資料４－３

採血基準に関する各種論文等（要約）一覧表

第１回WG提示各種論文等

資料番号	出典	対象	症例数	目的	結果
①	日本赤十字社	19年度全献血ドナー		19年度ドナー被害救済者対象	200ml献血において16～24歳までのVVR発生率は25歳以上に比較して頻度が高い。転倒率も同様の傾向にある。
②	河原班(18年度)	全血ドナー	18,726名	比重法とHb法との比較検討	比重検査の特異度低い（偽陽性、偽陰性高い）
		16-20歳初回全血献血ドナー	男性：47,038名 女性：43,194名	初回全血ドナーの年齢別、献血量別、重症度別にVVR発生頻度を比較	200ml献血男性ドナーでは16歳と比較し17歳-20歳のVVR発生率が高い。 200ml献血女性ドナーでは16歳-17歳と比較し18-20歳のVVR発生率高い。 400ml献血では男女ともに年齢間差はなかった。
		18-20歳全血献血ドナー	男性：14,191名 女性：12,503名	初回・2回目の献血方法別にVVR発生頻度を比較	初回200ml献血→2回目400ml献血は初回400ml→2回目400ml献血よりVVR発生率が高く、初回200ml献血によって2回目400ml献血時のVVRは防げない。
	河原班(19年度)	18年度全献血ドナー	男性：3,532,404名 女性：2,560,404名	献血基準拡大に伴う見込み	17歳400ml導入により全血総献血者数の0.73%増加するが、上限を69歳から74歳に引き上げることで0.11%増加に留まる。血小板献血を59歳から59歳へ引き上げにより45,534名増加が見込まれる。
		全血献血ドナー	男性：11,405名 女性：7,321名	比重法からHb法変更に伴う見込み	女性で1.44%のドナー減少、男性Hb13.0g/dlとすると1.04%のドナー減少
③	Transfusion2002	高校生全血ドナー（平均17歳）	白人：1,076名 アフリカ系：226名	若年ドナーのVVR発生リスク（人種別、性別、回数、体重別）	VVR発生率は白人8.2% vs アフリカ系1.2%で白人においては初回、低体重者、女性で多い。
④	Transfusion2006	高校生全血ドナー（平均17歳）	白人：7,274名	白人若年ドナーのVVR発生にリスク因子（性別、体重別、採血量別）	初回の17歳女性ドナーにおけるVVR発生率が高率である。
⑤	Transfusion2008	ドナーヘモビジランス	全血ドナー：6.014,472名 血小板ドナー：449,594名 赤血球ドナー：228,183名	2003年ARCドナーヘモビジランスより副作用解析	いずれの方法においても若年層ドナーでのVVR発生率は高く、月次変動は若年層が占める割合に依存する。→対策について
⑥	AABB2008			若年献血者の副作用及び傷害を軽減する方策	若年齢、初回献血、低体重、低血液量、女性、白人がVVRと相関。 これらの誘発因子を考慮し、副作用軽減に関する対策について検討。 傷害リスクを最小にするための勧告及び若年層への教育と同意に関する取り組みについて提案している。
⑦	血液事業2006	埼玉BCにおける全献血ドナー	男性：442,449名 女性：280,319名	全ドナーのうち、VVRによる転倒をきたした16名の解析とその対策	3年間で16名（0.002%）。全血男性ドナーに多い傾向。 10歳代と60歳代で同等に多い。水分摂取と30分休憩により10歳代の転倒者がゼロになった。
⑧	血液事業2006	埼玉BCにおける成分献血ドナー	成分ドナー：76,658名	成分ドナーにおけるVVR発生率の要因解析	初回女性（特に60歳以上）の成分献血でVVR高い。 初回成分献血の是非について

資料番号	出典	対象	症例数	目的	結果
⑨	Transfusion2008	豊橋BCにおける全献血ドナー	全血（男性：20,025名） （女性： 8,164名） 成分（男性：14,523名） （女性： 6,722名）	年齢、採血量、献血種類によるVVR発生率解析	女性（特に45歳以上、循環血液量少ない）の成分献血でVVR 発生率高い。（初回・再来での検討はされていない。）
⑩	FDA			血小板自動採血に対する指針	採血ドナー基準、管理他についての指針
⑪	血液事業	香川BCにおける全血ドナー	200mlドナー：63名 400mlドナー：62名	比重法とHb法の比較 （相関性）	比重適格者のHb（400ml：12.6−17.3g/dl、200ml：12.1−16.4g/dl)と妥当
			比重法（男性：23,985名） （女性：21,715名） Hb法（男性：22,749名） （女性：20.504名）	比重法とHb法の比較 （不適格者率、VVR発生率）	両法の不適格率に差はない。VVR発生率はHb法において男性で 発生率が減少したが女性では差がなかった。 →Hb法変更することによってVVR発生率は増加しなかった。
⑫	Transfusion2003	英国NBS	献血ドナー（男性：783名） （女性：730名）	比重法とHb法の比較 （相関性）	比重法は偽適格率が高い（特に女性）。 スクリーニング方法見直しが必要
⑬	自己血輸血学会2003	心臓血管外科自己血ドナー	8日で800ml採血：186名 7日未満400ml採血：44名 9日以上800ml採血：28名	自己血採血の採血間隔とHb回復、無輸血率	貯血間隔8日及び9日以上の2群で800ml貯血を行ったところ、1回目の Hb値は13.0g/dl及び13.5g/dl、術直前Hb値は1た。0g/dl及び11.2g/dlと 差異なく、無輸血率は81.7%及び92.9%であt
⑭	自己血輸血学会2004	自己血ドナー	男性13名、女性34名	400ml採血2週間後のHb回復度への影響因子	採血前Hb値と貯蔵鉄量がHb回復度に影響する。
⑮	Transfusion2004	ベルリン大学における全血ドナー	男性289名、女性237名	鉄剤服用による採血回数	20mg/日の服用により献血回数を男性で6回、女性で4回へ 上げることが可能であった。
⑯	血液事業			貧血と採血基準についての検討	鉄欠乏のない日本人男性のHb値下限は12.8～13.2g/dl、 女性は11.8～12.1g/dlであり、採血基準を見直す必要がある。
⑰	ARC			16歳以下の保護者に対する同意書	
⑱	佐竹班（15年度）	全国のBCによる献血ドナー	約6,000,000名	献血者の副作用データ解析	全献血者の1%に副作用、73%がVVR(全ての副作用で女性に高率）。 女性ではPC>PPP>400ml WB>、男性では採血種間差はない。 200ml採血で性差ない。 女性でのVVR頻度の増加分は対策により予防可能では？ →循環血液量に比する採血率の過重が原因と推察。
⑲	血液事業2006	埼玉BCにおける献ドナー	全血（男性：198,712名） （女性：320,943名） 成分（男性：100,457名） （女性：168,295名）	VVR高頻度群への予防対策と効果	全血（初回若年層）、成分（再来中高年女性）に30分以上の休憩、 水分摂取を促したところ、軽症のVVRは男女ともに低下したが、 重症例では男性では低下しなかった。 女性では血漿と400mlで有意に発生率が低下した。 若年男性の重症例では他の方策を考える必要がある。

資料番号	出典	対象	症例数	目的	結果
⑳	輸血学会2006	アンケート調査	集団献血高校生：400名 非集団献血高校生：450名 両群の教師：200名 父母：400名	16-17歳400ml採血への介入検討	情報提供前：400ml全血献血に67%、成分献血に61%に賛同 →情報提供後：400ml全血献血に77%、成分献血に74%賛同。 若年献血には適切な情報提供が必要である。

第2回WG追加各種論文等

資料番号	出典	対象	症例数	目的	結果
①*	日本赤十字社	19年度（16歳から19歳） 献血ドナー	16歳男性200ml：16,277名 16歳女性200ml：17,736名 17歳男性200ml：23,376名 17歳女性200ml：24,248名	19年度（16歳から19歳）献血ドナーにおける １歳刻みの副作用報告（被害救済者対象）	200ml献血において16～17歳の200ml全血でのVVR発生率は18から19歳よりむしろ低頻度であった。転倒率も同様もしくは若干低い傾向にあった。
②*	河原班ﾌﾟﾚｾﾞﾝ資料	17歳男性ドナー	男性：322名	17歳男性及び18-19歳男性における400ml採血による副作用、各種検査値改善度の比較検討	17歳男性における400ml全血採血は18-19歳の400ml全血と比してVVR発生率、Hb回復度に有意差はなく（むしろ低い傾向）安全に施行可能と考えられる。
③*	日本赤十字社	19年度全献血ドナー		年齢、性別、採血種類別採血副作用発生率	男性におけるVVR発生率は血漿採血と血小板採血の間でほぼ同様の傾向にあるが、女性では45歳以上血小板採血において血漿と乖離し、発生率が増加している。
④*	日本赤十字社	19年度複数回献血ドナー	男性11名	全血400ml複数回全血献血者のHb推移	4回献血者のHb推移では4回目の回復は落ちる傾向にある。
⑤*	厚生省血液研究事業 昭和59年度 研究報告集	複数回献血の安全性評価	男性307名 女性32名	3ヶ月間隔採血時のHb回復状況	男性では4回採血3ヶ月後の、女性では6ヶ月、9ヶ月後のHb値が初回前値と比較して有意に低下していた。
⑥*	日本赤十字社	全献血ドナー （平成16年10月～平成17年9月）		初回および再来献血者におけるVVR発生率 （採血種類別、性別）及び副作用総件数とその分類	全ての採血種間において初回ドナーは再来ドナーと比較して有意にVVR発生率が高く、特に男性で顕著である。成分献血においてはVVR歴よりも初回者の方が発生率が高いが、全血では初回者よりもVVR歴者でリスクが高かった。
⑦*	WHO	Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives(1994)		Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives(1994)	献血ドナーは男女とも18歳から65歳までの健常者であること。ドナー年齢の上限を設けていない、また親の同意があれば下限を16歳まで下げている国もある。
⑧*	WHO	Standard operating procedure		Standard operating procedure	**＜採血条件＞** ・採血間隔は3ヶ月以上あける ・体重が45Kg以上あること ・Hbが12.5g/dl以上であること （他） **＜同意について＞** ・血液の必要性 ・献血ボランティアの必要性 ・輸血を介する感染症について ・問診と正直な回答の必要性 ・安全な献血について ・献血血液の工程と使われ方について ・献血血液に行われる検査について

採血基準に関する各種論文

（第１回採血基準見直しの検討に係るﾜｰｷﾝｸﾞｸﾞﾙｰﾌﾟ提示分）

資料５

	項目	文献整理番号
1	400mL採血、成分献血の下限年齢の見直し	①、②、③、④、⑤、⑥
2	血小板成分採血の上限年齢	⑦、⑧、⑨、⑩
3	採血基準項目の「血液比重又は血色素量」を「血色素量」に改められないか	②、⑪、⑫
4	年間総採血量、採血回数、採血間隔	⑬、⑭、⑮
5	男性の血色素量最低値	⑯
6	インフォームドコンセント、ドナーの安全対策関連	⑤、⑥、⑩、⑰
7	その他（副作用全般）	①、④、⑥、⑦、⑧、⑨、⑱、⑲、⑳

19年度　年齢層別・男女別採血副作用発生件数

献血者年齢層／男女区分		VVR	VVR転倒	皮下出血	神経損傷	静脈炎	神経障害	穿刺部痛	その他	合計
16～19歳	男	5	15	8	1	0	2	0	7	38
	女	14	14	8	1	0	4	2	4	47
	小計	19	29	16	2	0	6	2	11	85
20～29歳	男	10	20	12	12	2	9	3	24	92
	女	33	20	13	16	2	8	6	19	117
	小計	43	40	25	28	4	17	9	43	209
30～39歳	男	12	16	11	31	4	15	9	23	121
	女	9	11	8	6	2	11	6	9	62
	小計	21	27	19	37	6	26	15	32	183
40～49歳	男	4	10	9	13	0	7	5	27	75
	女	8	7	4	7	1	5	2	7	41
	小計	12	17	13	20	1	12	7	34	116
50～59歳	男	7	5	7	6	0	4	3	10	42
	女	18	11	2	5	0	3	2	5	46
	小計	25	16	9	11	0	7	5	15	88
60～69歳	男	2	1	4	2	0	1	1	4	15
	女	5	5	2	2	0	0	0	2	16
	小計	7	6	6	4	0	1	1	6	31
年代別合計	男	40	67	51	65	6	38	21	95	383
	女	87	68	37	37	5	31	18	46	329
	合計	127	135	88	102	11	69	39	141	712

【参考】年齢層別・男女別献血者数

献血者年齢層／男女区分		献血者数(人)
16～19歳	男	171,258
	女	147,601
	小　計	318,859
20～29歳	男	654,236
	女	476,505
	小　計	1,130,741
30～39歳	男	944,094
	女	425,746
	小　計	1,369,840
40～49歳	男	816,948
	女	290,626
	小　計	1,107,574
50～59歳	男	543,530
	女	227,345
	小　計	770,875
60～69歳	男	168,722
	女	89,343
	小　計	258,065
年代別合計	男	3,298,788
	女	1,657,166
	合計	4,955,954

年齢性別採血副作用(平成19年度)

河原班　血小板採血基準拡大(年齢延長)関連

採血副作用件数(副作用1-5)

採血種類・性別／年齢		16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
200	男	745	223	155	94	68	46	23	17	8	4	2
	女	1,535	953	567	357	221	121	81	65	51	26	11
	男女	2,280	1,176	722	451	289	167	104	82	59	30	13
400	男	2,821	4,674	3,246	2,717	2,015	1,120	693	427	289	100	33
	女	1,514	2,206	1,183	1,005	719	468	353	312	382	190	52
	男女	4,335	6,880	4,429	3,722	2,734	1,588	1,046	739	671	290	85
PPP	男	97	274	245	251	235	186	157	124	272	158	100
	女	741	1,919	1,093	904	644	389	326	268	370	228	102
	男女	838	2,193	1,338	1,155	879	575	483	392	642	386	202
PC	男	207	817	633	860	826	632	538	405			
	女	571	1,573	1,084	955	792	570	497	424			
	男女	778	2,390	1,717	1,815	1,618	1,202	1,035	829	0	0	0

52,359

VVR件数(副作用1-5)

採血種類・性別／年齢		16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
200mL	男	688	213	148	87	59	43	17	11	2	0	0
	女	1,294	821	485	285	165	80	50	32	19	9	1
	男女	1,982	1,034	633	372	224	123	67	43	21	9	1
400mL	男	2,680	4,399	3,008	2,441	1,760	921	537	286	177	45	12
	女	1,405	2,010	1,067	879	618	390	283	255	309	150	43
	男女	4,085	6,409	4,075	3,320	2,378	1,311	820	541	486	195	55
PPP	男	62	155	131	132	113	89	65	51	112	58	34
	女	521	1,280	759	571	394	238	222	186	271	155	79
	男女	583	1,435	890	703	507	327	287	237	383	213	113
PC+PPP	男	113	405	310	392	375	276	232	176			
	女	400	1,017	737	634	531	382	342	319			
	男女	513	1,422	1,047	1,026	906	658	574	495	0	0	0

40,503

VVR転倒件数(副作用1-5)

採血種類・性別／年齢		16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
200mL	男	10	1	1	2	0	0	0	0	0	0	0
	女	20	9	4	0	1	1	0	1	0	0	0
	男女	30	10	5	2	1	1	0	1	0	0	0
400mL	男	45	74	40	49	25	26	10	6	6	0	0
	女	38	55	16	12	20	12	6	9	14	10	6
	男女	83	129	56	61	45	38	16	15	20	10	6
PPP	男	0	0	3	4	1	1	1	2	0	0	1
	女	4	21	12	5	11	0	2	3	3	1	2
	男女	4	21	15	9	12	1	3	5	3	1	3
PC+PPP	男	2	6	2	9	6	4	3	3			
	女	5	22	17	11	7	7	6	3			
	男女	7	28	19	20	13	11	9	6	0	0	0

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献血者数

採血種類・性別／年齢		16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
200mL	男	47,867	6,879	5,884	6,611	7,680	7,399	7,812	8,165	8,907	4,739	2,580
	女	77,296	61,090	50,306	52,509	48,690	35,505	28,678	25,689	27,733	15,538	6,567
	男女	125,163	67,969	56,190	59,120	56,370	42,904	36,490	33,854	36,640	20,277	9,147
400mL	男	107,177	230,977	228,788	307,542	341,513	301,881	262,572	213,351	181,239	82,713	32,031
	女	43,836	89,385	71,250	81,221	86,687	71,062	61,444	59,681	62,845	34,442	12,937
	男女	151,013	320,362	300,038	388,763	428,200	372,943	324,016	273,032	244,084	117,155	44,968
PPP	男	5,177	24,801	32,797	40,804	43,698	36,816	32,135	23,749	51,376	26,987	19,672
	女	16,703	66,545	56,308	49,051	40,257	27,964	21,760	16,198	21,334	12,513	7,346
	男女	21,880	91,346	89,105	89,855	83,955	64,780	53,895	39,947	72,710	39,500	27,018
PC+PPP	男	11,037	55,822	68,288	93,108	103,138	89,328	79,005	56,743			
	女	9,766	44,475	37,146	35,268	32,063	24,410	19,803	13,865			
	男女	20,803	100,297	105,434	128,376	135,201	113,738	98,808	70,608	0	0	0

4,955,954

採血副作用発生率(副作用1-5)

採血種類・性別／年齢		16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
200mL	男	1.56%	3.24%	2.63%	1.42%	0.89%	0.62%	0.29%	0.21%	0.09%	0.08%	0.08%
	女	1.99%	1.56%	1.13%	0.68%	0.45%	0.34%	0.28%	0.25%	0.18%	0.17%	0.17%
	男女	1.82%	1.73%	1.28%	0.76%	0.51%	0.39%	0.29%	0.24%	0.16%	0.15%	0.14%
400mL	男	2.63%	2.02%	1.42%	0.88%	0.59%	0.37%	0.26%	0.20%	0.16%	0.12%	0.10%
	女	3.45%	2.47%	1.66%	1.24%	0.83%	0.66%	0.57%	0.52%	0.61%	0.55%	0.40%
	男女	2.87%	2.15%	1.48%	0.96%	0.64%	0.43%	0.32%	0.27%	0.27%	0.25%	0.19%
PPP	男	1.87%	1.10%	0.75%	0.62%	0.54%	0.51%	0.49%	0.52%	0.53%	0.59%	0.51%
	女	4.44%	2.88%	1.94%	1.84%	1.60%	1.39%	1.50%	1.65%	1.73%	1.82%	1.39%
	男女	3.83%	2.40%	1.50%	1.29%	1.05%	0.89%	0.90%	0.98%	0.88%	0.98%	0.75%
PC+PPP	男	1.88%	1.46%	0.93%	0.92%	0.80%	0.71%	0.68%	0.71%			
	女	5.85%	3.54%	2.92%	2.71%	2.47%	2.34%	2.51%	3.06%			
	男女	3.74%	2.38%	1.63%	1.41%	1.20%	1.06%	1.05%	1.17%			

VVR発生率(副作用1-5)

採血種類・性別／年齢		16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
200mL	男	1.44%	3.10%	2.52%	1.32%	0.77%	0.58%	0.22%	0.13%	0.02%	0.00%	0.00%
	女	1.67%	1.34%	0.96%	0.54%	0.34%	0.23%	0.17%	0.12%	0.07%	0.06%	0.02%
	男女	1.58%	1.52%	1.13%	0.63%	0.40%	0.29%	0.18%	0.13%	0.06%	0.04%	0.01%
400mL	男	2.50%	1.90%	1.31%	0.79%	0.52%	0.31%	0.20%	0.13%	0.10%	0.05%	0.04%
	女	3.21%	2.25%	1.50%	1.08%	0.71%	0.55%	0.46%	0.43%	0.49%	0.44%	0.33%
	男女	2.71%	2.00%	1.36%	0.85%	0.56%	0.35%	0.25%	0.20%	0.20%	0.17%	0.12%
PPP	男	1.20%	0.62%	0.40%	0.32%	0.26%	0.24%	0.20%	0.21%	0.22%	0.21%	0.17%
	女	3.12%	1.92%	1.35%	1.16%	0.98%	0.85%	1.02%	1.15%	1.27%	1.24%	1.08%
	男女	2.66%	1.57%	1.00%	0.78%	0.60%	0.50%	0.53%	0.59%	0.58%	0.54%	0.42%
PC+PPP	男	1.02%	0.73%	0.45%	0.42%	0.36%	0.31%	0.29%	0.31%			
	女	4.10%	2.29%	1.98%	1.80%	1.66%	1.56%	1.73%	2.30%			
	男女	2.47%	1.42%	0.99%	0.80%	0.67%	0.58%	0.58%	0.70%			

VVR転倒発生率

採血種類・性別／年齢		16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69
200mL	男	0.021%	0.015%	0.017%	0.030%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%	0.000%
	女	0.026%	0.015%	0.008%	0.000%	0.002%	0.003%	0.000%	0.004%	0.000%	0.000%	0.000%
	男女	0.024%	0.015%	0.009%	0.003%	0.002%	0.002%	0.000%	0.003%	0.000%	0.000%	0.000%
400mL	男	0.042%	0.032%	0.017%	0.016%	0.007%	0.009%	0.004%	0.003%	0.003%	0.000%	0.000%
	女	0.087%	0.062%	0.022%	0.015%	0.023%	0.017%	0.010%	0.015%	0.022%	0.029%	0.046%
	男女	0.055%	0.040%	0.019%	0.016%	0.011%	0.010%	0.005%	0.005%	0.008%	0.009%	0.013%
PPP	男	0.000%	0.000%	0.009%	0.010%	0.002%	0.003%	0.003%	0.008%	0.000%	0.000%	0.005%
	女	0.024%	0.032%	0.021%	0.010%	0.027%	0.000%	0.009%	0.019%	0.014%	0.008%	0.027%
	男女	0.018%	0.023%	0.017%	0.010%	0.014%	0.002%	0.006%	0.013%	0.004%	0.003%	0.011%
PC+PPP	男	0.018%	0.011%	0.003%	0.010%	0.006%	0.004%	0.004%	0.005%			
	女	0.051%	0.049%	0.046%	0.031%	0.022%	0.029%	0.030%	0.022%			
	男女	0.034%	0.028%	0.018%	0.016%	0.010%	0.010%	0.009%	0.008%			

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（医薬品・医療機器等レギュラトリーサイエンス総合研究事業）
総括研究報告書

献血者の安全確保対策に配慮した採血基準の拡大に関する研究

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研究要旨

2002 年に成立した「安全な血液の安定供給に関する法律」においても、血液製剤の安全性確保と国内自給によるその安定供給は同法の理念にもなっている。さらに同法の国会審議において、献血者に生じた健康被害の救済の在り方について検討することが附帯決議の中でも求められている。いわば献血者は病に苦しむ人を救うという人類普遍の善意に基づいて献血という行為を行っている訳だが、こうした献血者の善意で現代医療は支えられているが、献血者の安全性をさらに向上するとともに医療現場に安定して血液製剤を供給するためには、最近の状況を踏まえて、科学的観点から改めて採血基準を再検討する必要がある。

採血基準に関しては現在、献血者の健康面への配慮と受血者にヘモグロビン量の多い血液供給をめざす観点から、内部基準の設定や検討が一部の血液センターにて実施されている。ヘモグロビン簡易測定法への全国的な切り替えに際し、適切な採血基準または内部基準を統一することが検討課題となっている。そこで、血液比重による採血適否判定とヘモグロビン簡易測定値の比較を行い、統一的な基準策定のための調査を実施した。

約２万人のデータを得た結果から、従来からの血液比重による採血適否判定とヘモグロビン簡易測定値では、血液比重では採血可能との判定にあるもののヘモグロビン簡易測定値では、採血ができないほど低値にある採血者も確認された。逆に、血液比重は 1.052 未満であるにもかかわらずヘモグロビン簡易測定値では、採血が十分可能な高値の献血者が存在することも明らかとなった。

この両者の差異を解消できる採血基準の策定が今後必要になる。

一方、献血に伴う血管迷走神経反応（VVR）等の副作用は、献血者に健康被害を及ぼすなどの負の側面があり極力その防止に努めるべき課題である。

本研究ではさらに、若年者に多いと言われている献血時の副作用の一つである血管迷走神経反応（VVR）に関して、現行採血基準における若年者の「初回献血の年齢別・献血方法別 VVR 反応発生状況」について調査するとともに、「初回献血は 200ml 献血を行ない２回目に 400ml 献血を行なった場合と、初回・２回目とも 400ml 献血を行なった場合の両者における、２回目 400ml 献血時の VVR 発生率」についての比較を行った。

また、待機的な手術に用いられる貯血式自己血では、その採血基準は一般献血の採血基準より厳格ではないことから自己血の採血時の有害事象を調査した。その結果、年齢、体重に関する献血基準の範囲外の症例で VVR を有意に発症しやすいということはなかったが、VVR 発症例で１回の採血量の循環血液量に対する割合は有意に高かった。採血基準の改定を検討する場合、採血量の循環血液量に対する割合を考慮すれば、現行の年齢、体重に関する規定を緩和できる可能性が示唆された。

少子高齢社会が急速に進展している今日、科学的根拠に基づく採血基準を設定するとともに、献血者の健康保護に十分配慮した血液事業の推進が求められている。

A．目的

献血人口の減少は少子高齢社会の進展により急速に進行している。自国の血液製剤需要は国内自給により賄うことがWHO（世界保健機関）をはじめとする国際的な認識である。しかし、わが国ではこのように献血人口が減少している現実を踏まえると、採血基準を見直すことにより必要量を確保することも血液の需給バランスを考える際のひとつの手段である。

血液事業はこうした医療現場が混乱しないように必要な血液製剤を絶えず供給するという使命を有するとともに、こうした量的確保に加えて献血者や受血者の安全性を確保し、製剤の品質向上に関しても大きな使命がある。

近年、従来より用いられていた血液比重による貧血の判定に替えてヘモグロビン簡易測定法による貧血の判定へと切り替える血液センターが増えている。

そこで、従来の血液比重による判定方法とヘモグロビン簡易測定法による判定方法を比較することにより、適切な採血基準を設定し、献血者の健康面への配慮と受血者にヘモグロビン量の多い血液供給をめざすに当って、科学的な根拠を示すことが本研究の目的のひとつである。

次に、今後益々進行する少子高齢化社会における輸血用血液の安定確保を図るために若年者の献血推進、特に400ml全血採血の推進のために必要な献血時の副作用の発生状況を詳細に調査し、その予防対策を講じるための基礎資料とすることが本研究のもうひとつの目的である。実際の献血者データを分析するとともにその採血基準が、一般献血の採血基準より厳格ではない待機的な手術に用いられる貯血式自己血の採血時の有害事象を調査することにより、現行の献血採血基準の範囲外における採血者の安全性を検討した。

B．方法

B－1．血液比重による採血適否判定とヘモグロビン簡易測定値の比較

全血採血の適否判定を現行どおり血液比重法にて行うと同時にHb値簡易測定を実施し、採血基準のあり方についての検討資料とするために、全血献血（200mL、400mL）希望者を対象にして、埼玉、愛知、福岡、岡山の4血液センターにて平成19年2月上旬～3月末日の期間に実施した。

そして、「①400mL献血者の男女別Hb分布」、「②比重測定にて1.052以上1.053未満として400→200mL採血に変更した献血者のHb分布」、「③200mL 献血者の男女別Hb分布」、そして「④1.052未満で不採血の場合のHb分布」について分析した。

B－2．若年献血者の全血採血におけるVVR反応の発生頻度について

1) 若年者の初回献血時VVR反応発生状況の調査では、全国7地域（北海道、宮城県、東京都、愛知県、大阪府、岡山県、福岡県）で平成17年1月～12月に献血をした16歳～20歳の献血者を対象とし、性別、年齢別、献血方法（200ml、400ml）、重症度別にVVRの発生率を調査した。2) 初回200ml献血を行なうことのVVR軽減効果については、当該期間に上記7地域で2回目の献血を行なった18歳～20歳の献血者のVVR発生状況を初回献血時の方法別に解析した。

2) 平成18年に東京都立駒込病院で自己血を採血した患者215例を対象にレトロスペクティブに解析した。患者背景、年齢、性別、体重、一回採血量、循環血液量などを調査し、採血に伴う合併症の有無とその要因について解析した。

（倫理面への配慮）

本研究は、個人を特定することなく献血に伴う副作用情報を分析するとともに、献血者の貧血情況を測定するものであり、貧血検査については献血の際の同意事項であるため倫理上の問題は生じない。また、データの取り

扱いについては「疫学研究に関する倫理指針(文部科学省・厚生労働省平成17年6月29日)」を遵守している。

C．結果

18,726名の献血者に対して血液比重による採血適否判定とヘモグロビン簡易測定値の比較を行った。そのうち有効数、18,705名（男性11,387名（60.9%）、女性7,318名（39.1%））について分析を行った。

年齢は、平均38.4歳（最年少16歳、最年長69歳）で、全体の血液比重値は平均値が1.05272、ヘモグロビン値が14.0であった。

希望する献血の種別については、200mL採血が3,107名（16.6%）、400mL採血が15,598名（83.4%）で、400mL採血を希望する献血者が多かった。しかし、実際の採血種類は、200mL採血が2,769名（14.8%）、400mL採血が13,562名（72.5%）、採血できなかった者が2,370名（12.7%）であった。

比重測定にて1.052以上1.053未満として400→200mL採血に変更した献血者のHb分布であるが、この情況に合致した献血者は398名であった。そのヘモグロビン値の平均値は、12.47g/dl(最小値10.2g/dl、最大値18.7g/dl)であった。

血液比重法の特性（血液比重測定法の感度、特異度、擬陽性率、擬陰性率など）を分析するために200mL採血と400mL採血に分け、前者は比重1.052が血液比重法による採血基準であることから、1.052以上と1.052未満に分けた。そして、もうひとつの採血基準であるHb値12g/dL以上の場合真の採血可能者、未満を真の採血不可能者とした。同様に400mL採血については、血液比重1.053とHb値12.5g/dLを基準数値に用いた。

そしてこれらを下記のように分類した。

200mL採血

	Hb値12g/dL以上	Hb値12g/dL未満	合計
血液比重1.052以上	真の採血可能者(a)	擬の採血可能者(b)	a+b
血液比重1.052未満	擬の採血不可能者(c)	真の採血不可能者(d)	c+d
合計	a+c	b+d	a+b+c+d

400mL採血

	Hb値12.5g/dL以上	Hb値12.5g/dL未満	合計
血液比重1.053以上	真の採血可能者(a)	擬の採血可能者(b)	a+b
血液比重1.053未満	擬の採血不可能者(c)	真の採血不可能者(d)	c+d
合計	a+c	b+d	a+b+c+d

その結果、以下のようになった。

200mL採血

	Hb値12g/dL以上	Hb値12g/dL未満	合計
血液比重1.052以上	2,595	137	2,732
血液比重1.052未満	37	0	37
合計	2,632	137	2,769

感度=2,595/2,632=0.986

特異度=0/137=0

擬陰性率=37/2,632=0.014

擬陽性率=137/137=1

陽性尤度比=真陽性率/擬陽性率=感度/（1−特異度）

=0.986/1=0.986

陰性尤度比=擬陰性率/真陰性率=(1−感度)/特異度

=0.014/0・・・計算不能

400mL 採血

	Hb 値 12.5g/dL 以上	Hb 値 12.5g/dL 未満	合計
血液比重 1.053 以上	13,126	370	13,496
血液比重 1.053 未満	1	65	66
合計	13,127	435	13,562

感度=13,126/13,127=0.9999

特異度=65/435=0.149

擬陰性率=1/13,127=0.00008

擬陽性率=370/435=0.851

陽性尤度比=真陽性率/擬陽性率=感度/（1−特異度）

=0.9999/0.851=1.1750

陰性尤度比=擬陰性率/真陰性率=(1−感度)/特異度

=0.0001/0.149=0.0007

献血者を対象としたデータが示すところは、若年者の血管迷走神経反応（VVR）の発生状況やその態様については、1)若年者の初回献血時の総 VVR 反応発生率は(軽症例＋重症例)、男性 200ml 献血時で平均 1.86%、400ml 献血時で 3.75%であった。年齢別では、200ml における 18 歳、19 歳、20 歳の発生率が（各々2.69%、2.37%、2.99%)、16 歳、17 歳（1.45%、1.62%）と比較して高い傾向が認められたが、400ml においては年齢間の発生頻度に違いはなかった。うち、重症 VVR の発生率は 200ml で 0.07%、400ml で 0.17%であった（年齢間に有意差なし)。女性の総 VVR 発生率は 200ml で平均 2.16%、400ml で 4.34%であった。年齢別の発生頻度は、200ml では男性同様に 18 歳、19 歳、20 歳の発生率が（各々2.23%、2.42%、2.76%)、16 歳、17 歳（1.72%、1.92%）と比較し高い傾向が認められたが、400ml では年齢間の発生率に有意差は認めなかった。うち、重症 VVR の発生率は 200ml で 0.13%、400ml では 0.28%あり、年齢間の発生率に有意差は認めていない。2）初回の献血方法別（200ml、400ml 別）に、2 回目の 400ml 時の VVR 発生率を見たところ、初回が 200ml で 2 回目に 400ml の場合（初回 200ml 群）の総 VVR の発生頻度は、平均 2.82%であり、初回献血から 400ml を行ない 2 回目も 400ml の場合（初回 400ml 群）の VVR 発生率と比較して 1.42%と有意に高い結果であった。重症 VVR の発生率も初回 200ml 群が 0.23%と、初回 400ml 群の 0.07%と比較し、有意に高かった。

女性における総 VVR の頻度は、初回 200ml 群が平均 2.95%であるのに対し、初回 400ml 群で平均 2.40%と、初回が 400ml の方にやや低い傾向は認めたが、統計的有意差はなかった。重症 VVR の頻度は初回 200ml 群（0.11%）、初回 400ml 群（0.20%）であり、両者間に統計学的有意差はなかった。

自己血採血に関するデータであるが、対象者群の総採血回数は 404 回、男性 88 例、女性 126 例、年齢は平均 59.9（19〜87）歳、体重は 58.3（37.0〜97.0）kg であった。基礎疾患は整形外科疾患の手術例が 42.3%ともっとも多く、次に脳外科手術例 31.2%であり、また、健常者である骨髄提供者が 11.6%を占めていた。

年齢分布は、70〜79 歳が 55 例（25.6%）、80 歳以上が 12 例（5.6%）で、これらは一般の献血基準の範囲外の年齢で、計 67 例（31.2%）を占めていた。

患者体重の分布と採血量については、献血の採血基準では 200mL 採血で、男性は 45kg 以上、女性は 40kg 以上、また、400mL 採血ではどちらも 50kg 以上が求められる。これらの基準を満たさない例は、男性で 3 例（1.4%）、女性で 6 例（2.8%）、全体では 9 例（4.2%）存在した。

1 回の採血量は 400mL がもっとも多く 42.3%を占め、採血回数は平均 1.9 回（1〜5 回）で、総貯血量は平均 579.3mL（200〜1200mL）であった。1 回の採血量の患者循環血液量に対する割合は、平均 8.2%（3.7〜9.4%）であった。

すべての症例のうち、採血時に有害事象が生じたのは 8 例（9 回）であり、本年はすべてが血管迷走神経反射（vasovagal reaction: VVR）であった。VVR 重症度はすべて I 度であった。1 例が 2 回 VVR を起していた。VVR 発生率は、実人数で男性 2.3%、女性 4.8%、延べ人数で男性 1.4%、女性 2.7%であった。いずれも女性に多い傾向があったが、統計学的な有意差は認めなかった。

VVR を発症した例と発症しない例の特徴を比較したところ、特に高齢者で VVR 発症例が多いということはなかった。体重、身長、循環血液量は VVR 発症例で低値をとる傾向にあったが、有意差は認めなかった。しかし、循環血液量に対する採血量の割合は VVR 発症例で有意に高かった。

D．考察

血液比重法と Hb 測定法を比較したところ、200mL および 400mL 採血とも“血液比重検査の特異度”が低かった。つまり、擬陰性となる確率は低いものの、擬陽性となる確率が高い検査であると言える。

陽性尤度比が 200 および 400mL 採血とも 10 以下と極めて低いことから、血液比重検査は“貧血がないと考えられる献血者の”確定“には適していない。一方、陰性尤度比については、200mL は計算不能で 400mL は 0.1 以下であることから、400mL 採血に関しては、血液比重検査は“貧血であると疑われる献血者”の“除外”には有用であると考えられる。なお、400mL 献血の採血適否に用いられる血液比重法に限っては、全体として見れば検査精度が優れていると考えられる。

献血者の採血に伴う有害事象であるが、初回採血時の採血量と VVR の関係を指摘した報告もあることから、比較的不安が大きいと考えられる初回は 200ml 献血を、2 回目以降 400ml 献血を行なうことで VVR の発生率が軽減できるとも考えられる。しかし、今回の我々の結果では、男性では初回 200ml 献血、その後に 400ml 献血を実施した群の VVR の発生率は、初回から 400ml 献血をした群のより有意に高く、女性では両者間に有意差がなかった。

男性では 1 回目に 200ml をした献血者が 2 回目に 400ml 献血を行なう時に 1 回目より倍の量を採血される心理的不安が働いたことも一つの要因であろう。これに対し、女性では比較的、精神的影響が少なかったとも考えられる。しかし、これらは主として欧米からの報告であるため、人種差による心理的影響の違いについても今後検討して行く必要がある。さらにこれらの要因を加え、若年者の VVR 発生率を更に明確にする必要があると考える。

自己血採血については、年齢が採血基準の範囲外であってもVVRの発生率が高いということは認められなかった。

また、体重が採血基準の範囲外においても、VVRの発生率が高いということも認められなかった。ただし、循環血液量に対する採血量の割合はVVR発症例で有意に高かったので、採血基準の改定を検討する際には循環血液量に対する採血量の割合を考慮する必要があるだろう。

循環血液量は体重と身長により推計できるが、現行の採血基準は体重のみの規定がある。体重も循環血液量を反映するが、体重があっても身長が低い場合は循環血液量が少ないので、両者を加味して一回採血量を決めることが望ましい。すなわち、循環血液量を考慮すれば、現行の採血基準における年齢、体重に関する規定を緩和できる可能性があるだろう。

一方、今回の調査結果は低循環血液量がVVRの発症の原因となっている可能性を示したものと思われる。したがって、循環血液量に対する採血量の割合が高い場合は、補液や経口摂取などで水分を補給することの意義があらためて確認されたものと思われる。

E．まとめ

ヘモグロビン（Hb）簡易測定装置導入に伴い、献血者の健康面への配慮と、受血者にHb量の多い血液供給をめざす観点から、内部基準の設定や検討が一部の血液センターにて実施されている。Hb簡易測定法への全国的な切り替えに際し、適切な採血基準または内部基準の統一については、①現行基準値は健常男性のHb値と比較して低いため基準値引き上げの是非、②200mL採血基準を400mLと同一基準に引き上げることの是非、③Hb値の上限値の設定などが検討課題となっている。

このような背景のもと本研究を実施したが、血液比重法では比重に関する採血基準に適合していても実際にHb値が低くHb値からすれば採血基準を満たさない少数の献血者からも採血していたことが明らかとなった。

献血者の健康保護を考えると、血液比重法に代えてHb測定法を導入する必要がある。そして今回の研究結果をもとに、現行の採血基準値の見直しや受血者にHbが多い血液製剤を供給するための方策などを検討していく必要がある。

一方、採血時の有害事象であるが、若年者が初回に400ml献血をした場合の総VVR発生頻率は概ね3～4%であり、年齢、性別による差は少なかった。しかし、一般献血者のVVR発生率が1%程度であることを考えると、ハイリスクの献血者と考えての慎重な対応が求められることが再確認された。

今回の研究結果により、少なくとも若年者に初回献血では200ml献血を行い、2回目以降に400ml採血を行なうことは、VVRの発生率の軽減には繋がらないとの結果は得られたが、若年者の献血推進、特に400ml全血採血の推進を行なうにはVVRの発生頻度は一般献血者の数倍であることを念頭に入れ、その検診、採血から接遇に至るまで細心の注意を払うべきと考える。

また、自己血採血時の有害事象は、現行の採血基準の範囲外の70歳以上の症例が31.2%含まれていたが、特にVVRの発生率が高いということはなかった。また、現行の採血基準の範囲外の低体重者が4.2%含まれていた。低体重の原因だけではVVRの発生率が高いことはなかったが、VVR発症例では循環血液量に対する採血量の割合が有意に高かった。

以上のことより、献血者の適格人口の増加を期待し、採血基準を見直す場合、循環血液量に対する採血量のことを考慮すれば、年齢は70歳以上でも十分、安全性は確保できる可能性がある。

F．健康危険情報

特になし

G．研究発表

1. 論文発表

予定あり

2. 学会発表

予定あり

H．知的財産権の出願・登録状況

(予定を含む)

1. 特許取得

特になし

2. 実用新案登録

特になし

3. その他

特になし

平成１９年度　厚生労働科学研究費補助金

（医薬品・医療機器等レギュラトリーサイエンス総合研究事業）

総括研究報告書

献血者の安全確保対策に配慮した採血基準の拡大に関する研究

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研究要旨

本研究班では献血年齢基準の見直しの観点から、1）17歳への400ml全血採血の導入、2）全血献血の上限年令(現行69歳)の見直し、3）血小板成分献血の上限年令(現行54歳)の見直しの可能性について導入効果（献血者の増加率）と安全上の問題を平成18年度の全国献血者のデータの基づき検討した。加えて「血小板の上限年令の見直しに関するアンケート調査」を50～54歳の血小板献血者を対象として実施した。

平成18年度に献血の受付をした男性3,532,404名、女性2,560,404名の計6,092,808名を対象として日本赤十字社の全国統一コンピューターシステムに入力されているデータを基に性別、献血方法別、年令階層別に献血者数、献血不適格者数、副作用発生状況を集計し、その結果を解析の基礎データとした。血小板献血の上限年令の見直しに関するアンケート調査は全国の7地域の血液センターで実施し、1,130名（男性739名、女性391名）からの回答が得られた。

その結果、1）17歳に400ml全血献血を導入することでは、年間に200ml献血換算46,684名分（男性28,961名、女性17,723名）に相当する増加が見込まれ、これは平成18年度の全血総献血者数（200ml換算）の0.73%（男性0.45%、女性0.28%）に相当した。献血時の副作用の発生率は17歳では男女とも18・19歳を比較しても同等以下であった。2）全血献血の上限年令を69歳から74歳に延長した場合に増加する献血者数は年間に200ml換算で6,573名であり、全血総献血者数の0.11%程度の増加しか見込まれないことがわかった。現行採血基準では最も高齢の60代献血者の副作用発生率を、他の年代と比較したが、同等以下の発生率であった。しかし、Hb値が基準値未満のため（Hb不足）献血不適格となった人数は男性60歳代が他の年代と比較して高いことがわかった。3）血小板成分献血の上限年令を現行の54歳から59歳に延長した場合には、年間45,534名の献血者の増加が見込まれた。50代の血小板献血者の副作用発生率は他の年代と比較しても発生率は同等以下の値であったが、Hb不足による献血不適格者数は男性で50代から高くなる傾向が認められた。「血小板献血の上限年令の見直しに関するアンケート調査」の結果では、90%以上の献血者が54歳以降も継続して血小板献血に協力したいと回答し、血小板献血の上限年令の見直しを行なうことには85%以上から賛成との回答が得られた。

このように年齢基準の見直しで比較的多数の献血者増が見込まれ、アンケート調査でも肯定的な回答が得られている血小板成分献血の上限年令の見直しを第一優先のテーマとして検討を進めるべきとの結論が得られた。

また、Hb基準値を引き上げた場合の献血者数への影響について血液比重による適否判定とHb簡易測定値をもとに検討した。

ヘモグロビン（Hb）簡易測定装置導入に伴い、献血者の健康面への配慮と、受血者にHb量の多い血液供給をめざす観点から、内部基準の設定や検討が一部の血液センターにて実施されている。Hb簡易測定法への全

国的な切り替えに際し、適切な採血基準または内部基準の統一について、特に「現行基準値は健常男性の Hb 値と比較して低いため基準値引き上げの是非と値」、「200mL 採血基準を 400mL と同一基準に引き上げることの是非」、「Hb 上限値の設定」が検討課題となっている。

血液比重測定法で採血適否判定を行い、同時に Hb 簡易測定も実施して、採血基準 Hb 値を引き上げた場合の採血数への影響を検討する。適切な採血基準として、参考資料　(内田立身：貧血と採血基準を考える～血液学的立場から～。赤十字シンポジウム 2007) をもとに、200・400mL 同一基準で男性 Hb≧13.0、女性≧12.5g/dL を仮定し算出した。

平成 19 年 2 月中旬～3 月下旬、血液センター（福岡ブロック、岡山ブロック、埼玉、愛知）で全血献血（200 mL,400mL）希望者を対象とし、血液比重法にて採血適否判定を行い、同時に Hb 値簡易測定をヘモキュー Hb201 プラスとその専用資材を用いて測定した。有効集計件数、男性 11,405 人、女性 7,321 人、計 18,726 人について解析を行った。なお Hb 簡易検査値は、当該検体の検査課機器測定値と大きく異なり、問診票と照合した結果 OCR 誤判読と判明したので、その点については訂正して解析した。また比重関連解析は、Hb 簡易検査判定をすでに導入していて比重同時測定を実施した岡山ブロックの一部のデータ（山口 BC 分）を除外し、総計 17,429 件を解析した。

その結果、比重測定 1.052 以上 1.053 未満を示し、400mL から 200mL に変更した献血者の簡易 Hb 平均値と標準偏差値は、男性 12.6±0.8 g/dL、女性 12.4±0.6g/dL で、現行の 200mL 採血基準の Hb12 g/dL 以上とほぼ合致する範囲であった。簡易測定 Ｈｂ値と検査課測定 Hb 値であるが、愛知 C では、検査課での血球計算測定は XE-2100 を使用し、4℃保存で採血翌日（約 24～32 時間後）に測定している。簡易測定法と同時に測定したものではないため、検査課測定値は参考データにとどまるが、同一検体の簡易測定 Hb 値と検査課機器 Hb 値の平均、相関係数を算定した。簡易 Hb 値は検査課機器と比較して、平均値で男性 0.4、女性 0.3 g/dL それぞれ低い値を示していた。相関係数は、男性は 0.923 と「非常に強い相関」を示したが、女性では 0.877 と「やや強い相関」の結果であった。献血申込者の簡易 Hb 値の平均と標準偏差値は、男性 14.9±1.1g/dL、女性 12.7±1.1 g/dL であった。男性で 13.0 g/dL 未満は 3.6%、女性で Hb12.5g/dL 未満は 37.9%であった。血液比重判定による男性献血者の簡易 Hb 値分布は、男性の 200mL 献血者数は 582 人（5.3%）で、10 代の占める比率が高い。400mL 献血は採血基準により、男女ともに比重測定法で 1.053（Hb 測定法で 12.5g/ｄL）以上と定められている。400mL 男性献血者では、Hb 簡易測定値で 13.0g/ｄL 未満は 241 人、逆に比重測定法で 1.053 未満と判定し Hb13.0g/dL 以上は 139 人存在した。Hb 簡易検査法に切り替え、判定基準値を 13.0g/ｄL 以上に設定すると、1.04%の減少が予測された。血液比重判定による女性献血者の簡易 Hb 値分布は、女性 200、400mL 献血者の Hb 値分布と年代別比率は、400mL 女性献血者では、比重測定にて 1.053 以上で、Hb 簡易測定値 12.5 g/dL 未満は 10.2%（310 人）含まれていた。逆に比重測定では 1.053 未満で、Hb12.5g/dL 以上を示した 400mL 献血希望者は 269 人であった。Hb 簡易測定法に切り替え、判定基準値（Hb12.5g/dL 以上）現行継続とした場合、41 人（1.44%）の減少が予測された。男性≧13.0、女性≧12.5g/dL 設定時の年代別採血不適率は、男性 400mL 献血希望者では Hb≧13.0g/dL とした場合、年代とともに不適率が上昇し、50 代（6%）、60 代（11.2%）で高く、全体では 3.5%が不適となった。200・400mL 同一判定基準を設定すると、200mL 希望男性の 6.7%が不適となった。女性に対し、200・400mL 同一判定基準（Hb≧12.5g/dL）を設定すると、10 代～40 代の不適率が高く、女性全体として 400mL 希望者で 35%、200mL 希望者で 42.6%が不適となった。献血申込者の簡易 Hb 値最高値は男性 20.0 g/dL、女性 18.7 g/dL であった。Hb 上限値の設定について、臨床的に精査が必要とされる数値を参考として男性 19 g/dL 以上、女性 17 g/dL 以上を設定した場合、不適率は男女ともに 0.08%であった。総蛋白量については、今回の検討対象者では、血中蛋白量が血液比重に

よる適否判定に影響したと考えられる例は認めなかった。

検討結果から、血液比重測定法と簡易 Hb 測定法はともに、手技を正しく行えば採血基準に従った適否判定に有用な手法と言える。H17 年に実施された簡易 Hb 測定機器評価試験で、検査課自動血球計数装置の測定値と比較して平均値がやや低いことが確認されている。今回の検討は、同一検体を 24～32 時間後に検査課機器**で測定した Hb 値であるが、簡易 Hb 値は平均値で男性 0.4、女性 0.3 g/dL それぞれ低い値を示していた。簡易 Hb 測定機器の誤差は±0.3 g/dL とされており、採血基準を下回る献血者からの採血が防止できる設定である。

Hb 測定法への切り替えに伴い、現行基準値は健常男性の Hb 値と比較して低いことから、基準値を 12.5 から 13.0 g/dL にひき上げた場合の採血予測を行ったところ、比重測定値 1.053 以上の判定時に比べ 1.04%の減少が予測された。女性では Hb を現行基準と同じ 12.5 g/dL と設定し、比重測定による判定と比較すると 1.44%の減少が予測された。女性において、簡易 Hb 測定機器導入で献血者予測が減少する理由として、測定機器が本来の Hb 値よりやや低めに表示するよう設定されていることも影響していると思われる。

200mL 採血数は減少傾向（H18 年：200mL 26%、400mL 74%）にある。受血者にとり供血者数は少ないほうが望ましく、200mL 採血は小児の輸血用に限定して採血している施設もある。200mL の採血基準を 400mL と同一基準にひきあげた場合、200mL 採血比率の低い九州地区ではほとんど影響がないと思われる。しかし、400mL 確保に苦慮している地域では、冬季の献血者減少時期など採血計画の変更が必要となる可能性がある。Hb 基準値の引き上げについては、今後予期しない感染症の流行や、供血者選択に新たな制限が加わる事態発生時などの血液確保も考慮して、検討されるべきであろう。

血液比重測定法は、基準値を満たすかどうかに限定した判定であるが、簡易 Hb 測定法では基準をはずれた献血申し込み者に対し、個々の状態に応じた健康指導が可能となる。Hb 簡易測定機器導入後は、この利点を生かした健康指導体制も望まれる。

また、本研究では献血に関する医学生の意識調査を行い、医学生の献血の現状、将来の予測、献血行動の関連因子を明らかにし、医学生に献血のプロモーションを行うことが献血者確保に有効か否かを予測した。2008 年 1 月 8 日から 2 月 1 日にかけて、東京医科歯科大学医学部医学科生を対象とした調査票調査を行い、299 名（全学生の 59%）から回答を得た。105 名（35%）が献血経験者であり、45 名（15%）がこの 1 年間に献血をしていた。今後 1 年以内に絶対献血すると回答したのは 31 名（11%）であった。今後献血する意志と関連する因子は献血経験の有無によって異なり、経験者では献血の継続性が、未経験者では義務感や後悔の念などが献血意志と関連するという結果となった。本学医学生の献血経験者率は低いが、献血率は高い。献血率の高さは、大学祭での献血バスによって初回献血者を常に確保していること、献血経験者が継続的に献血を行っていることによって維持されていると考えられる。献血未経験者の献血意志は TRA や TPB で説明可能であるが、経験者では「献血を継続しており、前回の献血で悪い印象がなく、特に阻害要因がないこと」が献血意志を高く保つ条件だと考えられる。医学生の献血に協力する気持ちは高く、プロモーション効果は十分にある。その際、未経験者では TRA や TPB に沿った戦略、経験者では毎回の献血で嫌なイメージを持たせないことに重点を置いた戦略を採る必要がある。また、献血バスの初回献血者確保に対する有効性も考慮すべきである。

注：　BC ; Blood Center
　　C ; Center
　TRA ; Theory of Reasoned Action
　TPB ; Theory of Planned Behavior

A．目的

少子高齢化社会の到来において献血可能人口の減少と高齢化による疾患構造の変化などにより血液需要量の増加が予測されるため、近い将来において血液の供給不足が懸念されるが、その対応策の一つとして献血年齢基準の見直しが考えられる。

そこで、本研究班では献血基準見直しの可能性が可能と考えられた3案、1) 17歳への400ml全血採血の導入、2) 全血献血の上限年令(現行69歳)の見直し、3) 血小板成分献血の上限年令(現行54歳)の見直しについて、導入効果（献血者の増加率）と安全上の問題の有無を平成18年度の全国献血者のデータの解析結果に基づき推定してみた。あわせて項目3）については、現行採血基準で血小板成分献血を行なっている50～54歳献血者を対象として、「血小板献血の上限年令の見直しに関するアンケート調査」を実施し、採血基準の見直しのための基礎資料を提供することが主たる目的である。

また、Hb基準値を引き上げた場合の献血者数への影響を知るために、血液比重による適否判定とHb簡易測定値の比較検討を行い、Hb簡易測定法への全国的な切り替えに際し適切な採血基準または内部基準の統一のためのデータを収集し、「現行基準値は健常男性のHb値と比較して低いため基準値引き上げの是非と値」、「200mL採血基準を400mLと同一基準に引き上げることの是非」、「Hb上限値の設定」などの妥当性を検討することがもう一つの研究目的である。

さらに医学生集団に対して集中的にプロモーションを行うことで献血者増加につながるかどうかを考察することを目的として研究を実施した。

B．方法

B－1．献血者の年令基準見直しに関する基礎的検討

平成18年度（平成18年4月～19年3月）に全国赤十字血液センター献血の受付をし、日赤全国統一コンピューターシステムに入力された男性3,532,404名、女性2,560,404名の計6,092,808名を対象として性別・献血方法別・年齢階層別に献血者数（実人数・延べ人数）、献血不適格者数、副作用発生状況について集計し、以後の解析の基礎資料とした。(献血者数は、男性3,212,704名、女性1,777,305名の計4,983,009名）併せて、全国7地域の血液センター（北海道、宮城県、東京都、愛知県、大阪府、岡山県、福岡県）で50歳～54歳血小板成分献血者を対象とした血小板献血の上限年令の見直しに関する意識調査を実施した。調査数は各施設200例（男性100例、女性100例）を目標とした。

B－2．血液比重による採血適否判定とHb簡易測定値との関係について

平成19年2月中旬～3月下旬、血液センター（福岡ブロック、岡山ブロック、埼玉、愛知）で全血献血（200mL,400mL）希望者を対象とし、血液比重法にて採血適否判定を行い、同時にHb値簡易測定をヘモキューHb201プラスとその専用資材を用いて測定した。有効集計件数、男性11,405人、女性7,321人、計18,726人について解析を行った。なお、上記の有効集計件数のうち当該検体の検査課機器測定値と大きく異なり、問診票と照合した結果OCR誤判読と判明したものを除外した17,429件を解析対象とした。

B－3．医学生の献血に対する意識調査

東京医科歯科大学医学部医学科1～6年生を対象に、授業間の休憩時間に調査票を配布する方法により、自記式調査票調査を行った。調査期間は、平成20年1月8日～2月1日で調査票の内容は、年齢、性別、学年、献

血行動（献血回数、献血場所、最近1年間の献血回数など）、献血に対する態度・イメージなど29項目である。

解析はSPSS 12.0J for Windowsを用いて行い、有意水準は0.05とした。

（倫理面への配慮）

本研究は、個人を特定することなく献血に伴う副作用情報を分析するとともに、献血者の貧血情況を測定するものであり、貧血検査については献血の際の同意事項であるため倫理上の問題は生じない。また、データの取り扱いについては「疫学研究に関する倫理指針(文部科学省・厚生労働省平成17年6月29日)」を遵守している。

C．結果

C－1．献血者の年令基準見直しに関する基礎的検討

17歳献血者への400ml全血採血の導入した場合の全血献血者の採血不適格者は、17歳男性の献血受付者数34,816名中、献血不適格者数は5,050名（14.5%）であり、17歳女性も献血受付者数53,188名中、献血不適格者数は20,728名（39.0%）と他の年代と比較して高い傾向が認められた。項目別に見ても、Hb不足（Hb値が基準値未満）、血圧、服薬、問診項目1（献血の永久不適項目に該当）、問診項目2（今回の献血は不可と判断される項目に該当）、事前検査、その他の全ての項目での不適格者数が他の年代と比較して高かった。

200ml全血献血者の年齢階層別副作用発生状況では、17歳男性の副作用発生率は1.19%であり、18～29歳の2.39%と比較して低い値であった。（18 19歳男性の副作用発生率は1.95%、2.79%）17歳女性の副作用発生率は1.75%であり、18～29歳の1.37%と比較すると高かったが、18歳、19歳の1.75%、1.81%との比較ではほぼ同等の値であった。

17歳に400m全血献血を導入した場合の献血人数(量)の増加の見込みであるが、平成18年度に200ml全血献血者を行なった17歳献血者のうち、どの程度が400ml全血献血の基準（体重、Hb値）を満たすかを調べた。17歳男性では29,765名中、400ml全血の献血基準（体重50Kg以上、Hb量12.5g/dl以上）を満たすのは28,961名（97.3%）であり、17歳女性では32,460名中、17,723名（54.6%）が体重・Hb量の両方の基準を満たすと推定された。

上記の献血者が全て400ml献血を行った場合には、年間に200ml献血換算で46,684名分（男性28,961名、女性17,723名）の献血量の増が見込まれるが、これは平成18年度の全血（200ml）換算総献血量6,378,490名の0.73%（男性0.45%、女性0.28%）に相当した。

全血献血の上限年令の見直しについては全血献血の献血不適格状況を見ると、男性におけるHb不足の比率は50代が0.19%、60～64歳は0.42%、65～69歳は0.69%と年令が増すとともに上昇する傾向があり、特に68歳・69歳のHb不足の率は0.93%、1.25%と高い値を示している。他の不適格項目の率は50代、60代で特に高い傾向はなかった。また、女性の50代、60代献血者の献血不適格者数は他の年代と比較して同等以下であった。200ml献血時の副作用発生状況、及び400ml献血時の副作用発生状況を見ると、男性では50代、60代献血者の発生率は他の年代と比較して低く、女性でも同様に50代、60代献血者の副作用発生率は他の年代と比較して低くかった。

全血の献血者数、献血率とも60歳から減少傾向を示している。そこで献血率と（男女計）と年齢についての回帰直線を求めたところ、200ml献血では、$Y=-0.04X+2.93$（$R^2=0.96$）、400ml献血では、$Y=-0.15X+10.61$（$R^2=0.97$）の式で表される負の相関関係が認められた。この回帰直線を用いて、全血献血の年齢基準の上限を74歳まで引き上げた場合の献血率についてシミュレーションを行なった。200ml献血では70歳で0.13%の献血率が73歳までに0.01%まで減少し、400ml献血では70歳は0.10%であるが

71歳で0.01%まで減少すると予測された。

血小板成分献血の上限年令の見直しについては、成分献血の受付者における献血不適格者状況を見ると、男性ではHb不足の率は、50～54歳で0.84%、54～59歳で1.12%、60～64歳で1.59%、64～69歳で1.69%と年齢を増すごと不適格の率も増加する傾向が認められたが、女性では50代・60代のHb不足の率は他の年代と比較して高くはなかった。

血小板成分献血（PC）を行なっている献血者の副作用の発生率は50～54歳の副作用発生率は男女とも他の年代と比較して同等以下であった。また、血漿成分献血（PPP）を行なっている献血者の副作用発生率を見ても男女とも50～69歳の副作用発生率は他の年代と比較して同等以下であった。

血小板成分献血の上限年令を現行の54歳から59歳迄延長した場合に献血者がどの程度増加するかをシミュレーションしてみた。年齢階層別の血小板成分献血者数は男女とも年齢を増すごとに献血者数が減少する傾向が認められている。45歳から54歳の間で、血小板献血者数（男女計の延べ人数）と年齢の関係について見てみると、$Y=-992.69X+65090.20$（$R^2=0.98$）で示す負の相関関係が認められた。

この回帰直線を用いて、血小板献血の上限年齢を現行の54歳から59歳まで引き上げた時に増加する献血者数を推定してみると、年間に45,534名の献血者の増加が見込まれ、これは18年度の総血小板成分献血者数775,148名の5.49%に相当人数であった。

また、全国7地域の血液センターで、現在血小板成分献血に協力をしている50歳～54歳の献血者を対象として血小板献血の上限年齢の見直しに関するアンケート調査を行なった。施設別の調査例数は　北海道188名、宮城県73名、東京都182名、愛知県123名、大阪府219名、岡山県177名、福岡県158名であり、合計は1130名であった（男性739名、女性391名）。年齢分布は50歳260名、51歳197名、52歳205名、53歳231名、54歳237名であった。

満54歳を越えてからの血小板献血については、男性で682名（92.3%）、女性で358名（91.6%）から今後も協力したいとの回答があった。血小板献血の上限年齢は54歳迄です。献血年齢の上限を引き上げについては、男性で661名（89.4%）、女性で337名（86.2%）から賛成の回答が得られたが、わからないとの回答も男性で68名（9.2%）、女性で47名（12.0%）あった。さらに賛成の場合、何歳までが適当と考えるかについては、男性では65歳未満との回答が225名（30.5%）最も多く、次いで60歳未満が207名（28.0%）であり、上限なしの回答は113名（15.3%）あった。女性では60歳未満との回答が153名（39.2%）と最も多く、次いで65歳未満が74名（18.9%）、上限なし41名（10.5%）の順であった。献血基準の見直しに関する意見は、「年齢に関係なく健康ならば献血可能」、「個人差があるので一律の年齢基準の設定は難しい」などの意見が多かった。献血基準の見直しに反対の意見は、3件あり、2件では（女性）血小板献血を行なった際に調子が悪くなったことを理由としていた。

C－2．血液比重による採血適否判定とHb簡易測定値との関係について

比重測定1.052以上1.053未満を示し、400mLから200mLに変更した献血者の簡易Hb平均値と標準偏差値は、男性12.6±0.8 g/dL、女性12.4±0.6g/dLで、現行の200mL採血基準のHb12 g/dL以上とほぼ合致する範囲であった。

簡易測定Hb値と検査課測定Hb値との関係については、愛知Cでは、検査課での血球計算測定はXE-2100を使用し、4℃保存で採血翌日（約24～32時間後）に測定している。簡易測定法と同時に測定したものではないため、検査課測定値は参考データにとどまるが、簡易Hb値は検査課機器と比較して、平均値で男性0.4、女性0.3 g/dLそれぞれ低い値を示していた。相関係数は、男性は0.923と「非常に強い相関」を示したが、女性で

は0.877と「やや強い相関」の結果であった。

献血申込者の簡易Hb値分布は、平均と標準偏差値は、男性14.9±1.1g/dL、女性12.7±1.1 g/dLであった。男性で13.0 g/dL未満は3.6%、女性でHb12.5g/dL未満は37.9%であった。

血液比重判定による男性献血者の簡易Hb値分布を求めたが、男性の200mL献血者数は582人（5.3%）で、10代の占める比率が高い。400mL献血は採血基準により、男女ともに比重測定法で1.053（Hb測定法で12.5g/dL）以上と定められている。 400mL男性献血者では、Hb簡易測定値で13.0g/dL未満は241人、逆に比重測定法で1.053未満と判定しHb13.0g/dL以上は139人存在した。Hb簡易検査法に切り替え、判定基準値を13.0g/dL以上に設定すると、1.04%の減少が予測された。一方、血液比重判定による女性献血者の簡易Hb値分布であるが、400mL女性献血者では、比重測定にて1.053以上で、Hb簡易測定値12.5 g/dL未満は10.2%（310人）含まれていた。逆に比重測定では1.053未満で、Hb12.5g/dL以上を示した400mL献血希望者は269人であった。Hb簡易測定法に切り替え、判定基準値（Hb12.5g/dL以上）現行継続とした場合、41人（1.44%）の減少が予測された。

男性≧13.0、女性≧12.5g/dL設定時の年代別採血不適率は、男性400mL献血希望者ではHb≧13.0g/dLとした場合、年代とともに不適率が上昇し、50代（6%）、60代（11.2%）で高く、全体では3.5%が不適となった。200・400mL同一判定基準を設定すると、200mL希望男性の6.7%が不適となった。女性に対し、200・400mL同一判定基準（Hb≧12.5g/dL）を設定すると、10代～40代の不適率が高く、女性全体として400mL希望者で35%、200mL希望者で42.6%が不適となった。

献血申込者の簡易Hb値最高値は男性20.0 g/dL、女性18.7 g/dLであった。Hb上限値の設定について、臨床的に精査が必要とされる数値*を参考として男性19 g/dL以上、女性17 g/dL以上を設定した場合、不適率は男女ともに0.08%であった。

総蛋白量については、今回の検討対象者では、血中蛋白量が血液比重による適否判定に影響したと考えられる例は認めなかった。

C－3．医学生の献血に対する意識調査

299名から回答を得た。内訳は1・2年96名（男72名、女24名）、3・4年113名（男65名、女48名）、5・6年90名（男59名、女30名、不明1名）であった。

現在までの献血回数が1回以上であると回答したものは105名（35%、n=299）であった。また、最近1年間に1回以上献血したと回答したものは45名（15%、n=296）であった。

将来の献血状況予測であるが、今後献血に協力する意向については、1年以内に絶対献血すると回答したものが31名（11%、n=289）であった。

回帰分析によって献血経験者ならびに未経験者の献血行動に関連する要因のモデルを作成したところ、経験者では「ここ1年間で何回献血しましたか」、「献血を続けることを止めようと考えたことがありますか」、「仮に献血する気持ちになった場合、確実に実行できると思いますか」の3項目、未経験者では「あなたにとって、献血は義務の1つですか」、「呼びかけられても献血しなかったとき、そのことを後悔することが多いですか」、「仮に献血する気持ちになった場合、確実に実行できると思いますか」、「問27. 近年、献血者数は増加していると思いますか、減少していると思いますか」の4項目で「今後献血に協力する気持ちはありますか」との間に有意に相関が見られた。

D．考察

若年者の献血基準であるが、欧米ではGoldmanらの報告によると16歳または17歳が下限と見受けられる。そこで、現在は200ml全血献血に限定されている17歳に400ml全血採血の導入をした場合に見込まれる増加率を調べたところ、全血総献血人数の0.75%（男性0.45%、女性0.28%）に相当する増加が見込まれている。なお、0.75%の増加は、平成18年度17歳の献血率4.7%に基づき試算したものであり、17歳の献血率が平成18年度の18・19歳の献血率の9.2%、9.9%により近づくならば、17歳献血者の占める比率は更に高くなることが考えられる。17歳の献血率が4.7%に留まっている要因の一つは、輸血用血液製剤の医療機関における需要の多くが400ml全血由来の製剤に移行し、200ml全血由来の血液製剤の需要が低下していることが考えられる。今後、若年者の献血推進（特に17歳）を進めて行くには、需要と供給のアンバランスが発生させない為にも17歳献血者に400ml全血献血を導入していくことが必要と考える。献血不適格者数は16歳、17歳が他の年代と比較して全ての項目で高値であったのは、初回献血者がこの年齢で多いことに起因すると考える。副作用の発生は若年者で高いといわれているが[1]、200ml献血時のVVR軽症例の発生頻度は17歳男性では1.05%であり、18歳～29歳の2.14%よりは低く、30代の1.01%とほぼ同等であった(18歳1.76%、19歳2.23%)。また、17歳女性の200ml献血時のVVR軽症例の発生頻度1.35%は、18歳～29歳の1.09%および他の年代と比較するとやや高い値であったが、18歳、19歳の1.39%、1.47%と違いはなった。

次に、全血献血の年齢の上限基準の見直しであるが、欧米では国により基準は異なり64歳から上限設定無しまで様々である。もし、本邦で74歳まで献血の上限年齢を引き上げた場合に見込まれる献血者数は年間6,573名で、全血総献血数の0.11%に限られることがわかった。これはカナダが2004年に献血の上限基準を見直した時に0.27%献血者が増加したとのGoldman報告[2]と比較しても低い値である。男性の68歳、69歳の献血者のHb不足の率が高値を示していることは、70歳以上の献血者が継続して全血採血を行なえるかの重要なポイントと考える。阿部らの報告では、赤血球系は70歳以降より急速に造血機能が低下し、骨髄有核細胞数が減少、脂肪髄の増加が認められるが、これらの年齢では日常生活活動能（ADL）の違いによりHb値は大きく異なるとしている。献血者は基本的にADLが高い母集団と考えられるが、現行採血基準で全血献血を行なっている65歳以上群のHb分布を調査し、他の年代と比較することも必要と考える。

血小板献血の上限年齢は54歳であるが、欧米では血小板成分献血の年令基準は全血献血の上限年齢を準用しており、採血の可否判定は検診医の判断に委ねられ、わが国より上限が高く設定されている。

そこで、現行の54歳の上限年齢を59歳に引き上げた場合に増加する献血者数を推定してみると、5.49%の血小板成分献血者数の増加に繋がる事がわかった。また、現在50歳～54の血小板成分献血者を対象として実施したアンケート調査では、90%以上の方は今後も血小板成分献血に協力すると回答し、85%以上の方が血小板献血の上限年齢は見直に賛成との回答が得られている。なお、血小板献血者数を年代別に見ると、男女とも年齢を増すごとに献血者数は減少しており、50～54歳の献血者は比較的献血に理解のある方が多く、そのことがアンケート結果に反映されているとも考えられる。今後は30代、40代の血小板献血者を対象としたアンケートも実施し、広い年代の意見をとりまとめることも必要と思われる。　50代以上の成分献血者のHb不足の率が高い点であるが、愛知県赤十字血液センター古田らは[4]、頻回の成分献血者で比重落ちの率が高いと報告している。成分献血時の事前採血の検体量や成分献血に用いるデスポーザブルキット内の残血などが要因の一つと考えられるが、成分献血を行なっている献血者の年代別のHb分布を調査し、年齢の要因が関与しているか否かを明確にすることは必要であろう。また、今回の集計結果ではVVRを含め、50代以上の献血者副作用の発生頻度は血小板・血漿献血ともは他の年代と比較して同等以下の率であったが、埼玉県赤十字血液センター溝口らは中年女性が血漿献血でVVRを発生した場合は回復が遷延する例を多く認めると報告している。高齢者の血小板献血におけるVVR回復時

間を調査し、回復時間の遷延の有無を確認しておくことも必要であろう。

血液比重による採血適否判定とHb簡易測定値との関係についてであるが、血液比重測定法と簡易Hb測定法はともに、手技を正しく行えば採血基準に従った適否判定に有用な手法と言える。H17年に実施された簡易Hb測定機器評価試験で、検査課自動血球計数装置の測定値と比較して平均値がやや低いことが確認されている。今回の検討は、同一検体を24～32時間後に検査課機器**で測定したHb値であるが、簡易Hb値は平均値で男性0.4、女性0.3 g/dLそれぞれ低い値を示していた。簡易Hb測定機器の誤差は±0.3 g/dLとされており、採血基準を下回る献血者からの採血が防止できる設定である。

Hb測定法への切り替えに伴い、現行基準値は健常男性のHb値と比較して低いことから、基準値を12.5から13.0 g/dLにひき上げた場合の採血予測を行ったところ、比重測定値1.053以上の判定時に比べ1.04%の減少が予測された。女性ではHbを現行基準と同じ12.5 g/dLと設定し、比重測定による判定と比較すると1.44%の減少が予測された。女性において、簡易Hb測定機器導入で献血者予測が減少する理由として、測定機器が本来のHb値よりやや低めに表示するよう設定されていることも影響していると思われる。

200mL採血数は減少傾向（H18年：200mL 26%、400mL 74%）にある。受血者にとり供血者数は少ないほうが望ましく、200mL採血は小児の輸血用に限定して採血している施設もある。200mLの採血基準を400mLと同一基準にひきあげた場合、200mL採血比率の低い九州地区ではほとんど影響がないと思われる。しかし、400mL確保に苦慮している地域では、冬季の献血者減少時期など採血計画の変更が必要となる可能性がある。Hb基準値の引き上げについては、今後予期しない感染症の流行や、供血者選択に新たな制限が加わる事態発生時などの血液確保も考慮して、検討されるべきであろう。

血液比重測定法は、基準値を満たすかどうかに限定した判定であるが、簡易Hb測定法では基準をはずれた献血申し込み者に対し、個々の状態に応じた健康指導が可能となる。Hb簡易測定機器導入後は、この利点を生かした健康指導体制も望まれる。

医学生の献血に対する意識調査であるが、今回の調査では35.1%（95%信頼区間29.9～40.7%）が献血をしたことがあるという結果となった。過去に行われた調査によると、19～29歳で献血経験のある人の割合は42.8%であり、この数値と比較すると本学医学生の献血経験者率は有意に低いことがわかる（$p<0.05$）。年齢が上がるにつれて献血経験の機会が増えると考えると、本学医学生の献血経験者率の低さは、回答者の平均年齢が22.3歳と若いことによるものだと推測できる。

一方、1年間の献血率（最近1年間に献血した人数を母集団の人数で除した数値）は15.2%（95%信頼区間11.6～19.7%）であった。日本赤十字社によると平成18年度の20～29歳の献血率は7.6%であり[1]、平成19年度もこの数値が維持されると仮定すると、医学生の献血率は一般の献血率に対して有意に高いと言える（$p<0.05$）。

また、今後の献血状況に関しては、「1年に以内に絶対献血する」と回答した10.7%（95%信頼区間7.6～14.8%）の人が必ず献血すると仮定し、平成18年度の20～29歳の献血率が平成20年度も維持されると仮定すると、平成20年度も本学医学生の献血率は一般よりも有意に高くなると考えられる（$p<0.05$）。

では、本学医学生の献血率が高い理由は何なのであろうか。調査票の分析の結果、最近1年間に献血した45名のうち19名（42%）が初めて献血をしており、この19名のうち14名（73.7%）が主な献血場所として「大学の献血バス」と回答していることや、最近1年間に献血した45名のうち17名（37.8%）が「1年以内に絶対献血する」、16名（35.5%）が「1年以内に献血するつもりでいる」と回答していることが分かった。これらのことから、本学医学生の献血率の高さは、献血経験者が継続的に献血することに加え、毎年10月に開催される大学祭での献血バスの活動による初回献血者確保によって維持されていると推測することができる。

これまでの考察から、本学医学生は「献血経験者率は低いが献血意志は高く、1度献血すると継続する可能性

が高い」という特徴を持つ集団であり、新規の献血者確保のための重要なターゲットとなり得ると結論づけることができる。

今後実際に医学生に対して献血のプロモーションを行う場合には、今回の調査結果で作成した献血意志関連モデルを参考にすると良い。未経験者のモデルでは、「あなたにとって、献血は義務の１つですか」、「近年、献血者数は増加していると思いますか、減少していると思いますか」が「規範意識」、「呼びかけられても献血しなかったとき、そのことを後悔することが多いですか」が「献血に対する態度」、「問25. 仮に献血する気持ちになった場合、確実に実行できると思いますか」が「統制感」とそれぞれのカテゴリーに入っており、TRA あるいはTPB の理論が当てはまることがわかる。一方、経験者のモデルはTRA やTPB の理論とは一致せず、「継続的に献血をしており、前回の献血でネガティブなイメージを持たず、特に阻害要因がなければ献血経験者は継続的に献血を行う」という構造になっていることがわかる。

よって、未経験者に対してはTRA およびTPB の理論に基づいた戦略を、経験者に対しては「毎回の献血で悪いイメージを持たせないこと」を念頭においた戦略を採ると良い結果が得られると考えられる。また、初回献血者の確保に関しては献血バスが大きな効果を持っていることも考慮すべきである。

E．まとめ

年齢基準の見直しで多くの献血者の増加が見込まれることから、血小板成分献血の上限年令(現行54 歳)の見直しを第一優先のテーマとして検討を進めるべきである。次に17 歳女性400ml 全血献血でのデータ収集が今後の課題となる。全血献血の上限年令の見直しについては、増加が見込まれる献血者数は少なく、60 歳以上で比重落ち率が増加していることを考慮すると、研究の優先順位は低いと考えられる。

献血経験や意識に関する医学生調査では、献血経験者率は低いものの、献血率・献血意志は高い集団であり、献血プロモーションによる効果は十分得られることが示唆された。また、プロモーションの際には献血経験の有無によって異なる戦略を採ることが望ましいことも明らかにされた。

F．健康危険情報

特になし

G．研究発表

1. 論文発表

予定あり

2. 学会発表

予定あり

H．知的財産権の出願・登録状況

(予定を含む)

1. 特許取得

特になし

2. 実用新案登録

特になし

3. その他

特になし

3

Vasovagal reactions in high school students: findings relative to race, risk factor synergism, female sex, and non-high school particpants

B.H. Newman

BACKGROUND: High school (HS) students have a high incidence of vasovagal reactions and are a good population for the study of vasovagal reactions.
STUDY DESIGN AND METHODS: Data from 1076 Caucasian students, 226 African-American students, and 157 nonstudents from HS blood drives in 2001 were entered into a database. Race, high-risk-factor synergism, the phenomenon of "survivorship," and female sex were evaluated. In addition, non-HS student participants were described.
RESULTS: Vasovagal reactions were 84 percent lower in African-American HS students than in Caucasian HS students (3 of 226 vs. 88 of 1076; 1.3 vs. 8.2 percent; $p = 0.0001$; relative risk, 6.2). In Caucasian HS students, first-time donor status increased the vasovagal reaction rate to 9.4 percent (vs. 3.6% in repeat donors, $p < 0.004$). Low weight (≤ 130 lb) increased the reaction rate to 13.6 percent (vs. 3.3% in weight > 81.2 kg, $p < 0.001$). Together they increased the reaction rate to 16.0 percent (vs. 3.2%, $p < 0.0001$). Females had more reactions than males (11.3 vs. 4.8%, $p < 0.001$), but the reaction rates equalized when donors under 150 lb were excluded (5.7 vs. 4.6%, $p = 0.66$).
CONCLUSION: African-American HS students had a significantly lower vasovagal reaction rate than Caucasian HS students. There was synergy among high-risk factors in Caucasian HS students. Female and male vasovagal reaction rates were similar when low-weight donors were excluded.

High school (HS) blood donors are young, frequently donate for the first time, and have a high incidence of vasovagal reactions. The high vasovagal reaction rate, which ranges from 8 percent to 11 percent,[1] makes them a unique population in which to study vasovagal reactions.

The following issues or questions were addressed in the present study. 1) Past studies have alluded to the possibility that African-American blood donors have fewer vasovagal reactions than Caucasians.[2,3] This study quantified the risk of a vasovagal reaction in Caucasian and African-American HS students. 2) Several measurable risk factors such as youth, low weight, and first-time donation status are associated with an increase in vasovagal reactions.[4-7] This study measured these risks and evaluated the degree to which they are additive. 3) Two recent studies reached different conclusions as to whether female sex increased the vasovagal reaction rate. One study found that confounding factors such as lower weight explained the higher vasovagal reaction rate in females,[7] while another study, although unpublished, found that female sex by itself was a risk factor (N.R. Haley, written communication, September 2000). This study addressed this question by evaluating female and male vasovagal reactions in four weight groups, which in a stepwise fashion eliminated lower weight donors. In addition to addressing these issues or questions, the study also evaluated non-HS participants to determine the extent of their participation, their demographics, and their vasovagal reaction rate.

ABBREVIATIONS: HS = high school; RR(s) = relative risk(s).

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MATERIALS AND METHODS

Phlebotomy

HS blood donations were collected on-site at Detroit metropolitan high schools. The donors were screened using a 40-question questionnaire, a mini-physical exam consisting mainly of vital signs, and a Hb-screening test. Accepted blood donors were subjected to a whole blood phlebotomy and collection of additional blood samples, which together did not exceed 535 mL. Blood donors rested on the donor bed after donation and were advised to spend 10 minutes at the refreshment site. All vasovagal reactions were recorded on the blood donor record, and an additional report was submitted if syncope occurred.

Data collection

Data from 1076 Caucasian HS students, 226 African-American HS students, and 157 nonstudent participants taken from randomly chosen Caucasian and African-American HS blood drives in 2001 were entered into a database (Excel 1997; Microsoft Corporation, Seattle, WA). The data entered consisted of the donor's age, race, sex, self-reported weight, blood donation status (first-time or repeat donation), a unique unit whole blood number, and the donor's reaction status. In addition, blood pressure results from 100 randomly selected Caucasian students were compared with 100 randomly selected African-American students.

Statistical analysis

Two-by-two contingency tables and a two-tailed Fisher Exact test were used to determine p values and relative risks (RRs) with 95 percent CIs. $p < 0.05$ was considered to be significant.

RESULTS

Demographics

Table 1 identifies the demographics of Caucasian and African-American HS students and nonstudent participants. Caucasian and African-American HS students were similar for mean donor age, percentage of females, percentage of first-time donors, and percentage of donors who weighed no more than 130 lb, but African-American HS students weighed slightly more (166 vs. 157 lb).

Nonstudent participants were 10.8 percent of the total number of participants. In comparison to HS students, they were significantly older (mean age, 44 vs. 17 years), had a lower first-time donor rate (9 vs. 79%-82%), weighed significantly more (180 vs. 157-166 lb), and had a lower percentage of donors under who weighed no more than 130 lb (10 vs. 22%–24%).

Comparison of vasovagal reaction rates

The vasovagal reaction rate was 8.2 percent (88 of 1076) in Caucasian HS students versus 1.3 percent (3 of 226) in African-American HS students ($p = 0.0001$; RR, 6.2; 95 percent CI, 2.0-19.3) versus 1.3 percent (2 of 157) in nonstudent participants ($p < 0.0004$). Eight syncopal reactions occurred in the Caucasian HS students, and none occurred in the other two groups ($p = 0.34$ with African-American students). Blood pressure results in Caucasian and African-American HS students were compared as a potential cause for the vasovagal reaction rate difference between the two groups. Table 2 shows a comparison of blood pressures in 100 randomly selected Caucasian HS students and 100 randomly selected African-American HS students. The differences were not significant.

Additive effects of high-risk factors in Caucasian HS students

The additive effects of risk factors could only be evaluated in the Caucasian HS students because the other two groups had very few reactions. Table 3 shows the effect of different risk factors. A first-time donor had a vasovagal reaction rate of 9.4 versus 3.8 percent in a repeat donor ($p < 0.002$; RR, 2.6). A low-weight donor ($\leq$ 130 lb) had a 13.6 percent vasovagal reaction rate versus 3.3 percent in a high-weight donor ($\geq$ 180 lb) ($p < 0.0001$; RR, 4.0). Adding both risk factors together increased the reaction rate to 16.0 versus 3.2 percent in donors who lacked these factors ($p < 0.004$; RR, 5.0). Since 45 percent of the Caucasian females weighed no more than 130 lb and only 5 percent of the males weighed no more than 130 lb, female sex was added last because of the confounding factor of low weight. The four factors increased the reaction percentage to 16.4 versus 3.8 percent in those who lacked these factors ($p < 0.01$; RR, 5.0).

TABLE 1. Blood donor demographics in Caucasian, African-American, and nonstudent participants

Population	Number	Mean age (years)	Females percentage	First-time donor percentage	Mean weight (lb)*	Percentage weighing no more than 130 lb
Caucasian HS students	1076	17	49	79	157 (150)	24
African-American HS students	226	17	47	83	166 (160)	22
Nonstudent participants	157	44	52	9	180 (180)	10

* Number in parentheses is median.

Repeat Caucasian donations (the "survival" phenomenon)

Repeat donors weighed more than first-time donors (163 vs. 155 lb), but the percentage of males and the percentage of females weighing no more than 59.0 kg in the two groups were statistically the same. Eighty-four percent of the repeat donors donated their second lifetime unit and 16 percent donated their third lifetime unit, based on a random sample of 50 HS blood donors. Repeat donors had a 60 percent reduction (3.8 vs. 9.4%) in their vasovagal reaction rate, but there was no synergistic benefit when additional factors such as "high weight" (weight ≥ 81.7 kg) or "male sex" or "both" were added to repeat donor status.

Vasovagal reactions in females

Table 4 shows the vasovagal reaction rate in Caucasian girls and boys at four different weight scenarios. Vasovagal reactions were higher in females than males when all donors were included (11.3 vs. 4.8%, p = 0.002) or when donors under 130 lb were excluded (9.4 vs. 5.0%, p = 0.018). Vasovagal reactions in females and males were similar when donors under 150 lb were excluded (5.7 vs. 4.6%, p = 0.66).

DISCUSSION

Caucasian HS students have a high predisposition toward blood donation-related vasovagal reactions because of their youth, high percentage of first-time donations, and lower weight.[4-7] Other studies have also shown that history of syncope and psychological factors can also increase vasovagal syncopal reaction rates.[8] The percentage of vasovagal reactions in first-time, mainly Caucasian HS donors has been reported to be as high as 8.7 times greater than in experienced blood donors.[1] Thus, Caucasian HS students represent an excellent population in which to study vasovagal reactions.

Two studies provided some evidence that African-Americans might have a lower predisposition for blood donation-related vasovagal reactions than Caucasians.[2,3] The present study is the first to quantify and compare the risk in two relatively equal groups of Caucasian and African-American HS students. African-American HS students have a vasovagal donor reaction that is 84 percent lower than Caucasian HS students (1.3 vs. 8.2%, p < 0.0001), and none of the eight syncopal vasovagal reactions occurred in the African-American group (0 vs. 0.74%, p = 0.34), although the differences in syncope between the two groups did not reach significance. Several studies have shown that elevated systolic blood pressure is protective against vasovagal reactions.[5-7] This potential explanation was studied but did not account for the differences between African-American and Caucasian vasovagal reaction rates (see Table 2).

Several studies have also demonstrated synergy among risk factors.[2,5,7] Graham[2] studied 352 Caucasian blood donors in 1957 (published 1961) in a hospital setting. The risk of a vasovagal reaction in his setting was

TABLE 2. Comparison of blood pressures in randomly selected Caucasian and African-American HS students

	Caucasian students	African-American students	p value*
Number	100	100	NA
Male percentage	61	52	0.2538
First-time percentage	73	85	0.0554
Mean BP†	115.6/71.3	117.4/71.6	0.36/0.84
Median BP	114/70	117/70	NA
Systolic BP ≤100 (%)	16	15	1.000
Systolic BP ≥140 (%)	7	13	0.2381
Diastolic BP ≤60 (%)	16	15	1.000
Diastolic BP ≥80 (%)	24	28	0.6289
Mean BP (females)	111.2/69.5	115/71.2	0.24/0.46
Mean BP (males)	118.4/72.5	119.6/72.5	0.62/0.71

* p < 0.05 is clinically significant.
† BP = blood pressure.

TABLE 3. Additive effects of risk factors in Caucasian HS students

Risk factor(s)	Vasovagal reaction rate (%)	p value*	RR (95% CI)
HS student	88/1076 (8.2)		
HS student; FT† donor (A1)	80/853 (9.4)	0.002	2.6 (1.3-5.3)
HS student; weight ≤130 lb (B1)	36/264 (13.6)	<0.0001	4.1 (1.9-8.6)
HS student; FT donor; weight ≤130 lb (C1)	35/219 (16.0)	<0.004	5.0 (1.2-20.4)
HS student; FT donor; weight ≤130 lb; female (D1)	32/195 (16.4)	<0.01	4.3 (1.1-17.6)
HS student; repeat donor (A2)	8/223 (3.6)		
HS student, weight ≥180 lb (B2)	8/239 (3.3)		
HS student; repeat donor; weight ≥180 lb (C2)	2/63 (3.2)		
HS student; repeat donor; weight ≥180 lb, male (D2)	2/53 (3.8)		

* Comparisons were made between A1 and A2, B1 and B2, etc.
† FT = first-time.

TABLE 4. Comparison of vasovagal reaction rates for females and males for four different weight groups

	Females*	Males*	p value†
≥110 lb			
All	51/523 (11.3)	27/553 (4.8)	0.002
First-time	55/422 (13.0)	25/433 (5.8)	0.0004
Repeat	4/101 (4.0)	2/120 (1.7)	1.000
≥130 lb			
All	32/341 (9.4)	27/537 (5.0)	0.018
First-time	29/266 (10.9)	23/417 (5.5)	0.011
Repeat	3/75 (4.0)	4/120 (3.3)	1.000
≥150 lb			
All	8/141 (5.7)	19/415 (4.6)	0.660
First-time	7/109 (6.4)	16/323 (5.0)	0.633
Repeat	1/32 (3.1)	3/92 (1.6)	1.000
≥180 lb			
All	1/44 (2.3)	7/191 (3.7)	1.0
First-time	1/34 (2.9)	5/138 (3.6)	1.0
Repeat	0/10 (0)	2/53 (3.8)	1.000

* Data presented as n (%).
† $p < 0.05$ is different.

quite high (15%), and a combination of factors increased the risk to 35 percent to 71 percent in some scenarios. Tomasulo et al.[5] and Kasprisin et al.[6] in blood center studies showed much lower risks. The risks in those two studies did not exceed 6.4 percent, even when risks were combined. The present study evaluated low-weight (≤ 59.0 kg) and first-time donation status in Caucasian HS students and found that low weight was a more significant factor than first-time donation status based on RRs (4.0 vs. 2.6) (see Table 3). Trouern-Trend et al.[7] found the same pattern in a study of vasovagal syncopal reactions. When low-weight and first-time donation status were combined, the risk was even greater (RR, 5.0). However, female sex barely affected the risk, when it was added as a fourth "risk" factor (RR, 4.3) because most of the "low-weight" individuals (< 130 lb) had already been excluded.

Repeat blood donors had a 60 percent decrease in vasovagal reactions (3.8 vs. 9.5%, $p < 0.004$) and adding other positive factors such as "high weight," "male," or "both" did not provide any additional benefit. Thus, repeat blood donation status alone is a good predictor for a low vasovagal reaction rate in HS students.

Female sex as a risk factor was evaluated by observing the vasovagal reaction rate in a stepwise fashion as lower weight donors were removed. The pattern clearly showed that lower weight (≤ 130 lb), which is much more common in females than in males (45 vs. 5%), was a major factor for increased vasovagal reactions in females. However, when donors under 150 lb were excluded, there were no differences between female and male vasovagal reaction rates. Thus, low weight is the main factor that causes a high reaction rate in females.

One limitation in this study was the low number of repeat donors. This influenced the RR ratios by increasing variability and decreasing precision. A second limitation was the size of the African-American population studied. It was too small to evaluate the causes of vasovagal reactions in the population.

In summary, this study showed that African-American HS students have a significantly lower vasovagal reaction rate than Caucasian HS students. There is synergy among high-risk factors and low weight is a more significant risk factor than first-time donor status. Although females have more vasovagal reactions than males, this is mainly due to lower weight, and the differences disappeared when donors under 150 lb were excluded. Repeat HS blood donors have 60 percent fewer vasovagal reactions, and a successful first-time donation is a good predictor of future success.

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Donor reactions in high-school donors: the effects of sex, weight, and collection volume

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BACKGROUND: The high incidence of donor reactions in first-time, 17-year-old Caucasian whole-blood donors makes this group ideal for the study of donor reactions.
STUDY DESIGN AND METHODS: Donor reaction rates were retrospectively evaluated in 7274 first-time, 17-year-old Caucasian whole-blood donors based on observations recorded at the collection sites. The effect of sex and weight on donor reactions was determined. In addition, a model was developed to estimate how different blood collection volumes would affect donor reaction rates.
RESULTS: The donor reaction rate was 12.0 percent (870/7274). Female donors overall had a higher donor reaction rate than male donors (16.7% vs. 7.3%) and also had a higher donor reaction rate than male donors at each 20-lb weight interval in the range from 110 to 189 lb. A model suggested that a change in the blood-unit volume from 450 to 500 mL would increase donor reaction rates by 18 percent in either female or male donors, whereas a reduction in the blood-unit volume from 500 to 400 mL would decrease donor reaction rates by 29 and 27 percent in female and male donors, respectively.
CONCLUSION: First-time, 17-year-old Caucasian female donors had a higher donor reaction rate than male donors overall and at equivalent donor weights. In the range of present US blood-unit volumes, a change in collection of as little as 50 mL could have a significant impact on blood donor reaction rates in high-school students.

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Clinical studies have evaluated the incidence of blood donor reactions[1] and have studied the correlation of donor characteristics such as weight,[2-6] age,[3-6] first-time or repeat donor status,[3-6] race,[6-8] and sex[3,4,6] to donor reaction rates. This study evaluated first-time, 17-year-old, Caucasian high-school students because these donors have a very high donor reaction rate of approximately 9 to 11 percent,[6,9] which is seven to nine times higher than the donor reaction rate in an experienced, general donor population.[2] We evaluated two nonfixed variables (sex, weight), but three variables (donor status, age, race) were fixed. We also developed a model for donor reaction rates as a function of sex and the ratio of whole-blood collection volume per donor weight, which allowed us to estimate the effects of various whole-blood collection volumes.

MATERIALS AND METHODS

Blood donor suitability and phlebotomy

High-school blood donors met acceptability criteria before being subjected to phlebotomy. The donors then lay in a supine position, and a 525-mL phlebotomy was performed in the antecubital fossa of the arm with a 16-gauge needle. The blood collection volume included 481 mL in a whole-blood unit, 33 mL in tubes for post-donation tests, and 11 mL trapped in the plastic tubing. Blood donor reactions observed at the collection site were recorded. A "donor reaction" was defined as the presence of any of the following symptoms or signs during or shortly after whole-blood donation: dizziness, diaphoresis (sweating), sudden weakness, hypotension, bradycardia, and syncope (faint). Approximately 97 percent of the reactions were nonsyncopal reactions.

Blood donor selection and data analysis

All high-school blood drive donor history records from 77 blood drives between October 1, 2003, and March 23, 2004, were reviewed. Donor selection was limited to 17-year-old, first-time, Caucasian donors who successfully donated a whole-blood unit. Studies have shown that African-American donors have a considerably lower donor

rate than Caucasian donors, so African-American donors were excluded from the study.[6,7] The decision to use successful donations and exclude unsuccessful donations was an arbitrary one. A total of 7274 donor history records were deemed suitable for evaluation.

Statistical analysis

Confidence intervals (CIs) for reaction rates were calculated as minimum-length intervals by integration of the Bayesian posterior with diffuse priors[10] with the assistance of computer software (the Solver tool in Microsoft Excel 2002, Microsoft Corp., Redmond, WA). Logistic regression was performed with Epi Info.[11] Proportion comparisons were done with the Fisher Exact test.

RESULTS

Donor weight distribution

Figure 1 shows a bell-shaped curve for male donors, with some skewing toward higher weights. In contrast, the curve for female donors appears truncated, suggesting that many Caucasian high-school female donors weighed less than 110 lb and could not donate blood.

Donor reaction rates in 17-year-old, first-time Caucasian blood donors

Table 1 shows the donor reaction rate for the total population and for each sex in 20-lb incremental weight groups. The donor reaction rate for the total population was 12.0 percent. Female donors had a 2.3-fold higher donor reaction rate than male donors, 16.7 percent versus 7.3 percent, and female donors had higher donor reaction rates within equivalent weight groups. Female donor reaction rates were 61 to 149 percent greater than male donor reaction rates, depending on the weight group. Figure 2 shows the donor reaction rates versus weight for female and male donors. Donor reaction rates appeared to decrease asymptotically as donor weights increased. Thus, logistic regression of reaction rate against a linear function of coded sex, reciprocal weight, and the product of coded sex and reciprocal weight—representing an interaction between sex and weight—was performed. The model was

$$\ln\left(\frac{r}{1-r}\right)=a+bs+\frac{c}{w}+\frac{ds}{w}, \quad (1)$$

where r is proportion of donors of coded sex s and weight w having a reaction; s = 0 if donor is male or 1 if donor is female; w is donor weight (lb); and a, b, c, and d are constants.

The coefficient d of the term representing sex–weight interaction was not significantly different from zero ($p = 0.09$ by a two-tailed test), so this term was omitted from the model. The remaining constants were found to have the following values: $a = -4.2941$, $b = 0.6120$, and $c = 284.1776$. All were significantly different from zero ($p < 0.0001$ by a two-tailed test). These constants yield the following formulas, which are plotted in Fig. 2.

$$\ln\left(\frac{r}{1-r}\right)=-4.2941+\frac{284.1776}{w} \text{ for male donors} \quad (2)$$

$$\ln\left(\frac{r}{1-r}\right)=-3.6821+\frac{284.1776}{w} \text{ for female donors.} \quad (3)$$

These formulas were used to give estimates of donor reaction rates at infinite weight, which were 2.5 percent for female donors and 1.3 percent for male donors. In a more practical context, the estimated donor reaction rates at 300 lb were 6.1 percent for female donors and 3.4 percent for male donors.

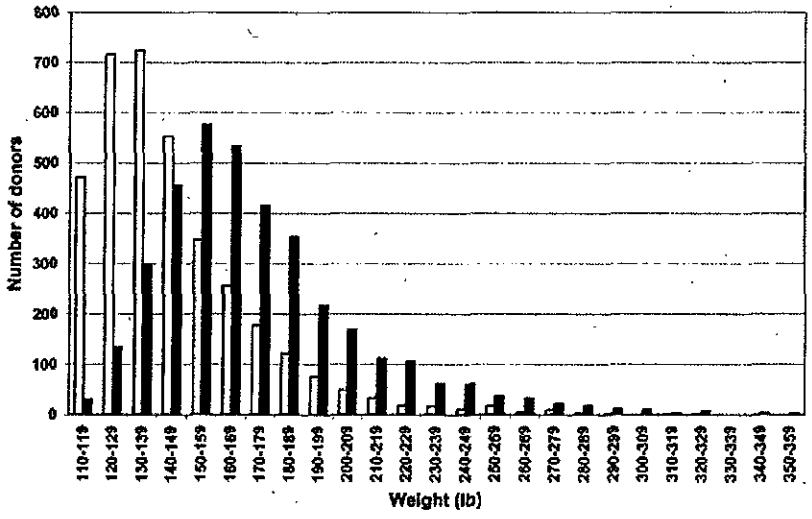

Fig. 1. Weights of first-time Caucasian high-school donors. (□) Female donors; (■) male donors.

Model for the effect of different blood-unit volumes on blood donor reaction rates

There is evidence that lower blood collection volumes are associated with lower reaction rates (see Discussion). We propose a unifying hypothesis that, for 17-year-old, first-time Caucasian donors, the donor reaction rate is a function of sex and the ratio of whole-blood collection volume to donor weight. Using the fact that Equations 2 and 3 were based on data obtained using a collection volume of 525 mL,

TABLE 1. Donor reaction rates in first-time, Caucasian high-school students

	Weight (lb)						
Donor sex	110-129	130-149	150-169	170-189	190-209	210+	Total
Female							
Number of reactions/number of donations	248/1187	206/1278	90/602	36/298	12/124	10/116	602/3605
Percent reactions	20.9	16.1	15.0	12.1	9.7	8.6	16.7
Male							
Number of reactions/number of donations	19/164	73/754	103/1108	39/768	15/386	19/489	268/3669
Percent reactions	11.6	9.7	9.3	5.1	3.9	3.9	7.3
Total							
Number of reactions/number of donations	267/1351	279/2032	193/1710	75/1066	27/510	29/605	870/7274
Percent reactions	19.8	13.7	11.3	7.0	5.3	4.8	12.0

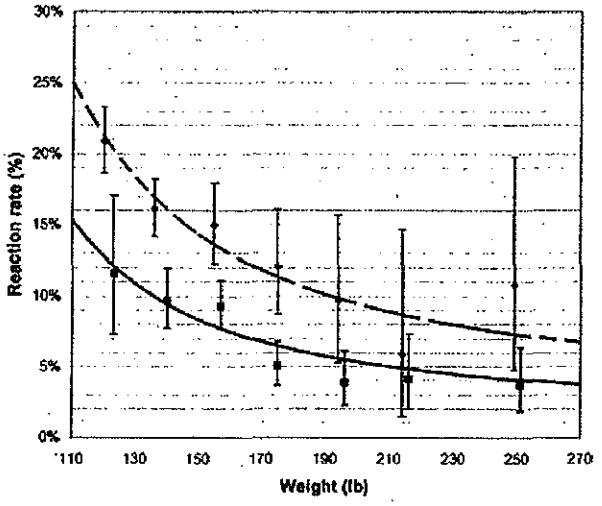

Fig. 2. Donor reaction rates in first-time Caucasian high-school students. Collections for each sex were grouped into 20-lb weight intervals for donor weights from 110 through 229 lb and a single interval for weights of 230 lb or more. The x coordinate of each group is the median weight, and the y coordinate is the reaction rate and its 95 percent CI. Curves were derived by logistic regression, as described under Materials and Methods. (◆) 95 percent CI, female donors; (■) 95 percent, male donors; (--) model, female donors; (—) model, male donors.

these equations were generalized to be consistent with the hypothesis

$$\ln\left(\frac{r}{1-r}\right) = -4.2941 + 0.5412907\frac{v}{w} \text{ for male donors} \quad (4)$$

$$\ln\left(\frac{r}{1-r}\right) = -3.6821 + 0.5412907\frac{v}{w} \text{ for female donors,} \quad (5)$$

where v is the blood collection volume in mL. When v = 525, Equations 4 and 5 are simplified to Equations 2 and 3, respectively.

The collection volume is the blood-unit volume plus the volume of blood in collection-set tubing and samples for testing. As previously stated, the latter is estimated to be 44 mL. Table 2 uses this estimate, the above model, and this study's donor weight distribution to give expected donor reaction rates at various blood-unit volumes. Table 3 compares the expected rates at different blood-unit volumes. The model suggests that an increase in the whole-blood unit volume from 450 to 500 mL would cause a 1.2-2.7 percent absolute increase in the donor reaction rate and a 17.9 to 18.2 percent relative increase in the donor reaction rate in first-time, Caucasian, high-school donors. Female donors had a greater absolute increase in the donor reaction rate (2.7 reactions per 100 collections vs. 1.2), but both sexes had similar relative increases of approximately 18 percent. A decrease in the whole-blood collection volume from 500 to 400 mL would decrease the donor reaction rate by 27 to 29 percent. Female donors would have a greater absolute decrease in the donor reaction rate (5.1% vs. 2.1%), but female and male donors would have a similar relative decrease (29% vs. 27%).

TABLE 2. Expected donor reaction rates at other collection volumes (reactions per 100 collections)

	Blood-unit volume (mL)						
Sex	500	481	450	400	350	300	250
Female	17.8	16.7	15.1	12.7	10.7	8.9	7.4
Male	7.8	7.3	6.6	5.7	4.8	4.1	3.5

TABLE 3. Expected effects of blood-unit volume changes on donor reaction rates*

	Blood-unit volume change (mL)		
Sex	450 to 500	500 to 400	500 to 250
Female	+2.7 (+17.9%)	–5.1 (–28.7%)	–10.4 (–58.4%)
Male	+1.2 (+18.2%)	–2.1 (–26.9%)	–4.3 (–55.1%)

* Absolute change in reactions per 100 collections (relative change).

DISCUSSION

Donor reactions are common. In a recent study, 7.0 percent of 1000 randomly selected interviewed whole-

blood donors had a donor reaction.[2] The rate was 2.5 percent based on observation at the collection site, but an additional 4.5 percent were found after a donor interview 3 weeks later. Approximately 97 percent of the donors had mild reactions, meaning that the donors had symptoms and signs such as dizziness, diaphoresis, pallor, and sudden weakness but did not faint. A 1-year follow-up showed that donors who had a reaction were 34 percent less likely than asymptomatic donors to return and donate again within a 1-year period.[12] Studies show that the blood donation return rates are even lower when donors had syncope.[13-15] Therefore, it is clear that a non-syncopal donor reaction decreases a donor's return rate, and syncope further decreases the return rate. Donor reactions are also a donor safety issue. One study showed a 14 percent injury rate in donors who progressed to syncope.[16] These injuries were often to the head and were generally minor, but lacerations and fractures occasionally occur. Serious injuries such as a closed-head injury are very rare but possible.

Three key factors associated with the probability of a donor reaction are weight,[2-6] age,[3-6] and first-time or repeat donor status.[3-6] Weight and age are the most important factors, and first-time or repeat donor status has marginal importance.[17] High weight, high age, and repeat status all protect donors against donor reactions. Caucasian donors have more risk for a donor reaction than African-American donors have.[6-8] Several studies have shown that female donors have more donor reactions than male donors,[3,4,6] but this was thought to be due to the female donor's smaller size because when female and male high-school donors over 149 lb were compared, the donor reaction rates were the same.[6] In addition, in 850 first-time, Caucasian donors from the same study, there were no differences in donor reaction rates when female and male donors in equivalent 20-lb weight groups were compared.[6] This study evaluated 8.6-fold more donors (7274 vs. 850) and detected large differences between reaction rates of female and male first-time Caucasian donors of similar weight.

Based on safety data for a 500 mL collection volume from a large blood center[18] and from the American Red Cross, most blood centers increased their whole-blood unit volume from 450 mL to a higher value. The American Red Cross collects 481 mL in each unit but 525 mL in total volume. This volume can be collected in any donor—even a donor with the lowest allowable weight, 110 lb (50 kg)—because it meets the AABB standard for a maximum whole-blood collection volume of 10.5 mL per kg of body weight.[19] Other blood centers collect two different whole-blood units—a 450-mL unit for low-weight donors and a 500-mL unit for donors weighing over approximately 120 lb.

A large blood center compared donor reaction rates in 282,000 donors who donated 450-mL whole-blood units and 547,000 donors who donated 500-mL whole-blood units.[18] The center did not detect a difference in donor reaction rates, which were 1.36 and 1.28 percent, respectively. But the subjects were from the general donor population, approximately 80 percent of whom were repeat donors and were much older and heavier than high-school students. A more sensitive study would have compared equivalent groups of very-high-risk donors such as the lower-weight female donors in this study, but this would have required entry of donor weight into the blood center's database, which is often not done.

In the donors studied here, the effect of two variables, sex and weight, on the reaction risk were determined. Three other variables, age, race, and first-time donor status, were fixed. It is probable but unproven that the bulk of the reactions in this group were caused by these five risk factors. Future studies could measure other factors that are thought to be associated with reactions such as a history of a donor reaction or being in the environment of a "group reaction." One could determine if there was an independent contribution from each variable by use of a logistics regression analysis, and such analysis could also quantify the contribution.

The model in this study, which relates the donor reaction rate in first-time, Caucasian high-school students to sex and the ratio of blood collection volume to donor weight, suggests that a 50-mL increase in whole-blood collection volume increased donor reaction rates by 18 percent. The model also suggests that a decrease in the blood-unit volume from 500 to 400 mL would decrease donor reaction rates by 29 percent in female donors and 27 percent in male donors, which is a very significant improvement. These lower rates are supported by Japanese data. The Japanese collect 400-mL (70% of collections) and 200-mL (30% of collections) units. They report a donor reaction rate of 0.6 to 0.7 percent based on 3.3 million whole-blood donations (H. Ikeda, Japanese Red Cross Society Central Blood Center, Japan; and M. Satake, Tokyo Red Cross Blood Center, Japan; written communications, 2003). Our data and model indicate that collecting 400-mL whole-blood units might be particularly effective in reducing donor reaction rates in young, low-weight, and first-time donors.

One limitation in this study was the lack of high-weight female donors. This made it difficult to show sex-related differences at high weights. A second limitation was that the data were based solely on observation of donors. In another study, a postdonation interview increased the number of reactions detected in a general donor population 2.3-fold, from 2.5 to 7.0 percent.[2] We do not believe that limiting the study to successful donations had an effect. The rate of unsuccessful donations in 4340 high-school students in the fall and winter of 2004 in our center was 5.0 percent (219/4340). It was 4.0 percent (21/525) in donors with a reaction and 5.2 percent (198/3815)

in donors with no reaction ($p = 0.21$). These data also challenge the perception that donor reactions are associated with more unsuccessful donations.

In conclusion, first-time, female Caucasian high-school students have a much higher donor reaction rate than male donors of equivalent weight. A model suggested that a change in the blood-unit volume from 450 to 500 mL would increase the donor reaction rate in this group by approximately 18 percent, and a decrease in the blood-unit volume from 500 to 400 mL would decrease the donor reaction rate by 27 to 29 percent. This kind of decrease in donor reaction rates would have a significant positive impact on safety and blood donor retention rates—particularly in first-time, lower-weight, high-school donors and other donors at high risk.

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5

The American Red Cross donor hemovigilance program: complications of blood donation reported in 2006

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BACKGROUND: The American Red Cross (ARC) initiated a comprehensive donor hemovigilance program in 2003. We provide an overview of reported complications after whole blood (WB), apheresis platelet (PLT), or automated red cell (R2) donation and analyze factors contributing to the variability in reported complication rates in our national program.

STUDY DESIGN AND METHODS: Complications recorded at the collection site or reported after allogeneic WB, apheresis PLT, and R2 donation procedures in 36 regional blood centers in 2006 were analyzed by univariate and multivariate logistic regression.

RESULTS: Complications after 6,014,472 WB, 449,594 PLT, and 228,183 R2 procedures totaled 209,815, 25,966, and 12,282 (348.9, 577.5, and 538.3 per 10,000 donations), respectively, the vast majority of which were minor presyncopal reactions and small hematomas. Regional center, donor age, sex, and donation status were independently associated with complication rates after WB, PLT, and R2 donation. Seasonal variability in complications rates after WB and R2 donation correlated with the proportion of donors under 20 years old. Excluding large hematomas, the overall rate of major complications was 7.4, 5.2, and 3.3 per 10,000 collections for WB, PLT, and R2 procedures, respectively. Outside medical care was recorded at similar rates for both WB and automated collections (3.2 vs. 2.9 per 10,000 donations, respectively).

CONCLUSION: The ARC data describe the current risks of blood donation in a model multicenter hemovigilance system using standardized definitions and reporting protocols. Reported reaction rates varied by regional center independently of donor demographics, limiting direct comparison of different regional blood centers.

Blood donation by healthy volunteers assures the availability of blood components for transfusion, which is a central tenet of modern health care. Accrediting and regulatory agencies (e.g., Joint Commission on Accreditation of Healthcare Organizations, Food and Drug Administration [FDA]) identify blood transfusion as a core function essential to quality medical care and promulgate specific requirements for appropriate use of blood components. Scientific efforts to improve blood safety have duly focused on the patient-recipient of blood transfusion and have substantially reduced the risk of infectious disease transmission. Similar scrutiny has not been applied to reducing the risk of blood donation, even though the infrequent occurrence of serious injury after blood donation may arguably now rival the residual risk of transfusion-transmitted infection.

ABBREVIATIONS: ARC = American Red Cross; LOC = loss of consciousness; R2 = automated red cell (donation).

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The blood supply depends entirely on the daily commitment of altruistic volunteers, who ostensibly gain little personal benefit from blood donation but are exposed to potential risk of discomfort, complications, and in rare cases, injury resulting from the collection procedure. Approximately 2 to 6 percent of all presenting donors experience a complication, most of which previously have been classified as light, mild, or minor reactions that resolve promptly but are still unpleasant for the donor.[1-5] Serious injury occurs infrequently, but typically results from a loss of consciousness (LOC), either at the donation site or after leaving the premises. Donor characteristics that correlate with higher syncopal complication rates after whole blood (WB) donation include young age, first-time donation status, low weight or total blood volume, female sex, and Caucasian race, although these may not all be independent predictors of reactions.[6-10] Changing population and donor demographics during the period 1996 through 2005 revealed that blood collection from young donors, aged 16 to 19 years, was increasing whereas blood donation rates by older individuals was declining.[11]

In light of these demographic trends, blood centers should continuously strive to improve the donation experience for all donors and should have an effective and comprehensive program to monitor donor complications as the keystone of a donor safety program. The importance of donor adverse reactions has been highlighted in the recent efforts by the AABB to initiate a US biovigilance program.[12] Our experience now provides a model system to assess the advantages and limitations of a national donor hemovigilance program.

Each year, the American Red Cross (ARC) has nearly 7 million encounters with individuals who present to donate WB or apheresis components to provide more than 40 percent of the US blood supply. The ARC established a national hemovigilance program to systematically analyze donor complications at its 36 blood regions. We describe annual hemovigilance data from 2006 and analyze factors contributing to variability in reported overall reaction rates in our system, which may serve as a basis for further improvements in hemovigilance efforts to protect healthy, volunteer blood donors.

MATERIALS AND METHODS

In 2003, ARC initiated a comprehensive hemovigilance program that prospectively collects data on events that occur at the time of donation, or that are reported later, including reports of donors receiving outside medical care. In mid-2005, the event definitions (Table 1) were modified to include citrate reactions for automated collections and the national reporting system was updated and fully implemented. This report describes data gathered in the first full calendar year of the modified program.

Collection site procedures

The 36 regional blood regions follow standard procedures for WB and automated collections from volunteer, allogeneic donors. WB is collected into 500-mL collection sets (Fenwal, Inc., Round Lake, IL; Pall Medical, Inc., East Hills, NY). The mean volume of collection is 517 ± 10 mL with trip scales and 524 ± 10 mL with electronic scales. Apheresis platelets (PLTs) are collected with one of three apheresis devices: Amicus (Baxter Healthcare, Round Lake, IL), Spectra (Gambro BCT, Lakewood, CO), or Trima (Gambro BCT). Automated red cell (R2) procedures for 2-unit red cell (RBC) collections are performed with Alyx (Fenwal, Inc.), Trima (Gambro BCT), or Haemonetics MCS+ 8150 (Haemonetics, Braintree, MA) systems. PLT procedures included plateletpheresis and plateletpheresis with infrequent plasma collection. PLT/plasma/RBC collections, plasma/RBC collections, and automated plasma and plasma/RBC collections were excluded from the analysis.

All adverse reactions occurring at the collection site are managed by collection staff, documented on the blood donation record according to the classification scheme (Table 1), and captured in a central electronic database. All donors are also instructed to contact the regional blood center if they experience problems or have concerns about their health after donation. Donor reactions or injuries reported by the donor or third parties after the donation event are managed by standard procedures, reviewed by a facility physician, and reported to the national hemovigilance program.

Classification scheme for donor complications

The standardized classification system for donor complications defines 15 reaction categories (Table 1). The scheme incorporates a severity rating (minor, major) for reaction types in most categories, and every category is further divided into whether or not the donor received outside medical care. Minor complications typically resolve within a short period of time (e.g., 30 min), and the donor recovers completely at the donation site and/or is managed solely by giving the donor instructions for care after an injury (e.g., hematoma) occurs. Major reactions typically require follow-up with the donor and review by ARC staff, either because they may be medically more serious or they may be more of a concern to donors (e.g., loss of bowel or bladder control during a short LOC), even if the reaction is not more medically significant than a minor complication. Presyncope defines a variety of symptoms (e.g., pallor, lightheadedness, dizziness, nausea) that may be related to vasovagal reactions, hypovolemia, or anxiety but do not progress to LOC. The small and large hematomas include true hematomas (e.g., a palpable mass), bruises, and infiltration at the venipuncture site. Reactions classified as "other" comprise a variety of

TABLE 1. Definitions of donor complications*

Complication	Brief description	
	Minor category	Major category
Systemic (syncopal-type):		
Symptomatic (presyncopal, prefaint)	Pallor, weakness, light-headedness, dizziness, diaphoresis, nausea/vomiting, no LOC.	
LOC	Short LOC: lasting less than 1 min.	Long LOC: lasting 1 min or more or complicated by seizures or convulsions or loss of bladder or bowel control.
Presyncopal or LOC with injury		Injury (e.g., head injury, fractures, abrasions, lacerations) associated with symptoms of prefaint or LOC.
Prolonged recovery		Symptoms of prefaint or LOC or other reaction that do not resolve within approx. 30 min.
Phlebotomy-related		
Hematoma	Small: involved area measures 2 × 2 in. or less.	Large: involved area measures more than 2 × 2 in.
Nerve irritation		Suggested by pain, tingling, numbness, or sharp shooting pains after phlebotomy.
Suspected arterial puncture		Suggested by rapid (<3 min) bleed time, pulsatile flow, and/or bright red blood.
Systemic (other)		
Citrate (automated procedures only)	Citrate reactions that persist despite intervention or are accompanied by additional symptoms such as nausea, muscle tightness, or cramping. Citrate reactions that involve perioral or peripheral tingling or numbness that resolves with reduced flow rate or calcium are not captured.	Symptoms of minor citrate plus prolonged or exaggerated muscle spasm (tetany), vomiting, chest tightness.
Allergic	Hives, itching, rash, or redness of skin.	Symptoms of minor allergic reactions, plus swelling of the face, neck, or throat; wheezing; or respiratory difficulty.
Other reaction	Symptom profile different from established categories (e.g., anxiousness, hyperventilation, headache).	Symptom profile different from established categories (e.g., chest pain, thrombophlebitis).

* Donor complications are classified according to type and severity (minor, major); cases in each minor and major complication category are further subclassified with respect to the need for outside medical care.

reactions or symptoms that do not otherwise fit into the established categories, including suspected thrombophlebitis and chest pain as major, other reactions. For every complication category, outside medical care is defined as medical advice or treatment provided by someone other than ARC staff (e.g., emergency medical services, a primary health care physician or specialist, or any health care professional), whether sought independently by the donor or at the advice of ARC staff. Donors may seek outside medical care for reactions that are common and self-limiting (e.g., large hematomas), as well as those that are medically more relevant to their well-being (e.g., syncope-related injuries).

National hemovigilance program

Every month, the hemovigilance program at the ARC National Headquarters Medical Office compiles and analyzes data on donor complications following WB and automated procedures that are either documented by collections staff at the time of donation or reported by the donor or a third party after the donation event, including cases that receive outside medical care. All major reactions (Table 1) that occur at the donation site and all reactions that are reported to the blood center after the donor leaves the site are captured on a standard case report form, investigated, and reviewed by the blood center physician and reported in a tally on a monthly basis to the National Medical Office. If a donor is referred for outside medical care by staff or later reports that he or she sought or received care from any outside health care provider, the complete blood donation record is reviewed by the National Medical Office and is maintained in a separate database. In this report, the actual medical care provided is not further differentiated and varies considerably from simple reassurance or advice to apply warm packs for the resolution of hematoma to administration of intravenous fluids and hospitalization.

Complications associated with allogeneic WB, apheresis PLT, and R2 procedures in 36 regions from January 1, 2006, to December 31, 2006, were analyzed; autologous and therapeutic collections were excluded. The analysis

also excluded 49 WB collection events in which a citrate reaction was recorded because these records most likely represent miscoding or misclassification of complications after WB donation, as well as 43 PLT donations and 45 R2 donations recorded for 16-year-old donors. Donor age was not recorded for 94 WB and 2 PLT donations.

Complications experienced by donors before the donation process or unrelated to phlebotomy (e.g., injuries caused by other accidents at the site) or experienced by individuals who did not donate blood (e.g., canteen volunteers) were excluded from the analysis. The denominator for the number of donations of each procedure type was the number of satisfactory collections plus the number of incomplete ("quantity not sufficient") collections. Donor complication rates were calculated per 10,000 collections for minor and major complications and for cases receiving outside medical care for different donor age groups.

Statistical analysis

Complication rates for different procedure types and among different age groups were compared by calculating odds ratios (ORs) and 95 percent confidence intervals (CIs; Instat, GraphPad, Inc., San Diego, CA). Linear regression and analysis of variance for the correlation between the proportion of young donors and monthly complications rates was performed with computer software (SAS Version 9.1.3, SAS Institute, Inc., Cary, NC).

A multivariate logistic regression analysis was performed to identify demographic variables that were independently associated with complications after WB, R2, or PLT donations using software (SAS STAT, SAS Institute, Inc.). There was an inverse and nonlinear relationship between donor age and the rate of complications, and complications were disproportionately represented in donors under age 20 and fairly constant above age 20. Consequently, the multivariate analysis considered the donors in the age groups as 16-year-olds, 17-year-olds, young adults (18- and 19-year-olds), and adults in each subsequent decade (e.g., 20-29, 30-39, up to 80+). A "STEPWISE" selection method was used to determine which effects entered the logistic regression model and also which effects remained in the model. A significance level of not greater than 0.05 was necessary for an effect to enter into the model and a significance level of not greater than 0.05 was necessary for an effect to remain in the model at any iteration step. The regression analyses for WB, PLT, and R2 procedures evaluated the independent variables (regional blood center, donor age, sex, donation status) and the dependent outcome (any complication). Outlier regions that performed fewer than 150 procedures in 2006 were not reported (three regions) in the R2 model. The ARC Institutional Review Board determined that the research was exempt under 45CFR46, 21CFR50.

RESULTS

Donations and donor complications at regional blood centers

In 2006, the donor hemovigilance program analyzed a total of 6,014,472 WB, 449,594 PLT, and 228,183 R2 collections, which were associated with 209,815, 25,966, and 12,282 adverse reactions (348.9, 577.5, and 538.3 per 10,000 donation), respectively. Minor symptomatic (presyncopal) reactions accounted for the majority of complications (258.3 per 10,000 collections) for WB, and small hematomas, for PLT and R2 donations (377.0 and 217.9 per 10,000 collections, respectively; Table 2). Excluding large hematomas, the overall rates of major complications were 7.4, 5.2, and 3.3 per 10,000 collections for WB, PLT, and R2 procedures, respectively (Table 2).

Regional and monthly variability in complications after WB donation

The complication rates observed for WB donation in the 36 regions demonstrated considerable regional and monthly variability; the systemwide mean was 348.9 ± 140.7 (range, 145.9-679.5) complications per 10,000 donations (Fig. 1). The overall WB complication rates in the 36 regions were normally distributed and 24 regions were within 1 standard deviation (SD) of the mean, and 34 regions were within 2 SDs of the mean (data not shown). For adverse reactions recorded by collection staff, mean monthly rates of reactions at the donation site varied over a wider range for the small- and medium-sized regions (approx. 57,000-207,000 WB collections per year) compared to the largest regions (with >208,000 WB collections per year).

Complication rates across the system demonstrated seasonal variation that was most pronounced for WB donation and strongly correlated with donor age. Specifically the rates of systemic (syncopal-type) complications (i.e., presyncope, LOC, injury, prolonged recovery) and the proportion of young donors (16-19 years old) for WB and R2 donations were higher in the spring and autumn compared to the winter and summer, whereas the rates of phlebotomy-related complications remained constant throughout the year (Fig. 2A). Systemic (syncopal-type) complications after WB donation correlated strongly with the proportion of donors less than 20 years old ($R^2 = 0.96$) and logistic regression demonstrated that the model explains a significant portion of the variation in the data ($F = 248.00$; $p < 0.0001$). Monthly variation was substantially less pronounced for systemic (syncopal-type) complications after automated collections (Fig. 2B) and did not correlate as strongly with the proportion of donors less than 20 years old as observed for WB ($R^2 = 0.58$; $p = 0.004$); no correlation was observed for PLT donations ($R^2 = 0.03$; $p = 0.58$).

TABLE 2. Rates of complications after WB and automated collections per 10,000 donations

Complications	WB (6,014,472)	Apheresis PLTs (449,594)	R2 (228,183)
Systemic (syncopal-type) complications			
Presyncopal (symptomatic, prefaint)	258.3	61.3	195.2
Short LOC	7.9	2.1	6.5
Major			
Long LOC	1.8	0.5	0.9
Prolonged recovery	2.4	0.8	1.0
Injury	1.1	0.3	0.1
Systemic (other) complications			
Citrate			
Minor		121.4	112.8
Major		2.2	0.4
Allergic (minor, major)	0.1	0.4	0.2
Other (minor, major)	0.6	1.0	1.0
All systemic			
Rate	272.1	190.1	317.9
Number of events	163,663	8,546	7,255
OR* (95% CI)	1.00	0.69 (0.68-0.71)	1.17 (1.15-1.20)
Phlebotomy-related complications			
Small hematoma	74.5	377.0	217.9
Major			
Large hematoma	0.4	9.4	1.9
Suspected nerve irritation	0.7	0.8	0.1
Suspected arterial puncture	1.1	0.2	0.4
Phlebotomy-related			
Rate	76.7	387.5	220.3
Number of events	46,152	17,420	5,027
OR (95% CI)	1.00	5.21 (5.12-5.31)	2.91 (2.83-3.00)
All reactions			
Rate	348.9	577.5	538.3
Number of events	209,815	25,966	12,282
OR (95% CI)	1.00	1.70 (1.67-1.72)	1.57 (1.54-1.60)
Major reactions			
Rate†	7.4	5.2	3.3
Number of events	4,443	232	76
OR (95% CI)	1.00	0.70 (0.61-0.80)	0.45 (0.36-0.57)
Outside medical care			
Rate	3.2	2.9	2.9
Number of events	1,903	132	66
OR (95% CI)	1.00	0.93 (0.78-1.11)	0.91 (0.72-1.17)

* ORs shown for univariate analyses compared to the rate for WB collections.
† Excluding large hematoma; univariate comparison of donation types.

Allogeneic WB donation and complications

The most common complications associated with allogeneic WB collections were systemic (syncopal-type) reactions (272.1 per 10,000 donations), most of which were mild symptomatic (presyncopal, prefaint) reactions that occurred at an overall rate of 258.3 per 10,000 donations (2.5%; Table 2). Of the major reaction categories, the most frequently reported was prolonged recovery (2.4 per 10,000 donations) or LOC for more than 1 minute (1.8 per 10,000 donations). The overall complication rate decreased with increasing donor age (Fig. 3) for both first-time and repeat donors (data not shown).

Young donors (<20 years old) accounted for 874,922 (14.5%) WB donations in 2006 and had a significantly higher reaction rate than older donors (Fig. 3). An analysis of complications in these young donors is presented elsewhere.[10] Multivariate analysis confirmed that regional blood center, age, sex, and first-time donation status are independent correlates for adverse events (Table 3). Donor age was the strongest independent predictor of complications; the effect of age effectively leveled off above age 40, although the differences between age groups was still significant. Other variables, including donor race, height, and weight, were not available on all donations for inclusion in this analysis. The overall complication rate was lower but the proportion of small hematomas was higher in the older age group (>60 years) compared to younger age groups (Fig. 3).

Overall, 1,903 WB donors had outside medical care documented after a complication, for a rate of 3.2 per 10,000 collections. Forty-six of these donors reported hospitalization after donation. The observed rate of reported outside medical care after WB donation was higher after first-time (5.7 per 10,000) compared to repeat (2.6 per 10,000) donations (OR, 2.2; 95% CI, 2.0-2.4). Major

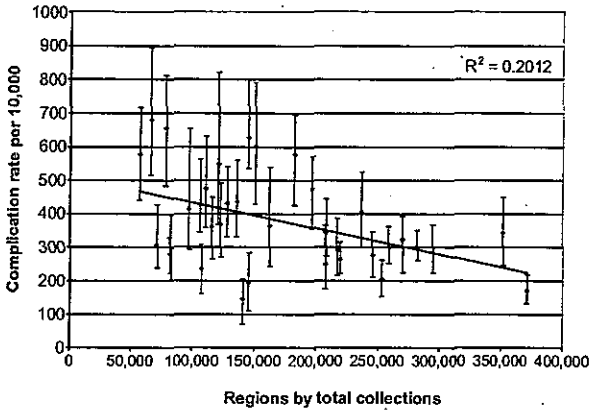


Fig. 1. Variability in rate of complications among ARC blood centers. The 36 regional blood centers are ordered by total collections in 2006 and plotted against their mean monthly overall complication rate per 10,000 collections. Bars show the maximum and minimum monthly complication rate for each center.

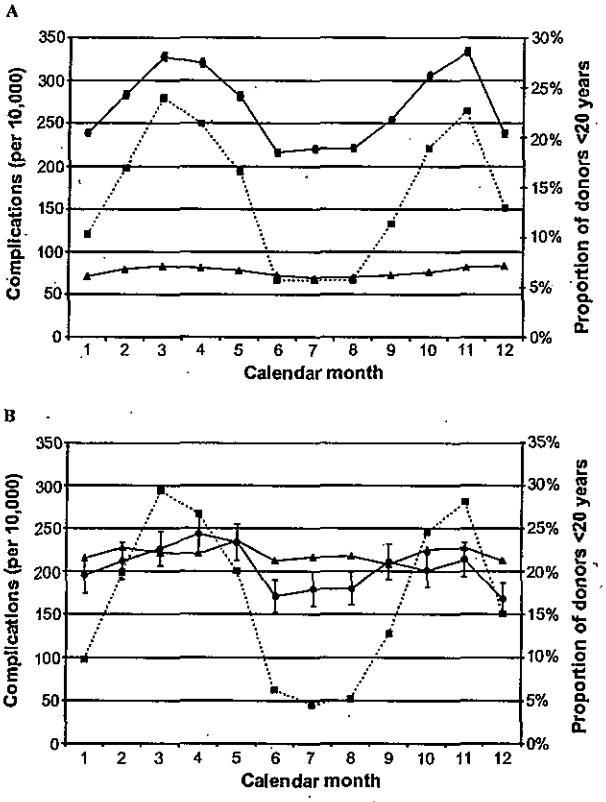


Fig. 2. Seasonal variability in donation-related complications correlates with the proportion of young donors. (A) WB; (B) R2. (●) Systemic (syncopal-type) complications; (▲) phlebotomy-related complications; (■, dotted line) proportion of donors less than 20 years old.

syncopal-type reactions (long LOC, LOC or presyncope with injury, prolonged recovery) accounted for approximately half (46%) of all reactions associated with outside medical care (Fig. 6A).

Automated collection procedures and donor complications

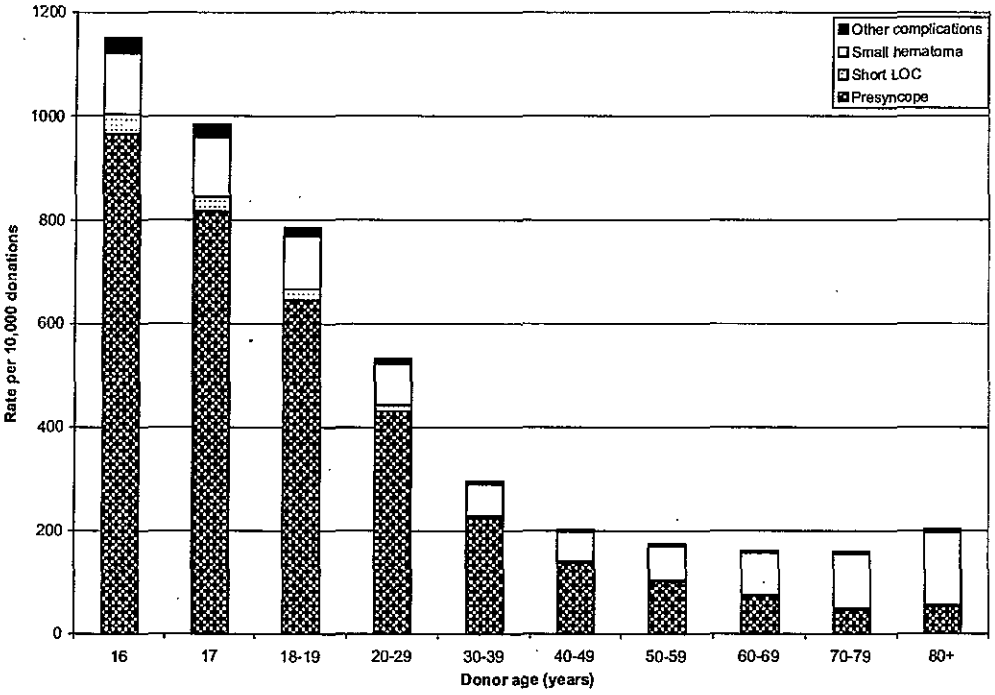
The most common complications associated with PLT and R2 donations were hematomas, followed by systemic citrate and syncopal-type reactions (Table 2). The rate of systemic reactions was lower for PLT donations (OR, 0.69; 95% CI, 0.68-0.71) and slightly but significantly higher for R2 donations (OR, 1.17; 95% CI, 1.15-1.20) compared to WB collections in a pairwise, univariate analysis (Table 2). The rate of major reactions, however, was significantly lower for both PLT (OR, 0.70; 95% CI, 0.61-0.80) and R2 (OR, 0.45; 95% CI, 0.36-0.57) collections. The rate of outside medical care was not significantly different for PLT and R2 (2.9 per 10,000) collections compared to WB (3.2 per 10,000) collections (Table 2).

As with WB donation, younger donors were more likely to experience complications after PLT (Fig. 4) and R2 (Fig. 5) collection, but the influence of age on the rate of donor complications was considerably less pronounced. Multivariate analysis confirmed that regional blood center, age, sex, and first-time donation status are independent correlates for adverse events (Table 3). Age was a strong independent predictor of complications, but there were no differences in complication rates in age groups above age 50 for R2 and above age 30 for PLT donation. Significant differences were observed among regional blood centers.

The observed rate of reported outside medical care was not different for WB (3.2 per 10,000) compared to automated procedures (2.9 per 10,000), but the composition of reaction types differed. Phlebotomy-related complications (large hematoma, possible nerve irritation) accounted for 39 percent of outside medical care reported after automated collections (Fig. 6B). Eight of these 198 donors reported hospitalization after donation.

DISCUSSION

A safe and adequate blood supply encampasses efforts to minimize the risk to the blood donor as well as the transfusion recipient. The present analysis represents the first report of the comprehensive ARC donor hemovigilance program. The data confirm the overall safety of blood donation and provide an estimate of risk currently associated with allogeneic WB and automated collection procedures. We have used the data internally for program and procedure development and have shared the data externally with various organizations to evaluate the impact of regulatory guidance and inform public policy. For



Donor age (years)	16	17	18-19	20-29	30-39	40-49	50-59	60-69	70-79	80+
Total donations	46,274	404,033	424,615	812,190	822,429	1,319,311	1,314,912	616,876	223,185	30,553

Fig. 3. Rates of donor complications associated with allogeneic WB donation. The overall rates are significantly ($p < 0.05$) different between each successive age group, except between the 60- to 69- and 70- to 79-year age groups.

example, the lower rates of serious reactions with automated PLT collections compared to WB collections served as the basis for a response to the FDA draft guidance on collection of PLTs by automated methods[13] to demonstrate that additional requirements for medical supervision at the collection site were unwarranted and would unnecessarily restrict PLT collection and availability. These data support the conclusions reached by others that plateletpheresis is associated with the lowest rate of systemic reactions compared to other collection procedures.[14]

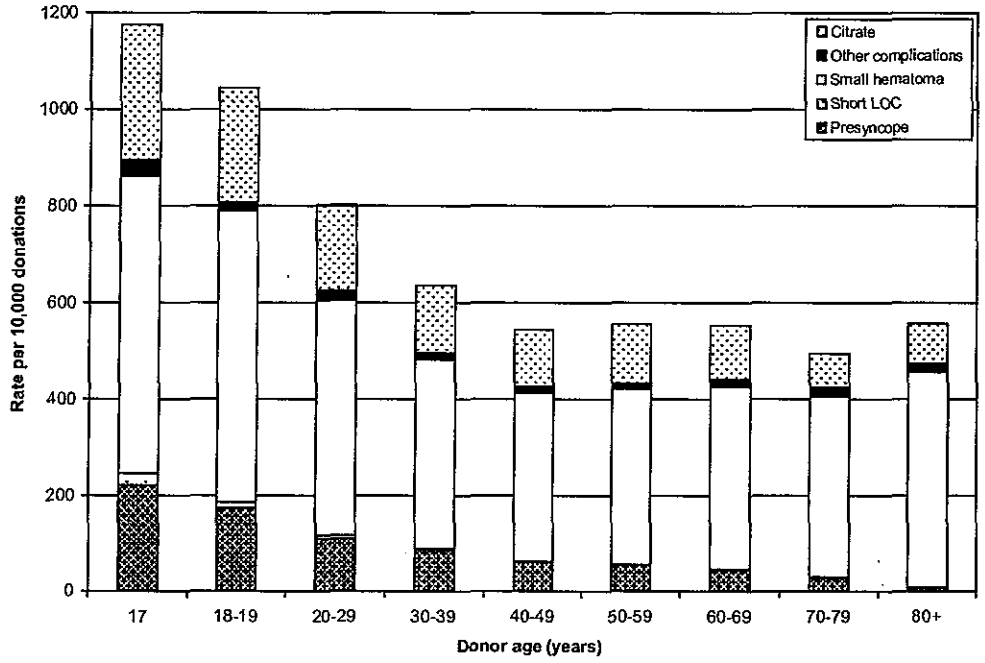
The AABB has proposed the establishment of a national biovigilance program that would include a donor adverse reaction component.[12] The national collection of donor complication data is currently constrained by the different definitions of reactions and data collection procedures in use by blood centers in the United States, which prevents direct comparisons between the complication rates reported by various blood collection agencies. We now demonstrate that even in a large multicenter system utilizing standardized protocols, considerable variability is apparent in reported reaction rates among different regional blood centers. Reaction rates are known to vary with donor age, gender, race, weight, and first-time donation status.[6-10] A major source of the variability we observed between regions relates to donor demographics, as evident by the strong correlation of higher reaction rates with the higher proportion of young donors in spring and fall compared to summer and winter. Nevertheless, we show that the blood region was also independently associated with complications separate from donor characteristics (age, donation status, and sex), suggesting that regional practices may affect the likelihood of reactions or the recognition and reporting of those reactions. Regional variability likely cannot be eliminated because of the inherent subjectivity in evaluating and recording donor complications. Any comparison of complication rates between different regional centers, for example, to evaluate staff performance or compare collection equipment, could be misleading. Despite the variability among regions, data from an individual region or a small subset of regions in a more controlled operational trial have proven useful to evaluate donor complications associated with implementation of new collection procedures or new equipment (data not shown). Further analysis of the regional variability may provide insight into practices consistently associated with lower complication rates.

TABLE 3. Multivariate logistic regression analysis of donor complications

	WB		R2		Apheresis PLTs	
Effect	Point estimate	95% Wald CI	Point estimate	95% Wald CI	Point estimate	95% Wald CI
Age (years)						
16	3.42	3.14-3.73	NA	NA	NA	NA
17	3.33	3.07-3.62	2.94	1.56-5.55	1.77	1.37-2.28
18-19	3.11	2.87-3.37	3.02	1.60-5.70	1.69	1.37-2.08
20-29	2.25	2.07-2.44	2.83	1.50-5.33	1.30	1.08-1.56
30-39	1.33	1.22-1.44	2.30	1.22-4.33	1.06	0.88-1.28*
40-49	0.95	0.88-1.03*	1.95	1.04-3.67	0.90	0.75-1.08*
50-59	0.84	0.78-0.92	1.84	0.98-3.46*	0.92	0.77-1.11*
60-69	0.80	0.73-0.87	1.81	0.96-3.41*	0.95	0.79-1.14*
70-79	0.80	0.73-0.87	1.69	0.89-3.23*	0.84	0.70-1.02*
80+	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Sex						
Male	0.56	0.55-0.56	0.64	0.60-0.68	0.53	0.52-0.55
Female	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Donation status						
First	2.00	1.98-2.02	1.33	1.25-1.40	2.04	1.83-2.28
Repeat	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Region						
A	0.90	0.86-0.94	3.61	2.72-4.80	1.99	1.75-2.26
B	2.00	1.90-2.10	1.18	0.16-8.83*	2.25	1.94-2.62
C	0.90	0.86-0.95	0.88	0.65-1.19*	0.98	0.85-1.13*
D	1.11	1.06-1.16	1.90	1.42-2.55	1.52	1.34-1.72
E	0.82	0.78-0.86	1.15	0.86-1.54*	1.83	1.61-2.08
F	2.12	2.01-2.24	5.34	3.72-7.68	1.58	1.34-1.85
G	2.46	2.35-2.58	3.52	2.60-4.77	2.48	2.18-2.83
H	0.84	0.80-0.88	1.00	0.72-1.38*	1.54	1.35-1.76
I	0.54	0.51-0.57	0.89	0.66-1.19*	2.12	1.87-2.40
J	0.85	0.81-0.90	1.18	0.87-1.60*	2.72	2.34-3.15
K	1.96	1.87-2.06	1.56	1.16-2.09	2.54	2.20-2.92
L	1.25	1.19-1.31	1.68	1.25-2.26	3.15	2.77-3.58
M	1.10	1.05-1.16	1.15	0.82-1.63*	1.68	1.45-1.96
N	0.44	0.42-0.47	0.26	0.18-0.36	2.13	1.82-2.48
O	0.82	0.78-0.86	NA	NA	0.75	0.64-0.88
P	1.40	1.33-1.46	NA	NA	1.37	1.20-1.57
Q	0.59	0.56-0.62	0.44	0.32-0.60	1.35	1.17-1.55
R	1.20	1.14-1.26	2.80	2.04-3.83	2.47	2.14-2.84
S	0.79	0.74-0.84	0.46	0.29-0.72	0.09	0.04-0.20
T	0.93	0.89-0.98	2.76	2.07-3.69	0.64	0.54-0.77
U	1.39	1.32-1.46	1.70	1.25-2.32	0.13	0.10-0.19
V	0.94	0.89-1.00	0.74	0.52-1.04*	2.98	2.55-3.48
W	1.98	1.89-2.07	2.00	1.49-2.67	1.84	1.61-2.10
X	0.62	0.59-0.66	0.24	0.16-0.37	2.29	1.95-2.68
Y	2.39	2.27-2.52	4.13	3.07-5.54	2.22	1.91-2.56
Z	1.24	1.17-1.30	1.91	1.39-2.63	0.81	0.70-0.94
AA	1.36	1.29-1.43	1.39	1.03-1.87	2.22	1.93-2.55
BB	1.33	1.27-1.40	4.53	3.37-6.08	2.69	2.35-3.09
CC	1.10	1.04-1.17	0.83	0.57-1.19*	0.44	0.34-0.56
DD	1.64	1.56-1.71	1.77	1.32-2.39	2.06	1.79-2.38
EE	1.30	1.24-1.37	1.01	0.70-1.45*	1.01	0.86-1.19*
FF	1.05	0.99-1.12*	1.24	0.91-1.70*	0.03	0.01-0.07
GG	1.10	1.05-1.15	1.81	1.35-2.43	1.44	1.26-1.63
HH	2.15	2.04-2.26	NA	NA	1.07	0.86-1.35
II	0.69	0.65-0.73	0.42	0.28-0.65	0.55	0.46-0.65
JJ	1.00 (referent)		1.00 (referent)		1.00 (referent)	

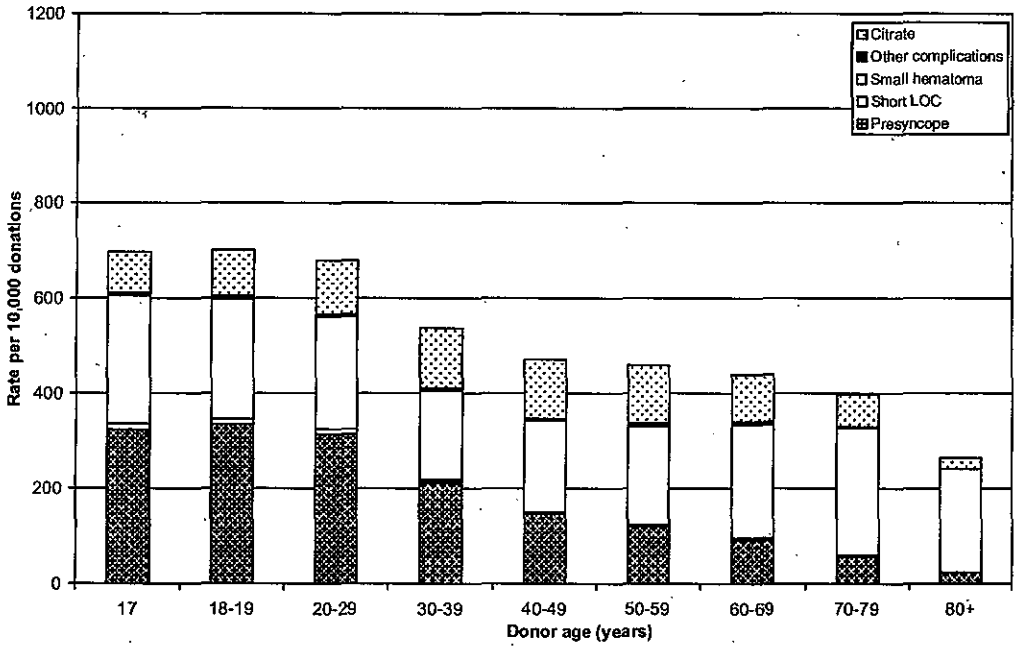
* Not significant.

Our experience also delineates the limitations of a national hemovigilance program and identifies opportunities for future improvement that may be tracked by the program. The approach to classify the type of complication rather than to capture specific signs or symptoms simplifies data collection, but we recognize that our definitions of donor complications are not mutually exclusive; for example, donors in the prolonged recovery category may also have had LOC as a feature of their reaction. This redundancy leads to having more than one code that can be used to describe a reaction; in addition, more than one type of reaction is possible. In both circumstances, staff is instructed to record the reaction based on the most severe symptoms. This subjectivity in evaluation and



Total donations	1,218	3,560	26,986	44,812	119,535	156,890	72,477	21,771	2,300

Fig. 4. Rates of donor complications associated with apheresis PLT donation. Differences in overall rates between successive age groups are different ($p < 0.05$) between 18- to 19-, 20-to 29-, and 30- to 39-year groups.



Total donations	18,578	20,814	29,580	30,392	51,141	50,291	21,747	5,178	417

Fig. 5. Rates of donor complications associated with R2 donation. Differences between overall rates between successive age groups are significant between the 20- to 29- and 30- to 39-year groups only.

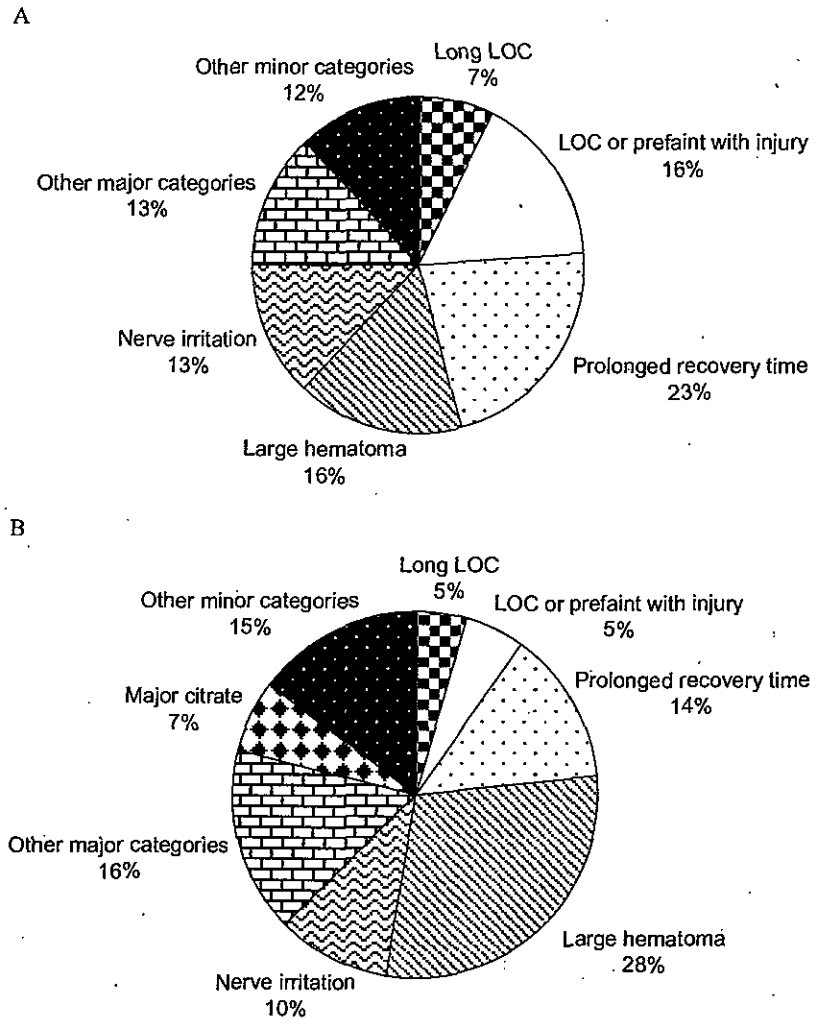


Fig. 6. Outside medical care reported after WB (A) and automated PLT and R2 collections (B). (A) WB (1,903 cases of outside medical care in 6,014,472 total WB collections; 3.2 per 10,000). (B) Automated (PLT, R2; 198 cases of outside medical care in 677,777 total automated collections; 2.9 per 10,000).

imprecision in coding undoubtedly contributes to regional reporting variability.

The utility of collecting systemwide data on hematomas and minor presyncopal reactions and the relevance of a distinction between short LOC and long LOC have been questioned. Hemovigilance efforts of a national system should be focused on moderate and severe reactions, which are more medically relevant than minor complications and require aggregation of data to evaluate trends and the effect of interventions on rare events. However, the common, minor reactions may provide important information if their rate serves as an indirect measure of the risk of more serious complications in individual blood centers. For example, an intervention that achieves even a small reduction in symptomatic (syncopal-type) reactions may predict a comparable reduction in the infrequent, but more serious syncopal-type complications including LOC with injury. This assumption, while logical, has not yet been proven because a large data set is needed to evaluate the effect of any preventive measure on infrequent but medically more serious complications. Regardless, even the common, mild complications are unpleasant for the donor and reduce the likelihood of return donation thereby serving as a surrogate measure of the donation experience.[15-17] Finally, we noted lower complication rates in young donors (<20 years) donating RBCs by apheresis compared to WB donations, providing a rationale for further study and for possibly expanding apheresis RBC donation programs in colleges and high schools.

Although blood collection establishments will likely not be able to eliminate all risk to healthy volunteer donors, they should continually foster a culture of safety and make a concerted effort to reduce the rate of donor complications, not only for the donors' health and well-being but also to enhance the likelihood of their future donation.[17] The ARC hemovigilance program provides estimates of the current risks associated with WB and automated collection procedures and lays the foundation of our efforts to improve the donation experience. Establishment of a national donor hemovigilance system may afford an opportunity for systematic improvement in donor safety in every collection center. Our experience, however, cautions against direct comparison of different blood centers in the absence of risk adjustment for donor demographics and consideration of differences in the identification, classification, and reporting of injuries.

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Advancing Transfusion and
Cellular Therapies Worldwide

ASSOCIATION BULLETIN #08-04

Date: August 28, 2008
To: AABB Members
From: J. Daniel Connor, MM, President
Karen Shoos Lipton, JD, Chief Executive Officer
Re: Strategies to Reduce Adverse Reactions and Injuries in Younger Donors

This Association Bulletin contains information for the membership on strategies that may mitigate the risk of injuries and adverse reactions in donors under 20 years of age. AABB is issuing this bulletin in anticipation of the renewal of high school and college blood drives. Blood collecting facilities may want to consider implementing some of these strategies in an effort to reduce the incidence of injuries and adverse reactions in this population of donors.

Association Bulletins, which are approved for distribution by the AABB Board of Directors, can include announcements of standards or requirements for accreditation, recommendations on emerging trends or best practices, and/or pertinent information. This bulletin does not contain specific recommendations, nor does it create a standard or accreditation requirement. It is based on reports from the AABB Younger Donors Adverse Reaction Working Group, which includes physicians, nurses, administrators, communications and legal experts, and representatives from AABB, America's Blood Centers, the American Red Cross, and Blood Centers of America. The working group reviewed and discussed available information and, on the basis of current practices, addressed three objectives: 1) reduce adverse reactions in young blood donors; 2) eliminate donor injuries related to adverse reactions; and 3) address donor education and consent issues related to young blood donors. The full texts of these reports, which are included as appendix 1 and appendix 2 to this bulletin, contain a number of strategies that may accomplish these objectives. Some of the suggested interventions are supported by studies and data, while others represent a common practice or, a practice that is expected, but not proven, to accomplish the stated objectives.

Background
Volunteer blood donations are the basis of the nation's blood supply. Donations are recruited from a healthy population that ranges in age from 16 (state law permitting) to 75 years or older. During the past several years, blood collection facilities have placed greater emphasis on donations from younger donors as donations from older donors are declining due to individual health issues and other eligibility barriers. Reports from blood collection facilities indicate that 10 to 20 percent of all whole blood collections in the

United States now come from blood donors who are less than 20 years old. In states where 16-year-olds are permitted to donate, the percentage of donations from this age group is even higher. The growth of this donation segment is related to the increase in blood drives at high schools. Blood donors of high school age generally embrace the opportunity to donate blood for a number of reasons; including their perception that donating is a "rite of passage," their attraction to the medical/technological aspects of blood donation, and the fact that they can often be excused from class. They are also ideal donors because they have lower deferral rates and, by experiencing donation early in life, they are more likely to continue donating in the future.

As data from young donors and high school drives accumulate, it has become clear that the rate of adverse reactions is more frequent in this group of donors – as much as five times the adult rate in some studies. Although serious syncopal reactions that can lead to donor injury are rare, they are proportionately elevated in this group. Moreover, age appears to be inversely related to the risk of suffering an adverse reaction. Several recent studies document this phenomenon as well as various strategies to reduce adverse reactions. These published results have drawn greater attention to this issue among blood collection facilities. Recognizing this new information and understanding the importance of assuring donors a safe and satisfying donation experience, blood collection facilities have joined forces to address safety for young blood donors.

Donor Adverse Reactions

The vast majority of blood donations are uncomplicated, with no side effects or discomfort. However, a small number of donors experience bruising and/or bleeding at the venipuncture site, mild nausea, or changes in consciousness, including dizziness, prefainting, fainting or syncope leading to collapse or convulsions. The working group focused specifically on change of consciousness reactions, such as syncope, that can lead to donor injury if the donor falls. Several factors influence the risk of complications after blood donation: inherent donor characteristics and predisposition toward reactions, blood collection staff skill and experience, blood drive set-up and environmental site features, and donor education before and after donation.

The literature, published studies and blood collection facility experience document donor characteristics that correlate with higher syncopal complication rates after whole blood donation. These include young age, first-time donation status, low weight, low blood volume, female gender, and Caucasian ethnicity. Young age, total blood volume, and first-time donation status are known to be independent risk factors and leading determinants of syncopal reactions.

Given these predisposing factors, the working group reviewed many field practices and literature reports on measures to reduce reactions, including the following.

- **Predonation education.** Measures in this area greatly affect donor understanding of what to anticipate and how to deal with discomforts that might arise from donation. This area is addressed more specifically below under Donor Education.

- **Blood drive environment and set-up.** Although few published data or information are available on best practices for drive set-up, the working group recognized the importance of adequate ventilation, electrical outlets, and physical space for managing adverse reactions. Specific actions discussed include:
  1. Procedures for site selection to ensure acceptable conditions that support operation and guidance on discontinuing operations if the conditions become unsuitable.
  2. Controlled donor flow and adequate staff or volunteer availability.
  3. Existence of a donation environment that can accommodate progressive recovery strategies.
  4. Donor escorts, especially from the chair/bed to the postdonation area (canteen).
  5. Predonation area for hydration and nutrition.
  6. Postdonation canteen/refreshment area.
  7. At the canteen site, adequate staff or volunteers who are trained in recognizing donation reactions.
  8. Separate areas for recovering donors who may feel anxious or sick.

  Additional practices and information relating to the listed strategies are contained in the appended reports.
- **Staff supervision and phlebotomist skills**. Training and supervision of collection staff are critical to the success of all blood drives and the safety of the donor. For high school drives, in particular, providing extra or experienced staff may mitigate the rate and impact of donor reactions. Blood collection facilities should regularly review collections staffing, training, and performance regarding managing reactions.
- **Interventions.** Various field practices are currently in place to prevent donor reactions, specifically in young donors. Although they are evolving practices, the following practices should be considered and evaluated by blood collection facilities.

  1. Donor Size/Age Criteria. The current eligibility requirement of a minimum weight of 110 lb and a whole blood collection limit of 10.5 mL/kg are sufficient to protect most donors. These criteria are based on the assumption that they would prevent drawing more than 15 percent of a donor's blood volume. Some blood collection facilities are considering changing those criteria to require that eligible donors have an estimated blood volume greater than 3500 mL. Other practices include raising the minimum weight to 120 lb for young donors or collecting a smaller volume of blood from young donors.

  2. Distraction Strategies. Distraction techniques such as audiovisual entertainment have been reported to be effective at putting donors at ease during collection, based on reductions in self-reporting of reactions.

  3. Hydration. In a few studies, donors who received water (500 mL, 30 minutes before donation) reported significantly fewer reactions. Blood

collection facilities may want to provide donors less than 20 years of age with beverages and encourage them to consume 500 mL of fluid within 30 minutes before phlebotomy.

4. Applied Muscle Tension (AMT). AMT is the repeated, rhythmic contraction of the large muscles of the arms and legs and has been shown to reduce presyncopal reactions in young donors. This technique is also easy to learn and safe to use.

5. Automated Collection Procedures. Automated two-unit red cell collections have a favorable safety profile compared to whole blood collections in young and first-time donors. The lower risk of reactions may be attributed in part to the saline (volume) replacement. Expansion and further study of apheresis red cell donation programs in high schools and colleges is recommended.

6. Postreaction Instructions. Under current standards, blood collection facilities must have a process for treating donor adverse events and providing for emergency care as necessary (BB/TS Standard 5.3.2.1). It is advisable to include information for both donors and families. This issue is addressed in more detail below under Donor Education.

Donor Injuries Resulting from Reactions

As it is a rare occurrence, there is no published information on injuries resulting from blood donor reactions. Available data come from injury claims at large collection programs. Current estimates predict approximately one serious injury per 200,000 donations. Injuries can occur when a donor has a syncopal reaction and collapses to the floor, causing facial or other fractures and lacerations. Reducing these syncopal reactions should, in turn, reduce these types of injuries. Other environmental and operational practices, including the use of additional staff and training in the management of reactions in the recovery area, are evolving. Reinforcement of canteen observation and escort policies and donor education about reaction recognition are also recommended. Placing recovering high school donors on floor mats to prevent falls and injury is another practice being evaluated. An accurate assessment of the impact of these measures awaits further collection of information on injury rates.

Donor Education

Predonation information, consent for donation and understanding how to manage postdonation issues are critical to providing a satisfying donation experience and ensuring that the donor returns for future donation. Because younger donors have different backgrounds, expectations, and legal issues relating to their donation, donor education and consent have special significance. Blood drives at high schools involve additional considerations for education, legal responsibility, and parent/guardian involvement.

Predonation anxiety is associated with increased rates of reactions. Addressing common donor fears and suggesting useful coping techniques allays donor anxiety and improves

attitudes toward self-efficacy (the belief that one has the capability to manage a situation) and future intention for blood donation. Predonation educational materials should be considered part of the consent process, in that information pertinent to the donation process, possible reactions, and interventions is imparted before the decision to donate. These materials will have greater impact if they are designed for the high school population, using age-appropriate language and graphics. They also may be presented in other adolescent-friendly formats, such as videos. Elements to be considered for inclusion in such materials include:

- A general statement that most donors have uneventful donations and most reactions, when they occur, are minor.
- A statement identifying which donors may be at increased risk for a reaction and why (for example, young, first-time, female, or low-weight donors may be especially at risk).
- A brief description of the donation process to inform first-time donors about the process and to alleviate anxiety about the unknown.
- Descriptions of possible techniques to prevent reactions and enhance coping skills, and a brief explanation of the possible benefits of adhering to these techniques.
- Statements describing blood collection facility policies on parent/guardian consent and confidentiality regarding test results, if applicable.

Blood collection facilities may want to consider targeting educational initiatives on adverse reaction prevention strategies, coping strategies to reduce reactions, responses to the management of delayed or prolonged donor reactions, and continuity of care after release from the donation site to the following groups:

- Chairpersons, drive sponsors, and high school officials.
- Training, recruitment and collection staff.
- High school students and their parents.
- School nurses.

Ideally, this information should be delivered close to the day of donation.

Postreaction Education and Care. Collection facilities must have a process for treating donor adverse events and providing for emergency care as necessary (BB/TS Standard 5.3.2.1). Measures to improve communication with parents/guardians or school nurses should improve the management of delayed reactions after leaving the site, and collection facilities may want to consider the following measures:

- Communication with parents/guardians if a donor experiences loss of consciousness or other reaction or injury, in accordance with state laws.
- Continuation of care for young donors who have had a reaction at the site or at home.

Consent and Confidentiality for Young Blood Donors

Informed consent practices for blood donation that successfully incorporate the principles of autonomy, veracity, beneficence, and non-maleficence have not been uniformly adopted. Consent to donate is not a simple signature on a form, but a broader process that involves education of the donor and, in some cases, the donor's parents/guardians. Moreover, consent for the collection of blood from 16- and 17-year-old minors, presents certain dilemmas and challenges. For example, state laws that allow 17-year-olds to consent to donate blood are generally silent on the minor's right to consent to subsequent medical treatment for an adverse reaction. States that allow 16-year-olds to donate often require parent/guardian permission/consent and, therefore, do not imply any emancipated status. Even though these states may recognize that minors have the decisional skills necessary to make informed health-care decisions, parents/guardians still have legal responsibility for their minor children.

Policies on notification of blood donors of test results must be carefully reviewed against state statutes relating to minors. In addition, minors are generally prohibited from participating in research without parent/guardian permission, although blood collection facilities may perform certain required or elective tests under research protocols that have been approved by an institutional review board.

Again, in providing adolescent donors (and parents/guardians) with information regarding the donation process and possible consequences (reactions), collection facilities are meeting an essential requirement of consent. Blood collection facilities may want to:

- Consult state statutes regarding age and consent requirements.
- Become familiar with the literature specific to adolescent/minor informed consent and assent.
- Provide information to both donors and parents/guardians as part of the consent process. Some facilities provide a parent/guardian consent form that functions as both informational brochure and consent documentation.
- Incorporate information specific to increased rates of reactions among certain groups such as young and/or first-time donors into the consent process.
- Incorporate statements regarding release of information to parents regarding medical care for reaction and/or positive test results, as applicable.

Summary and Conclusions

While most donations are uneventful, even a minor complication reduces the likelihood of a return donation. Serious injury following blood donation occurs infrequently among all donor age groups, but adolescent donors are disproportionately affected compared to older adults. Virtually all dimensions of the blood donation experience have some impact on the risk of complications. The working group has performed a comprehensive review of current views and practices involving adverse donation reactions in young donors. AABB believes that blood collection facilities may find this information useful in addressing the unique challenges presented by young donors and high school blood drives. Although zero risk may not be attainable even in adults, the rate of complications in minors calls for ongoing attention to a sustained operational effort that is continually focused on donation safety. AABB encourages blood collection facilities to continue to

monitor and report the effectiveness of interventions on blood donor reaction rates and injuries resulting from reactions. AABB's effort to establish a national hemovigilance program in the United States could provide not only a uniform reporting structure for adverse events after blood donation, but also the mechanism to monitor the effectiveness of efforts to prevent the rare but more medically serious donation-related complications.

Appendix 1.
Recommendations to Minimize the Risk of Reactions and Injuries among Adolescent Blood Donors

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Objectives

1. To review published data and reported efficacy of methods to enhance the donor experience and/or reduce donor complications.
2. To identify the different approaches that could be employed at blood centers to reduce donor complications at high school drives.

Executive Summary

Young (16- and 17-year-old) donors now represent a significant and increasing proportion of the whole blood donations to blood centers in the United States, accounting for about 8% of the whole blood donations or 450,000 whole blood collections to the American Red Cross (ARC) in 2006. However, young age, total blood volume, and first-time donation status are known to be independent risk factors and leading determinants of donation-related complications.[1-6] Even minor reactions or temporary deferrals decrease the probability of return donation,[6-9] and efforts to improve the donation experience are crucial to sustain the blood supply. The increasing dependence on recruiting and retaining young blood donors requires a committed approach to donor safety, especially on high school blood drives.

A multidimensional view of the donation experience recognizes several aspects that influence the risk of complications after blood donation: inherent donor characteristics and predisposition toward reactions, blood center staff experience and skill, blood drive set-up and environmental features, and donor education before and after donation. Donor characteristics that correlate with higher syncopal complication rates after whole blood donation include young age, first-time donation status, low weight, low blood volume, female gender, and Caucasian race. While these may not all be independent predictors of reactions, an additive effect of risk factors has been observed in Caucasian high school students.[5] Several interventions (eg, asking the donor to drink 16 oz of water shortly before donation, or using applied muscle tension or distraction techniques) have been used to improve the donation experience and/or reduce donor complication rates. However, no single measure has been shown to prevent a majority of systemic reactions or to prevent the rare but more serious complications, such as syncope-related injury after whole blood donation.

Consequently, blood centers should consider all factors that affect a donor's experience and influence the risk of complications before deciding which safety measures should be enhanced or introduced at the blood center. The effectiveness of safety initiatives should be monitored continuously, the resultant data should be peer reviewed, and the conclusions should be published to further our understanding of the efforts to improve the donation experience.

The working group recommends that blood centers consider one or more of the measures in the following areas and develop monitoring programs to continually assess safety:

I. Predonation education
II. Drive set-up and environment
III. Staff supervision and phlebotomist skills
IV. Interventions
    A. Donor eligibility criteria
        1. Deferring young donors with blood volumes below 3500 mL
        2. Raising the minimum acceptable donor weight
        3. Collecting a smaller volume of blood from young donors
    B. Distraction strategies
    C. Water ingestion
    D. Muscle tension
    E. Automated red cell collection procedures with volume replacement
V. Postreaction instructions to donor and parents

This report summarizes the available evidence on these different approaches to improve the donation experience, identifying expected benefits and limitations, providing directions for additional development and study, and estimating the impact on the donor base, to offer consensus-derived recommendations in each area.

I. Predonation Education

Efforts to address common donor concerns and provide useful coping suggestions were associated with improved scores on questionnaires that assessed donor attitude, anxiety, self-efficacy (the belief that one has the capability to manage a situation), and intention toward blood donation.[10] There are no published studies that evaluate the effect of blood donation recruitment materials on complication or return donation rates.

Some unpublished data and anecdotal experience suggest that educational initiatives may be effective at reducing donor reactions and equipping the donor and staff to better handle reactions to reduce their severity.

Recommendations

Educational efforts may be reasonably expected to improve the donation experience and could result in greater participation and more effective preparation. Such efforts would not be expected to have an adverse impact on the donor base.

Educational initiatives should target the following groups:

- Chairpersons and sponsors of drives.
- High school students and their parents.
    - Educational material directed at donors should contain prevention strategies or anticipatory guidance and content that address coping strategies to reduce reactions.
    - Educational material should be delivered close to the day of donation.
- School nurses.

- School nurses should be informed of the pathophysiology of donation-related adverse reactions and the care of donors who experience complications.
- In advance of the drive, donor centers should discuss with school nurses or administrators how to handle delayed or prolonged donor reactions and ensure continuity of care after release from the donation site.

- Training recruitment and collection staff.

The optimal delivery method for student education is unknown but may include the following formats:

- An educational DVD. A video format ≤10-minutes meets the students in their world and offers school administrators the ability to provide the education at their convenience.
- Podcast, downloadable eBook, or similar application.
- Blood center Web site.

II. Drive Set-Up and Environment

Blood centers should have systems in place to process donors efficiently and to provide good donor care regardless of age. Scant data exist on best practices for drive set-up, and sponsor groups are often challenged to find enough space to accommodate a blood drive. Most blood centers require site clearance before a blood drive. It is important to tour the location where the drive is held to ensure adequate ventilation, electrical outlets, and space for handling adverse reactions. In a recent Blood Centers of America (BCA) survey of 26 blood centers, nine centers responded that the drive set-up for high school drives differs from the set-up for regular drives (Nina Salamon, personal communication).

Recommendations

Supportive evidence does not exist to recommend more controlled or restrictive requirements for drive site set-up. However, blood centers are encouraged to share their experiences to identify and implement processes that may lessen the likelihood of adverse reactions.

A predonation hydration station or other mechanism to provide fluids to donors before donation should be part of the drive planning or set-up. Donors should be allowed to leave the area with bottles of water, which may require obtaining permission from the school administrators before the drive.

Blood centers should consider the following aspects of drive set-up that may mitigate adverse reactions at high school blood drives:

- Procedures for site selection to ensure acceptable conditions to support operations and guidance on discontinuing operations if the conditions become unsuitable.
- Controlled donor flow and adequate staff or volunteer availability. Arrival and departure patterns of students should be evenly spaced to minimize commotion. Access to the donation area should be limited to student donors, designated volunteers, and staff.
- Progressive recovery strategies (eg, dangling legs over the side of the bed with appropriate attention) before having the donor stand up after donation.
- Escorting donors through the process—in particular, from the chair/bed to the canteen. Consider asking the volunteers to escort the donors back to class.

- Predonation canteen table for fluid and food (see Water Ingestion, below).
- Postdonation canteen/refreshment area:
- Designated area and donor flow should allow for adequate time in the canteen after donation.
- Have donors lie on gym mats on the floor during the recovery and refreshment period after donation.
- Inform donors of the importance of staying in the canteen for an allotted time (eg, about 15 minutes) or until they feel well. Emphasize to staff the importance of instructing donors to stay in the recovery area for sufficient recovery time.
- Additional staff or volunteers who are trained in recognizing prereaction signs and symptoms can be assigned to the refreshment area.
- Area for recovery. Wheel chairs should be available. Mobile screens can be used to separate or partition areas for students who may feel anxious or sick.

III. Staff Supervision and Phlebotomist Skills

Employees in the collections department are crucial to the mission and success of the blood center and the safety of the blood donor, regardless of donor age. In one study, phlebotomists exhibiting high scores on a standardized social skills test were associated with reduced donor reaction rates.[11] Phlebotomy training was somewhat significant in this study.

Some donor centers try to mitigate adverse reactions at high school blood drives by including staff who are well trained to recognize signs of reactions and to take steps to prevent them, and by increasing the number of staff or other supervisory personnel at high school drives.

Recommendations

Although donor centers often report having "extra" or "more experienced" staff on high school blood drives, there is no industry benchmark for a staffing model or skill-set requirements. The importance of hiring practices and staff training in interpersonal skills as well as technical skills is recognized. Blood centers are encouraged to continually evaluate their training programs and staff performance.

IV. Interventions

A. Donor Eligibility Criteria

1. Deferring young donors with blood volumes below 3500 mL.
    - Postdonation syncope may be a manifestation of the typical "vasovagal" attack, but can be a manifestation of hypovolemia.
    - One study of whole blood donations showed that a donor blood volume below 4775 mL is an independent risk factor for faint and prefaint reactions.2
    - The risk of reaction decreases substantially with increasing blood volume in the ranges assessed.2 Five percent of donors in this study had blood volumes of less than 3500 mL, which guarantees that their 525-mL donations would be more than 15% of their blood volumes.
    - Implementing an additional requirement for minimum total blood volume (>3500 mL) may reduce the risk of faint and prefaint reactions. A bivariate analysis indicates that the difference in reaction rates based on donor blood volume is larger at a younger age than the

difference for donors older than 30 years of age. An intervention applied to young donors (<23 years of age) with low blood volumes (<3500 mL) might reduce reactions.

- Preliminary unpublished data (Hany Kamel, personal communication) have indicated that donors younger than 23 years of age whose blood volume is <3500 mL represent 9% of donors younger than 23 and 1.6% of all donors. The rate of moderate and severe reactions in this group is 1.7% (compared to a 0.33% overall rate of moderate and severe reactions). A policy of excluding donors <23 years of age with blood volumes <3500 mL is estimated to eliminate 20% of moderate and severe reactions in this age group (9% of all reactions).

2. Raising the minimum acceptable donor weight.
   - Trouern-Trend et al1 reported a reaction rate of 0.46% in donors weighing <120 lb compared to a rate of 0.14% in the reference group of donors weighing 150 to 179 lb.
   - In high school students, Newman et al12 reported a reaction rate of 16.9% in donors weighing <130 lb compared to a rate of 8.2% in donors weighing 130 lb or more. Donors weighing <130 lb represented 4.1% of all donors (118/2894).
   - In one study,6 22 of 32 (69%) injured 16- and 17-year-old donors who received outside medical care for donation-related injuries weighed >130 lb; only 4 of 32 (12.5%) weighed less than 120 lb. Selection criteria based on donor-reported weight, therefore, would be expected to prevent only a small fraction of the injuries sustained by adolescent donors.
3. Collection of smaller volume of blood from young donors.
   - Two abstracts13,14 demonstrated equivalent overall safety profiles for 450-mL and 500-mL whole blood collections. In these studies, donors were not stratified by factors known to predispose to systemic reactions (eg, age, weight, experience, etc). It is possible that any beneficial effect of collecting smaller volumes from young and/or low-weight donors may have been masked.
   - Tomasulo et al15 measured the weight of whole blood units collected in a 450-mL bag, calculated the percentage of blood volume removed, and reported donor reaction rates in different donor groups. Female donors who had 14% to 16% of their blood volume removed were more likely to experience a reaction than those who had only 10% removed. The authors concluded that donors weighing 110 to 119 lb had an increased reaction rate, which was attributed to collection volume.

<u>Recommendations (Donor Eligibility Criteria)</u>

Studies have identified subgroups at higher risk that may benefit from having different selection criteria. The current eligibility requirement for minimum weight of 110 lb and to limit collection to 10.5 mL/kg is sufficient to protect most, but not all, donors. This requirement was based on the assumption that it would prohibit drawing more than 15% of a donor's blood volume. Recent data suggest that this assumption is not accurate[2] and a new standard approach may be needed to limit whole blood collection to no more than 15% of the total blood volume for adolescent donors. Although the reduction in reaction rates for a given change in selection criteria can be estimated by multivariate analysis, it is not known if implementation of a given policy will achieve the predicted results. Blood centers are encouraged to evaluate the potential effectiveness of different donor selection criteria in preventing reactions and injury.

B. Distraction of the Donor During Collection

It is widely recognized that distraction techniques are effective at putting donors at ease during collection. In a small study the use of audiovisual distractions reduced the self-reporting of vasovagal reactions.[16] Some examples of easy-to-implement audiovisual distractions for donor drives include allowing the use of MP3 players or providing headsets with music, encouraging applied muscle tension activities, and placing donor chairs back to back.

Recommendations

Blood centers should provide education to donors on permissible activities for distraction that may increase their sense of control during the donation. Blood centers should instruct staff on the importance of distraction as a possible way to reduce reactions.

C. Water Ingestion

To date, two studies have been published on the effects of predonation hydration on blood donor reactions. In a randomized controlled trial, 83 male and female first-time donors (median age = 19) consumed 500 mL of water 30 minutes before allogeneic whole blood donation.[17] Results indicated that the donors who received water reported significantly fewer presyncopal reactions (eg, faintness, dizziness, weakness) as compared to those who did not hydrate. This finding was later confirmed in a study of nearly 9000 high school donors (17-19 years of age) who consumed 473 mL of water 0 to 30+ minutes before phlebotomy.[12] Based on donor reactions recorded on the health history form, reaction rates were reduced 21% by predonation hydration (water = 9.9% reaction rate; no water = 12.5% reaction rate). Additional analyses indicated that reaction rates were lowest for those who consumed water within 10 minutes of the phlebotomy, with reaction rates increasing with longer lag times.

Although there are only two published studies on the effects of predonation hydration on donor reactions, additional laboratory research has demonstrated that acute water loading increases blood pressure, peripheral vascular resistance, and cerebral blood flow, and can serve as an effective prophylaxis against vasovagal reactions in healthy individuals undergoing orthostatic challenge.[18-20]

Table 1. Summary of Reductions in Donor Reactions Observed as a Function of Predonation Water Loading vs Standard Donation Control

Study	Water	Control	Change
Hanson and France[17] (2004)	0.48 (BDRI, log units)	0.91 (BDRI, log units)	↓47%
Newman et al[12] (2007)	9.9 % (donor reactions)	12.5% (donor reactions)	↓21%

Note: The BDRI, or Blood Donation Reactions Inventory, is a self-report measure of donor reactions such as faintness, dizziness, weakness, etc. Elevations on this scale predict donor non-return over and above the effect associated with reactions recorded on the donor record.

Recommendations

Based on existing evidence that predonation hydration can help prevent presyncopal reactions in both male and female donors, does not interfere with the donation process, and is perceived by collection staff as easy to implement, donors should be provided with 500 mL of water or fluid and encouraged to consume the water approximately 10 minutes before phlebotomy.

D. Muscle Tension

To date, four studies have been published on the effects of applied muscle tension (AMT) on blood donor reactions.[21-24] Although AMT exists in many forms, it typically involves repeated, rhythmic contraction of the large muscles of the arms and legs. In the first study to apply this technique in the context of blood donation, a brief video was used to teach AMT to a small group (n = 37) of relatively inexperienced donors (ie, 0 to 2 prior donations).[21] Compared to controls who did not view the video, donors who learned AMT reported significantly fewer presyncopal reactions (eg, faintness, dizziness, weakness) following donation. Furthermore, those who said they used AMT throughout the donation had the fewest reactions.

The beneficial effects of AMT were confirmed and extended in a larger study of 605 young donors (mean age = 22; mean prior donations = 3.5).[22] In this study donors were randomly assigned to 1) standard donation, 2) AMT predonation (placebo control), or 3) AMT during donation (intervention). In both AMT conditions the donors learned the muscle tensing technique from a brief video presentation. To control for positive expectancy effects, participants in the AMT predonation (placebo control) condition were instructed to practice AMT from the time they sat down in the donation chair until just before needle insertion. Overall, the results indicated that AMT had a beneficial effect for female, but not male, donors. Specifically, female donors assigned to the intervention condition reported significantly fewer presyncopal reactions, required fewer donation chair reclines, and were more likely to produce a full unit of blood than females in the placebo or standard donation conditions (the placebo and standard donation conditions did not differ).

In a separate sample of donors (n = 467), presyncopal reactions were attenuated for both male and female donors assigned to the AMT intervention instead of either placebo control or standard donation (which did not differ).[23] Most recently, 1209 donors (50% female, mean age = 22, mean prior donations = 2.2) were randomly assigned to either standard donation or one of five forms of muscle tensing.[24] Donors assigned to AMT viewed a brief video depicting repeated muscle tensing of the 1) full body (arms, legs, and abdomen), 2) lower body only (legs and abdomen), 3) upper body only (both arms), 4) upper body only with distraction (both arms, but instructed to attend to nondonation arm), or 5) donation arm only. When compared to standard donation, full body AMT replicated prior effects of significantly lower reports of presyncopal reactions and fewer donor chair reclines. Similar benefits were observed for lower body AMT, but not upper body AMT, suggesting that tension in the legs and lower abdomen are important components of the beneficial effects of AMT. Upper body AMT with distraction was also associated with a significant reduction in presyncopal reactions, suggesting that AMT benefits may also derive, at least in part, from distraction.

In addition to research in the blood donation context, AMT has been used for decades to successfully treat patients with syncope related to blood and injury phobia[25-29] as well as other

causes of vasovagal syncope.[30-34] Laboratory studies suggest that AMT may help prevent syncopal and presyncopal reactions by increasing blood pressure and cerebral blood flow and oxygenation.[31,35-39]

Table 2. Summary of Reductions in Donor Reactions Observed as a Function of Applied Muscle Tension vs Standard Donation Control

Study	Muscle Tension	Control	Change
Ditto et al[21] (2003)	4.9 (BDRI units)	6.3 (BDRI units)	↓22%
Ditto et al[22] (2003)	All donors = 0.43 (log BDRI)	0.47 (log BDRI)	↓8%
	Female donors = 0.44 (log BDRI)	0.55 (log BDRI)	↓20%
Ditto and France[23] (2006)	0.35 (log BDRI)	0.45 (log BDRI)	↓22%
Ditto et al[24] (2007)	0.42 (log BDRI)	0.52 (log BDRI)	↓19%

Note: The BDRI, or Blood Donation Reactions Inventory, is a self-report measure of donor reactions such as faintness, dizziness, weakness, etc. Elevations on this scale predict donor non-return over and above the effect associated with reactions recorded on the donor record.

Recommendations

Based on existing evidence that AMT is easy to learn, safe to use, and effective at reducing or averting presyncopal reactions in young donors, donor and staff instruction in this technique is recommended. Different approaches are possible but should be focused on tensing the large muscles of the legs and abdomen during donation. Further study is encouraged to evaluate the effectiveness of the intervention in reducing reactions and injuries after donation.

V. Automated Red Cell Collection

The safety of automated collection of Red Blood Cells (RBCs) has been compared to whole blood donation.[40,41] In the American Red Cross experience, the vast majority of adverse reactions to Whole Blood (WB) and 2-unit RBC donation were minor, systemic complications (eg, prefaint, citrate reactions).[40] The overall rate of complications was marginally greater for 2-unit RBCs than for WB collections (320.3 vs 274.5 per 10,000 collections; odds ratio, 1.17 (95% CI, 1.15 to 1.20).

Table 3. Risk Factors for Donation-Related Complications*

Demographic Characteristic	Reaction Rate (/1,000 donations)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)
Blood volume < 3500 mL‡	34.9	4.47 (4.10-4.88)	2.88 (2.57-3.23)
Age = 17-18 years‡	39.6	4.19 (3.94-4.45)	2.78 (2.59-2.98)
Age = 19-24 years‡	27.4	2.87 (2.68-3.06)	2.39 (2.23-2.56)
First-time donor‡	27.5	2.80 (2.66-2.94)	2.20 (2.07-2.33)
Race = Caucasian ethnicity‡	14.3	3.42 (2.63-4.46)	2.15 (1.64-2.82)
Blood volume = 3500-4000 mL‡	23.5	2.97 (2.77-3.17)	2.09 (1.90-2.31)

*Donor reaction rates and odds ratios of combined mild, moderate, and severe reactions by donor characteristics compared to donors without reactions.[2]

†Includes age group, gender, donation history, race/ethnicity, estimated blood volume, pulse, systolic blood pressure, and blood center as covariates.

‡Compared to the reference group: blood volume >4775 mL; age 25-65; repeat donor, and Black, non-Hispanic ethnicity.

However, the rate of major systemic complications (loss of consciousness, loss of consciousness with injury, prolonged recovery, major citrate) in 2-unit RBC donations was lower compared to the rate in WB donations; in particular, for donors <20 years [odds ratio, 0.41 (95% CI, 0.32 to 0.53)].[40] Blood Systems demonstrated that manual WB collections have a low incidence of moderate and severe reactions (47.1 per 10,000 collections, 0.47%).[41] Single-unit RBCs collected by apheresis have the same safety profile (37.44 per 10,000 collections, $p > 0.20$). Two-unit RBC collections by apheresis and plateletpheresis collections have a significantly lower reaction rate (15.65 per 10,000 collections, $p < 0.00005$; and 14.84 per 10,000 collections, $p < 0.00005$, respectively).[41]

Automated 2-unit RBC collections have a favorable safety profile compared to whole blood collections, with a lower risk of major systemic complications compared to whole blood donation. This benefit is most pronounced among young and first-time donors, providing a rationale for further study and for possibly expanding apheresis red cell donation programs in colleges and high schools.

The apparent safety advantage of 2-unit RBC collections may be attributed to the saline replacement during such procedures or to the more stringent criteria for such donations (the hematocrit, height, and weight criteria used to select donors for 2-unit RBC donations are designed to select donors with larger red cell or total volumes than whole blood donors of smaller stature). Further analysis is needed to tease out the true impact of volume replacement.

Recommendations

The available evidence supports further study of expanding apheresis red cell donation programs in high schools and colleges.

VI. Postreaction Instructions to Donors and Parents

Donor centers must have procedures for postreaction care of donors (Standard 5.3.2.1).[42] Measures to improve communication with parents/guardians or school nurses may decrease the likelihood of delayed reactions after leaving the site, and donor centers should consider the following aspects:

- Communication with parents/guardians that the donor experienced a loss of consciousness or other reaction or injury, in accordance with state laws.
- Blood centers should ensure that donors who have had a reaction receive continued care while they are still at the collection site and after they reach home.

Conclusions and Future Directions

Blood centers should recognize all the dimensions of the donation experience that affect the risk of complications and consider one or more of the measures discussed in this report to enhance safety on high school drives. Blood centers should also monitor the effectiveness of their efforts to gauge progress and further refine their policies and procedures to protect donors and ensure a good donation experience. Although most donations are uneventful, even a minor complication reduces the likelihood of return donation. Serious injury following blood donation occurs infrequently among all donor age groups, but adolescent donors are disproportionately affected compared to older adults. In one study, the risk of syncope-related injury among 16- and 17-year-donors was 5.9 per 10,000 donations compared to 0.4 per 10,000 donations by individuals 20 years or older (odds ratio, 14.46; 95% CI, 10.43-20.04).[6] Although the initiatives that have been defined in this report to reduce donor reactions are predicted to also prevent some injuries, the actual benefit of any specific action may be difficult to measure given the rarity of the occurrence of donor injuries. Currently, it is also impossible to compare reaction rates across donor centers because of inconsistent definitions of what constitutes a reaction, different reporting criteria, and variability in how individual phlebotomists recognize and report adverse reactions. AABB's effort to establish a national hemovigilance program in the United States will provide not only a uniform reporting structure for adverse events after blood donation but also the mechanism to monitor the effectiveness of efforts to prevent the rare, but more medically serious, donation-related complications. Although zero risk may not be attainable even in adults, the rate of complications in minors calls for ongoing attention to a sustained operational effort that is continually focused on donation safety.

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Appendix 2.
Recommended Initiatives Concerning Education and Consent for Adolescent Blood Donors

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I. Initiatives to Improve Education of Adolescent Donors, School Personnel, and Parents

A. Adolescent Donors

Objectives

1. To reduce reactions and injuries of high school donors by educating them about maneuvers to prevent common reactions and injuries resulting from such reactions.
2. To identify elements for inclusion in predonation materials designed to reduce anxiety and provide coping techniques, thereby reducing reactions and injuries.

Background

Although many aspects of blood collection (such as screening, labeling, and testing) are highly regulated and standardized across collection facilities, many other facets of the collection process are unregulated and vary widely, such as the multitude of materials supplied to donors for recruitment and educational purposes. Specific challenges arising from the collection of blood from an adolescent population, including the high rate of reactions, may be addressed by improvements in predonation education of the adolescent donor to allay anxiety associated with the blood donation process and to promote coping skills.

The association of predonation anxiety with increased rates of vasovagal reactions is well documented.[1-4] Labus et al[3] used the Medical Fears Survey to assess the association of anxiety with the likelihood of fainting in a group of 364 volunteer blood donors and found that high scores best predicted fainting in first-time and experienced female donors. Efforts to address common donor fears and provide useful coping suggestions through predonation education were associated with improved scores on questionnaires that assessed donor attitudes, anxiety, self-efficacy (the belief that one has the capability to manage a situation), and intentions toward blood donation.[5] Studies to evaluate the effect of educational materials on the frequency of reactions are under way.

Recommendations

Although no published studies evaluate the effectiveness of donor educational material in reducing reactions, studies associating anxiety and fear with an increased rate of reactions suggest that interventions, including education, to reduce anxiety should have a positive effect. Therefore, predonation educational materials can be considered part of the consent process, so that information pertinent to the donation process, possible reactions, and interventions is imparted before the adolescent makes the decision to donate.

Educational materials for high school donors will likely have a greater effect if they are designed with age-appropriate language and graphics. In addition, educational materials may be presented in adolescent-friendly formats such as videos. Regardless of the format, elements to be considered for inclusion in predonation materials for students include the following:

- A general statement to the effect that most donors have uneventful donations and that most reactions, when they occur, are minor.
- A statement identifying which donors may be at increased risk for a reaction (eg, young, first-time, female, or low-weight donors) and why.
- A brief description of the donation process to alleviate anxiety about the unknown for first-time donors.
- Descriptions of possible techniques to prevent reactions and enhance coping skills. Also, a brief explanation of the possible benefit of each technique may boost compliance. Common techniques that have been used include the following:
  - Predonation hydration.
  - Receiving adequate sleep.
  - Receiving adequate nutrition.
  - Avoiding alcohol before and after donation.
  - Using applied muscle tension.
  - Using distraction techniques.
  - Using progressive recovery techniques (eg, dangling legs).
  - Complying with postdonation instructions and spending adequate time in the canteen.
  - Avoiding strenuous physical activity after donation.
  - Acknowledging anxiety and alerting blood collection staff of anxious feelings.
  - Becoming informed and asking questions.
- Statements describing blood collection facility policies on parental consent and confidentiality regarding test results, if applicable.

B. Parents of Adolescent Donors

Objectives

1. To involve parents by educating them about ways to reduce donation risk for their adolescent children.
2. To involve parents by educating them about the handling and treatment of reactions and involving them in decision-making when reactions occur.

Background

Parents of adolescent blood donors are in a unique position both to participate with their children in the decision to donate blood and, if reactions occur, to provide any needed care after their children return home.

Recommendations

It may be helpful to provide parents with information about blood donation, possible adverse reactions, and parental involvement in the event of an adverse reaction, even if parental consent for the donation is not required. The following should be considered for parental educational materials:

- Materials should include the same informational elements as student educational materials.
- Materials may include specific statements regarding the confidentiality of donor information, as applicable.
- Materials may include general instructions for supporting donors after common reactions such as hematomas or vasovagal episodes.
- Materials may be provided to the parent with consent documents when such documents are required.

C. School Personnel

Objectives

1. To involve school personnel by educating them about ways to reduce donation risk for their adolescent students.
2. To involve school personnel by educating them about the handling and treatment of reactions and involving them in decision-making when reactions occur.

Background

As employees of the school district, school health personnel have responsibility for the health of students on campus and, therefore, may serve as integral partners with the blood collection facility in the care of student donors. These health personnel may be involved in donor reactions either during the blood drive or after the collections staff have left the collection site. In either case, school personnel may have specific responsibilities to the student and parent in cases of student injury. Education of school personnel about the general process of blood donation, the possible reactions, and appropriate interventions and treatment is likely to be well received. Articles specific to blood donation and reactions are needed in the school health literature.

Recommendations

Blood collection facilities are encouraged to communicate with school officials before high school blood drives to establish policies and delineate responsibilities for student care during and after the blood drive. It may be useful for blood collection facilities to develop educational materials that target school health personnel; elements for consideration include the following:

- A general statement to the effect that most donors have uneventful donations and that most reactions, when they occur, are minor.
- A statement about which donors may be at increased risk for a reaction (eg, young, first-time, female, or low-weight donors) and why.
- A brief description of the donation process.
- A description of signs and symptoms of common donor reactions.
- A brief description of the appropriate handling of common donor reactions.

- A statement delineating the responsibilities of blood center personnel and school health personnel.
- A statement regarding confidentiality and release of information to parents, if applicable.

II. Initiatives to Address Consent Issues Specific to Adolescent Donors

Objectives

1. To provide blood collection facilities with information specific to informed consent of minor/adolescent donors.
2. To consider addressing increased rates of reactions in this age group in the informed consent process.

Background

The ethical substance of informed consent incorporates the fundamental principles of autonomy, veracity, beneficence, and nonmaleficence. The application of informed consent principles for both blood donors and blood recipients has been thoroughly addressed through peer-reviewed journal articles[6-8] and AABB publications.[9,10] However, the collection of blood from 16- and 17-year-old minors presents particular dilemmas and challenges with regard to traditional notions of informed consent.

Many states have long allowed 17-year-olds to consent to donate by specific state statute, but these statutes are silent on the issue of the minor's right to consent to subsequent medical treatment for an adverse reaction. Therefore, the consent process should take into account applicable state law provisions.

States that allow 16-year-olds to donate often require parental permission/consent. This situation allows the process of donation but does not imply any emancipated status because of the requirement for parental permission. Although 16- and 17-year-olds are sometimes recognized by state law as having the decisional skills necessary for making informed health-care decisions, parents and guardians still have legal responsibility, absent state law provisions to the contrary. This ambiguity is often handled by including the additional concept of assent, the notion that minors should be involved in health-care decisions in age-appropriate and developmentally appropriate ways.[8]

Specific issues arise when applying this distinction to blood donation. Blood collection facilities have traditionally adhered strictly to practices of confidentiality in notification of blood donors, including minors, of positive test results. Such policies need to be reviewed by blood collectors with specific attention to state statutes. The research setting presents similar issues. Minors are generally prohibited from participating in research without parental permission; however, blood collection facilities may perform certain required or elective tests under research protocols that have been approved by an institutional review board, and such protocols address the requirements for consent applicable to minors. Because statutes governing informed consent are state specific,

blood collection facilities are urged to consult legal counsel when addressing consent issues regarding minors.

In summary, it is vital to remember that consent is *not* a simple signature on a form, but a broader process that involves education of the donor and, in some cases, the parent. Providing adolescent donors (and parents) with information regarding the donation process and possible consequences meets an essential requirement of informed consent.

Recommendations

Blood collection facilities should consider the following:

- Consulting state statutes regarding age and consent requirements.
- Becoming familiar with the literature specific to adolescent/minor consent and assent.[7,8]
- Providing information to both donors and parents as part of the consent process. (Some facilities provide a parental consent form that functions as both informational brochure and consent documentation, when applicable.)
- Incorporating information specific to increased rates of reactions among groups such as young and first-time donors into the informed consent process.
- Incorporating statements concerning the release of information to parents about medical care for reactions and positive test results, as applicable.

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米国血液銀行協会
世界の輸血・細胞療法の発展

協会報　No.08－04

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宛先：　AABB 会員各位
差出人：　J.Daniel Connor, MM, 会長
　　Karen Shoos Lipton, JD, 最高責任者
件名：　若年献血者の副作用及び傷害を軽減する方策について

この協会会報には、20 歳未満の献血者の傷害及び有害反応のリスクを緩和する方策に関する会員向け情報が含まれる。AABB は、高校及び大学での移動献血の刷新を期待し、本会報を発行している。採血施設は、この献血者集団における傷害及び副作用の発生を軽減するため、いくつかのこれらの方針の実施を検討するとよいと思われる。

協会会報は、AABB 理事会が配布を承認したものであり、承認のための要件や基準の発表、新しい傾向またはベストプラクティスに関する勧告、関連情報などを含むことができる。本会報には、具体的な勧告は含まれず、基準や承認要件を作成するものではない。これは、AABB 若年献血者副作用作業部会の報告書に基づいている。同部会は、医師、看護師、運営者、広報及び法律専門家や米国血液銀行協会（AABB）、米国血液センター(America's Blood Centers)、米国赤十字社、米国血液センター（Blood Centers of America）からの代表者を含む。作業部会は入手された情報を検討及び協議し、現在の実践に基づき、1)若年献血者における副作用の軽減、2)副作用に関連した献血者の傷害の解消、3)若年献血者に関連した献血者教育及び同意の問題への対応、という三つの目標を取り上げた。これらの報告書の全文は、本会報の付属文書 1 と付属文書 2 に盛り込み、これらの目標を達成する可能性のある数多くの方策について記載している。いくつかの示唆された介入は、研究やデータの裏づけがあるが、その他については一般的な行為や期待される行為であり、ここに記載した目標を達成することを確証するものではない。

背景

自発的献血は、国の血液供給の礎である。献血は、16 歳（州法が認める）から 75 歳以上またはそれ以上の年齢幅にある健康な集団から募る。年齢の高い献血者からの献血は、個人の健康問題やその他の適格性を阻む壁によって減少しているため、過去数年間、採血施設は若年献血者からの献血をより重要視してきた。採血施設からの報告によると、現在米国のすべての全血採血のうち、10～20 パーセントは 20 歳未満の献血者から採取したものであるという。16 歳に献血資格を認める州では、この年齢群からの献血割合はさらに高くなっている。この献血層の伸びは、高校における移動献血の増加と関係している。高校生の献血者は一般に、多くの理由で献血の機会を受け入れる。その理由の中には、献血が「通過儀礼」であるという感覚、献血に関する医学的・

技術的側面への関心、多くの場合授業を免除される、などがある。また、延期率が低く、若いうちに献血を経験することにより、将来引き続き献血を行う可能性が高くなることから、理想的な献血者であるともいえる。

若年献血者及び高校における移動献血からのデータが蓄積されるにつれ、この献血者群の副作用率は他に比べてより高いことが判明し、ある研究によると成人の率の 5 倍も高いことが報告されている。傷害に至るまでの重篤な失神反応が献血者に生じることは稀であるが、このグループでは比較的高くなる。さらに、年齢は、副作用リスクと反比例するようである。最近のいくつかの研究で、この現象や副作用を軽減する各種の方策について報告されている。こういった結果が公表され、採血施設はこの問題に対する関心を高めている。このような新しい情報を認識し、献血者の安全を確保し、献血経験を満足させることの重要性を理解することで、採血施設は若年献血者の安全性を確保する取り組みを行なっている。

献血者の副作用

献血の圧倒的多数は問題なく、副作用や不快症状もない。しかし、少数の献血者は静脈穿刺部位にあざや出血が生じたり、軽い吐き気、またはめまい、気絶前症状、気絶または失神による虚脱またはひきつけなど、意識に変化が生じる。作業部会は、失神等、献血者が転倒した場合に傷害に至る可能性がある意識反応の変化をとくに重視している。献血後、合併症リスクに影響を及ぼすいくつかの因子として、反応に対する献血者の先天的な特徴や体質、採血職員のスキルと経験、移動献血の設定場所及び環境の特性、及び献血前後の献血教育が挙げられる。

文献、発表研究、及び採血施設の経験から、全血献血後の高い失神併発率は、献血者の特徴と相関することが報告されている。こうした特徴には、若年齢、初回献血、低体重、低血液量、女性、白人の民族性などが挙げられる。若い年齢、総血液量と初回献血の状況は、失神反応の主要な決定要素であり、独立したリスク因子である事が知られている。

これらの誘発因子を考慮し、作業部会は以下等の副作用の軽減対策に関する多くの現場体験や文献報告を検討した。

- 献血前教育。この分野の対処は、献血により生じる可能性のある不快症状の内容や対処方法に関する献血者の理解に影響を及ぼす。この分野は、献血者教育の下で、さらに具体的に記載されている。

- 移動献血の環境及び設置。移動献血の設置に関する最も良い実践については、利用可能な発表されているデータや情報はほとんどないが、作業部会は適当な換気、電気コンセント、副作用を管理するための健康診断スペースの重要性を認識している。具体的な対策として、以下のものが協議された。

1　作業を支持し、許容できる状況を確保するための設置場所選定手順および、その条件が不

適当になった場合の作業の中断に関する手引書。

2 献血者の流れの管理及びスタッフまたはボランティアの適当な配置。

3 継続した回復方策のためのスペースがある献血環境の存在。

4 献血者への付き添い。特に、イス・ベッドから献血後の場所（食堂）まで。

5 栄養補給・水分補給のための献血前の区域。

6 献血後の簡易食堂/軽食区域。

7 食堂区域で、献血副作用を見分ける訓練を受けた適当な職員またはボランティアを配置。

8 不安や気分不良を感じるかもしれない献血者の回復のための別エリア。

リストした方法に関連する追加的な実践及び情報については、付属の報告書に記載されている。

- **職員の管理及び採血者の技術。**採血職員に対する訓練と管理は、すべての移動献血の成功と献血者の安全に不可欠である。高校における移動献血では特に、特別なあるいは経験豊富なスタッフを配置することにより、献血者の副作用の影響と割合を軽減することができるかもしれない。採血施設は、副作用の管理に関して、採血職員の配置、教育訓練、及び仕事ぶりを定期的に精査するべきである。
- **介在。** 採血副作用、とくに若年献血者の副作用を防止するために、現在現場でさまざまな実践が行われている。実践は発展しているが、採血施設は以下の方策を検討し、評価すべきである。

1 献血者のサイズ/年齢の基準。現在の適格性要件である最低体重 110 ポンド（約 50 kg）、全血採血の上限 10.5 mL/kg は、献血者の多くを保護するのに十分である。これらの基準は、献血者の血液量の 15%を超えて採取することを妨ぐという推定に基づいている。一部の採血施設は、適格な献血者の推定血液量は 3500 mL を超える旨を要件とするために当該基準を変更することを検討している。その他の方策としては、若年献血者の最低体重を 120 ポンド(約 55 kg)までに引き上げる、または若年献血者からの採血量を引き下げる、などが挙げられる。

2 気分転換の方策。副作用の自己報告の減少に基づき、視聴覚の娯楽などの気分転換の手法は、採血中の献血者の気分を楽にする効果があることが報告されている。

3 水分補給。数例の研究では、水（献血 30 分前、500 mL）を摂取した献血者は、副作用が有意に減少したことが報告されている。採血施設は、20 歳未満の献血者に飲み物を提供し、献血前 30 分以内に液体 500 mL を摂取するよう勧めるとよいだろう。

4 筋伸張（Applied Muscle Tension; AMT）は、上腕や脚の大筋群を繰り返し、リズミカルに収縮させるもので、若年献血者の失神前反応を軽減させることが示されている。また、この手法は習得しやすく、安全に使用できる。

5 自動採血手順。2 単位赤血球の自動採取は、若年及び初回献血者において全血採血に比べ良好で安全な側面を持っている。副作用リスクがより低くなるのは、一部に、生理食塩水の代替によると考えられる。高校及び大学における血液成分分離装置による赤血球採取プログラムの拡大と、更なる研究を推奨する。

6　副作用後の指導。現在の基準では、採血施設は献血者の傷害を治療し、必要に応じて救急医療を提供する手順がなければならない（BB/TS 基準 5.3.2.1）。献血者とその家族に向けた情報を盛り込むよう助言する。この問題は、献血者教育の下にさらに詳細に述べる。

副作用の結果生じる献血者の傷害

稀なケースであることから、献血者の副作用から生じる傷害に関する情報は発表されていない。利用可能なデータは、大規模な採血プログラムでの傷害クレームから得ている。現在の推定では、献血 200,000 回に 1 回、重篤な傷害があると予想される。献血者が失神反応を示し、床に倒れ、顔面やその他の骨折及び裂傷を招く際に傷害が生じる。こうした失神反応を軽減することは、すなわちこのような種類の傷害を減らす。その他の環境上及び運営上の方策としては、回復場所において副作用を管理する追加スタッフの使用と訓練を実施することである。また、食堂での観察や付き添い方針の強化、副作用の認識に関する献血者教育も推奨される。回復時の高校生献血者を、転落や傷害を防止するため床マットに座らせることも、評価されているもう一つの方策である。これらの対策の影響の正確な評価は、負傷率に関する情報のさらなる収集を待つところである。

献血者の教育

献血前情報、献血の同意、および献血後の問題の管理方法に関する理解は、献血者に満足な献血経験を与え、献血者が将来再び献血することを確実にするために重要である。若年献血者の供血に関しては、異なる背景、期待、法的問題があるので、献血者教育と同意は特別な重要性を帯びている。高校における移動献血には、教育、法的責任、及び親/保護者の関与に関する追加的な問題が含まれる。

献血前の不安は、副作用率の増加に関連する。共通の献血者の不安に対処し、有用な対処方法を示唆することは、供血者の不安を和らげ、自己有効性（ある状況を管理する能力が自分にあるという確信）への姿勢や、献血に対する将来の意志を向上させる。献血前教育の資料は、献血意思の前に供血プロセス、潜在的な副作用、介入に関連した情報が提供される意味で、同意プロセスの一環と考えられる。こうした資料が、年齢に応じた言葉づかいやイラストなどを用いて高校生向きに作成されれば、より大きな影響を持つことになる。また、ビデオなど、その他にも青少年に親しみやすい形式で提示する場合もある。このような資料に盛り込む要素として、以下等が考えられる。

- 多くの献血者が無事に献血を行っており、副作用の多くは、起こったとしても、軽度である旨の一般的な記述。
- 副作用リスクが高くなる可能性があるのはどのような献血者か、及びその理由に関する記述（例：若年、初回、女性または低体重献血者はとくにリスクが高い可能性がある）。
- 初回献血者に対し、過程について知らせるための、また未知の不安を軽減するための、献血過程に関する短い記述。

- 副作用を予防し、対処する技術を高めるための考えられる技術に関する説明、及び、これらの技術を忠実に守ることで考えられる利点の短い説明。
- 該当する場合検査結果に関する守秘義務と親・保護者の同意についての採血施設の方針を記載する記述。

必要な場合、採血施設は、有害反応の予防方策に関する教育的な取り組みに焦点を当て、副作用の軽減方法に対処し、遅延性または長期的な献血者の反応の管理に対応し、献血場所から以下の集団に献血者を渡した後の看護の継続性を検討するとよいだろう。

- 会長、移動献血のスポンサー、高校関係者
- 教育訓練、募集及び採血の職員
- 高校生とその両親
- 学校看護師

理想的には、この情報は献血日が近くなってから配布する。

- 副作用後の教育と看護。採血施設は、献血者の有害事象に対し治療をし、必要に応じて救急治療を行うプロセスを有しなければならない（BB/TS 基準 5.3.2.1）。両親・保護者または学校看護師との連絡を強化するための対策は、献血場所を離れた後、遅れて生じる副作用の管理を向上させ、また、採血施設は、以下の対策を検討するとよいだろう。

- 州法に従い、献血者の意識消失またはその他の副作用あるいは傷害が見られた場合の両親親・保護者への連絡。
- 献血場所及び帰宅後に副作用が生じた若年献血者のケアの継続。

若年献血者の同意と機密性

自主性、真実性、慈善、無危害の原則をうまくとりいれた献血のインフォームド・コンセントの実施は、一律に採用されていない。献血の同意は、単に書類上の署名ではなく、献血者、場合によっては献血者の親/保護者への教育を含めたより広義のプロセスであることを銘記しておくことが重要である。さらに、16 歳及び 17 歳の未成年からの血液採取の同意には、ある種のジレンマと課題がある。例えば 17 歳の献血への同意を認めている州法は、有害反応の場合の後続的な医療処置にも未成年の同意権を認めるかについては、ほとんどの場合触れられていない。16 歳の献血を認める州法は、親・保護者の許可・同意を求める場合が多く、従って完全な自由を意味するものではない。こうした州が、説明を受けた医療行為の決定を行うのに必要な意思決定権を未成年に認めているとしても、親・保護者はかれらの未成年に対し依然として法定責任を負う。

検査結果に関する献血者への通知方針は、未成年に関する州法規定に照らして慎重に検討されな

ければならない。また、未成年は一般に、保護者の許可がなければ研究に参加することは禁じられる。しかし、採血施設は施設内倫理委員会が承認した研究プロトコルのもと、ある種の必要とされるまたは選択した検査を行うことができる。こうしたプロトコルは、未成年に該当する同意要件に対応している。

重ねて言うが、思春期献血者（及び親・保護者）に対し、献血プロセスや潜在的な結果（反応）に関する情報を提供することで、採血施設は必須の同意要件を満たしている。採血施設は、以下の実施を考慮すべきである。

- 年齢及び同意要件については、州法に従う。
- 思春期/未成年のインフォームド・コンセントについて具体的に記した文献に精通する。
- 同意プロセスの一環として、献血者と親・保護者の両方に情報提供する。一部の施設は、必要に応じて、情報提供のパンフレットと同意文書の両方の機能を兼ね備えた親・保護者の同意書を提供している。
- 若年かつ/または初回献血者は副作用率が高いという具体的な情報をインフォームド・コンセントのプロセスに組み込む。
- 必要に応じて、副作用及び陽性の検査結果に対する治療について、保護者に提供する情報に関する記述を盛り込む。

要約と結論

ほとんどの献血は問題なく終了するが、一方で軽度の合併症でさえ再献血の可能性を減少させる。献血後の重度の傷害は、稀ではあるがあらゆる年齢群の中で発生する。しかし思春期の献血者はそれよりも年上の大人の献血者と比べて過度に影響を受ける。実質的な献血経験の全ての局面は、合併症のリスクに何らかの影響を持つ。作業部会は、若年献血者の有害反応に関する現在の見解や実践について、総合的な検討を行った。若年献血者及び高校における移動献血がもたらす特殊な課題に対応する上で、採血施設にとって、この情報が有益となるかもしれないことを AABB は確信している。リスク・ゼロは成人においてさえ到達しがたいものであるが、未成年者の合併症率については、献血安全性に絶えず注意を集中する持続した運営上の努力に対し、継続した配慮が求められている。AABB は採血施設に対し、副作用から生じる傷害と献血者副作用率に関し、介在の有効性を継続して監視し、報告するよう勧告している。米国における国家ヘモビジランス・プログラムを策定しようとする AABB の取り組みは、献血後の有害事象に対する一貫した報告の枠組みとなるだけでなく、稀ではあるが医学的に重篤な献血関連の合併症を予防する取り組みの有効性を監視するためのメカニズムとなる。

附属文書 1

青年期献血者における副作用及び傷害リスクを最小にするための勧告

寄稿者：

米国血液銀行協会（AABB）若年献血者有害反応ワーキンググループ　会長 Robert Jones MD

Anne Eder, Hany Kamel, Christopher France, Diane Killion, Patsy Shipley, Pat Demaris, Nina Salamon, Dan Waxman.

目的

1　献血者の経験を高め、献血者の合併症を低減するための方法の公表されたデータ及び報告された有効性を再検討すること。

2　高校の移動献血における献血者の合併症を低減するために、血液センターで採用される可能性のある様々な手法を確認すること。

実行の概要

現在、米国の血液センターにおける全血献血では、若年（16 歳及び 17 歳）献血者が大きな割合を占め、その割合は増加しており、2006 年の米国赤十字社（ARC）における、全血献血件数の約 8%（45 万の全血採血）となる。しかし献血関連の合併症の主要決定因子として、若年齢、総血液量、初回献血が知られており、それらは独立したリスク因子である。軽度の副作用や一時的な供血延期でさえ献血に戻る可能性を減少させる。献血経験を改善する取り組みは血液供給を持続するために不可欠である。若年献血者の募集やその維持への高まる依存は、献血者の安全性、とりわけ、高校での移動献血に対する確実な取り組みを必要としている。

献血経験をさまざまな視点から捉えると、献血後の合併症リスクに影響を及ぼすいくつかの側面が明らかになる：副作用に対する献血者の先天的な特徴や体質、血液センターの職員の経験とスキル、移動献血の設営及び環境の特徴、献血前後の献血教育。全血献血後の失神の合併症率の上昇と相関関係をもつ献血者の特徴として、若年齢、初回献血であること、低体重、低血液量、女性、白人の民族性などが挙げられる。これらすべてが、副作用の独立した予測因子となるわけではないが、リスク因子との相加効果は白人高校生において認められている。献血経験の改善及び/または献血者の合併症発生率の軽減を目的として、いくつかの介入方法（例：献血直前に献血者に水約 480 mL（16 オンス）を摂取してもらう、または筋伸張や気分転換の手法など）が採られている。しかし、どの方法を採っても、大半の全身性反応の予防や、全血献血後の失神による傷害など、稀ではあるがはるかに重篤な合併症の予防には至っていない。

このため、血液センターは、献血者の経験や合併症リスクに影響を及ぼすあらゆる要素について検討した後、血液センターにどの安全対策を強化または導入するかを決定すべきである。また、安全対策の効果を継続的に監視し、結果データを仲間と再吟味すべきである。そして献血経験の改善への取り組みに対する我々の理解を促進するため結論を公表すべきである。

血液センターは以下の分野において一つまたは複数の対策を検討し、安全性の継続的評価を目的とした監視プログラムを策定するよう、ワーキンググループは勧告している。

I　献血前教育
II　移動献血の設営と環境
III　職員の管理と採血技術
IV　介入
　A　献血者の適格性基準
　　1　血液量が 3500 mL 未満の若年献血者の献血延期
　　2　献血者の最低許容体重の引き上げ
　　3　若年献血者からの血液採取量の引き下げ
　B　気分転換の手法
　C　水分摂取
　D　筋伸張
　E　容量置換を伴う自動赤血球採取手順
V　献血者と両親に対する副作用後の指示

本報告書は、献血経験の改善のために期待される効果と限界を見つけ出し、更なる開発と研究の方向性を提供し、献血者基盤への影響を推定し、および各分野においてコンセンサスに基づく勧告を行うためにこれらの異なるアプローチに関する入手可能な証拠を要約したものである。

I　献血前教育

献血者に共通する問題に取り組み、有用な示唆を与える努力は、献血者の態度、不安、自己効力感（ある状況を自分が管理する能力があるという信念）、及び献血に向ける意思を評価したアンケートのスコアの向上に関連していた。献血募集資料が合併症率や献血復帰率に及ぼす影響について評価する公表された研究はない。

いくつかの未発表データや不確かな経験は、教育的な取り組みが献血者の副作用を軽減させ、献血者と職員に副作用へのより良い対処を身につけさせることが、副作用の重症度を軽減するために効果的かもしれないと示唆している。

勧告

教育的な努力は、献血経験の改善が相当に期待でき、献血参加者の増加やより効果的な準備をもたらすだろう。そのような努力は、献血者基盤に有害な影響を及ぼすとは考えられない。

教育的な取り組みは、以下の集団を対象とすべきである。

- 移動献血の責任者及びスポンサー
- 高校生とその両親

- 献血者向けの教材には、予防戦略または副作用を軽減するために対処している戦略に関する事前ガイダンス及び内容を盛り込むこと。
- 教育資料は、献血日が近くなったら配布すること。

● 学校看護師
- 学校看護師は、献血関連の副作用の病態生理学や、合併症を経験する献血者の看護に関する知識があること。
- 移動献血前に、献血センターは遅延性または長期的な献血者副作用の対処方法について学校看護師または管理者と話し合い、献血者が献血場所を離れた後も看護の継続を確保する。

● 補充者及び採血職員の訓練

学生に教育する場合の最適な媒体は不明であるが、次の形式が含まれると考えられる。

● 教育用 DVD。それぞれの学生の状況に適う 10 分以内のビデオ形式で、学校管理者がそれぞれの都合に合わせて教育を行うことができるもの。
● ポッドキャスト、ダウンロード可能な電子ブック、または同様のアプリケーション。
● 血液センターのウェブサイト

II　移動献血の設営と環境

血液センターは、効果的な献血者手順及び年齢を問わず献血者への十分な世話を提供するシステムを処々に設けなければならない。移動献血の設営の最も良い実施については、データが不足しており、スポンサー集団は移動献血を行うのに十分な場所の確保に苦労する場合が多い。血液センターの多くは、移動献血を実施する前に現場清掃が必要である。適切な換気、電気コンセント、副作用を処置するための場所を確保するため、移動献血を行う場所を巡回してみることが重要である。最近、アメリカ血液センターグループ Blood Centers of America(BCA)が 26 の血液センターに対して実施した調査によると、高校の移動献血の設営は通常の移動献血の設営と異なる、と回答したセンターは 9 センターに及んだ（Nina Salamon、パーソナルコミュニケーション）。

勧告

移動献血の設営に、より制限されるか限定的要件の推奨を裏付ける証拠はない。しかし、血液センターに、副作用の可能性を低減するかもしれないプロセスを確認し実行するために、かれらの経験を共有することを奨励する。

献血の前に献血者に水分を与えるための献血前の水分補給場所やその他の仕組みなどが、移動献血の計画または設営の一部となるべきである。献血者が、水のボトルを持って献血場所を離れることを認め、その際には移動献血の前に学校管理者から許可を得ることが必要となる場合がある。

血液センターは、高校での移動献血における副作用を低減するよう、移動献血の設営において以下の側面を考慮する。

- 作業に適う許容条件を確保する場所選択手順及びそれらの条件が適さなくなった場合の作業の中断に関する手引書。
- 制御された献血者の流れ、及び十分な職員またはボランティアの有効性。動揺を最小限にするため、学生の出入りパターンを均等な間隔にする。献血エリアに入れるのは、学生の献血者、指定されたボランティア、及び職員に限定する。
- 献血者を献血後、立ち上がらせる前の段階的な回復方法（例：適切な配慮をしつつ、ベッドの側面から両足をぶらぶらする）。
- 特に、イス/ベッドから食堂までの間、献血者に付き添う。ボランティアに教室まで献血者に付き添う様に頼むことを考慮する。
- 水分および食物摂取のための、献血前の食堂テーブル（以下、「水分摂取」を参照）。
- 献血後の食堂/軽食場所：
- 指定の場所と献血者の流れは、献血後に食堂で十分な時間が取れるよう考慮する。
- 献血者を、献血後の回復と休憩期間の間、床の体操用マットに座らせる。
- 割当時間（例：約 15 分間）の間または献血者の気分が良くなるまで食堂にいる重要性を献血者に伝える。十分な回復時間の間、回復場所にとどまるよう献血者に指導することの重要性を職員に強調する。
- 副作用の兆候や症状を認識する訓練を受けた職員またはボランティアを追加して回復場所へ配置することが可能であること。
- 回復のための場所。車椅子の使用が可能であること。不安または気分が悪くなる可能がある学生のために、分割または場所を間仕切るための移動間仕切りの使用が可能である。

III　職員の監督および採血者の技術

採血部門の従業員は、献血者の年齢を問わず、血液センターの使命と成功及び献血者の安全にとって重要である。ある研究で、標準化社会技術テストで高得点を示した採血者は、献血者の副作用の減少と関連があった。採血訓練はこの研究において多少重要性があった。

一部の献血センターでは、副作用の兆候を認識しその予防対策措置が取れるように十分訓練を受けた職員を参加させることや、高校の移動採血の職員やその他の管理職員を増員することにより、高校での移動採血の副作用の軽減に努めている。

勧告

献血センターでは、高校での移動採血に関して、「追加の」または「より経験豊富な」職員を揃えていると報告する場合が多いが、手本となる人員配属または規定の技術要件のための業界基準はない。技能はもちろん雇用実践および職員教育訓練の重要性が認識されている。血液センターに教育訓練プログラムや職員の仕事ぶりを継続的に評価することを勧める。

IV　介入

A　献血者の適格性基準

1　血液量が 3500 mL 未満の若年献血者の供血猶予

- 献血後の失神は典型的な「血管迷走神経性」発作の兆候である場合があるが、血液量減少の兆候である場合もある。
- 献血者の血液量が 4,775 mL 未満である場合、失神反応及び失神前反応の独立危険因子であると全血献血に関するある研究は示した。
- 血液量を引き上げることにより副作用リスクは評価範囲でかなり低下する。この研究の献血者の 5%は血液量が 3500 mL 未満であり、このような献血者が 525 mL を献血すると、その献血者の血液量の 15%を超えることが確実である。
- 最低総血液量（>3500 mL）のための追加要件を実施することにより、失神及び失神前反応のリスクを軽減することができる。二変量解析は、献血者の血液量に基づく副作用率の差は、30 歳以上の献血者の差に比べて、若年者の方がより大きいことを示す。低血液量（3500 mL 未満）の若年献血者（23 歳未満）に介入を適用することにより、副作用が軽減される可能性がある。
- 予備的な未発表データ（Hany Kamel, パーソナルコミュニケーション）は、総血液量が 3500 mL 未満の 23 歳未満の献血者は、23 歳未満の献血者の 9%、全献血者の 1.6%を示している。この集団における中等度副作用及び重度副作用の率は 1.7%（中等度及び重度の全体の率 0.33%と比較して）である。血液量が 3500 mL 未満、23 歳未満の献血者を除く方針では、この年齢集団（全反応の 9%）で中等度及び重度副作用の 20%を排除できると推定される。

2　献血者の最低許容体重の引き上げ

- Trouern-Trend 等は、体重約 68 kg（150 ポンド）～約 81 kg（179 ポンド）の献血者の対照群の副作用率 0.14%に比較して、体重約 54 kg（120 ポンド）未満の献血者の副作用率は 0.46%であったと報告した。
- Newman 等は、高校生では、体重約 59 kg（130 ポンド）以上の献血者の副作用率 8.2%に比較して、体重約 59 kg（130 ポンド）未満の献血者では 16.9%であったと報告した。献血者の体重が約 59 kg（130 ポンド）未満は、全献血者の 4.1%であった（118/2894）。
- ある研究では、献血関連の傷害によって外部で治療を受けた 16 歳および 17 歳の献血者 32 名中 22 名（69%）が、体重約 59 kg（130 ポンド）を超えていた。32 名中、わずか 4 名（12.5%）が約 54 kg（120 ポンド）未満であった。献血者が報告した体重に基づく選択基準では、青年期献血者の傷害のうちのごく一部を予防するにすぎないと考えられる。

3　若年献血者からの血液採取量の制限

- 二つの要約は、450 mL 及び 500 mL の全血採取において同等の全体的な安全プロフィールを示した。これらの研究では、全身性の副作用が起こり易い要因（例:年齢、体重、経験など）により献血者を分類していない。若年及び/または低体重の献血者の採血量をより少なくする事に対するいかなる有益な効果も隠された可能性があり得る。
- Tomasulo 等は、450 mL バッグで採取した全血単位の重量を測定し、総血液量から除かれた血液量の割合を算定し、異なる献血者集団における献血者の副作用率を報告した。除かれた採血量が 14%から 16%であった女性献血者は、10%のみ除かれた者に比べて、副

作用を起こす可能性が高かった。体重が約 50 kg（110 ポンド）～約 54 kg（119 ポンド）の献血者は副作用率が高くなり、これは採血量に起因すると執筆者等は結論付けた。

勧告（献血者適格性基準）

研究は、異なる選択基準を持つことで恩恵を受けるかもしれない高リスクのサブグループを確認した。最低体重を約 50 kg（110 ポンド）、採取制限を 10.5 mL/kg にしている現在の適格性要件は、ほとんどの献血者を保護するために十分であるが、すべての献血者ではない。この要件が献血者の血液量の 15%を超える採血を防止することになるという推定にこの要件は基づいていた。最近のデータは、この推定が正確ではないことを示唆し、新しい標準的なアプローチでは、青年期献血者の全血採血を総血液量の 15%以下に制限することが必要となろう。選択基準における所定の変更での副作用率の減少は、多変量解析によって推定できるが、所定の方針の実施が予想結果を達成するかどうかは判明されない。血液センターに、副作用と傷害の予防において、異なる献血者選択基準の潜在的有効性を評価することを勧める。

B　採血中の献血者の気分転換

気分転換の手法は、採血中、献血者の気分を楽にする効果があることが広く認識されている。小規模な研究によると、視聴覚的な気分転換を用いると、血管迷走神経反応の自己報告が減少した。移動献血で実施しやすい視聴覚的な気分転換には、MP3 プレイヤーの使用の許可またはヘッドフォンでの音楽提供、献血者の筋伸張活動を奨励すること、ならびに献血者用椅子を背中合わせに置くことなどがある。

勧告

血液センターは、献血中に献血者の意識の制御を高めるかもしれない気分転換のために許される行動に関して、献血者に教育を提供すべきである。血液センターは、副作用を低減できそうな方法として、気分転換の重要性を職員に指導するべきである。

C　水分摂取

現在まで、献血者の副作用に対する献血前の水分補給の効果に関して二つの研究が発表されている。無作為化比較試験で、初回献血者男女 83 名（年齢中央値＝19 歳）に同種全血献血の 30 分前に水 500 mL を摂取させた。水を摂取した献血者は、水を摂取しなかった献血者に比較して、失神前反応（例：気を失いそうな感じ、めまい、脱力感）が有意に低い結果がしめされた。この所見は、採血の 0 分～30 分以上前に水 473 mL を摂取した高校生献血者（17 歳～19 歳）約 9000 名を対象にした研究で後に確認された。既往歴記入用紙に記録された献血者副作用に基づく副作用率は、献血前の水分補給によって 21%減少した（水＝副作用率 9.9%；水なし＝副作用率 12.5%）。さらなる分析では、採血の 10 分以内に水を摂取した人達の副作用率が最も低く、時間が遅れるにつれ副作用率が高くなることを示した。

献血前の水分補給が献血者の反応に及ぼす効果については、まだ二つの研究だけの発表であるが、

更なる実験研究では、急激な飲水負荷は血圧、末梢血管抵抗、及び脳血流を増加させ、起立性の問題がある健常人においては迷走神経反応の予防に役立つことが、実証された。

表 1

献血前の飲水負荷の機能と標準献血管理に認められた献血者副作用の低減に関するまとめ

研究	水	管理	変化
Hanson 及び France (2004)	0.48 (BDRI、ログ単位)	0.91 (BDRI, ログ単位)	↓47%
Newman 等 (2007)	9.9% (献血者副作用)	12.5% (献血者副作用)	↓21%

注：献血による副作用指標（Blood Donation Reactions Inventory; BDRI）は、気を失いそうな感じ、めまい、脱力感など、献血者の副作用に関する自己報告の測定である。この指標の上昇は、献血者記録に記録された副作用に関連する影響に加えて、献血者の献血復帰がないことを予想する。

勧告

献血前の水分補給が男女両方の献血者の失神前反応の予防に役立ち、献血の過程を妨げず、採血職員に実施しやすいと認識されているという既存の証拠に基づき、献血者に 500 mL の水または水分を与え、採血の約 10 分前に水を摂取するよう奨励するべきである。

D　筋肉の緊張

現在まで、献血者の反応に及ぼす筋伸張（Applied muscle tension; AMT）効果に関して、四つの研究が発表されている。AMT には多くの形があるが、両腕や両脚の大筋の反復する律動収縮などが一般的である。献血においてこの手法を適用した最初の研究で、比較的経験の少ない献血者（すなわち、過去の献血 0～2 回）の小人数のグループ（n=37）に対し、AMT を指導するために短いビデオが使用された。そのビデオを見なかった対照群と比較して、AMT を習得した献血者は、献血直後の失神前反応（例：気を失いそうな感じ、めまい、脱力感）が有意に減少したことを報告した。さらに、献血の間中 AMT を行った者は、反応が最も少なかった。

AMT の有益な効果は確認され、さらに大規模な、若年献血者（年齢中央値＝22 歳、過去の献血平均＝3.5 回）605 名を対象とした調査に広がった。本研究で、献血者を無作為に、1)標準的な献血、2)献血前に AMT を実施（プラセボ対照）、または 3)献血中に AMT（介入）、の群に割り当てた。両方の AMT は、献血者が短いビデオを見て筋伸張法を学ぶことが条件付けられた。肯定的な予測効果をコントロールするため、献血前に AMT を実施（プラセボ対照）が条件の参加者に、採血針が刺される直前まで、採血イスに座ったときから AMT を行うよう指導した。全体として、AMT は女性献血者に効果があり、男性献血者にはなかったという結果が示された。特に、介入が条件に割り当てられた女性献血者は、失神前反応が有意に低く、採血イスのシートを倒す必要性

が少なく、また、プラセボや標準的な献血が条件の女性に比べて全量まで血液が得られる可能性が高かった（プラセボ条件と標準的な献血条件では差がなかった）。

献血者（n=467）の独立サンプルでは、プラセボ対照または標準的な献血（プラセボ条件と標準的な献血条件では差がなかった）のどちらでもなく、AMT 介入に割り当てられた男女両方の献血者とも、失神前反応が弱まった。最近になって、献血者 1209 名（女性 50%、年齢中央値＝22 歳、過去の献血平均＝2.2 回）を無作為に、標準的な献血または筋伸張 5 パターンのうちの 1 つに割り当てた。AMT に割り当てられた献血者は、1)全身（両腕、両脚、および腹部）、2)下半身のみ（両脚と腹部）、3)上半身のみ（両腕）、4)気分転換をしながら上半身のみ（両腕、ただし献血に使わない腕に行うように指導）、または 5)献血する腕のみ、の反復する筋伸張を描いた短いビデオを視聴した。全身 AMT は、標準献血と比較して、失神前反応の報告を有意に減少させ、採血イスのシートを倒すことが少なくなり、先の効果が再現された。下半身 AMT では同様の効果が認められたが、上半身 AMT では認められず、両脚と下腹部の緊張は AMT 有益な効果の重要な要素であることが示された。気分転換をしながらの上半身 AMT も、失神前反応の有意な減少に関連があり、AMT の効果は、少なくともその一部が気分転換からも得られている可能性があることを示していた。

献血に照らした研究に加えて、血管迷走神経性失神のその他の原因と同様、血液や傷害恐怖症に関連する失神がある患者の治療の奏効に、何十年にもわたって AMT が使用されている。実験研究では、AMT は血圧ならびに脳血流を上昇させ、酸素供給をすることにより、失神や失神前反応を予防する助けとなることが示されている。

表 2

筋伸張の機能に認められた献血者反応の低減対標準献血管理に関するまとめ

研究	筋緊張	管理	変化
Ditto 及びその他 (2003)	4.9 (BDRI 単位)	6.3 (BDRI 単位)	↓22%
Ditto 及びその他 (2003)	全献血者＝0.43 (ログ BDRI)	0.47 (ログ BDRI)	↓8%
	女性献血者＝ 0.44（ログ BDRI)	0.55 (ログ BDRI)	↓20%
Ditto 及び France (2006)	0.35 (ログ BDRI)	0.45 (ログ BDRI)	↓22%
Ditto 及びその他 (2007)	0.42 (ログ BDRI)	0.52 (ログ BDRI)	↓19%

注：献血副作用指標（Blood Donation Reactions Inventory; BDRI）は、気を失いそうな感じ、めまい、脱力感など、献血者の副作用を自己報告するものである。この指標の上昇は、献血者記録に記録された副作用に関連する影響に加えて、献血者の献血復帰がないことを予想する。

勧告

AMT は習得しやすく、利用が安全で、若年献血者の失神前反応の低減または回避に有効であるという既存の証拠に基づき、この方法の献血者及び職員への指導を勧める。異なる手法を採ることは可能であるが、献血中、両脚及び腹部の大筋を緊張することを重視すべきである。献血後の副作用及び傷害の低減における介入効果を評価するため、さらなる研究を勧める。

V　自動赤血球採取

赤血球（RBC）自動採取の安全性は、全血献血と比較されてきた。米国赤十字社の経験では、全血（WB）及び 2 単位の RBC 献血に対する有害反応の大半が軽度で、全身性の合併症であった（例：失神前状態、クエン酸反応）。合併症の全体発症率は、WB 採取よりも 2 単位 RBC 採取のほうがわずかに高かった（10,000 回採取で 320.3 対 274.5；オッズ比、1.17（95%信頼区間、1.15 から 1.20）。

表 **3**　献血関連の合併症に対するリスク因子*

人口統計学的特性 ***	副作用発生率（献血 1,000 毎）	未調整オッズ比（95%信頼区間）	調整済オッズ比**（95%信頼区間）
血液量 3500 mL 未満 ***	34.9	4.47(4.10-4.88)	2.88(2.57-3.23)
年齢＝17 歳～18 歳 ***	39.6	4.19(3.94-4.45)	2.78(2.59-2.98)
年齢＝19 歳～24 歳 ***	27.4	2.87(2.68-3.06)	2.39(2.23-2.56)
初回献血者　***	27.5	2.80(2.66-2.94)	2.20(2.07-2.33)
人種＝コーカサス人種 ***	14.3	3.42(2.63-4.46)	2.15(1.64-2.82)
血液量＝3500～4000 mL　***	23.5	2.97(2.77-3.17)	2.09(1.90-2.31)

*副作用のない献血者と比べて、献血者の特徴別の献血副作用率と、軽度、中等度、重度反応を合わせたもののオッズ比

**共変量としての、年齢群、性別、献血履歴、人種/民族、推定血液量、脈拍、収縮期血圧、及び血液センターなど

***対照群と比較して：4775 mL 超の血液量；年齢 25～65 歳；献血リピーター、及び黒人、非ヒスパニック系の民族性。

しかし、2 単位 RBC 献血における重要な全身性合併症（意識消失、傷害を伴う意識消失、回復遅延、重いクエン酸中毒）率は、特に、20 歳未満の献血者[オッズ比、0.41（95%信頼区間、0.32 から 0.53）]で、WB 献血の副作用率に比べて低くなった。Blood Systems は、要手法による WB 採取は中等度及び重度の副作用の発生率が低いことを実証した（10,000 採取につき 47.1、0.47%）。血液成分分離装置により採取した 1 単位赤血球の安全プロフィールは同一である（10,000 採取につき 37.44、$p>0.20$）。血液成分分離装置による 2 単位赤血球採取と血小板フェレーシスによる採取の副作用率は有意に低下した（それぞれ、10,000 採取につき 15.65、$p<0.00005$；及び 10,000 採取につき 14.84、$p<0.00005$）。

自動 2 単位 RBC 採取は、全血採取に比較して安全プロフィールは良好であり、全血献血と比較して重大な全身性合併症のリスクが低くなる。この利点は、若年献血者及び初回献血者で最も顕著であり、大学や高校において今後のさらなる研究や、血液成分分離装置による赤血球提供プログラムの拡充のための根拠となっている。

2 単位 RBC 採取の明らかな安全性の強みは、そのような手順中の食塩水の置き換えまたはそのような献血のためのより厳しい基準（2 単位 RBC 献血の献血者選択に用いられるヘマトクリット、身長、体重の基準は、身長がより低い全血献血者よりも、赤血球量または総血液量が多い献血者を選定するように作られている）に起因している可能性がある。量の置き換えの本当の影響を探りだすため、さらなる分析が必要である。

勧告

利用可能な証拠は、高校や大学における血液成分分離装置による赤血球提供プログラムを拡大する更なる研究を支持する。

VI　献血者及び両親に対する副作用後の指導

献血者センターは、献血者の副作用後の看護のための手順がなければならない（AABB 標準書 5.3.2.1）。両親/保護者または学校看護師との意思疎通を改善する対策により、献血場所を離れた後、遅れて表れる副作用の可能性が低減されるかもしれない。献血者センターは、以下の面について考慮すべきである。

- 州法に従い、献血者が意識消失またはその他の副作用あるいは傷害を起こした場合の両親/保護者との連絡。
- 血液センターは、献血者がまだ献血場所にいる間または帰宅後に副作用を生じた場合、継続して看護が受けられる事を確実にすべきである。

結論と今後の方針

血液センターは、合併症リスクに影響を及ぼす献血経験のあらゆる面について認識し、高校における移動献血の安全性を高めるため、本報告書で論じた一つまたはそれ以上の対策について検討すべきである。血液センターは、進捗を測り、その取り組みの有効性の監視もし、献血者を保護する方針及び手順を改良し、満足できる献血経験を確保すべきである。献血のほとんどは無事に終了するが、軽度の合併症でも再来献血の可能性を減少させる。献血直後の重度の傷害は、あらゆる献血者年齢層の中でも稀に起こるが、青年期献血者はそれよりも上の年齢層の献血者と比べて過度に影響を受ける。ある研究で、失神に関連した傷害リスクは、20 歳以上の個人が 10,000 回献血につき 0.4 であるのに対し、16 歳及び 17 歳の献血者では 10,000 回献血につき 5.9 となった。（オッズ比、14.46；95%信頼区間、10.43－20.04)。献血者の副作用を軽減するために本研究で明確にされている試みは、いくつかの傷害の予防も期待できるが、献血者の傷害の発生が稀なことを考えると、いかなる特定の行為の実際の利点も測ることは難しいかもしれない。反応の定義が一貫していないことや報告基準が異なること、個々の献血専門家が副作用をどのように認識し、報告するか一定しないことから、今のところ、献血者センター間の副作用率の比較を行うことも不可能である。米国に全国ヘモビジランス・プログラムを策定するための AABB の試みは、献血後の副作用に対する統一した報告の枠組みとなるだけでなく、稀ではあるがより医学的に重篤な献血関連の合併症を予防する取り組みの有効性を監視するためのメカニズムともなる。ゼロリスクは成人においてさえ到達しがたいものであるが、未成年の合併症率については、献血安全性に継続して焦点を当てた持続した取り組みの成果に対して、継続して注意を向けることを要求する。

付属文書 2

青年期献血者の教育と同意に関する推奨される取り組み

寄稿者：
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I　青年期献血者、学校関係者及び両親の教育を改善するための取り組み

A　青年期献血者

目的

1　一般的な副作用及びそのような副作用から生じる傷害を予防する方法について彼らを教育する事により、高校生献血者の副作用と傷害を減少させること。
2　不安を軽減し、対処方法を提供するために献血前教材に盛り込む要素を特定し、それにより副作用及び傷害を軽減すること。

背景

血液採取の多くの側面（スクリーニング、表示、及び検査等）は採取施設全体で高度に規制され、標準化されているが、例えば募集や教育の目的で献血者に提供される山のような教材など、採血過程のその他多くの面は規制されず、ばらつきが大きい。青年期層からの血液の採取により生じる特定の問題は、高い副作用率も含めて、青年期献血者の献血前教育を改善し、献血プロセスに関連する不安を緩和し、対処技術を高めることによる取り組みが可能である。献血前不安は血管迷走神経反応の発生率の上昇と関連していることを示す文献は多い。Labus 及びその他は、医学的恐れに関する調査（Medical Fears Survey）により、364 名の自発的献血者集団を対象に、不安と失神の生じやすさとの関連性を評価し、初回者と経験を積んだ女性献血者において高スコアで最も失神が多いことを見出した。献血前教育を通じて、献血者に共通する恐れに対応し、有用な対処の提案を与える取り組みは、献血者の態度、不安、自己効力感（ある状況を自分が管理する能力が自分にあるという信念）、及び献血への意思を評価したアンケートのスコアの改善と関連した。教育材料が副作用の頻度に及ぼす影響を評価する研究も行われている。

勧告

副作用の低減のための献血者用教育材料の有効性を評価した発表研究はないが、不安や恐れが副作用率の増加にどのように関連するかを調べた研究は、教育を含めた不安を軽減するための介入が役立つことを示唆している。したがって青年期の若者が献血を決心する前に、献血プロセス、副作用の可能性、及び介入に関連した情報を与えられることになり、献血前教育の材料は同意プロセスの一環として考えることができる。

高校生献血者向け教育材料は、年齢に応じた言葉づかいやイラストを用いたものにすると、より大きな影響を持つことになるだろう。加えて、教育材料はビデオなど青少年に親しみやすい形式で示されるかもしれない。形式を問わず、学生向けの献血前の材料に盛り込む要素として、以下等が考えられる。

- 多くの献血者が無事に献血を行っており、副作用の多くは、起こったとしても、軽度である旨の一般的な記述。
- 副作用リスクが高くなる可能性がある（例：若年、初回、女性または低体重献血者はとくにリスクが高い可能性がある）のはどのような献血者か、及びその理由を特定する記述。
- 初回献血者向けに、未知のものに関する不安を緩和するための、献血プロセスの簡単な記述。
- 副作用を予防し、対処する技術を強化するために考えられる技術の説明。また、各技術の考えられる利点の簡単な説明は、従う気持ちを高める可能性がある。使われてきた一般的な技法として、以下が挙げられる。
  - ○ 献血前の水分摂取。
  - ○ 十分な睡眠の確保。
  - ○ 十分な栄養の摂取。
  - ○ 献血前後のアルコール回避。
  - ○ 筋伸張の利用。
  - ○ 気分転換の手法の利用。
  - ○ 段階的な回復手法の利用（例：足をぶらぶらする）。
  - ○ 献血後指導に従い、食堂で適度な時間を過ごすこと。
  - ○ 献血後、激しい身体運動を回避すること。
  - ○ 不安を認識し、採血職員に不安な気持ちへ注意を払ってもらうこと。
  - ○ 情報を得て、質問をすること。
- 該当する場合、親の同意に関する採血施設の方針、及び検査結果に関する守秘義務に関する記述。

B　青年期献血者の両親

目的

1　青年期の子供の献血リスクの軽減方法について両親を教育することで両親を関与させること。
2　副作用の対処及び処置について両親を教育することや副作用が生じた場合の意思決定へ両親を参加させることで両親を関与させること。

背景

青年期献血者の両親は、献血をするという決定において子供と一緒に関与し、かつ副作用が生じた場合には、子供が帰宅後にいかなる必要な看護も施すという両方の点で、特殊な立場にある。

勧告

献血に関して親の同意が要求されない場合も、献血、潜在的な副作用及び有害反応の際の親の関与に関する情報の両親への提供が役立つ可能性がある。以下は、親の教育材料のために考慮すべきである。

- 教材は、学生の教育材料と同一の情報要素を盛り込むべきである。
- 必要な場合、材料には献血者情報の守秘義務に関する具体的な記述を盛り込む場合がある。
- 教材には、血腫または血管迷走神経発作などの一般的な副作用後の献血者の援助のための一般的な指示を盛り込む場合がある。
- 親の同意が必要な場合、教材は同意文書と一緒に親に提供される場合がある。

C　学校関係者

目的

1　青年期学生の献血リスクを軽減する方法について学校関係者を教育し、関与させること。

2　副作用の対処及び治療について学校関係者を教育することや、副作用が起った時学校関係者を意思決定に参加させることで学校関係者を関与させること。

背景

校区の雇用者として、学校保健担当者は校内の学生の健康に責任を持つ。これにより、学生献血者の看護において採血施設の不可欠なパートナーになるかもしれない。移動献血中または採血職員が採血現場を去った後のいずれかで、献血者の副作用にこれらの保健担当者が関与する場合がある。何れにせよ、いずれの場合も学校関係者は、学生の傷害の場合、学生と親に対し特定の責任を負うかもしれない。献血の一般的な手順、可能性のある副作用、ならびに適切な介入及び治療に関する学校関係者への教育は、好評のようだ。献血や副作用に特定した記事が、学校保健教材の中に必要とされる。

勧告

採血施設に、高校での移動採血が実施される前に学校担当者と連絡をとり、移動採血中及び移動採血後の学生の看護に関する方針を策定し、責任を明確化することを奨励する。学校保健担当者を対象とした教育材料を作成することが、採血施設にとって、役立つ可能性がある。検討事項として、以下等が挙げられる。

- 多くの献血者が無事に献血を行っており、副作用の多くは、起こったとしても、軽度である旨の一般的な記述。
- 副作用リスクが高くなる（例：若年、初回、女性または低体重献血者）のはどのような献血者か及びその理由に関する記述。
- 献血過程に関する簡単な説明。
- 一般的な献血者の副作用に関する兆候と症状の記述。
- 一般的な献血者の副作用への適切な対処に関する簡単な説明。
- 血液センター職員及び学校保健担当者の責任を明確化する記述。

● 該当する場合、守秘義務及び両親への情報公開に関する記述。

II 青年期献血者に特有の同意の問題に取り組むための改善策

目的

1 未成年/青年期献血者のインフォームド・コンセントに特有の情報を採血施設に提供すること。

2 インフォームド・コンセントの過程で、この年齢層の副作用率の増加への対応を検討すること。

背景

インフォームド・コンセントの倫理的な内容には、自主性、真実性、慈善、非有害の基本原理が盛り込まれる。献血者と受血者の両者のためのインフォームド・コンセントの原理の適用は、専門家に再吟味された雑誌の記事やAABBの発行物を通して完全に述べられている。しかし、16歳及び17歳の未成年からの血液の採取は、インフォームド・コンセントの従来の考え方に関して、特定のジレンマと課題を提示している。

特定の州法によって多くの州が17歳の献血への同意を長い間認めているが、副作用のために次の医療処置に同意するための未成年者の権利の問題については触れていない。したがって、同意過程については該当する州法の規定を考慮すべきである。

16歳の献血を認める州法は、しばしば親の許可/同意を必要とする。この状況は献血の過程は認めるが、親の許可が要件となるため、どの様な解放された状況をも意味するものではない。16歳及び17歳は、情報に基づいて健康管理の決断をするために必要な判断能力を有すると州法で認められているが、両親及び保護者は依然法的責任があり、それとは反対に州法規定はない。この曖昧性は、同意に追加の概念を盛り込むことによってしばしば対処される。未成年は年齢及び発達に応じた方法で健康管理の決定に関与すべきであるという考え方である。

この区別を献血に適用すると、特定の問題が生じてくる。採血施設は従来、未成年を含む献血者の陽性の検査結果の通知に関し、厳密に守秘義務を貫いている。そのような方針は、州法に特定の配慮をしつつ採血者により見直されることが必要である。研究の場面でも、同様の問題が生じてくる。未成年は一般に、親の許可がなければ研究に参加することは禁じられる；しかし、採血施設は施設内審査委員会が承認した研究プロトコルの下、一部の必須または選択的な検査を実施する可能性があり、そのようなプロトコルは未成年に適用される同意の要件に対応している。インフォームド・コンセントを定める法律は州に特定するため、採血施設は未成年に関する同意の問題に対応する際は弁護士に相談することを求められる。

要約すると、同意は単に書類上の署名ではなく、献血者、場合によっては、親への教育を含めた、

より広義のプロセスであることを念頭に置くことが重要である。献血プロセスと起こり得る結果に関する情報を青年期献血者（及び両親）に提供することが、インフォームド・コンセントの必須要件に適う。

勧告

採血施設は、以下を考慮すべきである：

- 年齢及び同意要件については、州法に照らすこと。
- 青年期/未成年の同意及び承諾に特定した文献に精通すること。
- 同意プロセスの一環として、献血者と両親の両方に情報提供すること。（一部の施設は、適用できる場合、情報提供のパンフレットと同意文書の両方の機能を兼ね備えた親の同意書を提供している）。
- 若年者及び初回献血者のような集団では副作用率が高いという特定の情報をインフォームド・コンセントのプロセスに組み込むこと。
- 必要に応じて、副作用の治療及び陽性の検査結果について、両親に情報を公開する旨の記述を盛り込むこと。

[原著]

血管迷走神経反応による転倒の要因の解析と対策

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Analysis of factors which cause donors to collapse due to vasovagal reaction and prevention measures

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抄　録

血管迷走神経反応(VVR)は献血者の副作用として一番多く，献血者の約1%に起こる。VVRに伴う転倒は外傷に繋がり，その予防は献血者の安全を守る上で重要である。

埼玉県赤十字血液センターで2003年度から2005年度の3年間に起こったVVRに伴う転倒者16人について性別，年齢，献血種別について解析を行った。その結果，10歳代と60歳代に高い。成分献血では血漿献血者だけに転倒を認めた。全国統計でも同様の傾向がみられる。これらの群に注意をはらって，転倒を防ぐように努める必要がある。

10歳代の男性の全血献血者に特に転倒者が多かった。そこで，VVRの頻度が高い初回の献血者が集中する高校生の集団献血では，献血場所のすぐそばに椅子を用意して座らせ，30分以上の休憩と水分摂取を行うことによって転倒者が減少した。

Abstract

Among adverse events related to blood donation, vasovagal reaction (VVR) occurs most frequently and its incidence is around 1% of donors. Collapse related to VVR sometimes causes trauma to donors. It is important to prevent falls related to VVR for donor safety.

In order to decrease the incidence of falls linked to VVR, we analyzed the related factors in 16 donors who donated blood at Saitama Red Cross Blood Center between April 2003 and March 2006.

As a result, the risk factors of collapse are between 16 and 19 years of age and between 60 and 69 years of age, undergoing whole blood donation and plasmapheresis. The similar tendency was observed by the analysis of the nation wide study. We should, therefore, pay particular attention to these donors.

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In order to prevent male high school students from collapsing, we prepared a refreshment table next to the donation area and let them sit for at least 30 minutes. These procedures resulted in the decrease in the number of collapsing donors.

Key words: collapse of blood donors, vasovagal reaction, blood donation

はじめに

献血後の副作用は献血者の約1%に起こることが知られている[1]。その主なものは血管迷走神経反応(vasovagal reaction，VVR)，神経損傷と皮下出血である。VVRは全副作用のうち約75%を占める。VVRは転倒の原因となり，重篤な副作用に繋がる可能性がある。全国で年間約540万人の献血者がいるが，そのうちVVRによる転倒は100～150人の献血者に起こり，大きな問題と考える[2)-4)]。転倒事故を少なくするためにはVVRの発生率を下げる努力と転倒の直接的な予防策を立てる必要があると考える。

全血献血でVVRを起こしやすい人々は，①初回，②低体重，③若年，④白人，⑤若年初回の献血者では女性と報告されている[5)-7)]。一方，成分献血では①循環血液量の少ない人，②中高年の女性，③サイクル数の多い人等が上げられる[8)]。埼玉県赤十字血液センターの予備的な調査でも同様の傾向がみられ，中高年の女性の成分献血では1時間以上にVVRが持続する例が多い。

これらのVVRのハイリスクの献血者に2004年5月から①少なくとも30分以上休憩をとること，②水分を摂取することを勧めるパンフレットを渡している[9)]。その結果，VVRを起こす献血者は有意に減少したが，それによる転倒者の数は大きな変動を示さなかった。

そこで，VVRによる転倒者を減らす目的で2003年度から2005年度の3年間に埼玉県赤十字血液センターで発生したVVRに伴う転倒例16人についてその要因を解析し，その対策について検討したので報告する。

方　法

検討した献血者は2003年4月から2006年3月までの3年間に埼玉県赤十字血液センターに来訪した献血者722,768人(男性442,449人，女性280,319人，全血献血479,898人，成分献血242,870人)である（表1，表2）。それらの献血者のうち転倒した例は16人である（表3）。それらについて，性別，年齢，献血種別などについて検討した。

初回の若い男女の全血献血ではVVRが多いとされる。その献血者に転倒事故が起こる可能性が高い。とくにその中でも10歳代と20歳代の初回の男性を多く含む高校生献血あるいは専門学校生の集団献血では，転倒事故が起こりやすいと考えられる。埼玉県赤十字血液センターでは，そのような集団献血では多くの場合バスにおいて採血する。その場合に，図1に示すように，接遇の部屋をバスから離れたところに設営するのではなく，バスのすぐそばにテントで仮の接遇の場を造り，そこ

表1　2003年度から2005年度の献血種別による献血者数

献血種別	2003年度		2004年度		2005年度		合　計		総合計
	男	女	男	女	男	女	男	女	
200mL	14,248	36,428	13,751	37,329	12,522	37,517	40,521	111,274	151,795
400mL	84,593	24,897	85,229	23,197	85,992	24,195	255,814	72,289	328,103
血小板	19,678	7,966	20,743	8,169	21,647	7,879	62,068	24,014	86,082
血　漿	31,051	26,597	29,414	25,441	23,581	20,704	84,046	72,742	156,788
計	149,570	95,888	149,137	94,136	143,742	90,295	442,449	280,319	722,768

200mL：200mL献血　400mL：400mL献血　血小板：血小板献血　血漿：血漿献血

表2　2003年度から2005年度の年代別の献血者数

年代	2003年度		2004年度		2005年度		合計		総合計
	男	女	男	女	男	女	男	女	
10歳代	14,106	13,109	14,026	13,529	12,682	12,371	40,814	39,009	79,823
20歳代	31,227	26,761	30,167	25,541	28,279	24,045	89,673	76,347	166,020
30歳代	42,020	22,118	42,179	22,086	40,445	21,398	124,644	65,602	190,246
40歳代	30,753	13,477	31,277	13,636	31,224	13,847	93,254	40,960	134,214
50歳代	22,782	14,491	22,773	13,377	22,481	12,940	68,036	40,808	108,844
60歳代	8,682	5,932	8,715	5,967	8,631	5,694	26,028	17,593	43,621
計	149,570	95,888	149,137	94,136	143,742	90,295	442,449	280,319	722,768

表3　転倒者の年齢，性，献血種別および献血回数

年齢	性別	献血種別	献血回数
10歳代	男	200mL	初回
10歳代	男	200mL	2回目
10歳代	男	400mL	初回
10歳代	男	400mL	2回目
10歳代	男	400mL	2回目
10歳代	男	血漿	2回目
20歳代	男	400mL	3回目
20歳代	女	血漿	4回目
20歳代	女	200mL	3回目
20歳代	男	400mL	初回
30歳代	男	血漿	2回目
30歳代	男	400mL	13回目
30歳代	男	400mL	9回目
60歳代	女	400mL	13回目
60歳代	男	400mL	初回
60歳代	女	血漿	50回目

200mL：200mL献血　400mL：400mL献血
血漿：血漿献血

表4　献血者の性別と転倒者数および転倒率

	転倒者数	献血者数	転倒率
男性	12	442,449	0.0027%
女性	4	280,319	0.0014%

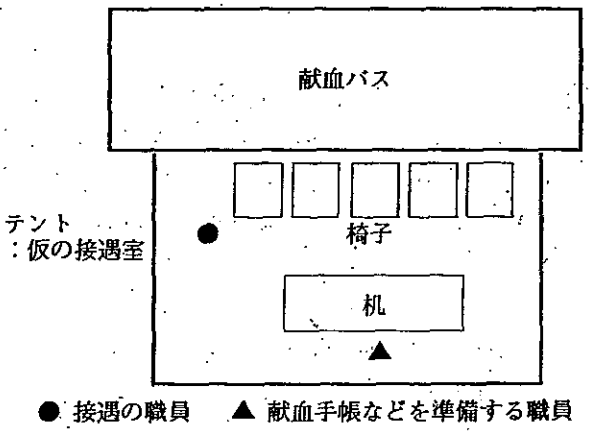

図1　高校生の集団献血の設営法

に1台のバスあたり約5脚の椅子を置き，さらに専門の職員を1人配置し，椅子に座ることと水分摂取を勧め，約30分後に献血手帳を渡すようにした。それによって，転倒事故が減少するか否かを検討した。

結　果

埼玉県赤十字血液センターにおいて，2003年度から2005年度の3年間にVVRに伴う転倒者は16人であった（表3）。その頻度は0.002%である。16人全員が治療のために医療機関を受診しているが，受診回数は1回受診が7人と多く，2回受診が3人，3回受診が2人，4回受診が1人，6回受診が1人，18回受診が1人，入院を要した献血者が1人であった。

転倒者と性別との関係をみると表4に示すように女性より男性に転倒率が有意ではないが高い傾向にある。このことはVVRが女性に多いことと対照的である[2)~4),9)]。さらに，性別と献血の種類を組み合わせてみると男性における全血献血におい

て転倒率が高い傾向がみられる（表５，表６）。また，その男性の全血献血の転倒者10人のうち初回の献血者が４人，２回目の献血者が３人とそれらで大半を占める（表３）。女性では成分献血の方が全血献血より転倒率が有意ではないが高い傾向がある（表５，表６）。

献血種別と転倒率の関係を調べると血小板献血で転倒した献血者は１人もいないので転倒率は0%となるが，それ以外で一番転倒率の低いのが200mL献血である。その値を１として，他の献血種別の転倒率を調べると，400mL献血が1.35倍と一番高く，ついで血漿献血が1.30倍と高い（表７）。

一方，転倒者を年齢別に同様の検討をすると40歳代と50歳代には転倒者がいない（表８）。転倒者がいた年代で一番転倒率の低いのは30歳代で，その値を１とすると，10歳代と60歳代がほぼ同じ転倒率を示し，それぞれ4.7と4.3と高い。20歳代は次に転倒率が高く1.5倍となる。

10歳代男性の全血献血の献血者に転倒者が多かったが，その多くが男性の高校生か専門学校生の集団献血で起こっている。そこで，10歳代の初回の男性を多く含む男性の高校生献血あるいは専門学校生の集団献血の場合に，転倒者を減らす目的でバスのすぐそばにテントで仮の接遇の場を造り，そこに１台のバスあたり約５脚の椅子を置き，さらに専門の職員を１人配置し，椅子に座ることと水分摂取を勧め，約30分後に献血手帳を渡すようにした（図１）。その結果，表９に示すように，その方法を開始後の３カ月間には約5,000人の高校生ならびに専門学校生の献血を行ったが，１人も転倒することはなかった。それ以前の３カ月間には約1,000人の献血者がいたが２人転倒した。さらに，2004年度の同時期の３カ月間にやはり約5,000人の献血をしたが，２人の転倒者がいた。

表５　男性献血者の転倒者数と転倒率

男　性	転倒者数	献血者数	転倒率
全　血	10	296,335	0.0034%
成分献血	2	146,114	0.0014%

表６　女性献血者の転倒者数と転倒率

女　性	転倒者数	献血者数	転倒率
全　血	2	183,563	0.0011%
成分献血	2	96,756	0.0021%

表７　献血種別と転倒者数および転倒率

献血種別	転倒者数	献血者数	転倒率	比　率
200mL	3	151,795	0.0020%	1
400mL	9	328,103	0.0027%	1.35
血　漿	4	156,788	0.0026%	1.30
血小板	0	86,082	0.0000%	0

200mL：200mL献血　400mL：400mL献血
血漿：血漿献血　血小板：血小板献血

表８　献血者の年代と転倒者数および転倒率

年　代	転倒者数	献血者数	転倒者率	比率
10歳代	6	79,823	0.0075%	4.7
20歳代	4	166,020	0.0024%	1.5
30歳代	3	190,246	0.0016%	1
40歳代	0	134,214	0.0000%	0
50歳代	0	108,844	0.0000%	0
60歳代	3	43,621	0.0069%	4.3

表９　高校生および専門学校生の集団献血における献血者数および転倒者数

1. 椅子をバスのそばに置く前の３カ月間（2005年７月27日～2005年10月26日）
   献血者数　1,142人　　転倒者数　２人
2. 椅子を置いてからの３カ月間（2005年10月27日～2005年１月23日）
   献血者数　4,988人　　転倒者数　０人
3. 前年同時期の３カ月間（2004年10月27日～2005年１月23日）
   献血者数　5,125人　　転倒者数　２人

考　察

転倒・転落は病院における医療でも医療事故の一つとして問題とされている。それを防ぐために，患者のリスクを分析し，それを点数化し，対策を検討する試みもなされている[10]。一方，献血者におけるVVRに伴う転倒はその頻度も少なく，その解析は十分行われてはいない。今回埼玉県赤十字血液センターにおいて2003年度から2005年度の3年間においてVVRに伴う転倒例の解析を行いその要因を調べた。

3年間の転倒者は16人で，献血者総数722,768人で除するとその頻度は0.002%である。埼玉県赤十字血液センターにおいて5秒以上の失神を伴う重症のVVRを起こした献血者の率は男性で0.03%で，女性で0.06%である。転倒率が0.002%であることは重症VVRを起こした献血者の約1/30～1/15に転倒が起こることを示している[9]。この転倒率は2003年度，2004年度，2005年度上半期の全国の統計の結果がいずれも約0.002%であることとも一致している[2)-4)]。米国においては，失神を起こしたVVRの頻度が0.09%であり，その14%が転倒するとのことであり，この値は埼玉県赤十字血液センターおよびわが国の全国統計の値とほぼ同じである[11]。

性別と転倒との関係を見ると，転倒者は男性に多い傾向がある。とくに埼玉県赤十字血液センターでは男性の全血献血での転倒者が多いのでその対策が必要であると考えた。しかし，全国統計では女性の転倒率の方が男性のそれより高い[2)-4)]。その理由は明らかでない。埼玉県赤十字血液センターにおける転倒者16人のうち10歳代の全血の献血者が一番多いことから10歳代の男性を多く含む高校生の集団献血で起こっている可能性があり，その解析と対策が今後必要であると考えた。

年齢と転倒率との関係を見ると，10歳代と60歳代が転倒のリスクが高いという結果であった。また逆に40歳代と50歳代は転倒のリスクが低いという結果であった。

一つのセンターの結果では転倒者の数も少なく，地域的な偏りもあることも考えられる。そこで，2003年度の日本赤十字社の全国統計をみるとやはり40歳代と50歳代は転倒率は0人ではないが他の年代より著しく低く，一番低い40歳代の転倒率を1とすると，10歳代が6.3，60歳代が3.6と高く，我々の結果と傾向は類似している。ただし，20歳代の転倒率が40歳代の3.7倍と我々の結果より高い値を示している[2)]。この傾向は，2004年度，2005年度の結果もほぼ同様である[3),4)]。

我々の結果から10歳代の男性の場合は初回の全血献血が転倒のリスクが高いと思われ（表3），それは男性の高校生あるいは専門学校生の集団献血の場で起こっている可能性が高い。

我々はVVRを防ぐためにVVRのハイリスクと考えられる①全血献血の初回の男女と，②中高年の成分献血の女性に対し，①30分間の休憩と②水分摂取を勧めるパンフレットを渡した[9]。それによって男女とも軽症のVVRの頻度は減少した。しかし，重症のVVRは女性の400mL献血と血漿献血で著明に減少したが，男性では，いずれの献血種別でも減少しなかった。とくに，200mL献血を行った献血者に重症のVVRの頻度が高かったが，それらの献血者にパンフレットを渡してもその減少がみられなかった[9]。200mL献血を行う男性は，高校生あるいは専門学校生の集団献血が多いことから，このパンフレットを渡す方策は男性の高校生あるいは専門学校生の集団献血では有効でないと考えられた。そこで，方法で述べたようなバスの周辺への椅子の設置，職員の配置，30分たってから献血手帳を渡す方策を考えた。その結果，表9に示すように転倒者を減少させるのに有用と考えられた。今後，さらに継続して，その効果をみていきたいと考える。

埼玉県赤十字血液センターにおいては10歳代の転倒者の割合は全転倒者の約40%であるが，2003年度の全国の統計を見ても10歳代の転倒者は約20人で全転倒者約100人の約20%を占めている。いずれにしても全国で10歳代の転倒者が多いが，これらの献血者に対し，我々の行った方策が全国で試され，有用であれば年間20～40人の転倒者が救われることになる。なお，全国の統計では20歳代の転倒率が60歳代と同程度に高く，10歳代と20歳代を合わせると全転倒者の40%を占めるので，20歳代の転倒者の要因を解析し，その転倒の対策を講じる必要があろう。

埼玉県赤十字血液センターのデータからは60歳代の転倒率が10歳代と同程度に高い結果であった。このように60歳代の転倒率が高いことは全国の統計からも明らかである[2)-4)]。VVRの頻度は60歳代で必ずしも高くないが，転倒率は高い。60歳代の転倒者に性差あるいは献血種別に差があるか等を検討する必要がある。当センターにおいて60歳代で転倒したのは全血献血と血漿献血で，血小板献血の献血者はいない。とくに，入院が必要であった献血者は64歳の女性で，血漿献血のリピーターであり，60歳代の血漿献血のリピーターの女性はとくに注意が必要であると考える。いずれにしても60歳代の献血者に対しては座るまで，看護師が付き添い，座らせ，必要な飲み物を取ってあげるなどの配慮が必要であろう。

成分献血では，転倒者は男女それぞれ2名ずつであるが，それらはすべて血漿献血のリピーターである。血小板献血は埼玉県赤十字血液センターでは初回の献血者には行っていないが，再来の血小板献血者でも転倒した献血者は1人もいない。血漿献血をした献血者では400mLの献血者と同程度の転倒率を認めている。転倒した献血者はいずれもリピーターであり，リピーターといえども十分な配慮をする必要がある。全国の統計でも血漿献血の方が血小板献血より転倒率は約4倍高い[2)]。VVRの頻度は血小板献血と血漿献血のそれと大きな違いはないが，転倒率でこのような差が起こる理由が何によるものか問題である。血小板献血と血漿献血の差異を調べてみると，血漿献血の方が献血者の条件がやや悪い。つまり，年齢制限については血小板献血は54歳以下であるが，血漿献血は69歳以下である。ヘモグロビン濃度は血小板献血では12g/dL以上であるが，血漿献血では女性では11.5g/dL以上である。また，ほぼ同程度の採液量であるが，それにかかる時間が血漿献血の方が血小板献血より短いことが多い。このようなことが，血漿献血の方が血小板献血より転倒率が高くなる要因である可能性がある。英国における年齢制限は血小板献血と血漿献血に差がなく，いずれも65歳以下である。ヘモグロビン濃度も血小板献血と血漿献血でその条件に差がなく，男性で13g/dL以上で，女性では12.5g/dL以上である[12)]。つまり，英国では，血小板献血と血漿献血の献血者の選択基準を同じにしている[12)]。また，成分献血は過去2年以内に全血献血を行い，大きな副作用のなかった献血者を受け入れている。さらに，成分献血の初回の献血者の年齢は60歳以下である。このような英国の基準の根拠は明らかでないが，わが国の基準を国際的な基準と比較し検討し直す必要があろう。

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[原著]

成分献血における血管迷走神経反応—性別，年齢，体重および献血回数の影響

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Vasovagal reactions in apheresis donors: the effects of sex, age, body weight and donation status

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抄　録

献血に関連して起こる副作用のうち血管迷走神経反応(VVR)の頻度が一番高く，全献血者の0.76%に起こる。成分献血者におけるVVRのリスク要因を明らかにするために，2004年6月から2005年4月までの11カ月間に埼玉県赤十字血液センターを訪れた成分献血者76,658人について，そのVVR発生率を性別，年齢，体重，献血回数との関係において検討し，同時期に訪れた全血献血者のそれと比較した。

その結果，女性の成分献血におけるVVR発生率は女性の全血献血および男性の全血献血と成分献血のVVR発生率より有意に高かった。初回の成分献血におけるVVR発生率は男性で4.7%，女性で7.4%であった。その頻度は，再来の成分献血のそれが男性で0.4%，女性で2.0%であるのに比べて著しく高く，初回の400mL献血のVVR発生率が男女それぞれ2.2%と2.6%であるが，これらよりも有意に高かった。初回の成分献血の是非について検討する必要があると考える。

Abstract

Among adverse events related to blood donation, the incidence of vasovagal reaction (VVR) occurs most frequently, involving around 0.76% of donors.

In order to clarify the risk factors of VVR in apheresis donors, we studied the incidence of VVR in 76,658 apheresis donors who visited Saitama Red Cross Blood Center for 11 months from June 2004 to April 2005 in relation to sex, age, body weight and donation status comparing with that of whole blood donors who visited our center during the same period.

As a result, the incidence of VVR in female apheresis donors was higher than that of female whole blood donors and that of male whole blood donors and

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apheresis donors. The incidence of VVR in male and female first-time apheresis donors is 4.7% and 7.4%, respectively. This incidence was significantly higher than that of male and female repeat apheresis donors, which is 0.4% and 2.0%, respectively, and was also significantly higher than that of male and female first-time 400mL whole blood donors, which is 2.2% and 2.6%, respectively. It is necessary to reconsider the enrollment of first-time donors for apheresis.

Key words: risk factors of vasovagal reactions, apheresis

はじめに

献血後の副作用は献血者の約1%に起こることが知られている[1]。その主なものは血管迷走神経反応(vasovagal reactions，VVR)，神経損傷と皮下出血である。VVRは全副作用のうち72%を占めると報告されている[1]。VVRは転倒の原因となり，重篤な副作用に繋がる可能性がある。VVRによる転倒は全国では年間100～150人の献血者に起こり，大きな問題と考える[2)-4)]。転倒事故を少なくするためにはVVR発生率を下げる努力と転倒の直接的な予防策を立てる必要がある。

全血献血でVVRを起こしやすい要因は，①初回，②低体重，③若年，④白人，⑤若年の初回献血では女性と報告されている[5)-10)]。一方，成分献血では①中高年の女性，②循環血液量の少ない人　③サイクル数の多い人がVVRを起こしやすいとされている[10),11)]。またMcLeodらは多数の血液センターのデータを集めた結果，初回の成分献血者もVVRを起こしやすいと報告している[12)]。

我々は成分献血者におけるVVRのリスク要因を明らかにする目的で，献血者の性別，年齢，体重および献血回数とVVR発生率との関係を検討した。

方　法

成分献血におけるVVRのリスク要因を明らかにするために，以下の検討を行った。

対象は2004年6月から2005年4月までの11ヶ月間に埼玉赤十字血液センターに来訪した献血者223,795人(男性136,901人，女性86,894人，成分献血76,658人，全血献血147,137人)であった（表1，表2，表3)。そのうち成分献血者について性別，年齢，体重，献血回数，献血種別とVVR発生率との関係について調査した。また，全血献血者について同様に調査し，成分献血と比較した。なお，埼玉県赤十字血液センターでは初回献血者に対して，原則として血小板献血は行っていないので，初回の成分献血者の結果は血漿献血者の結果である。

成分献血はほとんどの場合，献血ルームで行っている。全血採血は献血ルームと移動採血車で行っている。今回は全血献血におけるVVR発生率を献血ルームと移動採血車に分けては検討しなかった。

VVRの診断は，日本赤十字社の標準作業手順書に準拠した（表4)[13)]。標準作業手順書では表4に示すようにVVRを重症と軽症に分けているが，今回はその両者を併せた数を調査した。なお，献血場所から離れてから遅発性のVVRが起こるとされているが，今回は遅発性のVVRの調査は行わなかった[14),15)]。

表1　埼玉県赤十字血液センターにおける献血者数とVVR発生率(2004年6月～2005年4月)

性　別	男	女	計
献血者数	136,901	86,894	223,795
VVR発生数	696	1,086	1,782
VVR発生率	0.5%	1.2%	0.8%
初回献血者数	15,599	12,792	28,391
VVR発生数	319	260	579
VVR発生率	2.0%	2.0%	2.0%
再来献血者数	121,302	74,102	195,404
VVR発生数	376	－826	1,202
VVR発生率	0.3%	1.1%	0.6%

VVR発生率＝(VVR発生数÷献血者数)×100

成分献血に用いた採血機器の主なものは，CCS(ヘモネティクスジャパン株式会社,東京),TERUSYS(テルモ株式会社，東京)あるいはTERUSYS S(テルモ株式会社，東京)である。今回は採血機種とVVR発生率との関係は検討しなかった。

表2　埼玉県赤十字血液センターにおける全血献血者数とVVR発生率（2004年6月～2005年4月）

採血種類	200mL献血			400mL献血			総　計		
性別	男	女	小計	男	女	小計	男	女	計
献血者数	12,678	34,372	47,050	78,456	21,631	100,087	91,134	56,003	147,137
VVR発生数	96	205	301	407	206	613	503	411	914
VVR発生率	0.8%	0.6%	0.6%	0.5%	1.0%	0.6%	0.6%	0.7%	0.6%
初回献血者数	5,230	8,880	14,110	9,713	3,118	12,831	14,943	11,998	26,941
VVR発生数	76	120	196	212	81	293	288	201	489
VVR発生率	1.5%	1.4%	1.4%	2.2%	2.6%	2.3%	1.9%	1.7%	1.8%
再来献血者数	7,448	25,492	32,940	68,743	18,513	87,256	76,191	44,005	120,196
VVR発生数	20	85	105	194	125	319	214	210	424
VVR発生率	0.3%	0.3%	0.3%	0.3%	0.7%	0.4%	0.3%	0.5%	0.4%

VVR発生率＝(VVR発生数÷献血者数)×100

表3　埼玉県赤十字血液センターにおける成分献血者数とVVR発生率（2004年6月～2005年4月）

採血種類	血小板献血			血漿献血			総　計		
性別	男	女	小計	男	女	小計	男	女	計
献血者数	19,360	7,618	26,978	26,407	23,273	49,680	45,767	30,891	76,658
VVR発生数	69	180	249	124	495	619	193	675	868
VVR発生率	0.4%	2.4%	0.9%	0.5%	2.1%	1.2%	0.4%	2.2%	1.1%
初回献血者数	3	0	3	653	794	1,447	656	794	1,450
VVR発生数	1	0	1	30	59	89	31	59	90
VVR発生率	33.3%	0.0%	33.3%	4.6%	7.4%	6.2%	4.7%	7.4%	6.2%
再来献血者数	19,357	7,618	26,975	25,754	22,479	48,233	45,111	30,097	75,208
VVR発生数	68	180	248	94	436	530	162	616	778
VVR発生率	0.4%	2.4%	0.9%	0.4%	1.9%	1.1%	0.4%	2.0%	1.0%

VVR発生率＝(VVR発生数÷献血者数)×100

表4　VVRの重症度分類[12]

分類	症　状	血圧(max，mmHg) 採血前→測定最低値	脈拍数(/分) 採血前→測定最低値	呼吸数 (/分)
軽症	気分不良，顔面蒼白，あくび，冷汗，悪心，嘔吐，意識喪失(5秒以内)，四肢皮膚の冷汗	120以上→80以上 119以下→70以上	60以上→40以上 59以下→30以上	10以上
重症	軽度の症状に加え，意識喪失(5秒以上)，痙攣，尿失禁，脱糞	120以上→79以下 119以下→69以下	60以上→39以下 59以下→29以下	9以下

結　果

1．性別とVVR発生率との関係

男性ではVVR発生率は献血種別に関係なく，1%未満であった（表1，表2，表3，図1）。女性では全血献血におけるVVR発生率が1%以下であるが，400mL献血では女性が男性より有意に高かった。女性における成分献血では全体で2.2%，血小板献血で2.4%，血漿献血で2.1%と男性のそれより有意に高く，また，女性の全血献血のそれよりも有意に高かった。なお，女性の血小板献血と血漿献血の間にVVR発生率に有意差があるとはいえなかった。

献血回数を初回と再来に分けて，VVR発生率を検討した。400mL献血における初回者のVVR発生率は，男性で2.2%，女性で2.6%と再来者（男性0.3%，女性0.7%）より有意に高かった（表2，図2）。成分献血の初回者では男性で4.7%，女性で7.4%と，成分献血の再来者（男性0.4%，女性2.0%）や400mL献血の初回者に比べて有意に高かった（表3，図3）。ただし，埼玉県赤十字血液センターにおいては前述のように初回の成分献血者は血漿献血者だけである。また，初回の成分献血（血漿献血）ではVVR発生率は女性が男性より有意に高かった。再来の成分献血におけるVVR発生

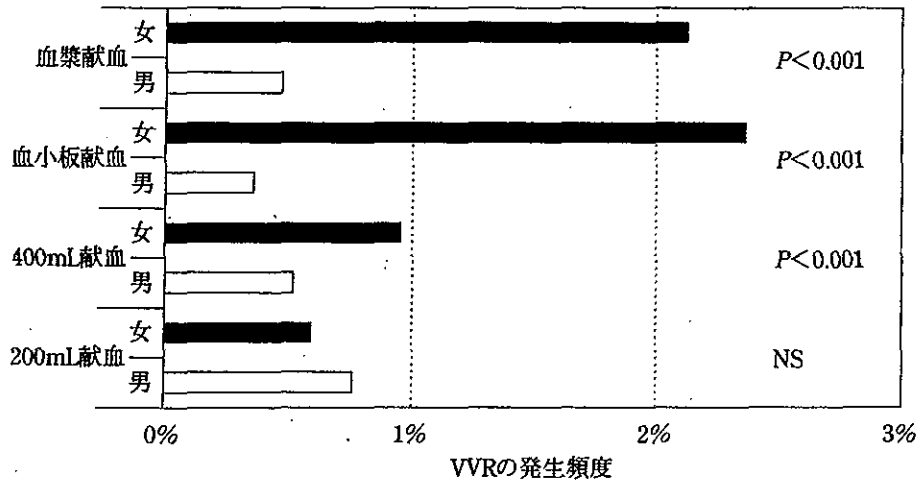

図1　性別ならびに献血種別ごとのVVR発生率

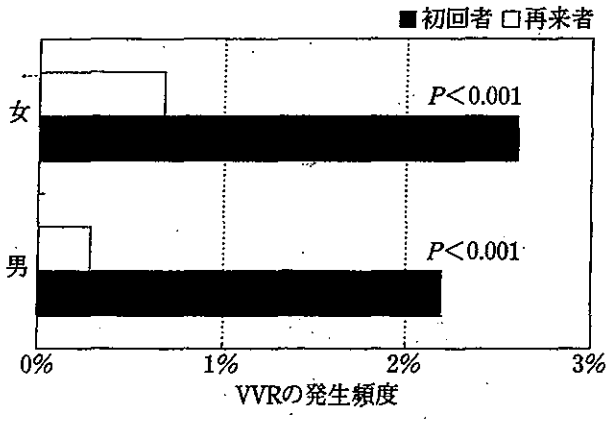

図2　400mL献血における献血回数とVVR発生率との関係

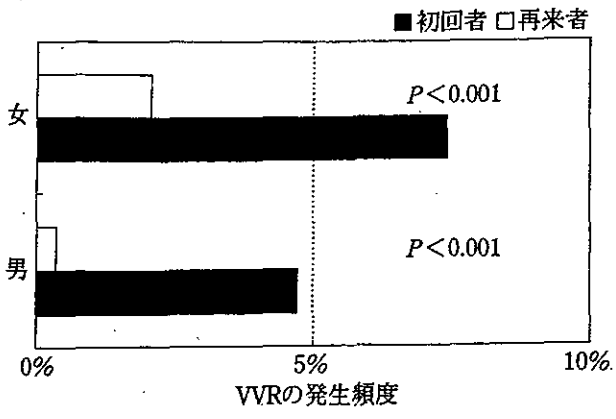

図3　成分献血における献血回数とVVR発生率との関係

率は血小板献血で1.1%，血漿献血で0.9%とほぼ同じ値であり（表3），いずれの場合もVVR発生率は女性が男性より有意に高かった。

2．年齢とVVR発生率との関係

400mL献血においては，いずれの年齢層においても男女とも初回献血者のVVR発生率が高かった（図4，図5）。また，男女とも若年層で高く，加齢と共に低下傾向を示した。

成分献血においても各年齢ともまた男女とも初回献血者のVVR発生率が再来のそれより高かった（図6，図7）。また，男女とも各年齢における初回の成分献血者のVVR発生率は初回の全血献血者のそれより高かった。男性においては初回も再来もVVR発生率は若年層で高い傾向がみられた。女

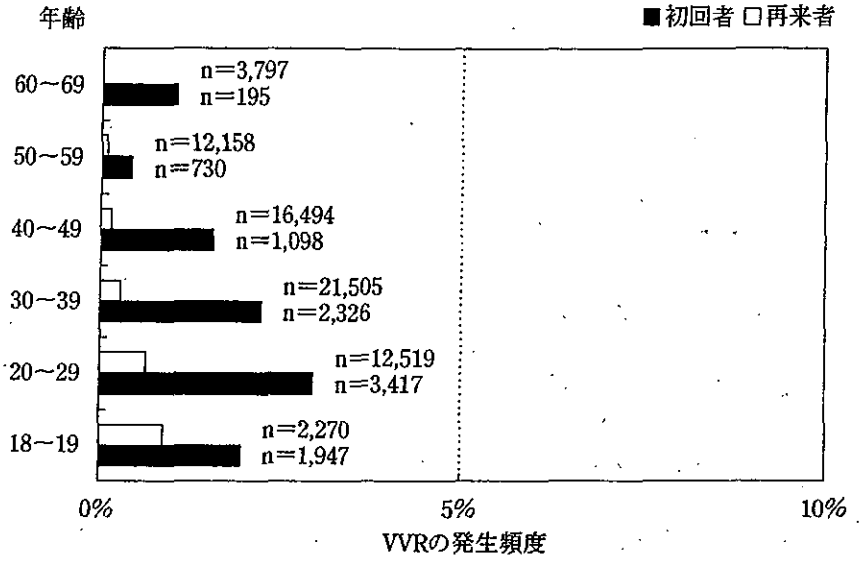

図4　男性の400mL献血におけるVVR発生率の献血回数と年齢との関係
n＝献血者数

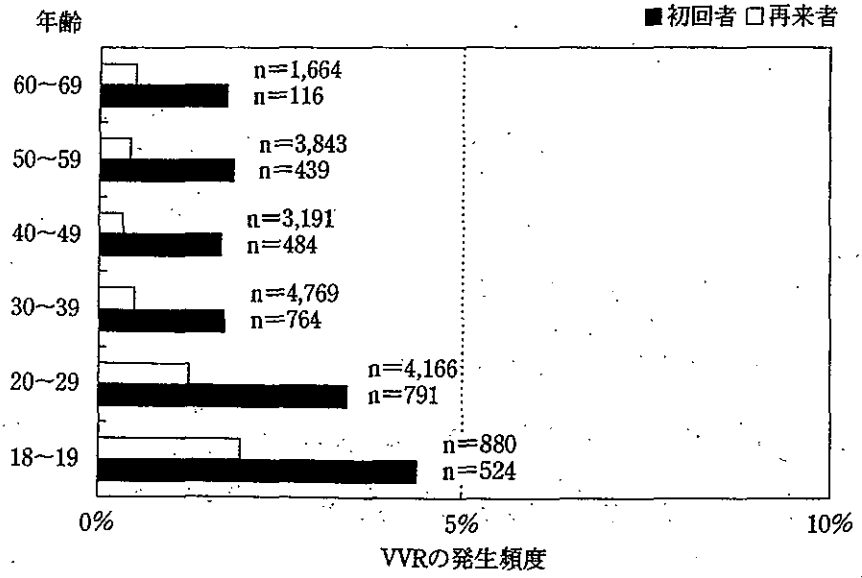

図5　女性の400mL献血におけるVVR発生率の献血回数と年齢との関係
n＝献血者数

性では，初回献血者のVVR発生率は非常に高く，すべての年齢層で5%を超えており，若年層でとくに高いという傾向はみられなかった。再来の成分献血の女性では，若年層にVVR発生率が高い傾向がみられた。

3．体重とVVR発生率との関係

（図8，図9，図10，図11）

400mL献血では，男女ともすべての体重において初回献血者が再来献血者よりVVR発生率が高かった（図8，図9）。さらに，男性では初回と再来の献血者いずれでも体重の少ない献血者にVVR発生率が高い傾向がみられた。一方，女性では初回および再来の献血者いずれでも体重とVVR発生率との関係は明らかでなかった。

成分献血では，すべての体重において，男女とも再来献血者より初回献血者でVVR発生率が高い

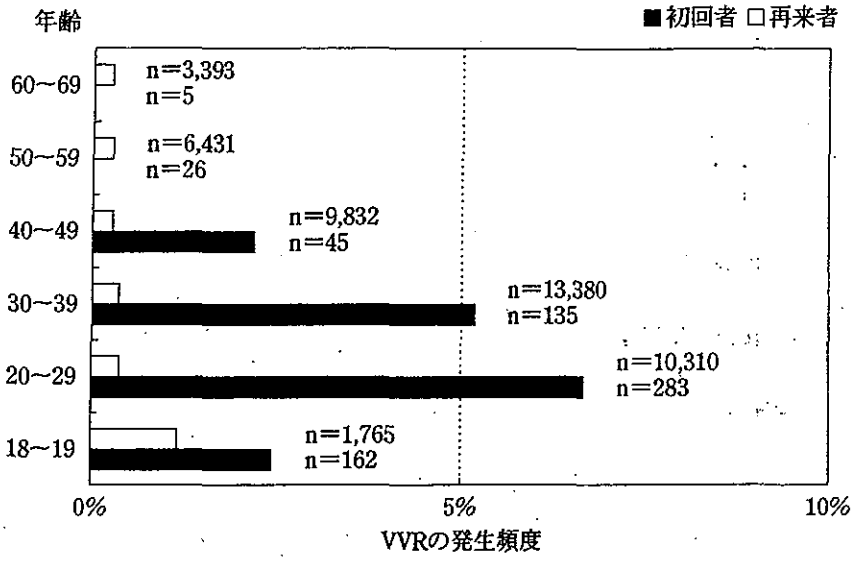

図6　男性の成分献血におけるVVR発生率の献血回数と年齢との関係

n＝献血者数

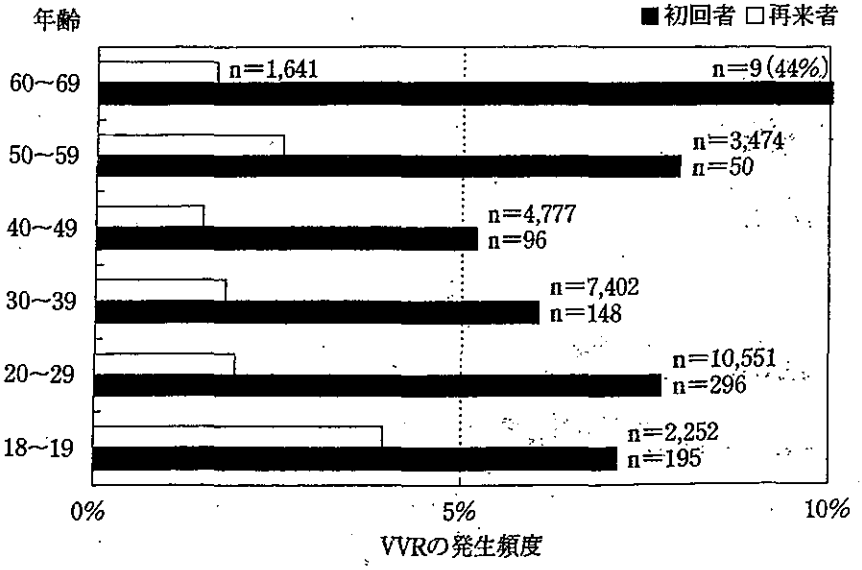

図7　女性の成分献血におけるVVR発生率の献血回数と年齢との関係

n＝献血者数

傾向がみられた（図10，図11）。また，男女ともほとんどの体重において初回の成分献血のVVR発生率は初回の全血献血のそれより高かった。初回献血者では男女ともVVR発生率と体重との間に一定の関係はみられなかった。再来の成分献血では，男性では体重が少ない献血者にVVR発生率がやや高い傾向があるが，女性ではその傾向は明らかでなかった。

考　察

Tomitaらは，全血献血におけるVVR発生率は男性で0.83%，女性で1.25%であり，成分献血では

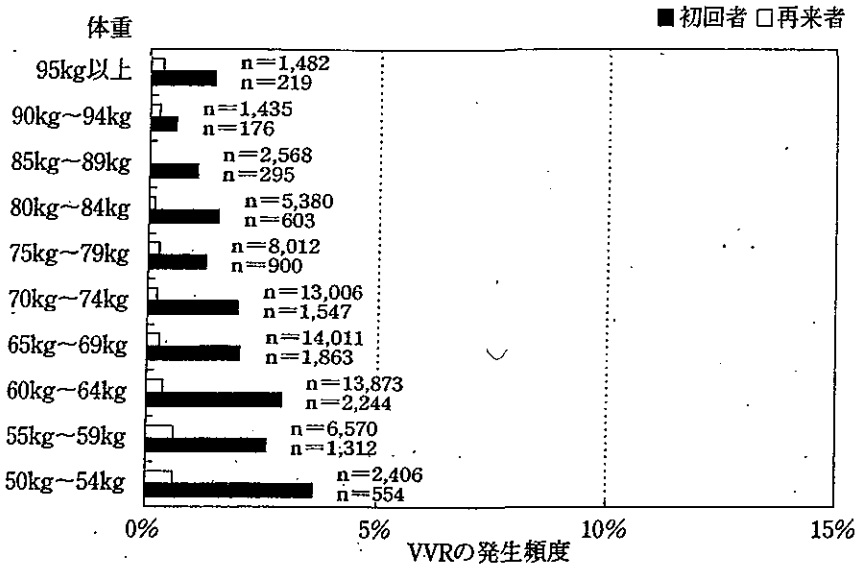

図8　男性の400mL献血におけるVVR発生率の献血回数と体重との関係
n＝献血者数

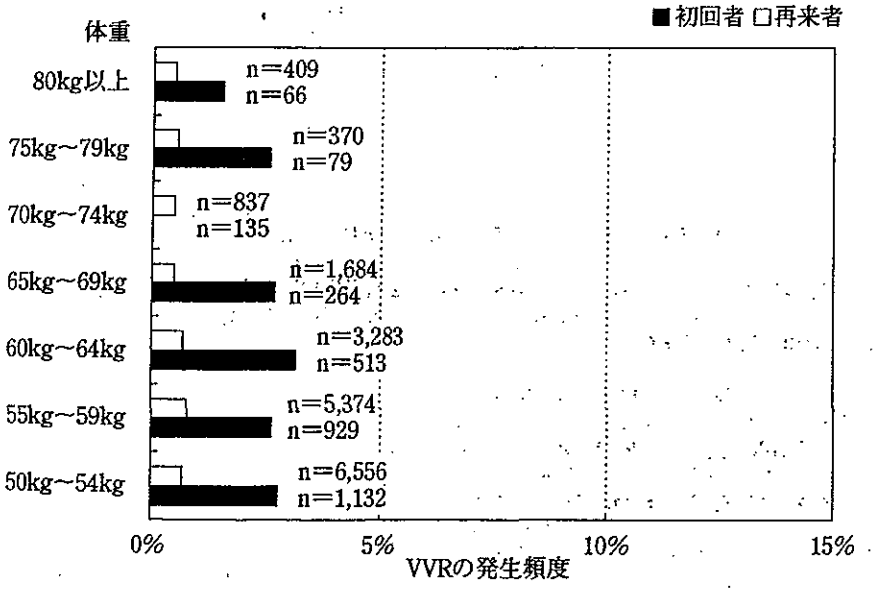

図9　女性の400mL献血におけるVVR発生率の献血回数と体重との関係
n＝献血者数

男性で0.99%，女性で4.19%という結果から女性の成分献血にVVR発生率が高いことを報告した。さらにVVRの要因を解析し，成分献血においては，①45歳以上の女性，②サイクル数の多い人，③循環血液量の少ない人にVVR発生率が高いと報告している。大坂らも成分献血では女性が男性よりVVR発生率が高いと報告している。その頻度は男性における血漿献血で1.2%，血小板献血で1.3%，女性における血漿献血で3.5%，血小板献血で4.7%であり，Tomitaらの報告に近い値である。Tomitaらの報告に対し，雑誌「Transfusion」の編集者は，成分献血では全血献血に比べて，献血に

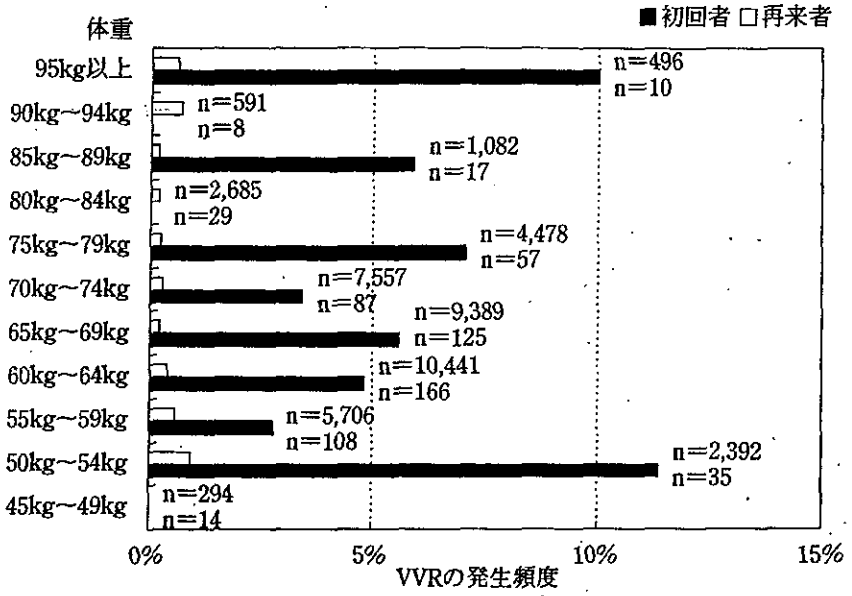

図10　男性の成分献血におけるVVR発生率の献血回数と体重との関係

n＝献血者数

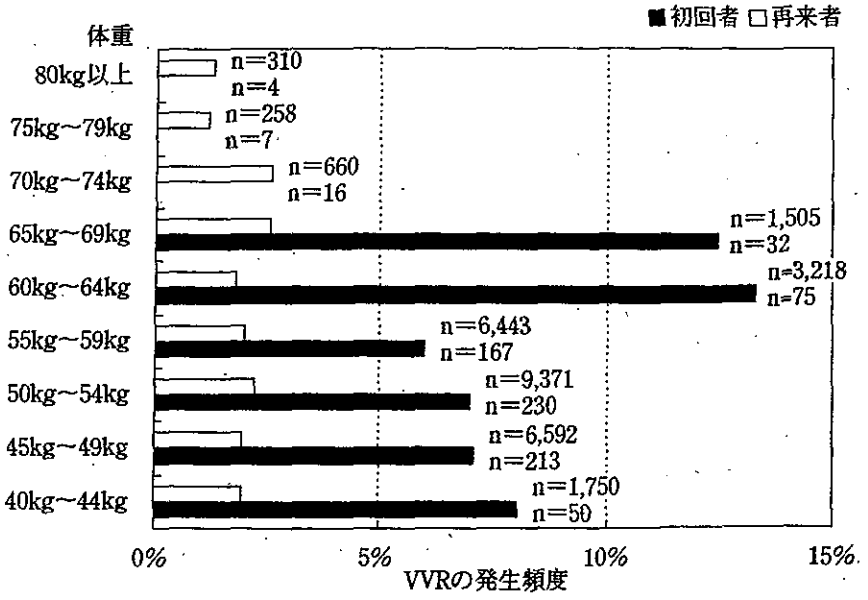

図11　女性の成分献血におけるVVR発生率の献血回数と体重との関係

n＝献血者数

要する時間が長いので，循環血液のバランスを回復するのに有利であり，成分採血装置の進歩により体外循環血液量も減少しているので，成分献血におけるVVR発生率は0.5%未満で低いと述べている[16),17)]。

われわれの検討では，成分献血において血小板献血および血漿献血で女性の方が男性よりVVR発生率が有意に高かった。この点はTomitaらあるいは大坂らの報告と一致する（図1）[10),11)]。つまり，女性であることが成分献血におけるリスク要因と考えられる。しかし，われわれの検討では女性の成分献血におけるVVR発生率は2.2%であり，Tomitaらの報告や大坂らの報告より低かった。Tomitaらは女性では中高年層でVVR発生率が高いと報告しているが，われわれの検討では再来の成分献血者では逆に若年層で高い傾向がみられた。また，Tomitaらは循環血液量が少ない女性でVVR発生率が高いと報告しているが，われわれの検討では再来献血者では循環血液量が少ないと考えられる低体重の献血者でとくにVVR発生率が高いことはなかった。Tomitaらの報告とわれわれの結果との差が何によるかが問題である。

今回のわれわれの検討で一番顕著な所見は，男女とも初回のVVR発生率が非常に高いことであった。つまり，初回の成分献血のVVR発生率が，男性で4.7%，女性で7.4%であり，再来の成分献血より有意に高く，さらに初回の400mL献血のそれよりも有意に高かった。Tomitaらはとくに初回者と再来者を分けたデータを示していないので，彼らの検討例にどの程度の初回献血者が含まれているのか，またそれが結果にどの程度影響しているのかが明らかでない。Tomitaらは45歳以上の女性の成分献血にVVR発生率が高いのは初回献血者が多いためではなく，多くは再来献血者であると述べているが，やはりVVR発生率を初回と再来に分けたデータは示されていない。大坂らの報告においても，初回および再来の成分献血のVVR発生率は示されていない。

McLeodらは米国の17の血液センターにおける成分献血の副作用を集めて報告した[12)]。各センターにおける献血者数は171人～2,519人と比較的少なく，総数は19,566人であった。その成分献血の80%を血小板献血が占め，7%が血漿献血，3%が顆粒球献血であった。彼らは副作用を静脈穿刺性(venipuncture)と非静脈穿刺性(nonvenipuncture)に分け，静脈穿刺性の副作用は神経損傷と血腫としている。一方，非静脈穿刺性の副作用にVVRとクエン酸中毒を含んでいる。非静脈穿刺性の副作用発生率は初回献血者が2.92%で，これは再来献血者が0.77%であるのに比べて有意に高いと報告している。また，採血機種によって副作用発生率が異なり，初回献血者ではHaemonetics(Haemonetics社)で5.08%と非常に高く，ついでSpectra(Gambro社)で3.04%，CS3000(Baxter社)では0.84%である。このHaemoneticsによる初回献血者の非静脈穿刺性の副作用発生率はわれわれの初回献血者のVVR発生率と同程度に高い。一方，再来献血者ではこれらの機種ごとのVVR発生率がそれぞれ0.80%，0.85%，0.64%とほぼ同じ値である。われわれの再来の成分献血者におけるVVR発生率が血小板献血で0.9%，血漿献血で1.1%であるが，これはMcLeodらの報告とほぼ一致する。McLeodは採血機器の違いによる初回献血者のVVR発生率の差異は，多数のセンターのデータを集めているので，センターの違いが大きく影響していると述べている。つまり，各センターで成分献血の初回としている献血者が以前に全血献血をしているかどうかを調査していないので，この点が影響している可能性を示唆している。成分採血機器には循環方式と間歇方式があり，現在のSpectraは2針法の循環方式であるが，McLeodらの報告した時のSpectraは単針法で採血するので間歇方式と思われる。Haemoneticsは現在も単針法の間歇方式で，体外循環血液量が305mLであるが，現在のSpectraとCS3000は2針法の循環方式でそれぞれ260mLと250mLとやや少ない。Haemoneticsではこの体外循環血液量が間歇的に体外に出るのに比べて，CS3000では献血者の循環血液量が減少することはない。今回われわれは採血機種とVVR発生率との関係を検討していない。しかし，われわれが用いた採血機器はすべて間歇方式であるので，McLeodらの報告したHaemoneticsと同じく循環血液量の減少が間歇的に起こるため，そのことが初回献血者にVVRが高頻度に起こったことと関係している

可能性がある。なお，Tomitaらの用いた採血機種はいずれもHaemonetics社のMCS-3PあるいはCCSであるので間歇方式であると思われる。今後，成分献血におけるVVR発生率を論ずるときに採血機種の差も調べる必要があると考える。

成分献血におけるVVR発生率と年齢との関係を見ると，いずれの年齢においても男女とも初回献血者のVVR発生率が再来献血者のそれより高く，また初回の全血献血のそれよりも高かった。とくに，60歳以上の女性で初回献血者9人のうち4人(44%)がVVRを起こしており，60歳代で献血が初めての女性に成分献血を適用することについて，至急検討する必要があると考える。Tomitaらは45歳以上の女性の成分献血にVVRが多いと報告しているが，われわれの検討では再来献血に限るとそのような傾向はみられなかった。むしろ，全血献血にみられるように加齢に伴って減少する傾向がみられ，その頻度は全年齢とも5%未満であり，初回の成分献血者のように非常に高いということはなかった。

成分献血におけるVVR発生率と体重の関係を見るとすべての体重において，初回献血者のVVR発生率は再来の成分献血や初回の全血献血のそれより高かった。また，その頻度もほとんどの体重で5%を超えており，初回献血者への成分献血の適用を再検討する必要があると考える。再来の男性では低体重の献血者でVVR発生率が高い傾向があるが，その頻度は全体重において1%以下であり，400mL献血のそれとほぼ同じ値である。現在のわが国の体重と採血量に関する基準では，成分献血者の安全性は十分確保されていると考えられる。Tomitaらの報告では，循環血液量の少ない女性でVVR発生率が4%を超えている。われわれは循環血液量を調べていないが，その算出値の大きな要素となる体重について調査した。その結果，再来の女性ではVVR発生率が低体重で非常に高いということはなかった。初回献血者では，すべての体重でVVR発生率が5%以上と非常に高いので，初回献血者の割合が多くなることの方がVVR発生数に大きな影響があるのではないかと考えられる。

われわれは初回の成分献血でVVR発生率が非常に高いことを認めたが，このことは献血者の安全上問題である。それとともに，一度VVRを起こした献血者はその後に献血をすることが少ないという報告もあり[8),18)]，血液の安定供給という点でも問題であると考える。英国の基準では，過去2年以内に全血献血を行い副作用のなかった人に成分献血を適用している[19)]。わが国でもそのようなことを考慮する必要があるのではないかと考える。また，採血機種によってVVR発生率に差があるかどうかも今後に残された問題である。

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(9)

Vasovagal reactions in apheresis donors

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BACKGROUND: The incidence rate of vasovagal reactions (VVRs) in apheresis is known to be higher in women than in men donors. VVRs in women apheresis donors were therefore analyzed to find out possible factors for their high incidence.

STUDY DESIGN AND METHODS: VVR incidence was compared between whole blood (WB) and apheresis donation in relation mainly to age and circulatory blood volume (CBV). In addition, blood pressure and pulse rate were measured during apheresis.

RESULTS: In WB donors, the VVR incidence was 0.83 and 1.25 percent, while in apheresis donors it was 0.99 and 4.17 percent in men and women, respectively. The VVR incidence decreased with age in WB donors, but age dependence was very weak in apheresis donors. In elderly women, the incidence increased with repeating cycle of apheresis. There were three different patterns of pulse fluctuation during apheresis, that is, stable (type A), increased rate during blood withdrawal (type B), and irregular pattern (type C). Elderly women donors and donors who suffered from VVRs mostly showed type B fluctuation. There was no particular fluctuation in blood pressure in relation to apheresis cycles.

CONCLUSION: The VVR incidence rate was particularly high in women apheresis donors over 45 years old and increased with repeating cycles of apheresis. Smaller CBV, high sensitivity of low-pressure baroreceptors, and citrate effects on cardiovascular reflex might be major factors involved in the high incidence of VVRs.

ABBREVIATIONS: CBV = circulatory blood volume; VVR(s) = vasovagal reaction(s); WB = whole blood.

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Blood donors occasionally have adverse reactions such as weakness, pallor, nausea, sweating, and fainting during or after blood withdrawal.[1,2] These symptoms are generally called vasovagal reactions (VVRs). The rate of incidence of VVRs has been analyzed mainly on the whole blood (WB) donors and reported to be higher in younger donors and at the first time of donation.[2-4] The contribution of other factors such as body weight and blood pressure is less clear. It has been reported for Japanese donors that there is no clear sex difference of VVR incidence in WB donors (1.70% in men, 1.85% in women), but that the rate of VVRs in apheresis is significantly higher in women (4.04%) than men donors (1.24%).[4] Failure of proper circulatory compensation by the autonomic nervous system may be an important factor responsible for the VVRs, but the mechanisms underlying these reactions are still mostly unclear. In the present study, therefore, the VVR incidence was demographically analyzed mainly on the apheresis donors in our blood center. In addition to this, blood pressure and pulse rate were measured to determine if characteristic alterations occurred during apheresis.

MATERIALS AND METHODS

The data accumulated from the voluntary blood donors were analyzed for the incidence of VVRs in the population of WB donors (a total of 20,025 men and 8,164 women during a 1-year period in 2000; including 200 and 400 mL phlebotomy) and in apheresis donors (14,523 men and 6,722 women; combined plasma [68.1%] and platelet collection [21.9%]), during the 3-year period 1999 to 2001. The equipment used for apheresis was either a multicomponent system (MCS 3P) or a component collecting system (Haemonetics, Tokyo, Japan). There was little functional difference between these machines. VVRs were judged from donor's symptoms described in the introduction by experienced nurses. VVRs were mostly relatively minor and syncopal episodes only occurred in a few percent of VVR donors. The VVR incidence rate was calculated for each age or for the circulatory blood volume (CBV) at a 100-mL step and averaged at each range indicated in the figures. Numerical values are expressed

as means ± SD. The data approximated most closely to normal distributions when examined with the Kolmogorov-Simirnov test. Significance of the difference was tested by with two-tailed, unpaired t-tests and the level of significance was set at $p < 0.05$.

The CBV (in mL) was estimated by following equations proposed by Ogawa et al.[5] for Japanese people:

$$CBV = 168H^3 + 50W + 444 \text{ for men}$$

$$CBV = 250H^3 + 63W - 662 \text{ for women}$$

where H is height (m) and W is weight (kg).

Blood pressure and pulse rate were measured automatically every 1 minute during apheresis in 42 men (19-67 years old) and 72 women (18-69 years old) with a automatic blood pressure monitor (Paramatec, PS-230). The reliability of the pulse rate measurement was confirmed by the simultaneous electrocardiograph measurements in three donors. All procedures were fully explained beforehand and carried out on donors who agreed to participate in the study.

RESULTS

In Fig. 1, the incidence of VVRs that occurred in WB and apheresis donation was compared between men and women donors of different ages. The incidence rate of VVRs associated with WB donation decreased with advancing age both in men and in women. In contrast, there was no such a clear tendency in VVRs in apheresis and the VVR incidence rate in apheresis was much higher in women than men, particularly in elderly donors. The mean incidence of VVRs of WB donors was 0.83 percent in men and 1.25 percent in women, while that of apheresis donors was 0.99 percent in men and 4.17 percent in women. These incidence rates were similar to those previously reported.[4]

The relationship between the VVR incidence and age in apheresis donors differed depending on the apheresis cycle (Fig. 2). In men donors, the incidence of VVRs that occurred during the first and second cycles decreased with age and was similar to the WB donation shown in Fig. 1, but it was independent of age at the third-fourth cycles. In women donors, the incidence also decreased with age at the first cycle, but it was independent of age at the second cycle and increased slightly with advancing age at the third to fourth cycles. There was a clear tendency for VVRs to occur at a later stage of apheresis with advancing age.

VVRs are known to occur more frequently in first-time donors than in repeated donors.[2-4,6] However, in women apheresis donors, there was no significant difference in the number of previous donations between healthy and VVR donors. Nearly all of the women apheresis donors over 45 years old who suffered from VVRs donated repeatedly (mean, 24.8 times) and VVRs were detected in only one first-time donor (1 of 45).

The high rate of VVRs in women donors in apheresis could partly be related to the fact that the CBV is significantly less (approx., 20%) in women than in men donors (Table 1). The mean CBV of the donors who suffered from VVRs was also slightly less (approx., 4%) than that of the control donors and the differences were significant ($p < 0.01$) both for men and for women donors.

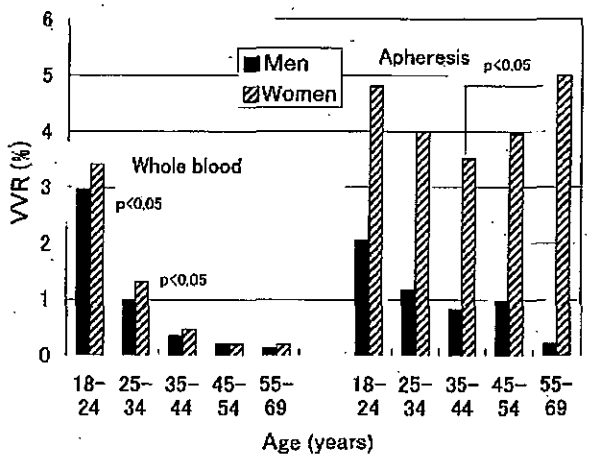

Fig. 1. VVR incidence rate in relation to age in WB and apheresis donors. Note that in men donors the incidence decreased with advancing ages both in WB and in apheresis donation, but that in women donors there was a large difference between WB and apheresis donation. The difference was significant ($p < 0.05$) between the younger three ranges of WB donors and men apheresis donors and also between 35- and 44- and 55- to 69-year-old women apheresis donors.

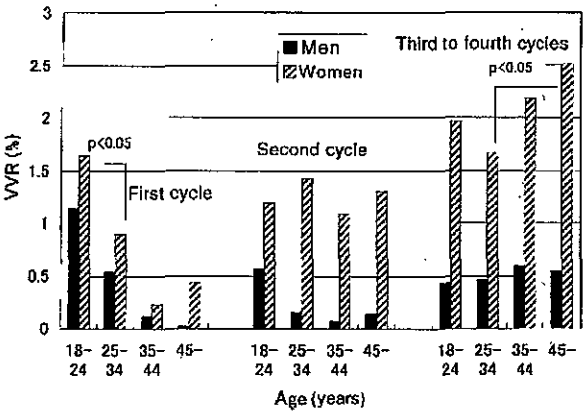

Fig. 2. The relationship between VVR incidence and age at different stages of apheresis. In younger donors, VVRs incidence did not differ much at different cycles of apheresis. In contrast, older donors tended to experience VVRs at a later stage of apheresis. A significant difference was indicated by the p value of less than 0.05. The difference between 18- and 24- and 25- to 34-year-old men donors at the second cycle was also significant ($p < 0.05$).

TABLE 1. CBV (mL) in WB and apheresis donors*

	Control	VVR donors
WB		
Men	4617.5 ± 536.4 (n = 1582)	4417.7 ± 496.8 (n = 168)
Women	3681.3 ± 520.2 (n = 668)	3475.5 ± 447.6 (n = 102)
Apheresis		
Men	4587.8 ± 505.0 (n = 1592)	4431.9 ± 431.5 (n = 144)
Women	3719.1 ± 546.7 (n = 734)	3584.7 ± 425.7 (n = 280)

* The values of control WB and apheresis donors were based on the data for 1- and 4-month periods, respectively. The differences of blood volume between control and VVR donors were statistically significant ($p < 0.01$) for WB and apheresis donors of both sexes.

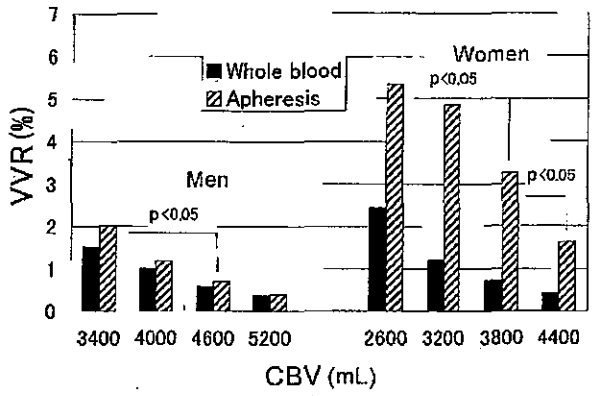

Fig. 3. VVR incidence in relation to CBV in WB and apheresis donation. The CBV was calculated by the equations described in the method. The significance of the difference is indicated by $p < 0.05$.

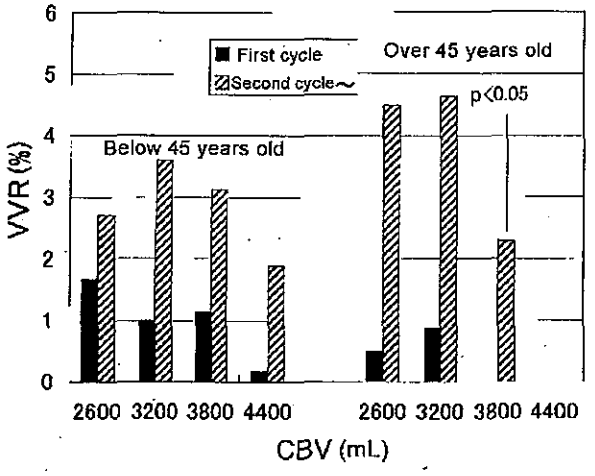

Fig. 4. VVR incidence in relation to CBV before (first cycle) and after the end of first cycle of apheresis (second cycle) in women donors below and over 45 years old. Note the higher incidence with smaller CBV and also after the first cycle of apheresis.

The relationship between the CBV and VVR incidence was compared in WB and apheresis donation (Fig. 3). In men, there was a tendency for the incidence of VVRs to decrease with larger CBV both in WB and in apheresis donors. In women apheresis donors, the CBV dependency was weaker in apheresis compared with WB donors.

CBV dependency of the VVR incidence was greater in older than young women donors. The incidence rate of women donors over 45 years old was 4.8, 2.8, and 0 percent with CBV of 2600 to 3700, 3800 to 4300, and greater than 4400 mL, respectively. In contrast, in the donors below 45 years old, it was 5.1, 3.6, and 1.9 percent, respectively. In men donors, such a clear difference was not detected.

The relationship between CBV and VVR incidence during the first and the second to fourth cycles of apheresis differed between women donors younger and older than 45 years old, as shown in Fig. 4. Below 45 years of age, approximately 25 percent of VVRs occurred at the first cycle relatively independent of the CBV, whereas over 45 years of age, only 10 percent of VVRs were observed at the first cycle. In women over 45 years old, the VVR incidence was much less in the donors having CBVs greater than 3800 mL.

VVR incidence during apheresis in women donors over 45 years old was relatively high (see Fig. 1), particularly at the later stage of apheresis (see Figs. 2 and 4). To investigate the possible mechanisms underlying these factors, blood pressure and pulse rate were measured during apheresis in 72 women (19-36 years old, n = 53; 40-69 years old, n = 19) and 42 men donors (19-27 years old, n = 27; 44-67 years old, n = 15).

Typical examples of blood pressure and pulse rate recorded during apheresis are shown in Figs. 5A and 5B, by averaging values obtained from five donors. Systolic blood pressure gradually decreased by about 15 mmHg in 10 to 15 minutes after starting apheresis and then became more or less steady. Diastolic pressure also decreased with time at the beginning but its degree was less than systolic pressure. Irregular fluctuations were often observed in diastolic pressure. No clear change was observed in relation to blood withdrawal and return both in systolic and in diastolic pressure. A particular pattern of blood pressure could not be used for prediction of VVR occurrence.

In contrast to blood pressure, blood withdrawal affected the pulse rate. Three different patterns of changed pulse rate were found during apheresis. One pattern was a reasonably stable rate throughout apheresis (type A), as shown in Fig. 5A. The second showed an increase in pulse rate during withdrawal and its recovery during return of

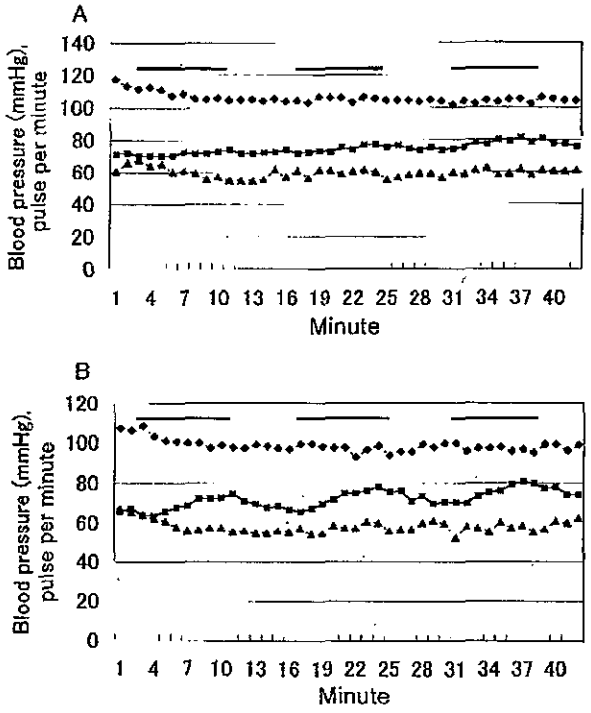

Fig. 5. Blood pressure and pulse rate measured every 1 minute during apheresis, averaging from five women donors whose pulse rate was stable (A) and increased (B) during blood withdrawal. (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

TABLE 2. CBV (mL) in donors showing stable pulse (type A) and fluctuating pulse rate (type B) during apheresis and in VVR donors*

Men	
Type A	4657.3 ± 284.3 (n = 20)
Type B	4347.1 ± 391.7 (n = 19)
VVR	4160.8 ± 458.6 (n = 2)
Women	
Type A	3819.1 ± 387.0 (n = 21)
Type B	3550.9 ± 341.1 (n = 41)
VVR	3535.6 ± 248.6 (n = 6)

* The differences of blood volume between type A and type B donors were statistically significant ($p < 0.05$) for both men and women donors. There was no difference in blood volume between VVR donors and type B donors.

blood (type B), as shown in Fig. 5B. The third was an irregular fluctuation without any clear relationship to blood withdrawal (type C, not shown). Types A, B, and C were shown in 31, 60, and 9 percent of women donors and 49, 46, and 5 percent of men donors, respectively. Women donors over 40 years old mostly (15 of 19) showed the type B fluctuating pattern, and there were only two each of donors showing types A and C, respectively. In contrast, in men donors over 40 years old, 40 percent were type B (6 of 15) and 60 percent were type A.

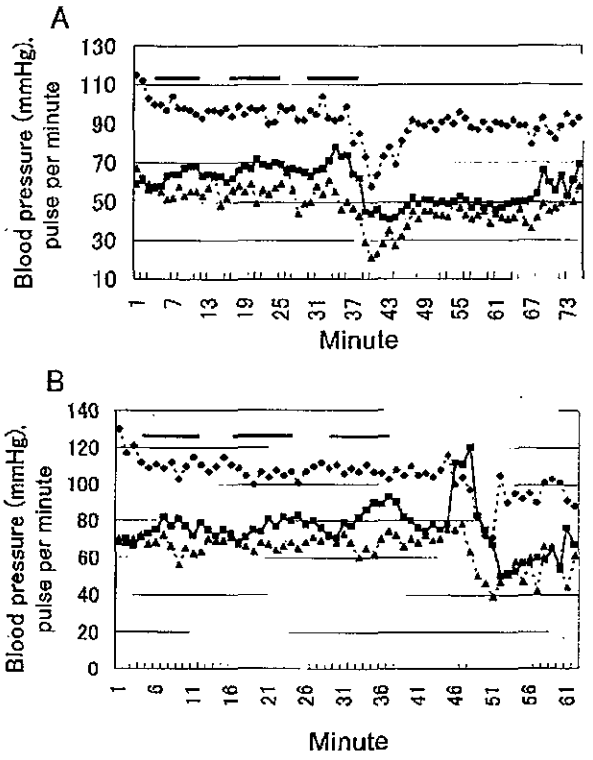

Fig. 6. (A) Blood pressure and pulse rate in a women donor (43 years old) who suffered from VVRs during the third cycle of blood withdrawal. VVRs were accompanied by tachycardia and lowered blood pressure, and then tachycardia was followed by prolonged bradycardia. The donor was laid down flat until recovery. (B) Another example of VVRs (a 20-year-old woman donor). VVRs occurred when she started to leave the bed and were accompanied by bradycardia and hypotension following transient tachycardia. Both donors showed an increase in pulse rate during blood withdrawal (indicated by horizontal bars). (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.

The mean CBV of the donors showing pulse rate fluctuations (type B) was less (about 7%) than those showing stable pulse rate (type A) both for men and for women donors (Table 2), and their differences were significant ($p < 0.05$).

The pulse rate data on VVRs were obtained from six women (20-43 years old) and two men donors (23 and 44 years old). They all showed the pulse rate fluctuations of the type B before the appearance of VVRs, as shown in two examples illustrated in Figs. 6A and 6B. The donors shown in Fig. 6 were kept in bed horizontally until they recovered, without medication. Typical VVRs were accompanied by marked bradycardia and periods of hypotension of various durations. The mean CBV of donors

who suffered from VVRs was similar to that of donors showing pulse fluctuations of type B both for men and for women (see Table 2).

DISCUSSION

The incidence of VVRs decreased with advancing age in the population of WB donors, both men and women donors, as previously reported.[2-4,6] A similar relationship was observed in men apheresis donors. However, no such a tendency was found in women apheresis donors. The VVR incidence of women apheresis donors was rather independent of age or even higher over 45 years old (see Fig. 1). This was not due to a high proportion of first-time donors in older women, because most donors over 45 years old were repeated donors.

The CBV was significantly (approx., 20%) less in women and it was also about 4 percent less ($p < 0.05$) in VVR donors than in healthy control donors. The VVR incidence tended to be higher with smaller CBV (see Figs. 3 and 4). It is possible in old donors that the actual CBV is less than that estimated solely from the height and weight determinations[7] and that the peripheral blood pool is small.[8] This may explain the larger effects of blood withdrawal in older donors. If stronger hypovolemia was a major factor in VVR incidence, it seems difficult to explain the difference in VVR incidence between WB and apheresis donors (see Figs. 1 and 3). Some other factors such as autonomic malfunction and hypocalcemia are more likely to be involved in higher VVR incidence in women, particularly older, apheresis donors.

A tachycardia was often observed during blood withdrawal without an associated change in arterial pressure. The ratio of the donors who showed such pulse rate fluctuations (type B) was higher in women than men and this difference was larger over 40 years of age. Furthermore, the VVR donors all showed type B fluctuations. Donors having smaller CBV have a tendency to produce tachycardia during apheresis (see Table 2). The increase in pulse rate usually became more marked with increasing cycles of blood withdrawal. This may have been due to an increased hypovolemia, because the extracorporeal blood volume increases with number of apheresis cycles. Tachycardia, without any significant changes in arterial blood pressure, has also been reported in response to a decreased venous return caused by lower-body negative pressure in humans[9,10] or by hemorrhage of up to 10 mL per kg blood in conscious dogs.[11] These responses are likely to be mediated by cardiopulmonary (low-pressure) baroreceptors, the sensitivity of which to hemorrhage is shown to be higher than those of carotid sinus (high-pressure) baroreceptors in dogs.[12] The mechanism causing the tachycardia during blood withdrawal is likely to be involved in triggering the patterns of VVRs by the circulatory control center.

In the apheresis, it is possible that the sensitivity of baroreceptor-mediated reflex is increased by a decrease in plasma Ca^{2+} concentration that is known to be caused by the supply of citrate during blood return.[12,13] This is probably one of the factors involved in the high VVR incidence in older women apheresis donors, whose VVR incidence is increased by repeating blood withdrawal and return. Not only the effects of blood withdrawal, but also the effects of citrate on the reflex mediated by cardiopulmonary baroreceptors would be stronger in the smaller CBV of old women donors. These factors may explain a high VVR incidence of elderly women donors and at later stage of apheresis.

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Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Blood Applications, Office of Blood Research and Review at 301-827-3524.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2007

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Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides you, blood establishments, and FDA staff with revised recommendations for the collection of Platelets by automated methods (plateletpheresis). This guidance is intended to help you ensure donor safety and the safety, purity, and potency of Platelets collected by an automated blood cell separator device. For the purpose of this document, Platelets collected by automated methods and resuspended in plasma will be referred to by the product name "Platelets, Pheresis." We consider the recommendations in this guidance document to provide appropriate criteria for a biologics license application or supplement for manufacturing Platelets, Pheresis, and provide guidance on preparing a manufacturing supplement for Platelets, Pheresis under Title 21 Code of Federal Regulations 601.12
(21 CFR 601.12).

This guidance applies only to the following Platelets, Pheresis components:

- Platelets, Pheresis (single, double, and triple collections);
- Platelets, Pheresis Leukocytes Reduced (single, double, and triple collections); and
- Platelets, Pheresis or Platelets, Pheresis Leukocytes Reduced collected concurrently with Plasma, Red Blood Cells (RBCs), and/or Source Plasma.[1]

This guidance replaces FDA's "Revised Guideline for the Collection of Platelets, Pheresis" dated October 1988. Also, this guidance finalizes the draft guidance, "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods" dated September 2005.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

[1] This guidance does not apply to plateletpheresis components collected concurrently during apheresis granulocyte collection procedures or plasma reduced apheresis platelets, which are not currently licensed products, or to platelets prepared from plasmapheresis as described in 21 CFR 640.22(b).

The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

If you have any questions about the effect of any portion of this guidance on a regulatory requirement, contact the Center for Biologics Evaluation and Research (CBER), Office of Blood Research and Review, Division of Blood Applications, at 301-827-3524.

II. DISCUSSION

A. Background

Plateletpheresis is the routine collection of platelets using an automated blood cell separator device, which results in the product Platelets, Pheresis manufactured from a high yield of platelets from a single donor. Transfusion of Platelets, Pheresis is effective for treating patients with platelet related insufficiencies, while limiting the recipient's exposure to platelets from multiple donors. In recent years, many improvements have been made in automated blood cell separator device technology, platelet storage stability, and blood cell counting methods, including:

- collection process efficiency;
- storage container characteristics; and
- accuracy of methods for determining a donor's pre-donation platelet count and component yields.

Automated blood cell separator devices are now capable of various plateletpheresis collection procedures including but not limited to the following:

- collection of double and triple platelet components obtained during a single procedure;
- use of in-process leukocyte reduction (Ref. 1);
- collection of concurrent plasma components (Ref. 2); and
- collection of concurrent RBC components (Ref. 3).

This document includes the following recommendations:

- Published research indicates that there is poor recovery of viable platelets stored at a pH of less than 6.2 (Refs. 4 and 5). Therefore, your process validation and quality control (QC) testing for Platelets, Pheresis should assure a pH at or above 6.2, to rule out a pH less than 6.2 on the date the product is issued or on the date the product expires (outdates). Note that we recommend that you adopt a stricter pH standard than that currently specified in 21 CFR 640.25(b)(2).
- You should include additional deferral criteria for donors of Platelets, Pheresis who have taken certain medications (see section III.A.) (Refs. 6, 7, and 8).

- To protect the safety of the donor, seven days should elapse after collection of a double or triple Platelets, Pheresis before the donor is eligible to donate Platelets, Pheresis again. In addition, first-time donors without a pre-donation platelet count should not undergo collection of a triple Platelets, Pheresis.
- Because of similarities between plateletpheresis and Source Plasma donation, you should follow the donor weight provisions for Source Plasma donors under 21 CFR 640.63(c)(6) (see Section III.A.).
- QC testing, as prescribed in 21 CFR 640.25(b)(1) through (3) requires that, each month, four units prepared from different donors be tested at the end of the storage period for platelet count, pH of not less than 6.0 when measured at the storage temperature of the unit, and volume. In addition, 21 CFR 211.160(b) requires that laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

We also note that bacterial contamination of blood components and associated transfusion risks is a continuing problem (Refs. 9 and 10). Bacterial contamination testing is a necessary part of process validation and quality assurance monitoring for Platelets, Pheresis.

B. Definitions

For purposes of the terms used in this guidance, the following definitions apply:

Actual platelet yield – The total platelet yield in the component, calculated by multiplying the platelet count of the sample times the volume of the component (platelet count x component volume = actual platelet yield).

Apheresis – Automated blood collection in which a device continuously or intermittently removes a small volume of whole blood, separates the components, collects certain components, and returns to the donor the uncollected remainder.

Automated blood cell separator – A device that uses a centrifugal or filtration separation principle to automatically withdraw whole blood from a donor, separate the whole blood into blood components, and return to the donor the remainder of the whole blood and blood components. The automated blood cell separator device is intended for routine collection of blood and blood components for transfusion or further manufacturing use.

Bacterial contamination testing – Testing conducted to determine whether a product contains viable contaminating bacteria.

Component – A part of a single donor's blood, such as platelets, separated from whole blood by physical or mechanical means. For Platelets, Pheresis, a component is a

transfusable product that may result from a single collection (resulting in one component), a double collection (resulting in two Platelets, Pheresis components), or a triple collection (resulting in three Platelets, Pheresis components).

Concurrent component – When a blood component, such as Platelets, is being collected during an apheresis procedure, a concurrent component is a different blood component (i.e., Plasma, RBCs) collected at the same time.

Dedicated donation – Platelets, Pheresis donated for a specific recipient.

Devices cleared or approved – Describes a device that has been cleared or approved by FDA pursuant to a 510(k) Premarket Notification (cleared device) or Premarket Approval Application (approved device). (See Title 21, United States Code, section 360c; Federal Food, Drug, and Cosmetic Act (FDCA), section 515 – Premarket Approval; and, FDCA, section 510(k)).

Donation frequency – Interval between a donor's collection procedures.

Process validation – Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

Qualification – A part of process validation that establishes confidence that a manufacturing device is capable of operating consistently (equipment installation qualification) and can be performed effectively and reproducibly (process performance qualification), and that the finished product meets all of the release requirements for functionality and safety (product performance qualification).

Residual White Blood Cell (WBC) count – The number of WBCs remaining in a Leukocytes Reduced component, calculated by multiplying the WBC count from a sample of the component times the volume of the component. In this document:

- references to residual WBC count testing apply when the Platelets, Pheresis will be labeled as Leukocytes Reduced.
- references to percent platelet retention apply to leukocyte reduction by filtration, provided there is access to a pre-filtration sample.

Rolling 12-month period – Continual assessment of a donor over a 12-month period. This is not a set 12-month period (i.e., calendar year).

Target platelet yield – The intended platelet yield programmed into an automated blood cell separator device, which may be based on the donor's platelet count and other factors.

Tolerance values – Minimum and maximum values (i.e., container volume; platelet concentration) described by the manufacturer as being acceptable. These values may also be described as specifications.

Weight/volume conversion – The total weight of the component minus the tare weight of the empty container divided by the specific gravity of the component equals volume of the component.

III. DONOR SELECTION AND MANAGEMENT

A. Donor Selection

Under 21 CFR 640.21(c), plateletpheresis donors must meet donor suitability criteria described in the biologics license application or supplement. These typically conform to donor suitability requirements (21 CFR 640.3) and recommendations applicable to donors of Whole Blood. In addition, we recommend:

- donor weight of at least 110 pounds (currently required for Source Plasma donors under 21 CFR 640.63(c)(6))
- Prior to the first donation, collect a sample for a platelet count.
- If you cannot test a sample for a platelet count prior to the first donation (for example, because the donor presents at a mobile collection site), you should collect a pre-donation sample and evaluate the donor's platelet count after the first collection.

You should not collect Platelets, Pheresis from donors who have ingested platelet inhibitory drugs recently enough to adversely affect platelet function in the product, or the safety of the donor. These recommendations include, but may not be limited to:

- Aspirin (ASA)/ASA-containing drugs/Feldene – two full medication free days prior to donation (Refs. 6 and 7)
- Plavix (Clopidogrel) and Ticlid (Ticlopidine) – 14 full medication free days prior to donation (Ref. 8).

When the drugs listed in this section are taken for a specific medical condition, donors should not discontinue taking drugs prescribed or recommended by their physicians in order to be eligible[2] to donate Platelets, Pheresis. However, we do not necessarily recommend deferral of such donors for all blood products, if the donors are in good health, and establishments may make eligibility determinations for donations of other products.

[2] We are using the terms "eligible" and "eligibility" in this guidance to refer to the donor suitability requirements described in 21 CFR 640.3 and 640.21(c).

B. Donor Management

1. Platelet Count

- You should collect a pre-donation sample from the donor for a platelet count. The device operator should enter that platelet count, or the one obtained immediately following initiation of the collection procedure, to more accurately set the target platelet yield parameters for each collection of Platelets, Pheresis. These steps should be consistent with the automated blood cell separator device manufacturer's directions for use.

- For any collection facility that cannot test a pre-donation sample for a platelet count (for example, a mobile collection site), you may use an average of previous historic platelet counts (as specified by the device manufacturer), or a default platelet count (either as recommended by the automated blood cell separator device manufacturer, or determined by using blood center specific values), to set the target platelet yield. You should not collect a triple Platelets, Pheresis from first-time donors who do not have a pre-donation platelet count available either prior to or immediately following initiation of the collection procedure. Concurrent components may be drawn if the donor meets eligibility requirements for those components.

- You should defer from donation donors whose platelet counts are less than 150,000 platelets/uL until a subsequent pre-donation platelet count indicates that the donor's platelet count is at least 150,000 platelets/uL.

2. Donation Frequency

To protect the safety of the donor:

- a donor should undergo no more than 24 Platelet, Pheresis collections in a rolling 12-month period.
- the interval between each collection of Platelets, Pheresis should be at least two days with no more than two procedures in a seven-day period.
- the interval between collection of a double or triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least seven days.
- the automated blood cell separator device should be set with a post-donation platelet count target of no less than 100,000 platelets/uL.

3. RBC Loss Prior to a Collection of Platelets, Pheresis

To protect the donor from significant RBC loss, we recommend that:

- you not allow a donor who has donated a unit of Whole Blood, a single unit of Red Blood Cells by apheresis, or a single unit of Red Blood Cells by apheresis concurrent with Platelets, Pheresis or Plasma in the previous 8

weeks to donate Platelets, Pheresis, unless the extracorporeal red blood cell volume during the Platelets, Pheresis collection is expected to be less than 100 mL (Ref 3).

- you not perform any collection procedure on a donor who has donated two units of Red Blood Cells by apheresis within the previous 16 weeks (Ref. 3).

4. Total Plasma Volume Loss Per Collection Procedure

The total plasma volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should not exceed:

- 500 mL (600 mL for donors weighing 175 lbs or greater), or
- the volume described in the labeling for the automated blood cell separator device (this volume may be more or less than the 500 mL or 600 mL volume stated in the above bullet).

IV. INFORMATION PROVIDED TO THE DONOR

Under 21 CFR 640.22(c), the collection procedure must be as described in the biologics license application or supplement. As part of the collection procedure, Platelets, Pheresis donors should receive information about the collection procedure and its associated risks. You should provide Platelets, Pheresis donors with the same information that is provided to a Whole Blood donor[3], plus the following information specific to the platelet collection:

- a description of the procedure for collection of Platelets, Pheresis and its associated risks.
- information about potential side effects of the procedure including possible effects as a result of solutions and/or treatment to reduce side effects such as treatment with a calcium replacement. Examples of side effects include anticoagulant effects (tingling and/or nausea), hypovolemia (decreased blood volume), fainting, and any other side effect as described by the automated blood cell separator device manufacturer.
- information indicating that there are limitations to the number and types of components that can be donated per year.

V. COMPONENT COLLECTION

Improvements in collection of Platelets, Pheresis have enabled blood establishments to obtain from a single collection procedure one, two, or three Platelets, Pheresis component(s) (and concurrent collection of Plasma, Source Plasma and/or RBC components).

[3] Refer to FDA regulations and guidance developed by FDA on this topic and available on the FDA website. http://www.fda.gov/cber/blood/bldpubs.htm

Under 21 CFR 640.22(c), the collection procedure must be as described in the biologics license application or supplement. In addition, the phlebotomy must be performed by a single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor's tissue (21 CFR 640.22(d)). A sterile connecting device may be used as described in the manufacturer's directions for the apheresis collection set. The automated blood cell separator device must perform in the manner for which it was designed (21 CFR 606.60(a)). Accordingly, your collection procedures should be consistent with the Operator's Manual, directions for use, and/or manufacturer's specifications. Specifications identified by the manufacturer may include, but not be limited to, the donor's platelet count, weight, height or hematocrit; the minimum/maximum volume of the storage container; platelet concentration per uL in the storage container, or actual platelet yield. In addition, supplies and reagents must be used in a manner consistent with instructions provided by the manufacturer (21 CFR 606.65(e)).

VI. VALIDATION OF THE COLLECTION PROCESS

The Current Good Manufacturing Practice (CGMP) regulations described in 21 CFR Parts 210 and 211 contain the minimum requirements for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing or holding of a drug to assure that the drug meets the requirements of the FDCA as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess (21 CFR 210.1(a)). These CGMP regulations also apply to Whole Blood and blood components (21 CFR 210.2(a), 211.1(b)) and supplement the CGMP regulations for blood and blood components contained in 21 CFR Part 606. As an element of CGMP, process validation "establishes documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics" (Ref. 11).[4] We recommend that establishing documentation of process validation include, but not be limited to, validation protocol development, installation qualification, process operator performance qualification, and product performance component qualification (Ref. 11).

Each device intended for the routine collection of Platelets, Pheresis must be cleared or approved by FDA for this purpose (see 21 CFR 864.9245). You should conduct validation of the collection process using each type of device used in your establishment prior to implementing routine collections.

In addition, your validation efforts should include the following manufacturing steps:

- cell counting
- pH measurement: we recommend that a pH meter or gas analyzer be routinely used rather than pH (nitrazine) paper.
- component weighing

[4] The requirement for process control is set forth in general terms in 21 CFR 211.100.

- sterile connecting method (Ref. 12)
- storage
- shipping

A. Equipment Installation Qualification

21 CFR 606.60(a) requires that equipment be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and must perform in the manner for which it was designed. Upon initial installation, the automated blood cell separator device should be qualified as described in the Operator's Manual or manufacturer's directions for use.

B. Validation Protocol

An integral element of the performance and documentation of process validation is the development of a validation protocol. You should refer to FDA's "Guideline on General Principles of Process Validation" (Ref. 11) as an outline for developing your validation protocol. The validation protocol should include at least the following:

- a description of the equipment to be used
- minimum/maximum acceptable values for the Platelets, Pheresis collection and/or component as specified by the automated blood cell separator device manufacturer
  - total volume (after removal of samples for hematological testing and bacterial contamination testing), including per component (container) from double and triple collections
  - actual platelet yield
  - residual WBC count (if Leukocytes Reduced) for the collection and components (if multiple components are collected), and percent platelet retention when applicable
  - concurrent component volume (Plasma or RBC), if applicable
  - pH measurement
- manufacturer's specifications or recommendations for processing parameters (i.e., actual platelet yield and concentration, weight or volume collected)
- description of supplies used in the collection (e.g., collection/storage containers, anticoagulants, etc.)
- failure investigation criteria
- personnel training criteria
- standard operating procedures for performing each element of the collection process
- documentation of the validation protocol criteria (all of the above)

C. Process Performance Qualification (Operator)

Each person engaged in the collection of Platelets, Pheresis must have adequate education, training, or experience to assure competent use of the automated blood cell separator devices involved (21 CFR 211.25(a)). Establishments must maintain applicable proficiency test results (21 CFR 606.160(b)(5)(v)).

We recommend that personnel training include the successful, consecutive, performance under supervision of an appropriate number of procedures, as defined by your facility. These procedures should result in the collection of Platelets, Pheresis meeting relevant component specifications.

D. Product Performance Qualification for Component Collection Process

Various mechanical and biological factors may influence the plateletpheresis collection process (i.e., the optical qualities of a donor's plasma, the donor's platelet count and platelet size, vascular access, and procedure duration) (Ref. 14). The objective of collection performance qualification is to verify that the automated blood cell separator device performs according to the manufacturer's claims when used, and through appropriate testing establishes confidence that the finished product produced by the specified process meets all release requirements for functionality and safety (Ref. 11). All components collected during the validation process can be released for transfusion provided that they meet minimum specifications as defined by the manufacturer, are labeled appropriately, and are otherwise suitable.

Process performance qualification should include testing for the actual platelet yield, pH, and volume; residual WBC count and percent platelet retention (for Leukocytes Reduced components) (See Table 1). We recommend that you assess the following at each collection site:

- **actual platelet yield** (platelet count multiplied by the volume):
  - determine actual platelet yield at collection.
  - follow the platelet pre-donation count recommendations in section III.B.1., and set an appropriate target platelet yield as recommended by the automated blood cell separator device manufacturer to maximize the likelihood that each transfusable component contains $\geq 3.0 \times 10^{11}$ platelets and the target collection type (single, double, triple) is achieved.
- **pH** as a measurement of quality after storage:
  - determine pH on the date the product is issued or on the date the product expires (outdates).
  - each transfusable component should have a pH ≥ 6.2
- **percent platelet retention**
  - perform when the automated blood cell separator device or filtration method is first put into use at an establishment and/or as recommended by the automated blood cell separator device manufacturer.
  - if leukocytes are reduced by filtration and there is access to both a pre-filtration and post-filtration sample, calculate percent platelet retention using pre- and post-filtration volume and cell content.
- **residual WBC count**:
  - perform when the automated blood cell separator device or filtration method is first put into use at an establishment and/or as recommended by the automated blood cell separator device manufacturer.

- perform within 48 hours of collection or per the manufacturer's directions for the cell counting methodology used (Ref. 15).
- conduct testing on the collection (parent container) and on the individual components from double and triple collections

- **volume**:
  - determine the volume after removal of samples for testing (i.e., cell count, bacterial contamination testing).
  - fill each storage container consistent with the manufacturer's minimum/maximum specifications.
  - equilibrate storage containers for double or triple collections $\pm$ 10 mL, or per the manufacturer's directions if different.

You also should qualify devices and perform failure investigations as follows:

- **Devices**:
  - complete product performance qualification for apheresis devices from different manufacturers, and for each model.
  - obtain data from all automated blood cell separator devices at each site for initial product performance qualification. If additional devices of the same model are added at the facility after qualification, include qualification data in monthly QC only.
- **Failure investigation**: Conduct an investigation for all component qualification failures, and when appropriate, initiate corrective action and follow-up measures (see 21 CFR 211.192; 606.100(c)). We understand that some failures may occur due to conditions **not** resulting from a failure of the process (e.g., automated blood cell separator device failures, donor reactions). In addition, you should:
  - investigate as qualification failures residual WBC counts that exceed the following:
    - single collection: $\geq 5.0 \times 10^6$ (collection)
    - double collection: $\geq 8.0 \times 10^6$ (collection), **and** $\geq 5.0 \times 10^6$ (either or both components)
    - triple collection: $\geq 1.2 \times 10^7$ (collection), **and** $\geq 5.0 \times 10^6$ (one, two or all three components).

  - However, each transfusable component from a double or triple collection of Platelets, Pheresis may be labeled as Leukocytes Reduced provided the residual WBC count on the component is found to be $< 5.0 \times 10^6$. investigate collections that fail to meet the percent platelet retention, if performed. However, the component may be transfused if the actual platelet yield is determined subsequent to filtration, and the component is labeled appropriately.

Variation in the actual platelet count might be due to the platelet counter used and the type of platelet count used at the time of collection (pre-donation or historic average). However, you should select a statistically sound sample size, based on 95% confidence that 75% of components (platelet yield) will meet the recommended results (see Table 1). For pH and recommended residual WBC count, you should select a statistically

sound sample size, based on 95% confidence that 95% of components (pH) or collections (residual WBC count) will meet the recommended results. Using the binomial statistic for example, a minimum of 60 components/collections should be tested, with zero process failures (93 tested with one process failure, 124 tested with two process failures, etc.) to qualify the process. Determine the sample size selection before starting the qualification process. For example, if you test 60 samples and encounter a failure, you should not continue with the testing of an additional 33 components. If you select a sample size of 93 and encounter a failure during testing, you may continue to test but there should be no additional failures. Similarly, if you select a sample size of 124 and encounter two failures, you may continue to test, but there should be no additional failures.

Table 1. Product Performance Qualification Criteria for the Platelet Component Collection Process

Test	Recommended Results	Target[1]	Allowable Process Failures[2] to achieve recommended results for a set of N tests[3]		
Actual platelet yield of transfusable component	$\geq 3.0 \times 10^{11}$	95%/75% *	N=11 **	N=18 **	N=23 **
			0	1	2
pH	≥ 6.2	95% / 95% ***	N=60	N=93	N=124
			0	1	2
Percent component retention	$\geq$ 85% component retention if performed ****	95%/95%	N=60	N=93	N=124
			0	1	2
Residual WBC count *****	Single collection: $< 5.0 \times 10^6$	95% / 95%	N= 60 collections	N=93 collections	N=124 collections
			0	1	2
	Double collection: Collection: $< 8.0 \times 10^6$ or Components: $< 5.0 \times 10^6$	95%/95%	N=60 collections	N=93 collections	N=124 collections
			0	1	2
	Triple collection: Collection: $< 1.2 \times 10^7$ or Components: $< 5.0 \times 10^6$	95%/95%	N=60 collections	N=93 collections	N=124 collections
			0	1	2

[1,2] Process failures only; non-process failures should be excluded.

[3] Corrective actions for exceeding allowable process failures

- if you select a sample size of 11 and find one failure, 17 additional samples would need to be tested with no additional failures.
- if you select a sample size of 60 and find one failure, 91 additional samples would need to be tested with no additional failures. If you select a sample size of 93 and find two failures, 157 additional samples should be tested with no failures. If you select a sample size of 124 and find three failures, 127 additional samples should be tested with no failures.

* 95% confidence that greater than 75% of the components meet the standard.

** The sample size numbers can be used in a sampling plan that should be representative of products collected on each machine type in each facility.

*** 95% confidence that greater than 95% of the components meet the standard.

**** Or per the container/automated blood cell separator device manufacturer's specifications

***** The stratified recommended results should ensure that the individual transfusable units will be $< 5.0 \times 10^6$ even with a 25% error in equilibration of the volume for double and triple collections.

E. Re-Qualification/Re-Validation

- Exceeding the allowable **process** failures of the collection process qualification may indicate that the process is not in control. You must investigate and correct the source of this failure (see 21 CFR 211.192, 606.100(c)) and should repeat validation.

- The manufacturer may provide re-qualification requirements for the automated blood cell separator device to be followed.

VII. QUALITY ASSURANCE AND MONITORING

Quality assurance (QA) is the sum of activities planned and performed to provide confidence that all systems and system elements that influence the quality of the component are functioning as expected (Ref. 13). When this is demonstrated, the process is considered to be in a state of control. Whether a process is operating in a state of control is determined by analyzing the day-to-day process and the data for conformance with the manufacturer's specifications and for variability.

You must have a quality control (QC) unit that has the responsibility and authority to approve or reject all components, containers, closures, in-process materials, packaging material, labeling and drug products and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated (21 CFR 211.22(a)). Thus, the QC unit's responsibilities include the review of production records, and the review of complaints involving the possible failure of a product to meet its specifications. (See, for example, 21 CFR 211.22, 211.192, 211.198, 606.100(c)). Please refer to FDA's "Guideline for Quality Assurance in Blood Establishments" (Ref. 13) for developing a QA and Monitoring program.

A. Standard Operating Procedures (SOPs) and Recordkeeping

1. Requirements for SOPs

- An automated blood cell separator device must "perform in the manner for which it was designed" (21 CFR 606.60(a)) during the collection or processing of apheresis components. Written SOPs must be maintained and must include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components (21 CFR 606.100(b)). Therefore, you must have written SOPs for each step in the collection of Platelets, Pheresis.

2. Additional Provisions Applicable to SOPs

- **Adverse reactions:** You must have a written SOP for investigating adverse donor and recipient reactions (21 CFR 606.100(b)(9)). In addition, you should have a written SOP for managing a cardiopulmonary emergency or

any other adverse reactions associated with donation, containing steps for contacting physicians, obtaining an emergency rescue squad response, and transporting the donor to the hospital.

- **Hematocrit**: If the final platelet collection contains more than 2 mL of packed RBCs, you should attach a sample of donor blood to the platelet storage container for compatibility testing to prevent the possibility of an adverse reaction during transfusion. In addition, you should hold the Platelets, Pheresis collection prior to distributing as Leukocytes Reduced until a residual WBC count of the transfusable component can be determined and found to be $< 5.0 \times 10^6$.

- **Component volume**: You should describe how to process components in the event the volume exceeds the automated blood cell separator device manufacturer's specifications. In addition, the volume in the storage containers from double or triple collections should be within ± 10 mL of each other or per the manufacturer's directions if different.

- **Samples for QC:** Containers for QC samples should be attached to the component/collection set using a sterile connecting device, to ensure the maintenance of the closed system.

- **Actual platelet yield**: The platelet yield from each collection of Platelets, Pheresis should be available to provide to the transfusion facility.

- **pH measurement**: Accurate pH measurement is time dependent, and samples should be tested within 1 hour of sampling, or as suggested by the manufacturer of the pH measurement system. We recommend that a pH meter or gas analyzer be routinely used rather than pH (nitrazine) paper. However, if you choose to determine pH measurements with nitrazine paper, the selected paper should read in increments of one-tenth units, or it may provide inaccurate measurements.

- **RBC loss**: You must have a written SOP for your collection procedure, including in-process precautions to measure accurately the quantity of blood removed from the donor (21 CFR 606.100(b)(5)). You should calculate the donor's RBC loss, which may include the residual RBCs remaining in the apheresis collection set after a collection of or discontinued collection of Platelets, Pheresis; the extracorporeal RBCs remaining in event of no RBC rinseback; the RBC loss from collection of tubes for testing; and/or collection of a concurrent RBC. You should record such RBC loss in the donor's record, in a manner that allows tracking of cumulative RBC loss over time.

- **Bacterial contamination testing**: You must maintain written SOPs and include all steps to be followed in the testing of blood and blood components (21 CFR 606.100(b)). Bacterial contamination testing should be performed using a culture based methodology, and using your established procedures.

- **QC failures**: You must thoroughly investigate any unexplained discrepancy or the failure of a batch to meet any of its specifications (21 CFR 211.192). You should define appropriate criteria for retesting of components, testing of additional components, final labeling, and disposition of components that fail to meet specifications.

- **Failure investigations**: (see 21 CFR 211.192; 606.100(c)) The criteria to assess in the performance of a thorough failure investigation (including the conclusions and followup) should include, but not be limited to: donor characteristics or specifications; operation and or performance of the collection device; adherence to SOPs; lot numbers of reagents or supplies; sample collection, handling, storage or shipping; operator performance, training or competency; and cell counting instrument performance including shifts or trends in controls.

- **Manufacturer's performance specifications**: You should state the acceptable tolerance specifications for the volumes, platelet concentration, and/or actual platelet yield for each storage container as described by the manufacturer. You should have a procedure addressing the handling of components that do not meet the manufacturer's performance specifications (e.g., use in research or further manufacture).

- **Labeling**:
  - The final component volume stated on the label should be determined after removal of samples for platelet count determination, QC, and/or bacterial contamination testing.
  - Platelets, Pheresis for transfusion should routinely contain $\geq 3.0 \times 10^{11}$ platelets. When special circumstances warrant their use, Platelets, Pheresis components containing less than 3.0×10^{11} platelets should be labeled with the actual platelet content.

- **Component Storage**:
  - If Platelets, Pheresis are stored at 20 to 24 °C, you must maintain a continuous gentle agitation throughout the storage period (21 CFR 640.25(a)). You should describe how temperature and agitation will be monitored, and the disposition of platelet components that are not stored properly.
  - You must follow the automated blood cell separator device manufacturer's directions for use (21 CFR 606.60(a)). If sterile connecting an additional container(s) is necessary, use a container(s)

designed to achieve and protect a sterile conduit. Because of differences in container specifications, you should use containers from the same manufacturer.

3. Recordkeeping

All recordkeeping requirements of 21 CFR Part 606, Current Good Manufacturing Practice for Blood and Blood Components, Subpart I (Records and Reports); Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart J (Records and Reports); and applicable provisions of 21 CFR 640.20 through 640.27, must be met.

B. Donor Monitoring

1. Platelet Counts

If the platelet count is known, you should notify your Medical Director when a donor has a post collection platelet count less than 100,000/uL, and you should defer the donor until his/her platelet count has returned to at least 150,000/uL.

Transient decreases in platelet counts have been reported in donors undergoing multiple collections of Platelets, Pheresis (Ref. 16). You should periodically review a donor's records to monitor platelet counts.

2. Adverse Reactions in Donors

Records must be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion and a thorough investigation of each reported adverse reaction must be made (21 CFR 606.170(a)).

3. Red Blood Cell Loss

- **Per collection**:
  - If the collection procedure needs to be discontinued for any reason before completion, and if the Operator's Manual allows, you should attempt to return RBCs to the donor.
  - Donor eligibility based on RBC loss (with or without RBC rinseback, and including all other types of donation) is described in Table 2.

Table 2: Recommendations for donor eligibility based on RBC loss per collection

Donor's Initial packed RBC loss	Donor's Second packed RBC loss within 8 weeks	Eligibility
Less than 200 mL	No donation or total from initial and second loss less than 200 mL	No deferral of donor for packed RBC loss; frequency of donation of Platelets, Pheresis as discussed in section III.B.2
Less than 200 mL	More than 200 mL but less than 300 mL total	Donor is not eligible to donate for 8 weeks from 2nd loss
More than 200 mL but less than 300 mL	NA	Donor is not eligible to donate for 8 weeks from initial loss
Less than 200 mL	Total loss from initial and second loss of more than 300 mL	Donor is not eligible to donate for 16 weeks from the 2nd loss
300 mL or more	NA	Donor is not eligible to donate for 16 weeks from initial loss.

- **Per 12 months**:
  Under 21 CFR 640.3(b), a person may not serve as a source of Whole Blood more than once in 8 weeks. In any such assessment, and in assessing a donor's RBC loss during the past rolling 12-month period, the RBC loss associated with the collection of Platelets, Pheresis, and including any other donation type (i.e., Whole Blood, RBC by apheresis), should also be considered.
- **Total plasma volume loss per 12 months**:
  The maximum volume (excluding anticoagulant) collected from a donor during a rolling 12-month period, and including any other donation type (i.e. Whole Blood, plasmapheresis) should not exceed:
  - 12 liters (12,000 mL) for donors weighing 110 – 175 lbs
  - 14.4 liters (14,400 mL) for donors weighing more than 175 lbs

  (Ref. 2).

C. Component Testing

1. Component Specification Check

- Actual platelet yield (volume x platelet count) must be determined after each collection (21 CFR 211.103).
- Weight/volume conversion is necessary to determine the volume of each collection. To convert weight to volume, divide the weight of the collection (the total weight minus the weight of the bag) by the specific gravity (1.03).

- Bacterial contamination testing: You should perform bacterial testing as specified by the storage container manufacturer (i.e., 7-day storage of Platelets, Pheresis, Leukocytes Reduced).

2. QC Monitoring

Under 21 CFR 211.160(b), laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures to assure that components and products conform to appropriate standards. One example of a scientifically sound statistical sampling and analytic plan is based on a binomial approach (see Table 1: Product Performance Qualification Criteria for the Platelet Component Collection Process). The sampling sizes described in Table 1 will confirm with 95% confidence a < 5% non-conformance rate for pH and residual WBC count, and < 25% non-conformance rate for actual platelet yield.

However, other statistical plans may also be appropriate, such as the use of scan statistics.

As part of your QC protocol you should:

- define a plan for non-selectively identifying collections to be tested. This should ensure testing of components collected on each individual automated blood cell separator device, each collection type, and each location.
- define sampling schemes for actual platelet yield (including volume determination) and pH, and residual WBC. We recognize that these sampling schemes may be mutually exclusive. However, the platelet yield of the collection (and designation of single, double or triple) should be made prior to performing the residual WBC count QC.
- test actual platelet yield (platelet count times the volume) and pH at the maximum allowable storage time for the container system used (or representing the dating period). Title 21 CFR 640.25(b) specifies that QC testing, including platelet count and measurement of actual plasma volume, be performed at the end of the storage period. We believe that such testing may be conducted "at issue" or within 12 hours after expiration. In addition, actual platelet yield and pH testing may be conducted on one storage container of a double or triple collection.
- include the residual WBC count (Ref. 1) for Leukocytes Reduced collections, if manufacturing leukocytes reduced products.
    - Perform the residual WBC count on the collection. For the purpose of labeling as Leukocytes Reduced (see 21 CFR 606.121(c)(1)), you may also perform a residual WBC count on the transfusable units for double and triple collections that fail the collection acceptance criteria listed (see below in this section).

  - Test for the residual WBC count within 48 hours after collection (Ref. 15), or per the manufacturer's directions for the cell counting methodology, to reduce aberrant results due to cellular deterioration and clumping.
  - Test for percent platelet retention, if leukocytes reduced by filtration.
- describe the criteria for investigation of failures during QC, including the factors to consider in categorizing a failure as process or non-process.
- have a method to document all calculations and test results.

We recommend that you consider the following QC results to be acceptable:

- pH $\geq$ 6.2. If one component from a double or triple collection is found to have a pH < 6.2, the corresponding component(s) from the collection should be retrieved and/or quarantined until they are tested and found to be acceptable.
- transfusable Platelets, Pheresis components $\geq 3.0 \times 10^{11}$ platelets.
- residual WBC count:
  - Single collection: $< 5.0 \times 10^6$ WBC
  - Double collection: $< 8.0 \times 10^6$ WBC
    Note: If $\geq 8.0 \times 10^6$, **but** each transfusable component is $< 5.0 \times 10^6$, this is not considered a collection failure.
  - Triple collection: $< 1.2 \times 10^7$
    Note: If $\geq 1.2 \times 10^7$, **but** each transfusable component is $< 5.0 \times 10^6$, this is not considered a collection failure.
- percent platelet retention should be $\geq$ 85% or per the manufacturer's specifications. Components with < 85% platelet retention may be distributed, but a failure investigation should be performed.
- negative for bacterial contamination testing, when performed.

D. Equipment/Supplies

Equipment must be observed, standardized, and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual (21 CFR 606.60(a)). Such equipment includes, but may not be limited to, the automated blood cell separator device, cell counting instrument(s), pH meter, scales and sterile connector.

All supplies (including containers) and reagents must meet all of the requirements described in 21 CFR 606.65.

E. Operator Training

Operators must have adequate training, education and experience, or combination thereof, to assure competent performance of their assigned functions (21 CFR 606.20(b)). We recommend that assessment of operators include scheduled

competency assessment and proficiency testing. In addition, we recommend that you develop and document appropriate training on component preparation and/or machine maintenance as updated information becomes available (Ref. 12).

F. Quality Monitoring

You should assess the following:

- total component volume and equal distribution of volume in double and triple component collection containers. This assessment should include checking the performance of the scale; the use of the tare weight of the empty containers/tubing; and the weight/volume conversion.
- component bacterial contamination testing: Rates of bacterial contamination of plateletpheresis should be monitored, and bacterial contamination rates that exceed 1:3000 (Refs. 10 and 12) should be investigated.

VIII. PROCESSING AND TESTING

A. Processing

Platelets, Pheresis must be processed as described in 21 CFR 640, Subpart C – Platelets (21 CFR 640.20-640.27).

B. Communicable Disease Testing

Donations of Platelets, Pheresis must be tested for communicable diseases (21 CFR 610.40, 640.5(a) through (c), 640.23). Platelets, Pheresis may be released or shipped prior to completion of communicable disease testing in accordance with 21 CFR 610.40(g).

You must test donations of human blood and blood components from a donor whose donations are dedicated to and used solely by a single identified recipient except that, if the donor makes multiple donations for a single identified recipient, you may perform such testing only on the first donation in each 30-day period (21 CFR 610.40(c)(1)(i)).

C. Expiration Date

The dating period for Platelets, Pheresis collected using an FDA cleared or approved collection container under a closed or functionally closed system will be specified by the collection container manufacturer.

In accordance with such instructions and our recommendation, Platelets, Pheresis collected in an open system expire 24 hours from the termination of the procedure if the integrity of the hermetic seal is broken during processing.

If the integrity of the hermetic seal is broken after collection, the Platelets, Pheresis expire 4 hours from the time of the integrity violation, or at the original expiration date, whichever is earlier (21 CFR 606.122(l)(2)).

IX. LABELING

An instruction circular must be available for distribution if the product is intended for transfusion (21 CFR 606.122).

Your container labels must comply with 21 CFR 606.121 and 610.60.

In addition:

- The label should include the estimated amount of anticoagulant in the component container.
- Platelets, Pheresis components for transfusion, containing less than 3.0×10^{11} platelets per storage container, should be labeled with the actual platelet content.
- A component from a double or triple Platelets, Pheresis may accurately be labeled as Leukocytes Reduced when the residual WBC count of the collection is $\geq 8.0 \times 10^{6}$ (double) or $\geq 1.2 \times 10^{7}$ (triple) **IF** the transfusable component is tested and found to have a residual WBC count $< 5.0 \times 10^{6}$.
- Platelets, Pheresis may be labeled (i.e., tie-tag) with the residual WBC count if counted and found to contain $< 1.0 \times 10^{6}$.

X. REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)

Licensed establishments must report changes to their approved application(s) in accordance with 21 CFR 601.12. For assistance in reporting your changes see FDA's "Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture." The information below is intended to assist you in determining which reporting mechanism is appropriate for a change to your approved BLA, as it applies to the manufacture of Platelets, Pheresis. You should prominently label each submission with the reporting category under which you are reporting your change, e.g., "Prior Approval Supplement;" "Supplement - Changes Being Effected in 30 Days;" "Supplement - Changes Being Effected;" or "Annual Report."

A. Prior Approval Supplement (PAS): Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes) (21 CFR 601.12(b))

Under 21 CFR 601.12(b), changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a Prior Approval Supplement (PAS).

Under this standard, the following kinds of manufacturing changes would fall within this category, warranting submission of your request to implement the following changes to your approved BLA as a PAS:

- if you currently hold an unsuspended, unrevoked BLA to manufacture blood components other than Platelets, Pheresis, and you intend to manufacture and distribute Platelets, Pheresis under that license.
- if you are currently approved to manufacture Platelets, Pheresis at a specific facility, and you intend to manufacture Platelets, Pheresis at a different facility, not under an approved Comparability Protocol. To submit a request for a Comparability Protocol see below.
- if you are approved to manufacture Platelets, Pheresis, but intend to change your manufacturing process in a manner that presents a substantial potential for an adverse effect on the product. FDA believes that such manufacturing changes include: change in storage conditions; change in anticoagulant; leukocyte reduction; and collection of an additional or different product.
- if you intend to collect Platelets, Pheresis using an automated blood cell separator device new to the market or new to your establishment.
- if you are requesting approval for a Comparability Protocol. The Comparability Protocol described in 21 CFR 601.12(e) is a supplement that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. A new Comparability Protocol, or a change to an existing one, requires approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect (21 CFR 601.12(e)).

  A Comparability Protocol is appropriate, but not required, if you wish to add multiple collection facilities under your direction and control, using the same process to manufacture Platelets, Pheresis. If you request approval for a Comparability Protocol, you should describe the procedures and processes that each new collection facility will implement to ensure conformance with the Comparability Protocol. You may identify one or more collection facilities for the purpose of validation and submission of the Comparability Protocol and supporting data to CBER for review. Approval of such a Comparability Protocol for future collection facilities justifies a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

  If you are using an approved Comparability Protocol, you should routinely review the procedures and specifications in the Comparability Protocol to assure that they remain current and consistent with the applicable application and current guidance. If modifications are required, you should contact FDA to discuss the change and to determine the appropriate reporting category.

- We consider the recommendations in this guidance document to provide appropriate criteria for a biologics license application or supplement for Platelets, Pheresis. You may use an alternative approach if such approach satisfies the requirements of the applicable statutes and regulations. Your alternative procedure(s) may be acceptable if you demonstrate that the resulting Platelets, Pheresis components meet applicable standards. We have determined that it may be adequate to determine the actual platelet yield at collection, and that re-determination of the actual platelet yield at issue or outdate is unlikely to provide additional relevant information. If you choose to discontinue determining the platelet count for QC testing as described under 21 CFR 640.25(b)(1), you must submit a request for an alternative procedure under 21 CFR 640.120.

You must not distribute in interstate commerce blood components made using a changed manufacturing process requiring a PAS until you have received our approval of your PAS (21 CFR 601.12(b)(3)).

B. Changes Being Effected in 30 Days (CBE-30) Supplement: Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Product Made Using the Change (21 CFR 601.12(c))

Under 21 CFR 601.12(c), changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a Changes Being Effected in 30 days (CBE-30) supplement.

You must submit your request to implement manufacturing changes with a moderate potential for an adverse effect to your approved BLA as a CBE-30 supplement under 21 CFR 601.12(c). The manufacturing changes described below are examples of changes that we believe fall within this category:

- certain software and hardware upgrades provided by the manufacturer to your cleared or approved automated blood cell separator device
- addition of concurrent plasma collection
- implementation of a new collection facility under an approved Comparability Protocol

You may distribute your blood components made using the change requested in your CBE-30 supplement in interstate commerce 30 days after we receive your supplement, unless we notify you otherwise (21 CFR 601.12(c)(4)).

C. Submission Inclusion Documents

1. PAS: To comply with the requirements in 21 CFR 601.12(b)(3), the following must be included in the supplement:

- identification of the components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and manufacturing site(s) or area(s) affected, and a detailed description of the manufacturing change (including device collection technology and the collection protocol(s)) (21 CFR 601.12(b)(3)(i) through (iii)). We recommend that this information be documented in a cover letter and FDA Form 356h. To permit assessment of the manufacturing change we recommend including copies of the following SOPs:
  - collection
  - informed consent
  - labeling including labels
  - donor qualification, deferral and adverse event follow-up
  - a description of training (or an example of training documents)
  - component manufacturing
  - monitoring donor RBC and plasma loss
  - failure investigation
  - quality control including sampling scheme, sample handling, tracking and trending
  - equipment standardization/calibration
  - quarantine and disposition of unsuitable products

Additionally, we recommend that the following SOPs, if already approved for other blood collection activities and unrevised, would not need to be submitted:

- sample preparation
- component storage and shipping
- donor arm preparation

- product labeling for each component, if changed (21 CFR 601.12(f)). We recommend submitting a Form FDA 2567 including Circular (unless already on file at FDA)
- a reference list of relevant SOPs (21 CFR 601.12(b)(3)(vii))
- relevant validation protocols and data (21 CFR 601.12(b)(3)(vi)). We recommend a summary of the validation protocol, including failure investigations.
- a description of the methods used and studies performed to evaluate the effect of the change and the data derived from such studies (21 CFR 601.12(b)(3)(iv) through (v)). We recommend submitting the following information and data:
  - the device manufacturer
  - the device type
  - blood unit number
  - component description (i.e., leukocytes reduced)
  - date of collection
  - date of testing
  - result interpretation(s)
  - the identity of the person performing the testing

- the identity of the collection facility
- evidence of QA oversight, and
- expected component specifications.

- Additionally, we recommend two months of QC data for actual platelet yield and volume, pH, and residual WBC count (if requesting approval for Leukocytes Reduced platelets).

We further recommend that you provide an agreement to summarize bacterial contamination testing results for the first two hundred and fifty (250) Platelets, Pheresis collections in your Annual Report.

2. Comparability Protocol: If you are an establishment with multiple manufacturing sites and wish to submit a comparability protocol to justify a reduced reporting category for a manufacturing change at multiple sites (see Section X.C.4 below), you must submit that protocol as a PAS (21 CFR 601.12(e)). In addition to the information listed in Section X.C.1 above , we recommend that you include the following:

- implementation plan
- proposed reporting category for changes made under proposed Comparability Protocol

3. CBE-30 submissions (excluding new facilities under an approved Comparability Protocol): Under 21 CFR 601.12(c)(3) and 601.12(b)(3)(i) through (vii), the following information must be included in your CBE-30 submission:

- identification of the Platelets, Pheresis components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and manufacturing site(s) or area(s) affected, and a detailed description of the proposed manufacturing change (including device collection technology and the collection protocol(s)). We recommend that you document this information in a cover letter and FDA Form 356h. To permit assessment of the documented manufacturing change, we recommend that you include copies of any new or revised SOPs.

- relevant validation protocols and data. We recommend that you submit a summary of the validation protocol, including failure investigation.

- the data derived from such studies. We recommend two months of QC data for actual platelet yield and volume, pH, and residual WBC count (if requesting approval for Leukocytes Reduced platelets).

4. CBE-30 submissions for new facilities under an approved Comparability Protocol: To comply with 21 CFR 601.12(c)(3) and 601.12(b)(3)(i) through (vii), the following information must be included:

- identification of the components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and new manufacturing site(s) or areas(s) affected, and a detailed description of the proposed implementation plan (manufacturing change including device collection technology and the collection protocol(s)). Additionally, we recommend that this information be documented in a cover letter and FDA Form 356h.

- relevant validation protocols and data. We recommend a summary of the validation protocol, including failure investigations to meet the requirement.

- the data derived from studies. We recommend two months of QC data for actual platelet yield and volume, pH, and residual WBC count (if requesting approval for Leukocytes Reduced platelets).

In addition, you should include the submission tracking number (STN) of the approved Comparability Protocol, or the STN(s) of changes to the SOPs associated with an approved Comparability Protocol.

D. Submission of Platelets, Pheresis Sample(s) to CBER

To obtain a biologics license under Section 351 of the Public Health Service Act for any biological product, the manufacturer must submit an application to CBER, and sample(s) representative of the product must be listed in the application (21 CFR 601.2(a)).

We recommend that:

- applicants with no prior experience in the collection of Platelets, Pheresis schedule submission of Platelets, Pheresis products to CBER.
- applicants who submit a CBE-30 for an additional facility under an approved Comparability Protocol generally would not need to submit Platelets, Pheresis products to CBER.

CBER may request the submission of product samples by other applicants, as necessary, during the review process or at any other time (21 CFR 610.2(a)).

E. Shipping Platelets, Pheresis Sample(s) to CBER

If CBER has requested you to submit a Platelets, Pheresis sample(s) to CBER, you should contact CBER Division of Hematology, Laboratory of Cellular Hematology at (301) 496-2577 to schedule delivery of the products to arrive prepaid. Platelets, Pheresis sample(s) should be shipped to the following address between 8:30 a.m. and 4:00 p.m. Monday through Friday, excluding Federal holidays:

Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
8800 Rockville Pike
Building 29, Room 323
Bethesda, Maryland 20892

We recommend that you enclose a pre-paid, self-addressed shipping label to allow return of shipping boxes and coolants, if desired.

We recommend that you ensure that the Platelets, Pheresis sample(s) arrives at CBER prior to the expiration time. The Platelets, Pheresis sample(s) should not expire on Friday or Saturday at midnight, or at midnight on the day before a Federal holiday.

Labeling and processing, including required testing for evidence of infection due to communicable disease agents (21 CFR 610.40), should be complete prior to shipment.

When shipping to us, you should follow your SOPs for collection, processing, storage and distribution of blood components intended for transfusion.

XI. CONTACT INFORMATION

You may direct questions specific to Platelets, Pheresis application submissions to the Division of Blood Applications. You may also direct questions to the Office of Communications, Training, and Manufacturers Assistance (OCTMA) as an initial general point of contact. Submit all registration forms (Form FDA 2830) and licensure applications/supplements to the Director, CBER.

Table 3: FDA Contact Information

Submissions: Registrations License Applications	Director, Division of Blood Applications Center for Biologics Evaluation and Research, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.
General Questions	Director, OCTMA, HFM-40, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-2000; Fax (301) 827-3843.
Application Submission	Director, Division of Blood Applications, Center for Biologics Evaluation and Research, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-3543; Fax (301) 827-3534.
Platelets, Pheresis Samples to CBER	Center for Biologics Evaluation and Research (CBER) Food and Drug Administration 8800 Rockville Pike Building 29, Room 323 Bethesda, Maryland 20892

XII. REFERENCES

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[原著]

事前検査におけるヘモグロビン測定の導入

香川県赤十字血液センター
内田 立身，窪田 明美，中西 幸美，安藤 浩子
西村 拓史，白井 隆，小河 敏伸，西尾由美子
細川 和浩，木村 史子，三枝 明子，本田 豊彦

Implementation of measuring hemoglobin concentration at pre-donation test

Kagawa Red Cross Blood Center
Tatsumi Uchida, Akemi Kubota, Yukimi Nakanishi, Hiroko Andoh,
Takuji Nishimura, Takashi Shirai, Toshinobu Ogoh, Yumiko Nishio
Kazuhiro Hosokawa, Humiko Kimura, Akiko Saigusa and Toyohiko Honda

抄　録

香川県赤十字血液センターでは2003年10月に，事前検査として血液比重にかわって，ヘモグロビン(Hb)測定法を導入した。Hb法の最大の利点はその定量性にあり，献血者にHb値を数字として提示することができ，Hb低値者，高値者に対する対応を明確にし得た。また，懸念されていたHb不足による献血不適格者数，VVR発症率も比重法施行時と大差がなかった。今回の検討で，Hb12.5g/dL以上がほぼ比重1.053以上に，12.0g/dL以上が1.052以上に相当すること，Hbと赤血球指数との関係から，赤血球が正色素性から小球性低色素性に変わるHb値が12.5～12.0g/dLであることから現行の採血基準は妥当であると考えられた。Hb法は測定装置がHbの表示まで時間を要すること，温度差による配慮が必要であるなどの欠点はあるが，定量性，均一性を重視するGMPからみても従来の比重法より優れていると結論した。

Key words: Pre-donation examination, Hemoglobin determination
Blood donation criteria, HemoCue hemoglobin analyzer

はじめに

香川県赤十字血液センターでは，2003年10月より，事前検査として硫酸銅法による比重測定にかわって，簡易ヘモグロビン(Hb)測定装置，ヘモキュウヘモグロビンシステム(以下Hb法)による方法に変更した。採血基準は，血液事業の根幹の一つであり，その判定には定量的なHb法が最も妥当と考えられるゆえである。自動血球算定装置がルーチン化したわが国において，貧血の診断はすべてHb，ヘマトクリット，赤血球数によっており，目視による比色法(ザーリ法)や比重法(硫酸銅法)は赤十字血液センターを除いて用いられていない。最近の献血の適否に関する世界の論文は，すべてがHb法を用いて判断しており[1)-3)]，比重法は

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検査法として教科書の記載すらない現状である[4]。

今回，比重法とHb法の比較，変更前後の献血不適格者の比率，副作用，とくに血管迷走神経反応(Vasovagal Reflex：以下VVR)の比率，また，200mL献血12.0g/dL以上，400mL献血12.5g/dL以上とされている採血基準の妥当性についても検討した。さらに，Hb法の有用性を生かして，不適格者のHb濃度別による個人指導のありかたについても検討したので，これらの成績を報告する。

方　法

簡易Hb法(ヘモキュウ)によるヘモグロビン測定は，あらかじめ試薬が充填された専用マイクロキュベットに10μLの末梢血をサンプリングしアナライザーにセットして，表示されるHb量を読み取る。Hb測定はアザイドメトヘモグロビン法により570nmと880nmからなる2波長様式によっている。

200mL献血申込者63名，400mL献血申込者62名において，血液比重測定と同時に自動血球計数装置(STKS)によるHb測定を行い両法の比較を行った。次に，平成14年4月1日から15年3月31日の間に比重法によって判定した献血者と平成16年4月1日から17年3月31日の間にHb法で判定した献血者において，本社採血基準による献血不適格者の比率，VVRの発症比率を比較検討した。また，献血申込者男性1,472名，女性771名のHb法によるHb濃度別度数分布を作成した。次に，STKSによって得られたMCV，MCH，MCHCとHb値の関係をみることにより，Hb法採用時の採血基準の妥当性を検討した。

Hb法(ヘモキュウ)を導入して1年6カ月経過した時点で，献血バスで実際に使用している看護師17名にアンケート調査を行った。

結　果

1．比重法とHb法の関係

400mL献血申込者のうち，血液比重1.053以上を示した献血者62名のHb値は12.6～17.3g/dLの範囲になり，その平均値±1SDは14.96±1.12g/dLであった。同様に比重1.052以上の200mL献血申込者63名は12.1～16.4の範囲で平均値は13.64±1.16g/dLであった。以上から，400mLの採血基準1.053以上またはHb12.5g/dL以上，200mLの採血基準1.052以上または12.0g/dL以上は両者ともcut off値として妥当であると考えられた。また，比重法の結果はHb値で幅広い範囲に分布し，定量性がないことも明らかとなった。

2．簡易Hb法と自動血球計算装置との相関

簡易Hb法(ヘモキュウ)と自動血球算定装置(Coulter STKS)によって測定した結果の相関を図1に示した。相関係数0.951(Y＝0.8893X＋1.59)の高い相関がみられた。

3．Hb法による献血者ヘモグロビンの度数分布

Hb測定の定量性を生かして献血者ヘモグロビンの度数分布が得られた（図2）。献血申込者の男性1,472名，女性771名の解析で最も頻度が高いのは，男性15.0～15.5g/dL，女性12.5～13.0g/dLであった。

4．比重法およびHb法による献血不適格者の比較

表1に比重法(平成14年4月1日～15年3月31日)とHb法(16年4月1日～17年3月31日)で判定した比重あるいはHb不足による献血不適格者の比率を示す。両者の年齢区分毎不適格率で大きな差異は認めなかった。200mL，400mLの合計において比重法の男性申込者は23,985名，うち不適格者数(率)151名(0.6%)，女性申込者は21,715名，うち不適格者4,404名(20.3%)，Hb法の男性申込者22,749名，不適格者数(率)151(0.6%)，女性申込者20,504名，不適格者数3,958名(19.3%)で，いずれも差異を認めなかった。400mL申込女性で40歳代では，多数の(26～30%)不適格者がみられた。また，400mL申込女性でHb12.5g/dL未満431名のうち10.0g/dL未満が43名(10.0%)，8g/dL未満も4名みられ，治療を必要とすると考えられた。

5．献血時副作用の比較

輸血副作用のうち採血基準が関係すると思われるvaso-vagal reaction(VVR)の発症率を比較した。ヘモキュウが用いられる献血バス200mL，400mL採血のVVRはHb法で男性が減少していたが，女性での頻度の差は認められなかった（表2）。いずれにしてもHb法を導入してVVRが増加することはなかった。

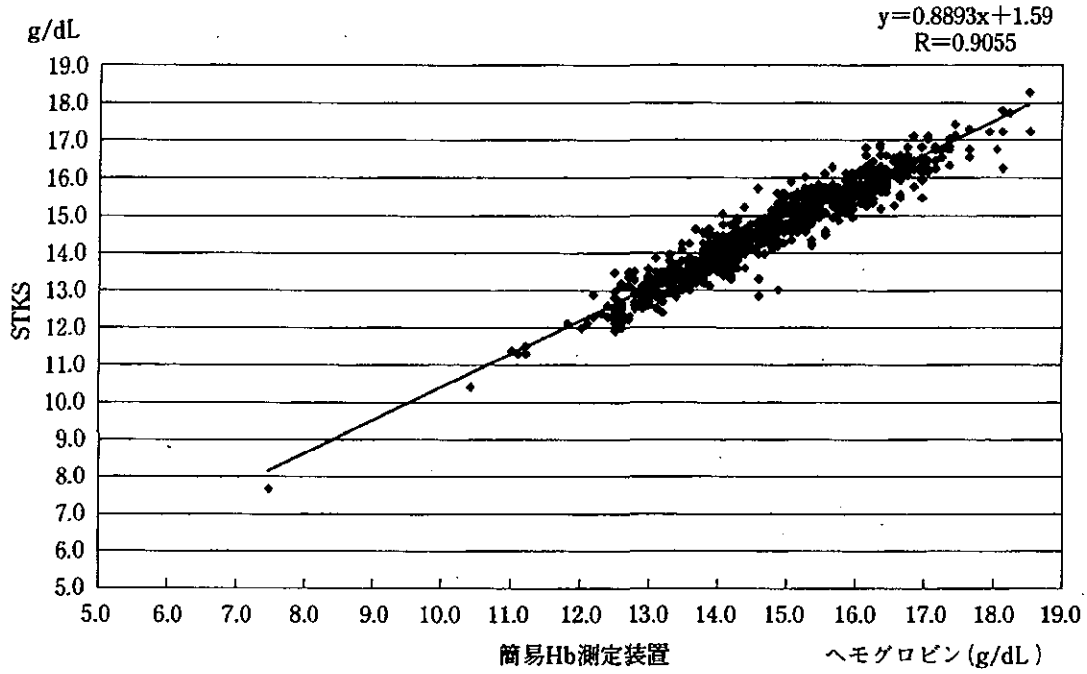
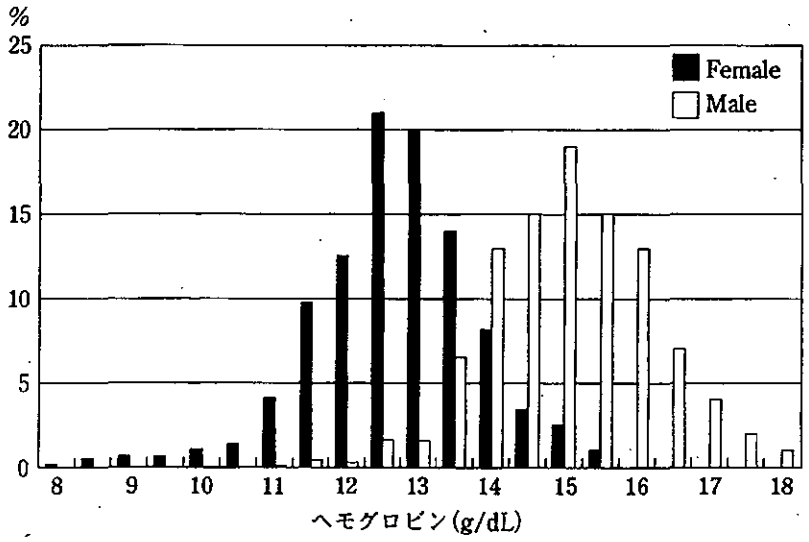


図1　簡易Hb測定装置(ヘモキュウ)と自動血球算定装置(STKS)との比較



献血申込者，男性1,472名，女性771名のヘモグロビン分布。男性で最も多いのは15.0～15.5g/dL，女性で最も多いのは12.5～13.0g/dLであった。

図2　献血申込者のヘモグロビン値の分布

6．ヘモグロビンと赤血球指数の関係

Hb値と赤血球指数(MCV，MCH，MCHC)の平均値の関係を表3に示す。Hbの低下に伴って赤血球指数も低下してくる。低下傾向が認められるのは男性で，MCV，MVH，MCHCともHb12.5g/dL未満から，女性12.0g/dL未満からであり，小球性低色素性の傾向が認められるのは男性が0.5g/dL高かった。以上から，Hbの低下にともなって赤血球は12.5～12.0g/dLで正色素性から小球性低色素性に変わることが判明した。

7．Hb低値による献血不適格者への対応

Hb測定の定量性を生かして献血者のHb値に応じた指導を行うこととした。Hb値10g/dL未満の献血者には医療機関を受診し治療を受けるよう医

表1　比重法およびHb法による献血不適格者の比較

			年齢区分	19～19	20～29	30～39	40～49	50～59	60～69	計
比重法	男性	200	申込数	1,091	286	346	550	517	210	3,000
			不適数	8	0	5	5	15	1	34
			不適率	0.7	0	1.4	0.9	2.9	0.5	1.1
		400	申込数	1,040	4,464	5,683	5,198	3,659	941	20,985
			不適数	5	14	21	29	30	18	117
			不適率	0.5	0.3	0.4	0.6	0.8	1.9	0.6
	女性	200	申込数	2,240	3,139	2,938	1,976	1,904	689	12,877
			不適数	399	602	689	448	239	67	2,444
			不適率	17.8	19.2	23.5	22.8	12.6	9.7	19.0
		400	申込数	601	1,923	2,097	1,923	1,771	523	8,838
			不適数	110	446	588	582	198	36	1960
			不適率	18.3	23.2	28.0	30.3	11.2	6.9	22.2
Hb法	男性	200	申込数	1,050	298	340	421	448	224	2,781
			不適数	7	1	1	4	5	8	26
			不適率	0.7	0.3	0.3	1.0	1.1	3.6	0.9
		400	申込数	1,147	4,183	5,510	4,832	3,373	923	19,968
			不適数	2	9	17	24	31	18	101
			不適率	0.2	0.2	0.3	0.5	0.9	2.0	0.5
	女性	200	申込数	2,422	2,579	2,825	1,762	1,510	612	11,710
			不適数	461	425	593	386	140	64	2,069
			不適率	19.0	16.5	21.0	21.9	9.3	10.5	17.7
		400	申込数	601	2,038	2,286	1,786	1,584	499	8,794
			不適数	176	454	596	467	163	33	1,889
			不適率	29.3	22.3	26.1	26.1	10.3	6.6	21.5

表2　比重法およびHb法によるVVR発症率の比較

		男　性	女　性
比重法	軽症	83	53
	重症	1	1
	計	84	54
	発症率（%）	0.44	0.43
Hb法	軽症	44	50
	重症	3	2
	計	47	52
	発症率（%）	0.27	0.44

師が指導し，12g/dL未満，10g/dL以上の献血者には食事指導用のパンフレットを作成し配布すると同時に，月に1度栄養士会による個別栄養指導も開設した。

8．Hb高値の献血者の頻度

採血可能であった男性1,472名，女性771名について（図2），Hb17.0g/dL以上の比率は，17.5＞Hb≧17.0：30例（3.0%），18.0＞Hb≧17.5：3例（0.3%），18.5＞Hb≧18.0：3例（0.3%），19.0＞Hb≧18.5：1例（0.1%）の計37例で，いずれも男性で女性にはみられなかった。また，赤血球指数は正常であった。

9．ヘモキュウ使用者のアンケート結果

ヘモキュウを使用している看護師のアンケート結果は以下のとおりであった。まず，利点としては①感染性廃棄物としての後始末が簡単になった（100%），②測定法が簡単である（74%），③献血者にHb値を示すことで説得力がある（63%），などであった。欠点としては①外気温や光線の影響

表3　Hbと赤血球指数の関係

Hb(g/dL)	男性			女性		
	MCV (fl)	MCH (pg)	MCHC (g/dL)	MCV (fl)	MCH (pg)	MCHC (g/dL)
16.0>Hb≧15.5	93±4	32±2	34±0			
15.5>Hb≧15.0	93±5	32±2	34±1	93±4	32±2	35±1
15.0>Hb≧14.5	92±3	32±2	34±1	92±3	32±1	35±0
14.5>Hb≧14.0	92±5	32±2	34±1	91±3	31±1	35±0
14.0>Hb≧13.5	92±4	32±2	35±1	91±1	32±1	35±0
13.5>Hb≧13.0	92±6	32±2	34±0	90±4	31±2	35±1
13.0>Hb≧12.5	92±5	32±2	34±1	90±3	31±1	34±0
12.5>Hb≧12.0	84±6	28±3	34±1	91±6	31±2	34±0
12.0>Hb≧11.5	83±5	28±2	34±0	87±5	30±2	34±1
11.5>Hb≧11.0*	77±0	25±0	33±0	83±5	28±2	34±0
11.0>Hb≧10.5				83±6	27±2	34±1

n=20 (*n=2)

を受けやすい(94%)，②測定に時間がかかる(94%)，③新たに精度管理が必要になった(69%)，などであった。

考　察

従来から採血基準として用いられている硫酸銅法による血液比重は，献血者を1.052未満，1.052以上(200mL)，1.053以上(400mL)と3区分して可否を判定するもので，各区分内に様々なヘモグロビン濃度が含まれる定性法であり，血液事業が始まって以来半世紀あまりずっと用いられている。しかしながら，比重法は測定者により±0.001程度のバラツキがあることが指摘されている[5]。一般に，赤血球沈降速度は，高温で促進，低温で遅延し補正が必要とされている[6]。佐野らの検討では，10℃で20℃に比し，0.001～0.002低い値，30℃で0.001～0.002高い値が得られるとしている[5]。また，Jamesら[7]は比重法の方がHb法よりも偽の適判定(false-pass)が多いことを証明した。以上から，現在のGMPに準拠した血液事業の理念からすれば，いつ，誰が，どう行っても一定した数値が得られるHb法の方が理想的であることは明白である。今回，簡易ヘモグロビン測定装置(ヘモキュウ)を導入して2年あまりになるので，従来の比重法との比較を様々の面から試みた。

ヘモキュウによるHb測定は，自動血球計算装置との相関で高い相関があり，とくに問題がないことが示された。これは過去の報告のとおりである[8)～10)]。また，比重法とHb法で献血不適格者の比率が異なるか否かを検討した。比重法とHb法の比較検討では，時期が異なるため厳密な比較ではないが，献血不適格者の増減はなく，現行の採血基準で有意の差はないと思われた。男性のVVRは，軽症でHb法の方が少なくヘモグロビン値以外の原因が考えられる。

Hb法の利点は，献血者のHb値を数字として表示できることであり，度数分布を知ることができる。この度数分布によって，女性献血申込者の中に，10g/dL未満の要加療者が不適格者の10%近くみられることが判明した。従来の比重法では，低比重以外の情報がなくそのまま放置されるわけであるが，Hb法ではHb値を提示できるので医療機関への受診を勧めることができた。また，10.0～12.5g/dLの方には栄養指導や食事のアドバイスができた。すなわち，貧血の予防と治療の双方を区別して指導することが可能である。

採血基準では，真性赤血球増加症(多血症)は採血しないことになっているが，比重法ではHb高値者を除外することができない。Hbを測定することによって，17g/dL以上は男性で3.7%にみられ，女性にはみられなかった。また，これらは白血球数，血小板数，赤血球指数が正常で，相対的(ストレス)赤血球増加症と考えられた。真性赤血

球増加症は白血球増加，血小板増加，小球性低色素性赤血球の傾向を示すことから，今回の検討で，Hb19.0g/dL未満で白血球数，血小板数，赤血球指数が正常であれば，採血可能と判断した．

今回Hb測定の定量性を生かして，従来の採血基準の妥当性を検討した。まず，比重法とHb法の比較で，1.052以上はHb12.1g/dL以上を，1.053以上はHb12.6g/dL以上を示した。また，Hb値の低下に伴って赤血球指数が低下してくるが，平均値の低下開始に相当するHb値は，小球性低色素性赤血球に移行する点で，女性の成分採血の際の可否判定に用いられているところである。低下開始点は男性12.5g/dL，女性12.0g/dLで，男性が0.5g/dL高かった。また，12.5g/dL以下の男性献血申込者の比率は0.6%と少なく，あえて男性の採血基準を引き上げる必要はないと考えられる。以上および米国FDAの基準[11]を勘案して，私たちはHb法の判定に男女差を設けず，従来の採血基準を用いることで問題がないと考えた。

今回用いたヘモキュウによるHb測定法は，英国のNational Quality Assessment Schemeの精度管理で正確性の保証が得られている[11]。また，静脈血採血と耳朶あるいは指尖毛細血管穿刺との間に差異があるとの議論がある。これは，サンプリングが不適切な場合で，血流が十分保たれ，穿刺が正確に行われた場合は有意の差がないとの見解が一般的である[12]。また，指尖穿刺の方が，静脈穿刺より正確性を欠くとの報告もある[13]。

献血の可否を決定する検査は，大別して，血液学的検査，生化学検査，感染症関連検査が行われている。生化学，感染症関連検査は1953年血液事業が開始されて以来，次々と改良，改善が加えられ，NAT検査の導入によって世界的水準を保つにいたっている。一方，採血基準の根幹である貧血の有無判定については，当初の硫酸銅による比重法が現在にいたるも用いられ，一向に改良の気配がない。その間，比重不足による献血不適格者は増加の一途であり，女性の400mL献血で本社の調査で，1990年 9.9%，2000年 18.1%，2003年21.3%である[14,15]。輸血によるウイルス性肝炎が激減したのと極めて対照的である。いうまでもなく比重法は測定者の目視による定性的判定法であり，温度・湿度の影響，使用滴下回数や蒸発，観察者の主観を無視できない。臨床の場においても，かつては比重法や比色法(ザーリ法)が用いられたが，現在はHb,ヘマトクリットに統一され，比重，比色によっている医療機関は皆無である。したがって，血液センターと医療機関の間で貧血に関するかぎり整合した議論が全くできていない。国は献血者の確保の推進として，献血の検査結果を健康診査，人間ドック，職場検診で活用するとともに，地域の保健指導に用いるよう求めているが[16]，比重で表示される献血不適格者の成績は利用し得ない状況である。以上から，血液センターにおいてもHb法を早急に導入し，定量的な評価によって献血者の健康を守る配慮をすべきである。

結　論

1．献血の可否判定にHb法を導入した。従来の比重法に比して，不適格者率，副作用発症率とも差異はなかった。

2．Hbおよび赤血球指数の度数分布から，従来の採血基準(400mL：12.5g/dL以上，200mL：12.0mg/dL以上)を用いて差し支えないことが判明した。

3．Hb低値の献血申込者に対して，Hb値に応じた栄養指導，医療機関への受診指導を行うことができた。

4．Hb法は定量性，客観性において比重法に優っており，Hb法に統一すべきであることを提言した。

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Statistical analysis of inappropriate results from current Hb screening methods for blood donors

Virge James, Keith F. Jones, Elizabeth M. Turner, and Robert J. Sokol

BACKGROUND: The objective was to apply statistical analysis to the false passes and fails that occur with the primary and secondary Hb-screening methods used at blood-donor sessions.

STUDY DESIGN AND METHODS: Venous samples from 1513 potential donors who had undergone primary $CuSO_4$ screening using capillary blood (Hb cut-offs: women, 125 g/L; men, 135 g/L) were tested at the session by a secondary method (HemoCue; cut-offs: women, 120 g/L; men, 130 g/L) and again at the base laboratory using another system (Beckman Coulter General S system), which generated the "true" Hb value.

RESULTS: False-pass and -fail rates for women and men, respectively, were 11.2 and 6.3 percent (women) and 5.2 and 1.8 percent (men) for $CuSO_4$; 1.9 and 3.7 percent (women) and 1.5 and 0.4 percent (men) for HemoCue; and 2.7 and 2.4 percent (women) and 1.8 and 0.2 percent (men) for a combined procedure that mimicked current practice of only testing $CuSO_4$ fails by HemoCue.

CONCLUSION: $CuSO_4$ Hb screening gives large numbers of false passes, particularly in women. Using venous samples, the majority correctly pass at the lower HemoCue cut-offs. The current dual-testing policy appears convenient for donor sessions, but because small percentages of false passes and fails represent large numbers of donors, every effort should be made to improve the accuracy of Hb screening.

Potential blood donors who attend donor sessions in the Trent Region (situated in the East Midlands, UK) initially undergo a health-screening survey. After passed this survey, they are subjected to primary Hb screening by the $CuSO_4$ gravimetric method carried out on finger-prick capillary blood, the cut-off levels for donation being set to correspond to Hb values of 125 g per L for women and 135 g per L for men.[1-3] To optimize blood-collection rates, UK regulations allow individuals who fail the primary $CuSO_4$ test to continue with the donation process if they pass the secondary Hb screening performed on a predonation venous sample using the HemoCue system.[2,4,5] With this method, donor acceptance or rejection is set at lower Hb levels: 120 g per L for women and 130 g per L for men.

We have recently become concerned that some donors are being bled inappropriately with these screening methods, whilst others with an acceptable Hb level are failing the tests. The purpose of this study is to determine whether this is the case and how to quantitate the problem by applying statistical analysis to the primary and secondary Hb-screening procedures used at our donor sessions, comparing them with a standard Hb measurement.

MATERIALS AND METHODS

Studies were carried out on potential volunteer blood donors attending routine donor sessions held throughout the Trent Region. All participants were fully informed of the purpose of the project and gave signed consent. The

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study had been formally approved by the Trent Multicentre Research Ethics Committee.

To avoid bias when selecting individual subjects for the study, a simple systematic sampling scheme was used at each donor session. Before screening, every n^{th} potential donor was approached for consent to enroll in the trial. If an individual declined, each subsequent person was approached until one consented. Subsequently, the next n^{th} individual was approached and so on. The value of n was controlled by the transfusion service staff at the screening station.

During quiet periods, n could be set at 1 so that every potential donor could be approached. During busier periods a larger value of n could be set, and at exceptionally busy times, sampling could be discontinued completely to avoid delaying the session.

Venous blood samples were collected from 730 women and 783 men who were potential donors who had undergone the primary $CuSO_4$ gravimetric Hb-screening test. All the venous samples, which included those from individuals who passed and failed $CuSO_4$ screening, were taken before any blood donation and tested at the donor session by the HemoCue method. These machines are calibrated to the International Council for Standardization in Haematology standard. The HemoCue results were used to construct a hypothetical screening test and were expressed as either a pass or fail in respect to cut-off Hb values of 120 g per L for women and 130 g per L for men.

A combined procedure that followed current practice was also applied. Thus, respondents were initially screened on the standard $CuSO_4$ test; those who passed were deemed to have passed the combined procedure. Those who failed the $CuSO_4$ test were considered to have passed the combined procedure if a subsequent HemoCue result was at least 120 g per L for women and 130 g per L for men.

The venous samples were tested again at the base laboratory with the Beckman Coulter General-S system (Beckman Coulter, High Wycombe, UK). These results were deemed to be the "true" Hb values against which the results of the $CuSO_4$, HemoCue and combined procedures could be compared.

Statistical methodology

In view of the known differences in Hb levels between men and women, data for the different sexes were analyzed separately. Because donor characteristics would be likely to vary considerably between individual donor sessions, any sampling biases with respect to donor age were adjusted by stratifying data for both men and women into quinquennial age bands and then testing to determine whether reweighting of the age-stratified data was necessary. This was achieved by chi-squared tests, comparing test and whole donor population data, and by a one-way ANOVA conducted for each of the women and men data sets with various Hb counts as the dependent variable and age category as the factor of interest.

The need to reweight was confirmed by both tests. A chi-squared value of 54.88 ($p < 0.0001$, $df = 10$) in respect to age distribution for women indicated that the test sample was severely under-represented in the 17 to 30 years age range, whereas for the age distribution for men, a chi-squared value of 18.60 ($p < 0.046$, $df = 10$) showed the test sample was under-represented in the 20-and-under ages. For the ANOVA, F values of 3.00 ($df = 10,724$, $p = 0.001$) for women and 2.23 ($df = 10,782$, $p = 0.015$) for men confirmed that in each case, Hb varied with age.

Reweighting to give reasonable donor population estimates was therefore carried out by calculating the stratified sample proportion of individuals possessing the appropriate attribute, together with its SE. This proportion is an unbiased estimator of the true population proportion possessing the desired attribute.[6,7] All values and standard errors were obtained using a statistical software package (SAS, SAS Institute, Cary, NC), and all proportions and standard errors were converted to percentages by multiplying them by 100.

The results of each screening test were compared to baseline Beckman Coulter Hb values of 125 g per L (women) and 135 g per L (men) for the $CuSO_4$ test and 120 g per L (women) and 130 g per L (men) for the HemoCue and combined procedures. The "false-pass" rates (i.e., the percentages of potential donors who would pass the relevant screening test but would fail the baseline Beckman Coulter test) were of particular interest.

RESULTS

Table 1 shows the results of the $CuSO_4$ Hb screening compared with the baseline Beckman Coulter values of 125 g per L (women) and 135 g per L (men). Table 2 (women)

TABLE 1. Results of $CuSO_4$ screening test compared with Beckman Coulter baseline at Hb levels of 125 and 135 g per L for women and men, respectively: population percentage estimates, stratum weighted by age

		Women		Men	
$CuSO_4$ result	Beckman Coulter result	Estimated percentage	SE	Estimated percentage	SE
Fail	Fail	12.4	1.3	3.9	0.7
Fail	Pass	6.3	0.9	1.8	0.5
Pass	Fail	11.2	1.3	5.2	0.8
Pass	Pass	70.1	1.8	89.0	1.1
Correct classification (%)		82.5		93.0	

TABLE 2. Results of screening tests for women compared with Beckman Coulter baseline Hb level of 120 g per L: population percentage estimates, stratum weighted by age

Screening test result	Beckman Coulter test result	$CuSO_4$ Estimated percentage	SE	HemoCue Estimated percentage	SE	Combined Estimated percentage	SE
Fail	Fail	6.0	1.0	6.0	0.9	5.3	0.9
Fail	Pass	12.7	1.3	3.7	0.7	2.4	0.6
Pass	Fail	1.9	0.6	1.9	0.6	2.7	0.7
Pass	Pass	79.4	1.6	88.4	1.3	89.6	1.2
Correct classification (%)		85.4		94.4		94.9	

TABLE 3. Results of screening tests for men compared with Beckman Coulter baseline Hb level of 130 g per L: population percentage estimates, stratum weighted by age

Screening test result	Beckman Coulter test result	$CuSO_4$ Estimated percentage	SE	HemoCue Estimated percentage	SE	Combined Estimated percentage	SE
Fail	Fail	2.2	0.5	2.0	0.5	1.7	0.5
Fail	Pass	3.6	0.6	0.4	0.2	0.2	0.2
Pass	Fail	1.3	0.4	1.5	0.4	1.8	0.5
Pass	Pass	93.0	0.9	96.2	0.7	96.3	0.7
Correct classification (%)		95.3		98.2		98.0	

and Table 3 (men) give the results of the individual $CuSO_4$ and HemoCue screening tests and of the combined procedures, comparing them with Beckman Coulter baseline values of 120 g per L for women and 130 g per L for men.

DISCUSSION

The UK requires a predonation Hb screening to be carried out on all potential donors, and only individuals with an Hb level at or greater than 120 g per L for women or 130 g per L for men proceed to donate.[8,9] However, accuracy of Hb-screening procedures at blood-donor sessions may be a problem, and our study, by quantitating this, provides data for informed debate (Tables 1-3). It also shows how such studies may be approached in the future. In the present case, statistical analysis without the need to reweight would have required an even larger sample size. This would have been impractical because the length of time it took to obtain the informed consent required by the Ethics Committee had a deleterious effect on the efficient running of many donor sessions, particularly busy ones. As a result, the test sample was not representative of the donor population as a whole. This, and because of clustering of sessions, made it important to reweight the data so that the test population truly reflected the whole donor population with regard to factors that affect screening outcomes, such as age and sex. Reweighting necessitated expressing the results in proportions (percentages) rather than as raw figures.

The primary purpose of Hb screening is donor protection, preventing an anemic individual from exacerbating their condition with potential ill effects. The secondary purpose is to ensure the patient receives a minimum infused Hb dose per RBC transfusion. Screening also acts as a nonspecific measure of the general health of the donor and may identify some conditions which could potentially be harmful to the recipient.[2]

Protocols with set cut-offs are not without problems: they cause administration and quality control costs, donor inconvenience, expense and anxiety as a result of medical follow-up of deferrals, as well as permanent loss of donors. Additionally, cut-offs need to be set to maximize donor safety but be balanced against the system's ability to collect an adequate blood supply, a particular concern when trying to exclude women with iron deficiency. Hb reference ranges vary with age, race, and sex, and are affected by altitude, smoking, and the site from which the sample is taken.[2,10] It has been suggested that, rather than having set cut-off values, a standard should be established whereby blood donations contain a "minimum Hb dose" of 50 g; this would allow individual blood centers to evaluate the appropriate safe Hb cut-off for their donors.[2]

The $CuSO_4$ gravimetric test has been the method of choice in the UK for primary Hb screening of potential blood donors for many years. It is fast, inexpensive, does not require a venous sample, and, although rigorous training and constant monitoring of session staff is necessary, does not need trained laboratory personnel. It does not, however, give a quantitative result, has a subjective endpoint, is difficult to quality control, and presents problems with the disposal of biohazardous material.[2] Although very anemic donors can, on occasion, pass the $CuSO_4$ test,[11] early reports suggested that the $CuSO_4$ method tended to give inappropriate failures, and thus significant numbers of such failed donors could be recovered with a revised Hb range or if an alternative screening method was applied.[2]

This is the rationale for the primary and secondary Hb-screening tests used in the UK. It is supported by several studies that show that many units of blood can be collected that would otherwise be lost. Figures of between 11 and approximately 50 percent recovery of donations with secondary screening are quoted.[2,12-14] The lowering of the cut-off Hb values for the secondary screening also helps. In one study, 29 percent of failed

donors passed the secondary test (HemoCue) at Hb cut-offs of 125 and 135 g per L (women and men, respectively); but with the cut-offs reduced to 120 and 130 g per L, this figure increased to over 44 percent.[14]

Initially there was concern that such a high proportion of donors, 11.2 percent of women and 5.2 percent of men in the present study, inappropriately pass the $CuSO_4$ screening test (Table 1); and, it should be noted that at these higher baselines, a HemoCue screening test would have considerably reduced the false-pass rates. Thus, the high false-pass rates in Table 1 do not mean that there is a similar proportion of donors being bled inappropriately. Examination of Tables 2 and 3 show that at baselines of 120 and 130 g per L, the $CuSO_4$ screening tests exhibit conservative false-pass rates similar in magnitude to the HemoCue procedure; only 1.9 percent of women and 1.3 percent of men who pass the $CuSO_4$ test have Hb levels less than 120 and 130 g per L, respectively, and should have been rejected as donors, indicating that, in practice, the current $CuSO_4$ cut-off levels can be tolerated. (The higher false-fail rates with the $CuSO_4$ test in Tables 2 and 3 are due to the higher cut-off settings.)

Tables 2 and 3 show that, had it been used in isolation, the HemoCue procedure would have classified 94.4 percent of women and 98.2 percent of men correctly at Hb levels of 120 and 130 g per L, respectively. Although this would appear to offer an improvement on the $CuSO_4$ test (set at 125 and 135 g/L for women and men, respectively), at present, the HemoCue procedure would be difficult to apply as a primary screening test on every potential donor because venous samples are preferred at our sessions. (HemoCue can be used on finger-prick blood, but capillary samples are known to give unreliable results[12,15] with all technologies and are thus unsuitable for secondary screening of blood donors.) Taking a venous sample from each person before donation could prove unacceptable to donors, slow down the donation process, as well as increase costs. Many studies have shown the excellent correlation between HemoCue and standard photometric methods in the laboratory,[14-18] and indeed we found the same in a prestudy evaluation of the analyzers used in this project. (In addition, HemoCue has a theoretic advantage over other photometric methods in that it incorporates a turbidity control, allowing more accurate results on lipemic samples.[2]) However, previous work has shown that accurate measurement of Hb level using the HemoCue system is difficult to achieve in the field.[19,20] There are several possible reasons for this; they include inadequate mixing of specimens,[19] sampling techniques, and operator performance,[20] rather than problems inherent to the methodology, and studies have shown that meticulous attention to sample mixing, mode of filling the cuvette, and continuous monitoring and training of staff can help to improve performance.[20]

Tables 1 through 3 show that the $CuSO_4$ and HemoCue screening tests are less accurate, compared with Beckman Coulter values, for women than men, with false-pass and -fail rates being higher for women than males. This has been recognized previously, and it was suggested that such differences in screening-test performance can be explained by the distribution of women and men donor Hb levels relative to the cut-off values for acceptance.[21] A comforting factor in our study, in spite of its relatively small sample size, is that the lowest false-pass levels were 109 g per L for women and 123 g per L for men. Although it was inappropriate to collect blood from such individuals by our current guidelines, these figures are not alarming; there were no clinical sequelae, as far as we are aware, in the donors, and the recipients would have obtained an adequate amount of Hb. The donors who had been inappropriately bled were contacted and informed.

The results of the "combined" screening procedures (Tables 2 and 3), which mimic current practice at donor sessions, respectively, show false-pass and false-fail rates of 2.7 and 2.4 percent, respectively, for women and 1.8 and 0.2 percent, respectively, for men. The false-pass rates for the combined procedure slightly exceed those for the HemoCue alone: 95-percent CIs for these differences in rate are approximately 1.6 and 0.8 percent for women and men, respectively. On the other hand, the false-fail rates on the combined procedures are slightly smaller than for HemoCue alone, with 95-percent CIs for these differences in rate of approximately 2.3 and 0.6 percent for women and men, respectively. It should be noted here that any false pass on HemoCue alone would also pass the combined procedure, regardless of the $CuSO_4$ test result. Consequently, the false-pass rate for the combined procedure must be at least as great as that for HemoCue alone.

In summary, compared with HemoCue alone, current practice trades off a slightly higher false-pass rate against a slightly lower false-fail rate, and so is still reasonable in spite of the error rates in the initial $CuSO_4$ screen, and they need not be changed until the problems of accurately measuring Hb in the field can be reduced or eliminated. Because approximately 2 million donations are collected annually in the UK, even small percentages of false passes and false fails at the Hb-screening stage represent a large number of individuals, and, consequently, any improvement in accuracy of Hb screening will be welcome.

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原　著

短期間の術前自己血貯血法の検討

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はじめに

医療レベルの向上に伴いその質が問われる現在，手術における同種血輸血の回避は患者の当然の選択肢となりつつある。心大血管手術においては，早くから多くの施設が積極的に自己血輸血を導入することにより，無輸血達成へ向けて努力している。無輸血達成率は自己血貯血量および貯血期間に比例するのは周知の事実である。しかし心大血管手術においては，長期の待期期間を設けられる場合がそれほどなく，術前の長期入院や通院も患者の負担が大きい。そこで当科では可及的に貯血期間を短縮し，貯血量を最大限に準備できる方法として，術前8日からの貯血開始を基本的に施行してきた。今回この貯血法を施行した186例を貯血期間が9日以上であった群と7日以下であった群とで比較検証し，また同種血輸血に至った例と無輸血例とを要因別に比較し，その成績と限界について検討した。

対象・方法

当科で1996年9月から2003年2月までに人工心肺を使用した心大血管手術例は427例であった。そのうち自己血貯血を施行したのは258例で，すべての人工心肺使用例中60.4％，全待期手術中73.5％あった。対象手術は冠動脈バイパス術，弁膜症手術，胸部大動脈瘤手術，先天性心疾患手術，その他であった。自己血貯血の適応は，原則として年齢が80歳以下で入院時Hbが10.0 g/dl以上の待期手術としており，非適応は感染性心内膜炎患者，透析患者，高度心不全患者，左主幹部病変を伴う不安定狭心症患者としている。貯血は全例入院中としている。自己血採血のプロトコールは，毎回採血前にHb値を測定し，10.0 g/dl以上であれば1週間ごとに400 ml採血している。保険適応内であればエリスロポエチン製剤（EPO）を6,000単位静脈投与を隔日投与，もしくは24,000単位の皮下注投与を隔週に投与した。また，鉄剤としてフマル酸第一鉄305 mgを毎日内服投与した。ここで論ずる貯血期間とは，初回自己血貯血開始日より手術前日までの日数とした。待期手術の患者は8日前に入院し，入院日に400 mlの貯血を行い，1週間後の手術前日にも400 ml貯血する（EPO投与は皮下注の場合は初回の1回のみ，静注の場合は計3回投与となる）という貯血法を186例に施行した（M群）。準緊急手術症例や心房中隔欠損症などの軽症例では貯血期間が7日以下で，400 mlのみの貯血で手術に臨み，これらは44例であった（S群）。術前の精査などで術前8日以前より入院可能であった患者においては，手術が決定した時点から貯血を開始した。このような症例で9日以上の貯血期間が得られたのは28例であった（L群）。これらの3群の無輸血率を比較するとともにM群において同種血輸血に至った例と無輸血例を性差，年齢，体重，EPO使用量，入院時Hb値，手術直前Hb値，人工心肺時間，手術時間，術式についておのおの要因別に比較した。検討において，

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術後から退院まで同種血輸血を施行しなかったものを無輸血例とした。手術時は全例回収洗浄式自己血輸血装置を用い，術後約12時間はドレーン排液も回収した。人工心肺は無血体外循環で手術終了時回路内血液を返血した。各群の数値は平均値±標準偏差で表し，統計学的検定はstudent-t，χ^2，分散分析を用い，p値＜0.05を有意差ありとした。

結果

各群の手術術式の内訳，およびその無輸血率は表1に示した。冠動脈バイパス術に貯血期間が短い傾向がみられたが，手術を急ぐ必要のある例が多かったためと思われた。おのおの3群間に有意差は認めなかったが，冠動脈バイパス術の無輸血率が低く，貯血期間の短い群にその傾向が強かった。各群の性差，年齢，体重，貯血期間，総貯血量，EPO使用量，入院時Hb値，手術直前Hb値，人工心肺時間，手術時間，無輸血率を表2，表3に示した。S群の貯血期間は1～7日，平均5.5±1.6日で，L群が9～28日，平均15.8±5.6日であった。総貯血量はM群で400～800 ml，平均770±103 ml，S群がすべて400 ml，L群が800～1,600 ml，平均1,029±249 mlであった。性差，

表1　対象手術と無輸血率

術式	例数			無輸血率		
	M群	S群	L群	M群	S群	L群
CABG	72 (63.7%)	29 (25.7%)	12 (10.6%)	72.2%	55.2%	91.7%
VD	76 (78.4%)	8 (8.2%)	13 (13.4%)	90.8%	87.5%	92.3%
TAA	14 (87.5%)		2 (12.5%)	78.6%		100 %
CHD	12 (63.2%)	7 (36.8%)		100 %	100 %	
その他	12 (92.3%)		1 (7.7%)	66.7%		100 %

CABG:冠動脈バイパス術，VD:弁膜症手術，TAA:胸部大動脈瘤手術
CHD:先天性心疾患手術

表2　対象群の比較1

	例数	性差 (M/F)	年齢 (years)	体重 (Kg)	貯血期間 (days)	総貯血量 (ml)	EPO投与量 (×1000 IU)
M群	186	119/67	63.1 ± 12.9	56.3 ± 9.1	8.0 ±0.0	770 ±103	20.9 ± 5.9
S群	44	28/16	62.7 ± 10.4	57.3 ±10.9	5.5 ±1.6	400 ± 0	3.8 ± 7.4
L群	28	18/10	61.6 ± 9.1	59.6 ± 9.6	15.8 ±5.6	1029 ±249	29.4 ±15.3

表3　対象群の比較2

	入院時Hb (g/dl)	手術直前Hb (g/dl)	人工心肺時間 (min.)	手術時間 (min.)	無輸血率	p value
M群	13.0± 1.4	11.0± 1.4	114 ± 70	246 ± 124	81.7%	0.047*
S群	12.9± 1.7	11.4± 1.4	99 ± 49	242 ± 155	68.2%	
L群	13.5± 1.3	11.2± 1.4	109 ± 35	223 ± 53	92.9%	0.231

年齢，体重，入院時Hb値，手術直前Hb値，人工心肺時間，手術時間において3群間に有意差は認めなかった。M群の無輸血率は81.7%で，S群の68.2%と比べ有意に高く（p=0.047），L群の92.9%と比べ低いものの有意差はなかった。M群において同種血輸血例と無輸血例を，性差，年齢，体重，貯血量，EPO使用量，入院時Hb値，手術直前Hb値，人工心肺時間，手術時間の各要因で比較したところ（表4），年齢，体重，入院時Hb値，手術直前Hb値，人工心肺時間，手術時間において有意差を認めた。M群の内で，2回目の採血前にHb値が10.0 g/dl以下，もしくは全身状態不良，採取困難な例で800 ml貯血できなかった例は15例（8.1%）あり，その無輸血率は66.7%と低い傾向にあったが，800 ml貯血例の無輸血率と有意差は認めなかった。また，術後出血再開胸や再手術を施行した例は9例あり，その無輸血率は44.4%と有意に低かった。術式では冠動脈バイパス術と弁膜症手術を比較すると前者で無輸血率が有意に低値であった（表5）。なお，全例において自己血廃棄例はなかった。

考察

心臓血管外科領域においては，他の領域に先がけて早くより同種血輸血回避に対する努力が試みられ，年々手術成績が向上するに伴い無輸血手術に対する関心は広がりつつある。無輸血達成へのもっとも効果的な方法として，術前貯血式自己血輸血が施行されるようになり[1]，人工心肺を使用する心大血管手術においては，現在ほぼ一般的な手法とされている[2]。しかしその適応や貯血期間

表4　M群における輸血例と無輸血例の要因別比較

要因		輸血例	無輸血例	P値
男女比	(M/F)	17/17	102/50	0.060
年齢	(years)	69.4 ± 8.2	61.7 ± 13.3	0.002 *
体重	(Kg)	51.7 ± 8.5	57.3 ± 9	0.001 *
貯血量	(ml)	741 ± 144	777 ± 91	0.067
EPO使用量	(×1000IU)	21.9 ± 4.6	20.6 ± 6.1	0.269
入院時Hb	(g/dl)	12.5 ± 1.5	13.1 ± 1.4	0.032 *
手術直前Hb	(g/dl)	10.0 ± 1.1	11.2 ± 1.4	<0.001 *
人工心肺時間	(min.)	173 ± 123	101 ± 42	<0.001 *
手術時間	(min.)	381 ± 211	216 ± 64	<0.001 *

表5　M群における無輸血率に影響する因子

	例数	輸血例	無輸血率	p value
800ml未完遂	15 (8.1%)	5	66.7%	
800ml完遂	171 (91.9%)	29	83.0%	0.221
再開胸(+)	9 (4.8%)	5	44.4%	
再開胸(-)	177 (95.2%)	29	83.6%	0.012 *
冠動脈バイパス術	72 (38.7%)	20	72.2%	
弁疾患手術	76 (40.9%)	7	90.8%	0.003 *

に関しては，施設間で一定していないのが現状である。施設間で手術方法，成績，麻酔科の方針，病院での輸血に対する取り組み，マンパワー等，あらゆる面で異なるので，自己血貯血に対する方針にも若干差が見られて当然である。長期の貯血期間を設け，多量の貯血量を準備できれば，無輸血率が飛躍的に向上するのは当然のことである。しかし心大血管手術においては，それほど長期の待期期間を経て手術となる症例は少ない。また病院の稼働率を考慮した場合，術前の入院期間は制約を受けるのが現状である。外来通院での貯血は理想的であるが，輸血部のようなユニットが独立している大規模な施設以外では，マンパワーの制限があったり，心疾患患者での外来採血は不安も多く，患者の術前の精神的負担も大きい。したがって，当施設もそうであるが，入院後の自己血貯血が原則となる。自己血貯血にEPO投与が効果的であることは多く報告され[3,4]，ほとんどの施設で使用されているが，保険基準で貯血量が800 ml以上で1週間以上の貯血期間が必要と定められている。この基準を満たし，かつ最短の貯血期間を設けるため，当科では術前8日からの入院および貯血開始を施行してきた。無輸血率は81.7％とある程度許容される成績ではあるが，やはり貯血期間の長い症例と比較すると，有意差はないものの低い傾向にあった。しかし貯血期間が1週間以内で，400 mlしか貯血できなかった症例（S群）よりは有意に良好な無輸血率であった。開心術にあえて貯血式自己血輸血をせず，良好な結果を示した報告もある[5]。しかし同種血輸血の安全性が100％確立されていない現在，多少とも自己血貯血やEPO投与の機会があり，無輸血の可能性が1％でも増えるならば，その選択肢は提供されるべきであろう[6]。この貯血法で同種血輸血に至った症例は，無輸血例に比べ，高齢で低体重，術前のHb値が低いという結果は当然考えられ，人工心肺時間および手術時間の長い例ほど輸血率が高いという結果も他の報告と同様であった[7]。この短期間で800 mlの採血は手術直前のHb値が他の報告に比べ著しく低く，平均が11.0 ± 1.4 g/dlであった。つまりEPO投与で，十分な造血効果が発揮されるには期間が短すぎるかもしれない。エリスロポエチンによる造血刺激を促すには最低3週間必要という報告も見られる[8]。しかし，われわれは以前1週間でも造血効果は有意に上がっている結果を報告している[4]。初回の開心術における貯血量は800 mlが至適であるという報告も見られる[9]が，その800 mlを採血した後の手術直前Hb値がどれだけ保たれているかも重要な要因と思われる。これは貯血期間と造血能に依存し，この術直前Hb値の低さはこの貯血法の限界であろうと考える。しかし術前の患者の全身状態に影響がない限り，手術前日でも400 mlの貯血は無輸血手術に有効と考える。出血再開胸や他の再手術を要した症例の無輸血率は著しく低かったが，これらの症例は貯血期間，量に関係なく同種血輸血を要したと考えられるので，初回手術に限れば無輸血率はもう少し良好と思われた。また，冠動脈バイパス術の無輸血率が弁膜症手術に比べ有意に不良であったのは，前者の方がバイパスグラフト採取などで有意に手術時間が長いこと，術前に抗凝固剤が投与されている例も多く，出血量が多いためと考えられた。この貯血法の妥当性を検討した場合，単独弁膜症手術，心房中隔欠損閉鎖術など，比較的人工心肺時間や手術時間の短い症例であれば，ほぼ満足すべき結果が得られる方法と思われた。少量の貯血量で十分と予想されても予想外に侵襲，出血が多くなることもあり，無輸血手術を第一義的に考えれば「最大限の貯血期間を設け，できうる限り多量の貯血を行う」ということに尽きると思われる。しかし，同種血無輸血を目指すあまり，患者に術前の負担を過剰にかけたくないという方針で，当科ではこのような貯血法を基本とした。すべての開心術に有効とはいえないまでも，長期の待期期間が設けられない症例に対し，比較的短期間の術前入院および貯血期間でほぼ良好な無輸血率を達成できる一手法として，今後も活用したいと考える。

結語

人工心肺を用いる心大血管手術において，貯血期間8日で800 mlを貯血する自己血貯血法を186例に施行し，無輸血率81.7％と比較的良好な成績を得られた。

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原　著

自己血400 ml採血後2週間のヘモグロビン値の回復度に与える影響因子の検討

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はじめに

我々は顎矯正手術の一つである上下顎同時移動術に対して，400 ml採血の貯血式自己血輸血と希釈式自己血輸血を併用し，同種血輸血を100 %回避している。本手術の対象となる患者は若くて健康であるが，低体重の女性が多いという特徴がある。当院では，自己血採血によって低下するヘモグロビン値（Hb値）をはじめとする種々の因子の回復を考慮し，予定手術日の3週間前に採血することを原則にしている[1]。しかし，患者の都合などにより術前2週間の採血を余儀なくされる症例もある。今回，手術2週間前に採血を行った患者のヘモグロビン値の回復度に影響を与える因子について検討した。

対象・方法

福岡歯科大学付属病院において，文書と口頭にて自己血輸血の説明を行い同意が得られ，手術の約2週間前に400 mlの自己血採血を施行した患者47名（男性13名，女性34名）を対象とした。自己血採血当日の採血前に検査血を採取し，Hb値，血清鉄値，フェリチン値，総鉄結合能（TIBC），不飽和鉄結合能（UIBC），血清総蛋白量（TP），血小板数（Plt），白血球数（WBC）を測定した。400 mlの自己血採血を行った後，フェジン® 80 mgを加えた1000 mlの晶質液輸液または300 mlの膠質液輸液を行い，さらに採血翌日から2週間，200 mg/dayの鉄剤を経口投与した[2]。入院後，手術前日に検査採血を行い，この時のHb値を術直前Hb値とした。循環血液量は，体格や性別によって大きく異なる[3]が，当院では，一律400 mlの採血を行っているため，採血後のHb値低下の程度も異なると考えられる。そこで，400 mlの自己血採血後，1000 mlの晶質液輸液または300 mlの膠質液輸液を行った時のHb値を予測できる，当科で用いている計算方法[4]を用いて採血後予測Hb値を算出した。循環血液量（CBV）をOgawa式[5]にて求め，図1に示す式にて採血後予測Hb値および予測Hb値の採血前Hb値に対する割合（α）を算出した。また，実測した術直前Hb値の採血前Hb値に対する割合（β）を求めた。さらに採血前の各検査データとβとの間の相関関係の有無を検討した。統計処理には分散分析（多重比較検定：Scheffe法），χ^2検定およびピアソンの相関係数の検定を用い，危険率1 %未満を有意差有りとした。

結果

対象患者全員の予測Hb値を算出したところ，その平均値は12.4 g/dlであった。採血前の平均Hb

福岡歯科大学診断・全身管理学講座麻酔管理学分野

・ 循環血液量(CBV) (g) $= \begin{cases} \text{男性}：0.168\times(\text{身長(m)})^3+0.05\times\text{体重(kg)}+0.444 \\ \text{女性}：0.25\times(\text{身長(m)})^3+0.063\times\text{体重(kg)}-0.662 \end{cases}$

・ 採血後予測Hb値 (g/dl) $=$ 採血前Hb値 (g/dl) $\times \dfrac{(\text{CBV}-0.4)}{\text{CBV}}$

・ $\alpha = \dfrac{\text{採血後予測Hb値 (g/dl)}}{\text{採血前Hb値 (g/dl)}}$

・ $\beta = \dfrac{\text{術直前Hb値 (g/dl)}}{\text{採血前Hb値 (g/dl)}}$

図1　αおよびβの算出方法
α：採血後予測Hb値の採血前Hb値に対する割合
β：実測した術直前Hb値の採血前Hb値に対する割合

表1　A群およびB群の患者背景と採血前検査値

		A群 (n=22)	B群 (n=25)
男女比	(男:女)	5 : 17	8 : 17
年齢	(歳)	23.1±6.9	24.2±3.9
身長	(cm)	162.1±7.9	163.8±11.1
体重	(kg)	53.9±7.3	57.7±13.3
血清鉄	(μg/dl)	88.1±31.1	84.8±27.3
フェリチン	(ng/ml)	51.6±37.5	49.9±57.6
総鉄結合能(TIBC)	(μg/dl)	281.5±38.8	288.4±31.1
不飽和鉄結合能(UIBC)	(μg/dl)	193.4±53.9	205.0±40.7
血漿総蛋白量(TP)	(g/dl)	7.1±0.4	7.1±0.4
血小板数	($\times10^4$/μl)	21.4±5.6	23.4±5.3
白血球数	($\times10^2$/μl)	54.4±11.2	62.2±14.2
採血前Hb値	(g/dl)	13.3±1.2 ＊	14.3±1.3

＊p<0.01　(Mean±SD)

A群：αが0.035以上増加した患者
B群：αの増加が0.035未満であった患者

値は13.8 g/dlであったので，αの平均は0.894となる。また，実測の術直前Hb値は12.8 g/dlであったのでβの平均は0.929となり，対象全員の（β－α）は，採血後2週間で平均0.035上昇していたことになる。このことからαが0.035以上増加した患者をA群とし，0.035未満であった患者をB群として比較検討した。A群は22名，B群は25名であり，群間の男女比，年齢，身長，体重には有意差は認められなかった。両群間の血清鉄値，フェリチン値，TIBC，UIBC，TP，Plt，WBCに

表2　C群およびD群の患者背景と採血前検査値

		C群 (n=5)	D群 (n=42)
男女比	(男:女)	2 : 3	11 : 31
年齢	(歳)	24.2±11.4	23.6±4.6
身長	(cm)	164.6±8.0	162.8±9.9
体重	(kg)	56.6±4.4	55.8±11.5
血清鉄	(μg/dl)	106.0±46.2 *	84.0±26.0
フェリチン	(ng/ml)	65.2±41.4	48.9±49.9
総鉄結合能(TIBC)	(μg/dl)	278.8±45.6	285.9±33.8
不飽和鉄結合能(UIBC)	(μg/dl)	172.8±86.3 *	202.7±41.0
血漿総蛋白量(TP)	(g/dl)	7.0±0.4	7.1±0.4
血小板数	($\times 10^4$/μl)	20.2±8.1	22.8±5.1
白血球数	($\times 10^2$/μl)	49.8±11.0	59.5±13.4
採血前Hb値	(g/dl)	13.2±1.8	13.9±1.3

* $p<0.05$　(Mean±SD)

C群：βが1以上であった患者
D群：βが1未満であった患者

有意差は認められなかったが，採血前Hb値はA群で有意に低い値を示した（表1)。しかし，採血前Hb値とβの相関関係については，決定係数（0.069)，相関係数（－0.093）と共に低く，相関関係は認められなかった。

次に，採血後2週間の術直前Hb値が採血前Hb値以上に増加したC群（$\beta \geqq 1$）とそれ以下にしか回復しなかったD群（$\beta < 1$）に分配し，比較検討した。C群は5名，D群は42名であった。両群間の患者背景に有意差は認められなかったが，血清鉄およびUIBCに有意差を認めた（表2)。しかし，採血前Hb値を含むその他の採血前検査値に差は認められなかった。血清鉄およびUIBCとβとの相関を見ると，相関係数はそれぞれ0.356，－0.359と低く，両者の間には，弱い相関関係しか認められなかった（表3)。

表3　患者背景および採血前検査値とβとの相関関係

	相関係数	p値
年齢	-0.199	0.226
身長	0.235	0.150
体重	0.135	0.414
血清鉄	0.356	0.026
フェリチン	0.227	0.166
総鉄結合能(TIBC)	-0.207	0.208
不飽和鉄結合能(UIBC)	-0.359	0.024
血漿総蛋白量(TP)	-0.047	0.780
血小板数	-0.096	0.564
白血球数	-0.301	0.062
採血前Hb値	-0.093	0.574

考察

上下顎同時移動術時には輸血が必要となるような出血が起こる場合があり，患者のQOLを考慮すると有効かつ安全な自己血輸血が望まれる。当院における本術式の出血量は，大部分の症例で600～800 mlであるが，1,000 ml以上出血する症例もあるため[1]；確実に同種血輸血を回避するために

は自己血貯血は必須である。我々は，本法に対して400 mlの自己血貯血を行っているが，他施設においても術前の貯血量は400 mlが主流となっている[6]。800 ml以上の貯血を行わないとエリスロポエチンは健康保険の適応外となるため使用できず，採血による貧血を回復させるためには，十分な期間をとる必要性がある。顎矯正外科手術は待機手術であり，大部分の患者は若く，健康状態は良好であるため外来採血が可能で，通常は比較的長く術前貯血期間をとることができるが，患者の時間的な都合や手術日の決定が遅延することなどにより期間を短縮せざるをえない場合もある。他領域の手術においては術前貯血量が800 ml以上必要となるような症例ではエリスロポエチンを併用して手術1週間前まで採血を行い，Hb値の低下もほとんど認められなかったという報告がある[7]。一方で，多少の貧血があっても術前400 ml貯血をした胃全摘術において100 %術中の同種血輸血が回避できたという報告[8]もあり，上下顎同時移動術を受ける患者では400 mlの貯血と術前貯血期間を十分とることで同種血回避率100 %をより確実に維持できると考えられる。

幹細胞の分化が始まって末梢血中に網状球として出現するのに要する期間は，約8日であり[9]，健康成人の生理的赤血球産生量は，全血量に換算すると1日30～40 mlである[10]。さらに，有効な造血刺激が加わると赤血球産生予備能は最大5～6倍まで亢進する[11]。これらのことからは，2週間の貯血期間は貧血回復には十分な期間であるように考えられる。しかし，今回検討した47例中400 ml採血後2週間で完全に元のHb値に回復したものは5例のみであったことから，臨床的には，採血から手術までの期間が2週間以上あることが望ましいと考えられる。症例数が少なかったこともあり，予測因子を明確にすることはできなかったが，採血前のHb値の低い症例の方がβが高かったことから，採血前Hb値が低いほど赤血球造血能が亢進する可能性が示唆された。これは，鉄欠乏性貧血患者は，貯血開始1～2週の早期から著明な造血能の亢進がみられるという新名主らの報告[12]と一致する。この理由として貧血患者では，貧血のない患者と比較して採血後の内因性エリスロポエチン濃度が高い[11]ことが考えられる。しかし，造血には，エリスロポエチンとともに材料となる鉄が必要である。C群の5症例は，D群の42症例と比較して，採血前Hb値には差がなく，血清鉄およびUIBCに有意差を認めた。フェリチン値には有意差は認められなかったが，その平均値はD群が48.9 ng/mlであったのに対しC群では65.2 ng/mlと高い傾向にあった。これは，貧血患者の方が早期のHb値の回復は速いが，完全に回復するためには貯蔵鉄量が関係する可能性がある。採血後全症例に量的には十分な鉄剤を投与しているので，採血前の貯蔵鉄量が関係する可能性は少ないように思われるが，鉄の吸収には個人差があり，採血前に貯蔵鉄量の多い患者の方が鉄の吸収度が高かったことが要因の一つとして考えられる。また，C群の採血前Hb値はD群のそれと有意差がなく，貯蔵鉄量は多かったことから考えて鉄を有効にHb生成に利用できている可能性が考えられる。しかし，今回は鉄剤投与後の貯蔵鉄量を測定していないため明らかにはできなかった。さらに検討を進めることで，顎矯正外科手術に対するより有効な術前貯血を行うことが可能となるものと考える。

結語

術前2週間に400 mlの採血を行った症例においてHb値回復に影響をおよぼす因子について検索した。採血前Hb値と貯蔵鉄量がHb値回復程度に影響を与えている可能性が示唆された。

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Daily doses of 20 mg of elemental iron compensate for iron loss in regular blood donors: a randomized, double-blind, placebo-controlled study

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BACKGROUND: A considerable number of regular blood donors develops an iron deficiency, and the exact amount of iron required to compensate for the iron loss from whole-blood donation in males and females is still unknown.

STUDY DESIGN AND METHODS: A total of 526 regular blood donors (289 male and 237 female) were randomly assigned to treatment with either 40 mg, 20 mg, or 0 mg per day of elemental iron as ferrous gluconate for a period of 6 months, during which one unit of whole blood was collected on four occasions (males) or three occasions (females). Hemoglobin level, serum ferritin, and soluble transferrin receptor levels were measured before each donation.

RESULTS: Daily doses of either 40 mg or 20 mg of elemental iron adequately compensated for iron loss in males, who gave blood at 2-month intervals, but did not result in a positive iron balance or an increase in storage iron as reflected by the logarithm of the ratio of transferrin receptor to ferritin concentration. In females, who donated at 3-month intervals, the same daily doses not only restored the iron balance but also led to an increase in storage iron. The number of gastrointestinal side effects due to iron supplementation (12%) was only slightly higher in both iron groups than in the placebo group.

CONCLUSION: The results of this study indicate that 20 mg of elemental iron per day can adequately compensate for iron loss in males and females who donate whole blood up to four (females) or six times per year (males).

The major side effect of whole-blood donation is iron depletion. In Germany, men are generally allowed to donate whole blood every 8 weeks and women every 12 weeks. However, the normal diet is usually unable to compensate for the resulting iron loss.[1,2] Consequently, a considerable number of regular blood donors develops a negative iron balance that may eventually progress to iron deficiency anemia.[3-7] Menstruating female donors are at a particularly high risk for chronic iron deficiency. Although this is well-known, only a few controlled, double-blind studies have dealt with the question of whether iron supplementation can prevent iron depletion in menstruating female blood donors.[8-11] There is evidence suggesting that daily doses of 40 mg of elemental iron as ferrous sulfate can sufficiently compensate for iron loss resulting from whole-blood donation and can improve iron status.[10,11] However, the question of whether a lower dose of iron is sufficient to compensate for iron loss in female donors is still open. In addition, controlled studies on iron supplementation in male donors are lacking. Most importantly, no valid measure of iron storage was used in early studies.[12,13] Today, serum ferritin and soluble transferrin receptor levels can be routinely measured and iron status can be much better assessed than previously.[14-17] The logarithm of the ratio of

ABBREVIATIONS: Fe^{2+} = elemental iron as ferrous gluconate; log(TfR/F) = logarithm of ratio of the soluble transferrin receptor to ferritin concentration.

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the soluble transferrin receptor to ferritin concentration (log[TfR/F]), which was shown to have a highly linear correlation to body storage iron, is currently the most precise measure of body storage iron available.[14,15] Here, we present the results of a double-blind study in which we randomly assigned regular male and female blood donors to treatment with 40 mg, 20 mg, or 0 mg (placebo) per day of elemental iron for 6 months.

MATERIALS AND METHODS

Selection of donors and study design

A total of 526 regular blood donors (289 male and 237 female) were enrolled in this study, which was approved by the Ethics Committee of Charité University Medical Center. Written informed consent was obtained from all volunteers. In accordance with the German guidelines for blood donor selection, all donors were determined to be healthy based on their history and had hemoglobin (Hb) concentrations of no less than 13.5 g per dL (males) or 12.5 g per dL (females). The investigational products consisted of identical capsules in blister packs containing 1.5 mg pyridoxal-phosphate, 2.25 µg cyanocobalamine, 400 mg ascorbic acid, 200 µg folic acid, and 75 µg biotin without (placebo) or with 20 mg of elemental iron as ferrous gluconate (Fe^{2+}) (Phyt-Immun GmbH, Homburg, Germany). Ascorbic acid was added to enhance iron absorption. Because most people believe in beneficial effects of vitamin supplements, the other selected vitamins were added for improved compliance. The form of iron used meets the European Community criteria for dietary foods for special medical purposes. The participants were randomized to one of three groups receiving either 40 mg Fe^{2+}, 20 mg Fe^{2+}, or 0 mg Fe^{2+} in two capsules once daily for 6 months. Hb, serum ferritin, and soluble transferrin receptor levels were determined before blood collection at each initial and follow-up visit. Each male volunteer was scheduled for a total of four visits, including a randomization visit before the first donation at Week 0 and three subsequent predonation visits at 2-month intervals. The females were scheduled for a total of three visits: a randomization visit at Week 0 and two predonation visits at 3-month intervals (Fig. 1). The intervals were chosen in accordance to the German guidelines, which allow six donations per year for male and four donation per year for female volunteers. Volunteers with hemoglobin concentration less than 13.5 g per dL (males) or 12.5 g per dL (females) were deferred, but not excluded from study. Compliance, which was defined as the ingestion of at least 90 percent of the capsules as prescribed, was checked by counting the returned capsules between blood donations.

Laboratory methods

Hemoglobin concentrations in fingerstick blood samples were determined by the acid methemoglobin method using a photometer (HemoCue B-Hemoglobin photometer, HemoCue, Großostheim, Germany). Ferritin and soluble transferrin receptor concentrations in serum were

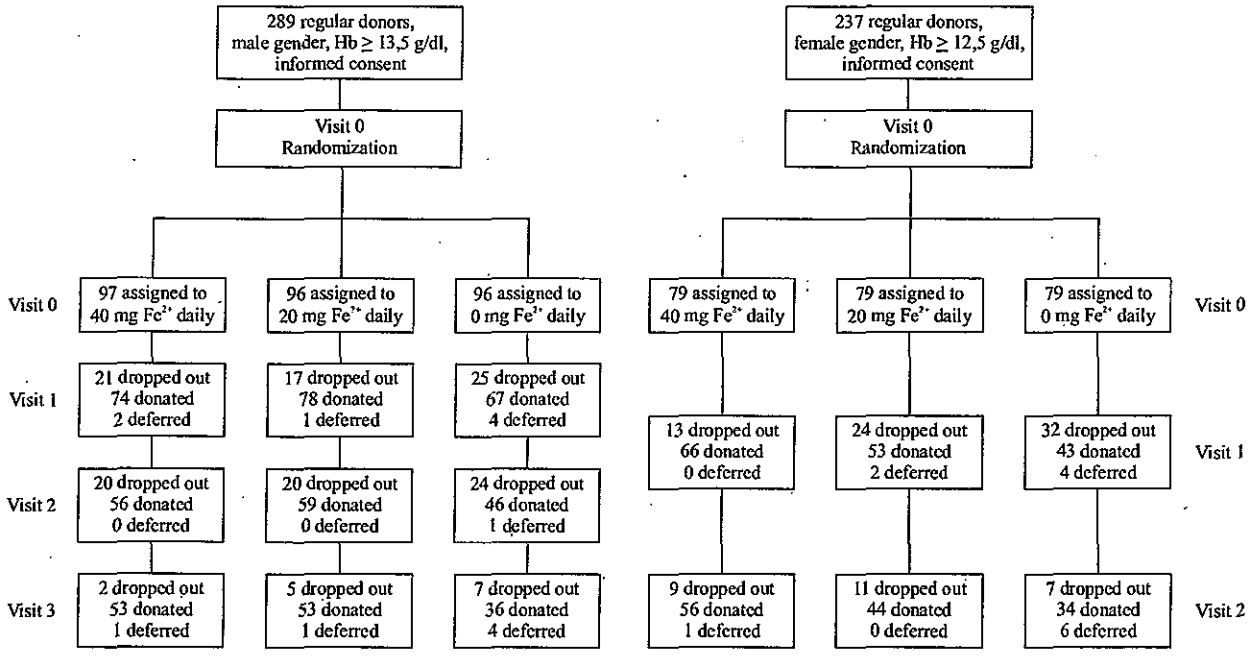

Fig. 1. Flow of participants during study.

determined by nephelometry using an automatic analyzer (BN Prospec, Dade Behring, Marburg, Germany).

Statistics

Sample-size calculation, randomization, and statistical analyses were performed using software (Stata for Windows, Stata Corp., College Station, TX). Based on the serum ferritin concentration, the required sample size was determined to be 49 males and 40 females per group, assuming a power of 0.9, a significance level of 0.0167 (Bonferroni adjustment for three groups), a smallest meaningful ferritin difference of 10 µg per L between groups, three (males) or two (females) follow-up measurements, a within-subject correlation coefficient of 0.8, and a standard deviation (SD) of 26 µg per L (males) or 22 µg per L (female) for serum ferritin. Assuming a dropout rate of 50 percent, we arrived at a final sample size of 98 males and 80 females per group.

The randomization plan was generated using block randomization with variable block length. Statistical analyses were performed as an intent-to-treat analysis for all participants coming for more than one visit using a linear regression model for longitudinal data (cross-sectional time-series regression model with generalized estimating equation analysis).[18] The logarithm of the ratio of transferrin receptor to ferritin concentration, an accepted measure of storage iron, was used as the outcome variable. To model the change in storage iron over time, we applied the difference values for log(TfR/F) and included the iron supplement as the predictor variable.

RESULTS

Males

Of the 289 male volunteers (age range, 19-67 years) enrolled in the study, 141 (49%) dropped out, yielding a dropout rate of 44 percent in the 40 mg of Fe^{2+} group, 44 percent in the 20 mg of Fe^{2+} group, and 58 percent in the placebo group ($p = 0.075$; Fisher's exact test). A total of 63 (45%) of the male dropouts withdrew before their second visit (Table 1). The mean interval between visits was 60 days. Deferral from donation because of unacceptable hemoglobin concentration values (<13.5 mg/dL) occurred in 14 of 825 visits (1.7%). This was more frequently the case in the placebo group than in the 20 mg and 40 mg iron groups (n = 9 vs. 2 vs. 3, $p = 0.022$; Fisher's exact test). Compliance was poor in roughly one-third of the male participants.

In the male placebo group, the mean serum ferritin concentration decreased from 35 µg per L at baseline to 21 µg per L at the final visit, the number of males with depleted iron stores (ferritin <12 µg/L) increased from 20 percent to 54 percent, and the mean concentration of soluble transferrin receptors rose slightly from 1.6 mg per L to 1.7 mg per L (Table 2, Fig. 2). In the male 20 mg iron group, serum ferritin decreased from 35 µg per L to 25 µg per L, whereas the median ferritin value changed only slightly (Table 2, Fig. 2); both the number of males with depleted iron stores (25%) and the transferrin receptor concentration (1.5 mg/L) remained nearly constant. In the male 40 mg iron group, the ferritin (33 µg/L) and transferrin receptor levels (1.5 mg/L) remained constant, whereas the number of individuals with iron depletion dropped from 26 percent to 13 percent.

The log(TfR/F) remained nearly constant in both iron groups, but rose continuously in the placebo group

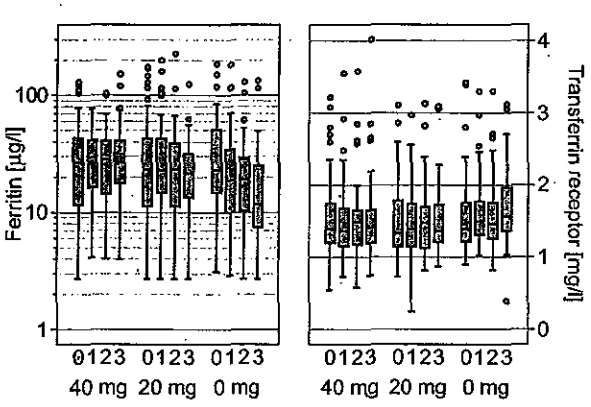

Fig. 2. Box-plot for the concentration of serum ferritin and soluble transferrin receptor in male donors.

TABLE 1. Reasons and numbers of dropouts during study

	Unknown		Gastrointestinal complaints		Poor compliance		Other	
Reason	(%)	(n/total)	(%)	(n/total)	(%)	(n/total)	(%)	(n/total)
Male donors								
40 mg iron	15.5	15/97	5.2	5/97	12.4	12/97	13.4	13/97
20 mg iron	18.8	18/96	6.3	6/96	16.7	16/96	3.1	3/96
0 mg iron (placebo)	20.8	20/96	6.3	6/96	21.9	21/96	11.5	11/96
Female donors								
40 mg iron	8.9	7/79	2.5	2/79	10.1	8/79	6.3	5/79
20 mg iron	20.3	16/79	6.3	5/79	11.4	9/79	6.3	5/79
0 mg iron (placebo)	24.1	19/79	3.8	3/79	10.1	8/79	11.4	9/79

TABLE 2. Serum ferritin concentration, number of donors with depleted iron stores (ferritin concentration <12 µg/L), and logarithm of the ratio of transferrin receptor to ferritin concentration (log[TfR/F]) for all donors with at least one follow-up visit

Visit number	Ferritin (µg/L) (mean ± SD)	Depleted iron stores (%)	Depleted iron stores (n/total)	log(TfR/F) (mean ± SD)
Male donors				
40 mg iron				
0	32.7 ± 27.5	26.3	20/76	1.54 ± 0.51
1	31.4 ± 18.8	16.2	12/74	1.47 ± 0.49
2	30.2 ± 20.8	17.9	10/56	1.50 ± 0.51
3	33.2 ± 26.7	13.0	7/54	1.52 ± 0.55
20 mg iron				
0	34.7 ± 36.3	25.3	20/79	1.48 ± 0.48
1	33.1 ± 33.3	21.8	17/78	1.46 ± 0.44
2	30.2 ± 32.7	25.4	15/59	1.47 ± 0.45
3	25.0 ± 19.8	24.5	13/53	1.52 ± 0.47
0 mg iron (placebo)				
0	35.1 ± 32.4	19.7	14/71	1.55 ± 0.50
1	27.5 ± 27.9	30.9	21/68	1.61 ± 0.45
2	24.9 ± 24.7	29.8	14/47	1.60 ± 0.52
3	21.4 ± 27.5	53.9	21/39	1.67 ± 0.53
Female donors				
40 mg iron				
0	19.3 ± 15.0	39.4	26/66	1.43 ± 0.65
1	28.5 ± 19.8	15.2	10/66	1.26 ± 0.49
2	31.4 ± 19.4	14.0	8/57	1.29 ± 0.54
20 mg iron				
0	20.0 ± 32.3	54.6	30/55	1.38 ± 0.46
1	23.3 ± 27.9	45.1	23/51	1.36 ± 0.42
2	23.5 ± 26.1	34.1	15/44	1.35 ± 0.49
0 mg iron (placebo)				
0	17.7 ± 15.0	48.9	23/47	1.39 ± 0.65
1	17.6 ± 14.5	44.2	19/43	1.40 ± 0.42
2	15.1 ± 12.3	48.7	19/39	1.55 ± 0.66

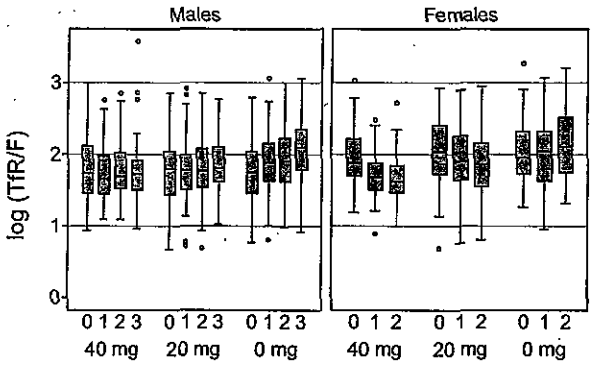

Fig. 3. Box-plots for the logarithm of the ratio of soluble transferrin receptor to ferritin concentration in male and female donors.

(Fig. 3), as was clearly demonstrated in the regression analysis (Table 3). The log(TfR/F) value increased by nearly 0.09 per donation in the placebo group, but changed only marginally in the two iron groups. Both iron groups differed significantly from the placebo group with respect to log(TfR/F).

Females

Of the 237 female volunteers (age range, 19-65 years) enrolled in the study, 96 (41%) dropped out, yielding a dropout rate of 28 percent in the 40 mg iron group, 44 percent in the 20 mg iron group, and 49 percent in the placebo group ($p = 0.015$; Fisher's exact test). A total of 69 (72%) of the female dropouts withdrew before their second visit (Table 1). The mean interval between visits was 88 days. Deferral from donation because of unacceptable dropout concentration values (<12.5 mg/dL) occurred in 13 of 546 visits (2.4%). This was the case more frequently in the placebo group than in the 20 mg and 40 mg iron groups (n = 10 vs. 2 vs. 1, $p = 0.001$; Fisher's exact test). Compliance was poor in roughly one-quarter of the female participants.

In the female placebo group, the mean concentration of serum ferritin decreased from 18 µg per L at baseline to 15 µg per L at the final visit, the number of females with depleted iron stores (ferritin <12 µg/L) remained constant (49%), and the mean soluble transferrin receptor concentration rose from 1.4 mg per L to 1.6 mg per L (Table 2, Fig. 4). In the female 20 mg iron group, serum ferritin increased from 20 µg per L to 24 µg per L, the number of individuals with depleted iron stores decreased from 55 percent to 34 percent, and the transferrin receptor concentration remained nearly constant (1.4 mg/L). In the female 40 mg iron group, ferritin concentration rose from 19 µg per L to 31 µg per L, transferrin receptor level fell slightly from 1.4 mg per L to 1.3 mg per L, and the number of individuals with iron depletion decreased from 39 percent to 14 percent.

The log(TfR/F) dropped in both iron groups, but rose continuously in the placebo group (Table 2, Fig. 3), as demonstrated by the regression analysis. The log(TfR/F) value increased by nearly 0.09 per donation in the placebo group (Table 3), but decreased by roughly 0.06 and 0.12, respectively, in the 20 mg and the 40 mg iron groups.

Side effects

Most donors (approx. 60%) did not report any side effects. There was no significant difference in the incidence of adverse effects between the three groups. In particular, the frequency of gastrointestinal complaints was low (11% in the 40 mg iron group, 13% in the 20 mg iron group, and 11% in the placebo group).

TABLE 3. Regression models for the change in log(TfR/F)

Predictor	Coefficient	95-percent confidence interval	p value
Male donors			
20 mg Fe^{2+}	−0.074	−0.121 to −0.028	0.002
40 mg Fe^{2+}	−0.118	−0.168 to −0.068	<0.001
Constant	0.091	0.058 to 0.123	<0.001
Female donors			
20 mg Fe^{2+}	−0.150	−0.238 to −0.061	0.001
40 mg Fe^{2+}	−0.209	−0.292 to −0.127	<0.001
Constant	0.086	0.018 to 0.153	0.012

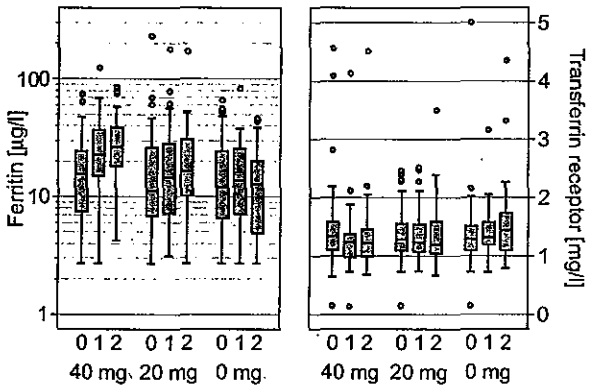

Fig. 4. Box-plot for the concentration of serum ferritin and soluble transferrin receptor in female donors.

DISCUSSION

Regular blood donation frequently leads to iron depletion, and it has been shown that iron supplementation can prevent this complication.[8,10,11] However, the exact dose needed to compensate for this type of iron loss remains unclear, and there is uncertainty as to whether iron supplementation is required in both male and female donors. Attempting to elucidate this complex issue more precisely, we monitored the logarithm of the TfR/F ratio as a measure of body storage iron in regular male and female whole-blood donors. The donors were randomly assigned to receive daily supplements containing selected vitamins plus 40 mg, 20 mg, or 0 mg of elemental iron. Dropout rates were marginally (male) or significantly (female) higher in the placebo group than in both iron groups. The reason for this finding is obscure.

Daily doses of 40 mg and 20 mg of elemental iron resulted in both a positive iron balance and an increase in storage iron in female donors and compensated for iron loss in males. This indicates that 20 mg of elemental iron per day is indeed sufficient to compensate for iron loss in both males and females. The differences in storage iron responses may be due to the shorter donation intervals in males (every 2 months) compared to females (every 3 months). It is likely that the ascorbic acid in the capsules may have increased the iron absorption by roughly 50 percent.[19] The question of whether the other vitamins may play any role in this context is speculative. The only reason for including these vitamins in the investigational products was our desire to improve the compliance rate.

In the present study, we monitored ferritin and soluble transferrin receptor levels as well as the logarithm of the TfR/F ratio. The latter variable, which was shown to have a highly linear correlation with body storage iron, is the most precise measure of body storage iron available.[14,15] Until now, body iron of blood donors was assessed mainly by measuring serum ferritin.[1,3,5-7] However, this variable is somewhat unspecific and may give false-high results in the presence of various underlying diseases.[2] In fact, if ferritin had been the only variable used for assessment of body storage iron, the effects of 20 mg elemental iron in males would have been underestimated in our study.

Interestingly, the number of side effects in the two groups treated with iron(II)-gluconate was only slightly higher than the number observed in the placebo group. In particular, the incidence of gastrointestinal side effects in the iron groups was very low (12%). Due to the slight risk of poisoning in children, iron capsules should be delivered in individual packages. Elemental iron preparations like carbonyl iron are preferred as an alternative by many experts due to the much higher lethal doses.[9,10,20,21] However, carbonyl iron is not available in the European countries. In comparison, bioavailabity of carbonyl iron is slightly lower than that of ferrous salts,[21] but side effects seem to be comparable: The incidence of gastrointestinal complaints for both preparations was reported much higher in two previous studies, probably due to the supplementation with higher doses of iron.[9,21] The utility of iron supplements for prevention of iron deficiency in menstruating female blood donors is currently being discussed.[20,22] However, others and we prefer a supplementation of iron for a short-term period after blood donation but not in general.

In conclusion, our results indicate that daily doses of 20 mg Fe^{2+} can adequately compensate for iron loss resulting from whole-blood donation in males who donate up to six times a year and in females who donate up to four times a year.

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2. 貧血と採血基準を考える
～血液学的立場から～

香川県赤十字血液センター
内田 立身

1．貧血の定義

貧血の定義について血液学の代表的な教科書をみると、①a reduction below normal in the concentration of hemoglobin or red blood cells in the blood[1] ②anemia is functionally best characterized by a hemoglobin concentration below normal[2] などの記載があり、健常人のヘモグロビンの下限値から判断するのが一般的である。米国人においては表1のような数字が用いられている[1) 2) 3) 4)]。この際、健常人として選ばれる対象のうち特に鉄欠乏状態の多い女性では血液学的に正常でない人が含まれ、下限域が低く算定される可能性があった。

表1 米国健常人のヘモグロビン(g/dL)下限値

	男性	女性	文献番号
WHO	13.0	12.0	3
Beutler E	14.0	12.3	1
Lee GR	13.2	11.6	2
NHANESⅢ	13.5	12.0	4

最近、Beutlerら[5] は米国人の貧血の定義としてNHANES-Ⅲ(The Third US National Health and Nutrition Examination Survey)[4] が行なったように、トランスフェリン飽和率16%以上、血清フェリチン10ng/mL以上の人を健常人として正常域の5%値未満を貧血としている(表2)。血液学的な貧血の定義として妥当な決め方である。

日本人の貧血の頻度について、私たちは「1981年～1991年」までの鉄欠乏の頻度を検索したことがあるが[6]、このデータをもとに鉄欠乏のない健常人を対象としてヘモグロビン値を求めたところ表3のとおりとなった。同じ方法で求められた斎藤ら[7] の成績とあわせると、鉄欠乏のない日本人のヘモグロビン下限値は男性12.8～13.2g/dL、女性11.8～12.1g/dLとなり、日本人成人の貧血の定義は男性13.0g/dL未満、女性12.0g/dL未満が妥当と考えられた。最近の日本人については鉄欠乏に関する正確なデータがなく、厚生労働省が行なっている「国民健康・栄養調査報告」などから鉄欠乏のない健常人のヘモグロビン値を求め、日本人の貧血の定義を定める必要がある。

表2 健常米国人のヘモグロビン(g/dL)下限値 (Beutler, 2006)

	男性(20～59歳)	女性(20～49歳)
白 人	13.7 (6,907人)	12.1 (2,966人)
アフリカ系	12.8 (434人)	11.1 (205人)

表3 鉄欠乏のない健常日本人のヘモグロビン値

	平均ヘモグロビン値	1標準偏差	5%正常分布値	文献
男性(284例)	14.8	1.0	12.8	6
女性(390例)	13.9	0.9	12.1	
男性 (26例)	15.0	0.9	13.2	7
女性(134例)	13.4	0.8	11.8	

2．日本人の貧血の頻度

私たちは、1981～1991年にかけて3,015名の女性で貧血の調査を行なった。その成績は、健常者43.6%、貯蔵鉄欠乏33.4%、潜在性鉄欠乏8.4%、鉄欠乏性貧血8.5%、その他6.5%

表4　日本人の貧血の頻度(%)（平成16年度国民健康・栄養調査報告から）

年齢	男性			女性		
	平均Hb±SD	Fr<10(%)	Hb下限値	平均Hb±SD	Fr<10(%)	Hb下限値
20～29	15.1±1.0	1.6	13.1	12.9±1.0	30.5	10.9
30～39	15.1±0.8	1.2	13.5	12.7±1.2	36.5	10.3
40～49	15.2±1.0	1.2	13.2	12.5±1.6	37.5	9.3
50～59	14.9±1.2	1.8	12.5	13.2±1.1	10.0	11.0
60～69	14.5±1.4	2.5	11.7	13.1±1.0	3.9	11.1
70≦	14.0±1.5	2.8	11.0	12.6±1.2	5.6	10.2
計	14.6±1.4	2.1	11.8	12.9±1.2	17.3	10.5

男性1,537名、女性2,634名の調査。

で40歳台前半では17.2％の鉄欠乏性貧血がみられた[6]。

その後、日本人についての詳細なデータがなく、特に女性の鉄欠乏性貧血の頻度をみるには毎年厚生労働省が行なっている国民健康・栄養調査から類推するのがよいと思われる[8]。表4はその成績である。高齢者を除くと男性の貧血は5.8％以下、鉄欠乏の頻度も2.5％以下であるが、女性は16.8％が貧血であり血清フェリチン低値(鉄欠乏)の頻度も高率であることから、ほとんどが鉄欠乏性貧血である。40歳台では25.0％に貧血があり同年代の半数（47.5％）が鉄欠乏状態にある。

また、香川県赤十字血液センターにおいて平成17年度に400mL献血を申し込んだ女性のうちヘモグロビン不足(Hb12.5g/dL未満)で献血ができなかった女性の比率[9]を表5に示すが、30～40歳台女性の約35％が献血できていない。また、日本赤十字社による全国的な調査によると[10]、平成17年に比重不足で献血できなかった人は485,746人で、これは東京都で１年間に献血できた人の数407,235人をはるかに凌駕するほどである。

表5　ヘモグロビン不足で献血できない女性の割合
（平成17年：香川県赤十字血液センター）

年齢	Hb<12.5g/dL
16～19	28.6%
20～29	32.6%
30～39	35.6%
40～49	35.3%
50～59	18.9%
60～69	17.5%
全体平均	19.4%（申込者数 9,963人）

わが国の女性の貧血の頻度は欧米に比して高い。米国の国民健康・栄養調査報告によると、20～40歳台の女性の鉄欠乏性貧血の頻度は5％、鉄欠乏状態は11％[11]、米国24血液銀行における2003年度の女性ヘモグロビン不足(12.5g/dL未満)の割合は平均で6.6％(1.3～13％)、Wisconsin州において17～49歳では21～23％である[12]。わが国のこれに対応する成績は400ml献血ができなかった女性が該当し、16～19歳で28.6％、20～29歳で32.6％、30～39歳で35.6％、40～49歳で35.3％であり[13]、どの調査をみても頻度は高いといわざるを得ない。

わが国で鉄欠乏の多い原因は鉄摂取量の不足にある。平成16年国民健康・栄養調査によると、男性の１日平均鉄摂取量は8.1mg、女性の１日平均は7.7mg（20～39歳で6.9～7.0mg)で必要量に比して少ない[8]。日本人の必要鉄摂取量は男性10mg、月経のある女性12mgであるが、その差2mgは全血にして10～12mLにしか相当せず、平均的月経量を30～40mLとして外国並に15～18mgは必要であろう。となるとわが国の月経のある女性は必要量の半分の鉄しか摂取していない。しかも鉄摂取量は過去の上記の調査によると年々減少してきている。

他方、米国における調査によると、白人男性で１日あたり17.2±0.3mg、女性で13.4±0.4mgで相当の開きがある[8]。採血基準を考える際には、以上のようなわが国の事情を勘案して決める必要がある。

3．採血基準をどう決めるか

日本の現状を踏まえて、わが国の採血基準をどう決めたらよいかについて以下に私見をまじえて述べたい。

代表的な国の採血基準を表6に示す。このうちEU諸国とオーストラリアは男女差があるが、米国とわが国は男女差がない。わが国の採血基準は1986年に改定され、200mL献血と400mL献血に分け、比重法かヘモグロビン法で判定するようになっている。現在、貧血の定義はヘモグロビンで記載されており、わが国の医療機関のすべてがヘモグロビン法で貧血を診断しているので、ヘモグロビン法に統一することが望ましい。また献血も400mL献血が主流になりつつあるので諸外国に倣い200mL、400mLを一本化して表記するのがよいと考えられる。

表6　各国の採血基準（400mL相当）

	男性	女性
Council of EU	13.5	12.5
Australia	13.0	12.0
U.S.A	12.5	12.5
日本	12.5	12.5

1)　ヘモグロビンの正常範囲から決める

鉄欠乏のない健常者から正常分布域を定め、5％正常値を求めると男性13.0g/dL、女性12.0g/dLとなり、これ以上を採血基準とする方法はわかりやすく貧血の定義とも一致する。

2)　貧血状態にない人から採血する

赤血球は鉄欠乏の進展に伴い、小赤血球化、低色素性化する。図1、図2は男性および女性におけるヘモグロビンと赤血球恒数との関係で、MCV・MCHが低下するのは男性で12.5g/dL、女性で12.0～12.5g/dLである[14]。また、鉄欠乏性貧血82例の私達の検討から、ヘモグロビンの分布域の上限は13.0g/dLであることをみると、現行の米国やわが国の基準である12.5g/dLは矛盾しない数字となってくる。

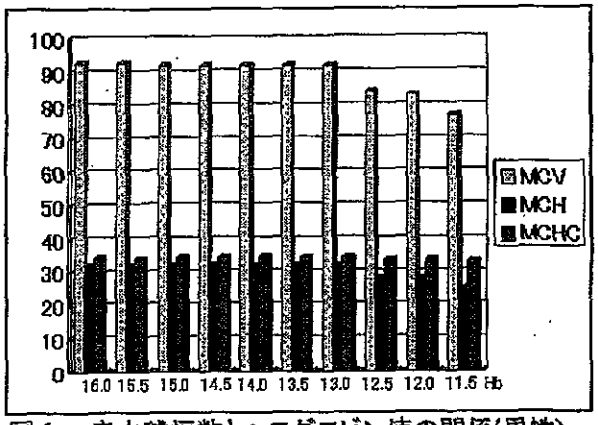

図1　赤血球恒数とヘモグロビン値の関係(男性)

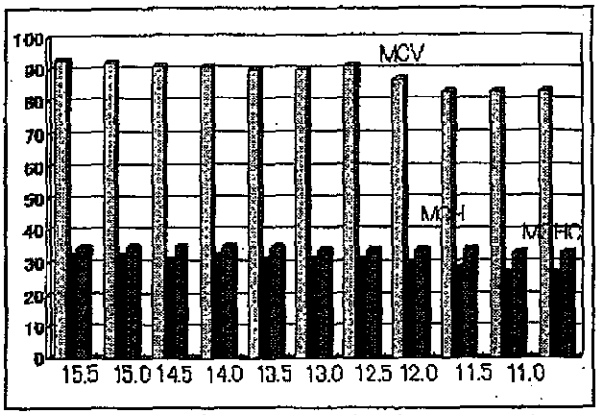

図2　赤血球恒数とヘモグロビン値の関係(女性)

3)　現在考えられる適切な採血基準は

上記を踏まえて採血基準について考察すると、わが国では鉄欠乏状態にある女性の頻度が高く、抜本的対策の見出せない現状では、貧血のない鉄欠乏からの採血をできるだけ避けるために女性の基準は12.0g/dLよりは12.5g/dLのほうが妥当と思われる。また、男性については貧血のない鉄欠乏はほとんどないが、12.5～13.0g/dLは貧血の人から採血することになり矛盾を生ずるので、13.0g/dLが妥当ではないかと思われる。

いずれにしても、採血基準の改定には正確なデータに基づく議論が必要である。それには、日本人の鉄欠乏性貧血、貧血のない鉄欠乏、鉄欠乏のない健常人の頻度（これは現行の国民健康・栄養調査の個々のデータから算出可能である）、献血申込者のヘモグロビン不足による男女別、年齢別不適格者の頻度などの解析によって決められるべきであろう。

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(17)

American Red Cross

Mid-America Division
Badger-Hawkeye Region
Heart of America Region
Midwest Region
North Central Region

Dear Parent or Guardian,

Your 16-year-old has expressed an interest in donating blood at an upcoming American Red Cross blood drive. The states of Illinois, Iowa, Kansas, Nebraska, Minnesota, Missouri and Wisconsin allow 16-year-olds to donate blood with written parental/guardian consent. We are asking for your support by completing the attached consent form.

Please read the attached forms: "What You Must Know Before Giving Blood" and "What You Must Know About NAT – A New Blood Test." If you have any questions about the information contained in these documents, please call 1-800-448-3543 – M-F: 8 am - 9 pm, Sat: 9 am - 1 pm, Sun: 4 pm - 8 pm – and press Option 6 to speak to a Red Cross donor health consultant.

We support each student's willingness to give blood and ask that you offer your encouragement too. Much like voting and driving a car, the opportunity to donate blood and save a life has become a right of passage for thousands of high school students. Becoming a blood donor is a very personal decision, and we understand that parents and students may be somewhat apprehensive about taking this step. This is completely natural, so we want to provide you with some additional information about donating blood.

Blood donation is a safe procedure using single-use sterile needles and supplies. To ensure that your student has a positive experience, we recommend that they follow these guidelines:

- Get a good night's sleep before the blood drive.
- Eat well and drink plenty of fluids in the days leading up to the blood drive, especially the day of the drive.
- Drink at least 16 oz of caffeine free fluid (2 cups) 3-4 hours before the donation and after.
- Be honest and accurate about their weight (donors must weigh at least 110 lbs).

While the donation process is safe, reactions can occur. Most reactions are mild and can include fainting or small bruises. Our staff is fully trained to work with first-time and younger blood donors, and to respond to any reactions. We hope you will encourage your student to support our blood drive. Since one blood donation can be separated into three components, your student has the potential to save as many as three lives with a single donation.

Please note that the FDA requires that donors are asked specific questions about their health history. This information helps ensure the safety of the blood donor and the blood recipient. These questions are asked privately and are completely confidential.

You should be very proud of your son or daughter's decision to donate at the upcoming drive. *Please help support this act of generosity by completing the consent form prior to the drive.* If you are not currently a blood donor, please consider making an appointment for yourself. For more information call 1.800.GIVE.LIFE or visit our website at givebloodgivelife.org.

Sincerely,

David C. Mair MD

David C. Mair, M.D., Senior Medical Director

Form:
Informed Parental Consent for Persons Not of a Legal Majority

What this form is about

This form provides staff with a mechanism for documenting a parent or legal guardian's informed consent for someone not of legal majority to donate blood or blood components.

Who should use this form

This form applies to all staff who obtain informed special consent from donors or parent/legal guardian.

Instructions

- Ensure the region-identifying information is on the form.
- Instruct the parent/legal guardian to
  - Print the name of the son, daughter, or ward in the space provided.
  - Print his or her name.
  - Sign the consent form.
  - Date the consent form.
- Affix a Whole Blood Number/Donation Identification Number (WBN/DIN) to the form.

Revision History

Revision Number	Summary of Revisions
1.0	Initial version
1.1	Developed and released prior to revision history requirement
1.2	Revised instructions for completion of form Reformatted signature, date, and WBN lines

Informed Parental Consent for Persons Not of a Legal Majority

Information

This form must be completed by a parent or legal guardian for blood donations by any person who has not yet reached the age of legal majority as defined by the laws of the state in which the donor makes the blood donation.

Questions or concerns about the blood donation process should be directed to

Department: **Donor Health Consultants**

Phone Number: **(800) 448-3543 (Press Option 6)**

Hours of operation: **M-F: 8am-9pm, Sat: 9am-1pm, Sun 4-8pm**

Parental Consent

I have received and read a copy of "What You Must Know Before Giving Blood" describing the overall blood donation process.

I have received and read a copy of "What You Must Know About NAT- A New Blood Test" describing additional test procedures and any research-related attachments.

I understand that in the event it becomes necessary to notify my son, daughter, or ward of test results, the American Red Cross will send those results directly to my son, daughter, or ward.

I understand the information provided to me and have had an opportunity to ask questions about the information it contains. I hereby give permission for my son, daughter, or ward, to make a voluntary donation of blood to the American Red Cross during his or her legal minority.

A signed consent from the Parent/Guardian will be required for each donation until the donor reaches the age of majority.

Donor Name [son, daughter, or ward] (print) _____

Parent/Guardian Name (print) _____

Parent/Guardian *Signature* _____ **Date:** MM / DD / YY

WBN/DIN →

American Red Cross Blood Services Washington, DC 20006	American Red Cross

WHAT YOU MUST KNOW ABOUT NAT

Possible Use of Donor Information and Blood Samples in Medical Research

The American Red Cross Blood Services mission is to provide a safe and effective blood supply for patients who need blood transfusions. As part of this mission, the American Red Cross may conduct research. Some research is conducted with other institutions, such as academic centers and biomedical companies.

Some examples of the types of research are:

- Studies relating to testing, storing, collecting and processing blood to increase the safety of the blood supply.
- Studies of new test methods for infectious agents carried in the blood, like Nucleic Acid Testing (NAT).
- Studies of ways to recruit blood donors and to evaluate donor eligibility.

Participation does not require additional blood to be collected or additional time.

By signing your Blood Donation Record, you are giving consent to allow us to use a portion of your blood donation and donor information for research like that listed above. Donor information for research will not include anything that would identify you as the donor, such as your name or Social Security Number (SSN).

Confidentiality

American Red Cross policy requires protection of the confidentiality of your donor identifying information, results of tests on your blood samples and information collected at the time of donation. Strict procedures are observed at all blood collection facilities to maintain the confidentiality of donor information.

Your donor identifying information will not be released to other institutions for research purposes without your consent. Your age, gender, general geographic location, and test results may be used to evaluate important information about disease or donor recruitment, but this information is combined with information about other donors and not identified with you.

While study results may be published, donor names and other identifying information will not be revealed, except as required by law. Records are kept, as required by State and Federal Laws. The Food and Drug Administration (FDA) may need to review and copy donor records in order to verify study data. The FDA, however, is committed to protection of the confidentiality of donor identity.

Testing and Storage

Blood samples used by researchers are coded. This means that your donor identifying information, including name and SSN, is not used in connection with research. Coded samples can be linked to information about donors' identity only by authorized Red Cross personnel who are required to follow Red Cross procedures to maintain confidentiality.

Some of your sample or information may be saved for future research on viruses or other agents that may be carried in blood. Samples linked to your identifying information may be used, either

now or in the future, for infectious disease testing, as described in What You Must Know Before Giving Blood or in other information about a specific research study that is being conducted today. Your identified sample and information will not be used for genetic testing or for research unrelated to blood safety without your consent.

You will be notified in person, by phone, or by letter, about any test results that may impact your health. You will receive information about how these test results may affect your health and future eligibility as a blood donor.

Possible Participation in a Follow Up Study
If your test results are positive or unexpected, Red Cross staff may ask you to participate in a follow up study. Participation is voluntary and of no cost to you.

Benefits
By using new infectious disease tests like NAT, you may find out sooner if you are infected by one of the agents being tested. This may be important to your health.

Risks
There is a very low chance that your blood sample may give a false positive or true positive infectious disease result. If this happens, the blood that you donate will not be used for transfusion and there is the likelihood that you may not be able to donate again. If you are donating for a specific patient and have a positive test result, your blood donation will not be available for that patient. If you are donating blood for yourself and have a positive result, your blood donation may not be available to you.

Your Right Not To Participate
You may refuse to participate now or at any time during the donation process. If you decide that you do not want your donation or donor information to be used for possible research like that listed above, you will not be able to donate today. It is very important to include all donors in such research in order to provide a safe and effective blood supply.

If you decide not to participate at this time, your decision will not change your future relationship with the Red Cross.

If you begin donating and then decide that you do not want to participate, you must notify the blood collection staff before you leave the collection site. If you decide to withdraw in the future, contact the Scientific Support Office at (301) 212-2801. However, test information collected before your withdrawal may still be used or disclosed after your withdrawal.

Questions
If you have any questions about your donation, please feel free to ask the ARC staff member performing your confidential health history interview. If you have questions later, you can contact the Blood Center at 1-800-652-9742.

If you have scientific questions, you can call the Scientific Support Office at (301)212-2801. If you have any questions about your rights as a research participant, call the American Red Cross Institutional Review Board Administrator at (301)738-0630.

You have been given this information sheet to read and will be offered a copy to keep.

American Red Cross Blood Services
Washington, DC 20006

What You Must Know Before Giving Blood

Thank you for coming in today!

This information sheet explains how **YOU** can help us make the donation process safe for yourself and patients who might receive your blood. **PLEASE READ THIS INFORMATION BEFORE YOU DONATE!** You will be asked to sign a statement that says you understand and have read this information today. **If you have any questions now or anytime during the screening process, please ask blood center staff.**

Accuracy And Honesty Are Essential

Your **complete honesty** in answering all questions is very important for the safety of patients who receive your blood. We will ask you for identification each time you try to donate. Please register using the same identifying information each time you donate (name, date of birth, etc.). **All information you provide is confidential.** Although your interview will be private, it may require more than one American Red Cross employee to participate in or be present at your health history and blood donation.

What happens when you give blood

To determine if you are eligible to donate we will:

- ask questions about your health, travel, and medicines
- ask questions to see if you might be at risk for hepatitis, HIV, or AIDS
- take your blood pressure, temperature, and pulse, and
- take a small blood sample to make sure you are not anemic.

If you are able to donate we will:

- cleanse your arm with an antiseptic. **(If you are allergic to Iodine, please tell us!),** and
- use a new, sterile, disposable needle to collect your blood.

While you are donating: (the donation usually takes about 10 minutes)

- you may feel a brief "sting" from the needle at the beginning.

After donating we will give you

- a form with post-donation instructions, and
- a number to call if you have any problems or decide after you leave that your blood may <u>not</u> be safe to give to another person.

What to expect after donating

Although most people feel fine before and after donating blood, a small number of people may have a(n)

- lightheaded or dizzy feeling
- upset stomach
- black and blue mark, redness, or pain where the needle was, and
- very rarely, loss of consciousness, or nerve or artery damage.

We will give you a number to call to report any problems or concerns you may have following your donation.

Why we ask questions about sexual contact

Sexual contact may cause contagious diseases like HIV to get into the bloodstream and be spread through transfusions to someone else.

Definition of "sexual contact":

The words "have sexual contact with" and "sex" are used in some of the questions we will ask you, and apply to any of the following activities, whether or not a condom or other protection was used:

- vaginal sex (contact between penis and vagina)
- oral sex (mouth or tongue on someone's vagina, penis, or anus), and
- anal sex (contact between penis and anus).

Continued on back

American Red Cross Blood Services
Washington, DC 20006

What You Must Know Before Giving Blood, Continued

Persons who should not donate

You should not give blood if you

- had hepatitis on or after the age of 11
- had malaria in the past 3 years
- met any of the conditions listed in the CJD Information Sheet
- were held in a correctional facility (including jail, lock up, prison, or juvenile detention center) for more than 72 straight hours in the last 12 months.
- have had sexual contact in the past 12 months with anyone who is sick with hepatitis or AIDS
- had or were treated for syphilis or gonorrhea or tested positive for syphilis in the last 12 months
- were raped in the last 12 months
- **have AIDS or have ever had a positive HIV test**
  AIDS is caused by HIV. HIV is spread mainly through sexual contact with an infected person, or by sharing needles or syringes used for injecting drugs.
- **done something that puts you at risk for becoming infected with HIV**
  You are at risk for getting infected if you
  - have ever used needles to take drugs, steroids, or anything not prescribed by your doctor
  - are a male who has had sexual contact with another male, even once, since 1977
  - have ever taken money, drugs, or other payment for sex since 1977
  - have had sexual contact in the past 12 months with anyone described above
  - received clotting factor concentrates for a bleeding disorder such as hemophilia
  - were born in, or lived in, Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria, since 1977.
  - since 1977, received a blood transfusion or medical treatment with a blood product in any of these countries, or
  - had sex with anyone who, since 1977, was born in or lived in any of these countries.
- have any of the following conditions that can be signs or symptoms of HIV/AIDS
  - unexplained weight loss (10 pounds or more in less than 2 months)
  - night sweats
  - blue or purple spots in your mouth or skin
  - white spots or unusual sores in your mouth
  - lumps in your neck, armpits, or groin, lasting longer than one month
  - diarrhea that won't go away
  - cough that won't go away and shortness of breath, or
  - fever higher than 100.5 F lasting more than 10 days.

Ineligible donors

We maintain a confidential list of people who may be at risk for spreading transfusion-transmitted diseases. By continuing this process, you consent to be entered in this confidential list of deferred donors if you are at risk for spreading such diseases. When required, we report donor information, including test results, to health departments, military medical commands, and regulatory agencies. Donation information may also be used confidentially for medical studies.

If you decide not to give blood

If you decide that you should not give blood, you may leave now.

Testing your blood

Your blood will be tested for hepatitis, HIV (the virus that causes AIDS), syphilis, and other factors. (There are unusual circumstances in which these tests cannot be performed.) You will be notified about test results that may disqualify you from donating blood in the future or that may show you are unhealthy. Your blood will not be used if it could make someone sick. (A sample of your blood or a portion of your donation might be used now or in the future for additional tests or other medical studies. Please tell us if you object.)

Though the tests we use are very good, they are not perfect. HIV antibodies may take weeks to develop after infection with the virus. If you were infected recently, you might have a negative test result, yet be able to infect someone. That is why you must not give blood if you are at risk of getting AIDS or other infectious diseases. **If you think you may be at risk for HIV/AIDS or want an HIV/AIDS test, please ask for information about other testing facilities. Please do not donate to get tested for HIV, hepatitis, or any other infections!**

Travel to or birth in other countries	Blood donor tests may not be available for some contagious diseases that are found only in certain countries. If you were born in, have lived in, or visited certain countries, you may not be eligible to donate.

American Red Cross Biomedical Services	Doc No ARC F6628CJD	Version 05/08

Form:
CJD Information Sheet

What this form is about

This form explains Creutzfeldt-Jakob disease to the donor.

Who should use this form

This form applies to collections staff.

Revision History

Revision Number	Summary of Revisions
07/04	Developed and released prior to revision history requirement
05/08	• Removed watermark so sheet can be printed from eDOCs or eBinder • Revised American Red Cross Logo • Placed into System 3 Document template

CJD Information Sheet

American Red Cross

Please do not donate if you—

- Since January 1, 1980 through December 31, 1996—
  - -Spent a total time that adds up to 3 months or more in any country(ies) in the United Kingdom (UK).
  - -The UK includes any of the countries listed in Table 1 below.
- Were a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military that spent a total time of 6 months on or associated with a military base in any of the following areas during the specified time frames—
  - -From 1980 through 1990 - Belgium, the Netherlands (Holland), or Germany
  - -From 1980 through 1996 - Spain, Portugal, Turkey, Italy, or Greece
- Since January 1, 1980 to present—
  - -Spent a total time that adds up to 5 years or more in Europe (includes time spent in the UK from -1980 through 1996 and time associated with the military bases in Europe as outlined above).
  - -The European countries that are affected are listed below in **Table 1** and **Table 2**.
  - -Received a blood transfusion in any country(ies) listed in **Table 1** below.
  - -Received an injection of bovine (beef) insulin made in any of the countries listed below.
- Ever received—
  - -A dura mater (or brain covering) transplant during head or brain surgery.
  - -Human pituitary growth hormone (brain extract).
- Any blood relative has had Creutzfeldt-Jakob disease. A blood relative is your mother/father, grandparent, sibling, aunt/uncle, or children.
- Have been told that your family is at risk for Creutzfeldt-Jakob disease.

If any of these apply to you, your donation cannot be accepted. If you have any questions, please ask us. We sincerely appreciate your support.

Table 1

United Kingdom			
♦ Channel Islands	♦ Falkland Islands	♦ Isle of Man	♦ Scotland
♦ England	♦ Gibraltar	♦ Northern Ireland	♦ Wales

Table 2

Europe		
♦ Albania	♦ Hungary	♦ Poland
♦ Austria	♦ Ireland (Republic of)	♦ Portugal
♦ Belgium	♦ Italy	♦ Romania
♦ Bosnia/Herzegovina	♦ Kosovo (Federal Republic of Yugoslavia)	♦ Serbia (Federal Republic of Yugoslavia)
♦ Bulgaria		♦ Slovak Republic (Slovakia)
♦ Croatia	♦ Liechtenstein	♦ Slovenia
♦ Czech Republic	♦ Luxembourg	♦ Spain
♦ Denmark	♦ Macedonia	♦ Sweden
♦ Finland	♦ Montenegro (Federal Republic of Yugoslavia)	♦ Switzerland
♦ France		♦ Turkey
♦ Germany	♦ Netherlands (Holland)	♦ Yugoslavia (Federal Republic includes Kosovo, Montenegro, and Serbia)
♦ Greece	♦ Norway	

###

American Red Cross Biomedical Services	Doc No 14.4.ja021	Version 1.1
Job Aid: **Medication Deferral List**	Approved by Quality Assurance	
	Approval date 05.04.06	

Please tell us if you are now taking or if you have EVER taken any of these medications:

- ☐ **Proscar® (finasteride) – usually given for prostate gland enlargement**
- ☐ **Avodart® (dutasteride) – usually given for prostate enlargement**
- ☐ **Propecia® (finasteride) – usually given for baldness**
- ☐ **Accutane®, Amnesteem®, Claravis®, or Sotret®, (isotretinoin) – usually given for severe acne**
- ☐ **Soriatane® (acitretin) – usually given for severe psoriasis**
- ☐ **Tegison® (etretinate) – usually given for severe psoriasis**
- ☐ **Growth Hormone from Human Pituitary Glands – used only until 1985, usually for children with delayed or impaired growth**
- ☐ **Insulin from Cows (Bovine, or Beef, Insulin) – used to treat diabetes**
- ☐ **Hepatitis B Immune Globulin – given following an exposure to hepatitis B**

  Note: This is different from the hepatitis B vaccine which is a series of 3 injections given over a 6 month period to prevent future infection from exposures to hepatitis B.
- ☐ **Unlicensed Vaccine – usually associated with a research protocol**

Please tell us if you are now taking or if you have taken any of these medications in the last 7 days:

- Clopidogrel
- Coumadin (warfarin)
- Heparin
- Plavix
- Ticlid
- Ticlopidine

IF YOU WOULD LIKE TO KNOW WHY THESE MEDICINES AFFECT YOU AS A BLOOD DONOR, PLEASE KEEP READING:

- If you have taken or are taking **Proscar, Avodart, Propecia, Accutane, Amnesteem, Claravis, Sotret, Soriatane, or Tegison**, these medications can cause birth defects. Your donated blood could contain high enough levels to damage the unborn baby if transfused to a pregnant woman. Once the medication has been cleared from your blood, you may donate again. Following the last dose, the deferral period is one month for **Proscar, Propecia, Accutane, Amnesteem, Claravis** or **Sotret**, six months for **Avodart** and three years for **Soriatane**. Tegison is a permanent deferral.
- **Growth hormone from human pituitary glands** was prescribed until 1985 for children with delayed or impaired growth. The hormone was obtained from human pituitary glands, which are found in the brain. Some people who took this hormone developed a rare nervous system condition called Creutzfeldt-Jakob Disease (CJD, for short). The deferral is permanent. CJD has not been associated with growth hormone preparations available since 1985.
- CJD has been reported in extremely rare cases in Australian women who took **gonadotropin from human pituitary glands** for treatment for infertility. Gonadotropin from human pituitary glands was manufactured and distributed outside the United States and was never marketed in the United States to treat infertility. Human chorionic gonadotropin which is used for fertility treatments in the United States is not derived from human pituitary glands and is not a cause for deferral.
- **Insulin from cows (bovine, or beef, insulin)** is an injected material used to treat diabetes. If this insulin was imported into the US from countries in which "Mad Cow Disease" has been found, it could contain material from infected cattle. There is concern that "Mad Cow Disease" is transmitted by transfusion. The deferral is indefinite.
- **Hepatitis B Immune Globulin (HBIG)** is an injected material used to prevent infection following an exposure to hepatitis B. HBIG does not prevent hepatitis B infection in every case, therefore persons who have received HBIG must wait 12 months to donate blood to be sure they were not infected since hepatitis B can be transmitted through transfusion to a patient.
- **Unlicensed Vaccine** is usually associated with a research protocol and the effect on blood transmission is unknown. The deferral is for one year.
- If you have taken **Clopidogrel, Plavix Ticlid, or Ticlopidine in the last 7 days**, these medications affect the portion of your blood called platelets. If you are donating platelets, your donated blood could contain high enough levels of the medications that it could affect the quality of the platelets that you give. Once the medication has been cleared from your blood, you may donate platelets again. Following the last dose, the deferral period is 7 days.
- If you have taken **Coumadin (Warfarin) or Heparin in the last 7 days**, these medications can affect the blood's ability to clot, which might cause excessive bruising or bleeding when you donate. Therefore, we ask that you be off of these drugs for 7 days prior to giving blood. Following the last dose, the deferral period is 7 days.

###

SECTION 1: Document Package Information

Transmittal Sheet Title: Revised health History Tables and Related Douments Number: 2522
Version: 1.0

Document Title: Time Period: May 2006

List Documents Here:	14.4.ja041, v-1.1	14.4.tbl010, v-1.4
14.3.019, v-1.3	14.4.ja049, v-1.2	14.4.tbl011, v-1.2
14.3.070, v-1.2	14.4.tbl001, v-1.3	14.4.tbl012, v-1.2
14.3.092, v-1.2	14.4.tbl002, v-1.3	14.4.tbl016, v-1.3
14.3.094, v-1.2	14.4.tbl003, v-1.4	14.4.tbl021, v-1.2
14.4.ja021, v-1.1	14.4.tbl004, v-1.4	14.4.tbl023, v-1.3
14.4.ja028, v-1.2	14.4.tbl005, v-1.2	14.4.tbl024, v-1.3
14.4.ja029, v-1.4	14.4.tbl006, v-1.3	14.4.tbl025, v-1.2
14.4.ja031, v-1.3	14.4.tbl008, v-1.2	14.4.tbl026, v-1.2
14.4.ja032, v-1.1	14.4.tbl009, v-1.3	
List Documents Here (continued):		
14.4.tbl027, v-1.2	14.4.tbl039, v-1.3	
14.4.tbl028, v-1.2	14.4.tbl044, v-1.3	
14.4.tbl029, v-1.4	14.4.tbl045, v-13.	
14.4.tbl030, v-1.2	14.4.tbl046, v-1.3	
14.4.tbl031, v-1.3	14.4.tbl047, v-1.3	
14.4.tbl033, v-1.2	14.4.tbl048, v-1.3	
14.4.tbl034, v-1.4	14.4.tbl201, v-1.1	
14.4.tbl035, v-1.2	14.4.tbl202, v-1.1	
14.4.tbl036, v-1.2	14.4.tbl208, v-1.1	

SECTION 2: Approvals

Your approval signifies that you have reviewed the documents according to the requirements for your functional area.

Signatory Name	Role	Signature	Date
Please print or type name here Pat Demaris	*Check role* Process Owner ☑ CEO/ Division VP ☐ None ☐	Pat Demaris	05/05/06
Anne Eder	Medical Office ☒ None ☐	Anne Eder	05/05/06
	Executive QA ☒ System QA ☐ BIT-QRM ☐ Testing Support QA ☐ Facility Quality Director ☐	Executive Quality	05.05.06

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平成１５年度　厚生労働科学研究費補助金（医薬品等医療技術リスク評価研究事業）
分担研究報告書

4．採血により献血者に起こる副作用・合併症の解析

—平成 14 年の全国データから—

分担研究者
佐竹　正博　（東京都赤十字血液センター）
中村　榮一　（東京都赤十字血液センター）

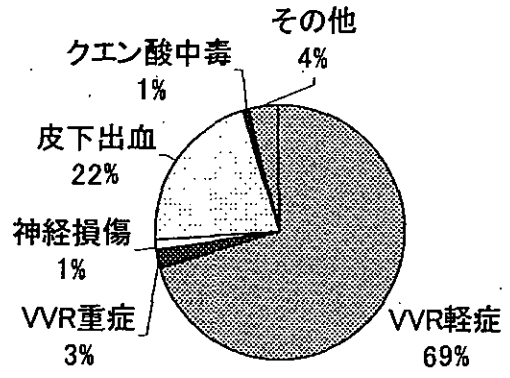
日本赤十字社では、献血時の採血によって献血者に起こる副作用や合併症のデータを集積しているが、ここでは全国の血液センターから集められた平成 14 年のデータをもとに解析を試みた。

まず、すべての採血種における全献血者の副作用の頻度を表に示した。

	VVR 軽症	VVR 重症	神経損傷	皮下出血	クエン酸中毒	その他	合計
%	0.73	0.026	0.011	0.23	0.011	0.039	1.04

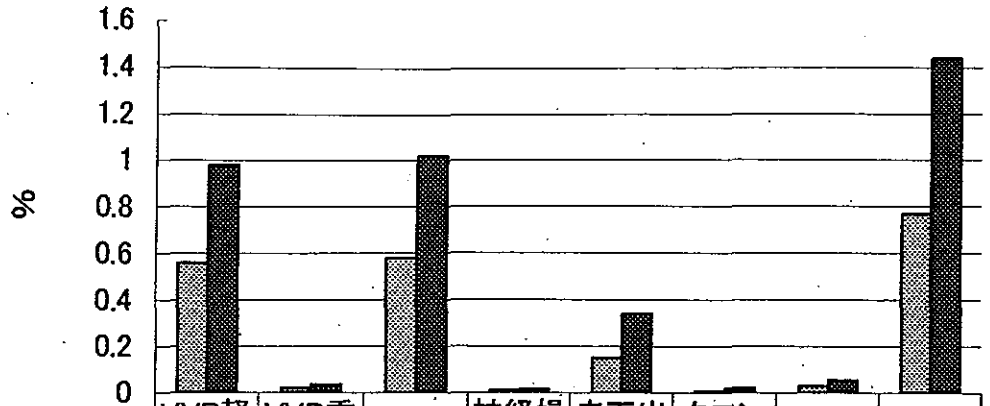
全献血者の約 1%に何らかの副作用が起こっており、その 73%は VVR（vasovagal reaction、血管迷走神経反応）である。献血者に長期にわたる愁訴・運動障害などを起こす可能性のある神経損傷が 1 万人に 1.1 人の確率で起こることは重大である。副作用の割合を示したのが図 1 である。VVR に次いで、皮下出血が 22%を占めている。

図 1.



これを男女別にみたのが次の図 2 である。

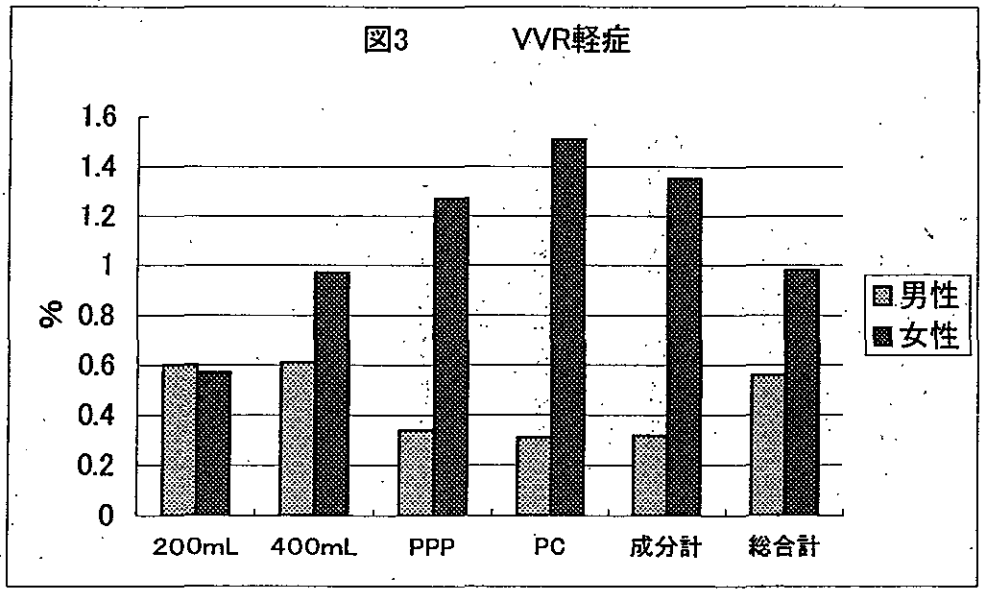
図2　　全ての採血



	VVR軽症	VVR重症	VVR計	神経損傷	皮下出血	クエン酸中毒	その他	合計
男性	0.56	0.021	0.58	0.0093	0.15	0.0051	0.029	0.77
女性	0.98	0.035	1.02	0.014	0.34	0.02	0.054	1.44

男女別でとくにパターンの大きな変化はないが、すべての副作用において女性のほうがその頻度が高い。しかしながら、これを採血種別にみていくと男女間でかなり大きな差があることがわかる。図3は比較的軽症のVVRの発生頻度を採血種別にみたものである。

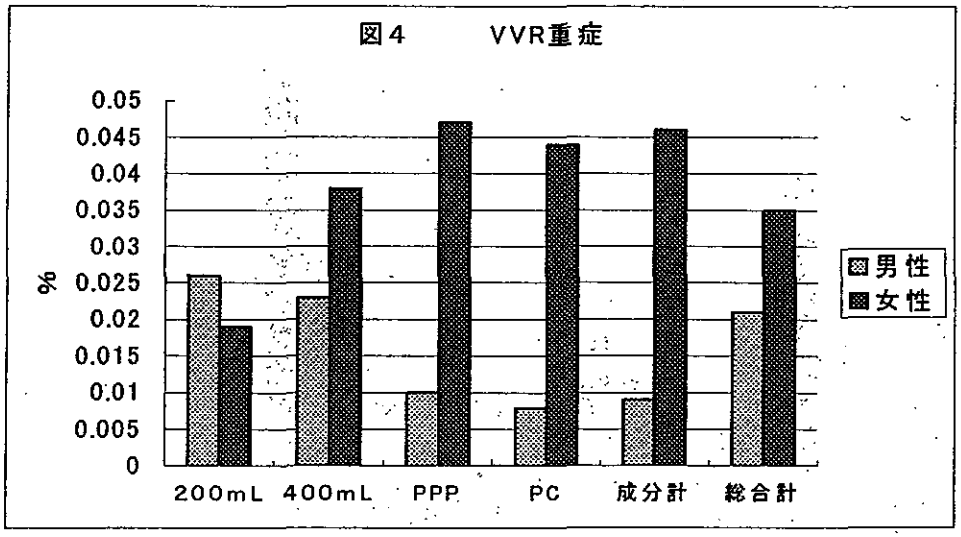
図3　　VVR軽症



200mL採血では男女ほぼ同じ頻度でVVRが起こっているが、400mLになると女性のほうが有意に多くなる。これは、女性のほうが一般に循環血液量が少なく、血管内のvolume lossによる症状が現れやすく、それがVVRに加算されて頻度が高くなったものと思われる。PCやPPPの成分採血になると、男性ではむしろVVRが少なくなっているのに対し、女性ではさらに頻度が高くなっている。女性で多くなるのは、前述のように血漿採取量の増加の影響が出ているものと思われるが、男性でかえって少なくなる理由は不明である。男性の場合、血漿採取量が循環血液量に影響を及ぼさない範囲では、専用椅子に1時間近くゆっくり座って採血を受ける成分採血の方が心理

的に余裕があり、VVR が起こりにくいこともあるのではないかと想像される。

重症の VVR では図 4 にように 200mL 採血ではむしろ男性の方が多い。成分採血では女性は男性の 5 倍ほど重大



な転帰をとりやすい。男女とも 200mL 採血では循環血液量に影響が出ることはほとんど考えられないので、この採血において男女の VVR の頻度がほぼ同じであることは、純粋に神経学的な機序のみで起こる VVR の頻度に性差はあまりないことを示すものといえる。図 5 は軽症と重症を合わせた全 VVR の頻度である。

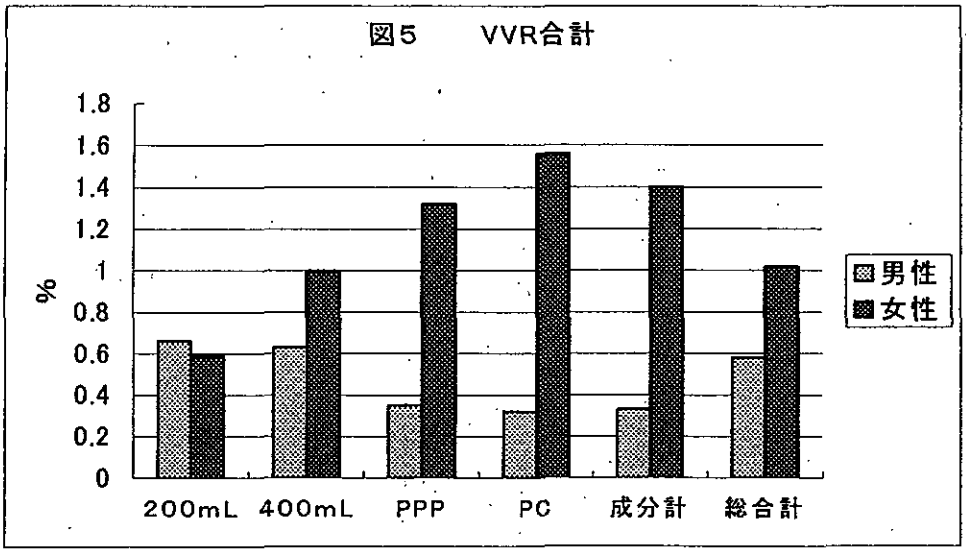
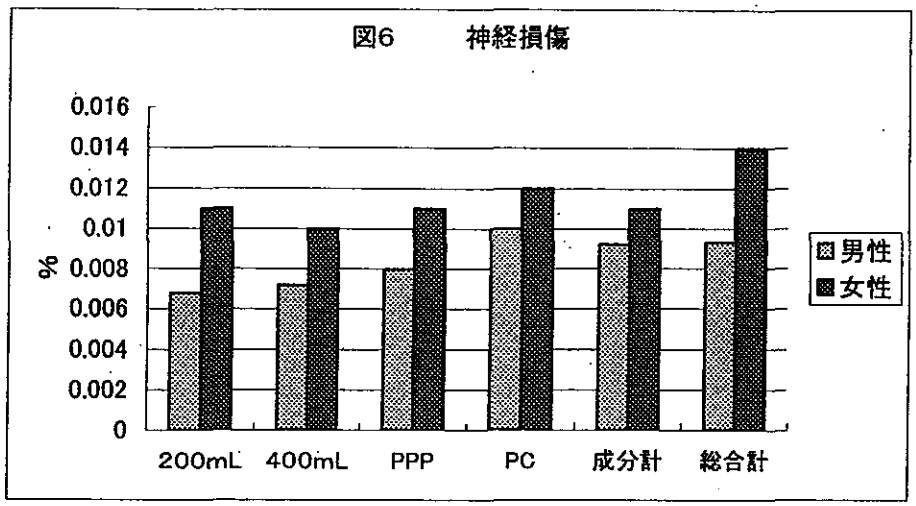
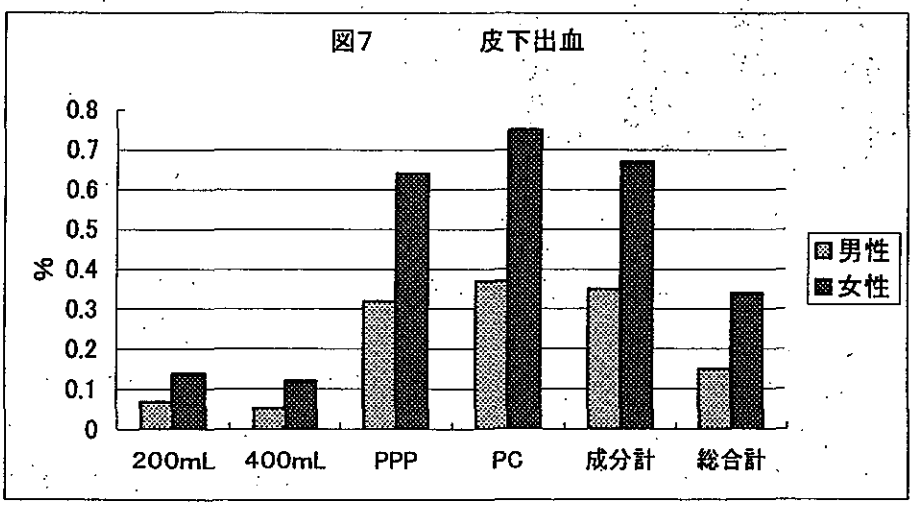


図6は神経損傷の頻度である。ここでは予想されるように採血種別による頻度の差はほとんどない。これはいっぽうでこのデータ収集が大きな片寄りのないものである事を示すものと思う。女性のほうがどの採血種別でも男性より頻度が高い。女性はより痛みに敏感であることが影響していると思われる。これは RSD(reflex



sympathetic dystrophy)などが女性に多いといわれる事などからも推察される。

図7は皮下出血の頻度である。特徴的なのは、200mL、400mL 採血ではどちらも同程度に頻度が低いのに対し、成分採血では約6倍ぐらい高いことである。これは、穿刺針が長時間静脈内に留置されている間に血管壁を傷つ



ける可能性が高いためであると考えられるが、さらに、長時間異物が挿入されていることにより、創傷の治癒機転が少なからず阻害される事もあるのではないかと考えられる。どの採血種でも女性は男性のちょうど2倍の報告がある。女性の方が美容上より気にしやすいこともあるだろうが、破綻血管からの止血について女性が本質的に弱点を持っている可能性はないだろうか。

図8はクエン酸中毒の頻度で、母集団は成分採血者のみとした。血漿採血（PPP）よりも血小板採血（PC）の方が遥かにクエン酸中毒を起こしやすい。これは採取血小板の凝集を防ぐために PC 採取の場合は ACD 輸注比を高く設定するためと、PC 採取の方が時間が長くかかるためと思われる。また、女性の方が圧倒的に頻度が高いのは、体格が小さいために循環血液量が少なく、クエン酸の血中濃度が高くなりやすいためと思われる。

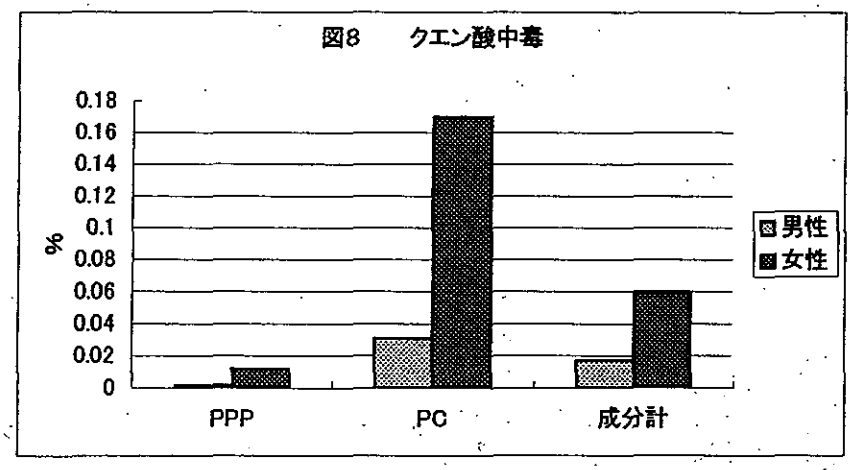


図9はその他の副作用である。

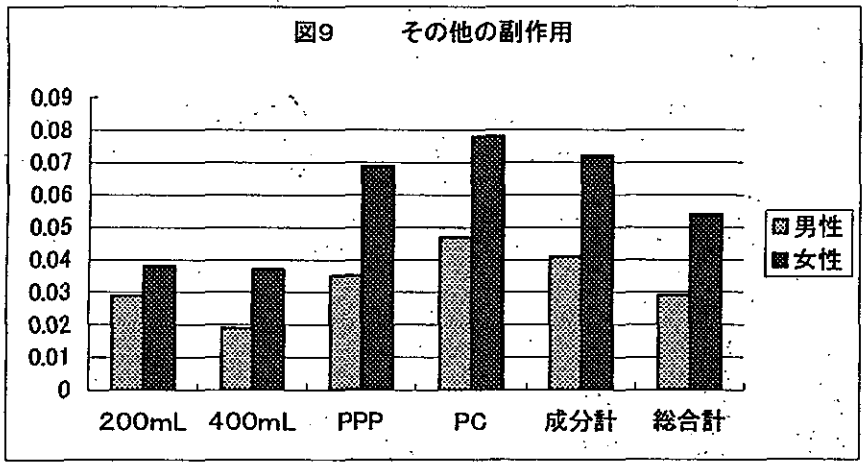
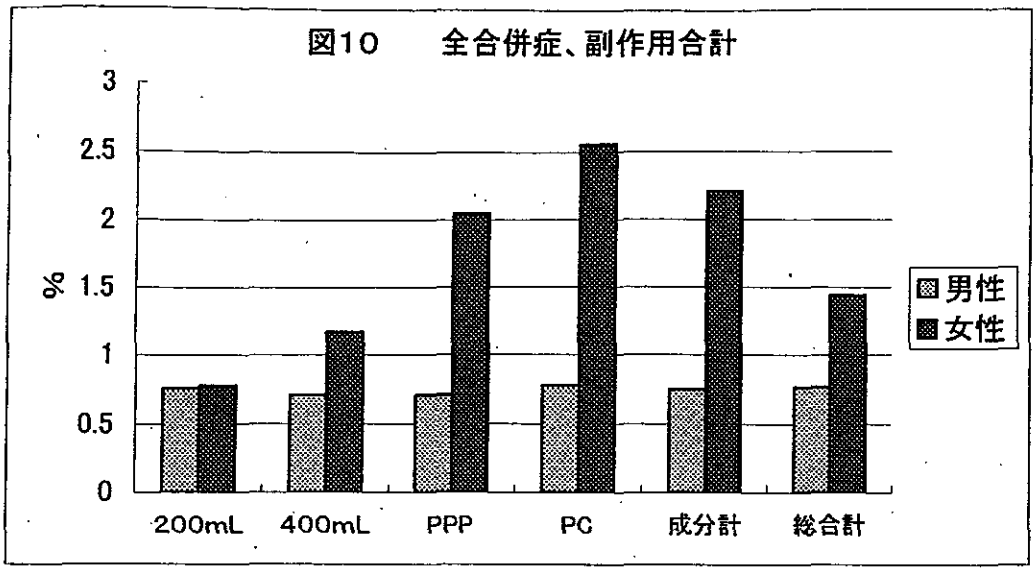
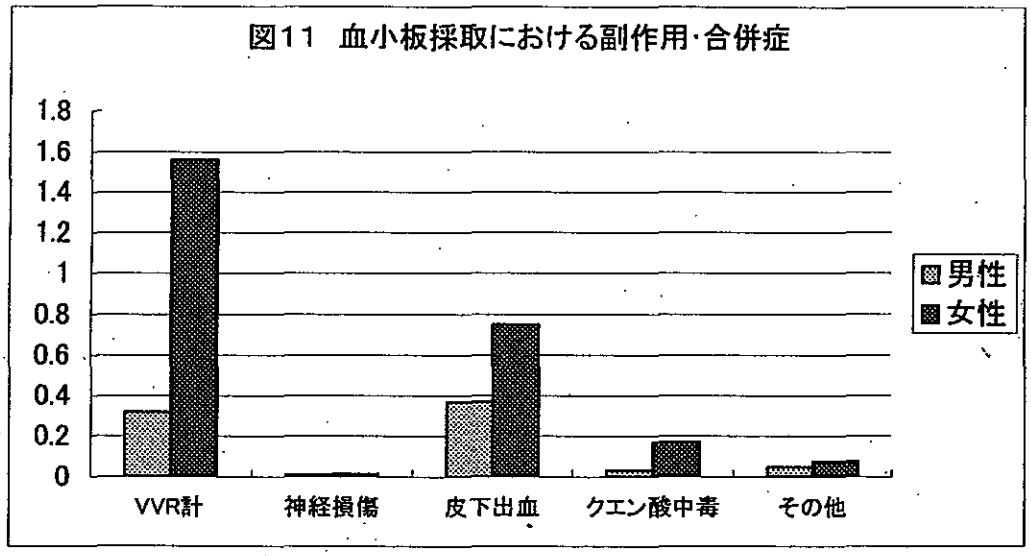


図10は、すべての採血副作用・合併症の合計の頻度を採血種別、男女別に合計したものである。おもしろいことに、男性ではすべての採血種でほぼ同じ合併症頻度を示す。これに対し女性では、200mL、400mL、PPP、PC の順に直線的に頻度が高まっていく。これに最も寄与しているのが VVR で、以下皮下出血、クエン酸中毒と続く。女性の PC 採血者において 2.5%もの献血者に副作用が出ている事実は注目されなければならない。血小板採取で起こる副作用をまとめると図11のようになり、女性においては VVR、次に皮下出血の順となる。成分採血後の止血法については改善の余地がある。





まとめ

全献血者の約1%に何らかの副作用･合併症が起こる。その73%はVVRであり、皮下出血が22%である。女性は男性の1.87倍合併症が起こりやすい。採血種別では、PC採血において最も頻度が高く、PPP、400mLと続く。これは女性にのみ認められる現象で、男性ではどの採血種別でも同じ頻度である。女性でこの頻度を高くしているのがVVR、次いで皮下出血である。

男性において、採血の環境･状況が異なるどの採血種でも頻度が同じであり、また200mL採血では男女の差はまったくないことは、この頻度が日本で不可避的に起こる採血合併症の頻度ではないかということを示唆する。いっぽう、女性での頻度の増加分は採血状況の何らかの改善によって防ぎうるものではないかということも示唆す

る。最も問題となるのはおそらく循環血液量に対する採血量の過重な負担であろう。現行の採血量・採漿量は、献血を継続していっても貧血に陥らない量、また急速脱血しても循環動態に影響を与えない量（循環血液量の12～13%）を基準に決められている。後者のよりどころとなるのは、健常者が安定した状態にあって脱血した場合のデータであると思われる。生理学的研究においてはこれは間違いのないデータであろうが、献血の場合は、問診において全身状態に問題のある献血者をお断りしているとはいえ、脱水や睡眠不足などあらゆる全身状態の献血者が採血を受け得る状況にある。このような献血者群から400mL以上採血した場合は、失神などの副作用は容易に起こるであろうと思われる。PC、PPP、400mL採血でのVVR増加分がこのような献血者群でのVVRの増加によるものかどうかについてはデータはないが、その可能性は十分にあると思われる。

十分に検討された現行の基準で採血を行っても1%もの献血者にVVRなどが起こっている。日赤の血液センターでは、これらの副作用を少しでも少なくするために、採血前後の水分補給、採血後の十分な休息、退出後の過ごし方での注意点の周知などに努めている。そして今回まとめられたデータをもとに、さらにどのような対策が適切であるかを現在検討中である。将来、献血時の採血量を増やす場合には、性差、体重、循環血液量、採血種別について十分に検討する必要がある。とくに女性での採血量については慎重に検討しなければならない。女性でのPC、PPP、400mL以上の採血では何らかの新たな基準が必要であろう。問診でのドナー選択と献血前後のドナーの処置法も再検討しなければならない。1年間に600万人の献血者から採血している状況から得られたデータは、小数の実験・麻酔例からのデータより重いものがあるのではないだろうか。

[原著]

血管迷走神経反応の予防の試み —ハイリスクドナーに休憩と水分摂取を勧めるパンフレットを渡したことの効果

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加賀 幸子，貫田多恵子，荒川 町子
柴崎 利明，山崎 健一，溝口 秀昭

Trial prevention of vasovagal reaction —The effect of handing pamphlets to high risk donors instructing them to take rest and drink water

Saitama Red Cross Blood Center
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Toshiaki Shibasaki, Kenichi Yamazaki and Hideaki Mizoguchi

抄　録

血管迷走神経反応(VVR)は献血者の副作用として一番多く，献血者の約1%に起こる。VVRを起こしやすい献血者のグループ(ハイリスクグループ)があることが知られている。

我々はVVRの頻度を減らす目的で，ハイリスクグループのうち①全血献血の初回の若年(10歳代と20歳代)の男女，②成分献血の中高年(50歳代と60歳代)の女性に対し，①休憩を30分以上取ること，②水分摂取をすることを勧めるパンフレットを手渡した。

その結果，パンフレットを渡すようになった2004年度と2005年度ではそれ以前の2002年度と2003年度に比し月ごとのVVRの頻度は低下した。2003年度と2004年度を比較すると軽症のVVRは男女とも低下した。重症のVVRは男性では低下しないが，女性では全体でも有意に低下し，血漿献血と400mL献血で有意に低下した。この方策は，VVRの減少に有効な方法と考えるが，若年男性の重症に対しては他の方策を考える必要がある。

Abstract

Among adverse events related to blood donation, vasovagal reaction (VVR) occurs most frequently and its incidence comprises around 1% of donors. It is well known that there are high risk populations who are susceptible to VVR.

In order to decrease the incidence of VVR, we prepared pamphlets that instruct donors to take rest for at least 30 minutes and to drink water after blood donation, and handed these pamphlets to 2 high risk group donors: first-time

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young whole blood donors and middle aged apheresis female donors. As a result, the incidence of VVR decreased after handing the pamphlets to high risk donors. Comparing the incidence of VVR before and after handing the pamphlets to donors, mild VVR decreased in both male and female donors. As far as the incidence of severe VVR is concerned, the incidence of VVR among male donors did not change, though the incidence of VVR among female 400mL whole blood donors and plasma apheresis donors decreased significantly. The pamphlets that we prepared effectively decreased the incidence of VVR but we must consider other methods of decreasing the incidence of severe VVR among young male donors.

Key words: blood donation, vasovagal reaction, rest, water intake

はじめに

献血後の副作用は献血者の約1%に起こることが知られている[1]。その主なものは血管迷走神経反応(vasovagal reaction, VVR)，神経損傷と皮下出血である。VVRは全副作用のうち約75%を占める。VVRは転倒の原因となり，重篤な副作用に繋がる可能性がある。VVRによる転倒は全国で，年間100～150人の献血者に起こり，大きな問題と考える[2)~4)]。転倒事故を少なくするためにはVVRの発生率を下げる努力と転倒の直接的な予防策を立てる必要がある。

全血献血でVVRを起こしやすい人々は，①初回，②低体重，③若年，④白人，⑤若年初回の献血者では女性と報告されている[5)~7)]。一方，成分献血では①循環血液量の少ない人，②中高年の女性，③サイクル数の多い人等が挙げられる[8)]。埼玉県の予備的な調査でも同様の傾向がみられ，中高年の女性の成分献血ではVVRが1時間以上持続する例が多い。

今回，VVRの発生率を低下させる目的で，VVRのリスクの高い献血者に対し，図1に示すような献血後に①30分以上の休憩することと，②水分摂取を勧めるパンフレットを渡し，そのVVR発生に対する効果を検討した。また同時に口答でもその内容を献血者に話すようにした。

方法と対象

対象とした献血者は2004年5月から2005年4月までの1年間に埼玉血液センターに来訪した献血者243,182人(男性149,271人，女性93,911人，全血献血159,186人，成分献血83,996人)であった（表

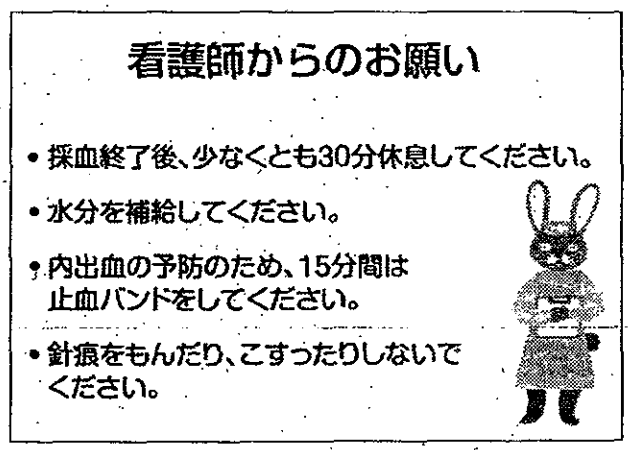

図1　VVRのハイリスクの献血者に渡すパンフレット

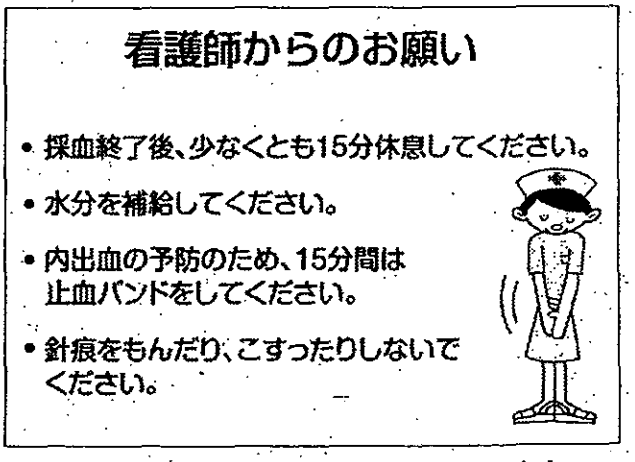

図2　VVRのローリスクの献血者に渡すパンフレット

1)。それらの献血者のうち，VVRのリスクが高いとされる初回の若年(10歳代と20歳代)の男女で全血献血をした人と再来の中高年(50歳代と60歳代)の女性で成分献血をした人に2004年5月から図1に示すようなパンフレットを渡した。その内容は献血後に①少なくとも30分以上は休憩することと，②水分摂取をすることを勧める内容である。それ以外の献血者に対しては図2に示すようなパンフレットを渡した。その内容の主なものは①少なくとも15分以上休憩すること，②水分摂取を勧める内容である。

パンフレットを渡し始めたのが，2004年5月であるので，年度の区切りを5月から次年度の4月までとした。つまり，2004年5月から2005年4月を2004年度とし，その月ごとのVVRの発生頻度とそれ以前の2002年度および2003年度の月ごとのVVRの発生頻度と比較した。2005年度の月ごとのVVR発生頻度も調べ比較した。

さらに，2003年度と2004年度のVVRの発生頻度についてその効果を男女別，献血の種類別，VVRの重症度別に比較検討した。

なお，比較の対照とした2003年度の献血者は総献血者数246,056人(男性149,898人，女性96,158人，全血献血161,757人，成分献血84,299人)であった(表2)。

VVRの重症と軽症の分類は表3に示すように，日本赤十字社標準作業手順書に準拠した[9]。つまり，軽症では気分不良，顔面蒼白，あくび，冷汗，悪心，嘔吐，5秒以内の意識喪失であり，重症になると，これらの症状に加え，5秒以上の意識喪失，けいれん，尿失禁，脱糞などが起こる。身体所見としては血圧の低下と徐脈，呼吸数の低下などがみられ，この重症例の一部に転倒例が含まれる。

結　果

図1あるいは図2のパンフレットを渡すようになった2004年度(パンフレットを渡すようになった2004年5月から2005年4月までとする)の各月のVVRの頻度は2002年度あるいは2003年度の各月のVVRの頻度に比し低い値を示した（図3）。つまり，2002年度と2003年度の各月のVVRの発生頻度はほとんどの月で1%を超えていたが，パンフ

表1　埼玉県赤十字血液センターにおける2004年度の献血者数

	全血献血		成分献血		総計
	200mL	400mL	PC+PPP	PPP	
男性	13,595	85,369	21,009	29,298	149,271
小計	98,964		50,307		
女性	36,910	23,312	8,243	25,446	93,911
小計	60,222		33,689		
総計	159,186		83,996		243,182

200mL：200mLの全血献血
400mL：400mLの全血献血
PC+PPP：血小板献血，PPP：血漿献血

表2　埼玉県赤十字血液センターにおける2003年度の献血者数

	全血献血		成分献血		総計
	200mL	400mL	PC+PPP	PPP	
男性	14,328	85,420	19,676	30,474	149,898
小計	99,748		50,150		
女性	37,138	24,871	7,946	26,203	96,158
小計	62,009		34,149		
総計	161,757		84,299		246,056

200mL：200mLの全血献血
400mL：400mLの全血献血
PC+PPP：血小板献血，PPP：血漿献血

表3　VVRの重症度分類[9]

分類	症　状	血圧(max，mmHg) 採血前→測定最低値	脈拍数(/分) 採血前→測定最低値	呼吸数 (/分)
軽症	気分不良，顔面蒼白，あくび，冷汗，悪心，嘔吐，意識消失(5秒以内)，四肢皮膚の冷汗	120以上→80以上 119以下→70以上	60以上→40以上 59以下→30以上	10以上
重症	軽度の症状に加え，意識喪失(5秒以上)，けいれん，尿失禁，脱糞	120以上→79以下 119以下→69以下	60以上→39以下 59以下→29以下	9以下

レットを渡すようになった2004年度の各月のVVRの発生頻度は1%未満となり，同様のVVRの低下傾向は2005年度でも持続していた。

男性の軽症のVVRの頻度は2004年度の発生率の方が2003年度の発生率に比し，全体で有意に低下した（図4）。軽症が大部分を占めるので，献血者全体でも有意に低下した。まずその献血の種類による違いをみると，血漿献血，血小板献血，400mLの全血献血，200mL全血献血のいずれでも有意に低下した（図4）。

女性の軽症のVVRの頻度は，2004年度の発生率は2003年度の発生率に比し，全体で有意に低下した（図5）。また，その献血の種類による違いをみると，血漿献血，400mL献血，200mL献血で有意に頻度が低下した（図5）。しかし，血小板献血では有意の頻度の低下は認められなかった。

男性の重症例で調べると，その頻度は2003年度も2004年度も0.03%と軽症例がそれぞれ0.7%と0.5%であるのに比べて，約1/10と少なかった。2004年度のVVRの発生率は2003年度の発生率と有意の差を認めなかった（図6）。また，いずれの献血種別でも差を認めなかった。とくに，200mL

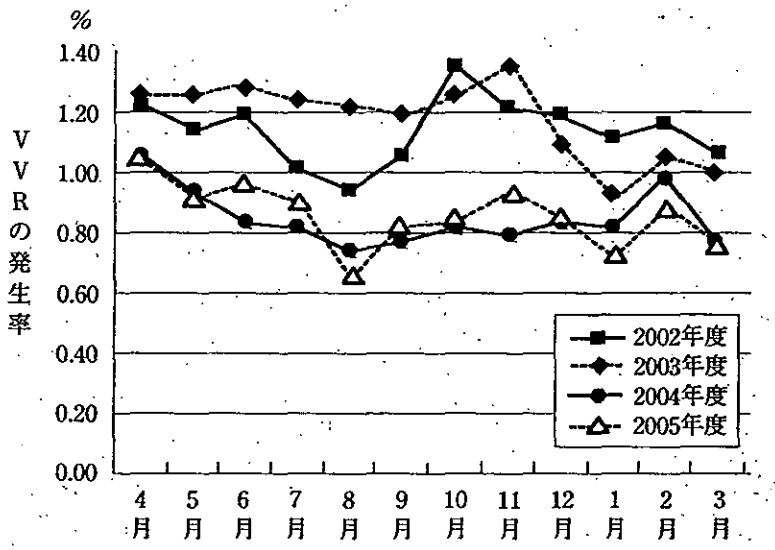

図3　VVRの発生率—2002年度，2003年度，2004年度，2005年度の月ごとのVVR発生率

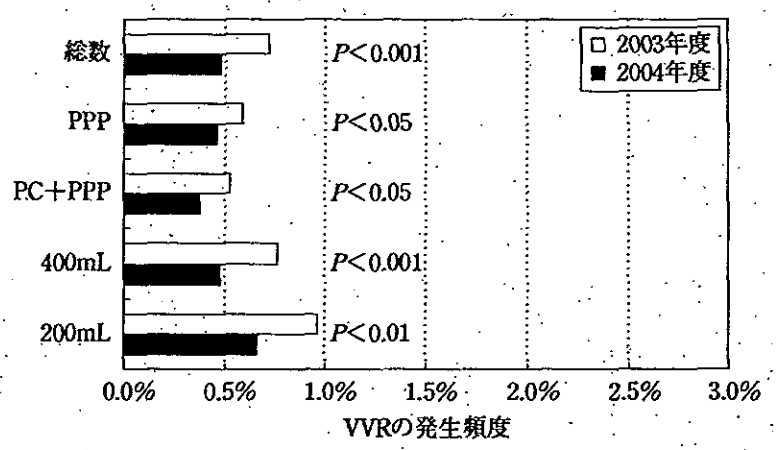

図4　埼玉赤十字血液センターにおける男性の軽症VVRの発生頻度の年度別の比較

PPP：血漿献血，PC+PPP：血小板献血　400mL：400mLの全血献血　200mL：200mLの全血献血

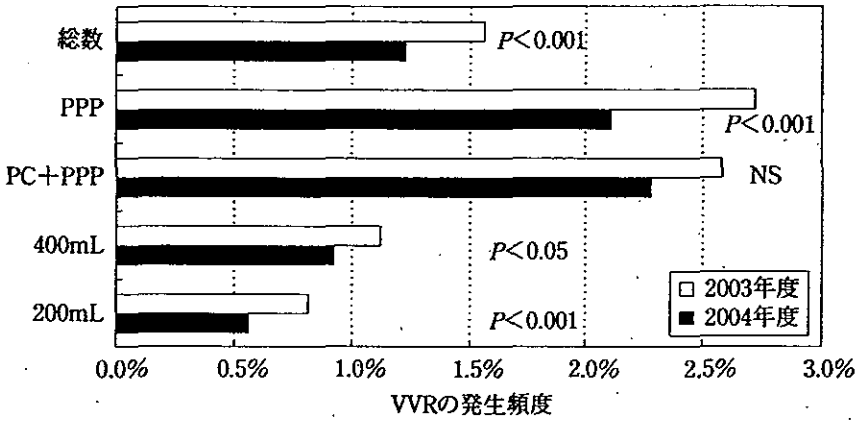

図5　埼玉赤十字血液センターにおける女性の軽症VVRの発生頻度の年度別の比較

PPP：血漿献血，PC+PPP：血小板献血　400mL：400mLの全血献血　200mL：200mLの全血献血　NS：有意差なし

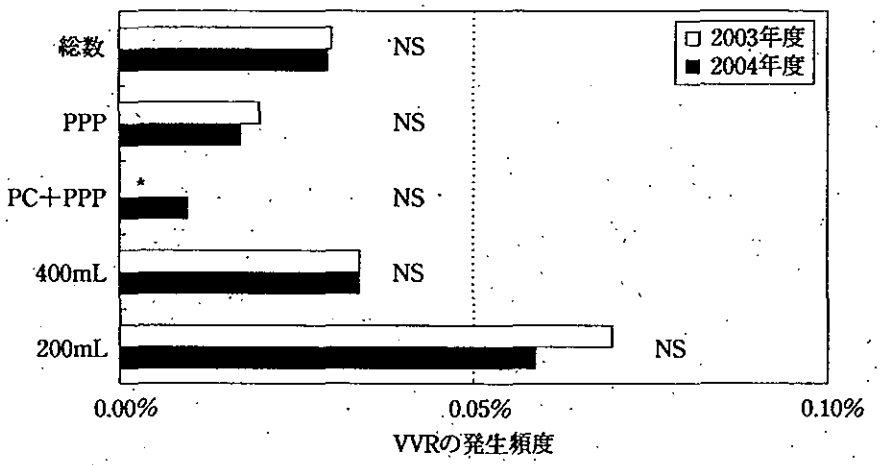

図6　埼玉赤十字血液センターにおける男性の重症VVRの発生頻度の年度別の比較

PPP：血漿献血，PC+PPP：血小板献血　400mL：400mLの全血献血　200mL：200mLの全血献血　NS：有意差なし

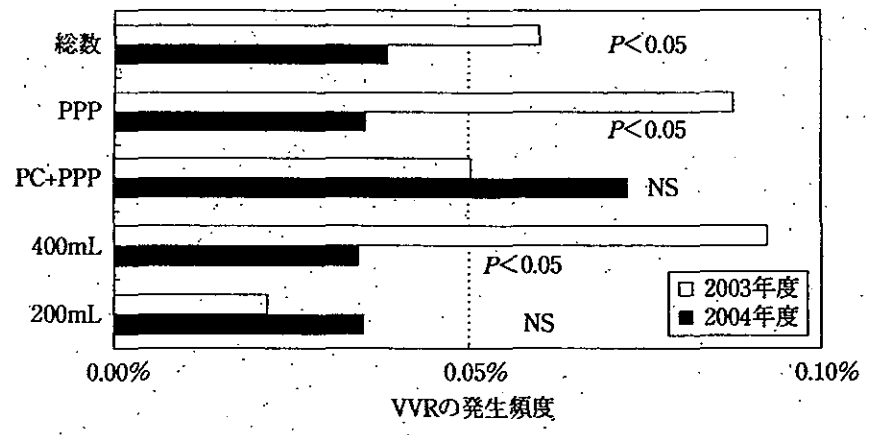

図7　埼玉赤十字血液センターにおける女性の重症VVRの発生頻度の年度別の比較

PPP：血漿献血，PC+PPP：血小板献血　400mL：400mLの全血献血　200mL：200mLの全血献血　NS：有意差なし

献血は高校生献血を多く含むと考えられ，重症例の発生は他の献血種別より高く，パンフレットを渡す効果はみられなかった。一方，女性の重症例では，2004年度の発生率は2003年度より全体，血漿献血および400mL献血いずれも有意に低下した（図7）。しかし，200mL献血と血小板献血における重症のVVRの発生頻度はパンフレットを渡しても有意の低下はみられなかった。

考　察

今回の結果から，初回の若い全血献血の男女と中高年の成分献血の女性に少なくとも30分の休憩と水分摂取を勧めるパンフレットを渡すことは男女ともVVRの発生頻度を低下させるのに有用と考える。医療機関における医療事故の防止には患者の協力を得ることが大切とされる。今回のパンフレットを献血者に渡すことはVVR予防に献血者の協力を求めるのに役立ったのではないかと考える。またそれだけではなく，採血を担当した看護師，接遇にあたる事務職員もそのパンフレットを持つ献血者に特別な配慮をした可能性もあり，それがVVR予防に有効であった可能性がある。他のグループの献血者には少なくとも15分休むように書いた紙を渡した。このこともVVRの全体の頻度を下げるのに効果があった可能性もある。

男性で重症のVVRについてはこの方法では頻度を低下させることはできなかった。とくに，初回の若年の男性を多く含む高校生あるいは専門学校生の集団献血ではこの方法が有効でない可能性が高い。そう考える根拠は，200mL献血における重症のVVRの頻度が他の献血より高く，この男性の200mL献血はほとんどが高校生の集団献血で行われているからである。その頻度がパンフレットを渡すことで低下していないことは，これらの献血者の重症のVVRの頻度をパンフレットを渡すことでは下げることができないと考えられる。現に，10歳代の男性の初回の全血献血者に限って検索すると，データは示していないが200mL献血も400mL献血も軽症のVVRの頻度は2003年度より2004年度の方が有意に低下したが，重症のVVRはいずれの場合も有意の減少はみられなかった。したがって，初回の男性の高校生あるいは専門学校生の集団献血では重症のVVRの頻度を低下させ，さらにそれによる転倒事故を減らすためには他の方策を考える必要があると思われる。我々は10歳代と20歳代の初回の男性を多く含む高校生献血あるいは男性の専門学校生の献血では，多くの場合バスにおいて採血する。その場合に，接遇の部屋をバスから離れたところに設営するのではなく，バスのすぐそばにテントで仮の接遇の場を造り，そこに1台のバスあたり約5脚の椅子を置き，さらに専門の職員を1人配置し，椅子に座ることと水分摂取を勧め，約30分後に献血手帳を渡すようにした。そのような工夫をすることによってVVRの発生頻度は大きく変わらないが，転倒者がいなくなった。このように接遇の部屋を採血場所にできるだけ近くにすることは他の血液センターでも推奨されている[10]。今後，その効果を長期的にみていきたいと考えている。

女性の重症のVVRの頻度は血漿献血，血小板献血および400mL献血で男性より高いが，それらの頻度がパンフレットを渡すことで著しく低下した。このことは本研究が目的とした成分献血のうち血漿献血には大きな効果があったと考える。しかし，血小板献血ではその頻度が減少しなかったことは，今後の問題と思われた。200mL献血における重症例の頻度は男性より低くパンフレットを渡すようになっても有意の変化はなかった。女性の場合は，男性で200mL献血を主に行う高校生の集団献血は埼玉県では行っておらず，多くはルームなどにおける個人の献血であると思われる。したがって，そのケアも行き届いている可能性が考えられる。そのことが200mL献血において男性の重症のVVRに比し，女性の重症のVVRの頻度が低い結果に繋がった可能性がある。

VVRの減少効果がパンフレットを渡した献血者だけに限定しているか否かについて一部の献血者で検討すると，データは示していないが，10歳代の男女とも200mL献血あるいは400mL献血において初回の献血者では2003年度より2004年度の方がVVRの発生は有意に減少したが，再来の献血者では有意の減少はみられていなかった。このことはこの群ではパンフレットを渡したことがVVRの発生を低下させたと考えられる。しかし，前述のよ

うにこの群でも重症のVVRの発生には効果はなかった。また，中高年の女性の成分献血では50歳代の初回の血漿献血をした献血者のVVRだけが2003年度より2004年度の方が有意に減少していたが，50歳代の再来あるいは60歳代の初回と再来では有意の減少は認められなかった。むしろ，若年の女性の血漿献血でVVRの減少傾向がみられていた。献血者を年齢別に分けるとその群に属する献血者数やVVRを起こした献血者数が少なくなり，その効果の判定が困難になった可能性もあるが，VVR予防のためのパンフレットを渡すという行為が献血者全員と職員のVVRに対する意識を高めたことも他の群のVVRの減少に関係した可能性もあると考える。

VVRのハイリスクグループを選び，VVRに対する対策を指示するパンフレットを渡すことは，VVRの減少に一定の効果を認めた。この方法が他センターでも有効であるか否かを検証していただくことが必要ではないかと考える。さらに，全国の血液センターにおける献血時の副作用を起こした例を集め，対策をたてることとそれぞれのセンターで有効とされる対策を集めて，それらの対策を全国のセンターで実施し，その有効性を検証することが必要であろう。

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(20)

原　著

16，17歳（高校生）を対象とする400m*l*全血と成分採血導入の可否—介入試験による検討

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若年者（16，17歳）からの400m*l*全血と成分献血についての意識調査を行った．高校生（集団献血実施校，非実施校），高校教諭，父母を対象に，両採血法に関する資料（情報）を提供し，その前後で同一内容のアンケートを行った．調査対象総数は1,450人，回答数（率）は1,177人（81%）であった．前調査では，400m*l*全血，成分の各献血法を「可」とするのは，それぞれ67，61%，「分らない」は28，35%であったが，この「分らない」の1/3～1/2が資料提供により賛成に転じ，後調査では「可」がそれぞれ77，74%に増加した．「反対」は前後の調査とも数～10%であった．

若年者での両採血の実施については，社会的な合意は大方得られており，適切な情報の提供のもとに実施可能であると考える．

キーワード：若年献血者，400mL献血，成分献血，介入試験

はじめに

少子高齢化が進むことにより，血液の供給面では献血者層，特に若い世代の献血者数と献血率の減少[1)2)]が，需要面では高齢受血者数と受血率の増加[3)]があり，需給の不均衡を生じることが懸念される．既に両者の関連を推計した報告[4)]があるが，その後に，献血年齢の上限が69歳に引き上げられ，医療技術の進歩や適正使用の推進により新鮮凍結血漿やアルブミン製剤の供給量は明らかに減少し，MAP加赤血球濃厚液のそれは微増に留まっている[5)]ことなどにより，現在は輸血用血液の需給の均衡は維持されているが，本質的な状況に変化はないと考えられる．

このような状況から，今後の血液の量的確保対策として，16，17歳を対象に400m*l*全血採血と成分採血の導入の是非を検討する必要があると考え，まず社会的な合意が得られるか否かの調査を2002年に行ったところ，過半数が賛意を表したが，「分からない」との回答者が20～30%認められた[6)]．そこで，これらの採血法に関する解説資料を提供して，「分からない」との回答者がその前後でどのように意識の変化を示すのかの，介入試験を試みたので報告する．

方　法

対象者は，集団献血実施校の高校生（A群）400人，非実施校の高校生（B群）450人，およびA，B両群の教諭（C群）200人と父母（D群）400人である．調査方法は，高校生では献血に関する

Table 1　Questionnaire

Question 1.	Recently, 400 m*l* whole blood donations from young persons (high school students) aged 16 or 17 have been discussed. What do you think of this idea?
	① Approve if he/she meets the criteria (body-weight etc.) defined by the Blood Collection Standards.
	② Approve at or over the age of 17.
	③ Approve at or over the age of 16.
	④ Unclear.
	⑤ Unacceptable. [Reasons：　　]
Question 2.	Recently, apheresis donations (collecting only platelets or plasma) from young persons (high school students) aged 16 or 17 have been discussed. What do you think of this idea?
	① Approve if he/she meets the criteria (body-weight etc.) defined by the Blood Collection Standards.
	② Approve at or over the age of 17.
	③ Approve at or over the age of 16.
	④ Unclear.
	⑤ Unacceptable. [Reasons：　　]

アンケート調査用紙（Table 1）を配布・記入し（前調査），次いで配布した解説資料を読んでもらった後に，再度同一内容のアンケート調査用紙に記入（後調査）を依頼し，回収した．教諭と父母については，同様な手順による記入を依頼し，郵送により回収した．

解説資料の内容[7]としては，循環血液量（体重）と安全な採血量の関係，過去15年間の献血者数，採血基準の概要，400m*l*採血と成分採血の概要，前述の2002年に実施した調査結果の要約を記載した．調査期間は2003年1～2月とした．

両調査について回答の得られたものを，対象者群別に，400m*l*全血と成分採血についてクロス集計し，さらにC，D群については献血経験の有無別に，A群は献血の種類（400m*l*と200m*l*全血献血）別にも比較検討したが，B群については献血歴の有無の調査は行わなかった．なお，回答は①「体重等の基準を満たしていればやってもよい」，②「17歳以上なら可」，③「16歳以上なら可」，④「分からない」，⑤「やるべきではない」（反対）であり，①②③を賛成群として集計した．有意差検定にはχ^2検定を用いた．

成　績

1）16・17歳の400m*l*献血について

有効回答数および回答率はA，B，C，D群順に337(84%)，383(85%)，167(84%)，290(73%)，総数1,177（81%）であった．前調査と後調査の群別クロス集計をTable 2に示す．前調査での①②③の賛成回答は，A，B，C，D群順に74，55，72，70%で，B群が他群より少なく（$p<0.005$），④「わからない」は各々25，42，16，22%で，B群が他群より多く（$p<0.005$），C群はA群より少なかった（$p<0.025$）．一方，⑤「やるべきではない」は各々1，3，13，8%で，A，B群はC，D群より少なかった（$p<0.005$）．

後調査では，賛成回答がA，B，C，D群順に83，69，83，76%に増加したが，それは各群の④の32～50%および⑤の8～36%が賛成回答に移動したためである．その結果④が16，28，10，17%へと減少し，⑤もわずかながら減少した．逆に賛成回答から⑤に変わったのは，B群の0.5%とD群の1%，④へは各々4，4，1，1%と少数であった．

後調査の対象群間差をみると，賛成回答ではB群はA，C群より（$p<0.005$），D群はA群より少なく（$p<0.025$），④ではB群は他群より多くなり（$p<0.005$），⑤は変化しなかった．

即ち，資料による介入効果がみられたのは，賛成回答の増加したA，B群（$p<0.005$）とC群（$p<0.025$）であり，A，B群での④の減少であった（$p<0.005$）．

献血歴別にみると（Table 3），C群の献血歴ありは130人(78%)，なしは36人，D群のありは175人(61%)，なしは114人であった．C群のあり，

Table 2 Opinion and change in opinion concerning the acceptability of 400 ml whole blood donations from young persons before and after reading a document about 400 ml whole blood donations by groups.

A group		after ①	②	③	④	⑤	before total (%)	
before	①	175	6	3	7	0	191 (57)	248 (74%)
	②	6	28	1	1	0	36 (11)	
	③	5	0	14	2	0	21 (6)	
	④	30	6	6	43	0	85 (25)	
	⑤	1	0	0	2	1	4 (1)	
after total (%)		217 (64)	40 (12)	24 (7)	55 (16)	1 (0)	337	

281 (83%)

Change in opinion from ④ to ①②③ : 42/85 = 49%
⑤ to ①②③ : 1/4 = 25%
⑤ to ④ : 2/4 = 50%

B group		after ①	②	③	④	⑤	before total (%)	
before	①	169	2	2	8	1	182 (48)	212 (55%)
	②	7	2	0	1	0	10 (3)	
	③	5	0	15	0	0	20 (5)	
	④	47	10	3	97	3	160 (42)	
	⑤	4	0	0	1	6	11 (3)	
after total (%)		232 (61)	14 (4)	20 (5)	107 (28)	10 (3)	383	

266 (69%)

Change in opinion from ④ to ①②③ : 60/160 = 38%
⑤ to ①②③ : 4/11 = 36%
⑤ to ④ : 1/11 = 9%

C group		after ①	②	③	④	⑤	before total (%)	
before	①	99	2	2	2	0	105 (63)	120 (72%)
	②	2	6	0	0	0	8 (5)	
	③	0	0	7	0	0	7 (4)	
	④	10	1	2	12	1	26 (16)	
	⑤	6	0	1	3	11	21 (13)	
after total (%)		117 (70)	9 (5)	12 (7)	17 (10)	12 (7)	167	

138 (83%)

Change in opinion from ④ to ①②③ : 13/26 = 50%
⑤ to ①②③ : 7/21 = 33%
⑤ to ④ : 3/21 = 14%

D group		after ①	②	③	④	⑤	before total (%)	
before	①	177	2	2	2	3	186 (64)	203 (70%)
	②	3	12	0	1	0	16 (6)	
	③	0	0	1	0	0	1 (0)	
	④	19	1	0	39	4	63 (22)	
	⑤	2	0	0	6	16	24 (8)	
after total (%)		201 (69)	15 (5)	3 (1)	48 (17)	23 (8)	290	

219 (76%)

Change in opinion from ④ to ①②③ : 20/63 = 32%
⑤ to ①②③ : 2/24 = 8%
⑤ to ④ : 6/24 = 25%

A group : Students in high schools giving mass blood donations
B group : Students in high schools notgiving mass blood donations
C group : Teachers in these schools
D group : Parents of these students

なし，D群のあり，なしの順に前調査の賛成は各々72，72，70，69%，④は各々16，14，22，21%，⑤は同様に12，14，8，10%で，献血歴の有無による差は認められなかった．後調査ではそれぞれが同じように④⑤から賛成へ変化し，同様の順に賛成が84，81，77，72%，④は各々11，6，15，19%となり，⑤はC群のありとD群のなしが5，9%になったが，C群のなしとD群のありは変化しなかった．資料による介入効果が認められたのはC群の献血歴ありの賛成回答の増加のみ（$p<0.025$）であった．

A群の献血種別による回答を，Table 4に示す．前調査の賛成回答は400mlと200ml献血者では各々79%，70%で差は無かったが，資料により400ml献血者の④の59%，200ml献血者のそれの46%が賛成回答へと変わり，後調査では賛成は各々90%，80%で，400ml献血者のほうが有意に多くなった（$p<0.025$）．即ち資料による介入効果は両者に認められるが400mlの方がより高かった（$p<0.025$，$p<0.05$）．

2) 16・17歳の成分献血について

有効回答数（率）はA，B，C，D群順に，336

Table 3　Opinion and change in opinion concerning the acceptability of 400 m*l* whole blood donations from young persons before and after reading a document about 400 m*l* whole blood donations by previous blood donations in C and D groups.

C group with previous blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	79	1	1	1	0	82 (63)	94 (72%)
	②	2	3	0	0	0	5 (4)	
	③	0	0	7	0	0	7 (5)	
	④	8	1	0	11	1	21 (16)	
	⑤	6	0	1	2	6	15 (12)	
after total (%)		95 (73)	5 (4)	9 (7)	14 (11)	7 (5)	130	

109 (84%)

Change in opinion from ④ to ①②③ : 9/21 = 43%
⑤ to ①②③ : 7/15 = 47%
⑤ to ④ : 2/15 = 13%

C group without blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	20	1	1	1	0	23 (64)	26 (72%)
	②	0	3	0	0	0	3 (8)	
	③	0	0	0	0	0	0 (0)	
	④	2	0	2	1	0	5 (14)	
	⑤	0	0	0	0	5	5 (14)	
after total (%)		22 (61)	4 (11)	3 (8)	2 (6)	5 (14)	36	

29 (81%)

Change in opinion from ④ to ①②③ : 4/5 = 80%

D group with previous blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	107	0	1	0	2	110 (63)	122 (70%)
	②	2	8	0	1	0	11 (6)	
	③	0	0	1	0	0	1 (1)	
	④	15	0	0	22	2	39 (22)	
	⑤	0	0	0	4	10	14 (8)	
after total (%)		124 (71)	8 (5)	2 (1)	27 (15)	14 (8)	175	

134 (77%)

Change in opinion from ④ to ①②③ : 15/39 = 38%
⑤ to ④ : 4/14 = 29%

D group without blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	68	2	1	2	1	74 (65)	79 (69%)
	②	1	4	0	0	0	5 (4)	
	③	0	0	0	0	0	0 (0)	
	④	4	0	0	18	2	24 (21)	
	⑤	2	0	0	2	7	11 (10)	
after total (%)		75 (66)	6 (5)	1 (1)	22 (19)	10 (9)	114	

82 (72%)

Change in opinion from ④ to ①②③ : 4/24 = 17%
⑤ to ①②③ : 2/11 = 18%
⑤ to ④ : 2/11 = 18%

C and D groups : see Table 2

Table 4　Opinion and change in opinion concerning the acceptability of 400 m*l* whole blood donations from young persons before and after reading a document about 400 m*l* whole blood donations by 400 m*l* and 200 m*l* whole blood donations at survey in A group.

400 m*l* donation		after ①②③	④	⑤	before total (%)
before	①②③	100	2	0	102 (79)
	④	16	11	0	27 (21)
	⑤	0	0	0	0 (0)
after total (%)		116 (90)	13 (10)	0 (0)	129

Change in opinion from ④ to ①②③ : 16/27 = 59%

200 m*l* donation		after ①②③	④	⑤	before total (%)
before	①②③	137	8	0	145 (70)
	④	26	31	0	57 (28)
	⑤	1	2	1	4 (2)
after total (%)		164 (80)	41 (20)	1 (0)	206

Change in opinion from ④ to ①②③ : 26/57 = 46%
⑤ to ①②③ : 1/4 = 25%
⑤ to ④ : 2/4 = 50%

A group : see Table 2

Table 5 Opinion and change in opinion concerning the acceptability of apheresis from young persons before and after reading a document about apherersis donations by groups.

A group		after ①	②	③	④	⑤	before total (%)	
before	①	163	4	0	8	0	175 (52)	230 (68%)
	②	3	26	1	3	0	33 (10)	
	③	5	1	16	0	0	22 (7)	
	④	31	8	3	64	0	106 (32)	
	⑤	0	0	0	0	0	0 (0)	
after total (%)		202 (60)	39 (12)	20 (6)	75 (22)	0 (0)	336	

261 (78%)

Change in opinion from ④ to ①②③ : 42/106 = 40%

B group		after ①	②	③	④	⑤	before total (%)	
before	①	162	3	1	7	0	173 (45)	198 (51%)
	②	4	4	0	1	0	9 (2)	
	③	5	0	11	0	0	16 (4)	
	④	62	9	4	103	2	180 (47)	
	⑤	0	0	0	2	5	7 (2)	
after total (%)		233 (61)	16 (4)	16 (4)	113 (29)	7 (2)	385	

265 (69%)

Change in opinion from ④ to ①②③ : 75/180 = 42%
⑤ to ④ : 2/7 = 29%

C group		after ①	②	③	④	⑤	before total (%)	
before	①	92	2	1	3	0	98 (59)	109 (66%)
	②	1	3	0	0	0	4 (2)	
	③	0	0	7	0	0	7 (4)	
	④	19	1	3	19	1	43 (26)	
	⑤	3	0	1	1	8	13 (8)	
after total (%)		115 (70)	6 (4)	12 (7)	23 (14)	9 (5)	165	

133 (81%)

Change in opinion from ④ to ①②③ : 23/43 = 53%
⑤ to ①②③ : 4/13 = 31%
⑤ to ④ : 1/13 = 8%

D group		after ①	②	③	④	⑤	before total (%)	
before	①	156	1	1	4	1	163 (56)	184 (63%)
	②	8	12	0	0	0	20 (7)	
	③	0	0	1	0	0	1 (0)	
	④	32	1	0	53	3	89 (30)	
	⑤	1	0	0	3	15	19 (7)	
after total (%)		197 (67)	14 (5)	2 (1)	60 (21)	19 (7)	292	

213 (73%)

Change in opinion from ④ to ①②③ : 33/89 = 37%
⑤ to ①②③ : 1/19 = 5%
⑤ to ④ : 3/19 = 16%

A, B, C and D groups : see Table 2.

(84%), 385 (86%), 165 (83%), 292 (73%) で, 総数1,178 (81%) であり, Table 5 に前調査と後調査の群別クロス集計を示す. 前調査では, A, B, C, D 群順に賛成が68, 51, 66, 63% で, 400 ml 献血に対する賛成回答より4~7% 少なかったが, 同様の傾向であり, B 群では他群より少なかった ($p<0.005$). ④「わからない」は各々32, 47, 26, 30% で, B 群が他群より多かった ($p<0.005$). ⑤「やるべきではない」は0, 2, 8, 7% と少数であり, A, B 群は C, D 群より少なかった ($p<0.005$).

資料読後には, ④では各群とも37~53% が, ⑤では A, B 群は変化なく C, D 群で各々の31, 5% が賛成回答に変ったことから, 後調査での賛成は A, B, C, D 群順に78, 69, 81, 73% に増加し, ④は各々22, 29, 14, 21% に減少し, C 群では⑤もわずかながら減少した. 賛成回答から⑤にかわったのは D 群の0.5% のみ, ④へは各々5, 4, 3, 2% であった. その結果, 後調査の対象群間差は, 賛成回答では B 群は A, C 群 ($p<0.01$, 0.005) より少なく, ④では B 群は他群より ($p<0.005$~0.05), A 群は C 群より ($p<0.05$) 多かった. ⑤では C, D 間以外はすべての群間に差を認めた ($p<0.005$~0.025).

即ち, 資料による介入効果はすべての群にみられ, 賛成回答は有意に増加 (A 群 ($p<0.01$), B, C 群 ($p<0.005$), D 群 ($p<0.025$)) し, ④は有意に減少 (A, C, D 群 ($p<0.01$), B 群 ($p<0.005$)) した.

Table 6　Opinion and change in opinion concerning the acceptability of apheresis from young persons before and after reading a document about apherersis donations by previous blood donations in C and D groups.

C group with previous blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	73	1	1	2	0	77 (59)	86 (66%)
	②	1	2	0	0	0	3 (2)	
	③	0	0	6	0	0	6 (5)	
	④	17	1	0	15	1	34 (26)	
	⑤	3	0	1	1	5	10 (8)	
after total (%)		94 (72)	4 (3)	8 (6)	18 (14)	6 (5)	130	

106 (82%)

Change in opinion from ④ to ①②③ : 18/34 = 53%
⑤ to ①②③ : 4/10 = 40%
⑤ to ④ : 1/10 = 10%

C group without blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	20	1	0	1	0	22 (61)	24 (67%)
	②	0	1	0	0	0	1 (3)	
	③	0	0	1	0	0	1 (3)	
	④	2	0	2	5	0	9 (25)	
	⑤	0	0	0	0	3	3 (8)	
after total (%)		22 (61)	2 (6)	3 (8)	6 (17)	3 (8)	36	

27 (75%)

Change in opinion from ④ to ①②③ : 4/9 = 44%

D group with previous blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	92	0	1	1	1	95 (54)	108 (62%)
	②	6	6	0	0	0	12 (7)	
	③	0	0	1	0	0	1 (1)	
	④	23	1	0	31	2	57 (33)	
	⑤	0	0	0	3	7	10 (6)	
after total (%)		121 (69)	7 (4)	2 (1)	35 (20)	10 (6)	175	

130 (74%)

Change in opinion from ④ to ①②③ : 24/57 = 42%
⑤ to ④ : 3/10 = 30%

D group without blood donation		after ①	②	③	④	⑤	before total (%)	
before	①	63	1	0	3	0	67 (59)	75 (66%)
	②	2	6	0	0	0	8 (7)	
	③	0	0	0	0	0	0 (0)	
	④	9	0	0	20	1	30 (26)	
	⑤	1	0	0	0	8	9 (8)	
after total (%)		75 (66)	7 (6)	0 (0)	23 (20)	9 (8)	114	

82 (72%)

Change in opinion from ④ to ①②③ : 9/30 = 30%
⑤ to ①②③ : 1/9 = 11%

C and D groups : see Table 2

献血歴別にみると（Table 6），C群の献血歴あり，なし，D群の献血歴あり，なし順に前調査の賛成は各々66，67，62，66%，④は各々26，25，33，26%，⑤は各々8，8，6，8%で，献血歴の有無による差は認められなかった．後調査では，賛成が各々82，75，74，72%，④は各々14，17，20，20%，⑤はC群献血歴ありのみ減少して5%になったが，後調査でも献血歴による差は認められなかった．一方，資料による介入効果が有意に認められたのは，C，D群ともに献血歴ありのみで，両群の賛成の増加（$p<0.005$，0.025）と④の減少（$p<0.025$，0.01）およびC群の⑤の減少（$p<0.05$）であった．

A群の献血種別による回答を，Table 7に示す．前調査の賛成率は400ml献血者では77%と200ml献血者の64%より多く（$p<0.025$），後調査では，400ml献血者の④の57%，200ml献血者の33%が賛成に変わったことから，後調査の賛成は各々88%と72%になった（$p<0.005$）が，介入効果が有意であったのは400ml献血者のみであった（$p<0.025$）．

3）反対意見の理由

⑤「やるべきではない」との回答の理由については，400ml，成分献血の導入に共通しており，C群では未だ成長過程にある，体力面での不安がある，大人（18歳あるいは20歳）になってからでよい，最近の高校生は弱くなっている，等が挙げられていた．またD群ではC群と同様の理由の他

Table 7 Opinion and change in opinion concerning the acceptability of apheresis from young persons before and after reading a document about apheresis donations by 400 m*l* and 200 m*l* whole blood donations at survey in A group.

400 m*l* donation		after ①②③	after ④	after ⑤	before total (%)
before	①②③	96	3	0	99 (77)
	④	17	13	0	30 (23)
	⑤	0	0	0	0 (0)
after total (%)		113 (88)	16 (12)	0 (0)	129

Change in opinion from ④ to ①②③ : 17/30 = 57%

200 m*l* donation		after ①②③	after ④	after ⑤	before total (%)
before	①②③	123	8	0	131 (64)
	④	25	50	0	75 (36)
	⑤	0	0	0	0 (0)
after total (%)		148 (72)	58 (28)	0 (0)	206

Change in opinion from ④ to ①②③ : 25/75 = 33%

A group : see Table 2

に，本人に正しい判断が望めない，成分採血時の感染が恐い，フィルター経由の環流（返血）は不可，との回答があった．これらの見解は資料を読んだ後でもほとんどの回答で変化はなく，献血経験の有無による差も認められなかったが，保護者の許可を条件とするとの⑤から④への変更が，C群に1人あった．

前調査の賛成回答から⑤への変更では，B群で量が多い，D群で正しい判断が望めない，他の方法を考えるべきとの理由が挙げられていたが，④への変更には理由の記載はなかった．

考　察

今後予測される血液不足対策としては，献血量の増量と使用適正化による量的抑制とが必要である．前者については，1986年の400m*l*全血採血と成分採血の導入，1999年の年齢の上限の69歳への引き上げとがあり，いずれも量的確保に効果的であった．今後の献血量の確保対策としては，先ずは現行の採血基準に該当する年齢層のより多くの参加を求める努力をすることであるが，さらには現在200m*l*の全血献血しかできない16，17歳の若年者（高校生）を対象にして，400m*l*全血と成分献血を導入することの是非を検討することである．

近年の年齢階級別の人口に対する献血率の推移をみると，毎年若年者ほど高い傾向にあるが，16～19歳の献血率は1985年をピークに以降の低下傾向が顕著である[1)2)]．このような低下傾向の理由の一つとして，医療機関の血液使用状況が200m*l*全血由来から400m*l*全血由来へと大幅に移行し，200m*l*全血由来の赤血球成分の使用量が激減してきていることから，日赤血液センターでは200m*l*全血採血を抑制する方針であることも挙げられる．しかしながら，献血のきっかけとして高校生献血を挙げる献血者が多いとの報告があり[6)]，高校生献血がその後の献血指向性に大きな役割を持っているといえることから，より合理的な高校生献血を推進することが必要と考えられる．

採血基準は，医学的な安全性とともに，社会的な合意が得られなければならない．1986年の採血基準改訂時には，400m*l*全血採血と成分採血時の安全性を循環血液量に対する採血量の比として検討し，それが12～13%以内（体重約50kgで400m*l*採血）であれば問題はないとされ[8)]，同様なことは他にも報告されている[9)]．このことは年齢には関係しないと考えられ，事実自己血輸血では16歳未満あるいは70歳以上でも採血が行われているが，特に年齢による問題点は指摘されていない．しかし，1986年の採血基準の制定時には社会的に受入れ易いことを考慮して，18歳以上とされた経緯がある．

今回のアンケート調査では，400m*l*全血献血で67%，成分献血で61%が，主に体重等の採血基準を満たしていれば16，17歳での導入に賛成していることから，現在では大方の合意は得られているものと考えられる．このことは，両採血法への理解が導入後20年近く大過なく行われてきていることから，より深まってきていることの表れと

もいえるであろう．さらに，前調査で400ml全血献血について「分らない」と回答した中の32～50%が，B群（献血非実施校）を含めて資料提供後に賛成に転じたこと，さらに成分献血についても同様に「分らない」との回答中の37～53%が賛成に変わったこと，しかも「やるべきではない」(反対者）の人数は少ないものの資料提供後には不変ないしわずかな減少であったことは，400ml全血や成分献血についての実態を理解することにより，賛成者が増加することを示している．また，C，D群（教諭，父母）では献血経験者の方が，またA群（献血実施校）では200ml献血者より400ml献血者のほうが，資料提供後の賛成への転換率が高かった．高校生の多くは初回は200ml献血であることも考慮すれば，献血経験が資料内容の理解をより容易にする効果があると考えられる．

海外での状況としては，欧米での採血基準（主に採血量と年齢）を各国のホームページ等で検索した結果，全血採血は体重50kg以上，採血量450～500mlの場合，年齢の下限は17あるいは18歳が多かったが，米国では一般には17歳[10]としているものの，ニューヨーク，カリフォルニア等の7州では16歳でも親の同意があればよく，またオーストラリアでも16，17歳の採血には親の同意を必要としている．なお，ニューヨーク州が16歳からとしたのは2005年4月であり[11]，今後はその他の州においても年齢の下限の見直しが行われるものと思われる．

以上のごとく，今回のアンケート調査結果や国外の状況からして，16，17歳での400ml全血および成分採血の実施は可能であると考える．本邦ではすでに200ml全血採血が16歳から行われている状況を踏まえれば，親権者の同意の必要性については今後検討すべき課題であろう．

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11) AABB：The New York State Department of Health recently granted New York Blood Center (NYBC) a variance to existing state regulations, permitting donations for the very first time from 16-year-old blood donors in New York. AABB Weekly Report, 11.(11)：7, 2005.

INTRODUCTION OF 400 ML WHOLE BLOOD AND APHERESIS DONATIONS FROM AGE 16 AND 17 (HIGH SCHOOL STUDENTS) INTO THE BLOOD PROGRAM —INVESTIGATION OF CHANGING OPINIONS BEFORE AND AFTER REVIEW OF EXPLANATORY DOCUMENTS—

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In order to obtain more blood for an increasingly aged society, a questionnaire survey was conducted to discover whether it would be socially acceptable to accept 400 m*l* whole blood (WB) and apheresis donations for the blood program from young persons of the age of 16 and 17 (mainly high school students), who are presently permitted to donate 200 m*l* WB only. We surveyed high school students who did and did not participate in mass blood donations in schools, their high school teachers, and parents. They were asked to reply to the same questions before and after reading documents explaining both blood donation types. The total number of respondents (rate) was 1,450 (81%). Before reviewing the documents 67% answered "acceptable" to 400 m*l* WB and 61% to apheresis, and 28% and 35% answered "unclear", respectively. One-third to one-half of those who ansewerd "unclear" changed their opinion to "acceptable" after reading the documents. This resulted in an increase of "acceptable" opinions to 77% for 400 m*l* WB and to 74% for apheresis. The proposal was "declined" by around 10% or less in both questions.

It is considered that the introduction of 400 m*l* WB and apheresis donations from young persons into the blood program would be commonly accepted after informed consent was obtained, and that the provision of suitable information on these donations can gain lead to an increase in acceptability.

Key words : Young donors, 400 m*l* donation, apheresis donation, intervention survey

採血基準に関する各種論文

（第2回採血基準見直しの検討に係るﾜｰｷﾝｸﾞｸﾞﾙｰﾌﾟ追加提示分）

平成19年度 10代年齢別採血副作用発生率

(1)

VVR発生件数

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	223	270	119	76
	女	304	353	354	283
	男女	527	623	473	359
400mL	男	−	−	1,347	1,333
	女	−	−	702	703
	男女	−	−	2,049	2,036
PPP	男	−	−	32	30
	女	−	−	224	297
	男女	−	−	256	327
PC+PPP	男	−	−	39	74
	女	−	−	156	244
	男女	−	−	195	318

VVR発生率

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	1.370%	1.155%	2.039%	3.196%
	女	1.714%	1.456%	1.872%	1.725%
	男女	1.549%	1.308%	1.912%	1.911%
400mL	男	−	−	2.673%	2.347%
	女	−	−	3.460%	2.985%
	男女	−	−	2.899%	2.534%
PPP	男	−	−	1.454%	1.008%
	女	−	−	3.484%	2.891%
	男女	−	−	2.966%	2.468%
PC+PPP	男	−	−	0.989%	1.043%
	女	−	−	4.544%	3.853%
	男女	−	−	2.644%	2.368%

VVR重症発生件数

採血種類	性別	16歳	17歳	18歳	19歳	
200mL	男	6	5	3	1	15
	女	10	14	8	3	35
	男女	16	19	11	4	50
400mL	男	−	−	51	41	92
	女	−	−	32	31	63
	男女	−	−	83	72	##
PPP	男	−	−	0	0	0
	女	−	−	7	9	16
	男女	−	−	7	9	16
PC+PPP	男	−	−	0	1	1
	女	−	−	5	13	18
	男女	−	−	5	14	19

VVR重症発生率

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	0.037%	0.021%	0.051%	0.042%
	女	0.056%	0.058%	0.042%	0.018%
	男女	0.047%	0.040%	0.044%	0.021%
400mL	男	−	−	0.101%	0.072%
	女	−	−	0.158%	0.132%
	男女	−	−	0.117%	0.090%
PPP	男	−	−	0.000%	0.000%
	女	−	−	0.109%	0.088%
	男女	−	−	0.081%	0.068%
PC+PPP	男	−	−	0.000%	0.014%
	女	−	−	0.146%	0.205%
	男女	−	−	0.068%	0.104%

VVR転倒発生件数

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	6	4	0	0
	女	2	6	6	6
	男女	8	10	6	6
400mL	男	−	−	21	24
	女	−	−	20	18
	男女	−	−	41	42
PPP	男	−	−	0	0
	女	−	−	2	1
	男女	−	−	2	1
PC+PPP	男	−	−	1	1
	女	−	−	3	2
	男女	−	−	4	3

VVR転倒発生率

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	0.037%	0.017%	0.000%	0.000%
	女	0.011%	0.025%	0.032%	0.037%
	男女	0.024%	0.021%	0.024%	0.032%
400mL	男	−	−	0.042%	0.042%
	女	−	−	0.099%	0.076%
	男女	−	−	0.058%	0.052%
PPP	男	−	−	0.000%	0.000%
	女	−	−	0.031%	0.010%
	男女	−	−	0.023%	0.008%
PC+PPP	男	−	−	0.025%	0.014%
	女	−	−	0.087%	0.032%
	男女	−	−	0.054%	0.022%

皮下出血発生件数

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	7	10	5	1
	女	46	54	32	32
	男女	53	64	37	33
400mL	男	−	−	33	49
	女	−	−	32	47
	男女	−	−	65	96
PPP	男	−	−	12	17
	女	−	−	82	115
	男女	−	−	94	132
PC+PPP	男	−	−	24	50
	女	−	−	39	84
	男女	−	−	63	134

皮下出血発生率

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	0.043%	0.043%	0.086%	0.042%
	女	0.259%	0.223%	0.169%	0.195%
	男女	0.156%	0.134%	0.150%	0.176%
400mL	男	−	−	0.065%	0.086%
	女	−	−	0.158%	0.200%
	男女	−	−	0.092%	0.119%
PPP	男	−	−	0.545%	0.571%
	女	−	−	1.275%	1.119%
	男女	−	−	1.089%	0.996%
PC+PPP	男	−	−	0.609%	0.705%
	女	−	−	1.136%	1.326%
	男女	−	−	0.854%	0.998%

穿刺部痛発生件数

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	3	5	2	1
	女	4	8	9	7
	男女	7	13	11	8
400mL	男	−	−	10	7
	女	−	−	6	5
	男女	−	−	16	12
PPP	男	−	−	2	0
	女	−	−	2	9
	男女	−	−	4	9
PC+PPP	男	−	−	0	5
	女	−	−	5	6
	男女	−	−	5	11

穿刺部痛発生率

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	0.018%	0.021%	0.034%	0.042%
	女	0.023%	0.033%	0.048%	0.043%
	男女	0.021%	0.027%	0.044%	0.043%
400mL	男	−	−	0.020%	0.012%
	女	−	−	0.030%	0.021%
	男女	−	−	0.023%	0.015%
PPP	男	−	−	0.091%	0.000%
	女	−	−	0.031%	0.088%
	男女	−	−	0.046%	0.068%
PC+PPP	男	−	−	0.000%	0.070%
	女	−	−	0.146%	0.095%
	男女	−	−	0.068%	0.082%

平成19年度:献血者数

採血種類	性別	16歳	17歳	18歳	19歳
200mL	男	16,277	23,376	5,836	2,378
	女	17,736	24,248	18,908	16,404
	男女	34,013	47,624	24,744	18,782
400mL	男	−	−	50,386	56,791
	女	−	−	20,288	23,548
	男女	−	−	70,674	80,339
PPP	男	−	−	2,201	2,976
	女	−	−	6,430	10,273
	男女	−	−	8,631	13,249
PC+PPP	男	−	−	3,943	7,094
	女	−	−	3,433	6,333
	男女	−	−	7,376	13,427

17歳男性の400mL全血採血に関する検討

【方法】

＜供血者の選択＞

1）採血時の満年齢が17歳であること

2）現行の400ml全血採血の基準を満たすこと

3）文書により本人および親権者の同意がえられること

4）各施設50名（北海道、宮城県、東京都、愛知県、大阪府、岡山県、福岡県）

＜検討項目＞

1)採取中・採取後の副作用の有無と採血後1週間以内の自覚症状の有無（アンケート調査）

2）赤血球採取前後の供血者の検査項目

採血前，採血3か月後に血球計数，血清鉄，TIBC，フェリチン値について検査

＜コントロール群＞

1）現行採血基準で400ml全血採血を行なっている18歳・19歳の献血者

2）各施設50名（北海道、宮城県、東京都、愛知県、大阪府、岡山県、福岡県）

*本研究は、試験プロトコール等について東京医科歯科大学の医学倫理委員会の承認を得ている

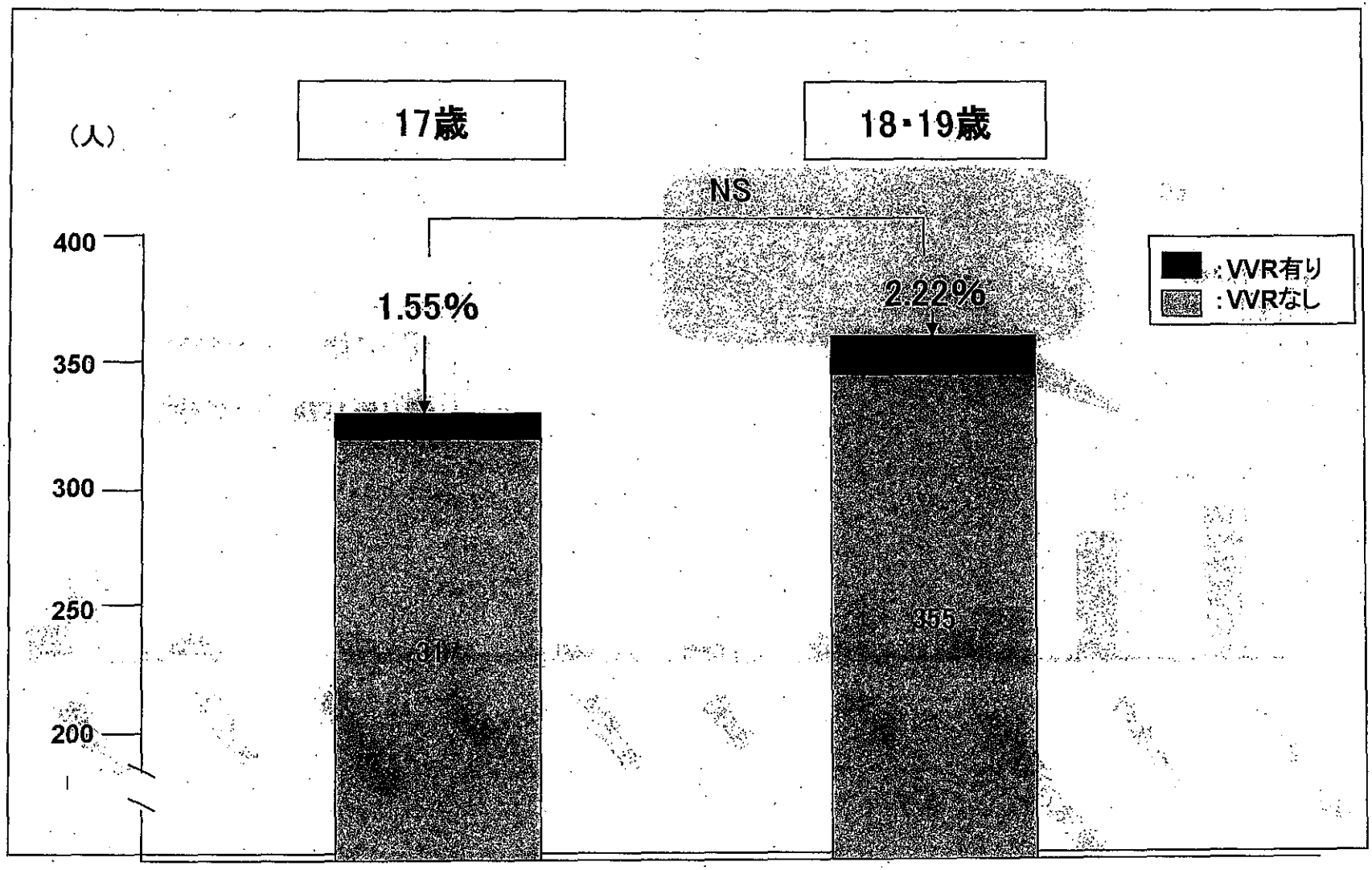
表1. 施設別400ml 採血例数

	17歳男性(検討群)	18・19歳男性(コントロール群)
北海道センター	45	46
宮城センター	43	57
東京都センター	65	58
愛知センター	43	45
大阪センター	53	57
岡山センター	21	45
福岡センター	52	55
計	322	363

【結果】　Ⅰ.供血者の背景

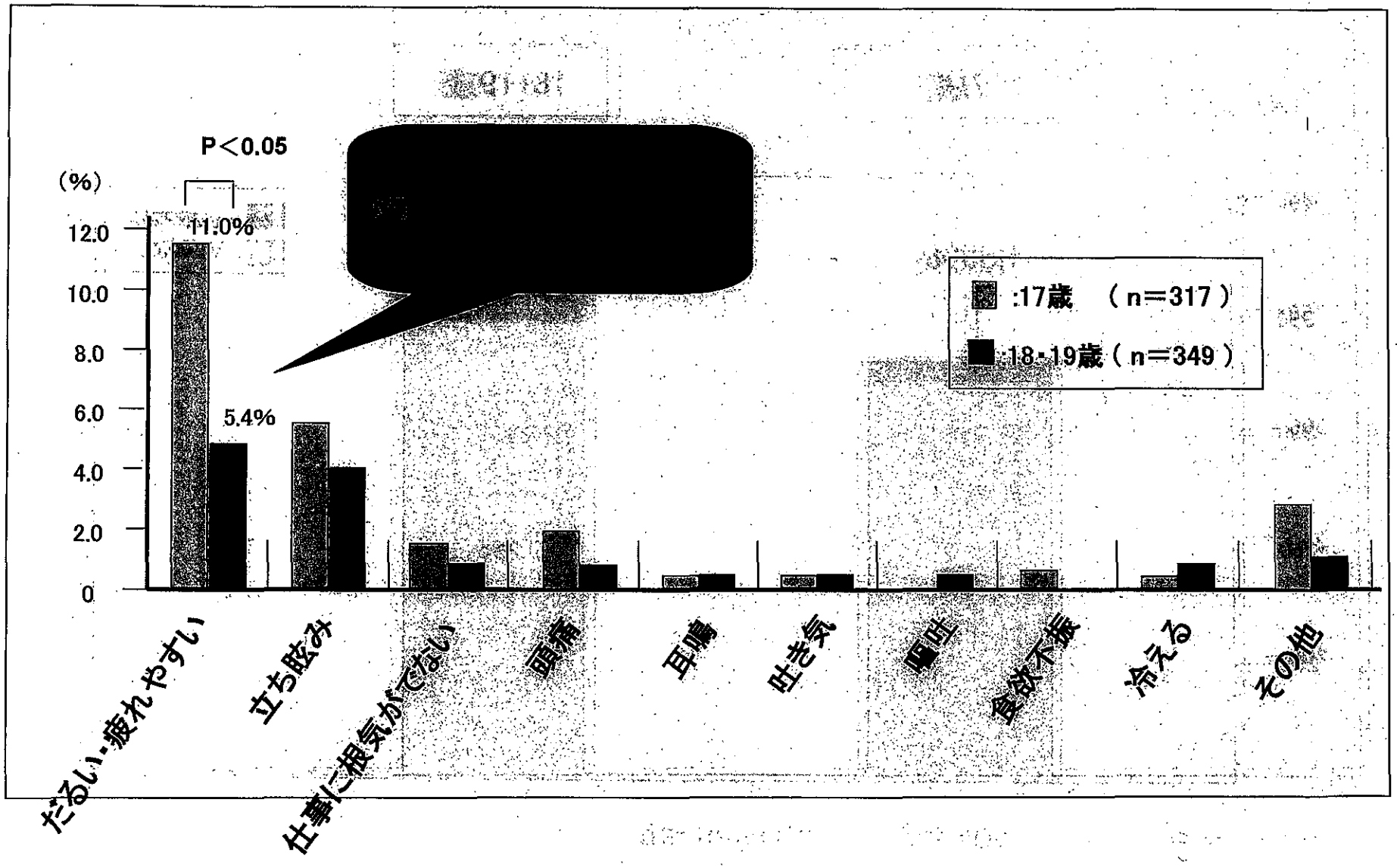
対象		17歳(検討群)	18･19歳(コントロール群)	有意差
例数		322	363	
年齢	(歳)	17.6 ± 0.3	19.0 ± 0.5	
身長	(cm)	171.1 ± 5.4	171.7 ± 5.6	NS
体重	(kg)	64.8 ± 10.2 (50 - 112)	64.6 ± 8.7 (51 – 98)	NS
循環血液量	(ml)	4526 ± 549 (3672 – 7074)	4529 ± 467 (3620 – 6276)	NS
採血量	(ml)	398.7 ± 19.2	399.2 ±13.9	NS
採血量/循環血液量	(%)	8.9 ± 1.0	8.9 ± 0.9	NS

有意差検定:Student t-test （$p < 0.05$）

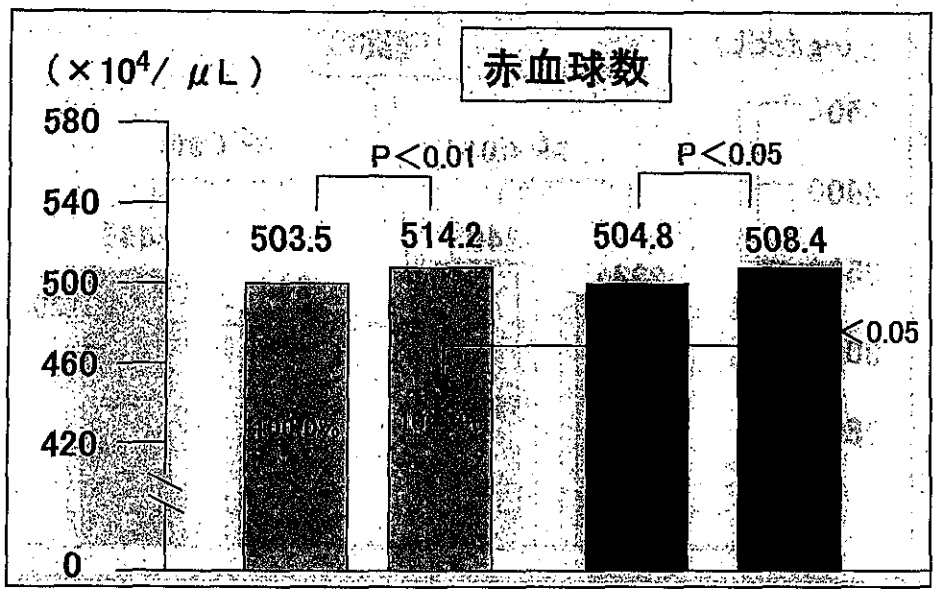


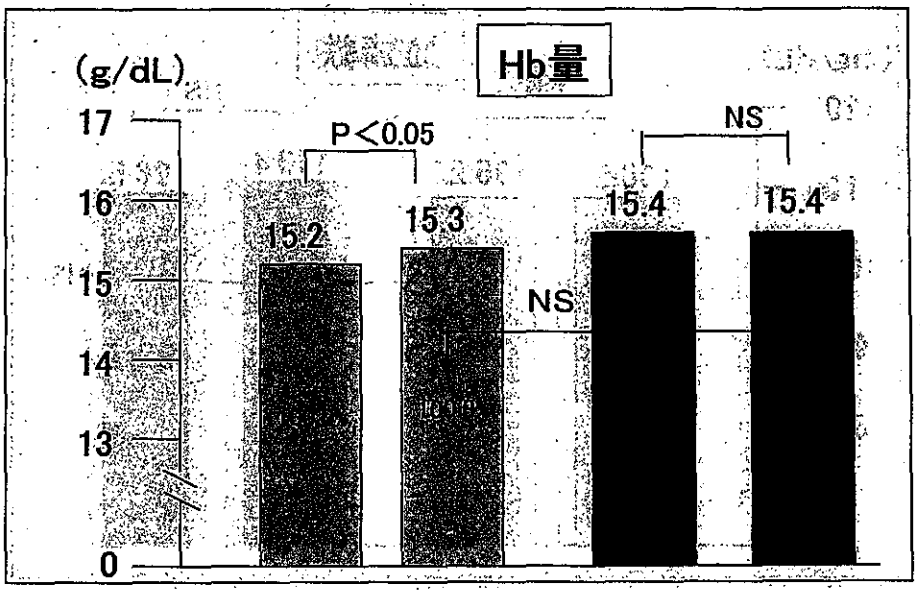
*全症例とも投薬することなく仰臥安静にて1時間以内に回復

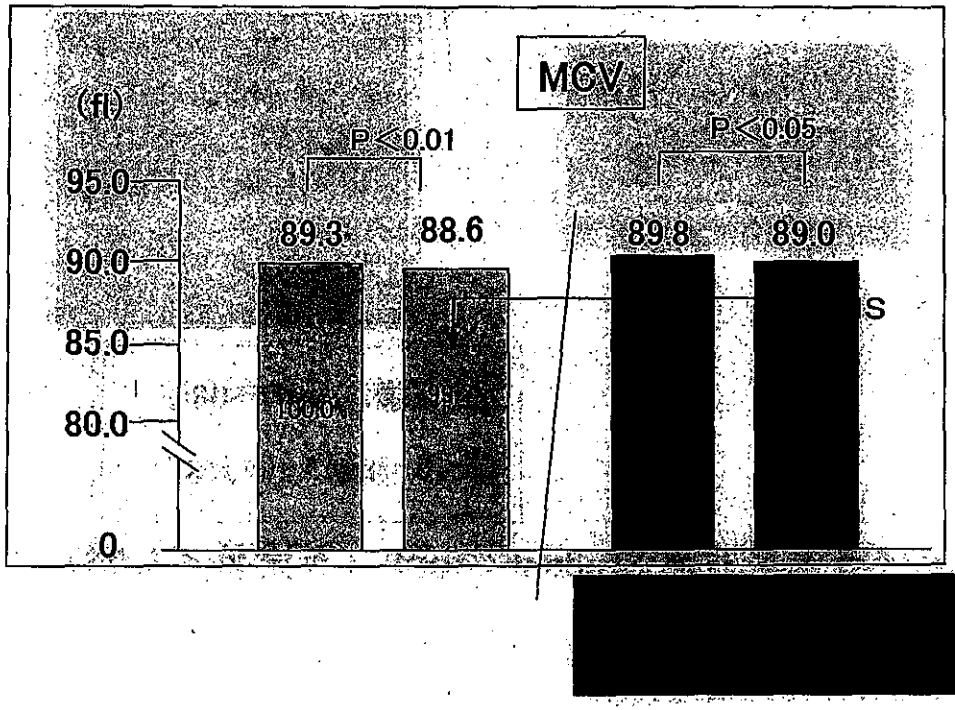
**有意差検定:2x2 Chi square test and Fisher's test ($p<0.05$)



*有意差検定:2x2 Chi square test and Fisher's test（p＜0.05）



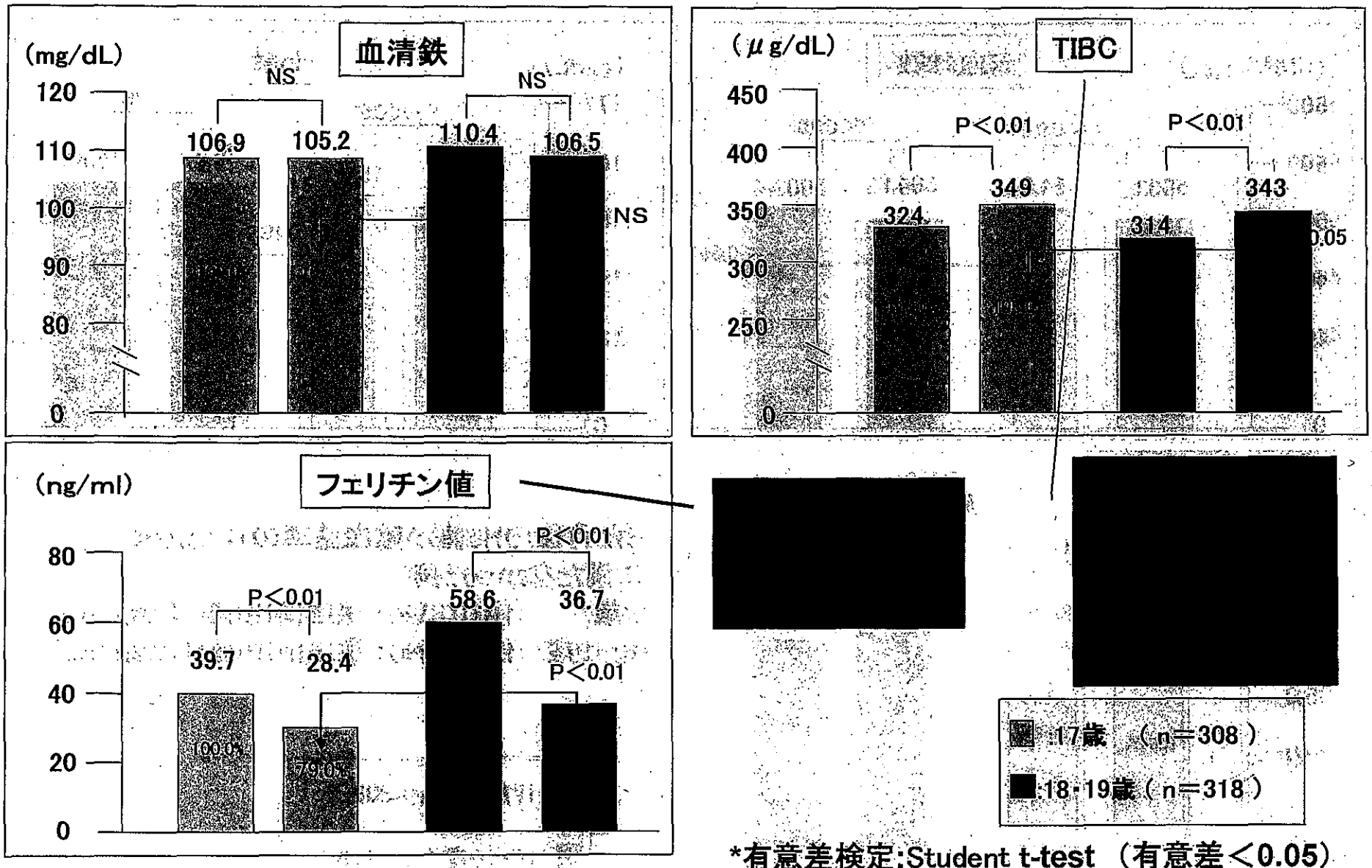




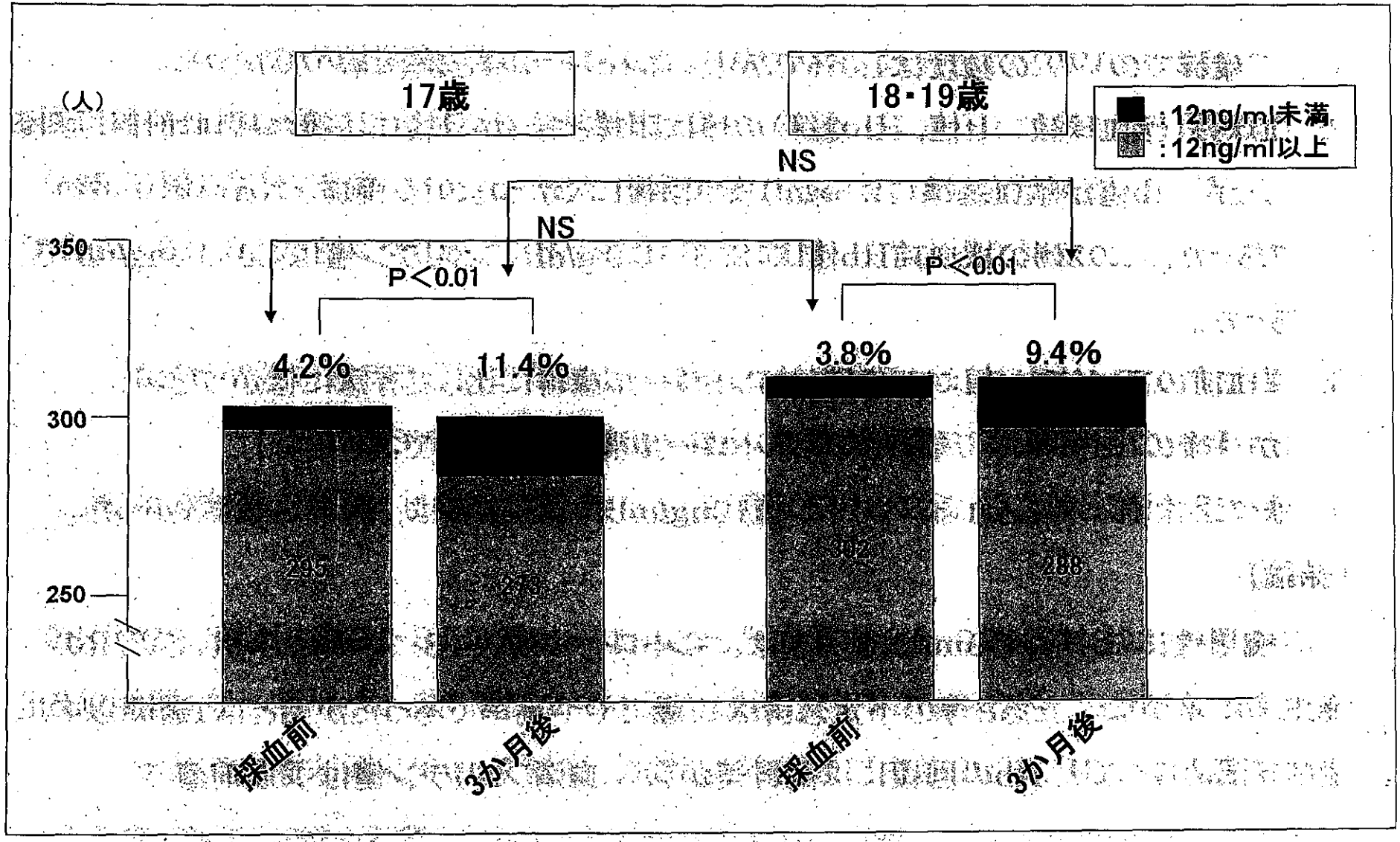
3か月後のHb値が献血基準の12.5g/dL
に満たなかった例
17歳:　1例(0.3%): 採血前Hb値(12.6g/dL)
18・19歳:1例(0.3%): 採血前Hb値(12.9g/dL)

■ :17歳　(n=308)
■ :18・19歳 (n=318)

*有意差検定:Student t-test　(p<0.05)



*有意差検定:Student t-test (有意差<0.05)



*有意差検定:2x2 Chi square test and Fisher's test（p＜0.05）

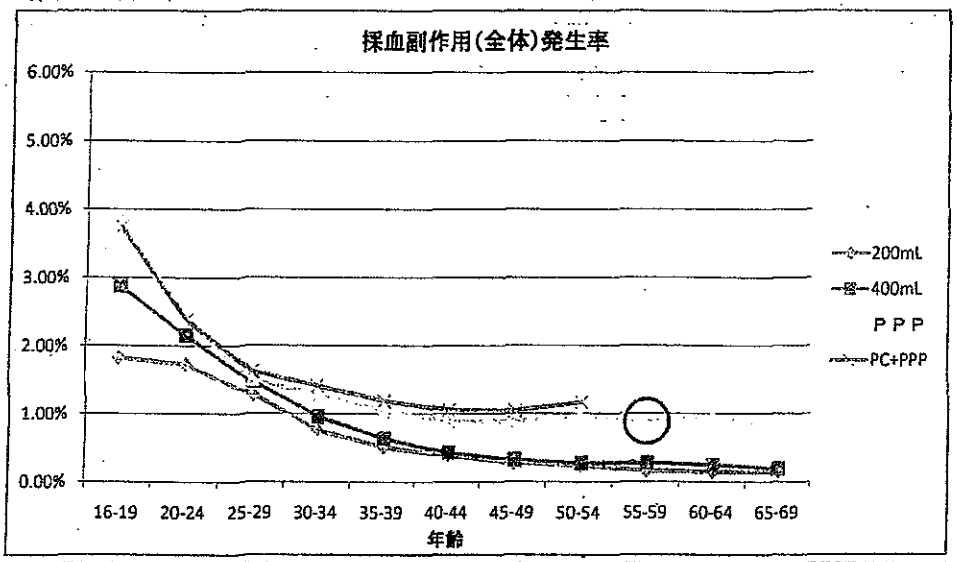
17歳男性の400ml全血採血（まとめ）

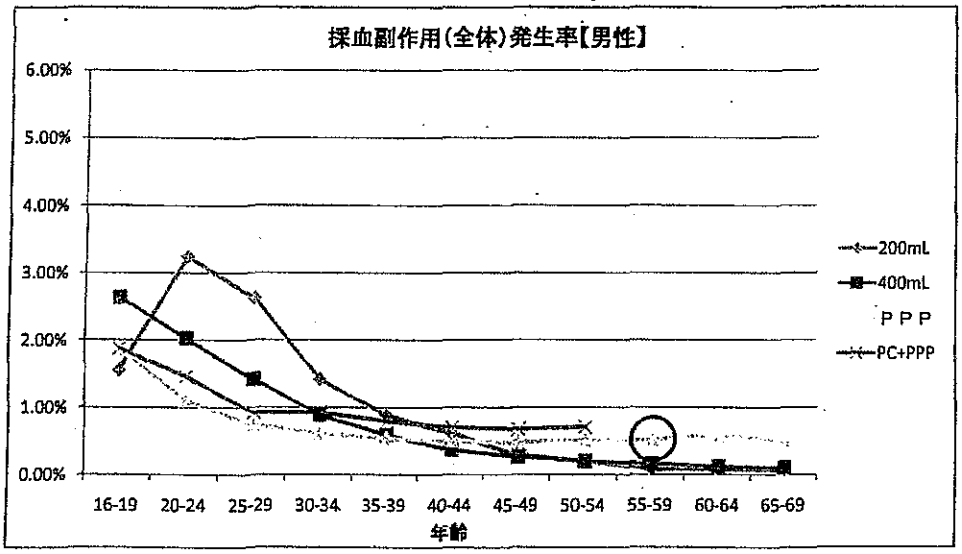
1. 17歳群でのVVRの頻度は1.6%であり、コントロール群と差を認めなかった。
2. 血球系（赤血球数，Ht値，Hb量等）の値は両群とも 3か月後には概ね採血前値に回復したが、Hb値が献血基準（12.5g/dl）まで回復しなかったのは 両群とも各1例（0.3%）であった。この2例の採血前Hb値は12. 6, 12.9 g/dl、フェリチン値は4.0, 6.3ng/ml であった。
3. 採血前のフェリチン値は17歳群はコントロール歳群に比して有意に低かったが、3か月後の回復率は17歳群ではコントロール群より速やかであった。
4. 鉄欠乏状態と考えられるフェリチン値12ng/ml未満の比率は，両群に差はなかった。

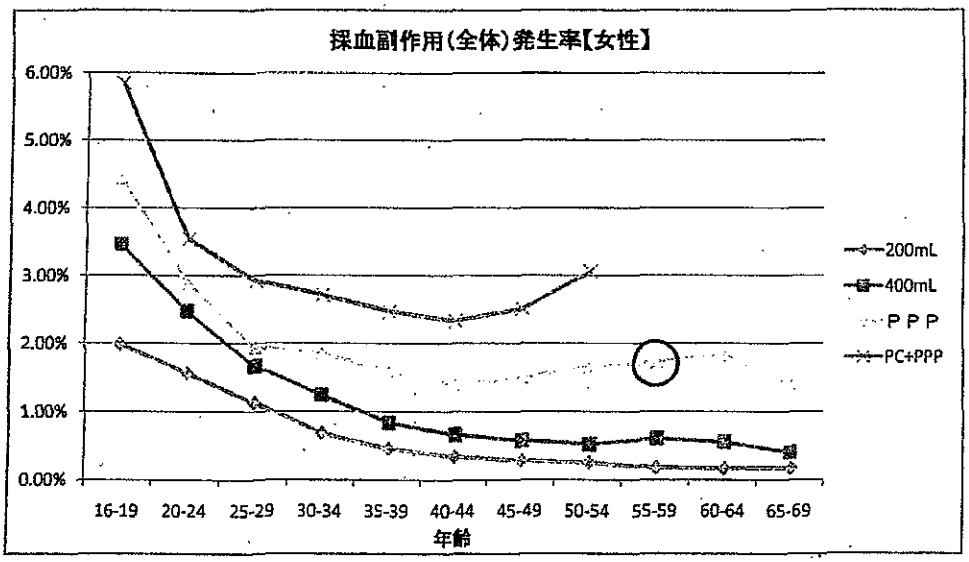
【結論】

17歳男性における400ml全血採血は、コントロール群の18･19歳と比較してVVRの発生率に差がなく、だるさ等の不定愁訴は17歳でやや高率であったが殆どは1週間以内に症状を認めなくなり、Hbの回復には両群差がなく、血清フェリチン値は採血前値でやや低い傾向は認めたが、回復はより速やかであることから、安全に施行可能と考える。

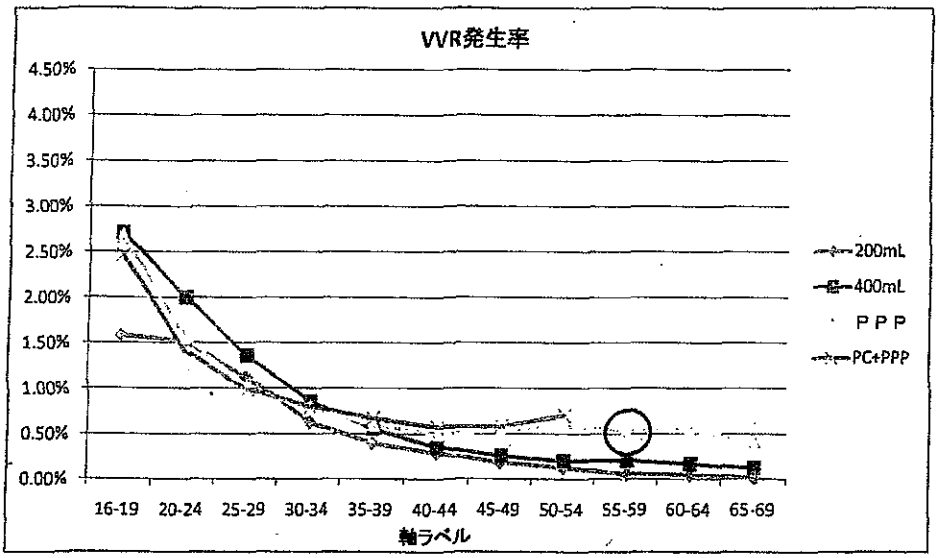
採血副作用発生率(年齢別・性別・採血種類別:平成19年度)

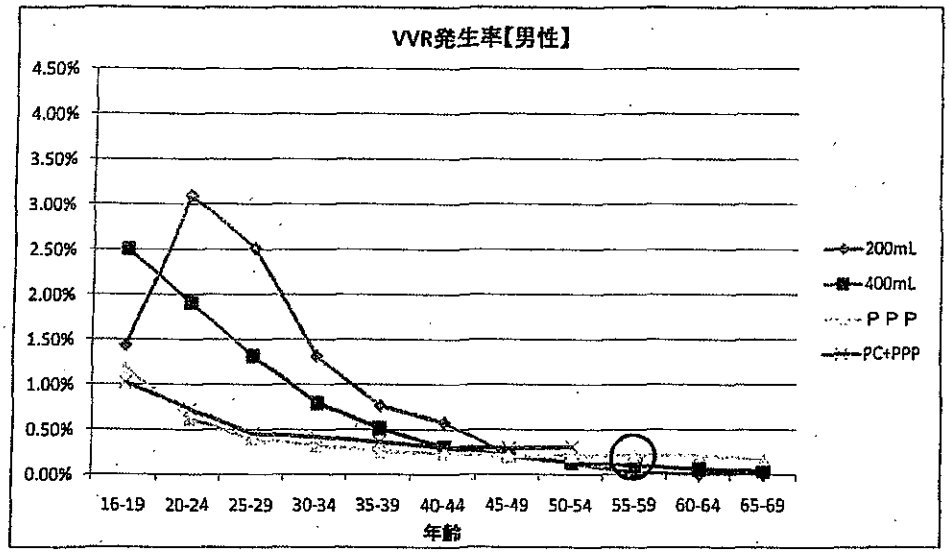


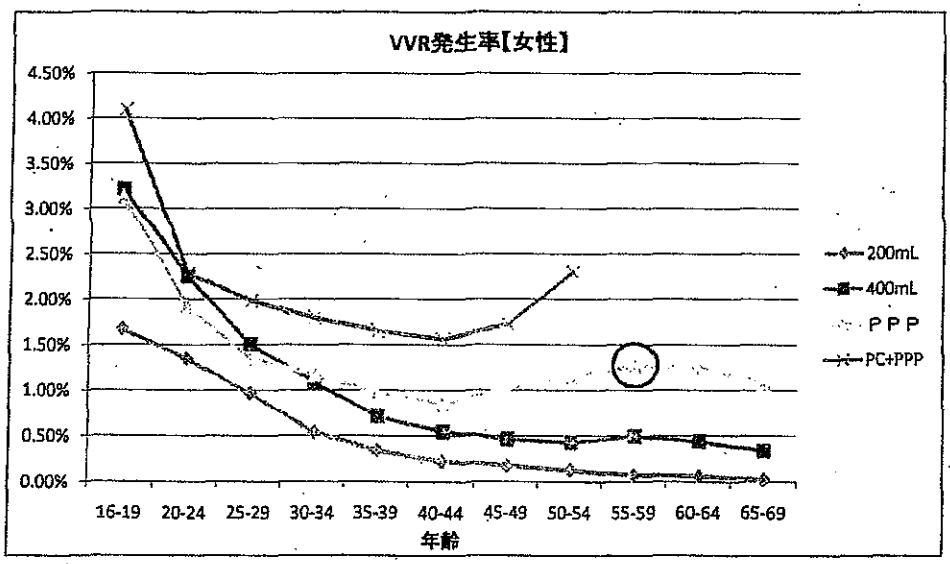




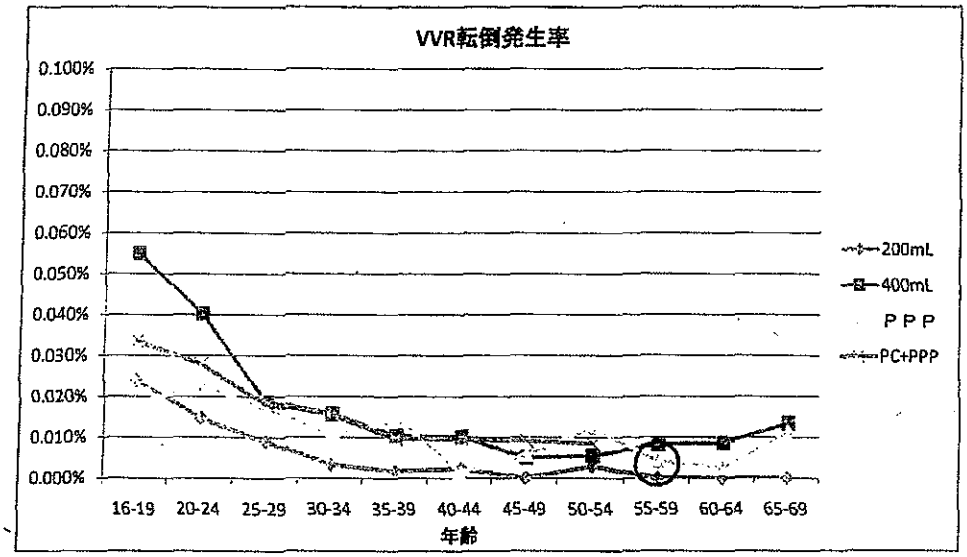
採血副作用発生率(年齢別・性別・採血種類別:平成19年度)

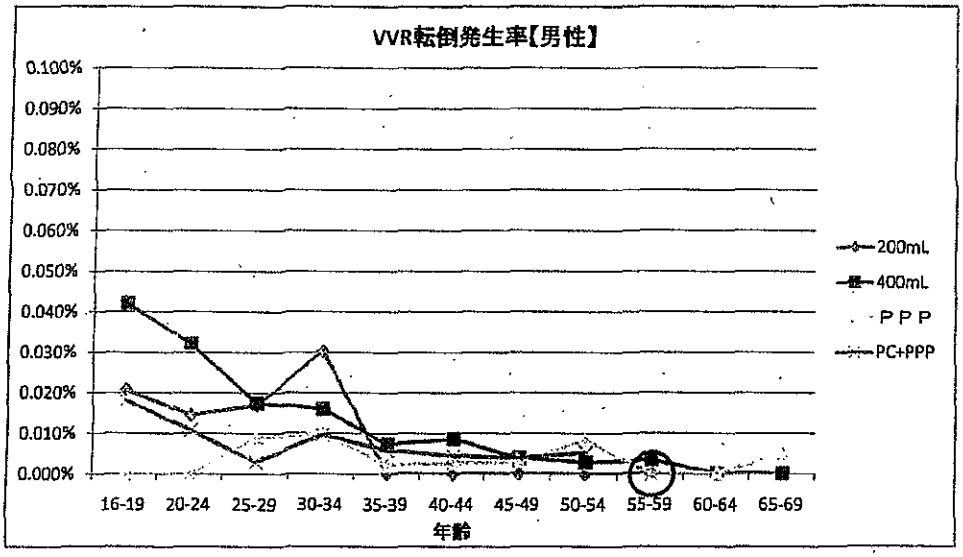


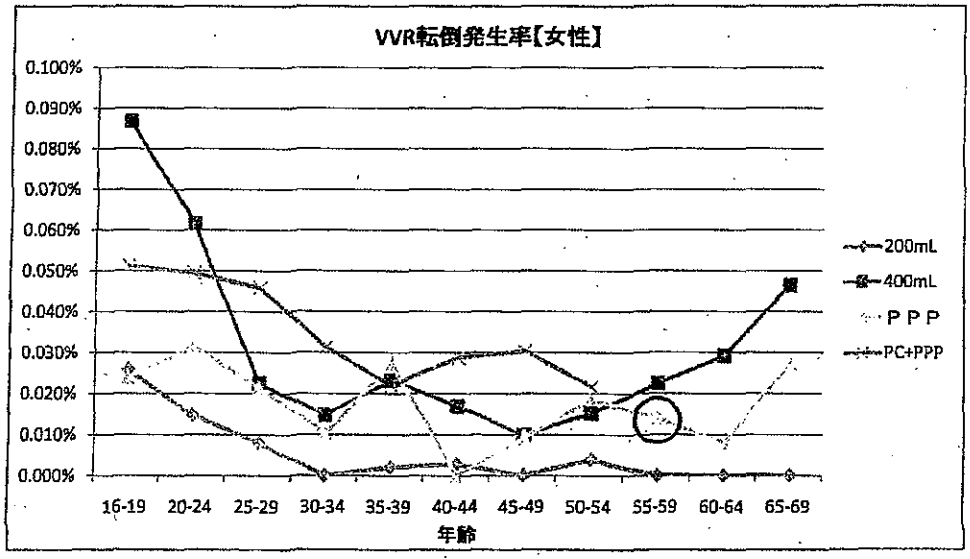




採血副作用発生率(年齢別･性別･採血種類別：平成19年度)





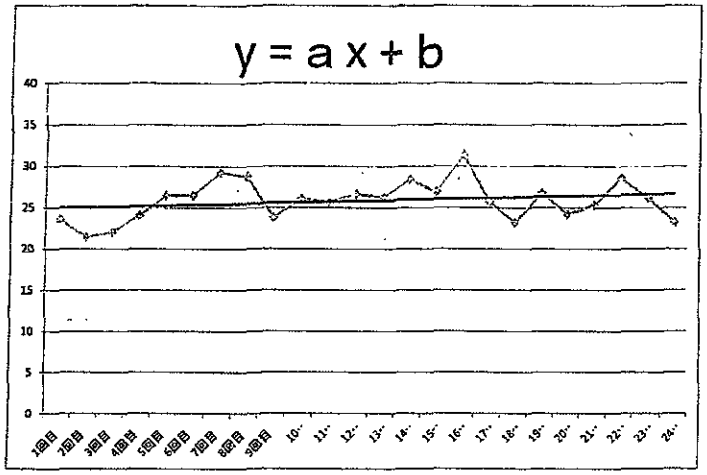


血小板数の推移

対象献血者　　：血小板献血を4年間で24回以上実施した献血者
対象データ　　：追跡開始から24回分のデータ(24回以上でも最初の24回分)

各対象献血者の24回分のデータから回帰直線を作成し、傾き(a)を求めた。

献血回数による血小板数の変化(全献血者)

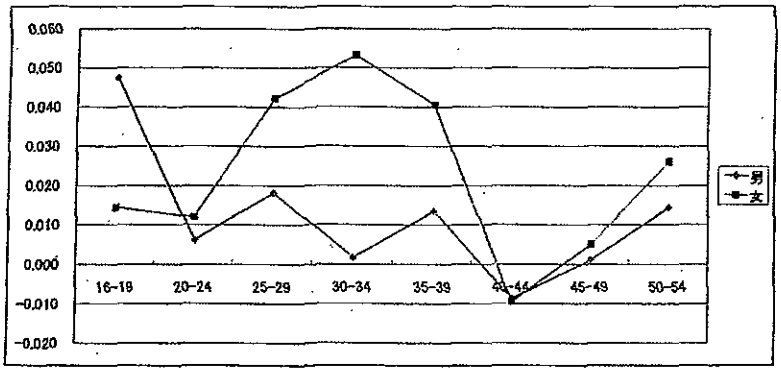


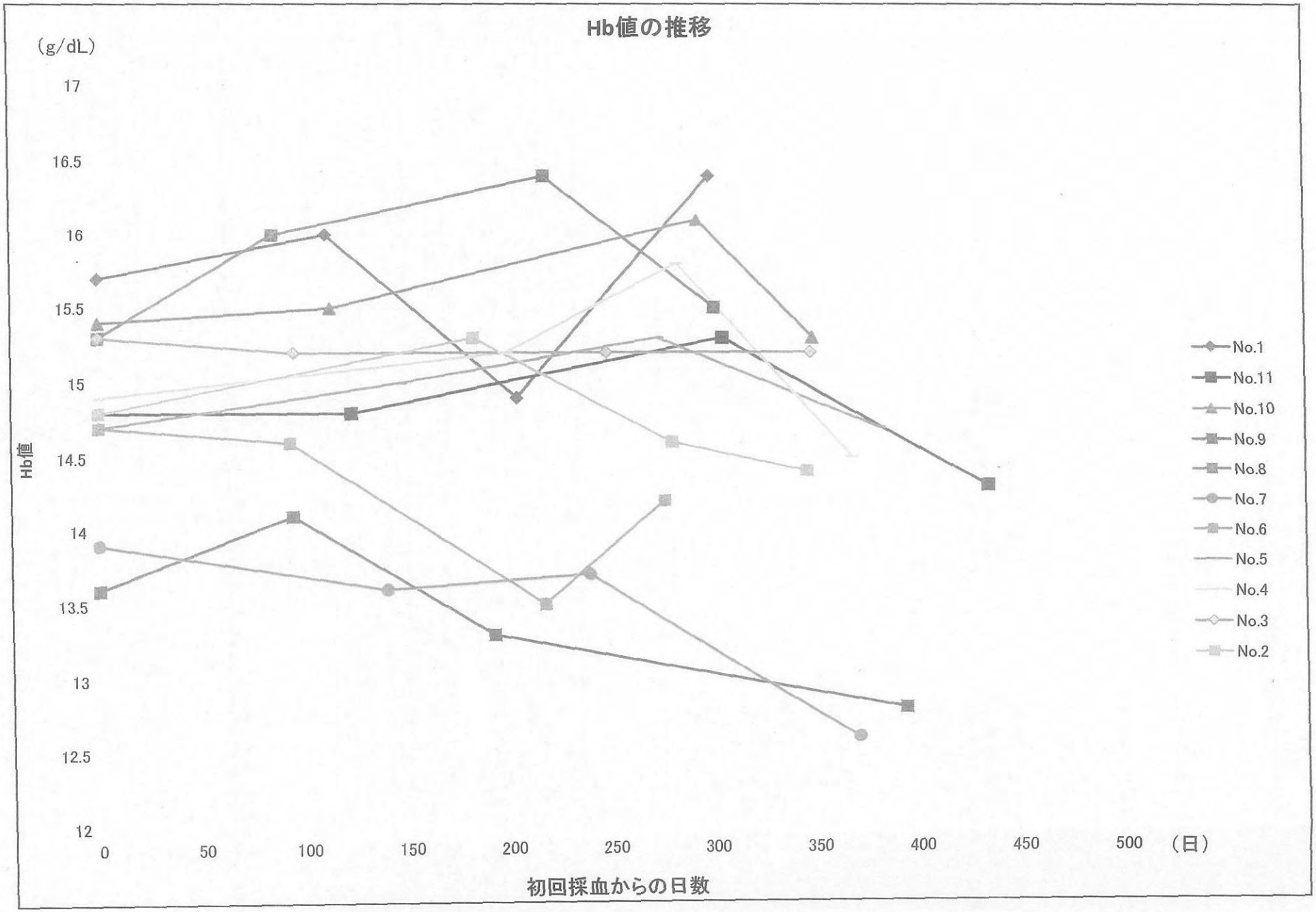
傾きaの加齢による変化

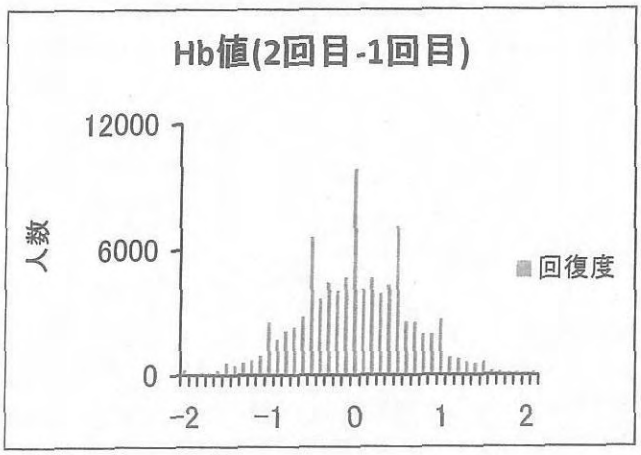
傾き(a)

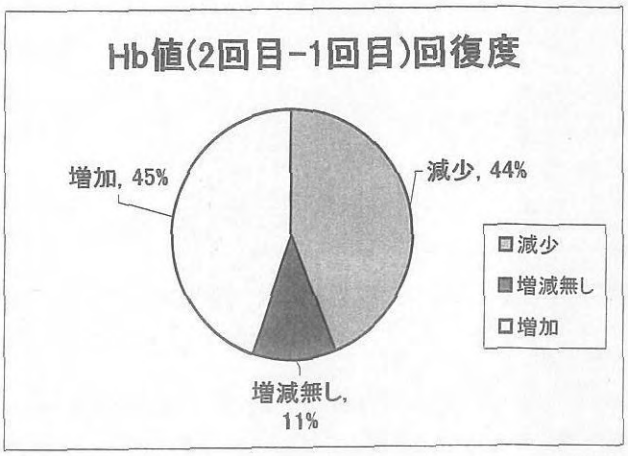
		PT(計)	16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54
合計	n	2737	88	324	479	538	467	410	321	110
	平均	0.010	0.042	0.007	0.021	0.008	0.016	-0.009	0.001	0.018
	SD	0.102	0.121	0.101	0.099	0.106	0.102	0.096	0.105	0.085
男	n	2403	73	270	414	473	425	364	289	95
	平均	0.007	0.047	0.006	0.018	0.002	0.014	-0.009	0.001	0.014
	SD	0.101	0.117	0.104	0.096	0.102	0.101	0.093	0.106	0.083
女	n	334	15	54	65	65	42	46	32	15
	平均	0.027	0.014	0.012	0.042	0.053	0.041	-0.010	0.005	0.026
	SD	0.111	0.140	0.088	0.110	0.124	0.108	0.116	0.100	0.100

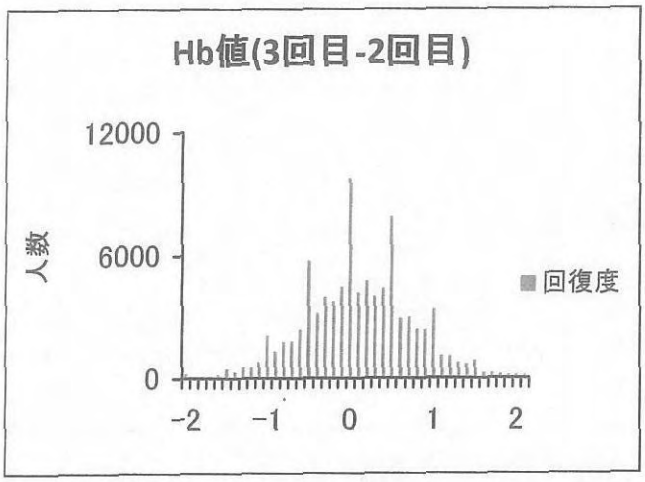
年齢	16-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54
男	0.047	0.006	0.018	0.002	0.014	-0.009	0.001	0.014
女	0.014	0.012	0.042	0.053	0.041	-0.010	0.005	0.026

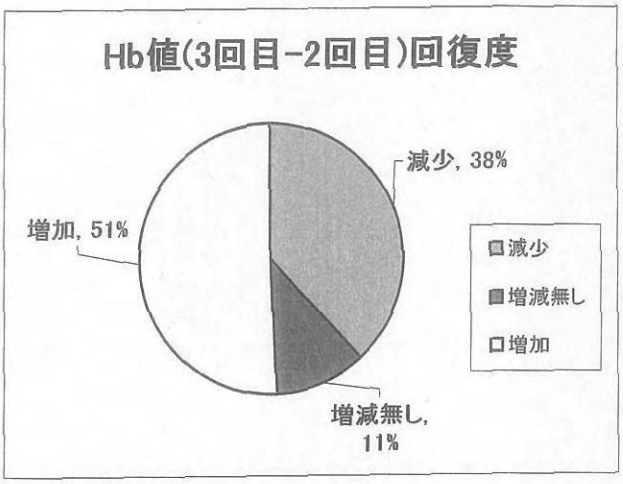


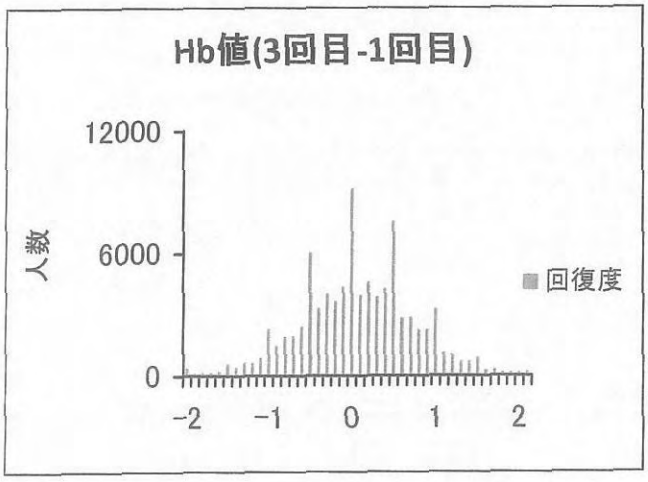

Hb値の推移
(g/dL)
17
16.5
16
15.5
15
14.5
14
13.5
13
12.5
12
Hb値
0
50
100
150
200
250
300
350
400
450
500
(日)
初回採血からの日数
No.1
No.11
No.10
No.9
No.8
No.7
No.6
No.5
No.4
No.3
No.2

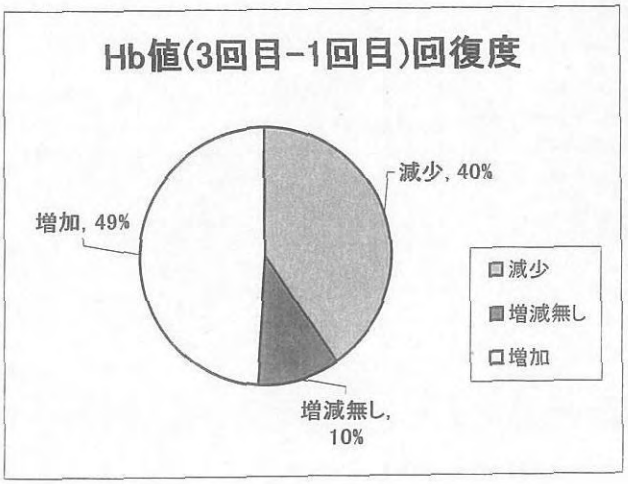

Hb値(2回目-1回目)
12000
6000
0
人数
-2
-1
0
1
2
回復度


Hb値(2回目−1回目)回復度
増加, 45%
減少, 44%
増減無し,
11%
減少
増減無し
増加


Hb値(3回目-2回目)
12000
6000
0
人数
-2
-1
0
1
2
回復度


Hb値(3回目−2回目)回復度
減少, 38%
増加, 51%
増減無し,
11%
減少
増減無し
増加


Hb値(3回目-1回目)
12000
6000
0
人数
-2
-1
0
1
2
回復度


Hb値(3回目−1回目)回復度
減少, 40%
増加, 49%
増減無し,
10%
減少
増減無し
増加

ii　副作用の発生状況については，表４－ａの各事項について，採血前，中，後（センター内に留まっている間）について問診し，さらに帰宅時調査用紙（表４－ｂ）を配付して１週間の身体状況について返答を求めた。また，対照として200ml採血者についても同様の調査を行った。

採血前所見の有無と採血中，後，１週間の副作用発生率との関係を男女別にみると，男性群では前所見有りの群でいずれもが，また女性群では前所見有り群の１週間の発生率のみが有意に高率であった。

400ml採血後にみられた副作用を，200ml採血（主に移動採血車）後のそれと比較すると，両者間には有意差が認められなかった（表５）。また，母体での200ml採血例に限って検討すると，採血中，１週間の所見には差がみられず，採血後の所見ではむしろ200ml採血例の方が有意に高率であり，また，初回400ml採血例と初回200ml採血例の比較でも採血中，直後の所見は初回200ml採血例の方が有意に高率にみられた。

iii　Hb値の回復状況について検討した結果は下記のごとくである。

約３か月間隔（３か月±２週間）の採血群中の男性群では，初回採血前値に比して12か月後（４回採血後３か月目）の値は有意（$P<0.001$）に低下していた。また，女性群では初回前値と６か月後（２回採血前），初回前値と９か月後（３回採血前）との比較では，それぞれ後者が有意（$P<0.001$）に低下していた（図1,2）。約４か月間隔（４か月±２週間）の採血群においては，男女両群ともに採血前値と4か月後(2回採血前）あるいは８か月後（３回採血前）との間には有意差は認められなかった。

iv　血清フェリチン値の回復状況について検討した成績は下記のごとくである。

約３か月間隔の採血群では，男女両群ともに前回

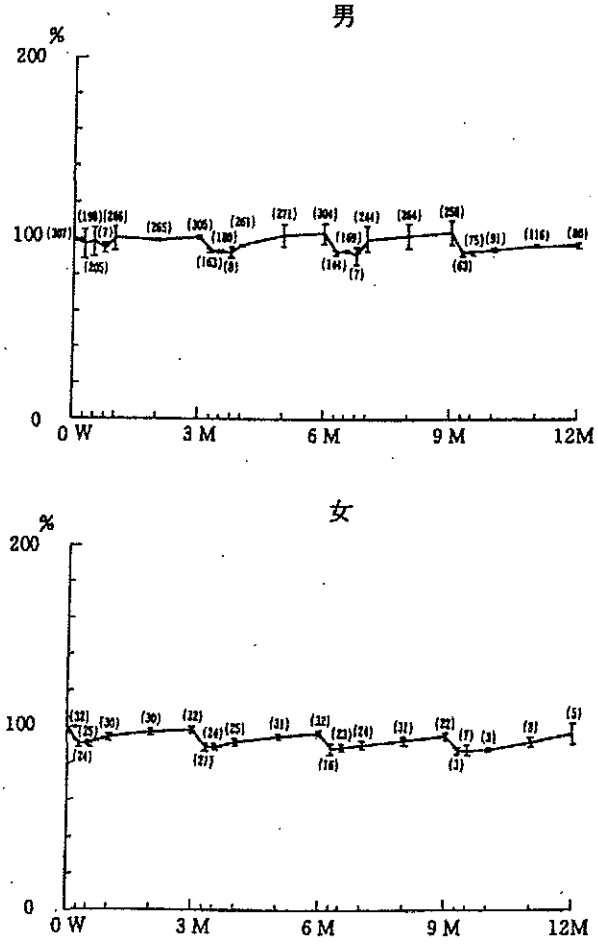


図１　３ケ月間隔採取時のヘモグロビンの回復状況（％）

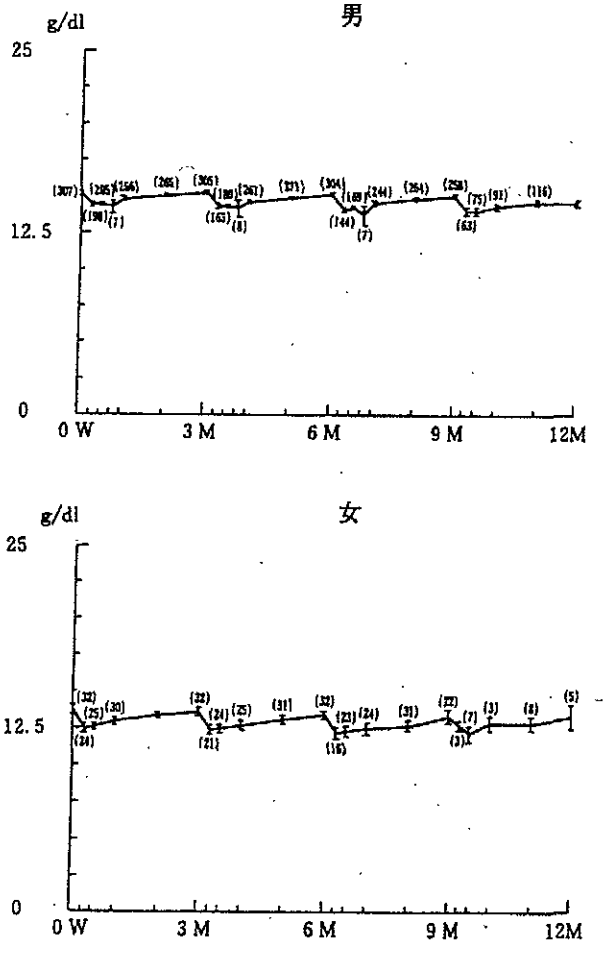


図２　３ケ月間隔採取時のヘモグロビンの回復状況（g／dℓ）

採血前および採血後1か月毎の検査の平均値（n＝供血者数）

（M ± SD）

		n	RBC (×10⁴)	Ht (%)	Hb (g/dl)	WBC	Platelet (×10⁴)	Serum Fe (μg/dl)	Ferritin (ng/ml)
0	400 ml 採血前	16	520.6 ± 34.7	46.0 ± 2.7	15.5 ± 0.8	6562 ± 2072	25.3 ± 5.7	153.5 ± 54.6	70.5 ± 41.2
1	1か月前	15	495.4 ± 30.7	45.3 ± 2.6	15.1 ± 0.7	6020 ± 1544	25.7 ± 4.8	114.8 ± 29.0	42.3 ± 27.6
2	2か月後	15	503.8 ± 27.2	46.1 ± 2.0	15.2 ± 0.5	6020 ± 1299	25.1 ± 4.9	137.0 ± 34.6	43.1 ± 24.3
3	400 ml採血3か月後	13	495.7 ± 35.4	45.3 ± 2.4	15.3 ± 0.9	6738 ± 1448	22.5 ± 4.0	155.5 ± 29.4	50.4 ± 23.9
4	4か月後	11	485.4 ± 35.7	44.2 ± 1.5	15.0 ± 0.7	5563 ± 1254	22.0 ± 4.6	144.0 ± 37.8	35.0 ± 19.6
5	5か月後	9	498.7 ± 30.0	45.4 ± 2.4	15.5 ± 0.9	6044 ± 1045	21.7 ± 7.8	129.8 ± 32.4	57.1 ± 31.3
6	400ml採血6か月後	11	518.2 ± 25.2	47.0 ± 2.8	15.8 ± 0.9	5900 ± 1238	25.1 ± 4.2	100.6 ± 18.2	42.3 ± 20.4
7	7か月後	7	496.1 ± 15.4	44.8 ± 2.2	14.9 ± 0.7	6300 ± 1800	23.7 ± 3.4	133.7 ± 51.0	43.5 ± 12.2
8	8か月後	8	518.5 ± 26.0	47.5 ± 2.8	15.5 ± 0.9	6025 ± 796	24.2 ± 7.3	157.3 ± 65.8	36.2 ± 16.0
9	9か月後	7	513.2 ± 17.8	45.8 ± 2.3	15.4 ± 0.7	7626 ± 1411	25.2 ± 4.1	153.4 ± 55.4	35.2 ± 21.0

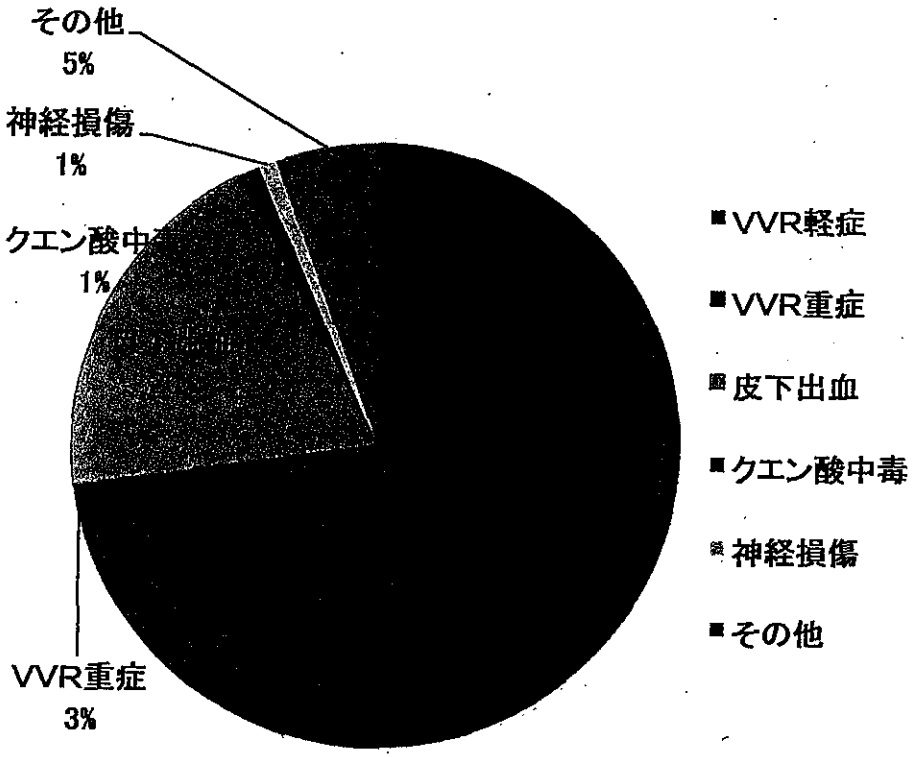
400 ml 採血平均値（男性）

★ P＜0.05

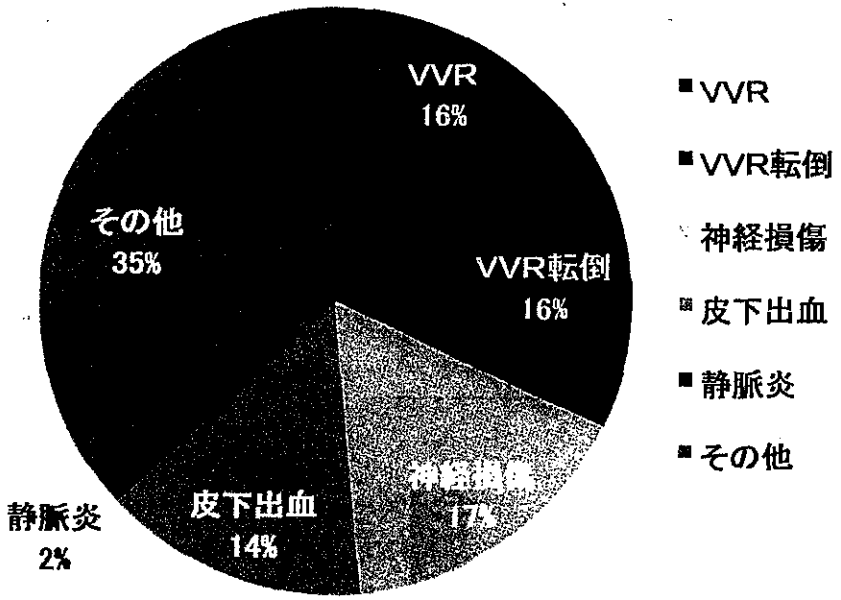
	1回目採血	1M後	2M後	2回目採血	1M後	2M後	3回目採血	1M後	2M後	3M後	6M後
血　圧	124 ±10.2 / 72.5 ±5.3 n＝4	121.5 ±20.3 / 78.5 ±14.8 n＝4	134 ±14.5 / 94 ±9.9 n＝4	125 ±12.9 / 85.5 ±6.0 n＝4	140 ±17.8 / 87.3 ±9.1 n＝4	133 ±7.4 / 94.5 ±4.4 n＝4	133 ±9.3 / 85.5 ±9.6 n＝4	129 ±7.6 / 82 ±2.8 n＝4	123.5 ±7.9 / 77 ±11.9 n＝4	130 ±8.2 / 84 ±7.1 n＝4	129.5 ±11.5 / 87 ±12.1 n＝4
脈　拍		81.8±7.5 n＝4	78±8.5 n＝4	70±10.6 n＝4	85.3±15.5 n＝4	79±6.8 n＝4	76.5±9.0 n＝4	72.5±5.7 n＝4	67.5±9.0 n＝4	73.8±10.0 n＝4	81.0±18.0 n＝4
比　重	1.056 n＝4	1.058±0.0005 n＝4	1.057±0.001 n＝4	1.059＋0.0008 n＝4	1.058±0.001 n＝4	1.059 n＝4	1.058±0.001 n＝4	1.059±0.001 n＝4	1.059±0.002 n＝4	1.060 n＝4	1.057±0.0015 n＝4
WBC ×10³	5.45±1.5 n＝4	5.55±0.4 n＝4	5.30±0.4 n＝4	6.0±2.6 n＝4	8.03±1.9 n＝4	5.33±0.8 n＝4	5.88±0.7 n＝4	5.48±1.0 n＝4	5.6±1.2 n＝4	7.13±1.4 n＝4	5.2±0.8 n＝4
RBC ×10⁴	4.945±0.2 n＝4	5.08±0.2 n＝4	4.985±0.3 n＝4	5.12±0.4 n＝4	4.76±0.3 n＝4	5.058±0.3 n＝4	4.715±0.3 n＝4	4.908±0.2 n＝4	4.905±0.3 n＝4	5.18＋0.3 n＝4	5.298±0.3 n＝4
Hb g/dl	15.6±0.7 n＝4	15.7±0.8 n＝4	15.2±0.5 n＝4	15.8±1.1 n＝4	14.8±0.8 n＝4	15.7±0.4 n＝4	★14.5±0.4 n＝4	15.0±0.5 n＝4	15.2±0.1 n＝4	16.1±0.3 n＝4	16.4±0.5 n＝4
Ht %	44.7±2.0 n＝4	46.4±1.8 n＝4	46.1±0.9 n＝4	47.4±3.3 n＝4	45.1±1.5 n＝4	47.3±1.3 n＝4	44.0±0.6 n＝4	46.1±1.5 n＝4	45.6±0.8 n＝4	★47.5±0.5 n＝4	★49.1±2.3 n＝4
P.LT ×10⁴	25.0±2.5 n＝4	30.4±4.2 n＝4	26.9±1.0 n＝4	26.2±3.4 n＝4	25.4±1.6 n＝4	27.3±3.9 n＝4	28.7±4.0 n＝4	27.4±4.2 n＝4	27.9±3.6 n＝4	26.7±3.2 n＝4	28.1±2.4 n＝4
Fe μg/dl	167±37.9 n＝4	144±41.2 n＝4	167.5±51.0 n＝4	121±15.2 n＝4	177.5±32.6 n＝4	178.5±21.9 n＝4	★112.5±18.1 n＝4	172.8±89.7 n＝4	★107.8±26.7 n＝4	118.3±25.3 n＝4	114.5±21.5 n＝4
鉄結合能 mcg/dl	364±37.2 n＝4	386±30.9 n＝4	396±24.9 n＝4	410±35.4 n＝4	386±38.3 n＝4	416±23.6 n＝4	394±57.5 n＝4	399±51.4 n＝4	396±41.6 n＝4	411±44.7 n＝4	386±39.4 n＝4
フェリチン ng/ml	89.9±32.9 n＝4	59.2±34.7 n＝4	59.2±24.1 n＝4	55.2±22.9 n＝4	★346±15.8 n＝4	45.2±26.5 n＝4	★38.7±18.6 n＝4	★19.6±7.2 n＝4	★24.5±13.2 n＝4	★39.3±24.1 n＝4	★41.5±16.0 n＝4

年令　21.3±1.0 才
身長　172±2.0 cm
体重　60.3±1.7 kg

採血副作用件数
（平成18年度）



医療機関に受診した採血副作用件数
（平成18年度）



副作用種類	VVR軽症	VVR重症	皮下出血	クエン酸中毒	神経損傷	その他	合計
発生件数	37,257	1,553	10,433	581	469	2,953	53,246
発生率(%)	0.75	0.03	0.01	0.21	0.01	0.06	1.07

副作用種類	VVR	VVR転倒	神経損傷	皮下出血	静脈炎	その他	合計
発生件数	118	114	120	105	12	256	725
発生率(%)	0.002	0.002	0.002	0.002	0.000	0.005	0.015

＊副作用1～5

採血副作用には、本採血前（不採血）の副作用も含む。

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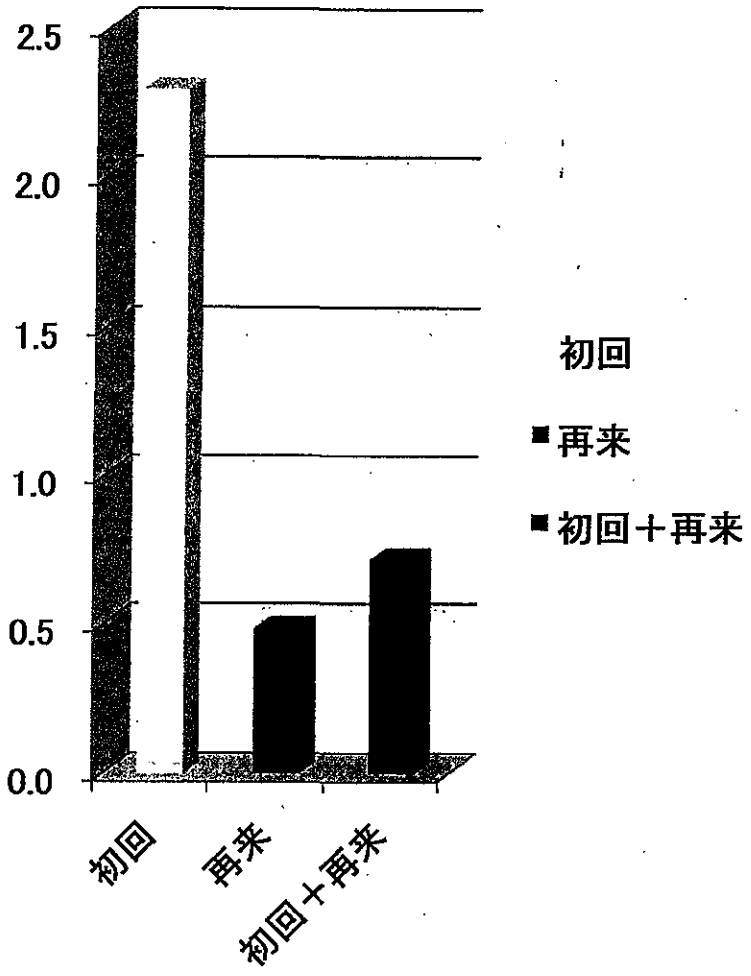
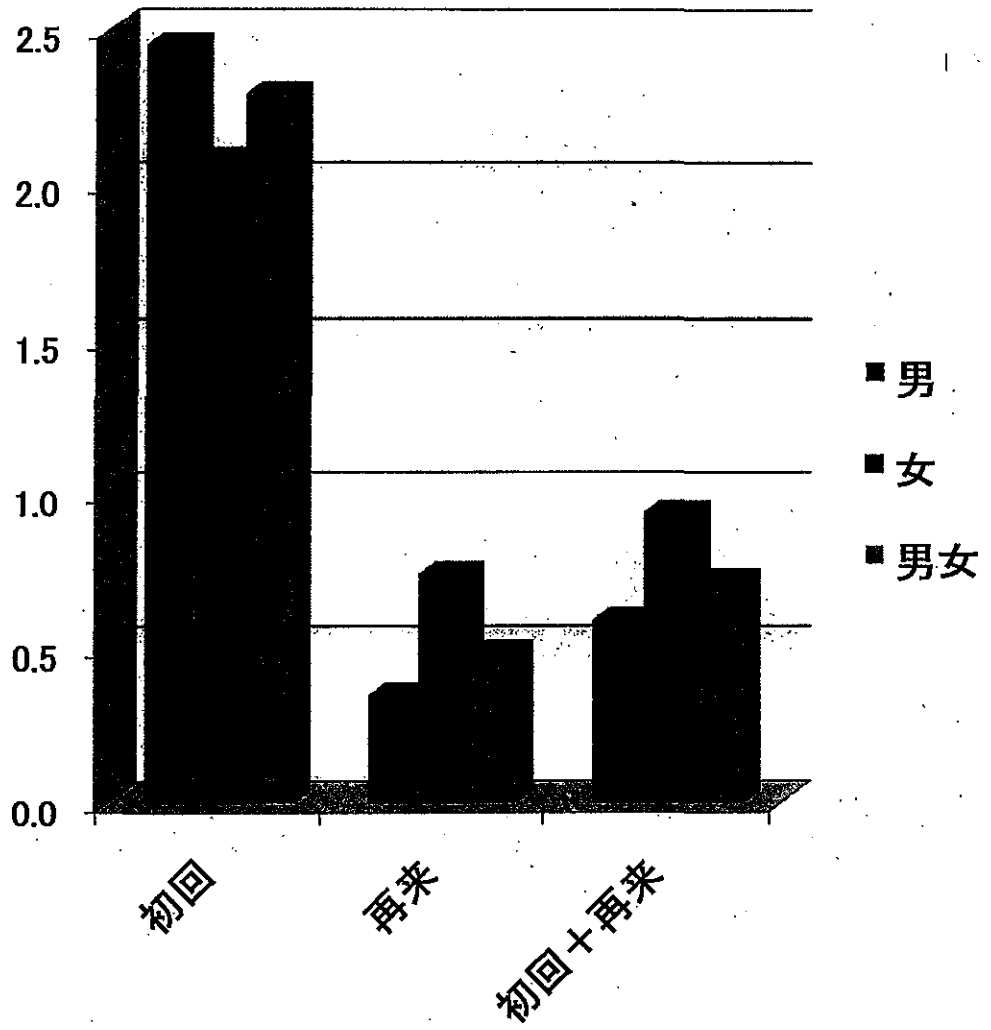
6

初回・再来とVVR発生率





平成18年1月～平成18年12月

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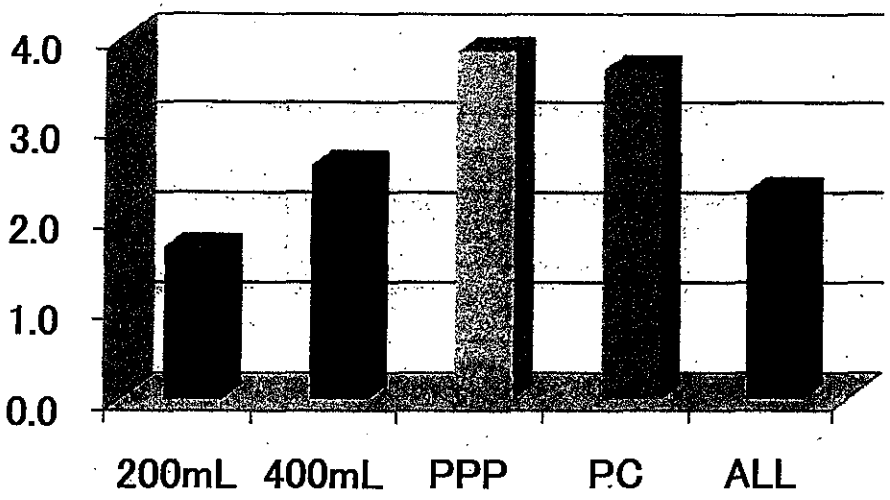
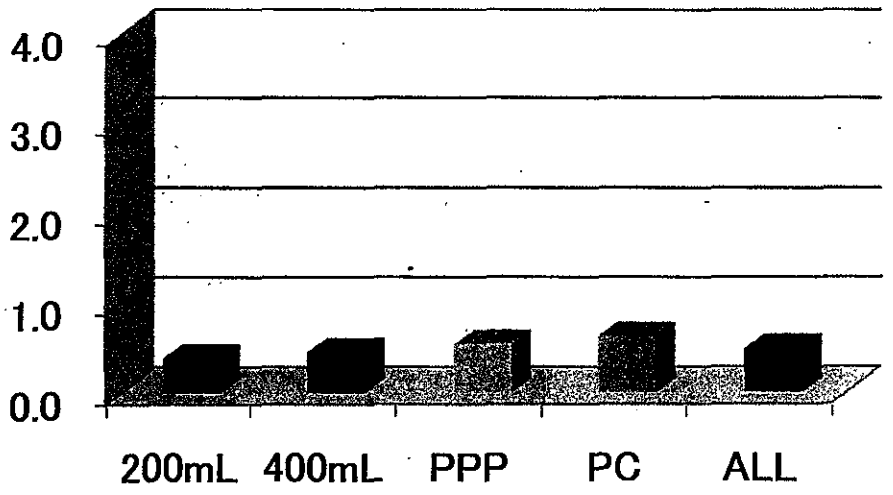
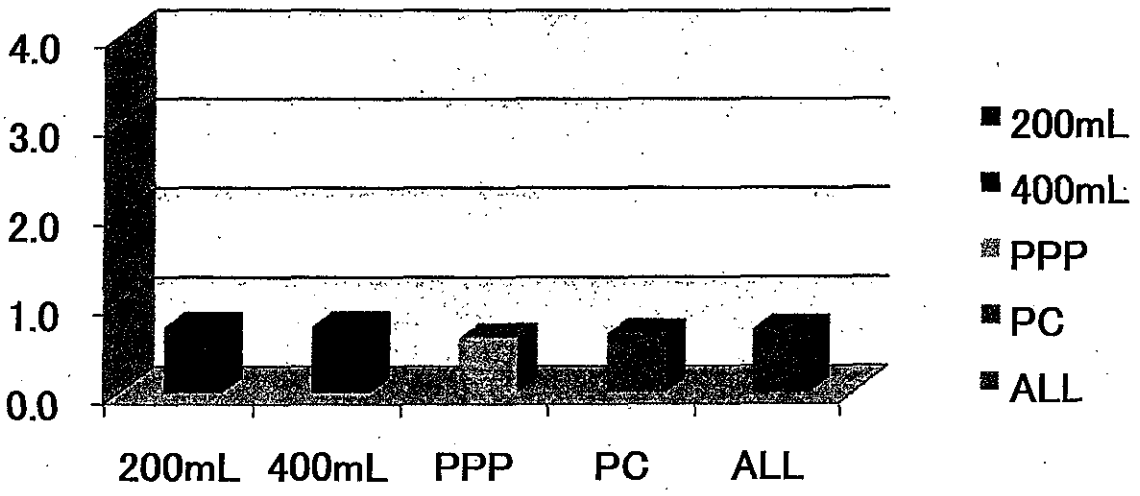
初回VVR発生率(%)



再来VVR発生率（%）



初回再来VVR発生率(%)



平成18年1月～平成18年12月

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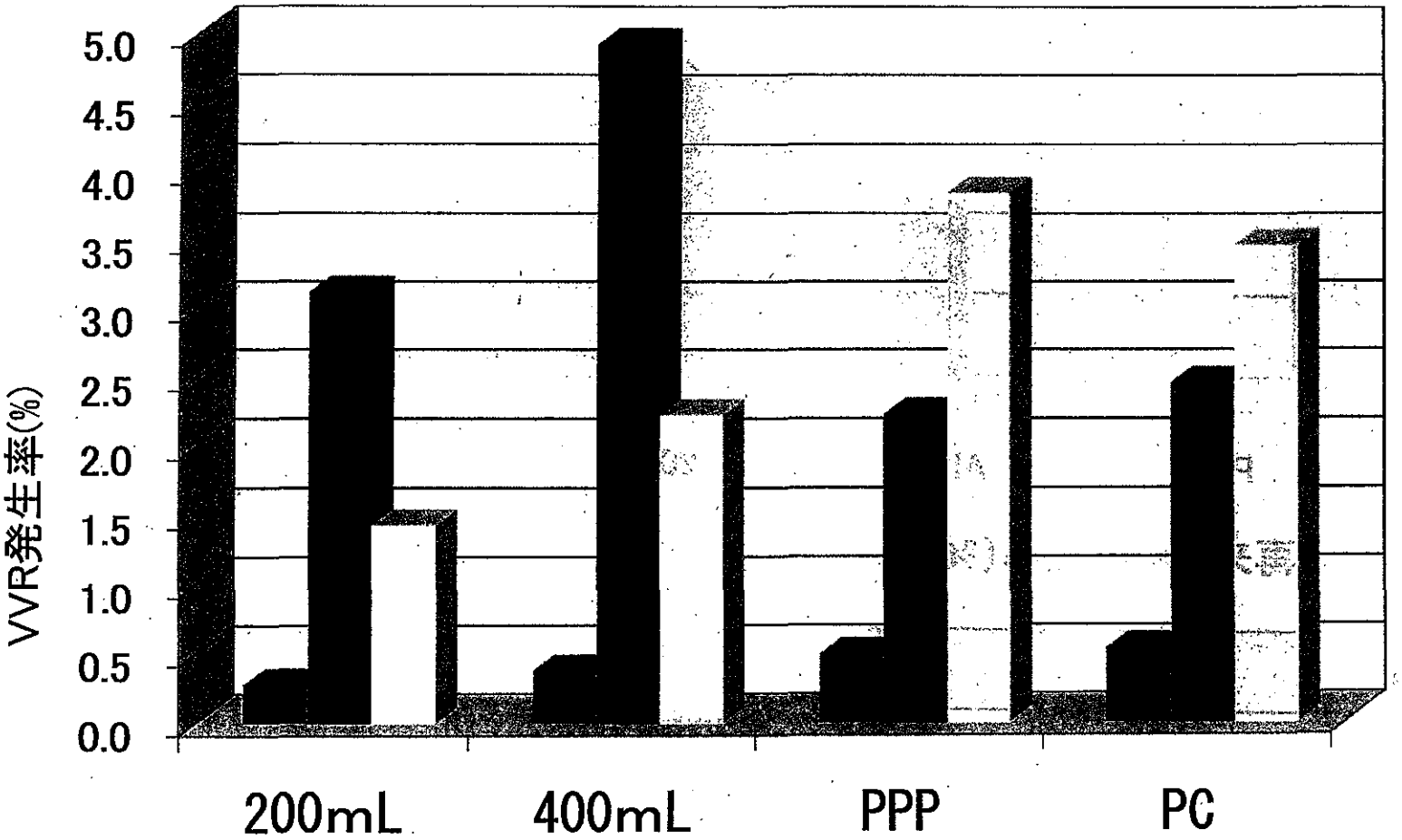
初回献血者、VVR歴あり献血者のVVR発生率(%)



	VVR歴なし	VVR歴あり	初回
200mL	0.28	3.13	1.43
400mL	0.38	4.93	2.23
PPP	0.50	2.24	3.85
PC	0.54	2.46	3.48

平成16年10月～平成17年9月

Japanese
Red Cross Society

WHO Technical Report Series, No. 840, 1994

Annex 2
Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (Requirements for Biological Substances No. 27, revised 1992)

Introduction

In 1976, a WHO Working Group on the Standardization of Human Blood Products and Related Substances (*1*) considered the need for international requirements for the processing and control of whole human blood and blood products. It emphasized that, as the quality of the source material played an important part in determining the quality of the final products, such requirements should cover all the stages in the process, from the collection of the source materials to the quality control of the final product. In response to the Working Group's recommendations, the Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products were published in 1978 (*2*). These Requirements were updated and revised in 1988 (*3*), and WHO recommendations concerning testing for antibodies to human immunodeficiency virus (HIV, *4*) were taken into account. This Annex contains a further revision of the Requirements, applicable to the quality control of blood, blood components and plasma derivatives.

A number of other WHO publications have dealt with whole blood and its components, among them guidelines intended mainly for blood transfusion services (*5*). Guidelines of a more general nature, such as the Guidelines for National Authorities on Quality Assurance for Biological Products, have also been published (*6*). The latter call for a quality-assurance system based on the existence of a national structure that is independent of the manufacturer and is responsible for granting licences for biological products, defining procedures for product release and setting up a post-marketing surveillance system. These Guidelines should be followed by any country having or wishing to set up an organization for the collection and fractionation of blood and blood components.

The names of the many experts who provided advice and data taken into account in this revision of the Requirements are listed in the Acknowledgements section, page 96.

General considerations

The setting up of an organization for the collection and fractionation of human blood and blood components calls for a great deal of expertise and considerable investment. Any country contemplating the establishment of such an organization should carry out a careful cost-benefit analysis to determine whether the investment is justified. A logical developmental sequence for a comprehensive organization starts with the collection and distribution of whole blood, progressing later to the separation of whole blood into components and then the fractionation of plasma pools. It is not always possible to be specific about the details of the procedures employed, the in-process controls or the tests applied at each stage of production, in particular for whole blood and component cells. In addition, although the general principle of fractionation of plasma is well established, there are in practice numerous variations in the details of the various production steps. Therefore, any country wishing to begin the collection and fractionation of blood and blood components should send personnel for training to a plant that is operating successfully. WHO may be able to help in arranging such training.

One of the basic questions to be answered by a country considering whether to start fractionation of plasma is whether there is a suitable donor population of sufficient size to guarantee an adequate supply of source material. It is not possible to set a lower limit for the quantity of source material that would be necessary to make such an operation economic because too many factors are involved. However, in order to maintain competence in production and to avoid certain contamination risks, it is important to have sufficient source material to maintain the fractionation facility in continuous operation.

In a comprehensive organization, the greatest expense is that involved in setting up the fractionation plant, but it is also possible to regard the collection of source material and its fractionation as quite separate operations. A country may wish to establish collection centres for separating the cell components and then send the plasma to an established fractionation plant in another country, from where the products could be returned to the original country. The costs of such an operation might be less than those involved in establishing and operating a fractionation plant.

The general prevalence of certain infectious diseases, such as various forms of hepatitis and parasitic diseases, and of HIV infection differs so markedly in different geographical regions that each national authority must decide for itself whether it is cost-effective to apply the most sensitive test to each blood donation and whether it is feasible to collect suitable source material. A brief protocol for the collection of source material is in any case mandatory (see Appendix). Great emphasis should be placed on the production of fractions by a process that experience has shown results in the least risk of contamination. For example, immunoglobulin prepared by the cold ethanol fractionation method of Cohn has a well established

clinical record of being free from contamination with HIV and hepatitis B virus (HBV), as have albumin products prepared by the same method, stabilized and heated for 10 hours at 60 °C (*5*). Nevertheless, extreme care is required in manufacture to ensure that these products are free from infectious viruses, and it cannot be assumed that different fractionation methods will be equally effective. When a fractionation process is introduced or significant modifications are made to an existing production process, the process or the modifications should be validated or revalidated by appropriate procedures, including the use of marker viruses and, where applicable, special *in vitro* and *in vivo* testing.

Blood can harbour a number of different viruses, and the use of medicinal products derived from human blood has led to transmission of viruses such as HBV and HIV. The risk of virus transmission by blood and blood products can be diminished by the testing of all individual donations. Policies for mandatory testing shall be determined by the national control authority, and should be reviewed regularly and modified according to the current state of knowledge.

Special care and appropriate measures approved by the national control authority must be taken to protect the health of the staff of blood collection and fractionation facilities.

The transport of source materials from blood collecting centres and hospitals to fractionation facilities requires special consideration. Refrigeration at the temperature range appropriate for the product must be efficient and reliable and proved to be so by monitoring. Thermal insulation must provide an adequate safeguard against a temporary failure of refrigeration. Containers of liquid source material should be filled so as to minimize frothing due to shaking. Because of the potentially infective nature of these biological materials, suitable protection should be provided against breakage, spillage and leakage of containers.

In these Requirements, the word "human" has been omitted from the names of products derived from human blood. Products of animal origin are immunogenic, and their administration to humans should be avoided whenever equivalent products of human origin can be used instead. The proper name of any blood product of non-human origin should include the species of origin.

These Requirements consist of four parts:

- Part A. Requirements for the collection of source materials
- Part B. Requirements for single-donor and small-pool products
- Part C. Requirements for large-pool products
- Part D. National control requirements.

Each deals with a separate aspect of collection, processing and quality control, but all the parts are intended to be taken together to constitute a single document. It will not be possible to rely on any blood product unless the relevant requirements for each step are complied with, and any attempt

to make them less stringent may have serious consequences for the safety of the final product.

Parts A-D are divided into sections, each of which constitutes a recommendation. The parts of each section printed in normal type have been written in the form of requirements, so that, if a health administration so desires, they may be adopted as they stand as definitive national requirements. The parts of each section printed in small type are comments or recommendations for guidance.

Should individual countries wish to adopt these Requirements as the basis for their national regulations concerning blood products and related substances, it is recommended that modifications be made only on condition that the modified requirements ensure at least an equal degree of safety and potency of the products. It is desirable that the World Health Organization should be informed of any such changes.

Increasing demand for blood products is resulting in the extensive movement of such products from one country to another. Internationally accepted requirements are therefore necessary so that countries without any regulations on blood products and related substances may refer to them when importing such products.

International Biological Standards and Reference Reagents

Rapid technological developments in the measurement of the biological activity of blood products and related substances require the establishment of international biological reference materials. The first two such materials (for anti-A and anti-B blood-typing sera) were established in 1950, and further reference materials have been established since. A number of materials are currently under investigation for use in the preparation of new standards.

The activity of blood products must be expressed in International Units where an International Standard exists. WHO publishes a list of such standards (revised from time to time and most recently in 1990) under the title *Biological substances: International Standards and Reference Reagents.*

Definitions

The following definitions are intended for use in this document and are not necessarily valid for other purposes.

Blood collection: a procedure whereby a single donation of blood is collected in an anticoagulant and/or stabilizing solution.

Processing: any procedure that takes place after the blood is collected.

Plasmapheresis, apheresis and cytapheresis: procedures whereby whole blood is separated by physical means into components and one or more of them returned to the donor.

Closed blood-collection and processing system: a system for collecting and processing blood in containers that have been connected together by the manufacturer before sterilization, so that there is no possibility of bacterial or viral contamination from outside after collection of blood from the donor.

Donor: a person who gives blood or one of its components.

Single-donor materials

Whole blood (sometimes referred to as "blood"): blood collected in an anticoagulant solution with or without the addition of nutrients such as glucose or adenine. Whole blood is collected in units of 450 ml.

Blood component: any part of blood separated from the rest by means of physical procedures.

Plasma: the liquid portion remaining after separation of the cellular elements from blood collected in a receptacle containing an anticoagulant, or separated by continuous filtration or centrifugation of anticoagulated blood in an apheresis procedure.

Plasma, frozen: a plasma separated more than 8 h after collection of the blood and stored below -20 °C.

Plasma, fresh-frozen: a plasma separated within 8 h of donation, frozen rapidly and stored below -20 °C (and preferably below -30 °C).

Plasma, platelet-rich: a plasma containing at least 70% of the platelets of the original whole blood.

Plasma, freeze-dried: any one of the above forms of plasma that has been freeze-dried for preservation.

Plasma, recovered: plasma recovered from a whole blood donation.

Cryoprecipitated factor VIII: a crude preparation containing factor VIII that is obtained from single units (or small pools) of plasma derived either from whole blood or by plasmapheresis, by means of a process involving freezing, thawing and precipitation.

Serum: the liquid part of coagulated blood or plasma.

Red cells: whole blood from which most of the plasma has been removed and having an erythrocyte volume fraction greater than 0.7.

Red cells suspended in additive solution: red cells to which a preservative solution, for example containing adenine, glucose and mannitol, is added to permit storage for longer periods; the resulting suspension has an erythrocyte volume fraction of approximately 0.6-0.7.

Red cells, washed: red cells from which most of the plasma has been removed by one or more stages of washing with an isotonic solution.

Red cells, leukocyte-depleted: a unit of a red-cell preparation containing fewer than 1.2×10^9 leukocytes.

Red cells, leukocyte-poor: a unit of a red-cell preparation containing fewer than 5×10^6 leukocytes.

Red cells, frozen: red cells that have been stored continuously at −65 °C or below, and to which a cryoprotective agent such as glycerol has been added before freezing.

Red cells, deglycerolized: frozen red cells that have been thawed and from which glycerol has been removed by washing.

Platelets: platelets obtained either by separation of whole blood, buffy coat or platelet-rich plasma or by apheresis and suspended in a small volume of plasma from the same donation.

Leukocytes: leukocytes obtained either by the separation of whole blood or by apheresis and suspended in a small volume of plasma from the same donation.

Large-pool products

Bulk material: plasma, powder, paste or liquid material prepared by the fractionation of pooled plasma.

Final bulk: a sterile solution prepared from bulk material and bearing the corresponding batch number. It is used to fill the final containers.

> In some countries, the final bulk is distributed into containers through a sterilizing filter. If the total final bulk is not distributed into containers in one session, each of the filling lots is given a sub-batch number.

Filling lot (final lot): a collection of sealed final containers that are homogeneous with respect to composition and the risk of contamination during filling and (where appropriate) drying or other further processing such as heat treatment. A filling lot must therefore have been filled and (where appropriate) dried in one working session.

Part A. Requirements for the collection of source materials

1. Premises

The premises shall be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance in accordance with accepted rules of hygiene. They shall comply with the requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products and in addition provide adequate space, lighting and ventilation for the following activities where applicable:

- The medical examination of individuals in private to determine their fitness as donors of blood and/or blood components and to provide an opportunity for the confidential self-exclusion of unsuitable potential donors.
- The withdrawal of blood from donors and, where applicable, the re-infusion of blood components with minimum risk of contamination and errors.
- The care of donors, including the treatment of those who suffer adverse reactions.
- The storage of whole blood and blood components in quarantine pending completion of processing and testing.
- The laboratory testing of blood and blood components.
- The processing and distribution of whole blood and blood components in a manner that prevents contamination and loss of potency.
- The performance of all steps in apheresis procedures, if applicable.
- The performance of labelling, packaging and other finishing operations in a manner that prevents errors.
- The storage of equipment.
- The separate storage of quarantined and finished products.
- The documentation, recording and storage of data on the donor, the donated blood and the ultimate recipient.

Mobile teams can be used for the collection of blood. Although the premises used by such teams may not comply with the more stringent requirements for centres built specially for the purpose, they must be adequate to ensure the safety of the donor, the collected blood or blood components and the staff participating in blood collection. The safety of the subsequent users of the premises should also not be forgotten.

2. Equipment

The equipment used in the collection, processing, storage and distribution of blood and blood components shall be calibrated, tested and validated before initial use, and shall be kept clean and maintained and checked regularly. The requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products shall apply in every particular.

The equipment employed to sterilize materials used in the collection of blood or blood components or for the disposal of contaminated products shall ensure that contaminating microorganisms are destroyed and shall be validated for this purpose. The effectiveness of the sterilization procedure shall be not less than that achieved by a temperature of 121.5 °C maintained for 20 min by means of saturated steam at a pressure of 103 kPa (1.05 kgf/cm^2 or 15 lbf/in^2) or by a temperature of 170 °C maintained for 2 h with dry heat.

All contaminated material should be made safe before disposal. Disposal should comply with the relevant local laws.

Tests for sterility are given in the revised Requirements for Biological Substances No. 6 (General Requirements for the Sterility of Biological Substances) (9, pp. 40–61).

3. Personnel

An organization for the collection of blood or blood components shall be under the direction of a designated and appropriately qualified person who shall be responsible for ensuring that all operations are carried out properly and competently. The director shall have adequate knowledge and experience of the scientific and medical principles involved in the procurement of blood and, if applicable, the separation of blood components and the collection of such components by apheresis.

The director shall be responsible for ensuring that employees are adequately trained and acquire practical experience and that they are aware of the application of accepted good practice to their respective functions.

The director should have the authority to enforce or to delegate the enforcement of discipline among relevant employees.

The persons responsible for the collection of the blood and blood components shall be supervised by licensed physicians who shall be responsible for all medical decisions, for review of the procedures manual and for the quality-control programme, including techniques, equipment, procedures and staff.

The personnel responsible for the processing, storage, distribution and quality control of blood, blood components and plasma shall be adequate in number and each member of the personnel shall have a suitable educational background and training or experience that will ensure competent performance of assigned functions so that the final product has the required safety, purity, potency and efficacy.

4. Donors

4.1 *Donor selection*

The provision of blood, blood components and plasma derivatives from voluntary, non-remunerated donors should be the aim of all countries.

In selecting individuals for blood donation, it is most important to determine whether the person is in good health, in order to protect the donor against damage to his or her own health and to protect the recipient against exposure to diseases or to medicinal products from the blood or blood products. It should be recognized that the donor selection process contributes significantly to the safety of blood products derived from large plasma pools. The following provisions apply to donations of blood or blood components not intended for autologous use.

The health of a donor shall be determined by a licensed physician or a person under the direct supervision of a licensed physician, and the donor shall be free from any disease transmissible by blood transfusion in so far as can be determined by history-taking and examination (see section 4.3). Donors shall be healthy persons of either sex between the ages of 18 and 65 years.

> In some countries, there is no upper limit to the age of the donor. With parental consent the minimum age may be lowered to 16 years.
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> Red blood cells from donors with glucose-6-phosphate dehydrogenase deficiency, sickle-cell trait or other inherited erythrocyte abnormalities may give rise to transfusion reactions under certain circumstances. Decisions regarding the suitability of such donors should be made by the national control authority.

A donor should be considered for plasmapheresis only where the procedures involved result in products or services shown to serve accepted medical purposes, including prophylaxis, therapy and diagnosis, as verified by valid scientific evidence. All donors should be certified as acceptable, at the time of each plasmapheresis procedure, by a registered physician or by trained personnel under the direct supervision of the physician.

Those eligible for apheresis donation include: (a) healthy persons who fulfil the general criteria for blood donors; (b) persons with antibody levels that have been increased, either naturally or by immunization; (c) subject to (a) above, persons with plasma that is of value for diagnostic or reference purposes; and (d) persons whose blood may be used in the preparation of certain vaccines.

> When a potential donor does not fulfil the general criteria for blood donation, the acceptance of her or him as a donor for a specific component of blood *should be at the discretion of the responsible physician. Where appropriate,* the physician should have access to an ethical committee.

Donor education and selection programmes are intended to prevent potentially infectious units of blood and plasma from being collected. It is essential that such programmes are comprehensible and readily accessible to all potential donors.

To reduce the likelihood of transmitting infections, all potential donors should be informed of factors in their history or behaviour that may increase their risk of being infected. The national control authority must determine the appropriate exclusion criteria for the country concerned.

Persons in the following categories shall be excluded from acting as donors:

- those with clinical or laboratory evidence of infectious disease, e.g. infection with hepatitis viruses, HIV-1 or HIV-2;
- past or present intravenous drug abusers;
- men who have had a sexual relationship with another man;

- men and women who have engaged in prostitution;
- those with haemophilia or other clotting-factor defects who have received clotting-factor preparations;
- sexual partners of any of the above.

In some countries, the sexual partners of those at risk of transmitting infections are excluded from acting as donors for only one year.

Persons who have received blood transfusions should be excluded from acting as donors for at least one year.

Donors should be made aware before donating blood that it will be tested for the presence of serological markers of infection. It is advisable that the right to test donations and the legal implications of testing donations should be clarified by the appropriate authority.

4.2 *Donation frequency and volume*

4.2.1 *Whole blood*

The frequency of whole-blood donations shall not exceed once every two months, with a maximum volume in any consecutive 12-month period of 3 l.

A standard donation should not be collected from persons weighing less than 50 kg.

A *standard donation* is 450 ml; an optimum blood/anticoagulant ratio is 7 to 1.

The frequency of donation may have to be modified on an individual basis. In general, premenopausal women should not donate blood as frequently as men.

4.2.2 *Plasma*

Plasma donors can be divided into three groups: those who donate at a frequency comparable to that allowed for whole-blood donations; those who donate two to three times as frequently as whole-blood donors; and those who donate at a maximum of twice a week. The first group shall be accepted on the basis of the general criteria for blood donors.

The maximum volume of plasma that may be removed from a donor during one plasmapheresis procedure shall be determined by the national health authority, and shall depend on whether the plasma is obtained by manual or automated plasmapheresis.

In some countries, the volume of plasma collected during a manual procedure is the quantity obtained from 1.0–1.2 l of whole blood. The volume of plasma collected during an automated procedure depends on the equipment used.

It is difficult to specify the maximum volumes of plasma that can be safely collected from donors until more definitive data are available on the effects of plasmapheresis on donors. The limits imposed in different countries vary, and depend on the nutritional status of the donor.

If a plasma donor donates a unit of whole blood or if the red blood cells are

not returned in an apheresis procedure, the next donation shall be deferred by eight weeks unless special circumstances warrant approval by the responsible physician of plasmapheresis at an earlier date.

In general, plasma collected by therapeutic plasmapheresis shall not be used for fractionation.

4.3 *Medical history*

4.3.1 *General*

Before each donation, questions shall be asked so as to ensure that the donor is in normal health and has not suffered, or is not suffering, from any serious illness.

A donor who appears to be suffering from symptoms of acute or chronic disease or who is receiving oral or parenteral medication, with the exception of vitamins, postmenopausal hormone therapy or oral contraceptives, shall not be accepted unless approved by a physician.

A donor who appears to be under the influence of any drug including alcohol or who does not appear to be providing reliable answers to medical history questions shall not be accepted.

4.3.2 *Infectious diseases*

Potential donors with a history that places them at increased risk of transmitting infection shall not donate blood or plasma for an appropriate time period. A donor shall be permanently excluded if one of his or her previous blood donations was believed to be responsible for transmitting disease.

> In most countries, questions concerning the signs and symptoms of HIV infection will be part of the routine assessment of medical history and appropriate monitoring for HIV, as defined by the national control authority, will be included. As a result of this assessment, a potential donor may be disqualified.

Donors shall not have a history of: positive laboratory test results for hepatitis or corresponding symptoms and signs; close contact with an individual with hepatitis within the previous year; receipt within the previous year of human blood or any blood component or fraction that might be a source of transmission of infectious agents; or tattooing, scarification or ear piercing (unless performed under sterile conditions) within the previous year.

> Acupuncture within the previous year may also present a risk if not carried out under sterile conditions.
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> In some countries, potential donors with a history of viral hepatitis or of a positive test for hepatitis B surface antigen (HBsAg) or antibodies to hepatitis C virus (anti-HCV) are permanently excluded. In others, such donors are accepted providing that recovery occurred more than one year previously and that the reaction for HBsAg and anti-HCV in a sensitive test is negative.

The requirements concerning viral hepatitis may be varied, at the discretion of the national control authority, according to the local epidemiological circumstances.

> The collection both of single-donor products (whole blood and its components) and of plasma for pooling for the manufacture of plasma fractions capable of transmitting hepatitis or HIV should be avoided if a group of potential donors shows a prevalence of acute or chronic hepatitis B, hepatitis C or HIV infection higher than that found in the general donor population. Specific approval may be given by national control authorities for the use of donations from such populations to provide plasma for the manufacture of hepatitis B vaccine or hepatitis B immunoglobulin.
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> In areas with a low incidence of transfusion-transmitted disease, whole blood or blood components should not be used for transfusion if obtained from source material collected in an area where there is a high incidence of blood-borne infectious disease.

Blood and plasma shall be tested for the presence of HBsAg, anti-HIV and anti-HCV by the methods described in Part B, section 7.2; the tests used should be approved by the national control authority or other appropriate authority.

Anyone whose blood has been shown to be reactive for infectious disease markers by approved screening tests shall be excluded as a donor. Selection as a donor may later be permitted if sufficient data are available from tests approved by the national control authority to indicate that the original results were non-specific.

National health authorities shall develop policies designed to prevent the transmission of infectious diseases based on the prevalence of these diseases in the donor population and the susceptibility of recipients to them.

> In countries where malaria is not endemic, donors of cellular blood products should have a negative history of malaria exposure during the previous six months and a negative history of clinical malaria, or a history of malaria prophylaxis if they have resided in, or visited, an endemic area within the three years preceding the donation. Such restrictions may be less important in countries where the prevalence of endemic malaria is high among both donors and recipients, except when blood products are required by visitors from non-endemic areas. Malaria history is not pertinent to plasma donation for source material that will be fractionated.

Particular attention should be paid to skin decontamination procedures before blood collection.

> Many parasitic, bacterial and viral diseases, including trypanosomiasis, toxoplasmosis, syphilis and brucellosis, can be transmitted by blood. Precautions shoud be taken to avoid blood collection during the viraemic phase of viral diseases like measles and rubella. Potential donors who have lived in or recently travelled to areas where human T-cell lymphotropic virus infections and haemorrhagic fever are endemic should be investigated for evidence of such infections.

Anyone who has received pituitary hormones of human origin should be permanently excluded as a donor because of possible infection with the agent causing Creutzfeldt-Jakob disease, although transmission of this agent through blood products has not been proved.

4.3.3 *Minor surgery*

Donors shall not have undergone tooth extraction or other minor surgery during a period of 72 h before donation.

4.3.4 *Pregnancy and lactation*

Pregnant women shall be excluded from blood donation. In general, mothers shall also be excluded during lactation and for at least six months after full-term delivery.

> The interval before blood donation is permissible after pregnancy may be shorter in some cases, e.g. six weeks after an abortion during the first trimester.
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> In some countries, donors are accepted when pregnant or during the period of lactation if their blood contains certain blood-group antibodies or is needed for autologous transfusion. The volume to be taken should be determined by the physician responsible.

4.3.5 *Prophylactic immunization*

Symptom-free donors who have recently been immunized may be accepted with the following exceptions:

- Those receiving attenuated vaccines for measles, mumps, yellow fever or poliomyelitis shall be excluded until two weeks after the last immunization or injection.
- Those receiving attenuated rubella (German measles) vaccine shall be excluded until four weeks after the last injection.
- Those receiving rabies vaccine for post-exposure treatment shall be excluded until one year after the last injection.
- Those receiving passive immunization with animal serum products shall be excluded until four weeks after the last injection.
- Those receiving hepatitis B vaccine need not be excluded unless the vaccine is being given because of exposure to a specific risk, in which case the donor shall be disqualified for at least 12 months after the last such exposure. If hepatitis B immunoglobulin has been administered, the period of deferral shall be at least 12 months because disease onset may be delayed.

4.4 *Physical examination*

As determined by the national control authority, physical examination of donors may include measurement of weight, blood pressure, pulse rate and temperature. If these are measured and the results lie outside the ranges recommended below, the donor concerned shall be accepted only if approved by the licensed physician in charge.

- *Blood pressure:* systolic blood pressure between 12 and 24 kPa (90 and 180 mmHg); diastolic blood pressure between 6.67 and 13.3 kPa (50 and 100 mmHg).
- *Pulse:* between 50 and 110 beats per minute and regular. Lower values may be accepted in healthy athletes with endurance training.
- *Temperature:* oral temperature not exceeding 37.5 °C.
- *Weight:* donors weighing less than 50 kg may donate a volume of blood proportionally less than 450 ml in an appropriate volume of anticoagulant, provided that all other donor requirements are met.

Donors shall be free from any infectious skin disease at the venepuncture site and of skin punctures or scars indicative of abuse of intravenous drugs.

4.5 *Additional requirements applicable to donors for plasmapheresis*

All phases of apheresis, including explaining to donors what is involved in the process and obtaining their informed consent, should be performed under the direct supervision of a licensed physician or by trained personnel reporting to such a physician.

4.5.1 *First-time plasma donors*

When prospective plasma donors present themselves to a centre for the first time, initial screening shall begin only after the procedure of plasmapheresis has been explained and the donor has given consent.

The following information shall be permanently recorded:

- Personal information and identification. If the donor is to participate in an ongoing programme, an effective means of identification is especially important. The use of identity numbers, photographs or other equally effective measures should be considered.
- A preliminary medical history as required for blood donors, covering infectious diseases and the donor's general state of health.

If there are no contraindications to plasmapheresis, preliminary laboratory tests shall be carried out, namely reading of the erythrocyte volume fraction or haemoglobin concentration, determination of total serum protein and screening for protein and sugar in the urine. The haemoglobin concentration or erythrocyte volume fraction of the donor's blood shall be within normal limits, as defined by the national control authority or the national blood transfusion authority.

> Many countries specify minimum haemoglobin concentrations of 125 g/l for women and 135 g/l for men, or, for microhaematocrit determinations, minimum erythrocyte volume fractions of 0.38 for women and 0.41 for men.

If normal values are also obtained in the other laboratory tests, evaluation of the potential donor by the physician begins.

> In some countries, specially trained non-physicians are permitted to conduct these routine examinations under the supervision of a physician.

Donors participating in a programme in which plasmapheresis is more frequent than is blood donation for those eligible for whole-blood collection shall be examined by a licensed physician on the day of the first donation, or not more than one week before that donation. This examination shall include measurement of temperature and blood pressure, auscultation of the heart and lungs, palpation of the abdomen, assessment of neurological signs, urine analysis and blood sampling for tests required by the national control authority. Liver function tests (e.g. for alanine aminotransferase), tests for HBsAg, anti-HIV and anti-HCV, and quantification of plasma proteins by electrophoresis or another suitable method shall also be included. The physician shall obtain informed consent after explaining the procedure of plasmapheresis and describing the hazards and adverse reactions that may occur. At this stage, donors shall be given an opportunity to refuse participation. If they consent, it must be on the condition that their legal rights to recover damages are not waived.

In some countries, the first plasmapheresis procedure may be performed before the results are available for the liver function tests, the serological tests for syphilis (if required by the national control authority) and the tests for HBsAg, anti-HCV and anti-HIV. The results of the tests for quantifying plasma proteins should be reviewed by the physician before subsequent plasmapheresis procedures.

4.5.2 *Donors who have undergone plasmapheresis previously in the same programme*

For donors who have already taken part in a plasmapheresis programme:

- The receptionist shall note the date of the last donation (at least two days must have elapsed since that time). No more than two donations shall be permitted within a seven-day period.
- The medical history and weight of the donor shall be recorded; blood pressure, temperature, pulse rate and haemoglobin concentration shall be measured by trained personnel. On the day of each donation, in addition to meeting the general requirements for donors, plasma donors shall be shown to have a total serum protein concentration of not less than 60 g/l.

The medical evaluation of plasma donors shall be repeated at regular intervals, as specified by the national control authority, and tests carried out as specified in section 4.5.3.

Whenever the result of a laboratory test is found to be outside the established normal limits or a donor exhibits any important abnormalities of history or on physical examination, the donor shall be excluded from the programme. The donor shall not be readmitted to the programme until the results of relevant tests have returned to normal and the responsible physician has given approval in writing. It is the responsibility of national health authorities to define normal ranges and standard deviations of test results on the basis of data from a sufficiently large sample of healthy individuals not undergoing plasmapheresis.

In the case of hepatitis C, the results of liver function tests frequently return to normal before rising again. Test results obtained over a period of adequate length must therefore be evaluated by the physician before the donor can be readmitted to the programme.

4.5.3 *Tests for plasma donors*

The following tests shall be performed at each donation:

- Measurement of haemoglobin concentration or erythrocyte volume fraction.
- Determination of total serum protein concentration, which shall be at least 60 g/l.
- An approved test for HBsAg, which shall be negative.
- An approved test for anti-HIV, which shall be negative.
- An approved test for anti-HCV, which shall be negative.

The following tests shall be performed initially and then every four months or after every 10 donations, whichever time interval is longer:

- If required by the national control authority, a serological test for syphilis, which shall be negative.
- Urine analysis for glucose and protein, which shall be negative.
- Serum protein electrophoresis: this shall be normal (unusual changes in a donor's results may be more significant than absolute values). The albumin and globulin concentrations may be calculated from the known total protein value, and shall be: albumin, minimum 35 g/l; IgM, minimum 0.5 g/l; IgG, between 5 and 20 g/l.
- Liver function tests.

  When determination of serum alanine aminotransferase is required, the enzyme concentration measured photometrically using approved reagents shall be no more than two standard deviations above an established normal mean.

4.6 *Donors for platelet and leukocyte apheresis*

In general, platelet and leukocyte donors shall meet the general criteria for donors and the specific criteria for plasma donors (sections 4.1–4.5). In addition, platelet donors should not have taken aspirin or other platelet-active drugs for at least 72 h before donation.

The requirements to be satisfied in the performance of plateletpheresis and leukapheresis in order to ensure that there is no danger to donors and that the products obtained are of satisfactory quality are under active investigation in many countries. The following recommendations may be useful as guidance.

On the day of each donation, donors for plateletpheresis should have an absolute platelet number concentration ("count") of not less than 200×10^9/l and donors for leukapheresis should have an absolute granulocyte number

concentration of not less than 3×10^9/l. Both types of donor should have a normal differential leukocyte count and haemoglobin level.

Although levels of circulating platelets and leukocytes recover promptly in donors, data are not at present available from which the maximum numbers of platelets and leukocytes that can be safely collected from donors can be defined. The long-term effects of the repeated removal of cellular elements are not known.

Leukapheresis may entail the administration of drugs to donors and their exposure to colloidal agents to enhance the yield of granulocytes. Appropriate precautions should be taken to protect donors, such as investigation for latent diabetes by means of a glucose tolerance test if a donor is to be given corticosteroids.

Leukapheresis should be performed as part of the treatment of a patient with chronic myeloid leukaemia only if approved by the patient's attending physician. It is inadvisable to use the leukocytes from such patients.

4.7 *Donor immunization and plasma for special purposes*

4.7.1 *Plasmapheresis in donors with naturally acquired antibodies and other types of medically useful plasma*

Plasma may be collected by plasmapheresis from donors who have acquired immunity through natural infection or through active immunization with approved vaccines for their own protection, and from donors with plasma useful for diagnostic purposes as a result of acquired or congenital underlying conditions.

Donors with medically useful plasma may be identified by screening whole blood donations and by examining patients convalescing from specific diseases or vaccinated individuals, e.g. veterinary students who have received rabies vaccine or military recruits who have been immunized with tetanus toxoid. Unnecessary immunizations can be avoided by this approach.

The following are examples of medically useful plasma:

- Antibody-rich plasma for control reagents in diagnostic tests, such as those for anti-HIV, hepatitis A and B, cytomegalovirus, rubella, measles and uncommon infectious agents; plasma should be collected in appropriately isolated premises when products are being prepared that are known to be capable of transmitting infection.
- Plasma containing antibodies to human cellular and serum antigens of diagnostic use, for example in HLA (human leukocyte antigen) typing reagents, erythrocyte typing reagents and immunoglobulin allotyping reagents.
- Plasma containing reagents useful for diagnostic tests, such as reagin, rheumatoid factors, heterophile antibody and C-reactive protein.
- Factor-deficient plasma for specific assays, such as factor-VIII-deficient plasma. Donors who have received factor VIII are at increased risk of transmitting hepatitis B, hepatitis C and HIV; their plasma should therefore be collected in appropriately isolated premises.

4.7.2 *Precautions to be taken when handling blood or blood products containing infectious agents*

All blood and plasma may contain unknown infectious agents and must be handled accordingly. In addition, special precautions must be taken when handling infected donors and blood products known to contain infectious agents. The precautions to be taken might include:

- isolation by means of the appropriate timing or location of the procedures, special labelling and quarantine of the products collected, use of protective packaging with double wrapping in impervious plastic;
- disinfection of all work surfaces and equipment with a disinfectant of known efficacy, such as freshly prepared 0.25% sodium hypochlorite solution;
- protection of staff by means of adequate training, avoidance of aerosols and use of gloves, gowns, masks and eye protection; it is strongly recommended that such staff also be protected by immunization with hepatitis B vaccine;
- fulfilment of the labelling, shipping and waste-disposal requirements appropriate to the etiological agents in question.

4.7.3 *Immunization of donors*

There is a clinically valid need for specific immunoglobulins and plasma for therapeutic, prophylactic and diagnostic uses. Deliberate immunization of healthy volunteers may be necessary in addition to collection of plasma from convalescent patients and donors selected by screening for high levels of specific antibodies. The immunization of donors requires informed consent in writing and shall take into consideration all the requirements of the previous sections.

Donors shall be immunized with antigens only when sufficient supplies of material of suitable quality cannot be obtained from other appropriate donors, from donations selected by screening, or in the form of safe and efficacious licensed monoclonal antibodies. Donors must be fully informed of the risk of any proposed immunization procedure, and pressure shall not be brought to bear on a donor to agree to immunization. Women capable of child-bearing shall not be immunized with erythrocytes or other antigens that may produce antibodies harmful to the fetus. Donors of blood and those undergoing plasmapheresis shall, if necessary, undergo investigations that can reveal hypersensitivity to a proposed antigen (see also Part B, section 6).

An approved schedule of immunization shall be used. Every effort shall be made to use the minimum dose of antigen and number of injections. In any immunization programme, the following shall be taken into consideration as a minimum: (a) the antibody assay; (b) the minimum level of antibody required; (c) data showing that the dose, the intervals between injections and the total dosage proposed for each antigen are appropriate; and (d) the criteria for considering a prospective donor a non-responder for a given antigen. No donor shall be hyperimmunized with more than one

immunizing preparation unless the safety of the multiple procedure is demonstrated.

Potential donors should be:

- informed by a licensed physician of the procedures, risks and possible sequelae and how to report any adverse effects, and encouraged to take part in a free discussion (which, in some countries, is achieved in small groups of potential donors);
- encouraged to seek advice from their family doctor before agreeing to immunization;
- informed that any licensed physician of their choice will be sent all the information about the proposed immunization procedure;
- informed that they are free to withdraw consent at any time.

All vaccines used for immunizing donors shall be registered or recognized by the national health authority, but may be administered at doses and with schedules differing from those recommended for routine prophylactic immunization. Erythrocyte and other cellular antigens shall be obtained from an establishment approved by the national control authority.

Donors shall be observed for approximately 30 min following any immunization in order to determine whether an adverse reaction has taken place. Because reactions often occur 2–3 h after immunization, donors shall be advised of this possibility and instructed to contact the facility's physician if a reaction is suspected in the first 12 h after immunization. Reactions may be local or systemic. Local reactions, which may be immediate or delayed, take the form of redness, swelling or pain at the injection site. Systemic reactions may include fever, chills, malaise, arthralgia, anorexia, shortness of breath and wheezing.

4.7.4 *Immunization with human erythrocytes*

Erythrocyte donors. A donor of erythrocytes for the purposes of immunization shall meet all the general health criteria for donors (see sections 4.3 and 4.4). In addition, the donor shall not have had a blood transfusion at any time.

The volume of erythrocytes drawn from a donor should not exceed 450–500 ml of whole blood in any eight-week period.

At each donation the donor shall be found to be negative for syphilis, HBsAg, anti-HIV, antibody to hepatitis B core antigen (anti-HBc), anti-HCV and antibodies to human T-cell lymphotropic viruses (anti-HTLV). The serum level of aminotransferases should be within normal limits as established by the national control authority.

Erythrocyte phenotyping shall be done for ABO as well as for C, D, E, c, e, Kell and Fy^a. Phenotyping for other specificities is often desirable and is recommended especially for Jk^a, Jk^b, Fy^b, S and s.

Ideally erythrocytes obtained for immunization purposes should be frozen for at least 12 months before use and the donor should be recalled and retested for anti-HIV, anti-HCV, anti-HBc, HBsAg and anti-HTLV before the stored cells are used for immunization.

Where suitable facilities for freezing erythrocytes are not available, national control authorities may authorize the use of cells from a single donor to immunize no more than three persons (preferably who have not previously had a blood transfusion) in an initial 12-month period, during which monthly determinations of anti-HIV, anti-HCV, anti-HBc, HBsAg and serum alanine aminotransferase should be made in both the donor and the recipients. If, after 12 months, the initial three recipients show no clinical or laboratory evidence of hepatitis, HIV infection or other blood-transmissible diseases, the donor may be considered acceptable for providing erythrocytes for immunization. As small a number of donors of erythrocytes should be used as possible.

Collection and storage of erythrocytes. Erythrocytes shall be collected under aseptic conditions into sterile, pyrogen-free containers in an appropriate proportion of an approved anticoagulant. They may then be dispensed in aliquots under aseptic conditions into single-dose, sterile, pyrogen-free containers for storage. The microbiological safety of the dispensing environment shall be validated.

Erythrocytes should be stored frozen for at least 12 months to permit retesting of donors for disease markers. The method selected should have been validated such that there is 70% cell recovery *in vivo*. Erythrocytes should be washed after storage to remove the cryoprotective agent.

Adequate sterility data to support the requested shelf-life for stored erythrocytes should be submitted by the manufacturer to the national control authority. A test for bacterial and fungal contamination should be made on all blood dispensed in aliquots in an open system (*9*). The test should also be performed on at least one single-dose vial from each lot of whole blood that has been stored unfrozen for more than seven days. The test should be made on the eighth day after collection and again on the expiry date. Cultures for the sterility test should be maintained for at least 14 days, with subculturing on day 3, 4 or 5.

Erythrocyte recipients. The following additional testing of erythrocyte recipients is necessary:

- The recipient should be phenotyped for ABO, Rh, Kell and Duffy antigens before immunization. Kell-negative and/or Fy(a-) persons should not receive Kell-positive or Fy(a+) cells except for the specific purpose of producing anti-Kell or anti-Fy^a. Only ABO-compatible erythrocytes may be transfused. Matching of Jk^a, Jk^b, Fy^b, S and s phenotypes is also desirable.
- Screening for unexpected antibodies by methods that demonstrate coating and haemolytic antibodies should include the antiglobulin method or a procedure of equivalent sensitivity.

Prospective erythrocyte recipients in whom antibody screening tests demonstrate the presence of erythrocyte antibodies (other than those deliberately stimulated through immunization by the plasmapheresis centre) should be asked whether they have ever been pregnant or had a

transfusion, a tissue graft or an injection of erythrocytes for any reason. This history should form part of the permanent record and should identify the cause of immunization as clearly as possible. Recipients should be notified in writing of any specific antibodies developed after injection of erythrocytes. The national control authority should be notified annually in writing of unexpected antibodies induced by immunization, and the immunized donor should carry a card specifying the antibodies.

Immunization schedules. Erythrocytes used for immunization purposes shall not be administered as part of any plasmapheresis procedure. Such immunization may be performed on the same day as plasmapheresis, but only after it and as a separate procedure.

To minimize the risk of infection to the donor, the immunization schedule should involve as few doses of erythrocytes as possible.

For primary immunization two injections of erythrocytes, each of about 1-2 ml and given three months apart, elicit antibody formation within three months of the second injection in approximately 50% of volunteers; the result is not improved by injecting larger amounts or giving more frequent injections.

It is advantageous to choose as donors of anti-D (anti-Rh_o) volunteers who are already immunized, since useful levels of anti-D are then usually attained within a few weeks of reimmunization. In some people, the level of antibody reaches its maximum within the first three weeks and will not increase after further immunization. In others, antibody levels may continue to rise for more than 12 months when injections of 0.5-1 ml of erythrocytes are given at intervals of five to eight weeks. About 70% of immunized volunteers eventually produce antibody levels well above 100 IU/ml. Once attained, such levels can be maintained by injections of 0.1-0.5 ml of erythrocytes at intervals of two to nine months, as required. If injections of erythrocytes are discontinued, antibody levels usually fall appreciably within 6-12 months.

The baseline antibody titre of every recipient of erythrocytes should be established, and the antibody response, including both type and titre, should be monitored monthly.

Erythrocytes to be used for immunization purposes should be selected, for each recipient, by a licensed physician.

Risks to recipients. Recipients of erythrocytes for immunization purposes may run the risk of:

- viral hepatitis (B and C) and HIV infection;
- other infectious diseases;
- HLA immunization;
- the production of unwanted erythrocyte antibodies that may complicate any future blood transfusion;
- a febrile reaction if the antigen dose is too great;

– the production of antibodies that may interfere with future organ transplantation if it is needed.

Record-keeping. Records of erythrocyte donors and of the recipients of their erythrocytes should be maintained and cross-referenced.

5. Collection of blood and plasma

A number of precautions must be taken in the collection of blood and plasma, as described in the following sections.

5.1 *Blood collection and apheresis procedures*

The skin of the donor at the site of venepuncture shall be prepared by a method that has been shown to give reasonable assurance that the blood collected will be sterile. Blood shall be collected into a container by means of an aseptic method. The equipment for collecting the sterile blood may be closed or vented provided that the vent is designed to protect the blood against microbial contamination.

With apheresis procedures, care shall be taken to ensure that the maximum volume of erythrocytes is returned to the donor by intravenous infusion. If the red cells cannot be returned to the donor, no further collection should be made until the donor has been re-evaluated. Several checks shall be made to ensure that donors receive their own erythrocytes, including identification of the containers of erythrocytes by donors before re-infusion. Haemolytic transfusion reactions are avoidable, since they are caused by the accidental infusion of incompatible erythrocytes. Personnel involved in reinfusion procedures should be adequately trained to prevent them. The signs and symptoms are hypotension, shortness of breath, stomach and/or flank pain, apprehension, cyanosis and haemoglobinuria.

If a haemolytic transfusion reaction occurs, the infusion of cells to all donors at the centre concerned should be discontinued until the identity of all containers of erythrocytes has been checked. Automated plasmapheresis is preferred to manual plasmapheresis in some institutions because of its greater safety.

5.1.1 *Summary of minimum general requirements for apheresis*

Equipment. This must be electrically safe and non-destructive for blood elements; disposable tubing must be used wherever there is blood contact. In addition, equipment must be accessible to detailed inspection and servicing and its decommissioning should not significantly interrupt the programme. It should also be provided with suitable automatic alarms.

Procedure. This must be non-destructive for blood elements and aseptic; there must be adequate safeguards against air embolism.

Disposables. These must be pyrogen-free, sterile and biocompatible (e.g. there must be no activation of enzyme systems).

5.1.2 *Adverse reactions*

Provision must be made to prevent and treat any adverse reactions in donors. As with any medical procedure involving the treatment of individuals, adverse reactions may occur with blood collection and plasmapheresis. Almost all such reactions are mild and transient, but an occasional serious reaction may occur. The possibility of adverse reactions, though remote, should be anticipated and adequate provision should be made to ensure that care is available to donors. Initial and continuing training in emergency care is mandatory for personnel. If any serious adverse reaction occurs, a physician should be called.

5.1.3 *Types of adverse reaction*

Vasovagal syncope. This is most likely to occur with new donors. The signs and symptoms are hypotension, bradycardia, syncope, sweating and (rarely) convulsions.

Local infection, inflammation and haematoma at the phlebotomy site. Reactions of this type are best prevented by adequate preparation of the venepuncture site and by training phlebotomists in proper methods of initiating blood flow. The symptoms are localized pain and redness and swelling at the phlebotomy site.

Allergic and anaphylactoid reactions. These may occur during the introduction of saline into the donor while red cells are being processed, or during reinfusion of red cells. The signs and symptoms are urticaria, burning in the throat, tightness of the chest, wheezing, pain in the abdomen and hypotension.

Systemic infection. Care should be taken at all stages of plasmapheresis to avoid the transmission of infectious organisms to the donor.

5.2 *Containers*

The original blood container or a satellite attached in an integral manner shall be the final container for whole blood and red cells, with the exception of modified red cells, for which the storage period after processing should be as short as possible and certainly not longer than 24 h. Containers shall be uncoloured and translucent and the labelling shall be placed in such a position as to allow visual inspection of the contents. They shall be sterilized and hermetically sealed by means of suitable closures so that contamination of the contents is prevented. The container material shall not interact adversely with the contents under the prescribed conditions of storage and use.

The specifications for containers should be approved by the national control authority (*10, 11*).

If sterile docking devices are not available, closed blood-collection and processing systems should be used to prepare blood components.

5.3 *Anticoagulants*

The anticoagulant solution shall be sterile, pyrogen-free and of a composition such as to ensure that the whole blood and separate blood components are of satisfactory safety and efficacy.

> Commonly used anticoagulant solutions are acid–citrate–glucose, citrate–phosphate–glucose and citrate–phosphate–glucose–adenine; the amount of adenine used varies in different countries. Solutions of adenine, glucose and mannitol used for red cell preservation may be added after removal of the plasma.
>
> For plasmapheresis, sodium citrate as a 40 g/l solution is widely used as an anticoagulant.

5.4 *Pilot samples*

Pilot samples are blood samples provided with each unit of whole blood or of red blood cells. They shall be collected at the time of donation by the person who collects the whole blood. The containers for pilot samples shall be marked at the collection site before the samples are collected, and the marking used must be such that the sample can be identified with the corresponding unit of whole blood. Pilot samples must be collected by a technique that does not compromise the sterility of the blood product.

> Pilot samples should be attached to the final container in a manner such that it will later be clear whether they have been removed and reattached.

5.5 *Identification of samples*

Each container of blood, blood components and pilot and laboratory samples shall be identified by a unique number or symbol so that it can be traced back to the donor and from the donor to the recipient. The identity of each donor shall be established both when donor fitness is determined and at the time of blood collection.

When blood-derived materials are transferred to a fractionation plant, the following details shall be provided by the supplier:

- name and address of collecting centre,
- type of material,
- donor identification,
- date of collection,
- results of mandatory tests,
- conditions of storage,
- other details required by the fractionator,
- name and signature of responsible person,
- date.

Part B. Requirements for single-donor and small-pool products

6. General considerations

These requirements for single-donor and small-pool products cover the methods used to prepare products directly from units of whole blood or of components collected by apheresis, starting with the testing of the units and proceeding to the separation of the various cell and plasma protein components. Among the products that may be prepared in small pools (12 donors or fewer) are cryoprecipitated factor VIII and platelets. In addition to tests on the units of whole blood that provide information on the safety, efficacy and labelling of the components, specific tests are included, where applicable, to ensure the quality of various components.

It is important to note that single-donor and small-pool products have certain specialized uses other than therapeutic application to correct deficits in patients. Although not dealt with further in these Requirements, these uses include the stimulation of plasma donors with red blood cells in order to raise antibody levels for the preparation of anti-D (anti-Rh_0) immunoglobulin (*12*) and special blood-grouping reagents. It is of the utmost importance that the donors of cells and plasma for such purposes be carefully studied both initially and on a continuing basis to minimize the likelihood of the transmission of infectious diseases to recipients. The use of red cells, stored frozen, that have been demonstrated to be free from infectious agents by retesting the donor 12 months after the initial collection reduces the risk of such transmission to volunteers for immunization.

Plasma donors may also be immunized with viral or bacterial antigens for the preparation of specific immunoglobulin products. All donor immunization procedures must be planned and carried out under the supervision of a physician who is familiar with the antigens being used and especially with the reactions or complications that may occur. Donors being immunized shall have been fully informed of all known hazards and shall have given their written informed consent to the procedures.

Donor immunization practices are considered in more detail in Part A, section 4.7.

Minimum general requirements for apheresis are summarized in Part A, section 5.1.1.

7. Production and control

7.1 *General requirements*

Single-donor and small-pool products shall comply with any specifications established by the national control authority. Cellular blood components and certain plasma components may deteriorate during separation

or storage. Whatever the method of separation (sedimentation, centrifugation, washing or filtration) used for the preparation of cell components, therefore, it is important that a portion of plasma protein sufficient to ensure optimum cell preservation be left with the cells, except when a cryoprotective substance is added to enable them to be stored for long periods in the frozen state, or additive solutions (for example containing adenine, glucose and mannitol) are used for the same purpose for liquid storage.

> The methods employed for component separation should be checked before they are introduced. The characteristics assessed might include yield of the component, purity, *in vivo* recovery, biological half-life, functional behaviour and sterility.
>
> The nature and number of such checks should be determined by the national control authority.

Immediately before issue for transfusion or for other purposes, blood components shall be inspected visually. They shall not be issued for transfusion if abnormalities of colour are observed or if there is any other indication of microbial contamination or of defects in the container.

Blood components shall be stored and transported at the appropriate temperature. Refrigerator or freezer compartments in which components are stored shall contain only whole blood and blood components. Reagents required for use in testing may be stored in a separate section of the same refrigerator or freezer provided that they have been properly isolated and are in suitable containers.

7.2 *Testing of whole blood and plasma*

7.2.1 *Sterility*

Each donation of whole blood intended for transfusion and each preparation of component cells constitutes a single batch. Single batches shall not be tested for sterility by any method that entails breaching the final container before the blood is transfused.

> The national control authority may require tests for sterility to be carried out at regular intervals on final containers chosen at random and at the end of the storage period. The purpose of such tests is to check on the aseptic technique used for taking and processing the blood and on the conditions of storage.

7.2.2 *Laboratory tests*

Laboratory tests shall be made on laboratory samples taken either at the time of collection or from the pilot samples accompanying the final container, labelled as required in Part A, section 5.

> In some countries, test reagents, in particular those used for blood-grouping and for detecting anti-HIV, anti-HCV and HBsAg, must be approved by the national control authority.

The results of the tests shall be used for ensuring the safety and proper labelling of all components prepared from units of whole blood.

7.2.3 *Tests for infectious agents*

Syphilis. Each donation of whole blood shall, if required by the national control authority, be subjected to a serological test for syphilis. If so tested, only units giving negative results shall be used for transfusion or component preparation.

Viral hepatitis. Each unit of blood or plasma collected shall be tested for HBsAg and anti-HCV by a method approved by the national control authority and only those giving a negative result shall be used (*13*). Units giving a positive result shall be so marked, segregated and disposed of by a method approved by the national control authority, unless designated for the production of a reagent or experimental vaccine in an area designed and segregated for such production.

In some countries plasma pools are also tested.

The label on the container or the record accompanying the container should indicate the geographical source of the blood or plasma as well as whether and how the material has been tested for HBsAg and anti-HCV.

Liver function tests, such as serum transaminase determinations, are used in some countries to detect liver damage that may be associated with hepatitis.

Anti-HIV-1 and anti-HIV-2. Blood for transfusion and for use in the preparation of blood components must be tested by a method approved by the national control authority for antibodies to HIV-1 and HIV-2 and be found negative. However, when other important factors outweigh the benefits of such testing (e.g. in emergencies) formal arrangements, approved in advance by the national control authority, should be in place that enable the prescribing physician to have access to an untested product. In all such cases, retrospective testing of the pilot sample shall be performed.

Other infectious agents. It is important for the national control authority to reassess testing requirements from time to time in the light of current knowledge, the prevalence of infectious agents in different populations and the availability of tests for serological markers of infection. For example, human retroviruses other than HIV have been described (HTLV types 1 and 2) and more may be identified in the future.

7.3 *Blood-grouping*

Each unit of blood collected shall be classified according to its ABO blood group by testing the red blood cells with anti-A and anti-B sera and by testing the serum or plasma with pooled known group A (or single subtype A_1) cells and known group B cells. The unit shall not be labelled as to ABO group unless the results of the two tests (cell and serum grouping) are in agreement. Where discrepancies are found in the testing or the donor's records, they shall be resolved before the units are labelled.

In countries where polymorphism for the D (Rh_o) antigen is present, each unit of blood shall be classified according to Rh blood type on the basis of

the results of testing for the D (Rh_o) red cell antigen. The D (Rh_o) type shall be determined with anti-D (anti-Rh_o) reagents.

> With the high-strength antisera and sensitive techniques now available, it is usually considered unnecessary to use the D^u test if the cells are found to be D-negative in routine testing.

7.4 *Red cells*

Whole blood for the preparation of all components shall be collected as described in Part A, section 5, and tested as described in Part B, section 7.2.

Red cells shall be processed under aseptic conditions and whenever possible in a closed system. The sterility of all components shall be maintained during processing by the use of aseptic techniques and sterile pyrogen-free equipment. The methods shall be approved by the national control authority, and a written description of the procedures shall be prepared for each product, covering each step in production and testing. Proposals for any procedural modifications shall be submitted to the national control authority for approval before they are implemented.

The following may be prepared for therapeutic purposes (see pages 40–41 for definitions):

- red cells;
- red cells suspended in additive solution;
- modified red cells:
  - red cells, leukocyte-depleted;
  - red cells, leukocyte-poor;
  - red cells, washed;
  - red cells, frozen;
  - red cells, deglycerolized.

7.4.1 *Methods and timing of separation*

Red cells shall be prepared from whole blood collected in plastic bags or in glass bottles.

> Multiple-plastic-bag systems with sterile docking devices are preferable because they minimize the risk of microbial contamination by providing completely closed systems. They are easy to handle and are disposable. The use of glass bottles is cheaper but has the disadvantage that the system is then an open or vented one, so that separation must be carried out under strictly aseptic conditions in sterile rooms or laminar-flow cabinets and microbiological monitoring is necessary. The same conditions also apply to the separation procedure when plasma is transferred from disposable single plastic bags to separate containers.

All surfaces that come into contact with the blood cells shall be sterile, biocompatible and pyrogen-free. If an open plastic-bag system is used, i.e. the transfer container is not integrally attached to the blood container and the blood container is opened after blood collection, the plasma shall be separated from the cells under conditions such that the original container is kept under positive pressure until it has been sealed. If the separation

procedure involves a vented system, i.e. if an airway is inserted into the container for withdrawal of the plasma, the airway and vent shall be sterile and constructed so as to exclude microorganisms.

In some countries, the sterility of products prepared in open systems is monitored by testing a sample of at least 2% of the units. The national control authority should approve the system used.

The final containers for red cells (but not necessarily modified red cells) shall be the containers in which the blood was originally collected or satellite containers attached in an integral manner. If pilot samples are detached from the blood container during removal of any component, such samples shall be reattached to the container of red cells. The removal and reattachment of the pilot samples shall be recorded conspicuously (with a signature) on the label of the unit. The final containers for all other components shall meet the requirements for blood containers given in Part A, section 5.2. If the final container differs from the container in which the blood was originally collected, it shall be given a number or other symbol to identify the donor(s) of the source blood. Whenever appropriate, the secondary final container shall be similarly labelled while attached to the primary final container.

The timing and the method of separation (centrifugation, undisturbed sedimentation or a combination of the two) will depend on the components to be prepared from the donation. When platelets and coagulation factors are being prepared from the same donation, the components shall be separated as soon as possible after withdrawal of the blood from the donor.

Separation should preferably be effected within 8 h of blood donation.

When platelets and coagulation factors are to be prepared, it is especially important that the venepuncture be performed in such a way as to cause *minimal tissue damage so as to prevent the initiation of coagulation.* The blood should flow freely without interruption and as rapidly as possible, and be mixed thoroughly with the anticoagulant.

If platelets are to be prepared from a unit of whole blood, the blood shall be kept at a temperature of 20–24 °C for up to 8 h until the platelet-rich plasma has been separated from the red blood cells.

Red cells may be prepared either by centrifugation or by undisturbed sedimentation before the expiry date of the original whole blood. Blood cells shall be separated by centrifugation in a manner that will not increase the temperature of the blood.

Sedimentation is the least expensive method for separation of red blood cells and does not require special equipment.

Repeated washing with saline and centrifugation and filtration are used to reduce the number of leukocytes and platelets and the volume of trapped plasma in red cells. Frozen red cells after thawing are also repeatedly washed with special solutions to remove cryoprotective agents while also preventing haemolysis.

7.4.2 *Expiry date*

The expiry date of whole blood and red cells prepared in a closed system from blood collected in acid-citrate-glucose or citrate-phosphate-glucose is generally 21 days after collection. The time of removal of plasma is not relevant to the expiry date of the red cells when the integrity of the container is not compromised.

The shelf-life of stored blood has been extended to 35 days by collecting the blood in acid–citrate–glucose supplemented with 0.5 mmol/l adenine or in a mixture of 0.5 mmol/l adenine and 0.25 mmol/l guanosine with extra glucose, and to 42 days by adding a solution containing adenine, glucose and mannitol. Recent studies indicate that it may also be possible to extend the shelf-life of stored blood to 35 days by collecting it in citrate–phosphate–glucose supplemented with 0.25 mmol/l adenine and extra glucose.

When red cells are prepared with very high erythrocyte volume fractions, an expiry date 14 days after collection is recommended in some countries because the cells may become glucose-deficient after this time. The erythrocyte volume fraction of red cells collected in citrate–phosphate–glucose–adenine should not exceed 0.9 if the expiry date is more than 21 days after collection.

The usefulness of acid–citrate–glucose is limited by the significant reduction in cell viability when the volume of cells collected is small, which is unavoidable for some donations.

Provided that sterility is maintained, the shelf-life of red cells is not influenced by the method of separation used. However, if an open system is used that does not maintain sterility, the expiry date shall be 24 h after separation and the cells should be used as soon as possible. Red cells and whole blood should be stored at 5 ± 3 °C and transported with wet ice in insulated boxes at 5 ± 3 °C. Care should be taken not to place containers directly on ice.

Refrigerated whole blood and red cells will warm up rapidly when placed at room temperature. Every effort should be made to limit the periods during which the products are handled at ambient temperatures in order to prevent the temperature from rising above 10 °C until they are used.

7.4.3 *Modified red cells*

Red cells, leukocyte-depleted and red cells, leukocyte-poor.

Because of the possibility of reactions, some countries require that red cells contain less than 2% of the leukocytes of the original whole blood.

Leukocyte depletion may be achieved by buffy-coat removal, freezing and washing, or by washing alone.

Leukocyte-poor red-cell concentrates are prepared by filtration.

Red cells, washed. Red cells can be washed by means of interrupted or continuous-flow centrifugation. If the first of these methods is used, the washing procedure shall be repeated three times.

Centrifugation should be carried out in refrigerated centrifuges. If such

equipment is not available, the washing solution should have a temperature of 5 ± 3 °C.

Red cells can also be washed by means of reversible agglomeration and sedimentation using sugar solutions.

Washed red cells should be transfused as soon as possible and in any case not later than 24 h after processing if prepared in an open system that does not maintain sterility, unless the national control authority has specified a longer shelf-life. They should be stored at all times at 5 ± 3 °C.

Requirements for pilot samples, labels and storage and transport temperatures are the same as those for unmodified red cells.

Red cells, frozen and red cells, deglycerolized. Red cells less than six days old are usually selected for freezing in order to minimize loss of yield due to haemolysis during processing.

Frozen red cells are red cells that have been stored continuously at low temperatures (-65 °C or below) in the presence of a cryoprotective agent. The red cells must be washed to remove the cryoprotective agent before use for transfusion. The methods of preparation, storage, thawing and washing used should be such as to ensure that at least 70% of the transfused cells are viable 24 h after transfusion. Storage at temperatures below -65 °C is usually necessary to achieve 70% recovery.

The cryoprotective agent in most common use is glycerol. The temperature of storage should be between −65 °C and −160 °C, depending on the glycerol concentration used.

The shelf-life of frozen cells below −65 °C is at least three years and may be much longer under certain circumstances, but the reconstituted (thawed and washed) red cells should be used as soon as possible and not later than 24 h after thawing unless a closed system is used.

Frozen cells are usually shipped in solid carbon dioxide ("dry ice") or liquid nitrogen, depending upon the glycerol concentration used. Deglycerolized red cells should be stored at a temperature of 1–6 °C and shipped at 5 ± 3 °C.

Requirements for pilot samples and labels are the same as those for unmodified red cells.

7.5 *Plasma*

Single-donor plasma shall be obtained by plasmapheresis or from units of whole blood that comply with the requirements of Part A, section 5, and Part B, section 7.2.

Fresh-frozen plasma and frozen plasma should be stored in carefully monitored freezers equipped with recording thermometers and audio and visual alarms to give warning of mechanical or electrical failure. If refrigeration is interrupted for longer than 72 h and the temperature rises above -5 °C, the product may no longer be considered as fresh-frozen plasma, although testing may indicate that reasonable amounts of factor

VIII remain if the plasma has not become liquid. Repeated thawing and freezing may cause denaturation of plasma constituents and cause prekallikrein activation.

7.5.1 *Plasma, fresh-frozen*

Fresh-frozen plasma shall be prepared by separating plasma from whole blood and freezing it rapidly within 8 h of collection.

Ideally, fresh-frozen plasma should be prepared by rapid freezing using a combination of solid carbon dioxide and an organic solvent such as ethanol. If this procedure is used, it should have been shown that the container cannot be penetrated by the solvent or substances leached from the container into the contents. Fresh-frozen plasma should be stored at or below −20 °C, and below −30 °C if to be used for transfusion purposes.

Before use for infusion, fresh-frozen plasma should be thawed rapidly at 30–37 °C. Agitation of the container and/or circulation of water at a temperature of 37 °C during the thaw cycle will speed thawing. Once thawed, fresh-frozen plasma must not be refrozen. It can be stored at ambient temperature and should be used within 2 h of completion of thawing.

Fresh-frozen plasma shall have an expiry date one year from the date of collection.

Before its expiry date, fresh-frozen plasma may be used for preparing cryoprecipitated factor VIII. It may be used for the preparation of other pooled plasma fractions (e.g. factors I, II, VII, VIII, IX and X) at any time, even after its expiry date.

7.5.2 *Plasma, frozen*

Frozen plasma is, by definition, a plasma separated from whole blood more than 8 h after the latter has been collected, but the delay should be as short as possible. Frozen plasma may be used directly for transfusion or fractionation, or it may be freeze-dried as single-donor units. Plasma may be combined in small pools before freezing if it is to be used to prepare freeze-dried plasma.

The national control authority should determine the specific requirements for frozen plasma.

If frozen or freeze-dried plasma is intended to be used directly in patients without further processing, the blood shall be collected in such a manner and in containers of such a type as to allow aseptic handling, e.g. by means of closed systems.

In some countries, frozen plasma is given an expiry date five years from the date of collection.

Whenever the container of frozen plasma is opened in an open procedure, the method of handling shall avoid microbial contamination; as an additional precaution, sterile rooms or laminar-flow cabinets can be used. Delay in processing shall be avoided, and the ambient conditions shall be regulated so as to minimize the risk of contamination.

Plasma may be pooled at any time after collection.

7.5.3 *Plasma, freeze-dried*

Freeze-dried plasma shall be made from single units or small pools of fresh-frozen plasma or frozen plasma.

The storage conditions and expiry dates of different forms of freeze-dried plasma shall be approved by the national control authority. The product normally has a shelf-life of five years when stored at 5 ± 3 °C, but this will depend on the source material, storage conditions and residual moisture in the product. Pooled freeze-dried plasma has a significant potential for the transmission of infectious diseases. This is likely to be substantially diminished by the introduction of viral inactivation procedures applicable to plasma.

7.5.4 *Plasma, recovered*

Recovered plasma intended to be pooled for fractionation shall not be used directly for transfusion; a preservative shall not be added.

Plasma may be separated from whole blood at any time up to five days after the expiry date of the blood. The method used for separation shall avoid microbial contamination. As an additional precaution, sterile rooms or laminar-flow cabinets can be used.

If the plasma has been pooled, it shall be stored and transported frozen at or below -20 °C.

7.5.5 *Plasma, platelet-rich*

Platelet-rich plasma is a preparation containing at least 70% of the platelets of the original whole blood.

The preparation shall be separated by centrifugation, preferably within 8 h of collection of the whole blood. The temperature and time of processing and storage shall be consistent with platelet survival and maintenance of function.

To achieve the desired haemostatic effect, platelet-rich plasma shall be transfused as soon as possible after collection, and not later than 72 h afterwards, unless stored at 22 ± 2 °C in containers approved for a longer storage period.

7.6 *Platelets*

Platelets shall be obtained by cytapheresis or from whole blood, buffy coat or platelet-rich plasma that complies with the requirements of Part A, section 5, and Part B, section 7.2. Aspirin ingestion within the previous three days precludes a donor from serving as a source of platelets.

Whole blood or platelet-rich plasma from which platelets are derived shall be maintained at 22 ± 2 °C until the platelets have been separated.

The separation shall preferably be performed within 8 h of collection of the whole blood. Blood shall be obtained from the donor by means of a single venepuncture giving an uninterrupted flow of blood with minimum damage to the tissue. It must have been demonstrated that the time and speed of centrifugation used to separate the platelets will produce a suspension without visible aggregation or haemolysis.

The national control authority shall determine the minimum acceptable number of platelets that should be present in the products prepared (e.g. 5.5×10^{10}).

A pH of 6.5–7.4 shall be maintained throughout storage of platelets. The volume of plasma used to resuspend platelets will be governed by the required pH of the platelet suspension at the end of its shelf-life, but shall be no less than 50 ± 10 ml.

Licensed artificial suspension media may be used to replace plasma.

Platelets stored at 5 °C are inferior to the same product stored at 22 ± 2 °C. Cold storage should be avoided where possible.

When stored at 22 ± 2 °C, platelet products shall be gently agitated throughout the storage period.

Platelet products with high platelet counts that are stored at 22 ± 2 °C may need to contain as much as 70 ml of plasma or more if the pH is to be maintained above 6.5 throughout the storage period. This period may be as long as seven days for containers made of certain special plastics, but it is prudent to restrict platelet storage to five days because of the risk of bacterial contaminants.

The product should be ABO typed and, in countries where D (Rh_o) is polymorphic, D (Rh_o) typed; it may also be desirable to know the HLA type.

The material of which the final container used for platelets is made shall not interact with the contents under normal conditions of storage in such a manner as to have an adverse effect on the product.

The requirements for labelling the final container are given in section 7.9. In addition to the customary data, the label shall bear: (a) the recommended storage temperature; (b) the statement that, when stored at 22 ± 2 °C, the platelets should be gently agitated throughout storage to obtain maximum haemostatic effectiveness; and (c) a statement to the effect that the contents should be used as soon as possible, and preferably within 4 h once the containers have been opened for pooling.

7.6.1 *Monitoring the quality of platelets*

Units randomly selected at the end of their shelf-life shall be tested on a regular basis. They shall be shown to have: (a) plasma volumes appropriate to the storage temperature; and (b) a pH between 6.5 and 7.4.

The number of units and of platelets to be tested shall be specified by the national control authority.

Some countries require there to be no visible contamination by red cells.

7.6.2 *Expiry date*

The expiry date of platelets processed in a closed system shall be 72 h after the original whole blood was collected, unless they are stored in a plastic container approved by the national control authority for a longer storage period.

Platelets prepared in an open system should be used within 4 h of preparation if stored at 22 ± 2 °C, unless the procedure used has been shown to allow a longer storage period.

Single-donor platelet concentrates may be pooled for one recipient under aseptic conditions before issue. Such small pools should be used as soon as possible, and within 4 h of preparation if stored at room temperature.

7.7 *Leukocytes*

Leukocytes are obtained by the separation of whole blood or by apheresis, and may contain a large number of platelets and red blood cells, depending on the method of preparation. When leukocytes are obtained from units of whole blood, such units shall comply with the requirements of Part A, section 5, and Part B, section 7.2.

The methods used to process leukocytes shall comply with the requirements and recommendations given in section 7.4.1 for the separation of red cells.

The label on the final container shall bear, in addition to customary data, instructions to use the leukocytes as soon as possible and in any case not more than 4 h after the container has been opened for pooling. The temperature of storage and transport shall be 22 ± 2 °C.

Leukocytes can be separated from blood by centrifugation, sedimentation or leukapheresis. To obtain a sufficient number, the leukocytes from units obtained from several healthy donors may have to be pooled.

Leukapheresis by continuous-flow filtration or centrifugation is the most efficient way of obtaining leukocytes, since it gives large numbers of high-quality cells from a single donor.

If centrifugation of whole blood is used, 30–60% of the leukocytes present in the original whole blood may be recovered.

Approximately 90% of the leukocytes present in the original whole blood can be separated by sedimentation of the red cells, accelerated by the addition of suitable substances with high relative molecular mass.

Leukocytes should be negative for cytomegalovirus.

The product should be ABO typed and, in countries where D (Rh_o) is polymorphic, D (Rh_o) typed; it may also be desirable to determine the HLA type. If not HLA typed, leukocytes should be irradiated.

The large number of red cells present in products prepared by some methods makes compatibility testing before transfusion necessary.

7.7.1 *Testing of leukocytes*

The number of units to be tested and the leukocyte yield (number) required shall be specified by the national control authority.

7.7.2 *Expiry date*

The expiry date of leukocytes shall be 24 h after collection of the original whole blood.

7.8 *Cryoprecipitated factor VIII*

Cryoprecipitated factor VIII is a crude preparation of factor VIII. It shall be obtained from single units or small pools of plasma derived either from units of whole blood that comply with the requirements of Part A, section 5, and Part B, section 7.2, or by plasmapheresis.

> The product may be prepared as a pool from a small number of donations, usually four to six but not exceeding ten. It may be freeze-dried. However, preparations of cryoprecipitated factor VIII carry the risk of viral transmission unless they have undergone specific virucidal procedures during manufacture.

The method of thawing and harvesting the cryoprecipitate shall have been shown to yield a product containing an adequate activity of factor VIII (see section 7.8.1).

In procuring source material for coagulation factors, the following technical considerations should be borne in mind:

- In order to prevent coagulation, venepuncture should performed in such a way that tissue damage is minimal. The blood should flow freely without interruption, and be mixed thoroughly with anticoagulant during collection.
- Microbial contamination should be avoided during separation of the plasma by using multiple-plastic-bag closed systems or laminar-flow cabinets if an open procedure is used.
- The recovery of factor VIII depends on the interval between venepuncture and freezing of the plasma, the temperature at which the plasma is held and the freezing method. While a useful product may be obtained with plasma frozen as late as 18–24 h after phlebotomy, freezing the plasma as early and as rapidly as possible is strongly recommended.
- Ideally, fresh-frozen plasma should be prepared by rapid freezing using a combination of solid carbon dioxide and an organic solvent such as ethanol. Fresh-frozen plasma should be stored at or below −20 °C. Contamination of the plasma by the solvent or leaching of substances from the container into the plasma should be avoided.
- If the temperature of the thawed plasma exceeds 2 °C, a high proportion of the factor VIII is lost in the supernatant. During thawing or separation of the supernatant plasma, therefore, the temperature should not be allowed to exceed 2 °C. The plasma may be separated while there is still a small quantity of the ice present in the plasma

container. Increasing the speed of thawing by circulating air or water at a temperature of 0 °C is believed to increase the yield of factor VIII.

7.8.1 *Testing of cryoprecipitated factor VIII*

Randomly selected units shall be tested for potency and sterility on a regular basis. The number of units to be tested shall be specified by the national control authority. The freeze-dried preparation shall dissolve without any signs of precipitation in the solvent recommended by the manufacturer within 30 min when held at a temperature not exceeding 37 °C.

The potency of cryoprecipitated factor VIII shall be compared with that of an appropriate plasma or intermediate-purity standard, by measuring its ability to correct the prolonged activated partial thromboplastin time of haemophilia A plasma or by another suitable method.

When cryoprecipitated factor VIII is produced from fresh-frozen plasma (frozen within 8 h of donation), the yield should be greater than 400 IU/l of starting plasma. Plasma frozen after this time will yield less cryoprecipitated factor VIII.

> In many laboratories, the average yield of factor VIII is 400 IU/l of starting plasma. The average yield of factor VIII as freeze-dried cryoprecipitate is then at least 300 IU/l of starting plasma. Whether this yield can be obtained elsewhere will depend on local technical possibilities. In some countries, the yields will be much lower, and the national control authority should decide as to the yield that is acceptable.

7.8.2 *Expiry date*

The frozen product shall be stored at or below -20 °C (if possible below -30 °C) and shall have an expiry date one year from the date of collection. The freeze-dried product shall be stored at 5 ± 3 °C and shall also have an expiry date one year from the date of collection. After thawing or reconstitution, cryoprecipitated factor VIII should be kept at 20–24 °C. It shall be used as soon as possible and in any case not more than 4 h after its container has been opened for pooling or reconstitution.

7.9 *Labelling*

After having been tested and before being issued for transfusion, units of single-donor and small-pool products shall be identified by means of container labels that clearly state at least the following information:

- the proper name of the product;
- the unique number or symbol identifying the donor(s);
- the expiry date, and when appropriate, the expiry time after reconstitution;
- any special storage conditions or handling precautions that are necessary;
- a reference to a package insert containing instructions for use, warnings and precautions;

- the name and address of the blood donor centre and, where applicable, the manufacturer and distributor;
- the average content in International Units of activity, where appropriate.

The results of red cell grouping shall be stated on the label of whole blood, red cells, fresh-frozen plasma (for clinical use), platelets and leukocytes but not necessarily on that of cryoprecipitated factor VIII.

Part C. Requirements for large-pool products

8. Introduction

A number of requirements common to albumin, plasma protein fraction, immunoglobulin preparations and coagulation-factor concentrates are given in Parts A and B, sections 3-7. However, for clarity, it has proved convenient to bring together in Part C certain specific requirements applicable to these products when manufactured on a large scale.

The source material for the large-scale preparation of blood products should comply with the relevant provisions of Parts A and B.

9. Buildings

The buildings used for the fractionation of plasma shall be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance in accordance with the requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products. They shall comply with the Guidelines for National Authorities on Quality Assurance for Biological Products (*6*) and in addition provide adequate space, lighting and ventilation for the activities listed below.

> Each of listed activities is an important integral part of the production procedure, and countries wishing to start manufacturing large-pool blood products and related substances should not do so unless adequate provision can be made for all of them.

9.1 *Storage of whole blood and plasma*

Whole human blood and plasma shall be stored frozen or refrigerated in separate facilities that are used only for this purpose. The source materials shall remain in quarantine until the results of testing show that they are suitable for introduction into the fractionation premises.

9.2 *Separation of cells and fractionation of plasma*

Cells shall be separated and plasma fractionated in a building isolated from those where non-human proteins or microbiological materials, such as vaccines, are manufactured or processed and separate from the animal house.

> In some countries, cell constituents are separated in an area separate from that where plasma is fractionated.

9.3 *Supply and recovery of ancillary materials*

Adequate facilities shall be provided for the supply of ancillary materials, such as ethanol, water, salts and polyethylene glycol.

Facilities for the recovery of organic solvents used in fractionation may also be provided.

9.4 *Viral inactivation*

A separate area shall be provided for all processing subsequent to the completion of viral inactivation procedures when these are carried out at a stage in production before aseptic dispensing and filling (see section 9.5).

9.5 *Freeze-drying, filling, packaging, labelling and storage*

Separate facilities shall be used for the freeze-drying, filling, labelling and packaging of containers. A separate area shall be provided for the storage of labels, package inserts and packages. Another separate area shall be used for the storage of final containers before dispatch.

9.6 *Keeping of records*

Adequate provision shall be made for keeping records of all donors, materials, fractionation steps, quality-control procedures and results, of the distribution of the final products and of the disposal of potentially infectious materials. Records should be retained for at least two years beyond the expiry date of the products to which they relate.

Some manufacturers might wish to extend this period to cover any future legal disputes.

9.7 *Quality control*

Separate facilities shall be provided for quality control, including haematological, biochemical, physicochemical, microbiological, pyrogen and safety testing.

9.8 *Disposal of infective material*

Provision shall be made for the suitable disposal of potentially infectious materials by autoclaving or incineration according to good manufacturing practices.

The disposal of these materials should comply with local legislation.

10. Equipment

Equipment used for the collection, processing, storage and distribution of source materials and large-pool blood products shall comply with the requirements of Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products.

Particular attention shall be paid to:

- The maintenance, monitoring and recording of the operation of continuously operating equipment, the validation of its reliability and the provision of stand-by equipment.
- The suitability and compatibility of the surfaces of all materials (e.g. filter medium, glass, stainless steel, plastic and rubber) that come into contact with the products.

  Metal surfaces that come into contact with proteins should be resistant to scratching. The surfaces of some materials can denature certain proteins or activate certain coagulation factors.

- The ease and efficiency with which equipment can be cleaned and, where necessary, sterilized. Any bactericidal agent used shall be capable of being completely eliminated before the equipment is used.

  Caution should be exercised in the use of detergents because of their possible effects on the final product; tests should be made to ensure that they do not have any adverse effect on it.

- The provision of suitable facilities for decontamination and for the disposal of potentially infective materials and equipment.

11. Provision of support services

A number of support services are essential for the fractionation of source materials.

11.1 *Water supply*

An adequate supply of suitable pyrogen-free water shall be provided for use during the fractionation process and for the reconstitution and/or dilution of the plasma fractions before filling and freeze-drying.

The two most commonly used types of water are pyrogen-free distilled water and pyrogen-free deionized water, each of which should be maintained at 80°C. Water preparation and delivery systems should be tested at regular intervals for endotoxin content and conductance. The water system should be a continuously circulating one and should have no dead ends.

Water for injections is generally used for the preparation of final products (*14*).

11.2 *Steam supply*

An adequate supply of steam shall be provided for the operation of sterilizing and cleaning equipment. The steam shall be clean and have the quality of water for injections.

11.3 *Other support facilities*

Other support facilities required are:

- A supply of electrical and thermal energy.

- A means of refrigeration for:
  - storing various source materials and fractions;
  - keeping the various fractionation areas at the correct temperature;
  - keeping the process equipment at the correct temperature;
  - storing final products under test;
  - storing final products awaiting dispatch.
- A system of ventilation providing the following two grades of filtered air:
  - air filtered to remove particles of 5 µm or greater in diameter, which shall be supplied to the entire work area; and
  - air passed through a filter with a retention capacity of more than 99.95% for particles greater than 0.5 µm in diameter, which shall be supplied at a positive pressure to areas where aseptic dispensing is to take place.

Other support facilities may include solvent recovery and a sewage disposal service. Sewage disposal must be carried out in accordance with the sanitary standards of the competent health authority.

Proteinaceous sewage from a plasma processing plant is highly nitrogenous and has a high biological oxygen demand; it should therefore not be discharged untreated.

These support facilities shall be located separately from the main process areas and in a place where the conditions (light, physical access, etc.) are conducive to the establishment of effective and routine preventive maintenance programmes. The equipment shall incorporate devices capable of monitoring and recording its operation so as to ensure the safety both of the material being processed and of the process operators. In this way a proper record of the operations of support facilities can be kept and, where necessary, entered into the process record of the product batches.

The equipment should be such as to ensure that both the fractionation process and the proteins are protected if the support services are interrupted. To this end, adequate spare equipment and emergency reserve systems should be available, serviced by engineering staff skilled in the maintenance and repair of such equipment.

12. Personnel

The plasma fractionation plant shall be under the direction of a designated qualified person who shall be responsible for ensuring that all operations are carried out properly and competently. The director shall have a good working knowledge of the scientific principles involved and shall be responsible for ensuring that employees are adequately trained, have adequate practical experience and are aware that accepted good practices should be applied in their work.

The personnel involved in quality-control functions shall be separate from those involved in production. The head of the quality-control department shall be responsible only to the director.

Where appropriate, personnel shall wear gowns, masks, boots, gloves and eye protectors.

Personnel should be medically examined at regular intervals. Those known to be carriers of specific pathogenic organisms that may adversely affect the product shall be excluded from the production area.

Vaccination against hepatitis B is strongly recommended for employees routinely exposed to blood or blood products.

13. Production control

13.1 *Fractionation of source materials*

The general conditions for the large-scale fractionation of source materials to prepare prophylactic or therapeutic blood products shall comply with Good Manufacturing Practices for Pharmaceutical (*7*) and Biological (*8*) Products and shall be approved by the national control authority.

Most physical and chemical techniques of protein separation may be used for the preparation of plasma fractions, provided that they yield protein preparations that have previously been shown to be safe and effective.

The fractionation procedures used shall give a good yield of products meeting the quality requirements of international or national authorities. Fractionation shall be carried out in such a manner that the risk of microbiological contamination and protein denaturation is minimized.

> The safety of fractionation steps may be increased by using protected or closed systems. Reproducibility may be increased by the use of automation.
>
> The biological characteristics of the products (such as antibody activity, biological half-life and *in vivo* recovery of the proteins) should not be affected by the fractionation procedures to the extent that they are unacceptable for clinical use.

Methods shall be used that exclude or inactivate pathogenic organisms, in particular hepatitis viruses and human retroviruses, from the final products intended for clinical use. Manufacturers shall validate the ability of their manufacturing processes to inactivate and/or remove potential contaminating viruses by the use of relevant model viruses.

There is increasing evidence that certain manufacturing procedures, coupled with strict control to ensure that the final product complies with precise specifications, result in a product free from HIV, hepatitis B and hepatitis C infectivity.

For coagulation products, viral inactivation and removal methods such as chromatography or treatment with dry heat, wet heat, steam under pressure, heated organic solvents or solvents/detergents shall be used, in combination with other methods that have been shown to be successful in reducing or eliminating the risk of HIV and hepatitis virus transmission.

Donor screening and viral inactivation procedures used in manufacturing plasma coagulation concentrates have significantly improved the safety of these products.

Fibrinogen prepared from plasma pools continues to carry a risk of infection unless it is treated to remove or inactivate viruses. Where large-pool, virally inactivated fibrinogen concentrates are not available, cryoprecipitated factor VIII prepared from individual units or small pools of plasma is preferred as a source of fibrinogen. Approximately 150 mg of fibrinogen is contained in the cryoprecipitate from one unit of plasma (200 ml) frozen within 8 h of collection from the donor.

The operating manual for the fractionation procedure shall specify the times of sampling of the products and the volumes to be taken at each stage of the process as well as the tests to be made on the samples.

Where appropriate, all materials used for fractionation shall be tested for microbiological contamination, identity, purity, endotoxin content and toxicity in accordance with *The international pharmacopoeia* (*14, 15*) or national pharmacopoeia.

Certain procedures, equipment and materials may introduce contaminants into the final product that can induce allergenic or immunogenic responses in recipients. The quantities of such contaminants in the final product shall be minimized. For example, where monoclonal antibodies are used for product purification, the residual concentration in the final product must be below clinically reactive levels.

> It is advisable to use air filtration under positive pressure during fractionation, to exclude airborne allergenic dust.

13.1.1 *Preservatives and stabilizers*

No preservatives shall be added to albumin, plasma protein fraction, intravenous immunoglobulin or coagulation-factor concentrates either during fractionation or at the stage of the final bulk solution. Antibiotics shall not be used as preservatives or for any other purpose in the fractionation of plasma.

To prevent protein denaturation, stabilizers may be added. Such substances shall have been shown to the satisfaction of the national control authority not to have any deleterious effect on the final product in the amounts present and to cause no untoward reactions in humans.

> Stable solutions of immunoglobulins may be prepared in approximately 0.3 mol/l glycine or 0.15 mol/l sodium chloride. In some countries, thiomersal and sodium timerfonate are not permitted as preservatives in intramuscular immunoglobulins.

13.2 *Storage and control of source materials*

At all stages of the manufacturing process, the source materials and resulting fractions shall be stored at temperatures and under conditions

shown to prevent further contamination and the growth of micro-organisms, to protect the identity and the integrity of the proteins and to preserve the biological activity and safety of the products.

If similar materials are stored together, the places allocated to them shall be clearly demarcated.

All source materials and resulting fractions shall be fully identified at all times; such identification shall include the batch number of all in-process fractions and final containers awaiting labelling.

13.2.1 *In-process control*

Source materials are subject to biological variability and the products resulting from protein separation will contain various amounts of other protein components of plasma. It is essential, therefore, to establish a monitoring system such that the safe operating limits of each process are maintained.

The main information collected is on variations in physical conditions (temperature, pH, ionic strength, timing, etc.) and in the number and species of contaminating organisms.

Owing to the numerous and interdependent factors involved, there are no universally accepted specifications for such in-process quality-assurance systems. For this reason, the information collected should be combined with data from previous experience with the same manufacturing process to ensure production control appropriate to the quality requirements of the final product.

13.2.2 *Record-keeping*

Records shall be kept of the performance of all steps in the manufacture, quality control and distribution of large-pool blood products and related substances (*7, 8*).

These records shall:

- be original (not a transcription), indelible, legible and dated;
- be made at the time that the specific operations and tests are performed;
- identify the person recording the data as well as the person checking them or authorizing the continuation of processing;
- be detailed enough to allow all the relevant procedures performed to be clearly reconstructed and understood;
- permit the tracing of all successive steps and identify the relationships between dependent procedures, products and waste materials;
- be maintained in an orderly fashion that will permit the retrieval of data for a period consistent with shelf-lives and the legal requirements of the national control authority and, if necessary, allow a prompt and complete recall of any particular lot;
- show the lot numbers of the materials used for specified lots of products;
- indicate that processing and testing were carried out in accordance with procedures established and approved by the designated responsible authority.

14. Control of albumin and plasma protein fraction

Source materials should be processed in such a manner that the albumin in the solutions manufactured will be changed as little as possible and will not cause undesirable reactions in the recipients. Source materials may contain either vasoactive substances or substances capable of generating or releasing endogenous vasoactive substances. Such substances may also be formed in the course of fractionation, and consequently contaminate the albumin and plasma protein fraction. To guard against this possibility, adequate in-process controls and the testing before release for prekallikrein activator activity are mandatory for albumin solutions of purity less than 95% (such as plasma protein fraction) containing 35–50 g of protein per litre. Such testing is also recommended for highly purified albumin products (purity greater than 95%).

Within 24 h of the start of filling, albumin and plasma protein fraction in solution shall be heated in the final container to 60 ± 0.5 °C and maintained at that temperature for not less than 10 h but not more than 11 h by a method that ensures uniform heat distribution throughout the batch. Although pasteurization at the final bulk stage may be possible, this approach requires careful validation before use.

Special attention should be given to microbial contamination of source material and intermediates, since soluble microbial substances, especially endotoxins, may accumulate in the finished albumin solution. In addition, it is possible that small amounts of endotoxin, present even in products for which satisfactory results have been obtained in tests for pyrogens, may have a cumulative effect in recipients receiving large product volumes in relatively short periods of time, as, for example, in therapeutic plasma exchange.

> In some countries, information is being collected about the usefulness of quantitative *Limulus* assays for the presence of endotoxin.

The in-process controls should be capable of detecting contamination with bacteria and moulds. In addition, care should be taken to ensure, by a method that shall be validated, that all equipment and reagents used in the manufacturing process are scrupulously clean and free from toxic materials.

14.1 *Stability of albumin solutions*

The stability of solutions of albumin and plasma protein fraction (that have been heated for 10–11 h at 60 °C) shall be tested by heating adequate samples at 57 °C for 50 h. The test solutions shall remain visually unchanged when compared to control samples that have been heated for only 10–11 h at 60 °C.

The thermal stability of albumin solutions shall be taken into consideration by the national control authority in determining the expiry dates.

The physicochemical quality of stored albumin solutions, as measured by the formation of dimers and particularly polymers, is influenced by:

— the quality of the starting plasma;
— the quality of the fractionation, particularly with respect to the degree of purity achieved and the number of reprecipitation and reheating procedures involved; and
— the storage conditions with respect not only to temperature and time but also to the physical state and concentration of the solutions.

With regard to the thermal stability of albumin solutions, the following general statements may be made:

- The addition of stabilizing chemicals is necessary. Commonly used products are sodium octanoate and sodium acetyltryptophanate.
- Albumin prepared from aged liquid or dried plasma is less stable than albumin made from fresh-frozen plasma.
- Reprocessing steps, such as reprecipitation and reheating, may reduce the stability of albumin solutions.
- On long-term storage, albumin solutions are more stable at 5 ± 3 °C than at 32–35 °C. Long-term storage above 30 °C should be avoided.

14.2 *Control of bulk material*

14.2.1 *Tests on bulk material*

Tests on the bulk powder or solution shall be made if the manufacturer sends the material to another institution for further processing. Samples for these tests shall be taken under conditions that do not impair the quality of the bulk material. Tests shall be carried out on a specially dissolved sample processed to a stage equivalent to the final product, after sterilization by filtration. The tests shall be those listed in sections 14.3.2 to 14.3.7 inclusive.

14.2.2 *Storage*

The bulk material shall be stored as liquid or powder in sealed containers under conditions that minimize denaturation and the multiplication of microbial agents.

14.3 *Control of the final bulk solution*

14.3.1 *Preparation*

The final bulk solution shall be prepared from bulk powder or by the dilution of concentrates by a method approved by the national control authority. It shall meet all of the requirements of sections 14.3.2 to 14.3.7 inclusive.

14.3.2 *Concentration and purity*

The albumin concentration in final bulk albumin solutions shall be between 35 and 265 g/l. Not less than 95% of the proteins present shall be albumin, as determined by a suitable electrophoretic method after the sample has been heated for 10–11 h at 60 °C.

The protein concentration in final bulk solutions of plasma protein fraction shall be at least 35 g/l. Plasma protein fraction shall contain at least 83% albumin and not more than 17% globulins. Not more than 1% of the protein in plasma protein fraction shall be γ-globulin.

14.3.3 *Hydrogen ion concentration*

The final bulk solution, diluted with 0.15 mol/l sodium chloride to give a protein concentration of 10 g/l, shall, when measured at a temperature of 20–27 °C, have a pH of 6.9 ± 0.5 (albumin) or 7.0 ± 0.3 (plasma protein fraction).

In some countries, different ranges of pH values and temperatures are permitted.

14.3.4 *Sterility and safety*

The final bulk shall be sterile. If required by the national control authority, it shall be tested for sterility; samples shall be taken for such testing in a manner that does not compromise the sterility of the bulk material. Part A, section 5, of the revised Requirements for Biological Substances No. 6 (General Requirements for the Sterility of Biological Substances) (*9*, p. 48) shall apply.

14.3.5 *Sodium content*

The final bulk solutions of albumin and plasma protein fraction shall have a maximum sodium concentration of 160 mmol/l.

14.3.6 *Potassium content*

The final bulk solutions of albumin and plasma protein fraction shall have a maximum potassium concentration of 2.0 mmol/l.

14.3.7 *Aluminium content*

The final bulk solutions of albumin and plasma protein fraction shall have a maximum aluminium concentration of 7.5 μmol/l (200 μg/l).

14.4 *Filling and containers*

The requiremens concerning filling and containers given in Good Manufacturing Practices for Biological Products (*8*) shall apply.

Special attention shall be paid to the requirement that solutions of albumin and plasma protein fraction in the closed final containers shall be heated to inactivate any infectious agents that may be present (see section 14, paragraph 2). In order to prevent protein denaturation, a stabilizer shall be added to albumin solution before heating (see section 13.1.1).

In some countries, the national control authority may authorize an interval longer than 24 h between filling and heating to 60 °C.

14.5 *Control tests on the final product*

The tests specified below shall be performed on representative samples from every filling lot. If the product is processed further after filling, e.g. by freeze-drying, the tests shall be performed on samples from each drying chamber.

14.5.1 *Identity test*

An identity test shall be performed on at least one labelled container from each filling lot to verify that the preparation is of human origin. The test shall be one approved by the national control authority. Additional tests shall be made to determine that the protein is predominantly albumin or plasma protein fraction as appropriate. The tests mentioned in section 14.3.2 shall be used.

14.5.2 *Protein concentration and purity*

The protein concentration and purity of each filling lot shall be within the limits prescribed in section 14.3.2.

> Tests to determine the concentration of additives (such as polyethylene glycol, porcine enzymes and reducing and alkylating agents) used during production shall be carried out if required by the national control authority.

14.5.3 *Sterility test*

Each filling lot shall be tested for sterility. Part A, section 5, of the revised Requirements for Biological Substances No. 6 (General Requirements for the Sterility of Biological Substances) (*9*, p.48) shall apply. Samples for sterility testing shall be taken from final containers selected at random after heating at 60 °C for 10–11 h.

> In one country, the sterility test is carried out at least 10 days after heating at 60 °C for 10 h. In some countries, the sterility test is carried out both before and after heating at 60 °C for 10 h.

14.5.4 *General safety test*

In some countries a general safety test may be required, whereby each filling lot is tested for extraneous toxic contaminants by appropriate tests involving injection into mice and guinea-pigs. The injection shall cause neither significant untoward reactions nor death within an observation period of seven days. The tests shall be approved by the national control authority.

> The tests generally used are the intraperitoneal injection of 0.5 ml into each of at least two mice weighing approximately 20 g and the injection of 5.0 ml into each of at least two guinea-pigs weighing approximately 350 g. In some countries, if one of the animals dies or shows signs of ill-health, such as weight loss, during a specified period, the test is repeated. The substance passes the test if none of the animals of the second group dies or shows signs of ill-health, such as weight loss, during that period.

14.5.5 *Freedom from pyrogenicity*

Each filling lot shall be tested for pyrogenicity by the intravenous injection of the test dose into three or more rabbits that have not previously received blood products. In general, the dose shall be at least equivalent proportionally, on a rabbit body-weight basis, to the maximum single human dose recommended, but not more than 10 ml/kg of body weight. For albumin at concentrations of 200 g/l and 250 g/l, the test dose for each rabbit shall be at least 3 ml/kg of body weight, and for albumin at concentrations of 35 g/l and 50 g/l and plasma protein fraction, 10 ml/kg of body weight.

A filling lot shall pass the test if it satisfies the requirements specified by the national control authority.

14.5.6 *Moisture content*

The residual moisture content shall, where appropriate, be determined by a method approved by the national control authority.

> The methods in use are: (a) drying over phosphorus pentoxide for at least 24 h at a pressure not exceeding 2.7 Pa (0.02 mmHg); and (b) the Karl Fischer method.

The acceptable moisture content shall be determined by the national control authority.

14.5.7 *Prekallikrein activator*

An assay shall be performed for prekallikrein activator. The product shall contain not more than 35 IU of prekallikrein activator per ml.

14.5.8 *Hydrogen ion concentration*

The final product, reconstituted if necessary and diluted with 0.15 mol/l sodium chloride to give a protein concentration of 10 g/l, shall, when measured at a temperature of 20–27 °C, have a pH of 6.9 ± 0.5 (albumin) or 7.0 ± 0.3 (plasma protein fraction).

> In some countries, different ranges of pH values are permitted.

14.5.9 *Absorbance*

A sample taken from the final solutions of albumin and plasma protein fraction, when diluted with water to a concentration of 10 g/l of protein and placed in a cell with a 1-cm light path, shall have an absorbance not exceeding 0.25 when measured in a spectrophotometer set at 403 nm.

14.5.10 *Inspection of filled containers*

All final containers shall be inspected for abnormalities, such as non-uniform colour, turbidity, microbial contamination and the presence of atypical particles, after storage at 20–35 °C for at least 14 days following heat treatment at 60 °C for 10 h. Containers showing abnormalities shall not be distributed.

The normal colour of albumin solutions may range from colourless to yellow or green to brown.

When turbidity or non-uniform colour raises the possibility of microbial contamination, testing should be done to isolate and identify the microorganisms.

14.6 *Records*

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 27–28) shall apply.

14.7 *Samples*

The requirements of Good Manufacturing Practices for Biological Products (*8*, page 29, paragraph 9.5) shall apply.

14.8 *Labelling*

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 26–27) and the national control authority's requirements for parenteral solutions shall apply.

In addition, the label on the container should state:

- the type of source material,
- the protein concentration,
- the oncotic equivalent in terms of plasma,
- that preservatives are absent
- the warning "Do not use if turbid",
- the sodium and potassium concentrations.

14.9 *Distribution and shipping*

The requirements of Good Manufacturing Practices for Biological Products (*8*) shall apply.

14.10 *Storage and shelf-life*

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 26–27) shall apply.

Final containers of albumin solution shall have a maximum shelf-life of three years if they are stored at or below 30 °C, and of five years if they are stored at 5 ± 3 °C.

Other storage conditions and shelf-lives may be approved by the national control authority.

Final containers of plasma protein fraction solution shall have a maximum shelf-life of three years if they are stored at or below 30 °C, and of five years if they are stored at 5 ± 3 °C.

Other storage conditions and shelf-lives may be approved by the national control authority.

15. Control of immunoglobulins

The final bulk solution of normal immunoglobulin shall be made from material from at least 1000 donors. If normal immunoglobulin is to be used for preventing or treating a particular infection, the titre of specific antibody should be measured.

> For normal immunoglobulins, a large number of donors are needed if the final product is to contain adequate amounts of the various desired antibodies.
>
> For specific immunoglobulins, whether intended for intravenous or intramuscular injection, the number of donors represented is less important because the requirement for specific antibody in the final product will be defined.

The immunoglobulin concentration in the final bulk of normal and specific immunoglobulin preparations for intramuscular use shall be 100-180 g/l. Concentrations lower than 100 g/l shall require the approval of the national control authority.

The immunoglobulin concentration in the final bulk of intravenous immunoglobulin shall be at least 30 g/l. If, in a specific immunoglobulin preparation, the concentration is lower than 30 g/l, it shall require the approval of the national control authority.

The immunoglobulin preparation shall be composed of not less than 90% of immunoglobulin, as determined by a method approved by the national control authority.

Tests shall be conducted on each filling lot of immunoglobulin solution to determine the proportion of aggregated and fragmented immunoglobulin. The recommended distribution shall be that at least 90% of the protein, other than proteins added as stabilizers to intravenous immunoglobulins, shall have the molecular size of immunoglobulin monomer and dimer. Not more than 10% shall consist of split products together with aggregates (oligomers of relative molecular mass equal to or greater than that of immunoglobulin trimer). This requirement shall not apply to products deliberately fragmented. The tests and limits shall be approved by the national control authority. Of the material having the molecular size of immunoglobulin monomer and dimer, most will consist of monomer. If a minimum level of monomer *per se* is to be established, the time and temperature at which samples must be incubated before analysis shall be specified.

> Gel-permeation chromatography and high-performance exclusion chromatography are useful techniques for determining molecular size distribution and can be standardized for making these measurements.

For intravenous immunoglobulin, the following tests shall be performed on a sample from each filling lot:

- A test for hypotensive activity.

An appropriate test is that for prekallikrein activator content. In some countries the kallikrein test is also used.

- A test for anticomplement activity.

  Several methods are available. The test method used and the maximum level of anticomplement activity permitted should be approved by the national control authority.

- A test for haemagglutinins by the antiglobulin (Coombs) technique.

  In such tests, group O D(Rh_0)-positive cells should be used to test for anti-D (anti-Rh_0); group A and group B D(Rh_0)-negative cells should be used for anti-A and anti-B, respectively.

  The purpose of the test is to ensure that the use of the product will not give rise to haemolytic reactions. The upper limit of activity should be specified by the national control authority.

15.1 *Potency of normal immunoglobulins*

A 160 g/l solution of normal immunoglobulin shall be prepared from final bulk solution by a method that has been shown to be capable of concentrating, by a factor of 10 from source material, at least two different antibodies, one viral and one bacterial, for which an international standard or reference preparation is available (*16*) (e.g. antibodies against poliomyelitis virus, measles virus, streptolysin O, diphtheria toxin, tetanus toxin, staphylococcal α-toxin).

For immunoglobulins formulated at an immunoglobulin concentration lower than 16%, the concentrating factor for antibodies from source material may be proportionally lower.

The immunoglobulin solution shall be tested for potency at the concentration at which it will be present in the final container.

Since preparations of normal immunoglobulins produced in different countries can be expected to differ in their content of various antibodies, depending upon the antigenic stimulation to which the general population has been subjected (either by natural infection or by deliberate immunization), at least two antibodies should be chosen for the potency test by the national control authority. The final product passes the test if it contains at least the minimum antibody levels required by the national control authority.

15.2 *Potency of specific immunoglobulins*

The potency of each final lot of specific immunoglobulin shall be tested with respect to the particular antibody that the preparation has been specified to contain. For intramuscular immunoglobulins, the following levels shall apply:

- For tetanus immunoglobulin, at least 100 IU/ml of tetanus antitoxin, as determined by a neutralization protection test in animals or by a method shown to be equivalent.
- For rabies immunoglobulin, at least 100 IU/ml of anti-rabies antibody,

as determined by an appropriate neutralization test in animals or by a method shown to be equivalent.

- For hepatitis B immunoglobulin, at least 100 IU/ml of anti-hepatitis antibody.
- For varicella zoster immunoglobulin, at least 100 IU/ml of anti-varicella zoster antibody, as measured by a comparative enzyme-linked immunosorbent assay or by a method shown to be equivalent.
- For anti-D (anti-Rh_0) immunoglobulin, the estimated potency shall be expressed in International Units and shall be not less than 90% and not more than 120% of the stated potency, and the fiducial limits of error shall be within 80% and 125% of the estimated potency.

The national control authority shall specify the antibody limits for other immunoglobulins.

After the potency tests, a test for immunoglobulin subclass may be performed. Different manufacturing steps have been shown to reduce the concentration of specific immunoglobulin subclasses (e.g. IgG1, IgG2, IgG3 and IgG4) in immunoglobulin preparations. The distribution of the four subclasses of IgG may be a factor in the efficacy of intravenous immunoglobulin preparations, since specific antibodies belonging to particular subclasses have been identified as being important in several infectious diseases.

In some countries the distribution of IgG subclasses has been measured by radial immunodiffusion. Enzyme-linked immunosorbent assays have also been described, and may be used if properly validated. Assays should be calibrated against the appropriate international reference materials.

15.3 *Sterility and safety*

Each filling lot shall be tested for sterility. Part A, section 5, of the revised Requirements for Biological Substances No. 6 (General Requirements for the Sterility of Biological Substances) (*9*, p. 48) shall apply.

In some countries a general safety test may be required, whereby each filling lot is tested for extraneous toxic contaminants by appropriate tests involving injection into mice and guinea-pigs. The injection shall cause neither significant toxic reactions nor death within an observation period of seven days. The tests shall be approved by the national control authority.

The tests generally used are the intraperitoneal injection of 0.5 ml into each of at least two mice weighing approximately 20 g and the injection of 5.0 ml into each of at least two guinea-pigs weighing approximately 350 g. In some countries, if one of the animals dies or shows signs of ill-health, such as weight loss, during a specified period, the test is repeated. The substance passes the test if none of the animals of the second group dies or shows signs of ill-health, such as weight loss, during that period.

15.4 *Identity test*

An identity test shall be performed on at least one labelled container from each filling lot to verify that the preparation is of human origin. The test shall be one approved by the national control authority.

Additional tests shall be made to determine that the protein is predominantly immunoglobulin.

The methods in most common use are radial immunodiffusion and electrophoresis.

15.5 *Freedom from pyrogenicity*

Each filling lot shall be tested for pyrogenicity by the intravenous injection of the test dose into three or more rabbits that have not previously received blood products. In general, the dose shall be at least equivalent proportionally, on a rabbit body-weight basis, to the maximum single human dose recommended, but not more than 10 ml/kg of body weight. The recommended test doses are 1 ml/kg and 10 ml/kg of body weight for intramuscular and intravenous preparations, respectively.

A filling lot shall pass the test if it satisfies the requirements specified by the national control authority.

15.6 *Moisture content*

The residual moisture content of a sample from each filling lot shall, where appropriate, be determined by a method approved by the national control authority.

The methods in use are: (a) drying over phosphorus pentoxide for at least 24 h at a pressure not exceeding 2.7 Pa (0.02 mmHg); and (b) the Karl Fischer method.

The acceptable moisture content shall be determined by the national control authority.

15.7 *Hydrogen ion concentration*

The final product, reconstituted if necessary and diluted with 0.15 mol/l sodium chloride to give a protein concentration of 10 g/l, should, when measured at a temperature of 20–27 °C, have a pH of 6.9 ± 0.5.

In some countries, a different range of pH values is permitted for intravenous immunoglobulins.

15.8 *Stability*

For immunoglobulin solutions, a stability test shall be performed on each filling lot by heating an adequate sample at 37 °C for four weeks. No gelation or flocculation shall occur.

Alternatively (or in addition), the molecular size distribution of the immunoglobulin or assays of enzymes such as plasmin (fibrinolysin) may be used, when shown to predict stability reliably and when approved by the national control authority.

15.9 *Records*

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 27–28) shall apply.

15.10 *Samples*

The requirements of Good Manufacturing Practices for Biological Products (*8*, page 29, paragraph 9.5) shall apply.

15.11 *Labelling*

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 26–27) shall apply.

In addition, the label on the container shall state:

- the type of source material;
- the protein concentration;
- the concentration of preservative, if any;
- "For intramuscular use only" (if the immunoglobulins are not specially prepared for intravenous use);
- "For intravenous use", when appropriate;
- for specific immunoglobulin, the content of specific antibody expressed in International Units or equivalent national units;
- for freeze-dried preparations, the name and volume of reconstituting liquid to be added.

The label on the package or the package insert shall show:

- the approximate concentration of electrolytes and excipients and, for intravenous preparations, the approximate osmolality;
- the buffering capacity when the pH of the diluted product is lower than that specified in section 15.7;
- the concentration of preservative, if any;
- the recommended dose for each particular disease or condition;
- the warning "Do not use if turbid";
- the sodium and potassium concentrations (if the immunoglobulin is intended for intravenous use).

15.12 *Distribution and shipping*

The requirements of Good Manufacturing Practices for Biological Products (*8*) shall apply.

15.13 *Storage and shelf-life*

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 26–27) shall apply.

Liquid immunoglobulin shall be stored at 5 ± 3 °C and shall have a shelf-life of not more than three years. Freeze-dried preparations shall be stored below 25 °C and shall have a shelf-life of not more than five years.

Other storage conditions and shelf-lives may be approved by the national control authority.

16. Control of preparations of coagulation-factor concentrates (factor VIII, factor IX and fibrinogen)

Factor VIII preparations are available as both frozen products and freeze-dried concentrates. The frozen products are usually derived from a single donation and consist of the cryoprecipitated factor VIII from the donor concerned prepared in a closed separation system. The control of this product and the freeze-dried product from fewer than 10 plasma donations is covered in Part B, section 7.8.1.

Generally, the small-pool product undergoes little or no purification and is handled and subdivided in such a way that many control tests are inappropriate. However, freeze-dried factor VIII concentrates prepared from more than 10 donations may be purified.

Source material for factor VIII preparations shall meet the general criteria for donor selection and testing for disease markers as specified in Parts A and B. It shall preferably be plasma frozen within 8 h of collection or frozen cryoprecipitate. Such material shall be kept frozen at such a temperature that the activity of the factor VIII is maintained.

16.1 *Tests on final containers*

16.1.1 *Sterility and safety*

Each filling lot shall be tested for sterility. Part A, section 5, of the revised Requirements for Biological Substances No. 6 (General Requirements for the Sterility of Biological Substances) (*9*, p. 48) shall apply.

In some countries a general safety test may be required, whereby each filling lot is tested for extraneous toxic contaminants by appropriate tests involving injection into mice and guinea-pigs. The injection shall cause neither significant toxic reactions nor death within an observation period of seven days. The tests shall be approved by the national control authority.

> The tests generally used are the intraperitoneal injection of 0.5 ml into each of at least two mice weighing approximately 20 g and the injection of 5.0 ml into each of at least two guinea-pigs weighing approximately 350 g. In some countries, if one of the animals dies or shows signs of ill-health, such as weight loss, during a specified period, the test is repeated. The substance passes the test if none of the animals of the second group dies or shows signs of ill-health, such as weight loss, during that period. For factor VIII and factor IX concentrates, the test dose should not exceed 500 IU of the coagulation factor per kg of body weight of the test animal.

16.1.2 *Freedom from pyrogenicity*

Each filling lot shall be tested for pyrogenicity by the intravenous injection of the test dose into three or more rabbits that have not previously received blood products. In general, the dose shall be at least equivalent

proportionally, on a rabbit body-weight basis, to the maximum single human dose recommended, but not more than 10 ml/kg of body weight.

The following test doses are suggested: factor VIII, 10 IU/kg of body weight; factor IX, 50 IU/kg of body weight; and fibrinogen, 30 mg/kg of body weight.

16.1.3 *Solubility and clarity*

Factor VIII preparations shall dissolve in the solvent recommended by the manufacturer within 30 min when held at a temperature not exceeding 37 °C. Factor IX preparations shall dissolve in the solvent recommended by the manufacturer within 15 min when held at 20–25 °C. The solutions, when kept at room temperature, shall not show any sign of precipitation or gel formation within 3 h of dissolution of the coagulation factors.

16.1.4 *Protein content*

The amount of protein in a final container shall be determined by a method approved by the national control authority.

16.1.5 *Additives*

Tests to determine the concentration of additives (such as heparin, polyethylene glycol, sodium citrate and glycine) used during production shall be carried out if required by the national control authority.

16.1.6 *Moisture content*

The residual moisture content shall be determined by a method approved by the national control authority. The acceptable moisture content shall be determined by the national control authority.

> The methods available are: (a) drying over phosphorus pentoxide for 24 h at a pressure not exceeding 2.7 Pa (0.02 mmHg); and (b) the Karl Fischer method.

16.1.7 *Hydrogen ion concentration*

When the product is dissolved in a volume of water equal to the volume stated on the label, the pH of the resulting solution shall be 7.2 ± 0.4.

> In some countries, different pH values are approved.

16.2 ***Test applicable to factor VIII concentrates***

Each filling lot shall be assayed for factor VIII activity by a test approved by the national control authority, using a standard calibrated against the International Standard for Blood Coagulation Factor VIII: Concentrate.

> The national standard and the manufacturer's house standard should be a concentrate rather than a plasma because the former has better long-term stability and provides more homogeneous assay results.

The specific activity shall be at least 500 IU/g of protein. The estimated potency shall be not less than 80% and not more than 125% of the stated potency. The confidence limits of error shall be not less than 64% and not more than 156% of the estimated potency.

16.3 *Tests applicable to factor IX concentrates*

16.3.1 *Potency*

Each filling lot shall be assayed for factor IX activity by a test approved by the national control authority, using a standard calibrated against the International Standard for Human Blood Coagulation Factors II, IX, and X in Concentrates.

Other coagulation factors may also be present in the final product, depending on the method of production, and products shall be assayed for all coagulation factors claimed to be present at a therapeutic level, including factors II, VII and X. The assay methods used for these factors shall be approved by the national control authority.

16.3.2 *Presence of activated coagulation factors*

A test for the presence of activated coagulation factors shall be carried out by a method approved by the national control authority.

In some countries, the non-activated partial thromboplastin times of normal plasma are measured after the addition of an equal volume of a number of different dilutions of the product under test.

In some countries, a test for the presence of thrombin is carried out by mixing equal volumes of the product under test and fibrinogen solution. The mixture is held at 37 °C and should not coagulate within 6 h. The usual range of concentrations of fibrinogen solution is 3–10 g/l.

16.3.3 *Alloantibodies*

A test shall be made for the presence of alloantibodies A and B by a method approved by the national control authority.

It is not possible to be specific about the tests for alloantibodies or to specify an upper limit for the titre.

16.4 *Test applicable to fibrinogen*

Each filling lot shall be assayed for clottable protein by a test approved by the national control authority.

Not less than 70% of the total protein should be clottable by thrombin.

16.5 *Identity test*

An identity test shall be performed on at least one labelled container from each filling lot of coagulation-factor concentrate to verify that the preparation is of human origin. The test shall be one approved by the national control authority.

For albumin and plasma protein fraction, additional tests shall be made to determine that the protein is predominantly albumin.

The methods in most common use are radial immunodiffusion and electrophoresis.

16.6 ***Records***

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 27–28) shall apply.

16.7 ***Samples***

The requirements of Good Manufacturing Practices for Biological Products (*8*, page 29, paragraph 9.5) shall apply.

16.8 ***Labelling***

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 26–27) shall apply.

In addition, the label on the container shall state:

- the content of the coagulation factor expressed in International Units, where they exist;
- the amount of protein in the container;
- the volume of diluent needed for reconstitution;
- a reference to a package insert giving instructions for use, warnings about the possible transmission of infectious agents and precautions.

16.9 ***Distribution and shipping***

The requirements of Good Manufacturing Practices for Biological Products (*8*) shall apply.

16.10 ***Storage and shelf-life***

The requirements of Good Manufacturing Practices for Biological Products (*8*, pages 26–27) shall apply.

Final containers of freeze-dried preparations of factor VIII and factor IX shall have a maximum shelf-life of two years if they are stored at 5 ± 3 °C. Final containers of fibrinogen shall have a maximum shelf-life of five years if they are stored at 5 ± 3 °C.

Other storage conditions and shelf-lives may be approved by the national control authority provided that they are consistent with the data on the stability of the products.

Part D. National control requirements

17. General

The general requirements for control laboratories in the Guidelines for National Authorities on Quality Assurance for Biological Products (*6*) shall apply.

The national control authority shall provide the standards and reference preparations necessary for the quality control of human blood and blood

products. Where appropriate, these standards should be calibrated against the relevant International Standard.

The national control authority shall have authority to approve the production and control methods used and settle all matters left for its decision or approval in Parts A, B and C.

The national control authority shall also have authority to approve the use of materials that carry potential risk and shall approve any new method of production and the preparation of any new product.

> New products or products prepared by new production methods may be monitored to confirm their efficacy and safety.

18. Release and certification

Human blood and blood products shall be released only if they satisfy the requirements of Parts A, B and C, wherever applicable.

A certificate signed by the appropriate official of the national control authority shall be provided at the request of the manufacturing establishment and shall state whether the product in question meets all national requirements as well as Parts A, B and C (whichever is relevant) of the present Requirements. The certificate shall also state the date of the last satisfactory potency test performed by the manufacturer, if applicable, the number under which the lot is released, and the number appearing on the labels of the containers. In addition, a copy of the official national release document shall be attached.

> The purpose of this certificate is to facilitate the exchange of human blood and blood products between countries.

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Appendix

Summary protocol for collection of source material

1. Name and address of collecting centre _____

   _____

2. Source material _____

3. Details of single donations, where applicable:
   (a) Donor identification _____
   (b) Date of collection _____
   (c) Volume in container _____
   (d) Results of tests for HBsAg _____
   (e) Results of tests for anti-HIV _____
   (f) Results of tests for anti-HCV _____
   (g) If applicable, results of tests for antibody to hepatitis B core antigen _____
   (h) If applicable, results of tests for alanine aminotransferase _____

4. Special information:
   (a) Anticoagulant used _____
   (b) Was the material collected for special purposes (e.g. as a source of specific antibodies)? _____
   (c) Precautions to be taken when using the material _____

5. Conditions of storage _____

6. Does the donation comply with existing agreements between the supplier and manufacturer? _____

7. Does the donation comply with the Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives published by WHO? _____

Name and signature of responsible person _____

Date _____

STANDARD OPERATING PROCEDURE

(Name of the Blood Centre)

Number	Effective Date	Pages	Author	Authorised by
SP 001		3		
Version	**Review Period**	**No. of Copies**	**Approved by**	**Date**
1	1 Year			

LOCATION	SUBJECT
Donor Room	Criteria for Donor Selection
FUNCTION	**DISTRIBUTION**
Assessing suitability of donor for blood donation	- Medical Officer in charge of Donor Area - Master File

1. SCOPE & APPLICATION

This SOP describes the criteria for a donor to be accepted for blood donation, for ensuring safety of donor as well as recipient. The purpose of donor selection is to identify any factors that might make an individual unsuitable as a donor, either temporarily or permanently.

2. RESPONSIBILITY

The Medical Officer is responsible for determining the suitability of donor for blood donation. He/She should confirm that the criteria are fulfilled after evaluation of health history questionnaire and medical examination including the results of pre donation screening tests.

3. REFERENCES

Technical Manual of American Association of Blood Banks- 13th edition, 1999 pgs 90-97, 103-110.

4. MATERIAL REQUIRED

- Donor Questionnaire
- Donor Card

5. PROCEDURE

CRITERIA FOR SELECTION OF BLOOD DONORS

A. Accept only voluntary/replacement non-remunerated blood donors if following criteria are fulfilled.

The interval between blood donations should be no less than three months. The donor shall be in good health, mentally alert and physically fit and shall not be a jail inmate or a person having multiple sex partners or a drug-addict. The donors shall fulfill the following requirements, namely:-

1. The donor shall be in the age group of 18 to 60 years
2. The donor shall not be less than 45 kilograms
3. Temperature and pulse of the donor shall be normal
4. The systolic and diastolic blood pressures are within normal limits without medication
5. Haemoglobin shall not be less than 12.5 g/dL
6. The donor shall be free from acute respiratory diseases
7. The donor shall be free from any skin disease at the site of phlebotomy
8. The donor shall be free from any disease transmissible by blood transfusion, in so far as can be determined by history and examination indicated above
9. The arms and forearms of the donor shall be fee from skin punctures or scars indicative of professional blood donors or addiction of self-injected narcotics

B. Defer the donor for the period mentioned as indicated in the following table:

CONDITIONS	PERIOD OF DEFERMENT
Abortion	6 months
History of blood transfusion	6 months
Surgery	12 months
Typhoid fever	12 months after recovery
History of Malaria duly treated	3 months (endemic) 3 years (non endemic area)
Tattoo	6 months
Breast feeding	12 months after delivery
Immunization (Cholera, Typhoid, Diphtheria, Tetanus, Plague, Gammaglobulin)	15 days
Rabies vaccination	1 year after vaccination
Hepatitis in family or close contact	12 months
Hepatitis Immune globulin	12 months

C. Defer the donor permanently if suffering from any of the following diseases:

1. Cancer
2. Heart disease
3. Abnormal bleeding tendencies
4. Unexplained weight loss
5. Diabetes
6. Hepatitis B infection
7. Chronic nephritis

. Signs and symptoms, suggestive of AIDS

9. It is important to ask donors if they have been engaged in any risk behaviour. Allow sufficient time for discussion in the private cubicle. Try and identify result-seeking donors and refer them to VCTC (Voluntary Counseling and Testing Center). Reassure the donor that strict confidentially is maintained.
10 Liver disease
11 Tuberculosis
12 Polycythemia Vera
13 Asthma
14 Epilepsy
15 Leprosy
16 Schizophrenia
17 Endocrine disorders

D. Private interview:

A detailed sexual history should be taken. Positive history should be recorded on confidential notebook.

E. Informed consent:

Provide information regarding:

1. Need for blood
2. Need for voluntary donation
3. Regarding transfusion transmissible infections
4. Need for questionnaire and honest answers
5. Safety of blood donation
6. How the donated blood is processed and used
7. Tests carried out on donated blood

N.B. This gives the donor an opportunity to give his/her consent if they feel they are safe donors

* Request the donors to sign on the donor card indicating that he is donating voluntarily.

6: DOCUMENTATION

Enter all details in the donor questionnaire form/card and computer