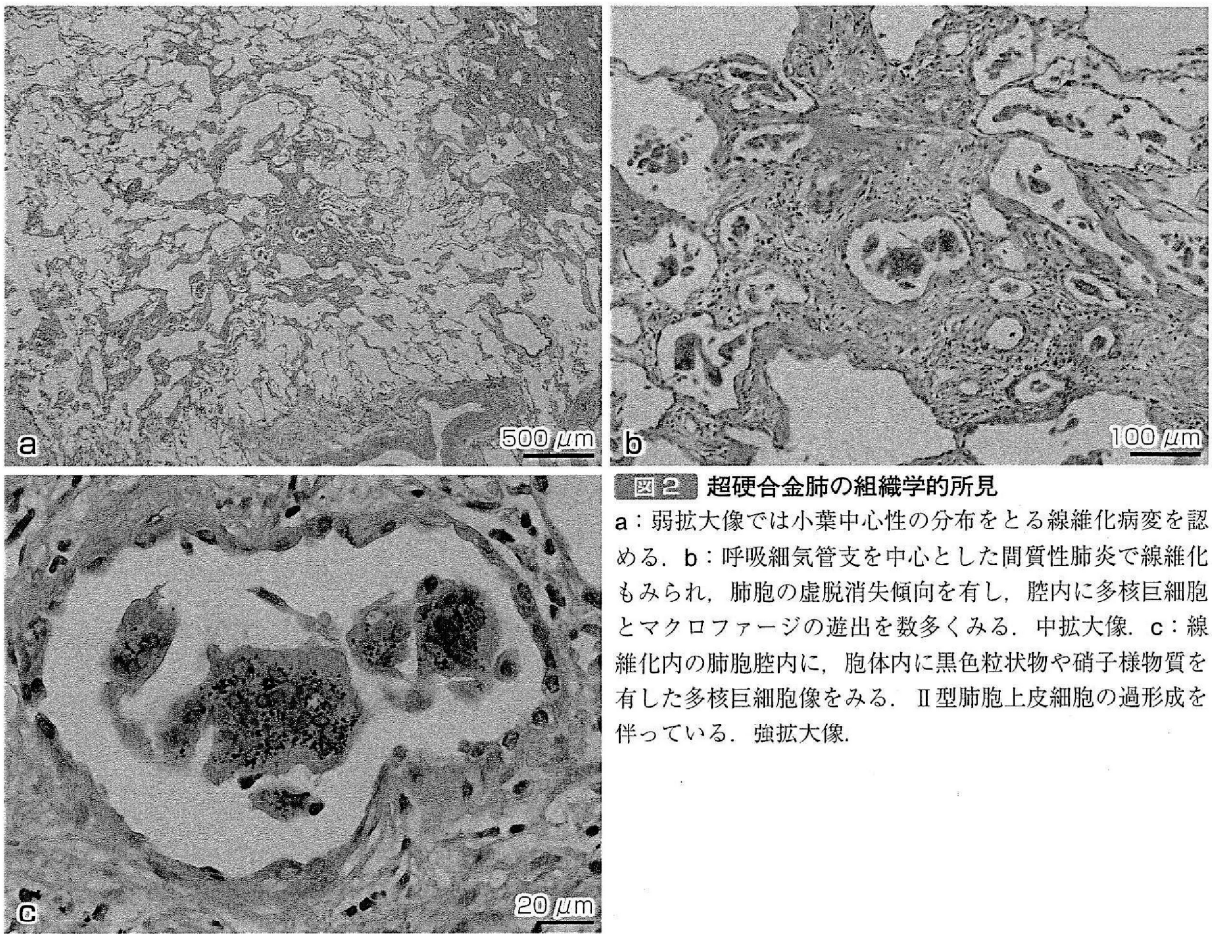

図2　超硬合金肺の組織学的所見
a：弱拡大像では小葉中心性の分布をとる線維化病変を認める．b：呼吸細気管支を中心とした間質性肺炎で線維化もみられ，肺胞の虚脱消失傾向を有し，腔内に多核巨細胞とマクロファージの遊出を数多くみる．中拡大像．c：線維化内の肺胞腔内に，胞体内に黒色粒状物や硝子様物質を有した多核巨細胞像をみる．Ⅱ型肺胞上皮細胞の過形成を伴っている．強拡大像．

Research on Cancer（IARC）の発がん性物質の評価の中で，超硬合金（コバルトと炭化タングステン）はGroup 2A（probably carcinogenic to humans）に分類されており肺癌の発症にも注意が必要である．

4 画像所見

胸部X線写真上は，ほぼ正常例から粒状影や網状影を認め，進行例では肺線維症がある．

胸部CT所見でAkiraは，汎小葉性・多小葉性の両側コンソリデーションあるいはすりガラス様陰影を報告している[13]．2009年の東京びまん性肺疾患検討会で超硬合金肺19例（GIPと小葉中心性の炎症線維化を認める14症例と，その他の病理組織型5例）についての検討が行われ，胸部CT所見として，小葉中心性結節およびすりガラス様濃度上昇を16例に認め，経過中気胸を7例に認めている．網状影や牽引性気管支拡張，上葉の容積減少も5例に認めている[12]．

5 組織学的所見（図2〜5）

超硬合金肺の代表的な病理組織所見として，GIPが挙げられる．GIPは，肺胞腔内にいびつで奇怪な（bizzare）多核巨細胞の出現をみる特異な間質性肺炎である．非特異性間質性肺炎non-specific interstitial pneumonia（NSIP）のように時間的空間的に均一な病変分布ではなく，程度の差こそあれ，小葉あるいは細葉中心性の間質性肺炎像の病変分布を認め，経過により線維化の程度が進み，その線維化は壁在型および閉塞型をとる．癒痕様病巣を呈することもある．外科的肺生検を行った症例の中には，上葉は細気管支周囲に黒色粒状物が目立つのみで，主に下葉にGIPを認めることもある．GIPでみられる多核巨細胞は，肺胞腔内に多数のマクロファージとともに散在したり，周囲を肥厚した間質に囲まれて腔内単独にみられることもある．多核巨細胞の胞体内には，数個から時に20個以上の核を認め，共食い性のcannibalistic，あるいは細胞内細胞cell in

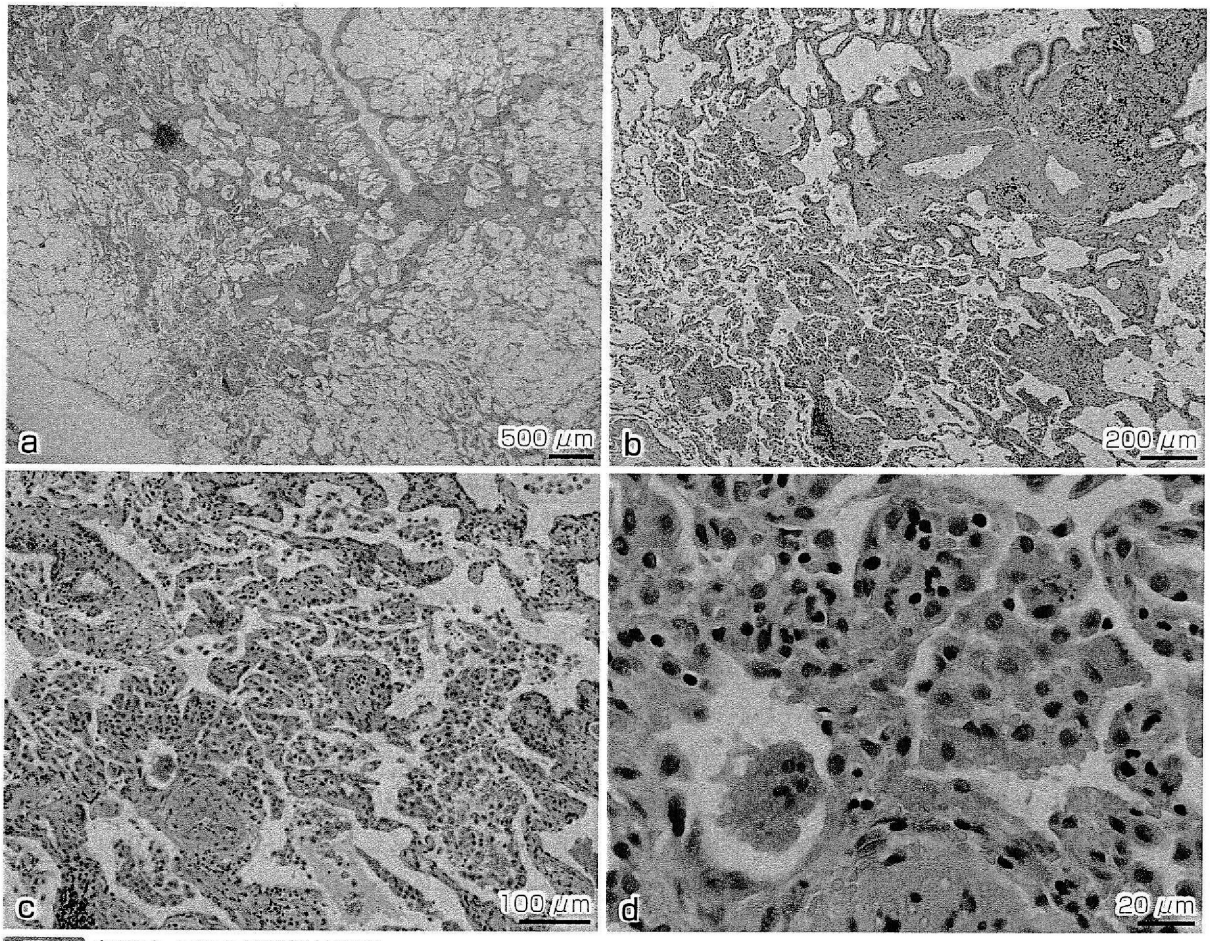

図3　超硬合金肺の組織学的所見

a：弱拡大像では小葉中心性の分布をとる線維化病変を認め，隣接病巣との接合もみる．b：肺胞腔内にはおびただしい数の細胞を認める．中拡大像．c：肺胞腔内にはマクロファージを主体とした細胞の遊出で，巨細胞が点在している．肺胞壁は小円形細胞の浸潤を伴う肥厚（胞隔炎）をみる．中拡大像．d：肺胞腔内のいびつな多核巨細胞とマクロファージの遊出．強拡大像．（長岡中央綜合病院 岩島　明先生ご提供）

cellなどと形容され，細胞内細胞陥入現象emperipolesisを示すこともある．また，巨細胞内には，取り込んだ粉じんの種類や量により，大小の黒色粒状物を認める．他の粉じんの影響が少ない場合には，黒色粒状物は目立たず，わずかに茶褐色の非常に細かい点状物を認めることがあり，この点状物が元素分析で超硬合金の構成成分であるタングステンやコバルトとして同定される．GIPでは，様々な程度の線維化をみ，その間質にはリンパ球など単核球の浸潤や時に好酸球も目立つ．また，肺胞腔裏打ちのⅡ型肺胞上皮の過形成を認める．肺胞を覆う細胞に多核化を認めることもある．気管支周囲に肉芽腫・類上皮細胞肉芽腫や器質化を伴う症例もあり，過敏性肺炎との鑑別が必要なことがある．曝露期間が長期になると，細胞浸潤が目立たない中で小葉中心性の瘢痕様の星芒状線維化形態を呈することもある．一部の超

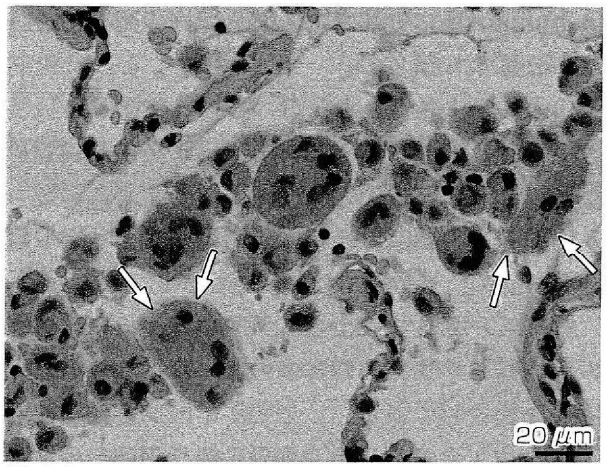

図4　超硬合金肺の組織学的所見

肺胞腔内の多核巨細胞とマクロファージ．多核巨細胞内には，非常に細かい茶褐色の粒状物を認める（矢印）．強拡大像．（岐阜市民病院 石黒　崇先生ご提供）

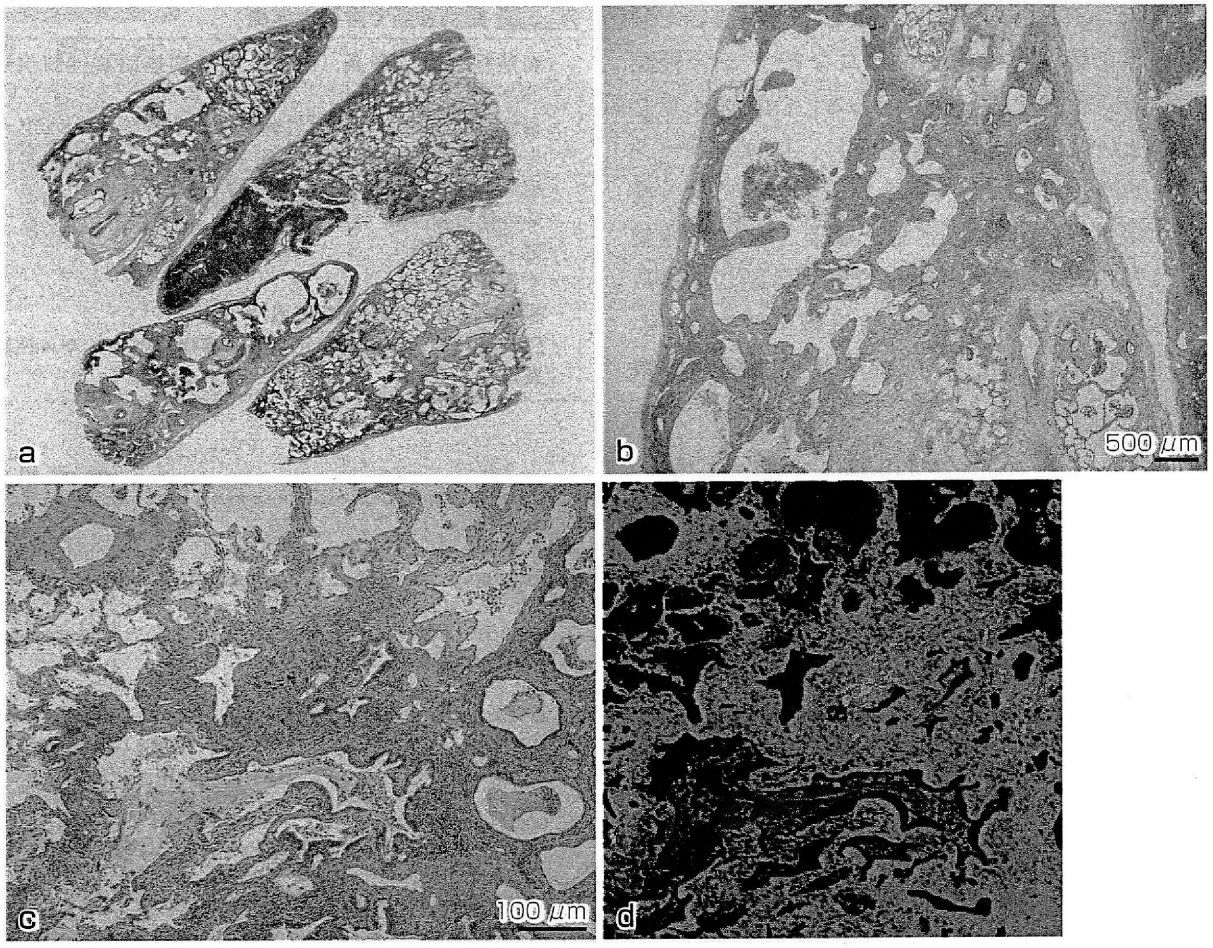

図5　蜂巣肺のびまん性肺線維症像を呈した超硬合金肺

a：ルーペ像．嚢胞化を伴った広い線維化の蜂巣肺を呈したUIP様像がみられる．b：呼吸細気管支～肺胞道部の嚢胞様拡張を呈したびまん性線維化の蜂巣肺形成をみる．弱拡大像．c：呼吸細気管支周囲の強い線維化で，肺胞が消失した線維化部には細胞浸潤が目立ち，小嚢胞化の腔は細気管支上皮で裏打ちされ，その腔内は細胞遊出が目立つ．中拡大像．d：cの連続切片の元素分析図．黄色部は超硬合金の主成分タングステンで，小葉中心の線維化部位や肺胞腔内の巨細胞に検出された．（神奈川県立循環器呼吸器病センター 小倉高志先生ご提供）

硬合金肺ではUIPパターンを認めるが，超硬合金の吸入が引き起こす病理組織は，時間経過によりGIPからUIPパターンに変化するのか，当初より他の組織型をとっていくのか，現在のところは明らかになっていない．

超硬合金肺の病理組織では，GIPが半数以上を占めるが，GIP以外にDIPパターンも報告されている[2]．いびつな多核巨細胞があまり目立たないで肺胞腔内に多数のマクロファージが存在している症例では，一見DIP様にみえるが，シート状に密接しているのではなくマクロファージは集簇しているものの，多くの細胞が個々に存在しているようにみえる．前述の東京びまん性肺疾患検討会では国内19例の超硬合金肺の検討でGIPおよび小葉中心性線維化病変を定型例として14例，非定型例5例（うちUIPパターン3例，慢性間質性肺炎と小葉中心性線維化1例，無気肺硬化型/上葉優位型肺線維症1例）であった[12]．

6 鑑別診断

超硬合金肺は，病理組織所見がGIPに固定されたものではなく，作業環境と個人の感受性，吸入物の量，超硬工具を使用して加工していた原材料や製品の影響も病理組織に反映される．肺胞腔内に多数のマクロファージが存在する場合にはDIPが，喫煙者で色素沈着を伴うマクロファージが存在する場合には呼吸細気管支炎を伴う間質性肺疾患respiratory bronchiolitis associated with interstitial lung disease（RB-ILD）が鑑別として挙げられ，リンパ球浸潤や肉芽腫形成，器質化を伴う場合には，過敏性肺炎の鑑別診断も必

要である．GIPをきたす原因として，前述した酸化チタンの吸入[9]や電子タバコなど[10]が今後臨床的にも問題となる可能性がある．GIPのような特徴的な病理組織所見を呈さずに，UIPパターンや慢性線維化が主体の肺病変である場合には，特発性間質性肺炎が鑑別診断上重要となる．職業歴，吸入歴を加味した総合的な鑑別診断が求められる．細気管支炎やびまん性汎細気管支炎 diffuse panbronchiolitis (DPB) として経過観察されていた症例もある．表1に重要な鑑別疾患をまとめた．

表1　鑑別診断で重要な疾患

- 剝離性間質性肺炎（DIP），喫煙関連間質性肺疾患（RB-ILD）
- 過敏性肺炎を含む間質性肺炎（UIPパターン，OPパターン，慢性線維化性肺炎）
- 細気管支炎，びまん性汎細気管支炎
- その他のじん肺（酸化チタン吸入など）
- 電子タバコ吸入
- サルコイドーシス
- 膠原病に伴う間質性肺疾患
- 巨細胞性肺炎（巨細胞を呈する麻疹などウイルス性肺炎）

7 発症メカニズム

超硬合金粉末の粒径は0.5～10数μm程度で，非常に細かく，近年超微粒子超硬合金も実用化されていて，経気道吸入で肺胞領域まで到達する．肺組織内で炭化タングステンとコバルトの相互作用により，活性酸素種が作られ，肺傷害を起こすことが報告されている[14]．超硬合金肺で免疫組織化学を行うと，小葉中心性の線維化巣ではCD163陽性マクロファージが多数分布しており，周囲にはCD8陽性リンパ球が存在する．マクロファージや多核巨細胞の胞体内に非常に細かい茶褐色の微粒子を認めることがあり，元素分析でタングステンやコバルトとして同定される[15]．ある種の異物に対して，多核巨細胞はマクロファージ単独に比べて補体関連の受容体を増加させて，貪食能を高めることが報告されている[16]．超硬合金粉じんに対する生体反応についてはさらなる解明が必要である[17]．

超硬合金肺は職業性肺疾患の一つであり，診断の際には詳細な職業歴と作業環境の情報を集めることが大切である．臨床医と確認しながら診断を確実なものにして頂きたい．

（森山寛史，岡本賢三）

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Clinical significance and applications of oscillometry

David A. Kaminsky[1,23], Shannon J. Simpson[2,23], Kenneth I. Berger[3], Peter Calverley[4], Pedro L. de Melo[5], Ronald Dandurand[6,7], Raffaele L. Dellacà[8], Claude S. Farah[9], Ramon Farré[10,11], Graham L. Hall[2], Iulia Ioan[12,13], Charles G. Irvin[1], David W. Kaczka[14], Gregory G. King[15,16], Hajime Kurosawa[17], Enrico Lombardi[18], Geoffrey N. Maksym[19], François Marchal[12,13], Ellie Oostveen[20], Beno W. Oppenheimer[3], Paul D. Robinson[21], Maarten van den Berge[22] and Cindy Thamrin[16]

[1]Dept of Medicine, Pulmonary and Critical Care Medicine, University of Vermont, Larner College of Medicine, Burlington, VT, USA. [2]Children's Lung Health, Telethon Kids Institute, School of Allied Health, Curtin University, Perth, Australia. [3]Division of Pulmonary, Critical Care, and Sleep Medicine, NYU School of Medicine and André Cournand Pulmonary Physiology Laboratory, Belleuve Hospital, New York, NY, USA. [4]Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK. [5]Dept of Physiology, Biomedical Instrumentation Laboratory, Institute of Biology and Faculty of Engineering, State University of Rio de Janeiro, Rio de Janeiro, Brazil. [6]Lakeshore General Hospital, Pointe-Claire, QC, Canada. [7]Montreal Chest Institute, Meakins-Christie Labs, Oscillometry Unit of the Centre for Innovative Medicine, McGill University Health Centre and Research Institute, and McGill University, Montreal, QC, Canada. [8]Dipartimento di Elettronica, Informazione e Bioingegneria – DEIB, Politecnico di Milano University, Milan, Italy. [9]Dept of Respiratory Medicine, Concord Repatriation General Hospital, Sydney, Australia. [10]Unitat de Biofísica i Bioenginyeria, Facultat de Medicina, Universitat de Barcelona-IDIBAPS, Barcelona, Spain. [11]CIBER de Enfermedades Respiratorias, Madrid, Spain. [12]Dept of Paediatric Lung Function Testing, Children's Hospital, Vandoeuvre-lès-Nancy, France. [13]EA 3450 DevAH – Laboratory of Physiology, Faculty of Medicine, University of Lorraine, Vandoeuvre-lès-Nancy, France. [14]Depts of Anaesthesia, Biomedical Engineering and Radiology, University of Iowa, Iowa City, IA, USA. [15]Dept of Respiratory Medicine and Airway Physiology and Imaging Group, Royal North Shore Hospital, St Leonards, Australia. [16]Woolcock Institute of Medical Research, The University of Sydney, Sydney, Australia. [17]Dept of Occupational Health, Tohoku University School of Medicine, Sendai, Japan. [18]Paediatric Pulmonary Unit, Meyer Paediatric University Hospital, Florence, Italy. [19]School of Biomedical Engineering, Dalhousie University, Halifax, NS, Canada. [20]Dept of Respiratory Medicine, Antwerp University Hospital and University of Antwerp, Belgium. [21]Woolcock Institute of Medical Research, Children's Hospital at Westmead, Sydney, Australia. [22]Dept of Pulmonary Diseases, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands. [23]These authors have contributed equally to this manuscript.

Corresponding author: David A. Kaminsky (david.kaminsky@uvm.edu)

Shareable abstract (@ERSpublications)
This paper provides a current review of the interpretation, clinical significance and application of oscillometry in respiratory medicine, with special emphasis on limitations of evidence and suggestions for future research. https://bit.ly/3GQPViA

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Abstract

Recently, "Technical standards for respiratory oscillometry" was published, which reviewed the physiological basis of oscillometric measures and detailed the technical factors related to equipment and test performance, quality assurance and reporting of results. Here we present a review of the clinical significance and applications of oscillometry. We briefly review the physiological principles of oscillometry and the basics of oscillometry interpretation, and then describe what is currently known about oscillometry in its role as a sensitive measure of airway resistance, bronchodilator responsiveness and bronchial challenge testing, and response to medical therapy, particularly in asthma and COPD. The technique may have unique advantages in situations where spirometry and other lung function tests are not suitable, such as in infants, neuromuscular disease, sleep apnoea and critical care. Other potential applications include detection of bronchiolitis obliterans, vocal cord dysfunction and the effects of environmental exposures. However, despite great promise as a useful clinical tool, we identify a number of areas in which more evidence of clinical utility is needed before oscillometry becomes routinely used for diagnosing or monitoring respiratory disease.

Introduction

The mechanical properties of the lungs are disrupted in many disease states and exposures and contribute to major respiratory symptoms such as dyspnoea. Both the clinical management and our understanding of

respiratory disease have benefitted from widely available tests like spirometry and the measurement of absolute lung volumes and gas transfer. However, these measurements require significant patient co-operation and a willingness to undertake maximal respiratory efforts. Oscillometry is a noninvasive method for measuring the mechanical properties of the respiratory system, which can enhance our understanding and management of lung disease [1]. Recently, the *European Respiratory Journal* published "Technical standards for respiratory oscillometry" [2], which reviewed the physiological basis of oscillometric measures and detailed the technical factors related to standardisation of equipment and test performance, quality assurance and reporting of results. Here we provide a review of the clinical significance and applications of oscillometry. We briefly review the physiological principles of oscillometric measurements and the basics of oscillometry interpretation, highlight potential clinical applications, and identify future work required for oscillometry to become routinely used in clinical practice.

The physiology and performance of oscillometry

Oscillometry measures the mechanical impedance of the respiratory system (Z_{rs}), representing the resistive and reactive forces that must be overcome to drive an oscillating flow signal into the respiratory system. The forces arise in the respiratory system from 1) the resistance of the airways and tissues to flow (R_{rs}), 2) the elastance (stiffness) of the lung parenchyma and chest wall in response to changes in volume (encompassed in reactance, X_{rs}), and 3) the inertance of accelerating gas in the airways (I_{rs}). Z_{rs} has generally been reported from a single frequency or over the frequency range of 5–40 Hz as an average across the whole breathing cycle (*i.e.* both inspiration and expiration). It has also been reported separately during the inspiratory and expiratory phases. These concepts and how they are measured by oscillometry are described in detail in the technical document. We provide a brief summary of these details in table 1, figure 1 and the supplementary material.

Much of the evidence for clinical utility of oscillometry, including the studies cited in the current document, have been collected using a wide range of equipment, protocols and reporting formats. Although there is increasing availability of commercial oscillometry devices, comparability across devices remains a challenge, especially with regards to differences in the frequency dependence of resistance and reactance at higher-than-normal impedance [3, 4]. As such, the applicability of existing reference equations (supplementary table S1) remains uncertain for abnormal disease states and across different devices and manufacturers. Until this is resolved, comparisons between healthy and diseased cohorts should ideally be made using the same device, and differences in results based on variability in equipment, protocols and reference values should be considered when interpreting data presented in this review. Efforts are currently underway by the Global Lung Function Initiative to gather data from around the world to develop more universal, robust reference equations that take into account specific equipment and protocols.

Additionally, while oscillometry is a simple test to perform in clinic, its interpretation remains a challenge for many. Further aspects need to be better established before oscillometry gains an evidence-based position in clinical practice, as summarised in table 2. Many of these aspects are highlighted in the following sections, but in particular it is important to note that establishing minimal important clinical differences to assess change in lung function over time is a crucial area for future research.

Oscillometry during infancy

Lung function measurements during infancy have largely been confined to a few specialist centres due to technical complexity, lack of commercially available equipment, and potential risks associated with the measurement (*e.g.* requirement for sedation). Additionally, the use of a face mask in infants complicates the interpretation of impedance data, since much of the measured R_{rs} may be attributed to nasal resistance [5]. To date, there is no evidence that impedance measurements in infants contribute to clinical decision-making. However, oscillometric studies have contributed to the pathophysiological understanding of respiratory disease in infants, particularly those with wheezing disorders, as described in the supplementary material.

Preterm birth and bronchopulmonary dysplasia beyond the neonatal intensive care unit

Emerging evidence suggests that oscillometry is a clinically useful measure of lung function in survivors of very preterm birth. Compared to preschoolers delivered at term, those born prematurely have increased R_{rs}, more negative X_{rs} and increased area of reactance (AX) and resonant frequency (f_{res}) [6]. Deficits are even greater in premature babies with bronchopulmonary dysplasia (BPD) [7–9]. X_{rs} measured in the first week of life has been shown to improve prognostication of respiratory outcome in very preterm infants on noninvasive respiratory support. Recently, EVANS *et al.* [10] showed that while all oscillometric outcomes were abnormal in those born very prematurely, X_{rs} was particularly sensitive at distinguishing term *versus*

TABLE 1 Summary of oscillometric parameters with a focus on the medium frequency range likely to be used in clinical practice (5–40 Hz)

Parameter	Physiological interpretation
Z_{rs}	Respiratory system impedance, reflecting the total forces related to resistance, elastance and inertance that must be overcome to drive airflow into and out of the lung. Z_{rs} broadly describes the mechanical properties of the entire respiratory system (airway, parenchyma and chest wall). Z_{rs} is not used in clinical practice *per se*. Rather, Z_{rs} is represented by its components, respiratory system resistance (R_{rs}) and reactance (X_{rs}) as described below.
R_{rs}	Resistance of the respiratory system, reflecting frictional losses both in gases as they flow along airways and in tissues of the lung and chest wall as they are stretched and deformed. R_{rs} at individual frequencies is denoted R_{rs_5}, R_{rs_8}, *etc.* Changes in R_{rs} at higher frequencies above ~5 Hz are reflective of changes in airway resistance, *i.e.* calibre, and thus sensitive to airway narrowing. As such, R_{rs} could be increased in clinical situations such as during bronchoconstriction, the presence of excessive mucous or mucous plugging, airway inflammation, and other causes of airway narrowing or obstruction. Tissue resistance becomes progressively more important as frequency decreases below 5 Hz, becoming dominant at normal breathing frequencies (~0.2 Hz) and lower.
Frequency dependence of resistance (*e.g.* $R_{rs_{5-20}}$)	R_{rs} is largely frequency independent over the medium frequency range among healthy individuals (except in very young children). However, in many respiratory diseases, increased upward inflection of resistance is often evident at low frequencies and therefore frequency dependence is increased. Clinically, the frequency dependence of R_{rs} is commonly quantified as the difference $R_{rs_{5-20}}$. This is thought to primarily be sensitive to heterogeneous narrowing in the peripheral airways, but it may also arise from substantial heterogeneity in narrowing of more central airways, heterogeneity of time constants reflecting airway *versus* parenchymal disease, and upper airway shunt flow (compliant regions proximal to resistance).
X_{rs}	Reactance of the respiratory system, reflecting respiratory system elastance (E_{rs}) due to the combined stiffnesses of the lung and chest wall tissues (below f_{res}; described below), and respiratory system inertance (I_{rs}) due to the mass of gas in the central airways (above the f_{res}). X_{rs} becomes "more negative" in lung disease, indicating the respiratory system becomes stiffer. X_{rs} is very dependent on lung volume, with X_{rs_5} having been demonstrated to be sensitive to airway closure and reflecting communicating lung volume. Intrabreath changes in X_{rs_5} are useful to detect expiratory flow limitation. To date, I_{rs} is not commonly used as a measure of lung disease clinically, but may be altered in conditions affecting gas flow in the upper and central airways.
f_{res}	Resonant frequency, where E_{rs} and I_{rs} make equal and opposite contributions to impedance, (*i.e.* where X_{rs} is zero). E_{rs} makes the major contribution to X_{rs} as frequency decreases below f_{res}, while I_{rs} dominates increasingly above f_{res}. The f_{res} of a healthy adult male is around 8 Hz but is usually higher in lung disease. In children, f_{res} is generally higher than 8 Hz and decreases with age.
A*X*	In contrast to R_{rs} in health, X_{rs} is frequency-dependent in the medium frequency range, the magnitude of which is exaggerated in lung disease. The area under the reactance curve (A*X*) is the area inscribed by the X_{rs} curve between the lowest measured frequency and f_{res}. A*X* is thus an integrative measure dominated by the lower frequency components of X_{rs}, determined predominately by E_{rs}, and affected by the point at which X_{rs} crosses the frequency axis (f_{res}), which is determined both by E_{rs} and I_{rs}. It has the advantage of having positive rather than negative units and is a measure that evaluates X_{rs} over a range of frequencies, with units of elastance hPa·L^{-1}. Assessing A*X* (considering X_{rs} at all frequencies below f_{res}) in the clinic is potentially more sensitive to changes in the elastic properties of the respiratory system than X_{rs} at a single frequency.

preterm preschoolers, suggesting a role for oscillometry in monitoring preterm lung disease. Deficits in oscillometric outcomes persist up to at least adolescence and correlate with respiratory symptoms [11, 12].

To date, only one study has measured oscillometry longitudinally in this population [13]. Interestingly, X_{rs} and A*X* deteriorated over time in those with BPD in parallel with declines in spirometry measures, and were found to decrease faster in those children exposed to environmental tobacco smoke and those with respiratory symptoms. Deterioration in these oscillometry outcomes was not associated with structural lung damage on chest computed tomography (CT) scans. The pathophysiology underpinning increased lung stiffness in this population remains unclear, but may reflect failed alveolarisation, structural damage to the parenchyma or inflammatory changes to the lungs.

Asthma

Oscillometric measurements can distinguish adult asthmatics from healthy controls [14–16], asthmatics with different degrees of airway obstruction [17], and between groups of adults with asthma compared to COPD [15, 18–21]. Oscillometry may be especially helpful in diagnosing asthma in patients with preserved spirometry as a more sensitive indicator of abnormal airway physiology [22]. However, while

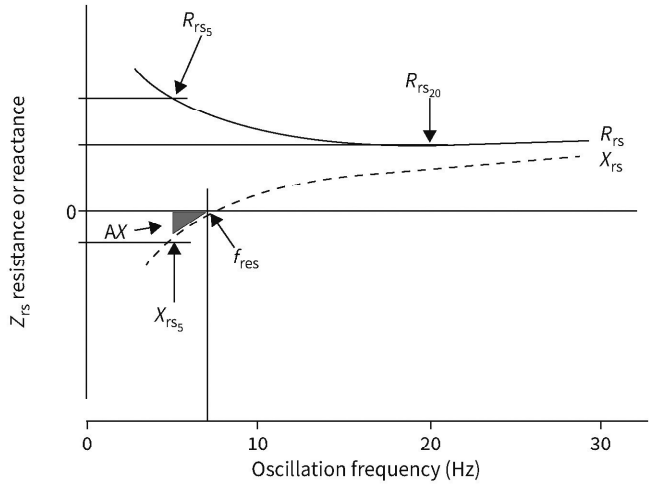

FIGURE 1 Impedance spectrum. Respiratory system impedance (Z_{rs}) is plotted against frequency. Z_{rs} is composed of a real component seen by resistance (R_{rs}) and an imaginary component expressed as reactance (X_{rs}). R_{rs} and X_{rs} at specific frequencies are noted by the frequency at which they are measured (*e.g.* R_{rs_5}=R_{rs} at 5 Hz, $R_{rs_{20}}$=R_{rs} at 20 Hz). The point at which X_{rs} crosses zero is the resonant frequency (f_{res}). Below f_{res}, X_{rs} is dominated by elastance, and above f_{res}, X_{rs} is dominated by inertance. An integrated measure of low frequency X_{rs} is the area inscribed by X_{rs} and Z_{rs}=0 starting at the lowest frequency up to f_{res}, known as the area of the X_{rs} curve, A*X*. The lowest frequency defining A*X* is shown at 5 Hz, but it may be estimated starting from any frequency. Note that the Z_{rs} spectrum shown is characteristic for a healthy adult. In healthy young children, the values and frequency dependence of R_{rs} would be relatively increased, X_{rs} would be more negative and f_{res} would be shifted markedly to the right (resulting in increased A*X*).

helpful in adults, the delineation between healthy controls and asthmatics using oscillometry is less clear in preschool-aged children, with several studies showing no difference between groups [23–25]. These conflicting findings may be due to differing diagnostic criteria, disease severity or degree of control in the paediatric populations studied who may have smaller differences between health and disease than adults.

Oscillometric outcomes other than resistance and reactance (such as A*X* and $R_{rs_{5-20}}$) may also be useful in supporting a diagnosis of asthma, predicting future loss of asthma control or monitoring clinical treatment changes. In particular, the term "small airway dysfunction" (SAD) has gained traction. The large ATLANTIS cohort revealed that $R_{rs_{5-20}}$, A*X* and X_{rs_5} were all strong contributors to SAD, with high prevalence in asthma compared to other physiological measures thought to reflect small airways [26]. However, a limitation of the study is that the definition of SAD relied on a statistical, data-driven approach, rather than an independent measure. It also is important to realise that no measures are specific for SAD, including $R_{rs_{5-20}}$, which is sensitive to heterogeneouis peripheral airway narrowing, but can also be affected by heterogeneity in the central airways and upper airway shunt (table 1). Furthermore, these relative contributions are likely dependent on disease. We urge caution in the strict interpretation of $R_{rs_{5-20}}$ as relating solely to small airways disease, especially when measured using devices that are known to be associated with enhanced frequency dependence of resistance [3, 27–29]. The clinical significance of $R_{rs_{5-20}}$ continues to be evaluated in terms of its mechanism [30, 31], prevalence [32] and correlations with measures of severity and control in both children and adults [26, 33, 34].

In addition, oscillometry has provided novel insights into the pathophysiology of asthma *via* the effects of lung volume on oscillatory mechanics, as well as short- and long-term variations in mechanics over time. These topics are further addressed in the supplementary material. These variations may be a marker of instability, and potentially useful to detect exacerbations or loss of control, particularly in a home telemonitoring setting [35]. Intrabreath changes in oscillometry parameters may also provide additional information beyond conventional parameters: in preschoolers it improved detection of acute obstruction and recurrent wheezers from healthy controls [36], while in adults with severe asthma it distinguished those with poor control from those with good control [37]. While oscillometry measures are generally altered in asthmatics at the population level, oscillometry is arguably of most benefit in clinical practice for the diagnosis of asthma (*via* bronchodilation or bronchoprovocation) and monitoring response to intervention, as discussed in the following sections.

TABLE 2 Gaps in knowledge and future needs in defining the clinical applications of oscillometry

Area of need	What we think we know	Identified gaps/research questions
Harmonisation of oscillometry devices [3]	Different metrics between commercial devices as measured impedance is increased.	Established standard testing procedures to compare devices. Encourage manufacturers to revise hardware and firmware/software design.
Normative values	Multiple reference populations to determine "normal", separate for children and adults.	Large, multicentre studies to determine multi-ethnic population normal values across all ages, equivalent to the Global Lung Function Initiative.
Minimal clinically important change	Short-term test variability over minutes and days; coefficient of repeatability values in children and adults. Longitudinal data in healthy people to understand variability and changes through life.	Correlations with clinical progression in disease populations. Minimally clinically important changes for each oscillometry index, which likely vary with disease and treatment.
Bronchodilator response	Cut-offs for significant bronchodilator responses, expressed for multiple indices in different ways, from individual studies in healthy people. Good discrimination between health and asthma. Higher sensitivity than spirometry in terms of response and identifying responders. Higher sensitivity than spirometry in identifying individuals with poor asthma control.	Determine the most useful way to express bronchodilator responses in the clinic. Consistency of such responses within subjects over time. Further studies on clinical correlates of bronchodilator responses, in both healthy and disease populations across all ages.
Standardisation of bronchial challenge testing protocol	Good feasibility in younger age groups. Variability across studies in terms of cut-offs. Higher sensitivity than spirometry in terms of response and identifying responders.	Determine value added to hyperresponsiveness measured by spirometry. Determine standardised cut-offs for the range of challenge agents. Potential feasibility of shorter protocols.
Phenotyping in obstructive diseases	Correlations of specific indices with symptoms, imaging and spirometry in terms of baseline measures, changes in response to treatment and prediction of treatment response.	Determine which indices provide the most clinically relevant information by reporting comprehensive, head-to-head comparison across the full range of indices, within disease populations, including patient-centred outcomes. Explore the role of new indices, such as those obtained from within-breath measurements. Sensitivity analyses within disease populations for oscillometry indices. Comprehensive studies correlating oscillometry measures with other phenotyping tools, such as lung imaging and histology. Determine correlations with known and emerging biomarkers of disease, particularly in response to treatment.
Grading severity of abnormalities	No data.	Assess degrees of deviation from normal in relation to statistical variation and clinical outcomes.
Home monitoring	Potential marker of airway instability in asthma. Sensitive detector of exacerbations in COPD, and utility as guide for intervention in subset of COPD patients (those with previous hospitalisation).	Role in exacerbation detection and guide for intervention in asthma. Role in prediction of disease progression and responses to treatment in asthma and COPD. Utility in other diseases.
Emerging clinical applications	Potential role in identifying lung function deficits in preterm children. Limited utility demonstrated thus far in cystic fibrosis in children, less data in adults. Potential role in detecting early changes in smokers. Potential utility in identifying pathological changes in obesity. Potential in monitoring progression after environmental exposures. Potential in diagnosis of vocal cord dysfunction. Potential role in titrating level of respiratory support in sleep and in COPD patients in the intensive care setting. Potential in identifying clinical progression in lung and bone marrow transplant patients, as well as interstitial lung disease and neuromuscular disease.	Larger clinical studies beyond proof of concept. Potential for aerosol generation to stratify risk of preventing spread of infection compared to spirometry.

Bronchodilator response testing

As discussed in the recent technical standards [2], cut-offs indicating a significant bronchodilator response (BDR) using oscillometric indices are reported in healthy adults and children (*i.e.* 40% decrease in R_{rs} at 5 Hz, 50% increase in X_{rs} at 5 Hz and 80% decrease in A*X* relative to baseline) (supplementary table S2) [2]. Recent work has shown results for BDR in adults [38, 39] that are similar to published data using different instruments [4], suggesting that BDR in oscillometry appears to be robust to different devices and populations. Nevertheless, given the diversity of age ranges, equipment and protocols, further work is still needed to best define a BDR, its significance relative to important patient outcomes and consistency of response over time.

Several studies have shown that a BDR based on oscillometric parameters is better than one based on forced expiratory volume in 1 s (FEV_1) at differentiating asthmatic from healthy children [40–42]. However, data relating to BDR in children with "early life" wheeze (*i.e.* no formal diagnosis of asthma) are less clear, with some studies reporting no differences in BDR between wheezy and non-wheezy preschoolers [43]. In adults, bronchodilation was identified more often using oscillometry than spirometry, and in one study changes in X_{rs} and A*X* (but not R_{rs}) correlated with spirometric responses and identified more subjects with poor asthma control compared to spirometry [44]. Other studies have shown that BDR assessed with oscillometry correlates with poor asthma control [14, 45].

Bronchial challenge testing

Oscillometry can also be used as an alternative to spirometry for conducting bronchial challenges in adults [46–58] and children [59–65]. A summary of studies to date attempting to define airway hyperresponsiveness (AHR) based on oscillometry is shown in supplementary table S3. Results vary widely, ranging from a 20 to 50% increase in R_{rs_5} and a 20–80% decrease in X_{rs_5}. Provocation studies in children are feasible in patients as young as 3 years old using oscillometry [59, 61]. However, conclusive data indicating which outcome measures and threshold values best reflect a positive bronchial challenge test are currently lacking in this age group. The main advantage of oscillometry for bronchial challenge testing is increased sensitivity of detecting bronchoconstriction, which might shorten the test and reduce the cumulative dose of the agent. However, there may be underestimation of the response occurring in the lungs in children during a challenge due to loss of the oscillatory flow into the upper and large airways, known as upper airway shunt [66]. More information about upper airway shunt is found in the supplementary material.

Deep breaths (*i.e.* inflation to total lung capacity (TLC)) during spirometry testing, or with some inhalation agents, potentially affect diagnosis, given both the bronchoprotective and bronchodilator effect of deep inhalation in health and in asthma [67–69]. Consequently, oscillometry may be more sensitive than spirometry for detecting AHR in mild asthmatic patients, given their maintained, albeit reduced, response to a deep breath, resulting in a lower provocative dose of methacholine [47, 70] and therefore a shorter testing protocol. However, since avoiding deep breaths may result in AHR even in healthy individuals [71], oscillometry may be less sensitive than spirometry in distinguishing healthy from asthmatic individuals. Of note, patients may prfer oscillometry over spirometry during bronchial challenge testing because they do not have to repeatedly take the deep breaths needed to perform spirometry.

AIIR detected by oscillometry is repeatable [47, 49, G1, 72] and correlates with responsiveness based on FEV_1 [73], but the correlations of spirometry and oscillometry are inconsistent. There is wide variability across studies, which may be explained by differences in methodology and study populations. However, it appears that oscillometric indices may provide additional information to spirometry. For example, some subjects report symptoms during bronchial challenge without accompanying changes in FEV_1, which may be related to the effects of deep inhalation mitigating changes in FEV_1; however, concomitant changes in R_{rs} and A*X* suggest there is narrowing and/or closure of small airways [74, 75] not detected by spirometry. In summary, oscillometry is a useful tool to detect airway narrowing before spirometry during bronchial challenge testing, but the correlations and thresholds of response are variable, and further studies are needed to determine if oscillometry indices are more clinically relevant than spirometry.

Treatment responses in asthma

In addition to treatment with bronchodilators, differences in R_{rs} and X_{rs} in response to different inhaled corticosteroids (ICS) [76, 77], montelukast [78], ICS/long acting β_2-agonist (LABA) formulations [79], and ICS *versus* ICS/LABA [80] have been demonstrated. In general, R_{rs}, X_{rs} and A*X* are more sensitive than spirometry [81]. Recent work has shown that oscillometry and other parameters related to peripheral airway function can be correlated with an improvement in symptoms for patients with poorly controlled asthma receiving ICS/LABA therapy [82]. One study has attempted to determine whether oscillometry

could distinguish any benefit of small *versus* large particle size ICS therapy based on peripheral *versus* central airway obstruction, respectively; however, this study only looked at the differential treatment effect on symptoms, not oscillometry, and used an arbitrary oscillometric definition of peripheral airway function [83]. Oscillometric indices are also sensitive to improvements in asthma in response to mepolizumab therapy [84]. These findings suggest an important role of oscillometry in identifying and monitoring treatment responses in asthma, complementary to traditional spirometry.

Thus, in asthma, individual oscillometry studies have demonstrated physiological correlations of specific indices with symptoms, imaging, spirometry, changes in response to bronchodilators, bronchial challenges and treatment, and prediction of treatment response. What needs to follow are larger scale trials beyond proof of concept that demonstrate actual clinical utility in terms of improving patient care in asthma, as well as what constitutes a minimal clinically significant difference in oscillometry parameters.

Cystic fibrosis

A number of studies in children with cystic fibrosis (CF) reveal normal oscillometric indices [85–87], with only one study of preschool children with CF reporting abnormal values [88]. Associations between oscillometric indices and other clinical parameters in children with CF are variable [25, 86, 88–92]. There are limited data on the use of oscillometry in adults with CF; however, by one report, resistance and reactance are abnormal in adults with CF and correlate with other measures of lung function [93]. Therefore, the clinical utility of oscillometry in CF remains uncertain, particularly when other clinical tests have shown superior ability to detect early CF lung disease and successfully monitor improvement in lung function with intervention.

COPD

Oscillometry may play an important role in the early detection of the adverse effects of smoking before COPD is diagnosed [94]. Several studies have found a high prevalence of abnormal Z_{rs} in smokers with normal spirometry, mainly in R_{rs} and X_{rs} near 5 Hz [95–98], with up to 60% of smokers with normal spirometry (FEV_1/forced vital capacity (FVC)>0.70) having some abnormality on oscillometry. Smokers also have greater prevalence of significant BDR compared to nonsmokers [38]. The clinical significance of these findings still needs to be determined by pathologic correlations and prospective clinical studies to establish relevance and utility.

Patients with COPD have significantly higher R_{rs} and more negative X_{rs} values than healthy people [99], changes that are proportional to the degree of airway obstruction [100]. Empirical studies demonstrate that X_{rs} is related to the degree of gas trapping and hyperinflation in the lungs and reflects the amount of communicating lung volume [101]. X_{rs} and f_{res} relate better to FEV_1, and measures of hyperinflation, *i.e.* inspiratory capacity/TLC and residual volume/TLC ratios, than do resistance measurements [102, 103]. Magnetic resonance imaging-derived measurements of abnormal gas mixing correlate best with $R_{rs_{5-19}}$ and AX in COPD patients [104]. Recent work with parametric response mapping by CT has demonstrated strong correlations with oscillometry-derived $R_{rs_{5-19}}$ in patients with COPD [105], which is presumed to reflect small airways disease (but may also reflect large airway heterogeneity). A similar finding has been shown using endobronchial optical coherency tomography, which demonstrated that $R_{rs_{5-20}}$ correlated with small airways pathology in heavy smokers and patients with COPD [106]. Oscillometric parameters likely related to gas trapping (*i.e.* X_{rs}) in patients with COPD correlated with changes in exercise capacity following completion of pulmonary rehabilitation [107]. Oscillometry may also help in the categorisation of COPD severity [108].

As in asthma, oscillometry parameters are sensitive to treatment in patients with COPD. For example, X_{rs} near 5 Hz rather than R_{rs} appears to be more sensitive to bronchodilators [109–113] or ICS/LABA combination treatment [114], or recovery from exacerbations [102, 115–117]. The magnitude of the BDR depends on the disease stage. In the earlier stages of COPD, improvements in oscillometric parameters are greater compared to healthy subjects and are related mainly to an increased bronchodilation of the central airways, improvements in ventilation homogeneity based on the slope of the resistive component of Z_{rs}, and total mechanical load [118].

Examination of intrabreath oscillometry has been especially significant in COPD, where it has been used to demonstrate evidence of tidal expiratory flow limitation (EFL_T). Reactance and resistance are higher during expiration compared to inspiration in patients with COPD [119–121], reflecting dynamic airway compression and expiratory airflow limitation [122]. The underlying mechanisms of airway collapse during tidal breathing are uncertain. An empirically defined threshold of the difference between inspiratory and expiratory X_{rs} has been shown to be a sensitive and specific method for detecting EFL_T [123, 124]. The inspiratory–expiratory difference in X_{rs} and its variability over time is also associated with worse dyspnoea [125]. This index is also

associated with more rapid deterioration in exercise capacity over time and an increased likelihood of exacerbations irrespective of the degree of spirometric impairment [126, 127]. EFL_T during tidal breathing is an important determinant of dynamic hyperinflation and its identification using oscillometry during noninvasive ventilation allows determining the lowest positive end-expiratory pressure (PEEP) able to abolish it. Recent preliminary studies showed that oscillometry can be incorporated in home noninvasive ventilators for abolishing EFL_T by continuously tailoring PEEP to varying lung mechanics [128] leading to reduced hypercapnia and ineffective efforts in stable COPD during nocturnal noninvasive ventilation [129]. Currently, some major limitations to the use of intrabreath monitoring of oscillometry are the lack of normative data and standardisation of analysis and reporting of data.

Oscillometry is often thought to be a better reflection of breathing conditions of everyday life than spirometry, as it directly assesses mechanical impediment to airflow during normal breathing, rather than following deep inhalation; this arguably makes it more useful in COPD, where dyspnoea often occurs even at rest, or where severely obstructed patients can have difficulties with forced manoeuvres. It also makes it amenable to home telemonitoring in COPD, in which feasibility and potential clinical utility has been demonstrated [130] (see supplementary material). Furthermore, the deep inspiration required in spirometry has variable effects on airway calibre in COPD, which may affect clinical correlations [131, 132]. Oscillometry has also revealed greater variations in lung function over time [133, 134] and greater bronchodilator responses in COPD than expected from spirometry [38], again shedding light on disease pathogenesis that goes beyond fixed airway obstruction and reversibility in the larger airways.

In summary, oscillometry may aide in earlier detection of smoking-related effects on the lung and adds insight into the pathophysiology of COPD; however, we still need more data to assess how oscillometry relates to clinical phenotypes of COPD (*e.g.* predominance of emphysema *versus* bronchitis) and how it will affect clinical management of patients with COPD.

Bronchiolitis obliterans

Because of its sensitivity to small airway disease, oscillometry has been used to study patients with or at risk of bronchiolitis obliterans. In children, post-infectious bronchiolitis obliterans can be detected by greater changes in X_{rs} compared to spirometry [135]. In adult lung and bone marrow transplant recipients, bronchiolitis obliterans syndrome may be detected earlier by oscillometry than by conventional spirometry [136–138]. The lack of a need for deep inspiration with oscillometry is also beneficial in patients in the acute postoperative lung transplant period.

Obesity

Impedance measured by oscillometry has been well studied in obesity [139–145]. The effects of obesity are most apparent in X_{rs}, which suggests that there is an increase in heterogeneous airway narrowing and in airway closure in the lung periphery, although increased stiffness of the chest wall can also contribute [146]. By contrast, there are minimal changes in spirometry and typically no changes in FEV_1/FVC ratio in obesity, with the exception of very severe obesity (>40 $kg \cdot m^{-2}$) [147].

In obesity, R_{rs} is increased, possibly due to reduced operating lung volume [148–150]. However, this is not the whole reason for this increase [140, 144, 151] as pulmonary circulatory congestion and airway oedema occur in obesity [152, 153] and are correlated with the magnitude of abnormality in both R_{rs} and X_{rs} [143]. These changes in airway function make interpretation of impedance in obesity difficult when assessing a patient with potential coexisting airway disease. Obese individuals with clinically and physiologically confirmed asthma have a more negative X_{rs} than obese, non-asthmatic individuals, probably because of enhanced peripheral airway closure [142, 146]. Changes in R_{rs} and X_{rs} with obesity and following bariatric surgery are more pronounced in the supine position with oscillometry being more sensitive to weight loss compared with spirometry [142, 146, 154]. The responses to methacholine bronchial challenge in obese subjects are different compared to non-obese subjects, particularly with regard to bronchoprotection [155] and exaggerated decreases in X_{rs} [139, 141, 155]. These nuanced differences cannot be easily determined with spirometry. Therefore, obesity is associated with a greater response to bronchoconstriction in terms of changes in the respiratory system elastic properties, but the clinical and pathophysiologic significance of these observations is uncertain.

In children, obesity has been found to be associated with a pattern different from that of obese adults (reduced FEV_1/FVC with normal or even increased FEV_1 and FVC), called "airway dysanapsis" [156]. Oscillometry may help distinguish the effects of obesity or asthma on the cause of a low FEV_1/FVC in children due to dysanapsis or airway narrowing [157]. Increased $R_{rs_{5-20}}$ and AX were also found in a cross-sectional study on overweight and obese adolescents [158]. Further research is needed to better