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# **Expiratory Flow Limitation in Intra and Extrathoracic Respiratory Disorders: Use of the Negative Expiratory Pressure Technique – Review and Recent Developments**

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Ahmet Baydur

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## **1. Introduction**

### **1.1. Definition**

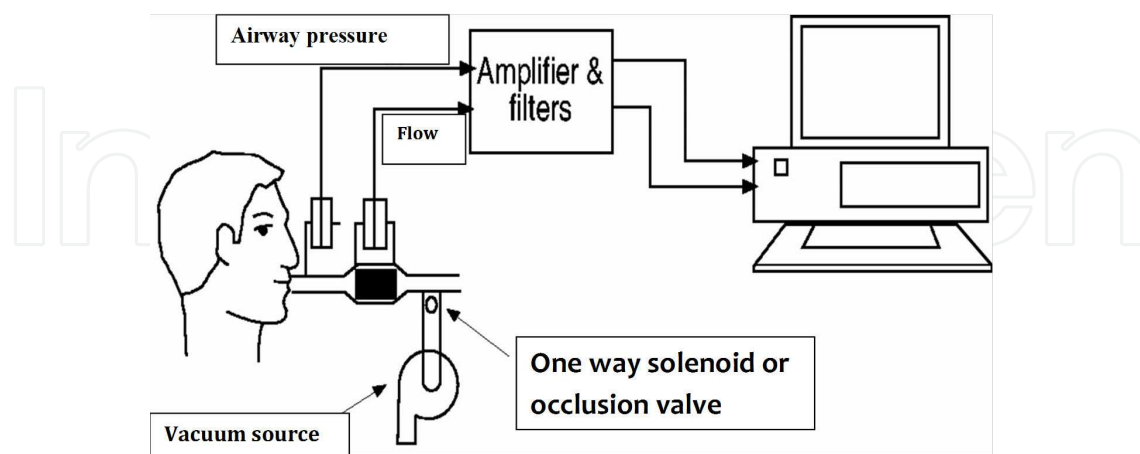
Expiratory flow limitation (EFL) is defined as an absence in increase in flow with application of negative expiratory pressure (NEP) during quiet breathing (Koulouris et al., 1994). The test is a simple, noninvasive, practical and accurate technique.

Application of the NEP technique provides a simple, rapid, non-invasive, and reliable test to detect tidal expiratory flow limitation; b) it does not require a body-box or cooperation on the patient's part; c) it can be applied in any posture, during mechanical ventilation, and during exercise; d) it provides new insights into the physiology and pathophysiology of several diseases and the symptom of dyspnea.

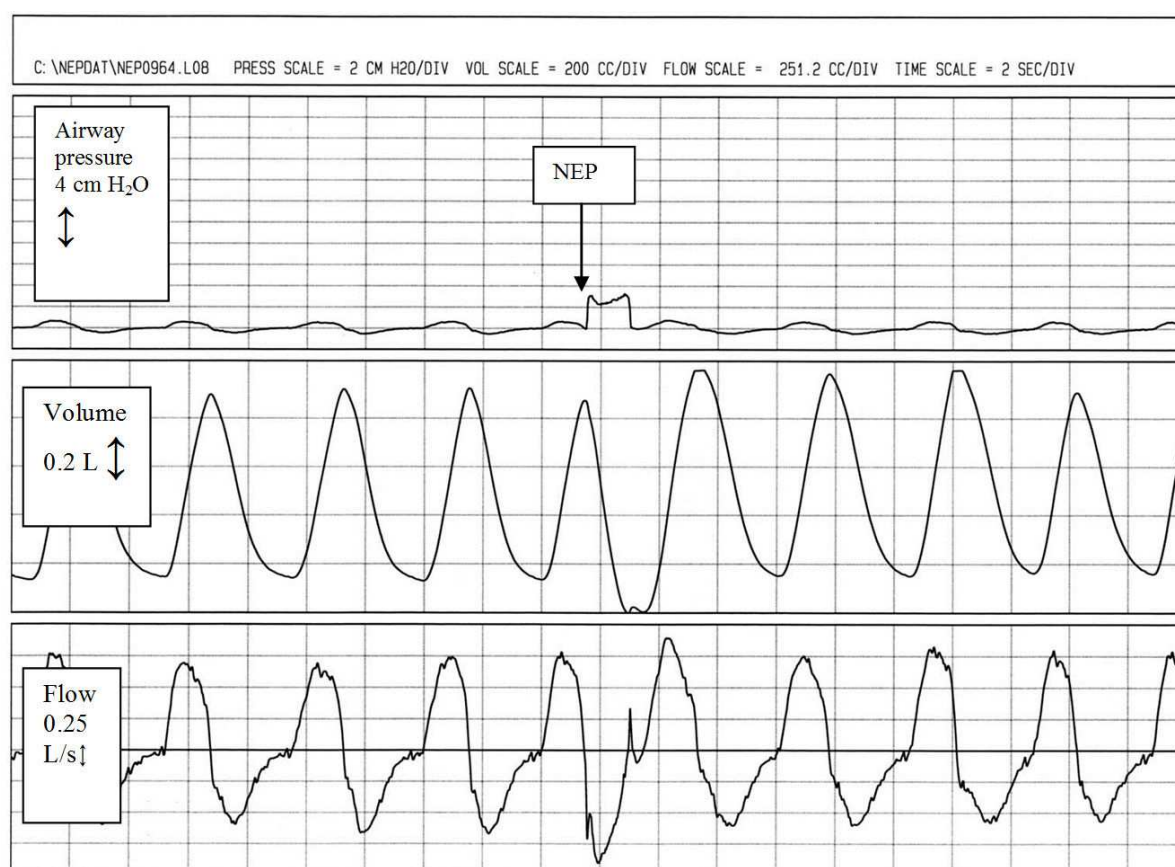
## **2. Negative expiratory pressure technique (NEP) – Methodology**

In the last 2 decades, expiratory flow limitation (EFL) in patients with various respiratory disorders has been studied extensively using the negative expiratory pressure technique (NEP). This method does not require performance of forced expiratory maneuvers or the body plethysmograph (D'Angelo et al., 1993; Koulouris et al., 1995; Valta et al., 1994). It consists of applying a small negative pressure (3–10 cm H<sub>2</sub>O, depending on the circumstances)

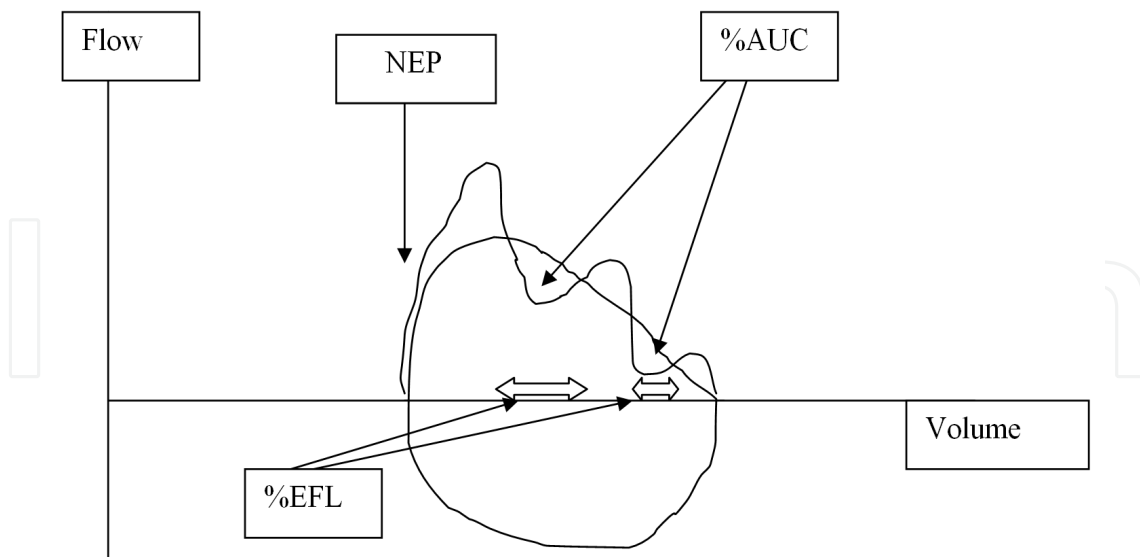
at the onset of tidal expiration and comparing the ensuing expiration flow-volume curve with that of the preceding control expiration (Figures 1-3).



**Figure 1.** Schema of negative expiratory pressure (NEP) setup to assess expiratory flow limitation (EFL).

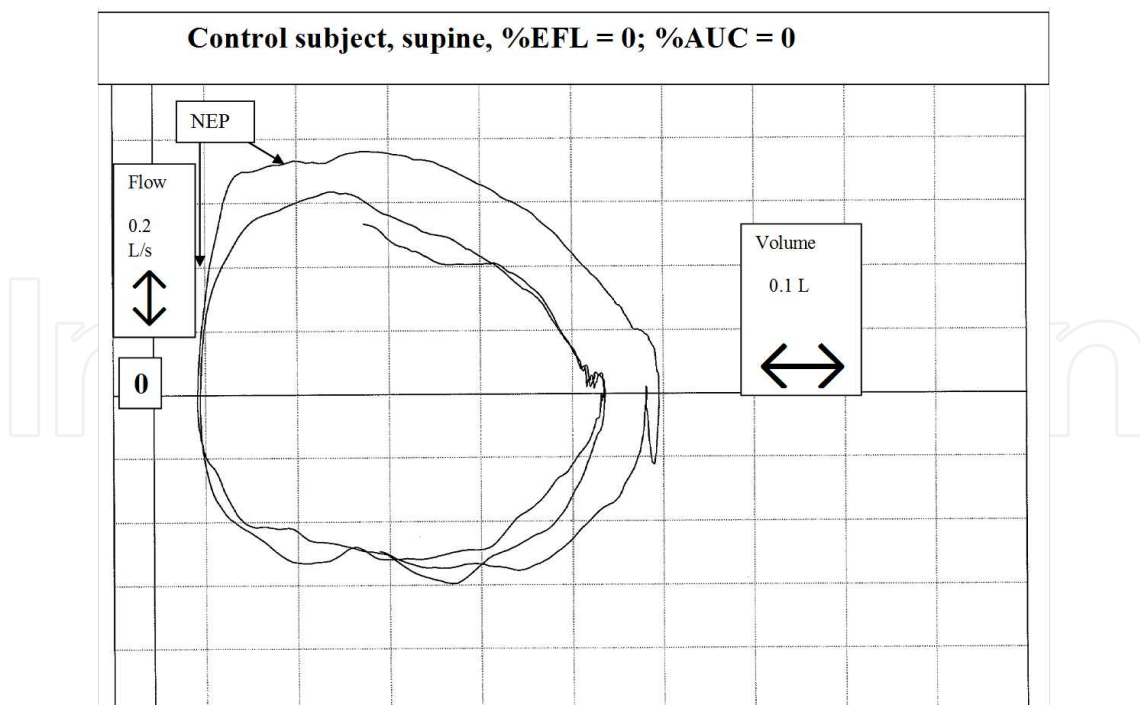


**Figure 2.** Tracings of airway pressure, volume and flow during quiet breathing. Application of negative expiratory pressure at the onset of expiration is indicated by NEP.



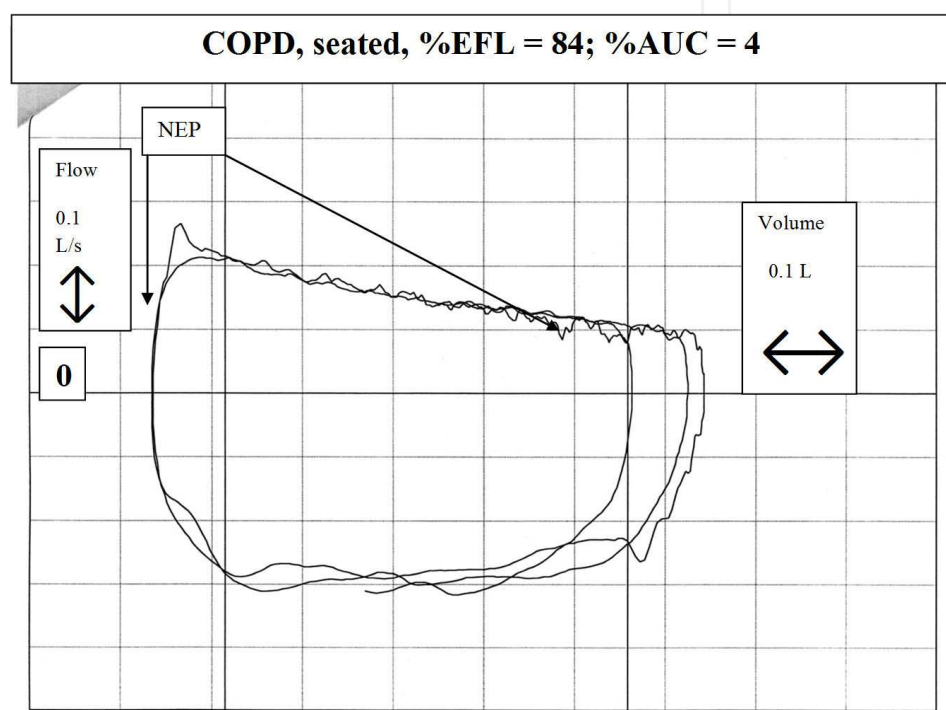
**Figure 3.** Schema of the control and NEP tidal flow-volume curves and how measurements of EFL% and AUC% were obtained.

As the driving pressure at the airway opening increases with application of NEP, expiratory flow should increase if the individual is not flow-limited (Figure 4).



**Figure 4.** Tracings of the control and NEP tidal curves in a healthy subject. Note increase in expiratory flow with application of NEP.

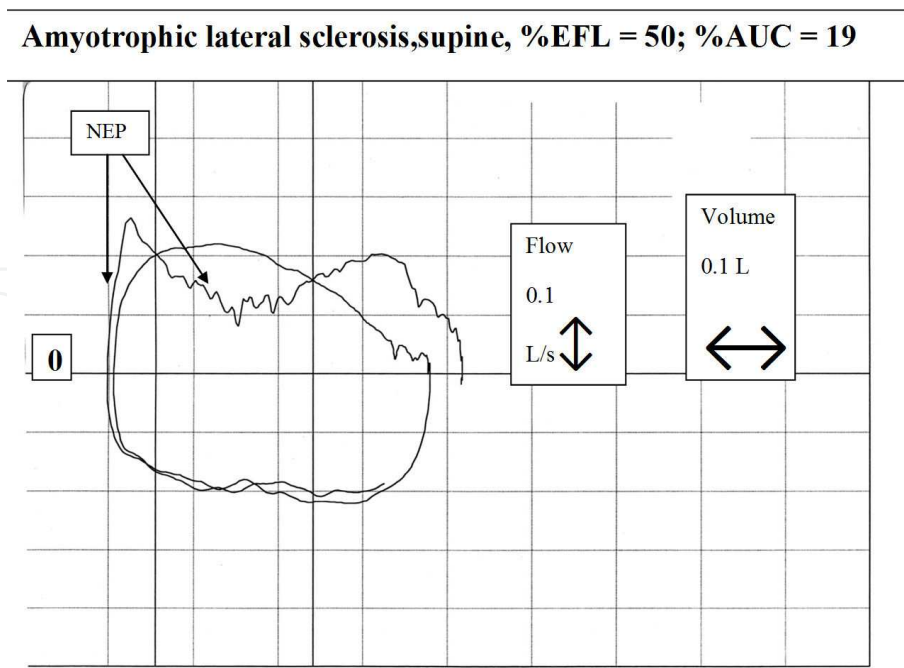
By contrast, intrathoracic EFL is demonstrated by a sustained absence in increase in flow during application of NEP (as occurs in COPD) (Figure 5). That is, in these individuals the control and NEP-generated tidal expiratory are superimposed on each other.



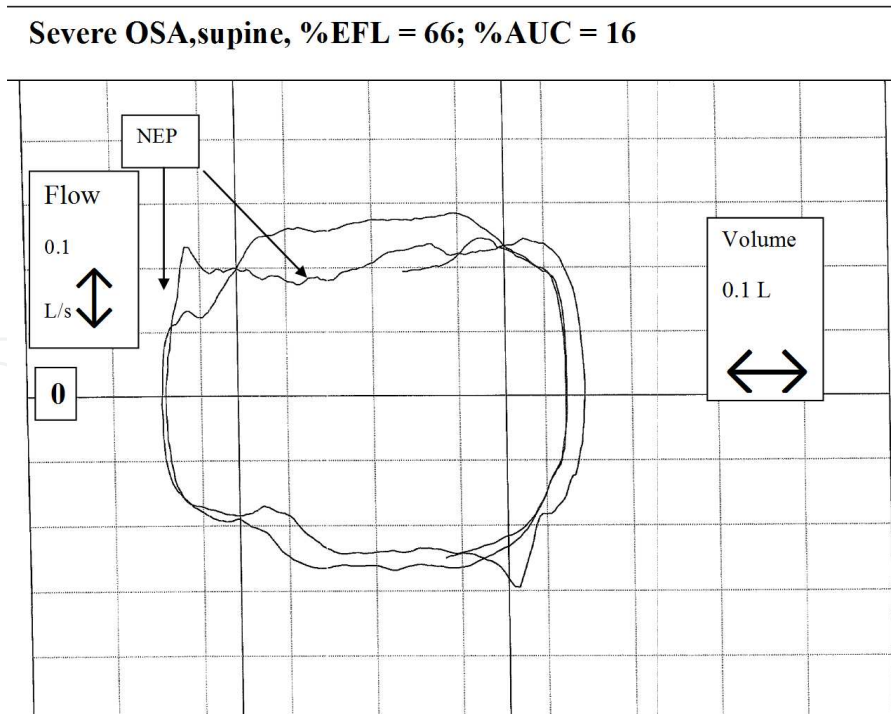
**Figure 5.** Tracings of control and NEP tidal curves in a patient with chronic obstructive pulmonary disease. Note absence of change in expiratory flow with application of NEP.

In obese individuals, some patients with restrictive respiratory disorders (Figure 6, individual with amyotrophic lateral sclerosis) and some subjects free of cardiorespiratory disease, application results in a reduction in the increase in flow or transient decrease below the control expiration. This finding is prevalent in patients with documented obstructive sleep apnea (Figure 7).

The NEP test is simple, noninvasive, practical and accurate. It has been validated by simultaneous determination of isovolume flow-pressure relationships (Valta et al., 1994).



**Figure 6.** Tracings of control and NEP tidal flow-volume curves in a patient with a chest wall disorder, in this case amyotrophic lateral sclerosis with bulbar involvement (but without obstructive sleep apnea). Note the decrease in expiratory flow below the control tidal expiration with application of NEP.



**Figure 7.** Tracings of control and NEP curves in a patient with severe obstructive sleep apnea. Note the sustained decrease of flow during application of NEP below the control expiratory tidal flow.



## 2.1. EFL in chronic obstructive pulmonary disease (COPD) and asthma

Fifty years ago, Hyatt (1961) suggested that patients with severe COPD may exhibit expiratory flow limitation (EFL) at rest. This phenomenon could be demonstrated by the finding that they breathed tidally along or above their maximal expiratory flow-volume curves. This pattern of tidal breathing leads to hyperinflation, increased work of breathing, impaired respiratory muscle function, hemodynamic compromise (Gottfried, 1991), and dyspnea (El-tayara et al., 1996; O'Donnell et al., 1987). A high prevalence of tidal EFL is found in patients with COPD (Baydur et al., 2004; Gottfried et al., 1991; Hyatt et al., 1961) (Figure 5). As many as one-third of patients were flow-limited in seated and supine postures in the report of Baydur et al. (2004). A smaller percentage of patients with asthma in remission exhibit EFL, almost always in the supine posture (Baydur et al., 2004; Boczkowski et al., 1997).

The NEP technique can be used to advantage in young children unable to perform forced expiratory volume maneuvers (Braggion et al., 1998; Goetghebeur et al., 2002; Jiříčková et al., 2009; Jones et al., 2000; Tauber, et al., 2003). Goetghebeur et al [10] described EFL in children aged older than 12 years with cystic fibrosis. These patients exhibited markedly decreased inspiratory capacity (IC) and forced expiratory volume at 1 sec (FEV<sub>1</sub>). The NEP technique has also been used to evaluate EFL in infants (Braggion et al., 1998; Jiříčková et al., 2009; Jones et al., 2000). Jiříčková et al. (2009), applying the NEP technique in newborns and pre-school children, found nearly half of their patients to be intrathoracically flow-limited. The same number of children, however, exhibited transient upper airway collapse (UAC). The authors did not specify, if in some children, the UAC may have obscured any underlying intrathoracic EFL (see below).

An advantage of using the NEP technique in the evaluation of intrathoracic EFL is the avoidance of variability in the forced expiratory vital capacity maneuver related to the pattern of inspiratory maneuver preceding forceful expiration. Fast inspiration followed immediately by forced expiration results in greater forced vital capacities (FVC) and peak expiratory flows (PEF) by generating higher elastic recoil; in contrast, performing a breath-hold between inspiration and expiration diminishes elastic recoil and results in lower FVC and PEF. This finding, observed in both in healthy volunteers (D'Angelo et al., 1993; Tzelepis et al., 1997; Wanger et al., 1996) and patients (Braggion et al., 1996; D'Angelo et al., 1994; D'Angelo et al., 1996; Wanger et al., 1996), has been ascribed to the viscoelastic properties of the lung (D'Angelo et al., 1991) and to greater activation of expiratory muscles (Tzelepis et al., 1997) occurring with fast maneuvers. The NEP method also avoids underestimation of lung volumes during rapid expiratory maneuvers due to gas compression (Ingram & Schiller, 1966; Koulouris et al., 1995). The technique also avoids incorrect alignment of the tidal and maximal expiratory flow-volume curves. Such alignment is usually made considering the total lung capacity (TLC) as a fixed reference point, and this assumption may not always be valid (Kosmas et al., 2004; Koulouris, 1997; Murciano et al., 2000).

The NEP technique has also been used to detect EFL during exercise (Koulouris et al., 1997). In normal young subjects, there is no evidence of EFL during submaximal exercise. By contrast, most patients with COPD exhibit NEP-generated EFL during light exercise. These findings are in agreement with exercise studies employing conventional forced expiratory

flow-volume curves (Beck et al, 1991; Grimby & Stiksa, 1970; Hyatt, 1961; Kosmas et al., 2004; Koulouris, 1997; Murciano et al., 2000; Stubbing et al., 1980; Younes & Kivinen, 1984). Patients with EFL exhibit progressive lung inflation, increased sensation of dyspnea, and reduced maximal oxygen uptake during exercise.

Manual compression of the abdominal wall has also been used to detect EFL (Ninane et al., 2001). It has the advantage of generating an increase in abdominal pressure (of about 15 cm H<sub>2</sub>O) that results in cranial displacement of the diaphragm into the thorax (provided it is relaxed) and a rise in pleural pressure (of about 6 cm H<sub>2</sub>O) without the use of a special device. It also does not depend on previous volume and time history, and relies on a modest increase in alveolar pressure rather than a vacuum applied at the mouth, thus avoiding artifact caused by upper airway collapsibility. One study of this maneuver resulted in an increase in tidal expiratory flow in normal subjects, while it exhibited EFL in half of 12 patients with COPD in both supine and seated postures, and in 4 additional patients in supine position alone (Ninane et al., 2001).

Expiratory flow limitation is more prevalent in the elderly and is related to the severity of dyspnea (de Bisschop et al., 2005). In general, EFL does not closely correlate with FEV<sub>1</sub> or FEV<sub>1</sub>/FVC (Eltayara et al., 1996). Older dyspneic individuals without cardiorespiratory disorders tend to be more flow limited than non-dyspneic persons (de Bisschop et al., 2005).

## **2.2. EFL in restrictive respiratory disorders**

In individuals with restrictive disorders (particularly those with infiltrative disorders, such as idiopathic pulmonary fibrosis) maximal expiratory flows are well preserved despite a marked decrease in lung volume (Bergofsky, 1995). Consequently, breathing occurs at low lung volumes (near residual volume) where maximal expiratory flows are relatively small. Furthermore, some patients with interstitial lung diseases exhibit a decrease in dynamic compliance with breathing frequency (Bergofsky, 1995; Fulmer et al., 1977). In some of these patients, including non-smokers, flow rates are reduced with respect to transpulmonary pressure (Fulmer et al., 1977; Gaultier et al., 1980; Murphy et al., 38). Baydur et al. (1997, 2004) did not find any patients with restrictive disorders who exhibited intrathoracic EFL in either body position. The absence of EFL can be attributed to the increase in elastic recoil associated with these disorders. Others, however, have described the presence of EFL in patients with cardiac failure (Duguet et al., 2000), acute respiratory distress syndrome (Koutsoukou et al., 2000), and pleural effusions (Spyratos et al., 2007).

## **2.3. EFL in sleep apnea; differences in FL pattern from COPD and asthma as assessed by the NEP method**

The NEP technique has also been used to assess upper airway collapsibility in patients with OSA, in which EFL has been described as a transient or sustained decrease in expiratory flow (frequently below the control tidal expiratory flow) during application of NEP (Baydur et al., 2004; Liistro et al., 1999; Van Meerhaeghe et al., 2004; Verin et al., 2002) (Figure 7).



Factors that contribute to OSA include increase in upper airway compliance (Isono et al., 1997), less negative critical (or closing) pressure of the passive upper airways as compared to snorers and normal subjects (related to structural soft tissue and bony changes) (Liistro et al., 1990), and smaller upper airway lumens during wakefulness and sleep, and greater pharyngeal airway length in OSA patients (Brown et al., 1985). Dyspnea in obese individuals is related to increased work of breathing related to decrease in FRC with resultant increase in intrathoracic EFL and intrinsic positive end-expiratory pressure, increased respiratory drive, and intermittent narrowing or collapse of the upper airway upon assuming the supine position (C.-K. Lin & C.-C. Lin, 2012).

Flow limitation can be assessed by computing the exhaled volume at specified time intervals during the application of NEP and expressed as percentage of the previous exhaled volume. Expiratory volumes at 0.2 and 0.5 sec after the application of NEP are significantly higher in awake healthy subjects than in awake patients with OSA (Insalaco et al., 2005; Romano et al., 2011). Expiratory volumes decline as disease severity increases., in these 2 studies, the exhaled volume at 0.2 sec exhibited a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to detect the presence of OSA of 81%, 93%, 98% and 53%, respectively (Insalaco et al., 2005; Romano et al., 2011). Sensitivity and negative predictive value both approached and reached 100% for moderate to severe [apnea-hypopnea index (AHI) 15-30], and severe (AHI >30) OSA, respectively. The authors concluded that FL measurements at 0.2 sec may be a useful screening test for suspected OSA (Insalaco et al., 2005; Romano et al., 2011).

Using a similar computational technique, Ferretti et al (2006) found that in awake OSA patients the exhaled volume during the first 0.5 sec after the onset of NEP averaged 20% and 31% less than snorers and control subjects, respectively, in supine posture (differences statistically significant). Under these conditions, an optimal cut-off value of 393 mL at NEP 0.5 sec exhibited a sensitivity, specificity, PPV and NPV of 76%, 74%, 84% and 64%, respectively. These differences were found to be less significant in the seated position. These authors concluded that while the NEP technique is potentially useful in evaluating upper airway collapsibility in OSA and its mechanisms while awake, it was not precise enough to differentiate simple snorers from those with OSA. Thus it cannot be recommended as a tool robust enough to screen obese patients or snorers for undergoing polysomnography (Ferretti et al., 2006).

### *2.3.1. Recent research by these authors*

In patients with both COPD and OSA, EFL due to the intrathoracic component may be obscured by the presence of upper airway collapse or narrowing which frequently leads to a reduction in expiratory flow below that of the preceding control breath during application of NEP. Furthermore, distinguishing EFL in OSA from that of COPD can be problematic because patients may exhibit overlapping or combined EFL patterns combining features of both conditions. Baydur et al. (2012) compared the ability of the NEP technique to distinguish individuals with COPD from those with OSA and non-OSA obesity. EFL was quantitated using the following methods (Fig. 2):

1. EFL was expressed as percentage of the expired tidal volume over which the NEP-induced flow did not increase above the immediately preceding tidal expiratory flow (EFL%) (Baydur et al., 1997, 2004; Eltayara et al., 1996; Koulouris et al., 1995) for each subject in both postures as the median of 10 acceptable NEP breaths (Figure 3).
2. The magnitude of the decrease in expiratory flow during NEP below the preceding control expiratory curve was expressed as the percentage of the area under the control curve (AUC%, Figure 3), modified from the method of Tamisier et al. (2005). This value was expressed as the median of the same 10 acceptable NEP breaths in each posture.
3. To further improve the discrimination between COPD and OSA, the ratio AUC% EFL% was computed as changes in EFL% and AUC% were not always of the same magnitude or direction. Thus, an increase AUC% EFL% would reflect a greater degree of upper airway EFL rather than intrathoracic EFL, while a decrease with preservation of EFL% would be more consistent with intrathoracic EFL. This quantity was expressed as an arbitrary unit, as the median of the same 10 acceptable NEP breaths in each posture.

This study was the first to quantitatively compare EFL in patients with COPD, non-OSA obesity and OSA in seated and supine postures. Its main findings were:

1. COPD patients exhibited the highest EFL% in seated posture, consistent with intrathoracic flow limitation. Percent EFL increased in all cohorts but COPD upon assuming the supine position.
2. While seated, when compared to other cohorts, OSA patients exhibited a greater tendency to upper airway collapsibility as evidenced by higher AUC% and AUC/% EFL% values, although median values exhibited variability of individual values that prevented differences between cohorts to be statistically significant. In supine posture, COPD patients exhibited the greatest AUC% but not AUC/% EFL%.
3. The AUC% method was able to only differentiate COPD patients from those with mild-moderate OSA in the seated position.
4. The AUC% method demonstrated higher AUC% in patients with OSA than in obese subjects, but was unable to clearly differentiate between the two groups because of overlapping values.

An increase in the AUC% and AUC/% EFL% reflects a greater degree of extrathoracic air-flow limitation (as occurs in obese and OSA subjects) while an increase in EFL% in the absence of an increase in AUC% indicates the presence of intrathoracic flow limitation (as in COPD). Thus, subjects with greater increases in AUC/% EFL% than in EFL% upon assuming supine posture exhibit an increase in upper airway resistance rather than intrathoracic air-flow limitation. At the same time, in patients with COPD, EFL% increases in supine position, a finding more likely to occur as FEV<sub>1</sub> decreases (Baydur et al., 1997, 2004; Eltayara et al., 1996; Koulouris et al., 1995). Variability in measurements using the NEP technique has been similarly reported by others (Hadcroft & Calverley, 2001; Walker et al., 2007) and is likely due to a number of factors, discussed below.

Percent AUC tended to be greater in OSA patients while seated indicating the presence of mechanisms maintaining upper airway patency while supine. By contrast, in COPD patients AUC% was greatest in supine posture, almost twice the value when seated. Thus, mechanisms preserving patency in supine COPD patients seem not to be as effective as in supine obese or OSA individuals. Reductions in lung volume (as occur in supine posture) result in decreases in caudal traction on the upper airway and concomitant increases in upper airway collapsibility (Owens et al., 2010; Squire et al., Thut et al., 1993; Van de Graaf, 1991). In addition, supine positioning promotes laryngeal edema and upper airway narrowing (Jafari & Mohsenin, 2011; Shepard et al., 1996). In COPD, mobilization of secretions when supine may have contributed to this finding. Yet, the finding of an overall increase in EFL% in supine position without concomitant increases in AUC% (or AUC/% EFL%) in most other cohorts indicated a greater degree of intrathoracic tidal EFL [as defined by Koulouris et al (1995)] than extrathoracic FL. This is likely related to decrease in lung volume when supine.)

The differing findings amongst cohorts can be explained thus: During early expiration, there is post-inspiratory inspiratory activity (PIIA) which may negate the effect of NEP. At the beginning of expiration, PIIA may oppose NEP (resistance posed by pliometric contraction [= lengthening] of the inspiratory muscles) (Shee et al., 1985). This implies that NEP should not be applied too early in expiration (when PIIA is high). In our subjects, NEP was applied immediately after the onset of expiratory flow so that PIIA is likely to have influenced variability of EFL within cohorts.

Our method for computing AUC% was similar to that of Tamisier et al. (2005) who devised a quantitative index corresponding to the ratio of the area under the expiratory flow-volume curves between NEP and control tidal volume. They did not, however, study subjects with mild OSA (BMI 5-15), and their control subjects were younger than ours. They also applied NEP near end-expiratory volume which stimulates activation of the genioglossus (Tantucci et al., 1998). This can change the area under the terminal portion of the NEP curve, affecting the quantitative index used to assess the upper airway collapsibility. Our results suggest that obese and OSA patients are more likely to experience upper airway narrowing while seated than COPD patients, indicating reduced PIIA and genioglossus activity in that posture.

There were some methodological limitations in this investigation. This study and those of others (Baydur et al., 2004, 2012; Insalaco et al., 2005; Liistro et al., 1999; Rouatbi et al., 2009; Van Meerhaeghe et al., 2004; Verin et al., 2002) assumed that upper airway collapsibility can be identified solely when expiratory flow during NEP decreases below the control curve. As such, detecting upper airway collapsibility only by computing the span of the preceding control tidal volume over which the NEP curve drops below the control breath may be misleading. It is possible that in this study some patients with upper airway narrowing may not have been identified if they exhibited only a reduction in the increase of expiratory flow (but still greater than the preceding control flow) during NEP.

Another limitation in this study was that sleep studies were not obtained in COPD patients and controls. Sleep-related disordered breathing (SDB) and nocturnal desaturations have been reported in COPD patients, giving rise to an “overlap syndrome” although not all SDB

could be classified as frank sleep apnea (Caterall et al., 1983; Aoki et al., 2005). Care was taken in this study, however, to exclude subjects with symptoms of sleep apnea. None of the obese COPD patients gave a history of symptoms of sleep apnea.

### 3. Conclusion

In conclusion, the EFL% and AUC% methods are useful in determining the magnitude of intrathoracic or extrathoracic FL in patients with COPD and OSA, but fail to distinguish cohorts on the basis of EFL quantification using the area under the curve method because of interindividual variabilities. In this respect, our findings were similar to those of Ferretti, et al. (2006). Pattern recognition of NEP tracings remains the best way to differentiate intrathoracic from extrathoracic EFL.

While the NEP method may be regarded as the new standard for the detection of tidal flow limitation (Koulouris, & Hardavella, 2011), further research should include its validation in conditions other than COPD that exhibit intrathoracic EFL. Comparison with other techniques such as the esophageal balloon, forced oscillation and abdominal compression (probably the easiest and least uncomfortable) methods should provide additional information in this regard. In the assessment of extrathoracic airway FL, the NEP technique offers a means to evaluate upper airway dynamics in patents with OSA, but is not able to differentiate snorers from those with OSA.

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### Abbreviation/Nomenclature list

AHI: Apnea-hypopnea index

AUC: Area under preceding control curve subtended by the NEP curve

BMI: Body mass index

EFL: Expiratory flow limitation

FEV<sub>1</sub>: Forced expiratory volume in 1 second

FRC: Functional residual capacity

FVC: Forced vital capacity

AUC: Area under control tidal curve subtended by the immediately following NEP curve

NEP: Negative expiratory pressure

OSA: Obstructive sleep apnea

PEF: Peak expiratory flow

PIIA, post-inspiratory inspiratory activity

V<sub>t</sub>: Tidal volume

T<sub>i</sub>: Inspiratory time

T<sub>e</sub>: Expiratory time

TLC: Total lung capacity

## Author details

Ahmet Baydur

Division of Pulmonary and Critical Care Medicine, Keck School of Medicine, University of Southern California, Los Angeles CA, USA

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