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

*Tadao Tomita, Miyuki Takayanagi, Kimie Kiwada, Akemi Mieda, Chiyoko Takahashi, and Tadayoshi Hata*

**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.

From the Japanese Red Cross Toyohashi Blood Center, Toyohashi, Japan; and the Department of Clinical Pathology, Fujita Health University, Toyoake, Japan.

*Address reprint requests to:* Tadao Tomita, MD, DPhil, Japanese Red Cross Toyohashi Blood Center, Higashiwaki 3-4-1, Toyohashi 441-8083, Japan. E-mail: ttomita@fujita-hu.ac.jp.

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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.

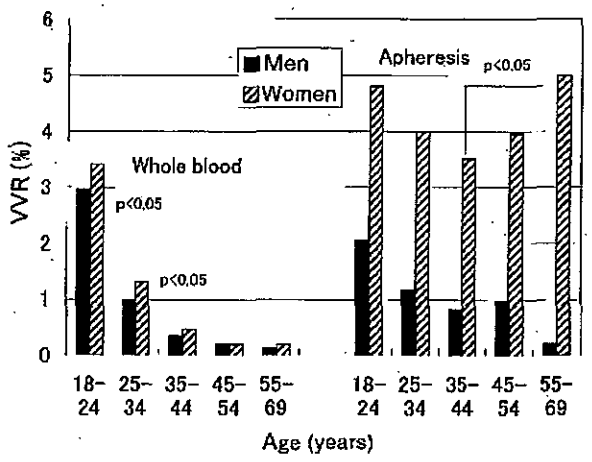


**Fig. 1. VVR incidence rate in relation to age in WB and apheresis donors. Note that in men donors the incidence decreased with advancing ages both in WB and in apheresis donation, but that in women donors there was a large difference between WB and apheresis donation. The difference was significant ($p < 0.05$) 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.**

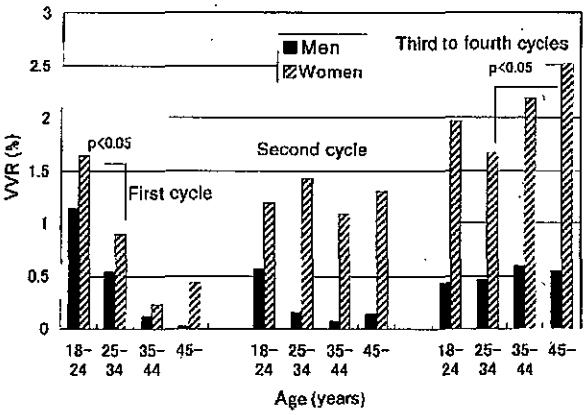


**Fig. 2. The relationship between VVR incidence and age at different stages of apheresis. In younger donors, VVRs incidence did not differ much at different cycles of apheresis. In contrast, older donors tended to experience VVRs at a later stage of apheresis. A significant difference was indicated 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.

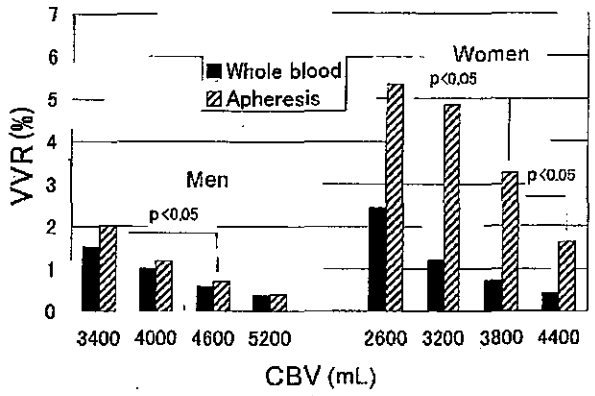


**Fig. 3. VVR incidence in relation to CBV in WB and apheresis donation. The CBV was calculated by the equations described in the method. The significance of the difference is indicated by $p < 0.05$.**

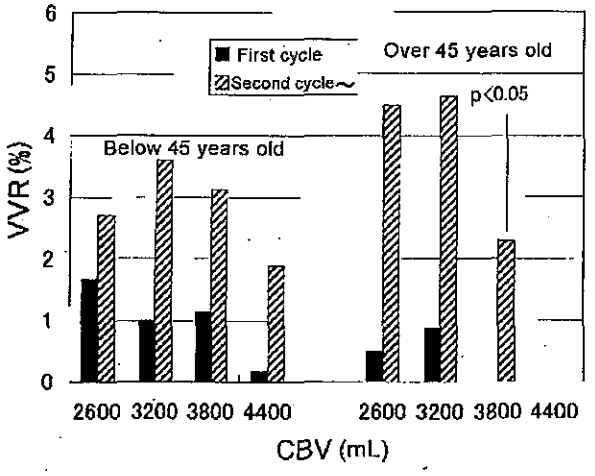


**Fig. 4. VVR incidence in relation to CBV before (first cycle) and after the end of first cycle of apheresis (second cycle) in women donors below and over 45 years old. Note the higher incidence with smaller CBV and also after the first cycle of apheresis.**

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

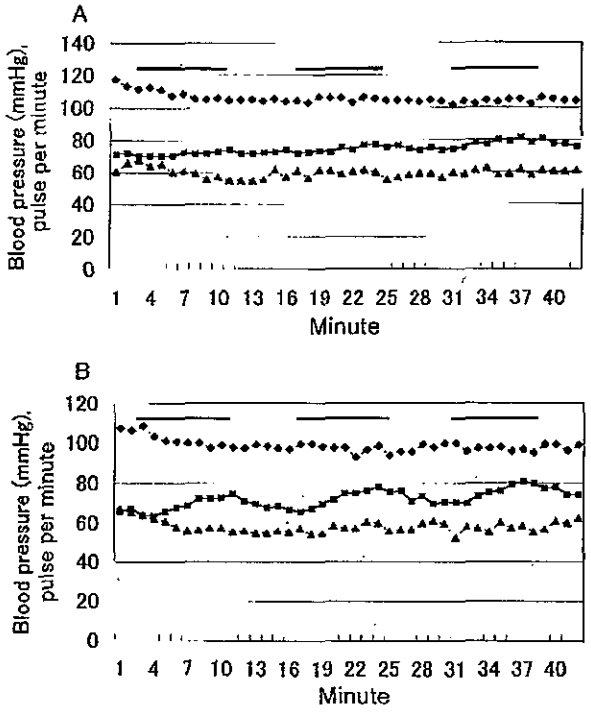


**Fig. 5. Blood pressure and pulse rate measured every 1 minute during apheresis, averaging from five women donors whose pulse rate was stable (A) and increased (B) during blood withdrawal. (♦) Systolic and (▲) diastolic blood pressure; (■) pulse rate.**

**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.

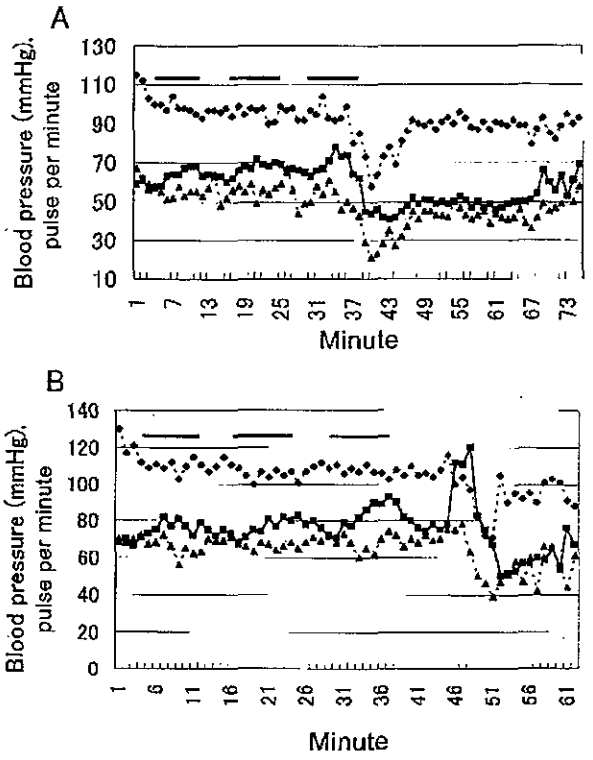


**Fig. 6. (A) Blood pressure and pulse rate in a women donor (43 years old) who suffered from VVRs during the third cycle of blood withdrawal. VVRs were accompanied by tachycardia and lowered blood pressure, and then tachycardia was followed by prolonged bradycardia. The donor was laid down flat until 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

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