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Review Article

The Role of Lung Function and the Importance to Measure Small Airways Modifications

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Abbrevations FOT (Forced Oscillation Technique); IOS (Impulse Oscillometry); SBNW (Single Breath Nitrogen Test)

Abstract

Normally in clinical practice the evaluation of lung pathophysiology follows a functional and mechanical evaluation primarily through spirometry and plethysmography. The Small Airways (SAW) are one of the most important targets for respiratory diseases and various studies underline their strict relations with chronic diseases like asthma or COPD, although it is nowadays recognized their role in a lot of other pathological entities. The evaluation of SAW is not always easy and often more than one functional test must be done. So, the possibility to known the "scenario" of available functional respiratory tests, both in clinical and research setting, represents a central point in the respiratory world. Moreover the correct interpretation of the lung function tests is necessary not only to better evaluate the actual clinical status of the respiratory disorders but also to allow the appropriate therapeutic choice. The aim of the current review is to direct the readers attention to the importance of lung function evaluation and its specific role both in clinical and research setting.

Introduction

In respiratory medicine one of the main points, other than clinical manifestations, is the lung pathophysiology. The lung is one of the more interesting organs that present a complex interaction between structures and function (anatomy and biophysics). Normally in clinical practice the evaluation of lung pathophysiology follow a functional and mechanic evaluation primarily through spirometry and plethysmography. The Small Airways (SAW) are one of the more important target for respiratory diseases and various studied underline their strict relations with chronic diseases like asthma or COPD, although it is nowadays recognized their role in a lot of other pathological entities [1]. SAW are defined as the peripheral airways having an internal diameter of less than 2 mm without cartilage [2]. The obstruction of the peripheral airways has proven to have little effect on the mechanical properties of the lung, though it has a guiding role in the ventilation distribution of the inhaled gases [3-5]. As because of the difficulty of reaching such a site, different and numerous techniques were developed in order to assess in vivo SAW physiopathological properties and to evaluate their changes in disease in a non-invasive manner, thus bringing light to the so called "silent zone" [1]. Next to the well-known body-plethismography and Forced Oscillation Technique (FOT), other methods, like the nitrogen washout test, were lately re-descovered and re-interpreted, while new ones, like the Impulse Oscillometry (IOS), have been developed, gaining more approval in the respiratory pathophysiological landscape (Table 1). Is already clear, that until now there is no test that presents a widely accepted cut-off value that can be used to measure and assess the severity of small airways alterations and also there isn't a test that represents the gold standard for clinical and experimental use. The objective of this review is to perform an overview of the actual major methods used to evaluate the SAW function and relative modifications in order to refresh the large instrumental options that pulmonologist have for their clinical and scientific use.

Static and dynamic lung volumes

It is largely known that isolated SAW alterations haven't measurable effect on the pressure-volume curve in experimental specimens [4] due to collateral alveolar ventilation [3] and that the peripheral airways have a marginal role in the total amount of pulmonary resistances [6], as it has been estimated that the obstruction of 75% of all SAW is required before an alterations can be identified by routine pulmonary functional tests [7].

Despite that, because of their physopathological characteristics, SAW represent the major site of airflow limitation [6] and of inhomogeneous ventilation distribution [3].

Table 1: Main tests to evaluate lung function.

Lung Function Test	Easy to use	Invasive	Level of clinical use
Spirometry	+++	-	+++
Plethysmography	+++	-	+++
FOT	+++	-	+
IOS	+++	-	+
SBNW Test	++	-	+
Esophageal balloon	+	+++	+

The + sign identifies the level of positive characteristics while – sign identify the level of negative characteristics. Three + represent the maximum level and one + the minimum, the same applies to -.

Our score is a priority score; created by the authors during the drafting of the paper, and related only to real life applicability of reported tests /methodic.

Among the 31 different forced expiratory variables that can be measured from the Maximal Expiratory Flow Volume maneuver, the Forced Expiratory Flow between 75% and 25% (FEF_{25-75}) of Vital Capacity (VC) and the forced expiratory flow at 50% of VC (FEF_{50}) are considered the most sensitive in detecting SAW abnormalities [8,9]. Their measurement reflects the most effort independent portion of the flow-volume curve [7], and a close agreement between the two parameters should be evidenced in the case of monotonous emptying of the lung with a single time constant [10]. As reported by Bar-Yishay et al., patients with peripheral obstruction haven't a linear relationship between flow and volume, thus implicating the presence of more than one time constant in order to describe the emptying of different zones of the lung [11]. The authors thus claim the independence of the FEF_{25-75} and FEF_{50} from the peripheral airway obstruction and the lack of correlation with severity disease, putting the two parameters almost at the same level and indicating the preference towards the FEF_{50} because of it's direct determination [11], while FEF_{25-75} appears to be more curve shape-dependent. FEF_{25-75} is in fact calculated considering the 75% and 25% points of the Forced Vital Capacity (FVC) on flow-volume curve, thus being directly dependent on FVC and presenting great variability in case of air trapping and bronchodilation [12]. The lower limit of normality for FEF_{25-75} is considered to be the 60% of predicted value [13]. FVC in turn results a poor indicator of air trapping and appears to be underestimated in case of Total Lung Capacity (TLC) increase for a given increase of Residual Volume (RV). Taking in account the considerations made, modifications from normality of FEF_{25-75} should be considered and interpreted with caution as a reflection of SAW impairment, both due to its intrinsic variability and dependence on other spirometricvolumes. Cohen J et colleagues observed a significant reduction of the FVC/SVC (slow vital capacity) ratio independently of FEV_1 (forced expiratory volume in 1 second) in patients with bronchiolitis obliterans that underwent lung transplantation suggesting the FVC/SVC as a parameter for detecting small airways obstruction [14]. A similar founding has been reported in subjects with eosinophilic versus non-eosinophilicsevere asthma [15].

The RV, obtained by body plethysmography through the modifications of mouth and airthight cabin pressure, appears to be elevated in case of premature airway closure and air trapping. It can be obtained through an easy-to-perform test, with a good reproducibility and low intra-patient variability [16]. Easy-to-perform has been referred to a real life and correlated to the possibility to have a good interaction between Doctor and Patients with a good result of the well done functional test. An elevation of RV/TLC ratio is considered the best measure of RV elevation and the first step of hyperinflation [12]. Stanescu in the past years described a new plethysmographic pattern characterized by a decrease in SVC and FEV_1, an increase in RV and RV/TLC and normal TLC and FEV_1/FVC [17]. This pattern has been proposed as an early detection of small airways disease. This alteration has been observed in the early stages of emphysema, elderly people and asymptomatic asthma [17]. Specific Airway Resistances (sRAW), also obtained by whole body-plethismography, appear not to be specifically related to SAW abnormalities [18].

The evaluation of static lung volumes as residual volume and total lung capacity permits only a quantitative characterization of hyperinflation and air trapping, without allowing a aren't able to detect minor changes and defects in distal airways conductance and ventilation pattern, permitting only a general volumetric characterization of air trapping [12]. Recently has been published that also in clinical practice, with all the well-known limitations, the sRAW utilization could be an interesting methods to evaluate the bronchodilatory effect in COPD subjects [19].

Forced Oscillation Technique (FOT) and Impulse Oscillometry (IOS)

The Forced Oscillation Technique (FOT) and the Impulse Oscillometry (IOS) are two non-invasive versatile tests that imply little patient collaboration and represent one of most important current research lines in lung physiopathology. FOT, firstly studied by DuBois et al. in 1956 [20], measures the impedance of the respiratory system to forced pressure oscillations produced by a loudspeaker. The impedance includes in itself two parameters: Resistance (Rrs) and Reactance (Xrs). Rrs is related to airway caliber, Xrs depends on the distributed inertance and stiffness of the respiratory system [21]. To derive its measures FOT uses the super-imposition of pressure fluctuations on the airway during subject's tidal breathing [22]. Goldman et al. confirmed the hypothesis that Rrs at frequencies higher that than resonance reflects large airway mechanical properties, while that at frequencies below resonance reflects the added influence of SAW. So it appears simple to study peripheral airway effects by comparing low and high frequency resistance [23]. Low frequency reactance appeared to be a useful and sensitive index of peripheral airway function; in fact it has been seen to increase and decrease in according to clinical symptoms in asthmatic patients that used respectively less or more inhaled corticosteroids [23]. The functioning principle of IOS is similar to FOT, as it derives directly from it and delivers a regular square wave of pressure 5 times per second emitting a continuous spectrum of frequencies that allows the determination of the mechanical behavior of respiratory system [12,23,24]. The advantages of IOS include good time resolution and continuous resolution in the frequency domain because the calculation is based on the Fourier integral rather than a Fourier series [25,26]. The so-called frequency dependence, an increase of Rrs at lower frequencies (<10-15 Hz), has been demonstrated in various obstructive lung disease like asthma, as related to obstruction at SAW level [23,27,28]. The decrease of Xrs at 5 Hz during expiration, found during FOT evaluation of flow limitation in COPD [29], as described by Claverley and Koulouris, has allowedto differentiate between

asthma and COPD [30]. An increase of Rrs at low frequencies has also been found to be strictly related to FEF_{25-75} in young asthmatics [31].

Takeda et al. reported that clinical symptoms and asthma control in asthmatics were strongly related with the parameters obtained by IOS [32]. Peripheral and proximal airway functions independently appear to contribute to health status, dyspnoea and disease control [32]. IOS results to be also a sensitive screening tool for the early detection of bronchial obstruction [33].

Oppenheimer et al., comparing the IOS technique with the dynamic compliance, observed that IOS can provide a non-invasive tool for assessment of distal airway function when spirometry is normal, which can be applied to various clinical settings including early diagnosis of COPD, asthma in clinical remission and occupational/ environmental irritant exposure [34].

There is no question that FOT and IOS keep the advantage on spirometry because of the ease with which these test can be performed , required little or no cooperation at all from the patients. This latter characteristic makes them feasible in pediatric environment too, were it has been demonstrated that with some technical refinements, the FOT measurement can reach the repeatability comparable to that of spirometry [21]. Moreover the amplitude of the oscillation do not alter the mechanical properties of the respiratory system, thus making this technique ideal in monitoring bronchoactive responses. The main weakness remains the inability to distinguish between obstructive and restrictive pattern [35].

Multiple and single breath nitrogen washout test

As deducted from previous studies, the SAW obstruction doesn't play a great role in lung mechanics modifications, while, on the other side, it effects the distribution of inspired gases if there is collateral ventilation like in the human respiratory system [3,36]. In order to assess the presence of distal ventilation inhomogeneity, in the 60's the Single Breath Nitrogen Washout Test (SBNW) was rediscovered and developed. It was firstly described by Fowler in 1949 [37], but largely ignored until Dolfuss et al. in '67 used it to measure the Closing Volume (CV) [38]. The record originated is made by a first steep increase of N_2 due to anatomical dead space of upper airways, than a plateau is reached reflecting the emptying of conductive and medium size airways (phase III) [38]. A final steep increase in N_2 concentration (phase IV) that normally occurs at the 25% of VC represents the CV, the lung volume that reflects the complete occlusion of the gravity dependent small airways. The CV is usually present near RV, being normal at about the 25% of VC. Although it has been seen a significant variation with age [39]. The SBNW represents a simple and sensible technique [40] to detect early closure of peripheral airwaysand while previously affected by poor reproducibility and predictivity [41], it is nowadays used in a lot of studies. The variability of CV can be ascribed to the incomplete filling or emptying of the lungs, the phase IV being influenced by expiratory flow and phase III by inspiratory flow [42,43]. In the last years the SBNW was used as a marker of airways dysfunction related to asthma severity [44] and to poor asthma control [45]. In the latter case Bourdin A and his colleagues found a relation between poor asthma control and an increase in CV and phase III slope [45]. Moreover J.C. In't Veen et al. reported an increase of CV in severe asthmatics with frequent exacerbations and a relation between CV and RV/TLC ratio increase when compared to severe asthmatics patients with well-controlled disease [46]. When the RV is summed to CV, Closing Capacity (CC) is obtained. It is always referred as the percentage of TLC (CC/TLC%). In COPD subjects the increase of CC and phase III slope correlates with airflow limitation [47]. However Timmins et al. proved that in COPD patients, the modest changes in SAW mechanics that occur after an ICS/LABA (Inhaled Corticosteroids/ Long Acting Beta2 Agonists) combination therapy were detected by FOT technique and not by SBWT [48]. Moreover CC/TLC appears to be less reproducible when compared to FEV_1 [49].

Recently, it was described a new way of assessing small airways alterations in a non-invasive way using the principles of Cosio et al. [7,50]: The Multiple Breath Nitrogen Wash-Out Test (MBWT). With respect to SBWT, MBWT has several major advantages as it is hardly affected by gravity [51], and it is not affected by airway closure below functional residual capacity, that is known to affect SBWT phase III [52]. Moreover it is capable of distinguishing the origin of ventilation heterogeneity, and so the implication of small airways. In fact in this case two different variables are detected, the Scond (index of conductive ventilation heterogeneity) and Sacin (index of acinar ventilation heterogeneity) [53,54]. It is important although to consider that age can play a role in the variability of detection of SAW abnormalities in lung diseases [55]. Both S_{acin} and S_{cond} have been observed to increase in smokers and COPD patients [56], while a reversibility of S_{cond} in relation to small airways was seen after smoking cessation in smokers without COPD [57]. In asthma, MBWT has been employed in airway challenging [58], and it showed a good relation in detecting SAW abnormalities independently of airway inflammation measured by Fractional Exhaled Nitric Oxide (FeNO) [59].

Due to the lack of the technique diffusion, nowadays is missing an international consensus standard of interpretation of SBWT and MBWT. However these non-invasive tests are capable of offering a reliable picture of small airways conditions both in asthma and COPD. The ability of interpretation of their numerous signals, next to other recent non-invasive techniques, has to bring novel insights in small airways pathophysiology.

Static/dynamic lung compliance and esophageal balloon

The esophageal balloon is perhaps at the same time the most invasive and most intriguing respiratory physiopathological technique of lung mechanics assessment. It represents still nowadays the gold standard for the measurement of transpulmonary pressure and permits the evaluation, when coupled with a pneumotacograph (flow and volume registration), of dynamic and static compliance. This test has been used principally for scientific scope and in intensive care unit as clinical test too. The pulmonary compliance is the result of the ratio between lung volume change and change in transpulmonary pressure ($C=\Delta V/\Delta P$) [60]. The esophageal balloon consists of a catheter linked to a pressure sampling equipment on one side, and the other extremity is represented by a soft balloon of 5-6 cm of length with a pressure transducer inside. The Pressure-Volume curve (PV curve) that is obtained is called "semi-static" because the test, when performed in conscious subjects, implies a minimal quote of muscle activity. The proper static PV curve is nowadays obtained only in emergency rooms and in invasively ventilated patients. It is not therefore a test that can be used in the everyday clinical practice.

It is known that the ratio between dynamic and static compliance decreases even in normal subjects when the breathing frequency exceeds 60/min. When small airway disease is present, both the dynamic compliance alone and the ratio are heavily reduced. This event is due to different time constants that characterize the uneven deflation of different lung zones, each with different and increased resistances. This ventilation heterogeneity increases more when breathing pattern changes [37,61,62]. A reduction in dynamic compliance is seen even when other lung functional parameters are in normal range [12]. The retractive pulmonary forces have been always studied by measuring the grade of the PV curve during tidal breathing. The S shape of the PV curve is due to the mechanical phenomena occurring at volumes close to RV and TLC. At low lung volumes this circumstance is thought to be related either to gas trapping secondary to the collapse of small airways [63] or to the balloon deformation by the mediastinal mass [64]. A closure of peripheral airways must be necessarily reflected by a modification in PV curve so the morphology of the curve at low lung volumes will not be influenced by artifacts but also by a closure of distal airways. Glaiser et al. confirmed that hypothesis in 1973 experimenting on animal models. Interestingly, the point at which the PV curve was leaving from the ideal exponential shape corresponded to the closing volume assessed with the ^{133}Xenon washout [65].

Conclusion

The lung function evaluations represent also today the cornerstone in respiratory diseases management. The basal spirometry must be performed in all patients with a smoking history and in front of subjects with a chronic obstruction disease plethysmography represent a mandatory test. Moreover, in presence of complex clinical cases, some other functional evaluations could be used in order to better understand lung function and pathological respiratory modifications.

References

1. Burgel PR, Bergeron A, de Blic J, Bonniaud P, Bourdin A. Small airways diseases, excluding asthma and COPD: an overview. Eur Respir Rev. 2013; 22: 131-147.
2. Ranga V, Kleinerman J. Structure and function of small airways in health and disease. Arch Pathol Lab Med. 1978; 102: 609-617.
3. Macklem PT. The physiology of small airways. Am J Respir Crit Care Med. 1998; 157: 181-183.
4. Brown R, Woolcock AJ, Vincent NJ, Macklem PT. Physiological effects of experimental airway obstruction with beads. J Appl Physiol. 1969; 27: 328-335.
5. Hogg W, Brunton J, Kryger M, Brown R, Macklem P. Gas diffusion across collateral channels. J Appl Physiol. 1972; 33: 568-575.
6. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet. 2004; 364: 709-721.
7. Cosio M, Ghezzo H, Hogg JC, Corbin R, Loveland M. The relations between structural changes in small airways and pulmonary-function tests. N Engl J Med. 1978; 298: 1277-1281.
8. McFadden ER, Linden DA. A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small airway disease. Am J Med. 1972; 52: 725-737.
9. Lebecque P, Kiakulanda P, Coates AL. Spirometry in the asthmatic child: is FEF25-75 a more sensitive test than FEV1/FVC? Pediatr Pulmonol. 1993; 16: 19-22.
10. Douglas RB. The mid maximum expiratory flow. Bull Eur Physiopathol Respir. 1980; 16: 283P-285P.
11. Bar-Yishay E, Amirav I, Goldberg S. Comparison of maximal midexpiratory flow rate and forced expiratory flow at 50% of vital capacity in children. Chest. 2003; 123: 731-735.
12. Konstantinos Katsoulis K, Kostikas K, Kontakiotis T. Techniques for assessing small airways function: Possible applications in asthma and COPD. Respir Med. 2013.
13. Burgel PR. The role of small airways in obstructive airway diseases. Eur Respir Rev. 2011; 20: 23-33.
14. Cohen J, Postma DS, Vink-Klooster K, van der Bij W, Verschuuren E. FVC to slow inspiratory vital capacity ratio: a potential marker for small airways obstruction. Chest. 2007; 132: 1198-1203.
15. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med 1999; 160: 1001-1008.
16. Contoli M, Bousquet J, Fabbri LM, Magnussen H, Rabe KF. The small airways and distal lung compartment in asthma and COPD: a time for reappraisal. Allergy. 2010; 65: 141-151.
17. Stänescu D. Small airways obstruction syndrome. Chest. 1999; 116: 231-233.
18. Burgel PR, Bourdin A, Chanez P, Chabot F, Chaouat A. Update on the roles of distal airways in COPD. Eur Respir Rev. 2011; 20: 7-22.
19. Santus P, Radovanovic D, Henchi S, Di Marco F, Centanni S. Assessment of acute bronchodilator effects from specific airway resistance changes in stable COPD patients. Respir Physiol Neurobiol. 2014; 197: 36-45.
20. Dubois AB, Brody Aw, Lewis Dh, Burgess Bf. Oscillation mechanics of lungs and chest in man. J Appl Physiol. 1956; 8: 587-594.
21. Robinson PD, Turner M, Brown NJ, Salome C, Berend N. Procedures to improve the repeatability of forced oscillation measurements in school-aged children. Respir Physiol Neurobiol. 2011; 177: 199-206.
22. Scichilone N, Contoli M, Paleari D, Pirina P, Rossi A. Assessing and accessing the small airways; implications for asthma management. Pulm Pharmacol Ther. 2013; 26: 172-179.
23. Goldman MD, Saadeh C, Ross D. Clinical applications of forced oscillation to assess peripheral airway function. Respir Physiol Neurobiol. 2005; 148: 179-194.
24. Smith HJ, Reinhold P, Goldman MD. Forced oscillation technique and impulse oscillometry [Chapter 5]. R. Gosselink, H Stam, Editors. In: Lung function testing: European respiratory society monograph. European Respiratory Society, Sheffield, UK. 2005; 31.
25. Fortney LR. Principles of Electronics: Analog and Digital, Harcourt Brace Jovanovich, San Diego 1987.
26. Tipler PA. Physics for Scientists and Engineers. 4th edn. WH Freeman/Worth, New York. 1999; 1.
27. Cavalcanti JV, Lopes AJ, Jansen JM, Melo PL. Detection of changes in respiratory mechanics due to increasing degrees of airway obstruction in asthma by the forced oscillation technique. Respir Med. 2006; 100: 2207-2219.
28. Grimby G, Takishima T, Graham W, Macklem P, Mead J. Frequency dependence of flow resistance in patients with obstructive lung disease. J Clin Invest. 1968; 47: 1455-1465.
29. Paredi P, Goldman M, Alamen A, Ausin P, Usmani OS. Comparison of inspiratory and expiratory resistance and reactance in patients with asthma and chronic obstructive pulmonary disease. Thorax. 2010; 65: 263-267.
30. Calverley PM, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. Eur Respir J. 2005; 25: 186-199.
31. Goldman MD, Carter R, Klein R, Fritz G, Carter B. Within- and between-day variability of respiratory impedance, using impulse oscillometry in adolescent asthmatics. Pediatr Pulmonol. 2002; 34: 312-319.

32. Takeda T, Oga T, Niimi A, Matsumoto H, Ito I. Relationship between small airway function and health status, dyspnea and disease control in asthma. Respiration. 2010; 80: 120-126.

33. Winkler J, Hagert-Winkler A, Wirtz H, Schauer J, Kahn T. [Impulse oscillometry in the diagnosis of the severity of obstructive pulmonary disease]. Pneumologie. 2009; 63: 266-275.

34. Oppenheimer BW, Goldring RM, Berger KI. Distal airway function assessed by oscillometry at varying respiratory rate: comparison with dynamic compliance. COPD. 2009; 6: 162-170.

35. Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, et al. ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003; 22: 1026-1041.

36. Hogg W, Brunton J, Kryger M, Brown R, Macklem P. Gas diffusion across collateral channels. J Appl Physiol. 1972; 33: 568-575.

37. Fowler WS. Lung function studies; uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. J Appl Physiol. 1949; 2: 283-299.

38. Dollfuss RE, Milic-Emili J, Bates DV. Regional ventilation of the lung, studied with boluses of ^{133}Xenon.Respir Physiol. 1967; 2: 234-246.

39. Buist AS, Ghezzo H, Anthonisen NR, Cherniack RM, Ducic S. Relationship between the single-breath N test and age, sex, and smoking habit in three North American cities. Am Rev Respir Dis. 1979; 120: 305-318.

40. Drummond GB, Milic-Emili J. Forty years of closing volume. Br J Anaesth. 2007; 99: 772-774.

41. Buist AS. Current status of small airways disease. Chest. 1984; 86: 100-105.

42. McFadden ER, holmes B, Kiker R. Variability of closing volume measurements in normal man. Am Rev Respir Dis. 1975; 111: 135-140.

43. Make B, Lapp NL. Factors influencing the measurement of closing volume. Am Rev Respir Dis. 1975; 111: 749-754.

44. Van Veen IH, Sterk PJ, Schot R, Gauw SA, Rabe KF. Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma. Eur Respir J. 2006; 27: 951-956.

45. Bourdin A, Paganin F, Préfaut C, Kieseler D, Godard P. Nitrogen washout slope in poorly controlled asthma. Allergy. 2006; 61: 85-89.

46. In't Veen JC, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. Am J Respir Crit Care Med. 2000; 161: 1902-1906.

47. Gennimata SA, Palamidas A, Karakontaki F, Kosmas EN, Koutsoukou A. Pathophysiology of evolution of small airways disease to overt COPD. COPD. 2010; 7: 269-275.

48. Timmins SC, Diba C, Schoeffel RE, Salome CM, King GG. Changes in oscillatory impedance and nitrogen washout with combination fluticasone/salmeterol therapy in COPD. Respir Med. 2014; 108: 344-350.

49. Vollmer WM, McCamant LE, Johnson LR, Buist AS. Long-term reproducibility of tests of small airways function. Comparisons with spirometry. Chest. 1990; 98: 303-307.

50. Verbanck S, Schuermans D, Van Muylem A, Paiva M, Noppen M. Ventilation distribution during histamine provocation. J Appl Physiol. 1997; 83: 1907-1916.

51. Prisk GK, Guy HJ, Elliott AR, Paiva M, West JB. Ventilatory inhomogeneity determined from multiple-breath washouts during sustained microgravity on Spacelab SLS-1. J Appl Physiol 1995; 78: 597-607.

52. Verbanck S, Schuermans D, Meysman M, Paiva M, Vincken W. Noninvasive assessment of airway alterations in smokers: the small airways revisited. Am J Respir Crit Care Med. 2004; 170: 414-419.

53. Dutrieue B, Vanholsbeeck F, Verbanck S, Paiva M. A human acinar structure for simulation of realistic alveolar plateau slopes. J Appl Physiol (1985). 2000; 89: 1859-1867.

54. Verbanck S, Schuermans D, Van Muylem A, Melot C, Noppen M. Conductive and acinar lung-zone contributions to ventilation inhomogeneity in COPD. Am J Respir Crit Care Med. 1998; 157: 1573-1577.

55. Verbanck S, Thompson BR, Schuermans D, Kalsi H, Biddiscombe M. Ventilation heterogeneity in the acinar and conductive zones of the normal ageing lung. Thorax. 2012; 67: 789-795.

56. Verbanck S, Schuermans D, Meysman M, Paiva M, Vincken W. Noninvasive assessment of airway alterations in smokers: the small airways revisited. Am J Respir Crit Care Med. 2004; 170: 414-419.

57. Verbanck S, Schuermans D, Paiva M, Meysman M, Vincken W. Small airway function improvement after smoking cessation in smokers without airway obstruction. Am J Respir Crit Care Med. 2006; 174: 853-857.

58. Verbanck S, Schuermans D, Van Muylem A, Paiva M, Noppen M. Ventilation distribution during histamine provocation. J Appl Physiol (1985). 1997; 83: 1907-1916.

59. Lehtimaki L, Kankaanranta H, Saarelainen S, Hahtola P, Jarvenpaa R. Extended exhaled NO measurement differentiates between alveolar and bronchial inflammation. Am J Respir Crit Care Med. 2001; 163: 1557-1561.

60. Salazar E, knowles JH. An analysis of pressure-volume characteristics of the lungs. J Appl Physiol. 1964; 19: 97-104.

61. Ingram RH, Schilder DP. Association of a decrease in dynamic compliance with a change in gas distribution. J Appl Physiol. 1967; 23: 911-916.

62. Woolcock AJ, Vincent NJ, Macklem PT. Frequency dependence of compliance as a test for obstruction in the small airways. J Clin Invest. 1969; 48: 1097-1106.

63. Butler J, White HC, Arnott WM. The pulmonary compliance in normal subjects. Clin Sci (Lond). 1957; 16: 709-729.

64. Agostoni E, Rahn H. Abdominal and thoracic pressures at different lung volumes. J Appl Physiol. 1960; 15: 1087-1092.

65. Glaister DH, Schroter RC, Sudlow MF, Milic-Emili J. Transpulmonary pressure gradient and ventilation distribution in excised lungs. Respir Physiol. 1973; 17: 365-385.