Eur Respir Rev 2011; 20: 121, 147–155
DOI: 10.1183/09059180.00001911

REVIEW

Physiological techniques for detecting expiratory flow limitation during tidal breathing

N.G. Koulouris and G. Hardavella

ABSTRACT: Patients with severe chronic obstructive pulmonary disease (COPD) often exhale along the same flow–volume curve during quiet breathing as they do during the forced expiratory vital capacity manoeuvre, and this has been taken as an indicator of expiratory flow limitation at rest (EFLT). Therefore, EFLT, namely attainment of maximal expiratory flow during tidal expiration, occurs when an increase in transpulmonary pressure causes no increase in expiratory flow. EFLT leads to small airway injury and promotes dynamic pulmonary hyperinflation, with concurrent dyspnoea and exercise limitation. In fact, EFLT occurs commonly in COPD patients (mainly in Global Initiative for Chronic Obstructive Lung Disease III and IV stage), in whom the latter symptoms are common, but is not exclusive to COPD, since it can also be detected in other pulmonary and nonpulmonary diseases like asthma, acute respiratory distress syndrome, heart failure and obesity, *etc.* The existing up to date physiological techniques of assessing EFLT are reviewed in the present work. Among the currently available techniques, the negative expiratory pressure has been validated in a wide variety of settings and disorders. Consequently, it should be regarded as a simple, noninvasive, practical and accurate new technique.

KEYWORDS: Dyspnoea, expiratory flow limitation, hyperinflation, reduced exercise tolerance, small airway injury

Some experts use the term ''chronic airflow limitation'' as a synonym for chronic obstructive pulmonary disease (COPD), to indicate the reduction in maximum expiratory flow that occurs in this disease (and indeed in other pulmonary diseases). Patients with severe COPD and other lung diseases often exhale along the same flow–volume curve during quiet breathing as they do during the forced expiratory vital capacity manoeuvre, and this has been taken as an indicator of flow limitation at rest. Consequently, the term ''tidal expiratory flow limitation'' (EFLT) is used to indicate that maximal expiratory flow is achieved during tidal breathing at rest or during exercise. This is characteristic of intrathoracic flow obstruction. The former term does not imply that EFLT actually occurs during tidal breathing [1]. The location of expiratory flow limitation is considered to be in the central airways (fourth to seventh generation) and move to the periphery during forced expiratory manoeuvres. It is located beyond the seventh (*i.e.* from the eighth onwards) generation during tidal breathing [2–5].

EFLT plays a central role according to a recent hypothesis on the transition from small airways disease to overt COPD in smokers [6–9]. EFLT implies inhomogeneity of ventilation distribution, with concurrent impairment of gas exchange and unevenly distributed stress and strain within the lung, which is amplified by tissue interdependence [7, 8] and may lead to small airway injury [6–9]. Initially, the latter is histologically characterised by denuded epithelium, rupture of alveolar airway attachments, and increased number of polymorphonuclear leukocytes [6–8]. Studies in which heliox (80% He/20% O_2) was administered in COPD and chronic heart failure patients also provided corroborative evidence that EFLT was located in the peripheral airways [2–5]. EFLT promotes dynamic pulmonary hyperinflation and intrinsic positive end-expiratory pressure (PEEPi) with concurrent dyspnoea and exercise limitation [9]. In fact, EFLT occurs commonly in Global Initiative for Chronic Obstructive Lung Disease stage III and IV patients, causing dynamic hyperinflation and severe dyspnoea [10]. It should

AFFILIATIONS
Respiratory Function Laboratory, 1st Dept of Respiratory Medicine, National and Kapodistrian University of Athens Medical School, ''Sotiria'' Hospital, Athens, Greece.

CORRESPONDENCE
N.G. Koulouris
Respiratory Function Laboratory
1st Dept of Respiratory Medicine
National University of Athens
Sotiria Hospital
152 Mesogeion Ave
Athens GR-11527
Greece
E-mail: koulnik@med.uoa.gr

Received:
Feb 14 2011
Accepted after revision:
May 11 2011

PROVENANCE
Submitted article, peer reviewed.

European Respiratory Review
Print ISSN 0905-9180
Online ISSN 1600-0617

be noted that the important role of expiratory flow limitation is not confined to COPD patients studied in a variety of clinical settings (during mechanical ventilation and exercise, correlation with dyspnoea, orthopnoea, and other lung function indexes, before and after bronchodilatation, and in various postures), but it is of significance for other respiratory and nonrespiratory diseases, such as asthma (stable asthma, during methacholine bronchoconstriction and during exercise), cystic fibrosis and bronchiectasis, restrictive lung disease, obesity, mechanically ventilated patients with acute respiratory failure and acute respiratory distress syndrome (ARDS), left heart failure, after single lung transplantation, euthyroid goiter, and for the assessment of bronchial hyperreactivity.

CLINICAL SIGNIFICANCE OF EXPIRATORY FLOW LIMITATION

The important role of EFLT in chronic dyspnoea and exercise impairment for a surprisingly wide range of clinical circumstances was highlighted by the techniques used to detect it, particularly by the use of the negative expiratory pressure (NEP) technique. EFLT measured with the NEP technique is a much better predictor of chronic dyspnoea than forced expiratory volume in 1 s (FEV_1), and FEV_1 is not a specific predictor of EFLT in COPD patients. These findings suggest that EFLT measured by the NEP technique may be more useful in the evaluation of dyspnoea in COPD patients than spirometric measurements [11].

The improvement of expiratory flow limitation after bronchodilator administration [12], which is mainly limited to patients who have expiratory flow limitation at rest and, therefore, usually exhibit a reduction of baseline inspiratory capacity, entails reduction in dyspnoea both at rest and during light exercise [13]. The fact that after bronchodilator administration there is a significant reduction of dynamic hyperinflation only in patients with expiratory flow limitation at rest further supports the usefulness of stratifying COPD patients in subgroups with and without expiratory flow limitation, in order to predict an improvement in dynamic hyperinflation [12]. COPD patients with expiratory flow limitation may experience less breathlessness after a bronchodilator, at least during light exercise, than those without expiratory flow limitation. This beneficial effect, which is closely related to an increase in inspiratory capacity, occurs even in the absence of a significant improvement of FEV_1 [13]. Though, in the past, bronchodilator testing focused on changes of FEV_1, the scrutiny of changes in inspiratory capacity in non-EFLT and EFLT COPD patients should provide useful information. In contrast, the detection of EFLT did not predict the changes in end-expiratory lung volume (EELV) or dyspnoea occurring after bronchodilation [14].

DIAZ *et al.* [15] found that inspiratory capacity was the only spirometric parameter in which there was almost no overlap between non-EFLT and EFLT COPD patients. In a group of 52 COPD patients, almost all the non-EFLT patients had normal inspiratory capacity, while all the EFLT patients had inspiratory capacity $<80\%$ predicted. Linear regression analysis performed separately for these EFLT and non-EFLT patients showed that in the EFLT patients the sole predictor of exercise capacity was inspiratory capacity (% pred), while in the non-EFLT the ratio FEV_1/forced vital capacity (FVC) (% pred) was the sole predictor. DIAZ *et al.* [16] also reported that in EFLT COPD patients the maximal tidal volume, and hence maximal oxygen consumption, were closely related to the reduced inspiratory capacity. The EFLT patients also exhibited a significant increase in arterial carbon dioxide tension and a decrease in arterial oxygen tension during peak exercise. O'DONNELL *et al.* [17] extended the findings of DIAZ and coworkers [15, 16], reporting that since the pathophysiological hallmark of COPD is expiratory flow limitation (occurring during exercise and, in advanced disease, even at rest), the latter promoted dynamic hyperinflation, which was correlated best with resting inspiratory capacity. Dynamic hyperinflation curtailed tidal volume response to exercise. The inability to expand tidal volume in response to increasing ventilatory demand contributed to exercise intolerance in COPD.

The main finding of these studies was that detection of EFLT plays an important role in identifying the factors that limit exercise tolerance, because resting expiratory flow limitation clearly separates two populations of patients with significant differences in exercise tolerance. More importantly, their detection provides useful information about the mechanisms limiting exercise tolerance. The detection of expiratory flow limitation during exercise should also be carried out using the NEP technique, as the conventional method for detecting flow limitation based on comparison of tidal with maximal flow–volume curves is not reliable [18]. In the presence of EFLT, dynamic hyperinflation appears to be the main determinant of exercise performance and the magnitude of resting inspiratory capacity, a well-recognised marker of dynamic hyperinflation, the best clinical predictor [15, 18].

Expiratory flow limitation may be absent at rest but can be developed and hence detected during any exercise level by the use of NEP. That explains the fact that COPD patients, who are not hyperinflated at rest, develop dynamic hyperinflation during exercise [18]. It should be noted here that there are instances when dynamic hyperinflation (reflected by a reduced inspiratory capacity) can occur in the absence of EFLT [19, 20], and the presence of EFLT may not necessarily result in dynamic hyperinflation if the available expiratory flow is sufficient to sustain resting ventilation without the need to increase EELV. This is reflected by the fact there are patients with EFLT and normal inspiratory capacity. Thus, measurement of inspiratory capacity and detection of expiratory flow limitation are complementary ways for assessing bronchodilator and exercise responsiveness in COPD patients.

It was found that almost all COPD patients who require mechanical ventilation are flow limited over the entire range of tidal expiration and that the supine posture promotes flow limitation [21–26]. Another study has shown that most patients with acute respiratory failure of pulmonary origin presented with EFLT while the ones with acute respiratory failure of extrapulmonary origin did not [24]. It was also found that most ARDS patients exhibit EFLT probably associated with small airways closure and a concomitant PEEPi [21]. The presence of EFLT, which implies concurrent cyclic dynamic compression and re-expansion of the airways, increases the risk of low lung volume injury. EFLT and PEEPi are also common in supine morbidly obese sedated–paralysed subjects after abdominal surgery [26]. This implies that the therapeutic administration

of external positive end-expiratory pressure to such patients must be monitored with concurrent assessment of expiratory flow limitation and PEEPi. Accordingly, it seems prudent to also apply external positive end-expiratory pressure in order to avoid peripheral airway closure and expiratory flow limitation. If there is no flow limitation, administration of external positive end-expiratory pressure should result in increased EELV without reduction of PEEPi and related work of breathing. Thus, assessment of expiratory flow limitation and PEEPi provide complementary information [23]. Therefore, the assessment of expiratory flow limitation in mechanically ventilated patients is a potentially useful bedside approach to provide information concerning respiratory mechanics.

Despite these potentially adverse consequences of expiratory flow limitation, its prevalence has not been extensively studied until recently, probably due to the lack of simple and non-invasive techniques. The scope of this work was to review the existing physiological techniques of assessing EFLT.

OESOPHAGEAL BALLOON TECHNIQUES

Fry method

The definition of expiratory flow limitation implies that in this condition a further increase in transpulmonary pressure will cause no further increase in expiratory flow [27]. Therefore, direct assessment of expiratory flow limitation requires determination of isovolume relationships between flow and transpulmonary pressure. In the 1950s, FRY *et al.* [28] were the first to develop such curves. The explanation of an isovolumic pressure flow curve lies in understanding its construction. Flow, volume and oesophageal pressure (P_{oes}) are measured simultaneously during the performance of repeated expiratory vital capacity efforts by a subject seated in a volume body plethysmograph, in which gas compression artefact is corrected. The subject is instructed to exhale with varying amounts of effort that are reflected by changes in P_{oes}. From a series of such efforts (~30) it is possible to plot flow against P_{oes} at any given lung volume [27]. The flow reaches a plateau at a low positive pleural pressure and once maximum flow for that volume is reached it remains constant, despite increasing P_{oes} by making expiratory efforts of increasing intensity.

Mead–Whittenberger method

The Mead–Whittenberger method directly relates alveolar pressure to flow [29]. Mead–Whittenberger graphs can be obtained by plotting the flow measured at the airway opening *versus* the resistive pressure drop during a single breath. In such a way the phenomenon of flow limitation is documented.

These techniques are technically complex and time consuming. Furthermore, these techniques are invasive because they require the insertion of an oesophageal balloon [28, 29].

CONVENTIONAL (HYATT'S) METHOD

Until recently, the ''conventional'' method used to detect expiratory flow limitation during tidal breathing was the one proposed by HYATT [30] in 1961. It involves superimposing a flow–volume loop of a tidal breath within a maximum flow–volume curve. This analysis and the ''concept of expiratory flow limitation'' have been the kernel for understanding respiratory dynamics. Flow limitation is not present when the patient breathes tidally below the maximal expiratory flow–volume (MEFV) curve. According to this technique, normal subjects do not reach flow limitation even at maximum exercise [1, 31]. In contrast, flow limitation is present when a patient breathes tidally along or higher than the MEFV curve. Patients with severe COPD may exhibit flow limitation even at rest, as reflected by the fact that they breathe tidally along or above their maximal flow–volume curve [1, 27–31]. However, the conventional method to detect flow limitation based on comparison of maximal to tidal expiratory flow–volume curves suffers from several methodological deficiencies. These include the following.

1) Thoracic gas compression artefacts. Volume should be measured with a body-box, instead of using, as is common practice, a pneumotachograph or a spirometer in order to minimise such errors [32]. Consequently, in practice, flow limitation can be assessed only in seated subjects at rest.

2) Incorrect alignment of tidal and maximal expiratory flow–volume curves. Such alignment is usually made considering the total lung capacity (TLC) as a fixed reference point. This assumption may not always be valid [33, 34].

3) Effect of previous volume and time history. Comparison of tidal and maximal flow–volume curves is incorrect, since the previous volume and time history of a spontaneous tidal breath is necessarily different from that of an FVC manoeuvre. Therefore, it is axiomatic that comparison of tidal with maximal flow–volume curves is problematic. In fact, there is not a single maximal flow–volume curve but rather a family of different curves, which depend on the time course of the inspiration preceding the FVC manoeuvre [35–37].

4) Respiratory mechanics and time constant inequalities are different during the tidal and maximal expiratory efforts, again making comparisons of the two flow–volume curves problematic [38–40].

5) Exercise may result in bronchodilation or bronchoconstriction and other changes of lung mechanics, which may also affect correct comparisons of the two flow–volume curves [41].

6) Patient cooperation. Another important limitation of the conventional method is that it requires the cooperation of the patient. This is not always feasible [33, 34].

In fact, it has been clearly demonstrated in several studies [12, 18, 42, 43] comparing the NEP with the conventional technique that the latter is not accurate. As a result, the use of the conventional method is no longer recommended, because from the above theoretical and practical considerations, and from experimental data, it appears that the detection of expiratory flow limitation based on comparison of tidal and maximal flow–volume curves is not valid, even when a body-box is used.

NEP TECHNIQUE

In order to overcome these technical and conceptual difficulties, the NEP technique has been introduced [11, 18, 33, 42]. The NEP technique was first applied and validated in mechanically ventilated intensive care unit (ICU) patients by concomitant determination of isovolume flow–pressure relationships [23, 44]. This method does not require performance of FVC manoeuvres, collaboration on the part of the patient

or use of a body-box. It can be used during spontaneous breathing in any body position [45], during exercise [18, 46, 47], and in ICU settings [21–26]. With this technique the volume and time history of the control and test expiration are axiomatically the same.

Briefly, a flanged plastic mouthpiece is connected in series to a pneumotachograph and a T-tube (fig. 1). One side of the T-tube is open to the atmosphere, while the other side is equipped with a one-way pneumatic valve, which allows for the subject to be rapidly switched to negative pressure generated by a vacuum cleaner or a Venturi device. The pneumatic valve consists of an inflatable balloon connected to a gas cylinder filled with pure helium and a manual pneumatic controller. The latter permits remote-controlled balloon deflation, which is accomplished quickly (30–60 ms) and quietly, allowing rapid exposure to negative pressure during expiration. Alternatively, a solenoid rapid valve can be used. The NEP (usually set at about -5 cmH_2O) can be adjusted with a potentiometer on the vacuum cleaner or by controlling the Ventouri device. Airflow is measured with the heated pneumotachograph and pressure at the airway opening is simultaneously measured through a side port on the mouthpiece (fig. 1). Volume is obtained by digital integration of the flow signal, and correction of electrical drift is mandatory [42]. While performing the testing, the subjects should be watched closely for leaks at the mouthpiece. Only those tests in which there is no leak are valid [48]. EFLT is assessed while seated upright in a comfortable chair or, if needed, lying supine on a comfortable couch, at least 2 h after eating or taking coffee. Patients are asked to breathe room air through the equipment assembly with the nose-clip on (fig. 1). Each subject has an initial 10–15 min trial run, in order to become accustomed to the apparatus and procedure. The flow, volume and pressure are continuously monitored on the computer screen. When regular breathing is resumed, a series of test breaths are performed, with regular breaths in between the test breaths, in which NEP is applied at the beginning of expiration and maintained throughout the ensuing expiration [42].

The NEP technique is based on the principle that, in the absence of flow limitation, the increase in pressure gradient between the alveoli and the airway opening caused by NEP should result in increased expiratory flow. By contrast, in flow-limited subjects application of NEP should not change the expiratory flow. Our analysis essentially consists in comparing the expiratory flow–volume curve obtained during a control breath with that obtained during the subsequent expiration in which NEP is applied [23, 42].

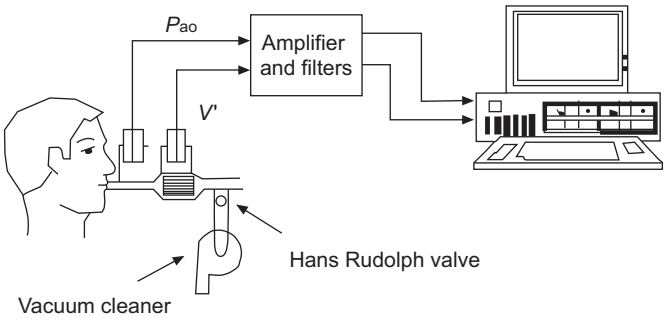

FIGURE 1. Schematic diagram of equipment set-up. P_{ao}: pressure at the airway opening; V': gas flow. Reproduced from [42] with permission from the publisher.

Subjects in whom application of NEP does not elicit an increase of flow during part or all of the tidal expiration (fig. 2b and c) are considered flow limited. By contrast, subjects in whom flow increases with NEP throughout the control tidal volume range (fig. 2a) are considered not flow limited (non-EFLT). If EFLT is present when NEP is applied, there is a transient increase of flow (spike), which mainly reflects sudden reduction in volume of the compliant oral and neck structures. To a lesser extent a small artefact due to common-mode rejection ratio of the system of measuring flow may also contribute to the flow transients [11, 42]. Such spikes are useful markers of expiratory flow limitation.

The degree of flow limitation can be assessed using three different EFLT indices: 1) as a continuous variable expressed as a percentage of tidal volume in both seated and supine positions (fig. 2) [42]; 2) as a discrete variable in the form of three categories of classification, *i.e.* non-EFLT both seated and supine, EFLT supine but not seated, and EFLT both seated and supine [42]; and 3) as a discrete variable in the form of a five-category classification (five-point EFLT score) [11].

In all studies employing the NEP technique, the latter was not associated with any unpleasant sensation, cough or other side-effects [11, 18, 23, 42]. The finding of O'DONNELL *et al.* [49] that application of -9.7 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ of expiratory assistance for 4 min during inspiration and expiration caused unpleasant respiratory sensation can be attributed to negative pressure application differences. NEP, usually set at -5 cmH_2O level, is applied only during expiration at five- to 10-breath intervals.

In subjects without obstructive sleep apnoea syndrome (OSAS), assessment of intrathoracic expiratory flow limitation with NEP is valid in almost all instances, even when NEP at levels of -5, -10, and -15 cmH_2O was applied [50]. However, there is a potential limitation of the NEP technique, which concerns normal snorers and patients with OSAS [50–53]. With NEP, expiratory flow shows a transient drop below control flow, reflecting a temporary increase in upper airway resistance. After this transient decrease in flow, expiratory flow with NEP usually exceeds control flow, showing that there is no intrathoracic flow limitation. Occasionally, flow with NEP remains below control throughout expiration, reflecting prolonged increase in upper airway resistance. In this case, the NEP test is not valid for assessing intrathoracic flow limitation. However, this phenomenon is uncommon in non-OSAHS subjects without obstructive sleep apnoea/hypopnoea syndrome (OSAHS) [50]. Furthermore, valid measurements may be obtained with repeated NEP tests using lower levels of NEP (*e.g.* -3 cmH_2O).

Turning this apparent drawback into an advantage, LIISTRO *et al.* [52] and VERIN *et al.* [53], in OSAHS patients with no evidence of intrathoracic obstruction, found a significant correlation of the degree of flow limitation expressed as a percentage of tidal volume in the supine position, with desaturation index and apnoea/hypopnoea index.

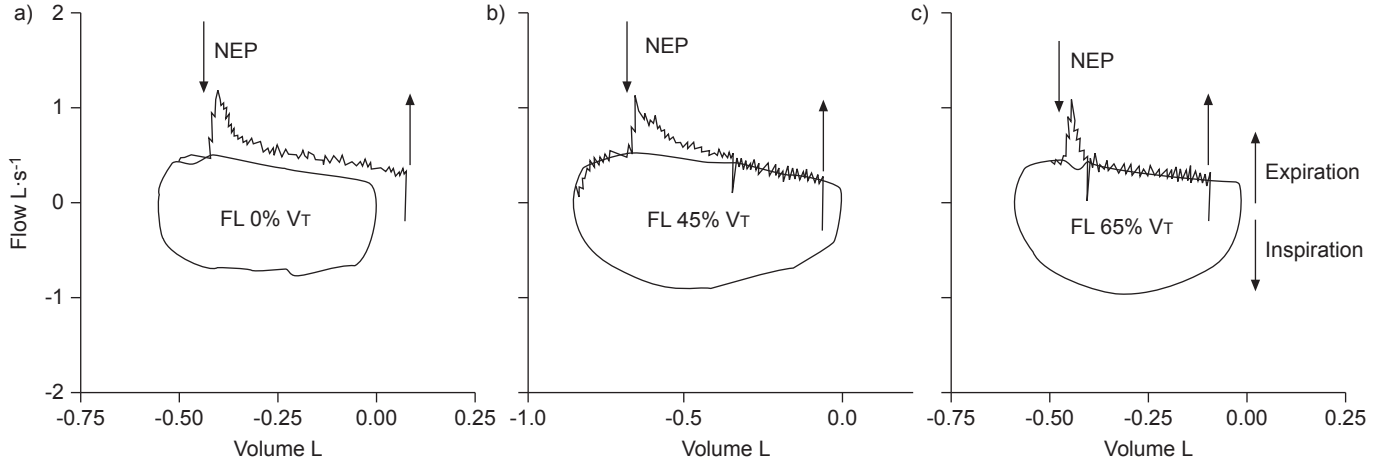

FIGURE 2. Flow–volume loops of test breaths and preceding control breaths of three representative chronic obstructive pulmonary disease patients with different degrees of flow limitation: a) not flow limited, b) flow limited over less than 50% of tidal volume (*V*T) and c) flow limited from peak expiratory flow. Arrows indicate points at which negative expiratory pressure (NEP) was applied and removed. Reproduced and modified from [11] with permission from the publisher.

The use of the NEP technique during tidal flow–volume analysis studies have led to realisation of the important role of expiratory flow limitation in exertional dyspnoea and ventilatory impairment for a surprisingly wide range of clinical circumstances, *e.g*. before and after bronchodilation, exercise, ICU, and heliox administration at rest and during exercise [9, 54, 55]. To date, no study has questioned the reliability and accuracy of the NEP technique. Currently, therefore, the NEP technique can be regarded as the new gold standard to detect EFLT, if one takes into account the pros and cons of each available technique. It is a novel, simple, noninvasive, useful research and clinical lung function tool.

Alternatively, in non-OSAHS and OSAHS patients [50, 53], in whom there is a consistent upper airway collapse in response to the application of NEP, EFLT can be assessed by: 1) submaximal expiratory manoeuvres initiated immediately from end-tidal inspiration; or 2) squeezing the abdomen during expiration.

SUBMAXIMAL EXPIRATORY MANOEUVRES

PELLEGRINO and BRUSASCO [56] proposed an alternative technique to detect expiratory flow limitation. EFLT was inferred from the impingement of the tidal flow–volume loop on the flow recorded during submaximally forced expiratory manoeuvres initiated from end-tidal inspiration in a body-box (fig. 3). After regular breathing with no volume drift, the subject performs a forced expiration from end-tidal inspiration without breath holding (partial expiratory manoeuvre). Care is taken to coach the subjects not to slow down the inspiration preceding the partial forced manoeuvre, thus minimising the dependence of forced flows on the time of the preceding inspiration. A deep inspiration to TLC recorded soon after the gentle forced manoeuvre allowed the loops to be superimposed and compared at absolute lung volume. Flow limitation is defined as the condition of tidal expiratory flow impinging on the maximal flow generated during the gentle forced expiratory manoeuvre. Since this method requires a body-box, measurements cannot be made in different body postures, ICU, or during exercise testing.

SQUEEZING THE ABDOMEN DURING EXPIRATION

Workers in Brussels, Belgium have shown that manual compression of the abdomen coinciding with the onset of expiration can be used as a simple way of detecting flow limitation at rest [57] and during exercise [58]. With one hand placed on the lower back of the patient and other applied with the palm at the level of the umbilicus perpendicular to the axis between the xiphoid process and the pubis, the operator first detects a respiratory rhythm by gentle palpation and then after warning the subject applies a forceful pressure at the onset of expiration. As in the NEP technique, the resulting expiratory flow–volume loop recorded at the mouth is superimposed on the preceding tidal breath (fig. 4). Failure to increase expiratory flow indicates flow limitation. This technique produces clear differences between normal subjects and patients with COPD. The presence of flow limitation during exercise

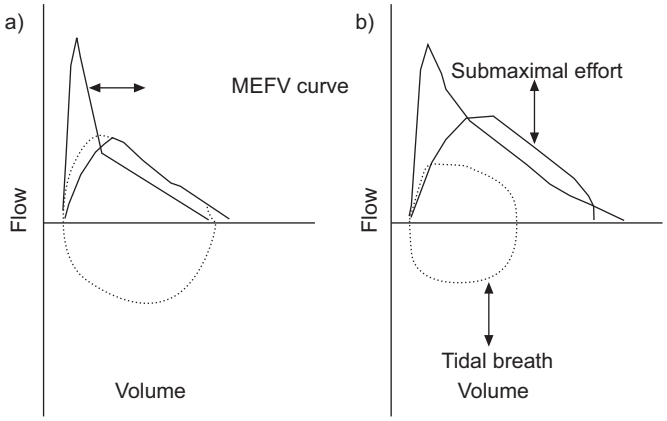

FIGURE 3. Graphical representation of the method used to detect expiratory flow limitation by comparing tidal to submaximal effort flow–volume loops started from end-tidal inspiration. a) A patient is expiratory flow limited, as tidal expiratory flow impinges on submaximal forced expiratory flow. b) A subject is not flow limited, as tidal expiratory flow is much less than submaximal forced expiratory flow. MEFV: maximal expiratory flow–volume. Reproduced and modified from [56] with permission from the publisher.

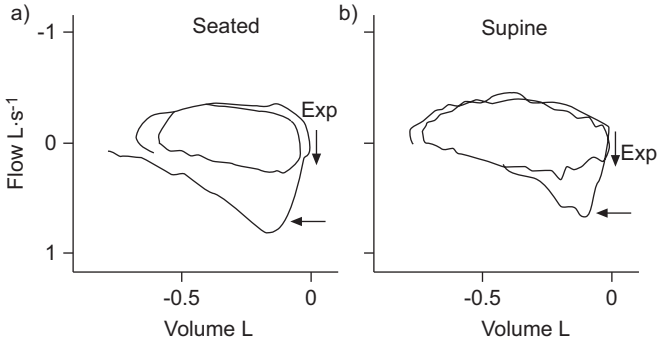

FIGURE 4. Flow–volume loops of test breaths and preceding control breaths of a representative chronic obstructive pulmonary disease patient with different degrees of flow limitation in seated and supine posture: a) the patient was not flow limited in the seated position and b) was flow limited in the supine position. Arrows indicate points at which manual compression of the abdomen was applied. Exp: expiration. Reproduced and modified from [57] with permission from the publisher.

detected during exercise in COPD patients was associated with increases in EELV [58]. Interestingly, not all subjects with COPD exhibited flow limitation when lung volume changed, a finding which requires confirmation. The method is appealingly simple, not influenced by upper airway compliance and, like the NEP method, it avoids problems with the preceding volume history of the test breath. Despite initial concerns about the possibility that gas compression in the alveoli would produce false-positive results, this does not seem to be a practical problem. However, unlike the NEP method, it is virtually impossible to squeeze at the precise moment of expiration. Thus far, this technique has not been widely applied, despite its relative simplicity.

FORCED OSCILLATION TECHNIQUE

A recent approach for detecting EFLT has been the forced oscillation technique (FOT), previously applied to look at the frequency dependence of resistance in a range of lung diseases and now available commercially in a modified form using impulse oscillometry [59, 60]. The principle here is that flow limitation will only be present in patients with obstructive pulmonary disease during expiration. Normally, oscillatory pressures generated by a loudspeaker system at the mouth are transmitted throughout the respiratory system, and by studying the resulting pressures which are in and out of phase with the signal, both the respiratory system resistance and reactance (a measure of the elastic properties of the system) can be

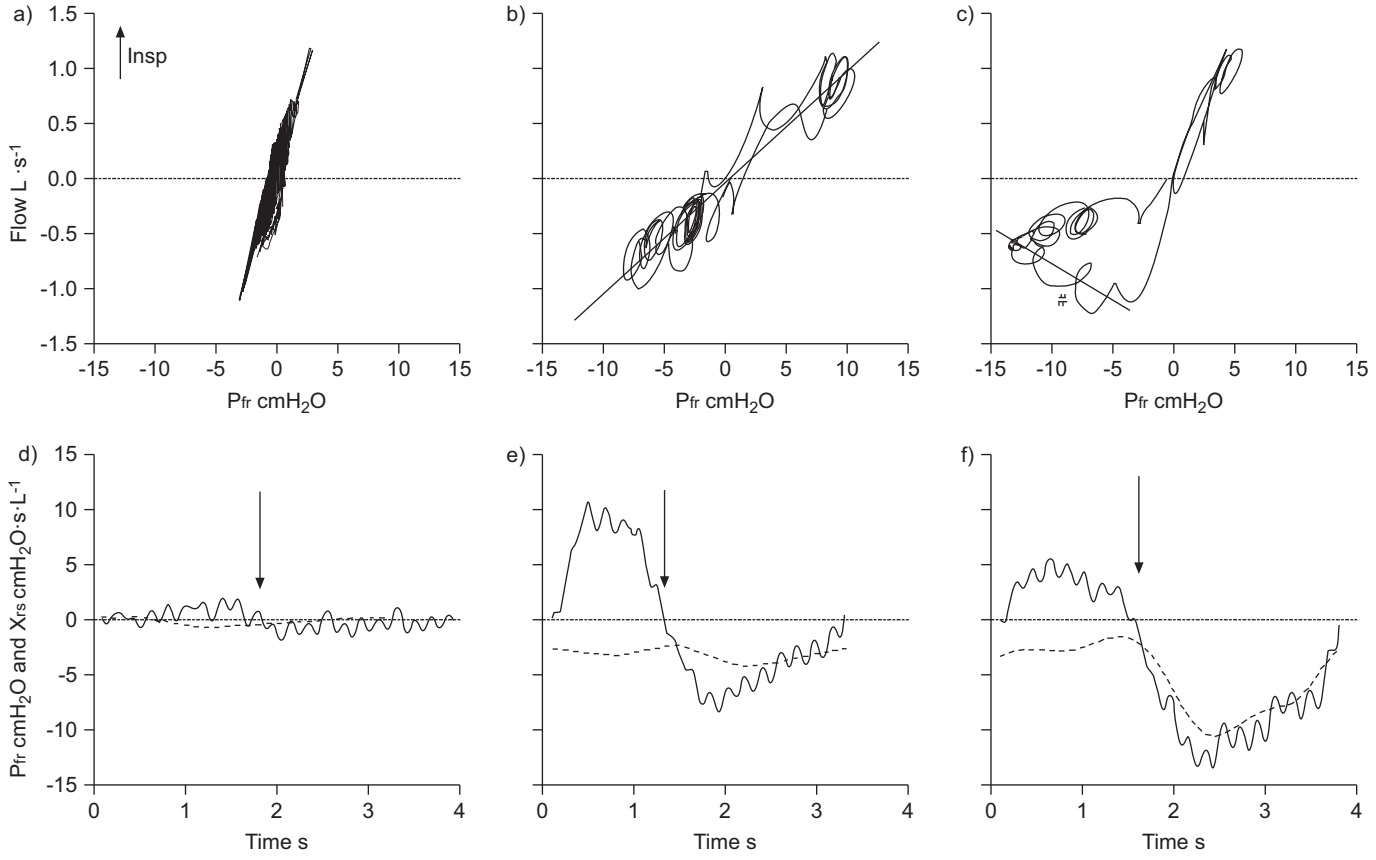

FIGURE 5. The Mead and Whittenberger graphs (a–c) obtained by plotting the airway opening flow *versus* the resistive pressure drop (P_{fr}) during a single breath. Data from a, d) a healthy subject, b, e) a chronic obstructive pulmonary disease (COPD) patient not flow limited and c, f) a flow-limited COPD patient. The regression lines in the left and in the middle graph represent airway resistance at breathing frequency. In the right graph expiratory flow limitation is demonstrated by the presence of a region in which airway opening flow is decreasing while P_{fr} is increasing. Traces obtained during forced oscillation technique application (d–f) show the corresponding time courses of P_{fr} (continuous line) and respiratory system reactance (X_{rs}; dashed line). The arrows indicate end inspiration, *i.e.* time before this point is inspiration, afterwards is expiration. Insp: inspiration. Reproduced from [60] with permission from the publisher.

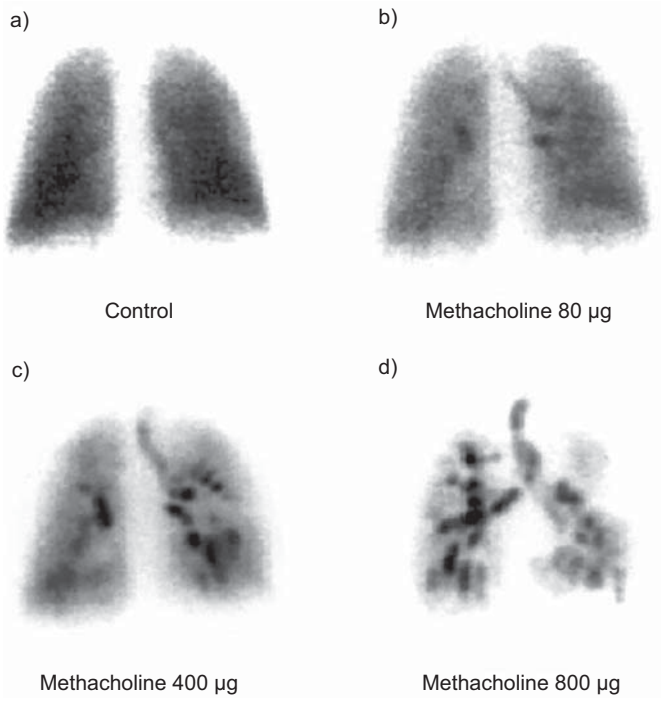

FIGURE 6. Typical example of posterior–anterior scans of the lungs after inhaling Technegas on day 1 (control; a) and after increasing doses of methacholine (b–d). Note the enhanced distribution of the Technegas in the central areas of the lungs even with the smallest dose of the constrictor agent. Reproduced from [20] with permission from the publisher.

computed. When flow limitation occurs, wave speed theory predicts that a choke point will develop within the airway subtended by that ''unit'' of the lung. In these circumstances, the oscillatory pressure applied at the mouth will no longer reach the alveoli and the reactance will reflect the mechanical properties of the airway wall rather than those of the whole respiratory system. As a result, reactance becomes much more negative and there is a clear within-breath difference between inspiration and expiration (fig. 5). DELLACÀ *et al*. [60] used this property to investigate the distribution of changes in within-breath reactance in normal subjects and COPD patients who were instrumented with balloon catheters. In a recent study, DELLACÀ *et al*. [61] found a good agreement between NEP and FOT, despite the fact that the FOT method may detect regional as well as overall EFLT. NEP detects the condition in which all possible pathways between airway opening and the alveoli are choked. When this occurs, the total expiratory flow is independent of the expiratory pressure, a condition of ''global'' expiratory flow limitation. In contrast, FOT assesses the amount of the lung that is choked during expiration only. This measures ''regional'' flow limitation, and a threshold value may indicate when the regional flow limitation reaches the condition of ''global'' flow limitation. Therefore, when ''global'' expiratory flow limitation is reached, the two techniques should produce the same response [61].

Like the other methods, this technique is independent of the previous volume history of the breath tested but unlike them can give breath-by-breath data continuously and provide an aggregate estimate of the probability of flow resistance being present in an individual. It can be used during exercise and can be automated, which may offer a widespread application for the detection of expiratory flow resistance in the ICU and routine physiology laboratory. It does appear to hold considerable promise but, to date, only a few studies to detect EFLT with this method have been reported. Conversely, FOT is very complex, expensive, as it requires the special FOT equipment, and time consuming.

TECHNEGAS METHOD

Technegas is an aerosol of ^{99m}Tc-labelled carbon molecules with small diameter (<0.01 µm) [20] capable of depositing even in the most peripheral regions of the lung. PELLEGRINO *et al*. [20] used the inhalation of Technegas to reveal sites (''hot spots'') of EFLT after induced bronchoconstriction in asthmatic patients. During forced expiration, the flow-limiting segment is known to be located first in the large intrathoracic airways and then to move peripherally. However, the present scintigraphic technique cannot precisely define the anatomical location of the flow-limiting segment during tidal breathing. Therefore, what the hot spots represent appears to be uncertain. The authors claim that this technique is useful to detect ''regional'' EFLT well before the NEP and submaximal expiratory manoeuvre techniques (fig. 6).

BREATH-BY-BREATH METHOD

The most recent method used to detect EFLT is the one using breath-by-breath quantification of progressive airflow limitation during exercise applied in stable COPD patients [62]. The authors have noted that during heavy exercise in COPD patients, dynamic airway compression leads to a progressive fall in intrabreath flow. This is manifested by an increasing concavity in the spontaneous expiratory flow–volume (SEFV) curve. The new method consists of quantifying the SEFV curve configuration breath by breath during incremental exercise utilising a computerised analysis. For the SEFV curve for each breath, points of highest flow and end expiration were identified, to define the diagonal of a rectangle. Fractional area within the rectangle below the SEFV curve was defined as the ''rectangular area ratio'' (RAR). RAR <0.5 signifies concavity of the SEFV curve. However, this method may be useful only during exercise because inspection of SEFV curve during resting breathing is not a reliable means of detecting EFLT [48]. Severe COPD patients often exhibit a mechanically active expiration. This necessarily affects the shape of SEFV curve, making it concave with respect to the volume axis, even in the absence of EFLT [63].

CONCLUSIONS

In conclusion, the newer aforementioned techniques represent a substantial advance on traditional approaches comparing tidal and maximal flow–volume loops, or even the more robust, but time-consuming, method of determining partial expiratory flow–volume loops. By freeing both parts, the doctor and the patient, from the limitations of oesophageal balloon catheters and the body plethysmograph, they have opened up a new era in understanding modern physiological principles like the EFLT [9, 54, 55]. Among the available physiological techniques to detect EFLT, the NEP should probably be regarded as the new gold standard. This view is supported by the data obtained from the application of NEP in

a wide variety of settings [9, 54, 55]. However, extensive comparisons between these different methods are needed before the best ''test'' or combination of techniques can be unequivocally recommended to correctly assess EFLT.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Pride NB. Tests of forced expiration and inspiration. *In:* Hughes JMB, Pride NB, eds. Lung Function Tests: Physiological Principles and Clinical Applications. London, WB Saunders, 1999; pp. 3–25.
2 Pecchiari M, Pelucchi A, D'Angelo EM, *et al.* Effect of heliox breathing on dynamic hyperinflation in COPD patients. *Chest* 2004; 125: 2075–2082.
3 Brighenti C, Barbini P, Gnudi G, *et al.* Helium-oxygen ventilation in the presence of expiratory flow-limitation: a model study. *Respir Physiol Neurobiol* 2007; 157: 326–334.
4 D'Angelo E, Santus P, Civitillo MF, *et al.* Expiratory flow-limitation and heliox breathing in resting and exercising COPD patients. *Respir Physiol Neurobiol* 2009; 169: 291–296.
5 Pecchiari M, Anagnostakos T, D'Angelo E, *et al.* Effect of heliox breathing on flow limitation in chronic heart failure patients. *Eur Respir J* 2009; 33: 1367–1373.
6 Milic-Emili J. Does mechanical injury of the peripheral airways play a role in the genesis of COPD in smokers? *COPD* 2004; 1: 85–92.
7 Milic-Emili J, Torchio R, D'Angelo E. Closing volume: a reappraisal. *Eur J Appl Physiol* 2007; 99: 567–583.
8 D'Angelo E, Koulouris NG, Della Valle P, *et al.* The fall in exhaled nitric oxide with ventilation at low lung volumes in rabbits: an index of small airway injury. *Respir Physiol Neurobiol* 2008; 160: 215–223.
9 Calverley PMF, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. *Eur Respir J* 2005; 25: 186–199.
10 Gennimata SA, Milic-Emili J, Palamidas AF, *et al.* Evolution of peripheral airways disease (PAD) to overt chronic obstructive pulmonary disease. *COPD* 2010; 7: 269–275.
11 Eltayara L, Becklake MR, Volta CA, *et al.* Relationship between chronic dyspnoea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 154: 1726–1734.
12 Tantucci C, Duguet A, Similowski T, *et al.* Effect of salbutamol on dynamic hyperinflation in chronic obstructive pulmonary disease patients. *Eur Respir J* 1998; 12: 799–804.
13 Boni E, Corda L, Franchini D, *et al.* Volume effect and exertional dyspnoea after bronchodilator in patients with COPD with and without expiratory flow limitation at rest. *Thorax* 2002; 57: 528–532.
14 Hadcroft J, Calverley PMA. Alternative method for assessing bronchodilator reversibility in chronic obstructive pulmonary disease. *Thorax* 2001; 56: 713–720.
15 Diaz O, Villafranca C, Ghezzo H, *et al.* Role of inspiratory capacity on exercise tolerance in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Respir J* 2000; 16: 269–275.
16 Diaz O, Villafranca C, Ghezzo H, *et al.* Breathing pattern and gas exchange at peak exercise in COPD patients with and without tidal expiratory flow limitation at rest. *Eur Respir J* 2001; 17: 1120–1127.
17 O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770–777.
18 Koulouris NG, Dimopoulou I, Valta P, *et al.* Detection of expiratory flow limitation during exercise in COPD patients. *J Appl Physiol* 1997; 82: 723–731.
19 Tantucci C, Ellaffi M, Duguet A, *et al.* Dynamic hyperinflation and flow limitation during methacholine-induced bronchoconstriction in asthma. *Eur Respir J* 1999; 14: 295–301.
20 Pellegrino R, Biggi A, Papaleo A, *et al.* Regional expiratory flow limitation studied with technegas in asthma. *J Appl Physiol* 2001; 91: 2190–2198.
21 Koutsoukou A, Armaganidis A, Stavrakaki-Kalergi C, *et al.* Expiratory flow limitation and intrinsic positive end-expiratory pressure at zero positive end-expiratory pressure in patients with adult respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; 161: 1590–1596.
22 Koutsoukou A, Bekos B, Sotiropoulou CH, *et al.* Effects of positive end-expiratory pressure on gas exchange and expiratory flow limitation in adult respiratory distress syndrome. *Crit Care Med* 2002; 30: 1941–1949.
23 Valta P, Corbeil C, Lavoie A, *et al.* Detection of expiratory flow limitation during mechanical ventilation. *Am J Respir Crit Care Med* 1994; 150: 1311–1317.
24 Armaganidis A, Stavrakaki-Kalergi K, Koutsoukou A, *et al.* Intrinsic positive end-expiratory pressure in mechanically ventilated patients with and without tidal expiratory flow limitation. *Crit Care Med* 2000; 28: 3837–3842.
25 Alvisi V, Romanello A, Badet M, *et al.* Time course of expiratory flow limitation in COPD patients during acute respiratory failure requiring mechanical ventilation. *Chest* 2003; 123: 1625–1632.
26 Koutsoukou A, Koulouris N, Bekos B, *et al.* Expiratory flow limitation in morbidly obese postoperative mechanically ventilated patients. *Anesthesiologica Scandinavica* 2004; 48: 1080–1088.
27 Murray JF. Ventilation. *In:* Murray JF, ed. The Normal Lung: the Basis for Diagnosis and Treatment of Pulmonary Disease. 2nd Edn. London, WB Saunders, 1986; pp. 83–119.
28 Fry DL, Ebert RV, Stead WW, *et al.* The mechanics of pulmonary ventilation in normal subjects and patients with emphysema. *Am J Med* 1954; 16: 80–97.
29 Mead J, Whittenberger JL. Physical properties of human lungs measured during spontaneous respiration. *J Appl Physiol* 1953; 5: 779–796.
30 Hyatt RE. The interrelationship of pressure, flow and volume during various respiratory maneuvers in normal and emphysematous patients. *Am Rev Respir Dis* 1961; 83: 676–683.
31 Leaver DG, Pride NB. Flow–volume curves and expiratory pressures during exercise in patients with chronic airways obstruction. *Scan J Respir Dis* 1971; 77: 23–27.
32 Ingram RH Jr, Schilder DP. Effect of gas compression on pulmonary pressure, flow, and volume relationship. *J Appl Physiol* 1966; 21: 1821–1826.
33 Stubbing DG, Pengelly LD, Morse JLC, *et al.* Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. *J Appl Physiol* 1980; 49: 511–515.
34 Younes M, Kivinen G. Respiratory mechanics and breathing pattern during and following maximal exercise. *J Appl Physiol* 1984; 57: 1773–1782.
35 D'Angelo E, Prandi E, Milic-Emili J. Dependence of maximal flow–volume curves on time-course of preceding inspiration. *J Appl Physiol* 1993; 75: 1155–1159.
36 D'Angelo E, Prandi E, Marrazzini L, *et al.* Dependence of maximal flow-volume curves on time course of preceding inspiration in patients with chronic obstructive lung disease. *Am J Respir Crit Care Med* 1994; 150: 1581–1586.
37 Koulouris NG, Rapakoulias P, Rassidakis A, *et al.* Dependence of FVC manoeuvre on time course of preceding inspiration in patients with restrictive lung disease. *Eur Respir J* 1997; 10: 2366–2370.
38 Melissinos CG, Webster P, Tien YK, *et al.* Time dependence of maximum flow as an index of nonuniform emptying. *J Appl Physiol* 1979; 47: 1043–1050.

39 Fairshter RD. Airway hysteresis in normal subjects and individuals with chronic airflow obstruction. *J Appl Physiol* 1985; 58: 1505–1510.

40 Wellman JJ, Brown R, Ingram RH Jr, *et al.* Effect of volume history on successive partial expiratory maneuvers. *J Appl Physiol* 1976; 41: 153–158.

41 Beck KC, Offord KP, Scanlon PD. Bronchoconstriction occurring during exercise in asthmatic patients. *Am J Respir Crit Care Med* 1994; 149: 352–357.

42 Koulouris NG, Valta P, Lavoie A, *et al.* A simple method to detect expiratory flow limitation during spontaneous breathing. *Eur Respir J* 1995; 8: 306–313.

43 Boczkowski J, Murciano D, Pichot M-H, *et al.* Expiratory flow limitation in stable asthmatic patients during resting breathing. *Am J Respir Crit Care Med* 1997; 156: 752–757.

44 Jones MH, Davies SD, Kisling JA, *et al.* Flow limitation in infants assessed by negative expiratory pressure. *Am J Respir Crit Care Med* 2000; 161: 713–717.

45 Dimitroulis J, Bisirtzoglou D, Retsou S, *et al.* Effect of posture on expiratory flow limitation in spontaneously breathing stable COPD patients. *Am J Respir Crit Care Med* 2001; 163: A410.

46 Kosmas EN, Milic-Emili J, Polychronaki A, *et al.* Exercise-induced flow limitation, dynamic hyperinflation and exercise capacity in patients with bronchial asthma. *Eur Respir J* 2004; 24: 378–384.

47 Murciano D, Ferretti A, Boczkowski J, *et al.* Flow limitation and dynamic hyperinflation during exercise in COPD patients after single lung transplantation. *Chest* 2000; 118: 1248–1254.

48 Baydur A, Milic-Emili J. Expiratory flow limitation during spontaneous breathing. Comparison of patients with restrictive and obstructive respiratory disorders. *Chest* 1997; 112: 1017–1023.

49 O'Donnell DE, Sanii R, Anthonisen NR, *et al.* Effect of dynamic airway compression in breathing pattern and respiratory sensation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1987; 135: 912–918.

50 Baydur A, Wilkinson L, Mehdian R, *et al.* Extrathoracic expiratory flow limitation in obesity and obstructive and restrictive disorders; effects of increasing negative expiratory pressure. *Chest* 2004; 125: 98–105.

51 Tantucci C, Duguet A, Ferretti A, *et al.* Effect of negative expiratory pressure on respiratory system flow resistance in awake snorers and non snorers. *J Appl Physiol* 1999; 87: 969–976.

52 Liistro G, Veritier C, Dury M, *et al.* Expiratory flow limitation in awake sleep-disordered breathing subjects. *Eur Respir J* 1999; 14: 185–190.

53 Verin E, Tardif C, Portier F, *et al.* Evidence for expiratory flow limitation of extrathoracic origin in patients with obstructive sleep apnoea. *Thorax* 2002; 57: 423–428.

54 Dueck R. Assessment and monitoring of flow limitation and other parameters from flow/volume loops. *J Clin Monit Comput* 2000; 16: 425–432.

55 Johnson BD, Beck KC, Zeballos RJ, *et al.* Advances in pulmonary laboratory testing. *Chest* 1999; 116: 1377–1387.

56 Pellegrino R, Brusasco V. Lung hyperinflation and flow limitation in chronic airway obstruction. *Eur Respir J* 1997; 10: 543–549.

57 Ninane V, Leduc D, Kafi SA, *et al.* Detection of expiratory flow limitation by manual compression of the abdominal wall. *Am J Respir Crit Care Med* 2001; 163: 1326–1330.

58 Abdel KS, Serste T, Leduc D, *et al.* Expiratory flow limitation during exercise in COPD: detection by manual compression of the abdominal wall. *Eur Respir J* 2002; 19: 919–927.

59 Dellacà RL. Measurement of respiratory system impedances. *In:* Aliverti A, Brusasco V, Macklem PT, *et al.*, eds. Mechanics of Breathing. Milan, Springer, 2002; pp. 157–171.

60 Dellacà RL, Santus P, Aliverti A, *et al.* Detection of expiratory flow limitation in COPD using the forced oscillation technique. *Eur Respir J* 2004; 23: 232–240.

61 Dellacà RL, Duffy N, Pompilio PP, *et al.* Expiratory flow-limitation detected by forced oscillation and negative expiratory pressure. *Eur Respir J* 2007; 29: 363–374.

62 Ma S, Hecht A, Varga J, *et al.* Breath-by-breath quantification of progressive airflow limitation during exercise in COPD: a new method. *Respir Med* 2010; 104: 389–396.

63 Koulouris NG, Valta P, Lavoie A, *et al.* Expiratory flow limitation during tidal breathing. *Eur Respir J* 1995; 8: 1624.