REVIEW

Auto-PEEP in respiratory failure

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ABSTRACT

Intrinsic positive end-expiratory pressure (auto-PEEP) is a common occurrence in patients with acute respiratory failure requiring mechanical ventilation. Auto-PEEP can cause severe respiratory and hemodynamic compromise. The presence of auto-PEEP should be suspected when airflow at end-exhalation is not zero. In patients receiving controlled mechanical ventilation, auto-PEEP can be estimated measuring the rise in airway pressure during an end-expiratory occlusion maneuver. In patients who trigger the ventilator or who are not connected to a ventilator, auto-PEEP can be estimated by simultaneous recordings of airflow and airway and esophageal pressure, respectively. The best technique to accurately measure auto-PEEP in patients who actively recruit their expiratory muscle remains controversial. Strategies that may reduce auto-PEEP include reduction of minute ventilation, use of small tidal volumes and prolongation of the time available for exhalation. In patients in whom auto-PEEP is caused by expiratory flow limitation, the application of low-levels of external PEEP can reduce dyspnea, reduce work of breathing, improve patient-ventilator interaction and cardiac function, all without worsening hyperinflation. Neurally adjusted ventilatory assist, a novel strategy of ventilatory assist, may improve patient-ventilator interaction in patients with auto-PEEP. *(Minerva Anestesiol 2012;78:201-21)*

Key words: Respiration, artificial - Positive-pressure respiration, intrinsic - Pulmonary disease, chronic obstructive.

In 1982, Pepe and Marini reported the "spontaneous development of positive end-expiratory pressure" in three mechanically-ventilated patients.[1] Two of these patients had chronic obstructive pulmonary disease (COPD) and one had developed airway disease following a thermal injury. The investigators called this spontaneous positive end-expiratory pressure "auto-PEEP".[1] They noted that auto-PEEP could severely depress cardiac output by increasing intrathoracic pressure.[1] Since that early study a wealth of information on auto-PEEP in patients with acute respiratory failure has been published. In this review we will discuss the physiologic basis of auto-PEEP, how to detect and measure auto-PEEP, its clinical implications, and therapeutic strategies. Areas of active research and controversial topics will be highlighted throughout the review.

Physiologic basis of auto-PEEP

In healthy subjects who are breathing at rest the lung volume at end-exhalation approximates the relaxation volume (Vr) of the respiratory system – *i.e.*, the lung volume where the opposing elastic forces of the lungs and chest wall are equal.[2, 3] When these opposing forces are equal expiratory flow is zero (Figure 1). In some mechanically ventilated patients, however, expiratory flow at end-exhalation is not zero. Unless these patients are actively exhaling, persistent expiratory flow at end-exhalation indicates that end-expiratory lung volume (EELV) is larger than Vr. Under these circumstances, the tidal volume delivered by the ventilator will cause a progressive increase in end-inspiratory lung volume (EILV) and EELV (breath stacking). The increase in lung volume is accompanied by a progressive increase

in the caliber of the intrathoracic airways (the larger lung volume will tend to keep the intrathoracic airways open) [4] and a progressive increase in elastic recoil of the lung and, less so, of the chest wall.[5] The combined increase in airway caliber and elastic recoil will result in a higher expiratory flow.[4] When the pressure-volume and pressure-flow relationships are approximately linear,* the expiratory flow at a given time "t" is given by the following equation:[8]

$$\dot{V}exp(t) = \frac{E \cdot V(t)}{R}$$

Where $\dot{V}exp(t)$ and $V(t)$ are the instantaneous expiratory flow and lung volume at a given time "t", and E and R are the elastance and the resistance of the respiratory system. From this equation it is clear that the progressive increase EILV and EELV will continue until the expiratory flow has increased sufficiently to expel the delivered tidal volume within the available time for exhalation (T_E) (Figure 1).[8] At that point, EELV stabilizes above Vr.[5] The volume of gas above Vr remaining in the lungs at the start of a new mechanical inflation (Vtrapped) can be calculated as follows:[8]

$$Vtrapped = \frac{VT}{e^{T_E/\tau} - 1}$$

Where V_T is tidal volume and □ is the time constant of the respiratory system (the product of resistance by compliance).[8] Stated differently, when: (a) the pressure-volume and pressure-flow relationships are approximately linear and (b) the expiratory muscles are not contracting, then mean expiratory flow (V_T/T_E) and the time constant of the respiratory system determine the increase in EELV above Vr.[8]

An increase in EELV above Vr is commonly referred as dynamic pulmonary hyperinflation.[5] Dynamic pulmonary hyperinflation (a "volume" phenomenon) is almost invariably associated with an increase in the end-expiratory elastic recoil of the respiratory system (a "pressure" phenomenon). Such increase in end-expiratory elastic recoil has been called auto-PEEP [1] or intrinsic-PEEP.[10] Auto-PEEP has been reported in all mechanically ventilated patients with COPD, and in more than one-third of patients with acute respiratory failure with no history of COPD [11] – including patients with ARDS, sepsis, and respiratory muscle weakness.[11-14] A common mechanism for the development of auto-PEEP is an increase in the expiratory time constant of the respiratory system (see below).[5]

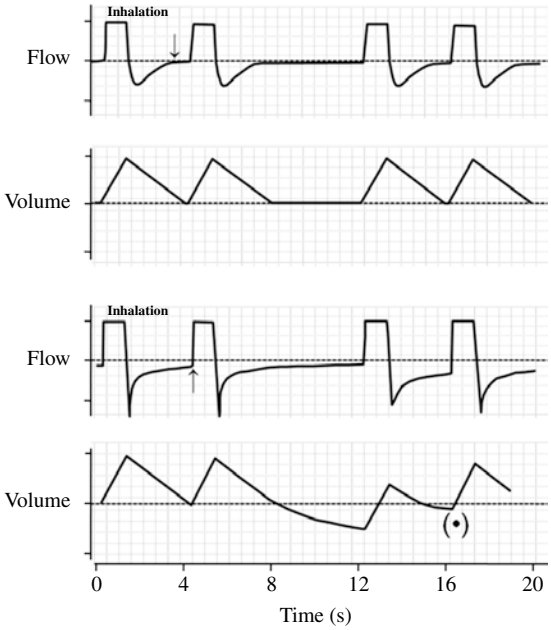

Figure 1.—Schematic representation of the flow/time and volume/time relations in a healthy subject (upper panel) and in a patient with COPD (lower panel). Both are ventilated with controlled mechanical ventilation (CMV) with a respiratory rate of 15 breaths/min, inspiratory time (T_I) of 1 s, and expiratory time (T_E) of 3 s. A 3-second delay in mechanical inhalation occurs after the second CMV breath.
In the healthy subject, expiratory flow returns to zero (□) before the end of exhalation. Therefore, during the additional time available for exhalation no flow is recorded. This finding suggests that at the end of each exhalation the lung volume approximates the relaxation volume of the respiratory system – *i.e.,* the lung volume where the opposing elastic forces of the lungs and chest wall are equal.
In the patient with COPD, expiratory flow is still present at the end of exhalation (□). When the duration of T_E is doubled (second CMV breath), expiratory flow continues throughout exhalation and still it does not return to zero at the onset of the next breath. The persistence of expiratory flow at the onset of the next breath indicates that the lung volume is still greater than the relaxation volume of the respiratory system (hyperinflation) and that alveolar pressure is positive – *i.e.,* the elastic recoil pressure of the respiratory system is increased. Such elevation in elastic recoil pressure is referred as auto-PEEP. Resumption of CMV (last two breaths) is associated with incomplete lung emptying (•).

* Lung mechanics are not strictly linear [5-7] nevertheless, as long as tidal volume is not excessive and there is no expiratory flow limitation the linearity approximation is acceptable.

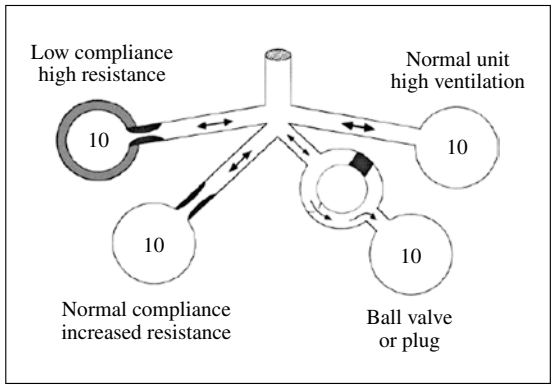

Figure 2.—Schematic representation of the mechanisms involved in the development of auto-PEEP. Auto-PEEP can occur in normal lung units as a result of increased ventilation *(upper right),* one-way valve physiology (*e.g.,* mucus plug, *lower right*), or a long expiratory time constant (product of compliance and resistance, *upper and lower left*). As illustrated in the left upper and lower lung units, the same auto-PEEP value (in all these examples auto-PEEP is 10 cm H_2O) may be associated with hyperinflation *(lower left),* or it may not be associated with hyperinflation *(upper left)* depending on the mechanism responsible for the prolongation of the time constant (from Marini JJ *et al.*).[42]

Other mechanisms include decreases in T_E, increases in tidal volume, increased external flow resistance and persistent inspiratory muscle activity during exhalation (Figure 2).[5, 15 **]

Auto-PEEP caused by increases in expiratory time constant and expiratory flow limitation

As stated above, compliance and resistance of the respiratory system are important determinants of expiratory flow during passive exhalation.[8] If the compliance is increased, such as in patients with COPD, the driving pressure that expels gas from the lung will be reduced. A reduced driving pressure diminishes expiratory flow. Similarly, expiratory flow can be reduced when resistance is increased. Increased resistance can result from a fixed reduction in the lumen of the airways ("ohmic" resistance) such as in obstructive bronchiolitis, asthma (including "glottis braking") [16] and upper airway obstruction. Increased resistance can also result from airway narrowing during exhalation. Airway narrowing during exhalation causes expiratory flow limitation (EFL) – a condition where an increase in transpulmonary pressure at a given lung volume cannot increase expiratory flow.[17] EFL always occurs during forceful exhalation – even in healthy subjects.[18] EFL can also occur during resting breathing.[18] In the latter case it entails a pathological tendency of the small airways to cave in because of damage to the elastic scaffold surrounding the airways (*e.g.*, COPD) [18] or because of increased weight of the lung (*e.g.*, ARDS) [12] or of the respiratory system (*e.g.*, obesity).[9, 19] EFL during resting breathing occurs in 60% of clinically stable patients with COPD,[20] and always during acute exacerbations.[5] Patients with EFL experience true "air trapping" whereby activation of the expiratory muscles increases alveolar pressure without increase in expiratory flow.[5, 21] An additional mechanism responsible for EFL is the, so-called, wave speed limitation [22, 23] – *i.e.*, the tracheobronchial tree cannot adjust an airflow more rapidly than the velocity at which pressure travels along the airways.[24] The speed of wave propagation decreases with a reduction in the cross-sectional area of the airways, a raise in gas density, and a decrease in airway wall elastance.[24] An extreme form of impediment to expiratory flow occurs when there is complete collapse of the small airways during exhalation with obliteration their lumen. In this case expiratory flow ceases and closing volume encroaches into EELV (see excellent review by Milic-Emili *et al.*).[25]

The effect of compliance and ohmic resistance on expiratory flow can be mathematically summarized in terms of time constant: □ = resistance x compliance. Time constant describes the exponential decrease of lung volume during passive exhalation.[1, 26] In healthy subjects a model of the respiratory system with one time constant is sufficient to describe passive exhalation. In contrast, patients with lung diseases, such as patients with acute respiratory failure, have considerable regional difference in the mechanical properties of the lungs. This heterogeneity precludes the description of lung mechanics with a single time constant.[26] Moreover, in any intubated patient, the additional

** Some exceptions to this rule include patients with ARDS where EELV can be less than predicted yet auto-PEEP may be present, and some patients with COPD during resting breathing in whom the loss of elastic recoil of the lungs causes the relaxation volume to move to a higher volume (static hyperinflation) even in the absence of auto-PEEP [9].

resistance of the ventilator circuit further negates a single time constant.[5] In addition, for patients with EFL, expiratory flow becomes independent of driving pressure (be it elastic recoil or expiratory muscle contraction), and resistance becomes effort-dependent. In other words, in presence of EFL it is not possible to calculate the expiratory time constant. Patients with increased time constants and with EFL are at risk of developing auto-PEEP because of the increased time required to exhale to Vr.

Auto-PEEP caused by a decrease in T_E

When T_E is too short, auto-PEEP follows. For example, healthy subjects have a time constant of about 0.2 s (compliance =0.1 L/cm H_2O and resistance =2 cm $H_2O \times L^{-1}$).[5] Considering that it takes a time interval equal to one time constant for the passive exhalation of 64% of volume, a T_E>4 time constants (*i.e.*,>0.8 s in healthy subjects) is necessary for complete passive exhalation.[5] In the clinical setting, a short T_E can result from the patient's own breathing pattern or from the ventilator settings – including the use of high ventilatory frequencies and prolonged inspiratory time (T_I). Prolonged T_I can result from the use of low inspiratory flow rates or end-inspiratory pauses.[5] End-inspiratory pauses promote auto-PEEP due to shortening T_E and by decreasing end-expiratory elastic recoil.[5] The latter phenomenon is caused by stress relaxation.[5]

Auto-PEEP caused by persistent inspiratory muscle activity during exhalation

In asthmatic patients, postinspiratory activity of the diaphragm and rib cage inspiratory muscles can brake expiratory flow.[9] As a result lung volume at end-exhalation does not fall to Vr.[9] The active increase in EELV may maintain airway patency and minimize flow limitation during bronchoconstriction. Postinspiratory activity of the inspiratory muscles has also been reported in obese patients [9] and even in healthy volunteers.[15]

Auto-PEEP caused by an increase in tidal volume

Large tidal volumes during controlled or assisted mechanical ventilation (and during spontaneous respiration) increase the elastic recoil at end-inhalation. This increase in elastic recoil enhances the driving pressure that expels gas from the lung at the beginning of exhalation. When the lung volume decreases, however, the driving pressure will decrease as well. If T_E is relatively short for the patient's time constant, auto-PEEP will occur despite the initial high expiratory flow rate.[27]

Auto-PEEP caused by an increase in external flow resistance

The time constant of a patient who is intubated and mechanically ventilated is affected by flow resistance that is external to the patient. The increase in external resistance is due to the resistance of the endotracheal tube (particularly when the tube has concretions or is partially bent),[28] and also of the ventilator tubing, exhalation valves and external PEEP.[5] Even in an intubated patient with healthy lungs total expiratory resistance (across lungs, endotracheal tube, and exhalation valves) may exceed 10 cm H_2O/L/s (normal, <4 cm H_2O/L/s), enough to cause measurable auto-PEEP when the minute ventilation exceeds 20 L/min.[21]

Implications of auto-PEEP

Auto-PEEP has detrimental effects on the respiratory system (respiratory mechanics, respiratory muscles, patient-ventilator interaction and gas exchange), on the cardiovascular system and on patient's monitoring.

Respiratory mechanics, respiratory muscles, patient-ventilator interaction and gas exchange

In most instances auto-PEEP is associated with increased EILV.[5] When excessive, increased EILV can cause alveolar overdistension, reduce lung compliance, and increase the elastic work of breathing. The positive pressure in the alveolus at the end of exhalation means that the patient has to first generate negative inspiratory pressure equal in magnitude to this level of pressure before inspiratory flow can be initiated – *i.e.*, threshold inspiratory load.[29]

During assisted modes of ventilation – where ventilatory assistance is triggered by changes in airway pressure or airflow – the threshold load of inspiration associated with auto-PEEP can promote dyspnea and poor patient-ventilator interaction including delayed triggering and ineffective trigger efforts.[27] Poor patient-ventilator interaction has been associated with greater use of sedation,[30] sleep disruption,[31] prolonged duration of mechanical ventilation,[32] and overall worse prognosis.[33]

In addition to increased elastic and threshold work of breathing, auto-PEEP impairs respiratory muscle function by worsening the length-tension relationship of the respiratory muscles by decreasing the zone of apposition (decreased "bucket handle" movement of the lower rib cage) [9, 29] and by impairing inspiratory muscle perfusion.[34] It is likely that the alveolar overdistension caused by auto-PEEP can increase the risk of barotraumas.[29]

Auto-PEEP can contribute to hypoxemia in patients requiring mechanical ventilation [35] possibly as a result of inhomogeneous distribution of inspired gas between lung units with different time constants.[12, 35]

Circulation

The rise in intrathoracic pressure associated with auto-PEEP can decrease venous return (decreased preload) and it can increase pulmonary vascular resistance and, thus, right ventricular afterload.[36] In addition, during partial ventilator support, auto-PEEP can augment left ventricular afterload due to the increased negative intrapleural pressure generated by the patient when he/she triggers the ventilator. All these phenomena can severely decrease cardiac output.[1, 35]

Overzealous manual ventilation during cardiopulmonary resuscitation can cause auto-PEEP. This can be sufficiently severe to precipitate electromechanical dissociation and the return of spontaneous circulation after the resuscitative (and ventilatory) efforts are discontinued – so called autoresuscitation or Lazarus phenomenon.[37-39]

All the cardiovascular effects of auto-PEEP may be exaggerated in COPD because the abnormally compliant lungs transmit a high fraction of alveolar pressure to the intrathoracic vessels.[1] Stated differently, the hemodynamic and energetic costs of auto-PEEP and the risk of barotrauma mostly correlate to increases in lung and chest wall volume (dynamic hyperinflation) rather than increases in alveolar pressure for itself.[40] Therefore the stiffer the lungs or chest wall the lesser the hemodynamic, energetic and barotrauma consequences of auto-PEEP.

Monitoring

Static compliance of the respiratory system in ventilator-supported patients is calculated by dividing V_T by the difference between plateau pressure measured at the airway during an occlusion at end-inspiration and the external PEEP applied by the ventilator. In patients with auto-PEEP, this calculation can underestimate true static compliance by up to 48%.[10, 29] To avoid this error, static compliance must always be calculated as a ratio between tidal volume and plateau pressure minus end-expiratory occlusion pressure.[29]

When auto-PEEP causes ineffective efforts (non-triggered breaths) errors in estimating the patient's respiratory rate will follow.

Respiratory muscle strength is usually assessed by measuring maximum inspiratory pressure ($P_{I,max}$). In patients with auto-PEEP the inspiratory muscles must first overcome that threshold load. This means that the recorded $P_{I,max}$ underestimates the total pressure developed by the inspiratory muscles, yet it represents the portion of $P_{I,max}$ available to generate airflow.[29]

Dynamic hyperinflation associated with auto-PEEP magnifies the respiratory variation of arterial pulse pressure.[41] This can cause a pathologic *pulsus paradoxus* (>10 mmHg) and it can cause fluctuations in the pulse oximetry tracing in the absence of constrictive pericarditis, restrictive cardiomyopathy and other cardiac pathologies.[41] The increase of intrathoracic pressure associated with auto-PEEP can also falsely elevate pulmonary artery wedge pressure.[1] Failure to recognize this overestimation

may lead to inappropriate fluid restriction or unnecessary vasopressor therapy.[1]

When to suspect the presence of auto-PEEP

Auto-PEEP (and dynamic hyperinflation) should be suspected in any patient with persistent expiratory flow at end-exhalation as displayed in the ventilator monitor or inferred from the auscultation of wheezing that continues to end-exhalation (Figure 1).[42] When expiratory muscle recruitment is present, expiratory flow at end-exhalation can result from a combination of auto-PEEP plus active exhalation [43-45] or active exhalation alone.[46] Even when exhalation is passive, the magnitude of end-expiratory flow bears little relation to the magnitude of auto-PEEP in a given patient over time or among patients.[42] A given end-expiratory flow can result from moderate localized obstruction or widespread severe obstruction. End-expiratory flow will be greater when some communication between hyperinflated alveoli and distal airway – albeit difficult – is still present than when airways open during inhalation but seal before end-exhalation is completed or when airways are completely occluded (*e.g.*, mucus plugs) and alveoli receive some gas through collateral ventilation.[41]

Other situations when auto-PEEP (and dynamic hyperinflation) should be suspected include the presence of poor patient-ventilator interaction,[27] high plateau pressures,[10, 29] fluctuations in the pulse oximetry tracing,[41] pathologic *pulsus paradoxus* [41] and development of hypotension or electromechanical dissociation following endotracheal intubation and commencement of manual or mechanical ventilation.[37-39]

Measurement of auto-PEEP

Auto-PEEP can be estimated by measuring the changes in airway pressure (Paw) at end-exhalation (static auto-PEEP) or the changes in Paw or esophageal pressure (Pes) at the start of inhalation (dynamic auto-PEEP). The methods to measure auto-PEEP vary whether the patient is passively ventilated or is actively breathing: [5, 29]

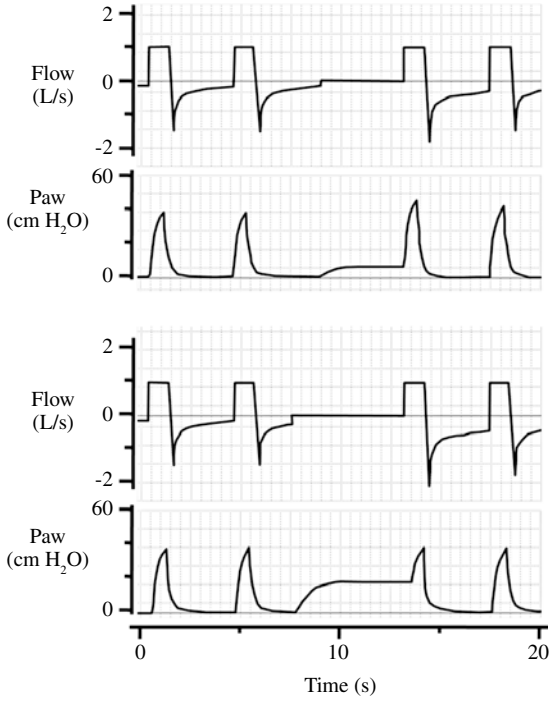

Figure 3.—Schematic representation of the measurement of static auto-PEEP by single-breath end-expiratory airway occlusion in a mechanically ventilated patient with COPD during controlled mechanical ventilation (CMV). In the upper panel the end-expiratory airway occlusion is carried out exactly when the third CMV breath should have taken place. The recorded static auto-PEEP is 8 cm H_2O. In the lower panel end-expiratory airway occlusion is carried out shortly after the start of exhalation. The recorded static auto-PEEP is 22 cm H_2O. End-expiratory airway occlusion carried out too early during exhalation produces an overestimation of static auto-PEEP.
Paw: airway pressure.

Measurement of auto-PEEP in passively ventilated patients

Measurements of "static" auto-PEEP in passively ventilated patients

End-expiratory airway occlusion method.—This method requires the occlusion of the airway at end-exhalation (Figure 3). The end-of-occlusion to pre-occlusion difference in Paw is known as static auto-PEEP. The end-of-occlusion Paw to atmospheric pressure difference is known as total-PEEP. If no external PEEP is used, static auto-PEEP and total-PEEP are equivalent. When auto-PEEP is present, the rise in Paw during the occlusion maneuver should continue until a plateau is reached, usually in less than 4 s.[5] The

delayed plateau in Paw is caused by stress adaptation phenomena and by time-constant inequalities.[5] In other words, static auto-PEEP represents the average measurable auto-PEEP within a non-homogeneous lung after equilibration of alveolar pressure among patent lung units with varying time constants. This technique cannot detect the contribution of increased alveolar pressure distal to airways that are completely occluded during exhalation.[47] For this reason, some experts advocate the measurement of end-inspiratory plateau airway pressures as a more sensitive tool to monitor the potential perils of dynamic hyperinflation over the more approximate estimations of auto-PEEP with the end-expiratory occlusion method.[42, 47] (Measurements of plateau pressure to estimate dynamic hyperinflation can be used even in patients who gently trigger the ventilator).[42]

Timing and location of occlusion are important technical aspects of the end-expiratory airway occlusion method. During controlled mechanical ventilation (CMV), airway occlusion must occur at the end of the set exhalation period, just before the ventilator's inspiratory flow is supposed to start. Occlusions applied too early during exhalation overestimate auto-PEEP (Figure 3) – or suggest its presence when no auto-PEEP exists. Most modern ventilators are equipped with an end-expiratory airway occlusion hold option that occludes the expiratory port at the end of the ventilator respiratory cycle. Occlusions can be also performed manually. Auto-PEEP values recorded with manual occlusions are accurate as long the occlusion is applied within the last 0.5 s of T_E.[5] In patients with severe asthma the end-expiratory airway occlusion method can occasionally produce unexpectedly low values of static auto-PEEP, presumably because widespread airway closure precludes correct measurement of alveolar pressure at end-exhalation.[47]

Occlusion of the airway at the exhalation port is associated with gas compression within the ventilator tubing plus humidifier.[5] This artifact can cause an underestimation of auto-PEEP ranging from 2 to 9 cm H_2O.[48] Strategies that can decrease this artifact include the use of shorter ventilator tubes and the removal of the humidifier during the occlusion maneuver.[5] Alternatively, the artifact can be reduced by using a pneumatic valve at the airway opening.[5]

Measurements of "dynamic" auto-PEEP in passively ventilated patients

Paw change preceding inspiratory flow.—Dynamic auto-PEEP is measured as the increase in Paw from end-exhalation to the point corresponding to the onset of inspiratory flow (Figure 4).[10]This method presupposes that the rise in Paw preceding inspiratory flow mirrors the pressure needed to counterbalance the elastic recoil of the respiratory system at end-exhalation.[10] Due to time constant inequalities between lung units, the end-expiratory elastic recoil may not be distributed homogeneously.[49] It follows that auto-PEEP measured as the increase in Paw pre-

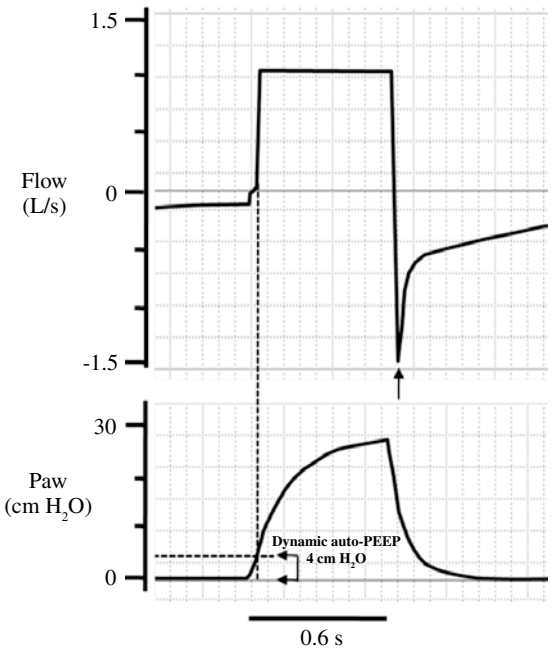

Figure 4.—Measurement of dynamic auto-PEEP as the increase in airway pressure (Paw) from end-exhalation to the point corresponding to the onset of inspiratory flow in a patient with COPD and pneumonia during controlled mechanical ventilation. The recorded dynamic auto-PEEP is 4 cm H_2O. Of interest, expiratory flow exhibits an initial peak – or supramaximal flow transient (□) – followed by a sharp decline. Whenever a supramaximal flow transient is detected, expiratory flow limitation should be suspected (see text for details).

ceding inspiratory flow represents the pressure required to start inspiratory flow in lung units with the shortest time constants and the fastest exhalation (minimum auto-PEEP). This characteristic of dynamic auto-PEEP raises several points. First, dynamic auto-PEEP underestimates the magnitude of static auto-PEEP, at times by as much as 90%.[50] Second, the true clinical impact of auto-PEEP can be misjudged if only dynamic auto-PEEP is considered.[5] Finally, the difference between dynamic and static auto-PEEP – often reported as the ratio of dynamic to static auto-PEEP or "inequality index" [12] – can estimate the severity of time constant inequalities of the respiratory system.[50] In a study of paralyzed, mechanically ventilated patients, Maltais *et al.*[50] reported a smaller inequality index in patients with airway obstruction, 0.36±0.06, than in patients without airway obstruction, 0.87±0.05.

Measurement of auto-PEEP in actively breathing patients

Measurements of "static" auto-PEEP in actively breathing patients

End-expiratory airway occlusion method: occlusion of one breath.—This method is identical to the occlusion method used in passively ventilated patients (Figure 3).[51] Correct timing of occlusion and the patient's own inspiratory effort make this technique potentially inaccurate and impractical (see below).

End-expiratory airway occlusion method: occlusion of several breaths.—This method requires occlusion of the airway for several breaths starting from end-exhalation.[46, 52, 53] A plateau in Paw between inspiratory efforts indicates equilibration of alveolar and airway opening pressures

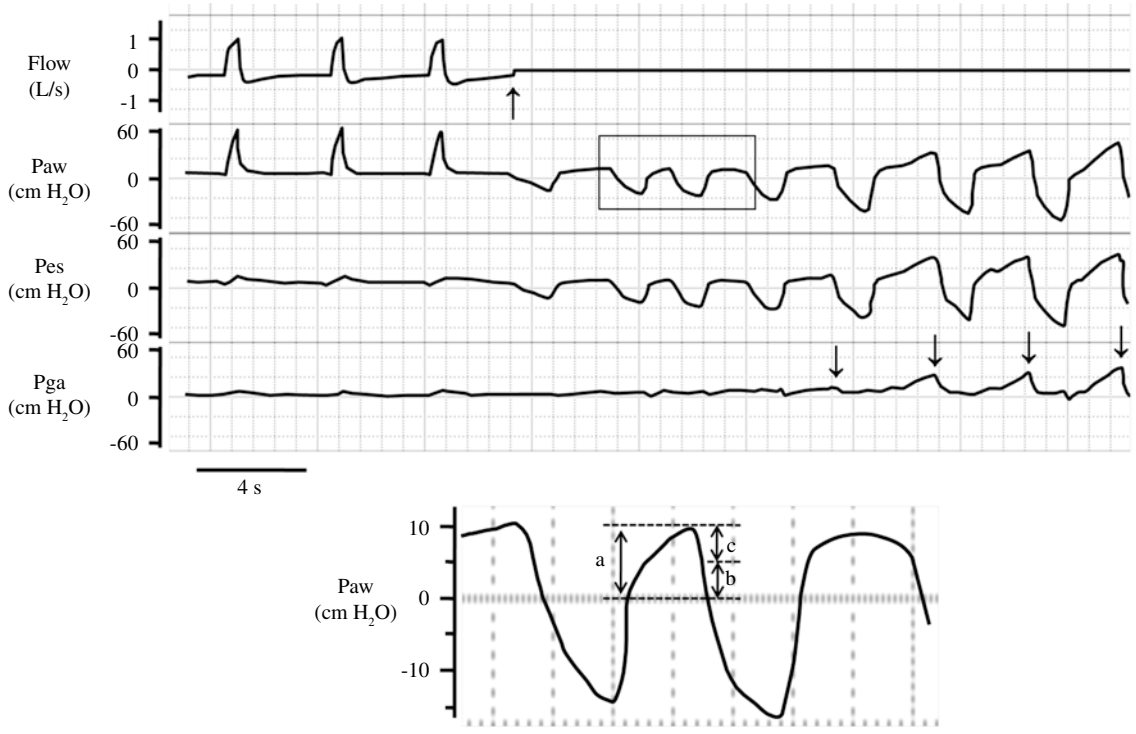

Figure 5.—Upper panel: Tracings of flow, airway pressure (Paw), esophageal pressure (Pes) and gastric pressure (Pga) in a patient recovering from acute respiratory failure while receiving assist-control ventilation and external PEEP of 5 cm H_2O. Following the third assisted breath, the airway was manually occluded (□) at end-exhalation and it was maintained closed for several consecutive efforts. During the first three occluded exhalations the plateau in airway pressure is 10 cm H_2O (inset, lower panel). This is the value of total PEEP (a). Considering that external PEEP (b) was set at 5 cm H_2O the resultant static auto-PEEP (c) is 5 cm H_2O (a-b=c). Measurement of static auto-PEEP in spontaneously breathing patients is often unsatisfactory due to the frequent recruitment of the expiratory muscles during the occlusion maneuver as reflected by the progressively increase in Pga at end-exhalation during the last four occluded breaths (□).

and relaxation of the respiratory muscles.[53] This plateau pressure represents the elastic recoil of the total respiratory system (static auto-PEEP). If the patient is receiving external PEEP or continuous positive airway pressure (CPAP), the end-expiratory Paw during unconcluded breathing is subtracted from the end-expiratory plateau in Paw during airway occlusion (Figure 5).[53]

Unfortunately, measurement of static auto-PEEP in actively breathing patients is often unsatisfactory or impossible for several reasons. First, expiratory muscle contraction can increase end-expiratory alveolar pressure and Paw independently of underlying pulmonary hyperinflation (Figure 5). Second, patients react to end-expiratory occlusions in an unpredictable manner.[29] Third, the variability of neural T_E (a common occurrence in a spontaneously breathing patient) [46] has unpredictable effects on the time available to exhalation and, thus, on the level of auto-PEEP the patient experiences when the airway is not occluded. Finally, the arithmetic approach of subtracting total PEEP from external PEEP to obtain static auto-PEEP can be used only in the absence of expiratory flow limitation.

Measurements of "dynamic" auto-PEEP in actively breathing patients

Paw change preceding inspiratory flow.—This method cannot be used to detect dynamic auto-PEEP because any evidence of dynamic auto-PEEP is hidden by the negative deflection in Paw taking place when the patient triggers the ventilator.

Pes change preceding inspiratory flow ("counterbalance method").—This technique requires the insertion of an esophageal balloon catheter system to estimate changes in pleural pressure. Dynamic auto-PEEP is measured as the deflection in Pes from the beginning of inspiratory effort to the onset of inspiratory flow (Figure 6).[45, 46] The Pes-counterbalance method is based on several assumptions.[29] First, the end-expiratory alveolar pressure represents the elastic recoil pressure of the relaxed respiratory system. Second, the change in Pes from the beginning of inspiratory effort to the onset of inspiratory flow reflects the inspiratory muscle pressure required to counterbalance the end-expiratory elastic recoil of the respiratory system. Finally, it assumes absent expiratory muscle contraction at end-exhalation. If expiratory muscle contraction is present at end-exhalation, the decrease in Pes at the start of inhalation will reflect, in part, the relaxation of the expiratory muscles rather than inspiratory muscle contraction alone.[29]

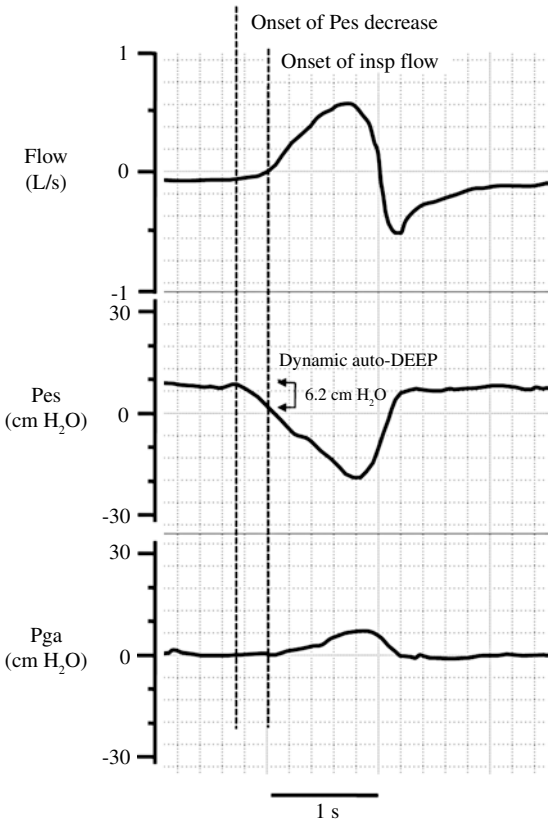

Figure 6.—Recordings of flow, esophageal pressure (Pes) and gastric pressure (Pga) illustrating the esophageal pressure counterbalance method for measuring dynamic auto-PEEP during spontaneous respiration in a patient undergoing a weaning from mechanical ventilation. The first vertical line indicates the onset of inspiratory effort – as determined by the decrease in Pes. The second vertical line indicates the onset of inspiratory flow. Dynamic auto-PEEP is measured as the negative deflection in Pes from the start of inspiratory effort to the onset of inspiratory flow. The gastric signal is flat during exhalation suggesting absent expiratory muscle recruitment.

Several methods to correct for expiratory muscle recruitment have been proposed.[43, 46, 55-57] Appendini *et al.*[55] suggested that dynamic auto-PEEP can be obtained by measuring the

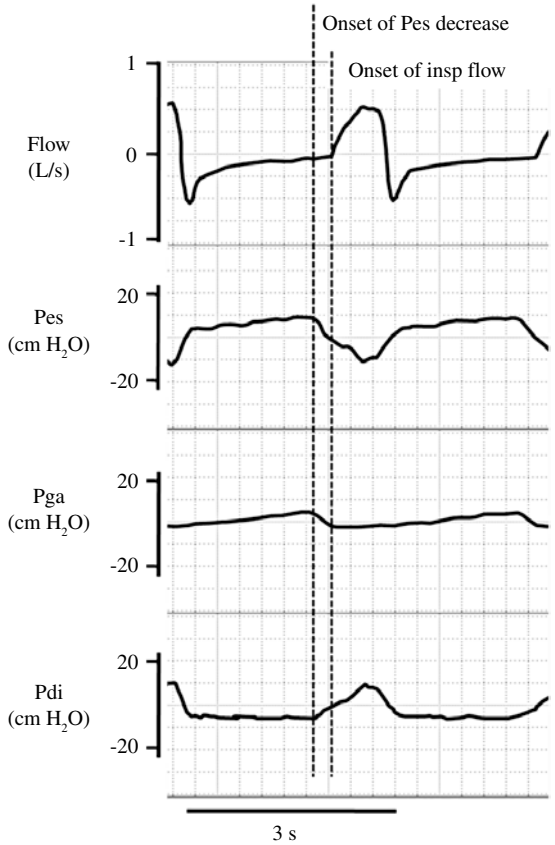

Figure 7.—Experimental recordings illustrating the method of Appendini *et al.*[55] used to calculate dynamic auto-PEEP during spontaneous unconcluded breathing in a patient with active expiratory muscle recruitment (expiratory rise in gastric pressure). From top to bottom tracings of flow, esophageal pressure (Pes), gastric pressure (Pga) and transdiaphragmatic pressure (Pdi). The first vertical line indicates the onset of inspiratory effort – as determined by the increase in Pdi. The second vertical line indicates the onset of inspiratory flow. Pga increases through most of exhalation. At the onset of inspiratory effort (increase in Pdi, first vertical line), Pga becomes less positive. With the method of Appendini *et al.*, dynamic auto-PEEP is calculated by subtracting the negative deflection in Pga from the negative deflection in Pes during the interval between the onset of increase in Pdi until the onset of inspiratory flow.

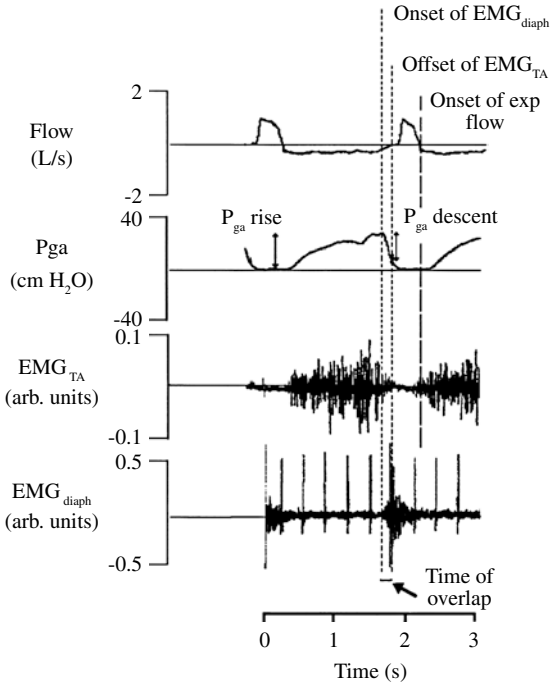

Figure 8.—Tracings of flow, gastric pressure (Pga), electromyogram of the transversus abdominis (EMG_{TA}) and electromyogram of the diaphragm (EMG_{diaph}) in a healthy subject receiving pressure support ventilation of 20 cm H_2O in whom airflow limitation was induced with a Starling resistor. During the descent in gastric pressure there is a simultaneous decrease activity of the transversus abdominis and an increase activity of the diaphragm, as measured from their respective EMG signals. (From Parthasarathy *et al.*).[48]

rise in transdiaphragmatic pressure (Pdi) from the beginning of inspiratory effort to the onset of inspiratory flow (Figure 7).[55] This approach is based on the assumption that during the interval of auto-PEEP measurement the decrease in Pga results only from expiratory muscle relaxation. A theoretical problem with this method is that it ignores that a decrease in Pga due to expiratory muscle relaxation could be accompanied by an increase in Pga due to diaphragmatic contraction (Figure 8).[29, 43] The relative magnitude of these two processes cannot be accurately apportioned.[5, 29]

Lessard *et al.*[46] proposed that the contribution of expiratory muscle contraction to auto-PEEP could be estimated by measuring the increase in Pga between its end-inspiratory level and its maximal level at end-exhalation (Figure 9). The assumption here is that the diaphragm has no phasic activity during exhalation and thus functions as a passive membrane during exhalation; consequently, the effect of contraction of all expiratory muscles is reflected by an increase in Pga, which in turn is transmitted to the alveolar space. This method may also be in error since it underestimates activity of the expiratory intercostal muscles if their force generation is poorly transmitted to the abdominal cavity.[29, 46] In addi-

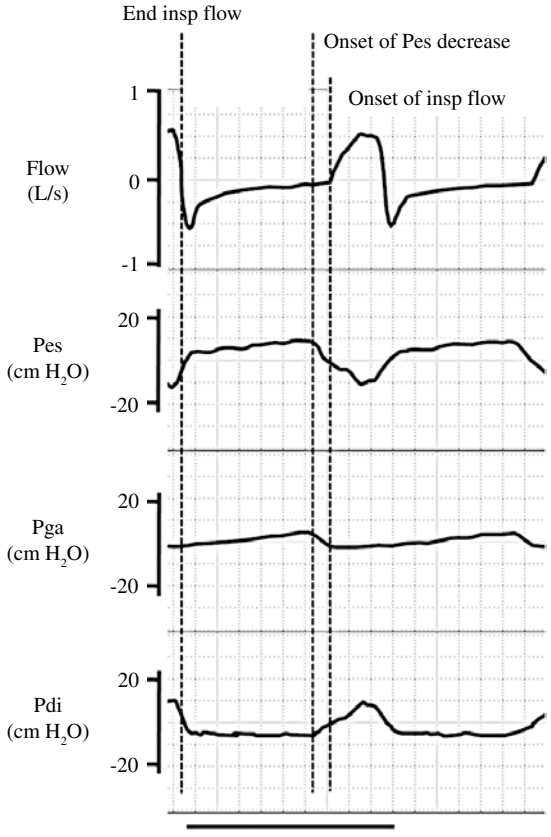

Figure 9.—Experimental recordings (same as Figure 6) illustrating the method of Lessard *et al.*[46] used to calculate dynamic auto-PEEP during spontaneous unconcluded breathing in a representative patient with active expiratory muscle recruitment. From top to bottom tracings of flow, esophageal pressure (Pes), gastric pressure (Pga) and transdiaphragmatic pressure (Pdi). The first vertical line indicates the end of inspiratory flow. The second vertical line indicates the abrupt decrease in Pes. The third vertical line indicates the onset of inspiratory flow. The extent of active expiratory muscle recruitment is quantified as the expiratory rise in Pga from the end of inspiratory flow (first vertical line) to its maximal level at end-exhalation (second vertical line). (In most patients with active expiratory muscle recruitment the maximal level of Pga at end-exhalation coincides with the abrupt pressure decay in Pes).[46] With the method of Lessard *et al.*, dynamic auto-PEEP was calculated by subtracting the expiratory rise in Pga from the negative deflection in Pes during the interval between the abrupt decrease in Pes until the onset of inspiratory flow.

tion, this approach may be inaccurate since it ignores postinspiratory activity of the diaphragm, which will hinder the transmission of abdominal pressure;[29] however, such activity is uncommon in patients with COPD.[46, 54]

Parthasarathy *et al.*[43] compared the two proposed methodologies obtaining electromyographic (EMG) recordings of the transversus abdominis muscle in healthy subjects receiving pressure support ventilation. To bring on contraction of the transversus abdominis muscle, airflow limitation was induced with a Starling resistor. The investigators found that the correction factor of Lessard *et al.*[46] (the expiratory increase in Pga) correlated well with transversus abdominis EMG activity (r=0.70 to 0.95). In contrast, the correction factor of Appendini *et al.*[55] (the early inspiratory decrease in Pga) showed a weaker correlation with transversus abdominis EMG activity (r=0.04 to 0.53). More recently, Zakynthinos *et al.*[57] compared the two proposed methodologies constructing Campbell diagrams in 15 patients who required ventilator support. These investigators found that the correction factor of Appendini *et al.*[55] (the early inspiratory decrease in Pga) performed better than the correction factor of Lessard *et al.*[46] (the expiratory increase in Pga). The differences between the methods were, however, small (2-3 cm H_2O). In summary, the studies on dynamic auto-PEEP [43, 46, 55, 57] highlight the complexity of its measurement and underscore the fact that there is still no consensus on the optimal method to correct for the effect of expiratory muscle activity on the measurement of dynamic auto-PEEP.[58]

An additional confounding factor when calculating dynamic auto-PEEP is the breath-to-breath variability in the duration of neural T_E.[46] This phenomenon causes a variable duration of lung emptying, which, in turn, can cause large fluctuations auto-PEEP even over short periods of time.[27, 46] Systematic investigations of this additional confounder in the determination of dynamic auto-PEEP are not available.

Respiratory inductive plethysmography technique. With this technique dynamic auto-PEEP is estimated by identifying the level of external PEEP necessary to increase thoracic gas volume.[59, 60] This approach is appropriate for patients with EFL – *i.e.*, in patients without EFL any level of external PEEP should increase lung volume, and precludes accurate determination of auto-PEEP.[61] Factors to consider when using this technique include the difficulty to maintain stable calibration of the inductive plethysmo-

graph over time and the fact that application of excessive external PEEP can trigger expiratory muscle recruitment and, thus, may prevent clear changes in lung volume from taking place.[52]

Detection of expiratory flow limitation

Supramaximal flow transient at the beginning of exhalation

EFL should be suspected when the expiratory flow exhibits an initial peak – or supramaximal flow transient – followed by a sharp decline (Figure 4). It has been reasoned that the supramaximal flow transient is caused by the rapid expulsion of gas from the collapsing tracheobronchial tree.[62, 63]

Peak airway pressure while increasing external PEEP

When patients are receiving volume cycled ventilation the application of low-levels of external PEEP will cause little-to-no changes in peak and plateau airway pressures (Figure 10) [51] and little-to-no changes in end-expiratory lung volume [5] when auto-PEEP is primarily due to EFL. This happens because low-levels of external PEEP do not reach the alveoli until a "critical" pressure is exceeded – the so called waterfall phenomenon.[52, 61] In contrast, when auto-PEEP is not due to EFL, the application of low-levels of external PEEP will cause a more or less equivalent rise in peak and plateau airway pressures (Figure 10) (see below).[51]

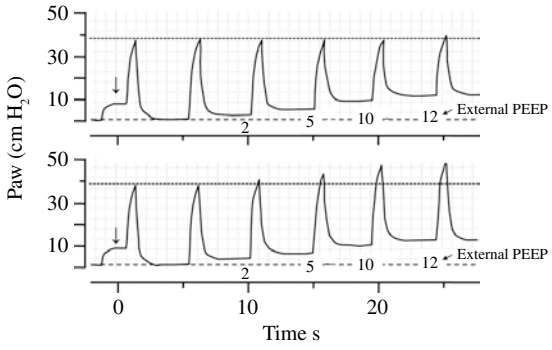

Figure 10.—Schematic representation of airway pressure (Paw) versus time during controlled mechanical ventilation as external PEEP is increased from 0 to 12 cm H_2O in a patient with expiratory flow limitation (upper panel) and in a patient without expiratory flow limitation (lower panel). In both patients static auto-PEEP determined by the end-expiratory airway occlusion technique (□) is 10 cm H_2O. In the presence of expiratory flow limitation (upper panel), peak airway pressure (dotted line) increases only when external PEEP was 12 cm H_2O. In the absence of expiratory flow limitation (lower panel), application of external PEEP caused a proportional increase in peak airway pressure. The qualitative responses to external PEEP seen with peak airway pressure would be expected to occur also with plateau pressure (see text for details).

Tidal volume while increasing external PEEP

When auto-PEEP is primarily due to EFL – and patients are receiving pressure-cycled ventilation – application of low-levels of external PEEP will cause little-to-no changes tidal volume.[42] In contrast, when auto-PEEP is not due to EFL, application of low-levels of external PEEP will cause an immediate decrease in tidal volume.

Removal of low levels of PEEP

When auto-PEEP is primarily due to EFL, removal of low levels of external PEEP cause minimal-to-no increases in driving pressure and thus minimal-to-no increases expiratory flow (waterfall phenomenon).[52, 61] In contrast, when auto-PEEP is not due to EFL, removal of low levels of external PEEP will increases driving pressure and expiratory flow (Figure 11).

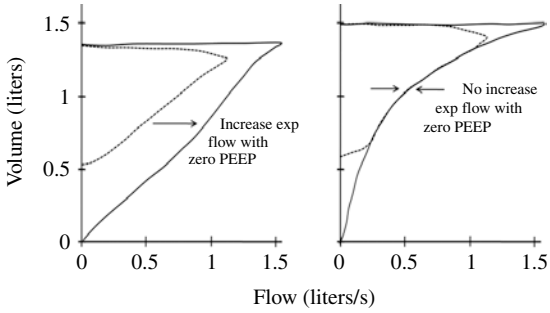

Figure 11.—Representative expiratory volume-flow plots during passive exhalation in a patient with ARDS (left panel) and a patient with COPD (right panel) while receiving external PEEP of 5 cm H_2O (dotted line) and while receiving no external PEEP (solid line). In the absence of PEEP, expiratory flow increased in the patient with ARDS. In contrast, with and without PEEP there was no change in expiratory flow in the patient with COPD. The absent effect of low level of PEEP on expiratory flow is suggestive of expiratory flow limitation (modified from Rossi A *et al.*[5]).

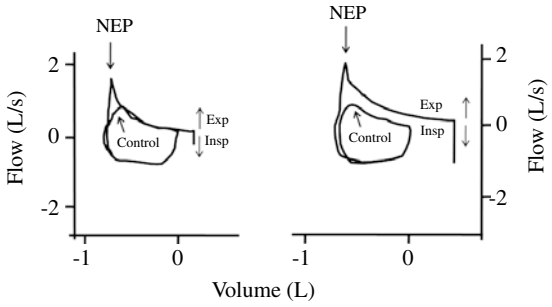

Figure 12.—Flow-volume plots of a sedated patient with COPD during control breaths superimposed to flow-volume plots recorded during application of negative expiratory pressure (NEP) at the onset of exhalation while supine (left panel) and while semi-recumbent (right panel). In the supine position application of NEP produced a transient increase in flow at the onset of exhalation, with no change thereafter. In contrast, application of NEP while the patient was semi-recumbent produced an increase in flow over the entire course of exhalation. This pattern indicates presence of airflow limitation in the supine position and not in the semi-recumbent position (see text for details). (Modified from Koulouris *et al.*[65]).

Negative expiratory pressure technique

This technique can be used during spontaneous and supported breathing.[64] It consists in applying a small negative pressure at the airway opening (usually -5 cm H_2O) during exhalation.[64] When EFL is present, NEP does not increase expiratory flow either during the whole tidal exhalation or during part of it. A transitory "spike" in flow may arise due to sudden displacement of gas from the compliant upper airways during the swift decompression (Figure 12).[65] When EFL is absent, NEP increases expiratory flow.[64, 65] Using this technique, Koulouris *et al.*[65] reported that EFL may be present while patients are supine and absent while semi-recumbent. NEP is well tolerated without untoward effects except, in rare occasions, mobilization of secretions.[29]

Gentle epigastric pressure technique

In ambulatory patients with COPD the lack of an increase in expiratory flow during a gentle compression of the abdominal wall at the umbilical level can accurately detect EFL at rest [66] and during exercise.[67] Whether this simple technique could be used in ventilated patients remains to be determined.

Monitoring auto-PEEP

Monitoring has been defined as the act of performing frequent measurements of a biological signal over time. The frequency with which these measurements should be performed depends from the biological signal being monitored. For instance, monitoring the cardiac electrical signals requires a much greater number of measurements per unit of time than monitoring urinary output. One important goal of monitoring is to tailor therapeutic intervention(s) according changes in the monitored biological signal and clinical status. Unfortunately, no user-friendly strategy to monitor fluctuations in auto-PEEP (or dynamic hyperinflation) over time is yet available.

Therapy of auto-PEEP

Strategies to reduce or eliminate auto-PEEP

One or more therapeutic strategies can be used according to the mechanism responsible for auto-PEEP (Table I). One of the most valuable strategies is the reduction in minute ventilation – even if this means development of permissive hypercapnia.[68]

In patients with auto-PEEP ventilated with volume-cycled modes (*e.g.*, and the volume-cycled form of assist-control ventilation), clinicians often increase inspiratory flow to decrease inspiratory time. This is done in the hope of prolonging the time available for exhalation. Increases in inspiratory flow, however, commonly lead to an increase in respiratory rate [69, 70] and the anticipated reduction in T_E could increase auto-PEEP. Laghi *et al.*[70] studied this phenomenon in 10 patients with COPD while receiving assist-control ventilation with a back-up rate of one breath per minute (Figure 13). As expected, an increase in flow from 30 to 90 L/minute increased the respiratory rate from 16±1 to 21±2 breaths per minute. Despite the rise in rate, auto-PEEP decreased from 7±1 to 6±1 cm H_2O. The decrease in auto-PEEP was the result of a paradoxical increase in T_E, which permitted extra time for lung deflation. The investigators reasoned that the shortened inspira-

TABLE I.—*Therapeutic strategies to reduce or resolve auto-PEEP according to the underlying pathophysiologic derangement and mode of mechanical ventilation.*

Cause of auto-PEEP	Therapy according to mode of mechanical ventilation	
	Volume-Cycled Ventilation	Pressure-Cycled Ventilation
High minute ventilation (i)	– Decrease minute ventilation: decrease respiratory rate plus decrease tidal volume in volume-cycled modes and decrease inspiratory pressure and T_I in pressure-cycled modes; may allow permissive hypercapnia – Temporary disconnection of patient from ventilator in cases of ventilator-related hypotension – Control agitation, fever and pain *(ii)*	
Short T_E (iii)	Eliminate inspiratory pause	
	Increase inspiratory flow	Decrease T_I
Reduce expiratory flow limitation	Low-levels of external PEEP	
Increased expiratory time constant	Bronchodilator therapy	
Persistent inspiratory muscle activity during exhalation	Bronchodilator therapy (?)	
Large tidal volume	Decrease tidal volume	Decrease inspiratory pressure
Increased external flow resistance	Large bore endotracheal tube Avoid heat-and-moisture exchangers	

T_E = expiratory time; T_I = inspiratory time; (i) decrease in minute ventilation is usually the most effective strategy to decrease auto-PEEP [42;68]; (ii) to decrease causes minute ventilation; (iii) Increasing T_E beyond 4 s is probably futile in decreasing auto-PEEP [76].

tory time due to the increase inspiratory flow combined with time-constant inhomogeneity of COPD caused over-inflation of some lung units to persist into neural exhalation. Continued inflation during neural exhalation could stimulate the vagus, which prolongs expiratory time.[69]

Strategies to minimize adverse events associated with auto-PEEP

Respiratory complications

In patients where auto-PEEP is primarily due to EFL, application of low levels of external PEEP (*i.e.*, external PEEP < static auto-PEEP) can reduce the effort to trigger the ventilator.[51, 71] The physiologic phenomena responsible for the reduced effort to trigger the ventilator are probably the following. At the end of inhalation, lung volume is "increased" by the delivered tidal volume. This (transient) increase in lung volume enlarges the cross sectional area of the airways. This increase in the cross-sectional area of the airways at end-inhalation will carry over to the beginning of exhalation. In other words, patients with EFL are not necessarily "flow limited" from the very start of exhalation:[62] the volume-associated increase in the cross sectional area of the airways will suffice to maintain some degree of airway patency despite the tendency of the compliant small airways to narrow during exhalation. Application of low levels of external PEEP in these patients will, of course, add some resistance to exhalation. Yet, as long as lung volume has not decreased to a critical level during exhalation, the lumen of the compliant small airways (though smaller than expected) will be sufficient to maintain a brisk expiratory flow. As exhalation progresses, the lung volume and the cross — sectional area of the airways will decrease. When the volume-associated decrease in cross — sectional area of the airways is sufficient for EFL to occur airflow will slow down. The region where EFL occurs becomes the "choke point" for the system.[21] Adding low levels of external PEEP downstream from the choke point may not slow expiratory flow significantly [60] (or at all),[60] even though the intraluminal pressure distal to the choke point has increased – waterfall phenomenon (Figure 11).[52, 61] In patients with EFL, external PEEP might dilate those small airways that have become severely narrow during exhalation.[21] As long as external PEEP is high enough to eliminate the choke point – but not higher than alveolar pressure – decompression of previously flow-limited units will take place. That is, external PEEP and auto-PEEP are not algebraically additive.[21, 60, 71] Additional mechanisms for

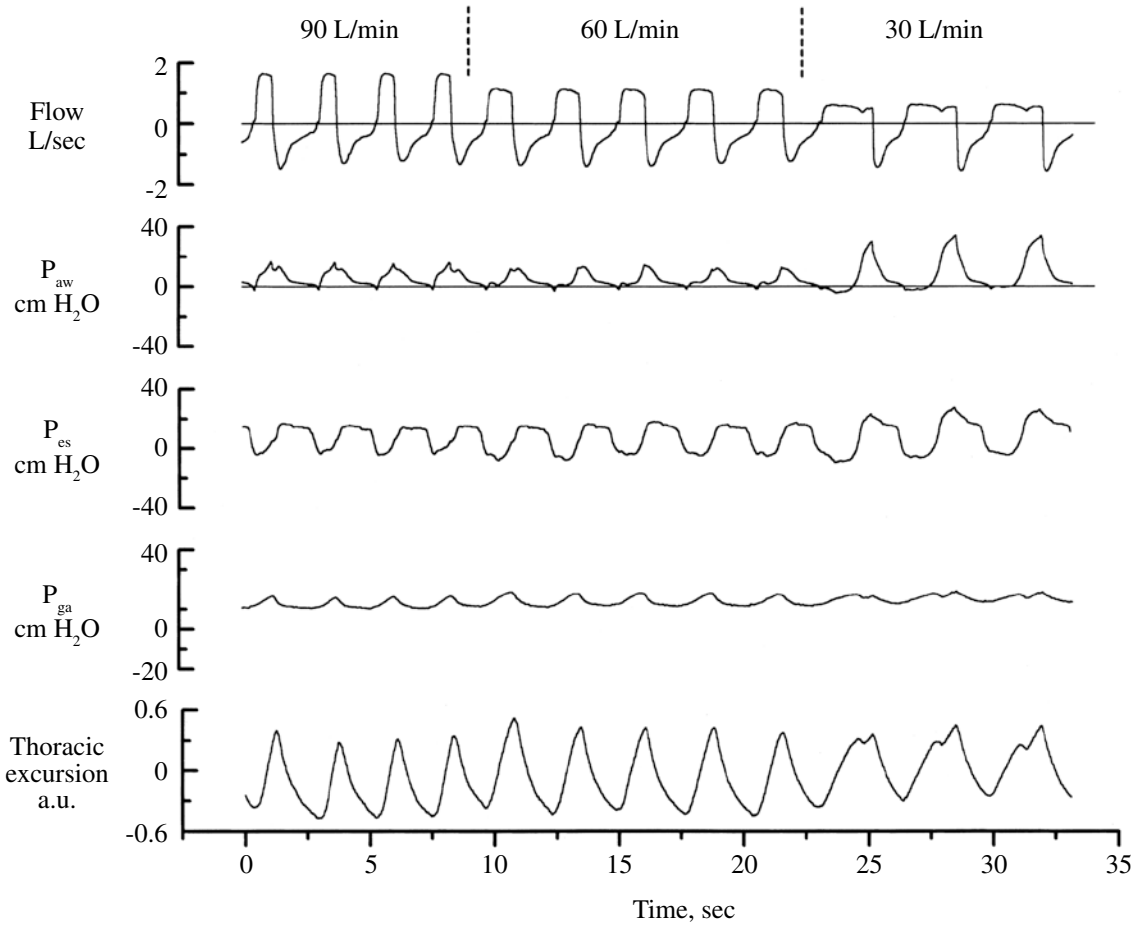

Figure 13.—Continuous recordings of flow, airway pressure (Paw), esophageal pressure (Pes), gastric pressure (Pga), and the sum of rib-cage and abdominal motion, in a patient receiving assist-control ventilation at a constant tidal volume. Decreases in inspiratory flow from 90 L/min to 60 and 30 L/min led to decreases in frequency (26, 23, and, 18 breaths/min, respectively), but the time for exhalation decreased (1.6, 1.5, and 1.3 s, respectively); increases in auto-PEEP (13.3, 14.4, and 15.6 cm H_2O, respectively) and end-expiratory lung volume indicate dynamic hyperinflation. Decreases in flow from 90 L/ min to 60 and 30 L/min led to increases in the swings in Pes from 16.8 to 19.5 and 21.5 cm H_2O, respectively. The higher airway pressures at lower flow settings represent continued mechanical inflation into neural exhalation. (From Laghi *et al.*).[70]

this "paradoxical" deflation with the application of external PEEP (Figure 14) include reopening of sticky airways that had completely collapsed [60] and improvement of wave speed limitation.[22, 60]

Once external PEEP is set above some critical value, however, the association lung volume-PEEP reverts to that observed in patients without airflow obstruction [51] or in patients with increased ohmic resistances (Figure 14).[60, 72] At that point PEEP will cause hemodynamic deterioration.[21] In patients with COPD receiving CMV, external PEEP of less than 80-85% of (static) auto-PEEP does not significantly affected hemodynamics or lung volume.[73]

In patients where auto-PEEP is primarily due to an increase in ohmic resistance the application of even modest levels or external PEEP can be detrimental.[21, 72] In these patients, resistance to expiratory flow is greater than normal throughout exhalation. Hence, the application of external PEEP is an additional "back pressure" to the expiratory flow that – from the very start of exhalation – is already encumbered by the increased

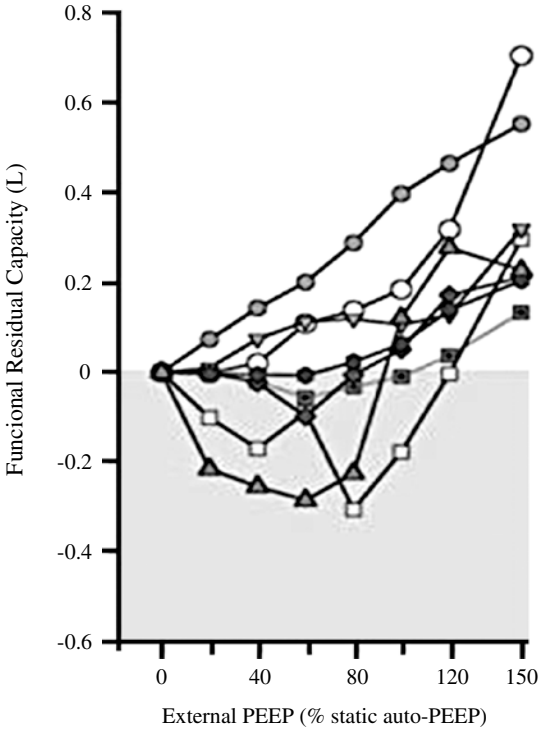

Figure 14.—Changes in functional residual capacity (FRC; inductive plethysmography) as external PEEP is increased from zero cm H_2O to 150% of static auto-PEEP in eight patients with obstructive lung disease (four with asthma and four with COPD). Patients were receiving invasive volume-cycled controlled mechanical ventilation with tidal volume set at 6 mL/kg, respiratory rate of 9 breaths/min and inspiratory flow of 40 L/min. The reference FRC (FRC = 0.0) was the FRC recorded on zero PEEP.
As external PEEP was increased, three patients demonstrated a paradoxical response to external PEEP (decrease in FRC), two patients experienced a biphasic response (initially FRC does not change and then increases) and two patients experienced an overinflation response (linear or quasi-linear increase in FRC as soon as external PEEP was administered; see text for details). (From Caramez MP *et al.*)[60]

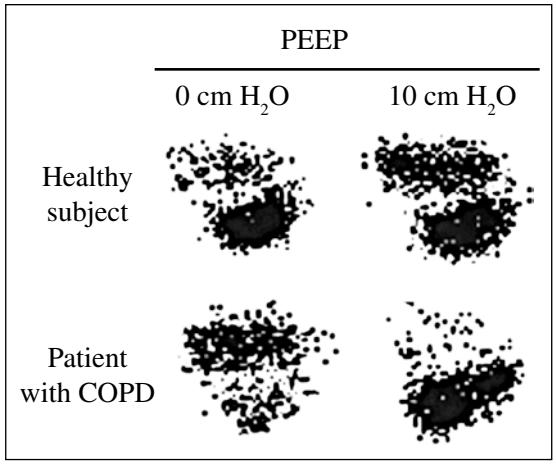

Figure 15.—Ventilation scans obtained with radioactive krypton (^{81m}Kr) in a healthy subject (upper panels) and in a patient with COPD (lower panels). Both were resting in the left decubitus position, and were initially breathing with a PEEP of 0 cm H_2O (left panels) and then with a PEEP of 10 cm H_2O (right panels).
When PEEP was 0 cm H_2O, ventilation was predominantly distributed to the dependent lung regions in the healthy subject and to the non-dependent lung regions in the patient with COPD. When PEEP was 10 cm H_2O, ventilation was evenly distributed throughout the lung of the healthy subject. In the patient with COPD, PEEP of 10 cm H_2O restored ventilation to the dependent portion of the lung probably because PEEP did not allow the collapse of dependent airways. (Modified from Shim C *et al.*)[78]

ohmic resistance.[21] This back pressure is transmitted to the alveoli and causes a parallel increase in central and alveolar pressures.[21] If the tidal volume remains constant, alveolar pressure will have to increase as much as the applied external PEEP to compensate for the drop in driving pressure.[21] For example, in a classic investigation, Tuxen [72] reported that in six patients with severe obstruction, peak airway pressure and lung volume increased in direct proportion to the level of external PEEP applied. Worsening hyperinflation was associated with hypotension and decreased oxygen delivery.

It has been reasoned that greater lung volumes caused by the application of external PEEP could increase the cross sectional area of the airways and, thus, could decrease airway resistance.[21]. Despite this potential fall in airway resistance, total work of breathing may change little because of the increased elastic recoil. In addition, hyperinflation can worsen the force-length relationship of the respiratory muscles.[21]

In patients with respiratory failure, flow-limited and non-flow limited units can coexist.[21, 60] When EFL physiology prevails, application of low levels of external PEEP will minimally increase the mean end-expiratory alveolar pressure and lung volume.[21, 60, 73] At the same time low levels of external PEEP will narrow the pressure gradient between alveoli and central airways (Palv – Paw) at end-exhalation.[21] In addition, low levels of external PEEP can decrease the "inequality index" (improvement of the regional inhomogeneity in auto-PEEP) with a parallel improvement in oxygenation.[12]

In patients where EFL physiology prevails low levels of external PEEP will maintain a patent (or nearly patent) pathway between the central airway and the alveolar compartment at the start of inhalation. This means that contraction of the inspiratory muscles will translate into an immediate (or near immediate) inspiratory flow. Not surprisingly, application of low external PEEP in patients in whom EFL physiology prevails reduces the effort required by the patient to trigger the ventilator,[51, 74] to start inspiratory flow during weaning from mechanical ventilation,[53] and improves patient-ventilator interaction.[51]

In patients where non-EFL physiology prevails, application of external PEEP will cause a proportional increase in alveolar pressure, hyperinflation and the attendant impairment of inspiratory muscle function, hemodynamic compromise, and risk of barotraumas.[60, 72] The coexistence of EFL and non-EFL physiology may explain why low levels of external PEEP are occasionally detrimental in patients with COPD in whom EFL should be the main cause of auto-PEEP.[60, 72] Coexistence of EFL and non-EFL physiology is also the likely explanation for the beneficial effect of low levels of external PEEP in some patients with asthma,[60, 75] particularly during the resolution phase of an episode of acute severe obstruction.[76]

In summary, the major goal of using external PEEP in patients with airflow obstruction is to decrease workload [77] and dyspnea.[53] In these patients, titration of external PEEP should continue until dyspnea has improved, respiratory drive has decreased [71] or until peak and/or plateau airway pressure demonstrate a sizeable increase (volume-cycled ventilation) (Figure 10) [21, 60] or tidal volume starts to decrease (pressure-cycled ventilation).[42] In patients with COPD receiving CMV, replacement of auto-PEEP with external PEEP (of 50-100% of measured static auto-PEEP) may improve ventilation perfusion matching (Figure 15) [78] and oxygenation without any effect on cardiac output.[79]

Neurally adjusted ventilatory assist (NAVA) is a novel strategy of ventilatory assist that uses diaphragm electrical activity to control timing and level of assist [80] – *i.e.*, with NAVA the ventilator is not triggered by a pneumatic signal generated by patient's effort such as airway pressure or inspiratory flow. Whether NAVA could improve patient-ventilator synchrony in patients with auto-PEEP has been the focus of several recent investigations.[81-83] Spahija *et al.* [81] compared the physiologic response to pressure support ventilation (PSV) and NAVA in 14 mechanically ventilated patients. Twelve patients had COPD and had auto-PEEP levels ranging from 3 to 12 cm H_2O. All patients were ventilated with the lowest tolerable level of PSV (PSV-low) and with PSV set 7 cmH_2O higher than the PSV-low (PSV-high). NAVA was titrated to achieve a peak airway pressure similar to the one with PSV-low (NAVA-low) and a peak airway pressure similar to the one with PSV-high (NAVA-high). The breathing pattern with PSV and NAVA were comparable at low levels of support. At high levels of support PSV was associated with larger tidal volumes and lower breathing frequencies than with NAVA. In addition, NAVA-low and NAVA-high reduced delays of ventilator triggering and ventilator cycling. NAVA abolished wasted inspiratory efforts observed with PSV in 6 patients. In the study of Spahija *et al.*,[81] expiration with PSV was set to start when inspiratory flow was 5% of peak flow. Such a low threshold could have worsened hyperinflation when patients with COPD were on PSV and could have overestimated the benefit of NAVA.[82]

More recently, Piquilloud *et al.*[82] compared PSV and NAVA in 22 patients, 36% of whom had obstructive pulmonary disease. In this study, expiration with PSV was set to start when inspiratory flow was 25-30% of peak flow. Despite the more favorable cycling-off settings with PSV, NAVA was still superior to PSV in terms of trigger delays and expiratory synchrony.[82] NAVA reduced by half the number of patients with asynchrony index >10% and completely eliminated ineffective effort or late cycling. Improved patient-ventilator interaction (reduction of overassistance) with NAVA as compared to PSV has also been reported in patients recovering from acute respiratory dis-

tress syndrome.[83] Whether better patient-ventilator interaction with NAVA could decrease sleep disruption,[31] shorten the duration of mechanical ventilation [32] and improve overall prognosis [33] remains to be determined.

Hemodynamic complications

In patients with auto-PEEP, intravascular fluid expansion can increase blood pressure and cardiac output.[1] Prompt disconnection from the ventilator can resolve hypotension due to auto-PEEP. If that is the case mechanical ventilation should be restarted with lower minute ventilation (Table I). When hypotension is unresponsive to ventilator disconnection, tension pneumothorax should be suspected.[76]

Future developments

Thirty years after the pioneering work of Pepe and Marini,[1] a large body of physiologic data has produced a growing awareness of the mechanistic role of auto-PEEP in the development of respiratory failure and a host of respiratory and non-respiratory complications. Future research in this field should improve our knowledge of the following:

— how to easily identify the structure-function relationship responsible for the development of auto-PEEP;[84]

— how to quantify auto-PEEP when the small airways of some lung compartments occlude during exhalation;

— develop computer technology for the display and processing of physiologic signals, making the measurement of auto-PEEP easier and faster.[85] Faster measurements of auto-PEEP would allow, for the first time, true moment-by-moment monitoring of auto-PEEP – a biological signal that can widely fluctuate with episodic tachypnea, changes in airway resistance and, when patients receive pressure-cycled ventilator modes, with episodic changes in tidal volume.[86] Development of monitoring capabilities represents the necessary step in the design of outcome studies based on the individualized care of patients with auto-PEEP.

— Identify the most appropriate ventilator mode and setting for a given lung disease and mechanism of auto-PEEP;[84, 87]

— assess the impact of therapeutic strategies designed to reduce or eliminate auto-PEEP – and the adverse events caused by auto-PEEP – on a patient"s clinical outcome in terms of short-term and long-term morbidity,[88] resource utilization and survival.[89]

Conclusions

Identification of auto-PEEP and management of patients with auto-PEEP remains a challenging task for the intensivist. This review illustrates the major importance of auto-PEEP and the mechanisms by which externally applied PEEP can be useful in these patients. To date it is unknown whether the use of externally applied PEEP may improve the overall clinical management and outcome of ventilated patients with auto-PEEP. Ongoing investigations are being conducted to address some of these controversial issues.[84, 85, 87, 89]

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