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REVIEW ARTICLE

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Intrinsic positive end-expiratory pressure ($PEEP_i$)

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Introduction

Positive end-expiratory pressure (PEEP) is one of the most frequently discussed topics in critical care medicine. However, alveolar pressure can remain positive throughout expiration without PEEP set by the ventilator whenever the time available to breathe out is shorter than the time required to decompress the lungs to the elastic equilibrium volume of the total respiratory system (V_r). The end-expiratory elastic recoil (Pel,rs) due to incomplete expiration has been termed auto PEEP, occult PEEP [1], inadvertent PEEP [2], endogenous PEEP, internal PEEP and intrinsic PEEP [3, 4] owing to its similarity and contrast with PEEP set by the ventilator.

The purpose of this article is to provide a comprehensive review of the studies on this interesting aspect of critical care medicine, from the underlying physiological mechanism(s) to the clinical and therapeutic implications, through measurement and monitoring in the intensive care setting.

Physiology

The physiological mechanisms leading to intrinsic PEEP are closely related to factors determining the end-expiratory lung volume and the rate of lung emptying.

The *functional residual capacity* (FRC) is defined as the amount of gas in the lungs and the airways at the end of expiration [5]. In normal subjects, during tidal breathing, the elastic energy stored in the respiratory system during the preceding inspiration is sufficient for an expiration and FRC is determined by the opposing elastic forces of the lungs and the chest wall. Under such circumstances, expiratory flow becomes nil, and remains nil for an appreciable time (i.e. the end-expiratory pause) before the onset of the next inspiration: FRC corresponds to the elastic equilibrium volume of the total respiratory system (V_r). Pulmonary hyperinflation defines an increase in FRC above predicted values. Pulmonary hyperinflation can be due, for example, to loss of lung elastic recoil and airway closure at higher volumes. *Dynamic pulmonary hyperinflation* (DPH) defines an increase in FRC above V_r due to the presence of dynamic forces at the end of expiration: (a) increased flow resistance (and expiratory flow limitation); (b) short expiratory duration; and (c) increased post-inspiratory inspiratory muscle activity [6, 7]. Abnormally increased flow resistance, often associated with expiratory flow limitation, is by far the major mechanism leading to DPH in mechanically ventilated patients and in patients with acute respiratory failure (ARF) in

general. In addition, short expiratory time (TE) can be an important mechanism of DPH in conditions such as inverse ratio ventilation and spontaneous rapid shallow breathing. Intrinsic PEEP ($PEEP_i$) is a systematic corollary of DPH, reflecting the end-expiratory Pel,rs (Fig. 1) [2, 7].

Internal and external factors causing DPH and $PEEP_i$

Basically, three factors cause $PEEP_i$ and determine its magnitude in mechanically ventilated patients and during weaning: (a) the patient's respiratory mechanics (respiratory system resistance and compliance); (b) added resistance (endotracheal tube and ventilator tubing and devices); and (c) ventilatory pattern (due to the ventilator setting, the patient ventilatory demand or a combination of both). For the purpose of this article, patient's respiratory mechanics and breathing pattern are classified as internal factors, whereas added resistance and ventilator settings are referred to as external factors (Table 1). In most instances, internal and external factors are related and synergetic in causing $PEEP_i$ and determining its magnitude.

Another factor that promotes $PEEP_i$ is the end-inspiratory pause (in general, <0.4 s) commonly used in the ICU to improve gas exchange [8]. It should be noted, however, that the end-inspiratory pause causes not only an increase in inspiratory time, and hence a decrease in TE at a given frequency, but also a decrease in the pressure available to produce expiratory flow. During the pause there is a decrease in Pel,rs, the driving pressure for expiration [9].

Flow resistance

The mechanism by which abnormally increased flow resistance causes DPH is self-evident. Excessive flow resistance actually delays the rate of lung emptying such that expiration cannot be completed within the time actually available for breathing out. Under such circumstances, inspiration (or mechanical lung inflation) starts before full decompression of the lungs, and FRC stabilises above V_T. The usual end-expiratory pause is then replaced by a change in flow direction, from expiration to inspiration (Fig. 2).

In mechanically ventilated patients and during weaning, total flow resistance is given by: (a) airway and respiratory tissue resistance, (b) added resistance of fine-bore endotracheal tube (ETT), and (c) ventilator tubing, circuits and devices. It has been shown that ETT resistance in vivo is further increased by compression and kinking of the tube as well as by secretions in the lumen [10, 11, 12].

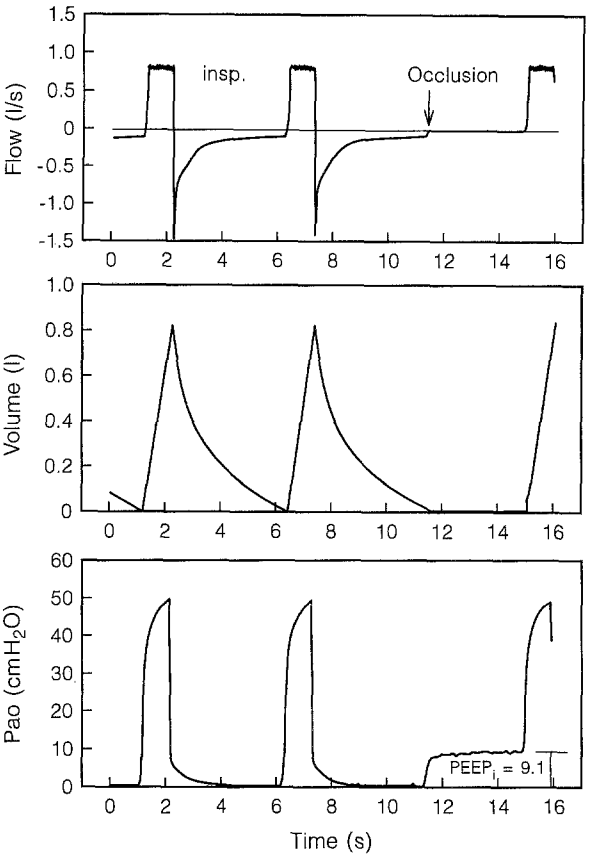

Fig. 1 Representative record with measurement of $PEEP_i$ by end-expiratory airway occlusion EEO in a mechanically ventilated patient with acute exacerbation of COPD during controlled ventilation with constant inspiratory flow. *Top* to *bottom:* records of flow, volume, and pressure at the airway opening P_{ao}. Inspiration is upward. The *continuous line* in the *upper panel* indicates zero flow. The first mechanical inflation is regular, namely without EEO: end-expiratory pressure is apparently atmospheric. In contrast, at the end of the second tidal expiration, the expiratory circuit of the 900 C Siemens ventilator is occluded using the end-expiratory hold button of the ventilator and P_{ao} becomes positive, reflecting the end-expiratory elastic recoil of the respiratory system due to incomplete expiration. The value of $PEEP_i$ is provided by the difference between the EEO P_{ao} plateau and atmospheric pressure. Visual detection of the plateau on P_{ao} provides direct evidence of absence of leaks in the circuit, respiratory muscle relaxation, and equilibration between alveolar and tracheal pressure

Table 1 Determinants of DPH and PEEP (T_I inspiratory time, T_{TOT} total time)

Internal	External
Respiratory mechanics	*Added flow resistance*
Flow resistance	Fine bore endotracheal tube
Expiratory flow limitation	Ventilator tubing and devices
Respiratory system compliance	*Ventilator setting*
Breathing pattern	Frequency
Frequency of breathing	I:E
T_I/T_{TOT}	Inflation volume
Tidal volume	End-inspiratory pause

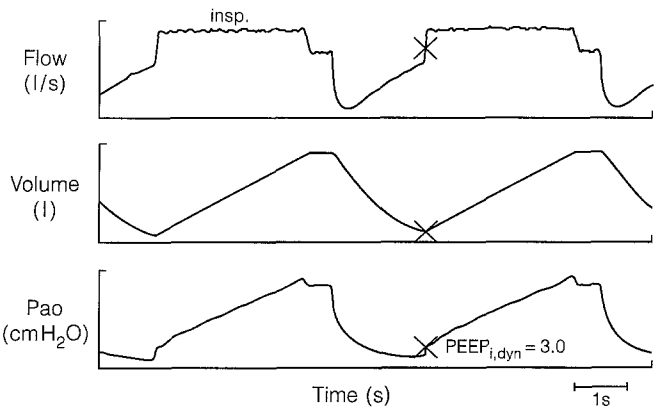

Fig. 2 *Top* to *bottom*, records of flow, volume, and P_{ao} in a mechanically ventilated patient during inverse ratio ventilation. There is no end-expiratory pause, but the end-expiratory flow is suddenly cut by the onset of the mechanical lung inflation, indicating that expiration was not completed and that the end-expiratory tidal volume was above the elastic equilibrium volume (dynamic pulmonary hyperinflation, DPH). Inspiratory flow is preceded by the onset of the positive pressure swing delivered by the ventilator. At zero flow, i.e. the beginning of inspiration, P_{ao} is already positive, i.e. 3 cmH_2O. This pressure was needed to counterbalance part of the end-expiratory elastic recoil in order to start inspiration and corresponds to dynamic intrinsic PEEP ($PEEP_{i,dyn}$)

Expiratory flow limitation

In patients with advanced chronic obstructive pulmonary disease (COPD), increased flow resistance due to the inflammatory process in the bronchial wall, mucus in the lumen and bronchospasm is not the only cause of retarded expiration. The destruction of lung parenchyma causes loss of alveolar septa (attachments) which support the small airways [13], while excessive pulmonary hyperinflation can determine positive pleural pressure throughout expiration [2, 10, 14]. Under such circumstances, poorly supported small airways are dynamically compressed during expiration, giving rise to expiratory flow limitation [14–19]. At its extreme, dynamic compression of the airways becomes airway closure. Air trapping, a well recognised event in advanced COPD, is the result of both the closure of small airways and the abnormally low expiratory flows through compressed airways.

DPH is mainly determined by expiratory flow limitation in COPD patients, which has important implications for treatment. First, after the very beginning of expiration, expiratory flow is extremely slow and the time required for a complete expiration can be abnormally long. For example, in some patients with acute exacerbation of COPD, 20–30 s of relaxed expiration was not sufficient to reach an end-expiratory pause [14, 20, 21]. Second, expiratory flow cannot be increased by application of positive pressure on the chest wall or of negative pressure at the mouth, or by contraction of abdominal (expiratory) muscles. Finally, as will be further discussed, application of moderate levels of PEEP will not increase lung volume until a "critical" value, somewhat lower than $PEEP_i$ has been exceeded [17, 22].

Respiratory compliance

Increased airway resistance and expiratory flow limitation are not the only 'intrinsic' mechanisms causing 'occult' PEEP. Respiratory compliance must also be taken into account. In patients well adapted to the ventilator, the respiratory muscles are relaxed throughout most of the ventilatory cycle and the elastic recoil stored in the respiratory system (Pel,rs) during the preceding inspiration provides the pressure driving expiratory flow. Total flow resistance is the opposing force.

Low compliance increases the expiratory driving pressure and hence the rate of lung emptying. This explains why mechanically ventilated patients with pulmonary oedema or adult respiratory distress syndrome (ARDS) have low levels of DPH and $PEEP_i$ in general, although total flow resistance has been found to be abnormally high, particularly in the early stages [11, 23, 24]. It has not yet been documented or sufficiently clarified whether expiratory flow limitation can also exist in critically ill patients without COPD.

Ventilator setting

While the terms 'occult' and 'inadvertent' PEEP stress clinical implications due to the lack of recognition of $PEEP_i$, the therms 'intrinsic' and 'auto' PEEP stress the role of patient respiratory mechanics in determining DPH and $PEEP_i$. However, the role played by 'extrinsic' factors should also be emphasised. The magnitude of $PEEP_i$ also depends on: (a) the amount of volume to be exhaled, and (b) expiratory time, determined by (i) the ventilator frequency setting and (ii) the I:E ratio (Table 1). Ventilatory variables become internal factors when the patient is controlling the breathing pattern, as may be the case not only during weaning, but also during assisted ventilation.

$PEEP_i$ and ventilatory modes

To some extent, the presence and magnitude of DPH and $PEEP_i$ are influenced by the ventilatory mode. In particular, the difference between controlled and assisted modes can be important.

$PEEP_i$ and controlled ventilation

Most measurements of $PEEP_i$ reported in the literature were obtained during controlled ventilation. In Table 2, we report the range and prevalence of $PEEP_i$ in a nonselected consecutive series of patients during controlled ventilation with the same ventilator setting (e.g. $V_T = 12-10$ ml/kg, $f = 12-15$ breaths/min, $I:E = 1:2-3$) from some of our previous publications [10, 20, 23, 25].

As predicted, the highest values of $PEEP_i$ were found in patients with airway diseases, particularly COPD patients, in whom DPH and $PEEP_i$ were essentially caused by expiratory flow limitation. $PEEP_i$ can be significantly reduced by changing the ventilatory setting, but will never totally disappear. $PEEP_i$ has also been systematically found, albeit at low levels, in stable COPD [26–30] and cystic fibrosis (CF) [31] patients. In patients without chronic airway disease, external factors such as endotracheal and ventilator tubes, exhalation valves and the ventilator setting can play an important role in determining both the presence and the magnitude of $PEEP_i$ [23, 25]. In this connection, the high prevalence of $PEEP_i$ reported in patients with polytrauma, namely 28/50 patients (56%), in whom intrinsic factors such as high ventilatory demand were also probably involved, is noteworthy [32].

$PEEP_i$ and inverse ratio ventilation

A clear example of DPH and $PEEP_i$ entirely caused by the ventilator setting may be seen during inverse ratio ventilation (IRV). This is a particular form of controlled ventilation, which is generally pressure controlled (PC-IRV), with a longer inspiratory phase than usual followed by a short expiration [33–37]. IRV is sometimes used in patients with severe hypoxaemia and respiratory failure, often after conventional CV has failed to maintain a satisfactory P_aO_2 [33]. $PEEP_i$ is present during IRV as an "occult PEEP" because of incomplete expiration (Fig. 2). The presence of $PEEP_i$ can explain the improvement in P_aO_2 observed in patients on IRV and the sometimes unexpected drop in cardiac output (CO) [34]. Not surprisingly, less PEEP than during CV is required to increase P_aO_2 during IRV since a certain amount of $PEEP_i$ is already present [37]. In addition, the conclusion that IRV decreases the risk of barotrauma because of the lower peak cycling pressure is questionable. It is true that alveolar pressure and mean airway pressure (MAP) may be much higher than expected due to DPH, and hence the risk of barotrauma is unchanged if not increased. The lower peak cycling pressure observed during IRV than during CV is the result of the lower resistive pressure drop due to the generally slower end-inspiratory flow, while the end-inspiratory alveolar pressure will approximate the level occurring with a similar amount of PEEP [36].

Table 2 Magnitude and prevalence of PEEP in mechanically ventilated patients (*$PEEP_i$* intrinsic positive end-expiratory pressure (cmH_2O), *COPD* chronic obstructive pulmonary disease, *CF* cystic fibrosis, *ARDS* adult respiratory distress syndrome, *CPO* cardiogenic pulmonary oedema, *Other* patients with ARF of extrapulmonary origin

Diagnosis	No.	$PEEP_i$ (range)	Prevalence
COPD	45	2.6–22	45/45 (100%)
CF	1	11	1/1 (100%)
Asthma	3	13.5–20	3/3 (100%)
ARDS	28	1.0–8.1	15/28 (58%)
CPE	10	1.0–6.0	8/10 (80%)
Other	10	1.0–4.1	5/10 (50%)

Another particular form of controlled ventilation is high-frequency ventilation (HFV). $PEEP_i$ reaching approximately 9 cmH_2O was found in COPD patients ventilated with high-frequency jet ventilation [38].

$PEEP_i$ and assisted ventilation

During assisted ventilation, i.e. assist/control ventilation (ACV), synchronised intermittent mandatory ventilation (SIMV), and pressure support ventilation (PSV), the inspiratory muscles are active at the beginning of inspiration, and even throughout inspiration, so as trigger the mechanical breath [39, 40]. Expiration is mostly passive and hence is controlled by the mechanical properties of the respiratory system, as is the case with CV, together with the added resistance of ETTs and ventilator circuits, and by the ventilator setting. Therefore, in general, the mechanisms leading to DPH and $PEEP_i$ during ACV, SIMV, and PSV do not differ from those during CV. However, with assisted ventilatory modes, random and erratic inspiratory efforts can either trigger undesired ventilatory cycles or interrupt expiration in the early phase in such a way that there is a sudden reduction in the expiratory phase leading to a dramatic rise in the magnitude of $PEEP_i$. This has been described by Braschi et al. during SIMV [41], and Fernandez et al. during ACV [42].

$PEEP_i$ and spontaneous breathing

It has been recognised that rapid shallow breathing (RSB) is a common characteristic of patients with ARF from respiratory causes. RSB can occur during the early stage of ARF and is also a common sign of unsuccessful weaning [43]. Although DPH and $PEEP_i$ have not been measured on wide scale in patients breathing spontaneously, there can be little doubt that the short TE determined by RSB may be associated with high levels of $PEEP_i$ particularly in COPD patients, as illustrated in Fig. 3. In addition, with the shortening of the expiratory phase, inertial fac-

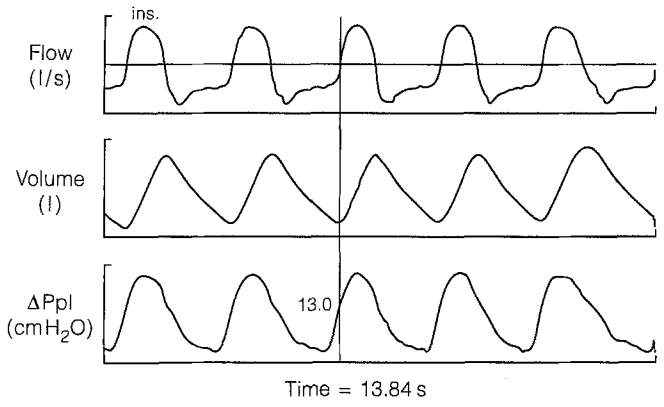

Fig. 3 Representative record (flow, volume, and pleural pressure, ΔP_{pl}, from top to bottom) in an intubated, spontaneously breathing patient with acute exacerbation of COPD. The expiratory flow is abruptly cut at the end of expiration, whilst P_{pl} swing (namely the inspiratory effort) had already begun. The difference between the point corresponding to the onset of the change in P_{pl} and the point of zero flow on the P_{pl} tracing, represents $PEEP_{i,dyn}$) which had to be counterbalanced by the contracting inspiratory muscles in order to start inspiration. In this patient, the inspiratory muscles had to develop 13 cmH_2O before the inspiratory flow could start. Tidal volume amounted to 0.3 l frequency was 35 breaths/min, minute ventilation was 10.5 l/min

tors due to the moving mass of the respiratory system could also be a cause of hyperinflation. It is not possible to provide a quantitative estimation, because inertial factors are generally disregarded. Nevertheless, these may become relevant as regards very rapid breathing.

In spontaneously breathing patients, respiratory muscle activity could affect DPH and $PEEP_i$ in terms of both increased post-inspiratory muscle activity (PIIA) and expiratory muscle contraction. The former has been found in normal subjects and asthmatics during induced bronchoconstriction [44], whereas the latter has been observed during stable COPD [29, 45] and during application of continuous positive airway pressure [46]. In critically ill patients, there has only been one recent report of abdominal (expiratory) muscle activity [47].

Implications

Just over 10 years ago, Pepe and Marini [1] made the brilliant observation that in a few mechanically ventilated patients who were well adapted to the machine cycle and for whom no PEEP was set by the ventilator, airway occlusion at the end of tidal expiration revealed positive end-expiratory alveolar pressure. This was termed auto PEEP and occult PEEP [1], i.e. $PEEP_i$ (Fig. 1). Subsequent research has shown that $PEEP_i$ is quite common in mechanically ventilated patients [25] (Table 2). The implications of $PEEP_i$ in mechanically ventilated patients partly depend on the mode of ventilation.

Controlled ventilation (CV)

$PEEP_i$ [1] has three major consequences during controlled ventilation: (a) a drop in cardiac output due to the impediment in cardiac filling determined by the positive intrathoracic pressure; (b) a potentially greater risk of barotrauma due to the high alveolar pressure; and (c) an error in the computation of respiratory compliance.

$PEEP_i$ and haemodynamics

Although it is widely accepted that $PEEP_i$ can unduly increase alveolar and intrathoracic pressure and hence reduce cardiac output, few measurements of haemodynamics in patients with significant levels of $PEEP_i$ [3, 36, 48], have been reported in the literature since the original observation by Pepe and Marini [1].

$PEEP_i$ reduces cardiac output [36], whereas a reduction in $PEEP_i$ increases cardiac output [48]. Unrecognised $PEEP_i$, i.e. occult PEEP, may lead to misinterpretation of haemodynamic data, generating erroneous interpretation of the patient's volemic status [1]. High levels of DPH and $PEEP_i$ can be associated with reduced cardiac filling and also significant cardiac arrhythmia, which are reversed by a reduction in DPH and $PEEP_i$.

$PEEP_i$ and barotrauma

Pulmonary barotrauma, defined by the presence of extra-alveolar air in locations where it is not normally found, is a well-recognised and teared event in mechanically ventilated patients [50, 51, 52]. In patients with high levels of DPH and $PEEP_i$, conventional tidal volume (i.e. 10–15 ml/kg) may shift ventilation toward the upper flat portion of the volume-pressure curve of the lungs, thus exposing terminal airspaces to the risk of overdistension and rupture. However, to our knowledge, no studies have been conducted to date showing a direct relationship between $PEEP_i$ and increased incidence of pulmonary barotrauma. It has been suggested that PEEP and $PEEP_i$ may help in preventing ventilatory induced lung injury [52, 54]. $PEEP_i$ prevents end-expiratory alveolar collapse and allows a smaller than usual tidal volume to be used to ventilate the lungs, thus reducing the shear forces between lung units with different regional degrees of inflation [52, 54]. However, this interesting suggestion, which puts $PEEP_i$ in a new perspective, requires further clinical investigation.

$PEEP_i$ and measurement of respiratory compliance

As shown by Jonson et al. [55] and our work [3], if $PEEP_i$ is not recognised and measured, a significant error is introduced in the calculation of static respiratory compliance ($C_{st,rs}$), a variable which is commonly used not only to assess the status and progress of ARF in mechanically ventilated patients, but also to set PEEP at the ventilator [56]. Traditionally, $C_{st,rs}$ is computed from the following equation:

$$C_{st,rs} = V_T/(P_{plat} - PEEP) \quad (1)$$

but the correct equation is as follows

$$C_{st,rs} = V_T/(P_{plat} - PEEP - PEEP_i) \quad (2)$$

where V_T is the tidal volume from the end-expiratory position and P_{plat} is the plateau pressure measured during end-inspiratory airway occlusion [1]. It has been shown that true compliance may be underestimated by up to 100% and 30% in COPD [25] and ARDS [23] patients, respectively, if $PEEP_i$ is not taken into account (i.e. Eq. 1 vs Eq. 2). In this context, it should be noted that due to the interdependence of several non-constant factors (Table 1), the magnitude of $PEEP_i$, and hence the extent of the error in the computation of compliance, is difficult to predict. It has to be stressed that most modern microprocessor-equipped mechanical ventilators that can display the on-line computation of respiratory compliance do not take $PEEP_i$ into account and thus provide incorrect and therefore useless, if not misleading, information.

Assisted ventilation and weaning

In patients with ARF during assisted ventilation and weaning, the implications of DPH and $PEEP_i$ are important in terms of the energetics of breathing [57]. First, dynamic hyperinflation profoundly alters the capacity of the inspiratory muscles to sustain a load due to length-tension considerations as well as changes in the geometrical arrangement [58]. Second, $PEEP_i$ is an *inspiratory threshold load* [59] which must be counterbalanced by the contracting inspiratory muscles in order to create sub-atmospheric pressure in the central airways and hence either trigger the mechanical breath or generate inspiratory flow. In these circumstances, the conventional equation of motion becomes:

$$P_{appl}(t) = PEEP_i + [V_T(t)/C_{dyn}] + [R_{TOT} \cdot V_I(t)] \quad (3)$$

where P_{appl} is the total pressure applied to inflate the respiratory system, V_T is tidal volume, C_{dyn} is dynamic respiratory compliance, R_{TOT} is total flow resistance, and V_I is the inspiratory flow rate, at any instant (t).

During assisted ventilation, the triggering pressure is set at very low levels, e.g. 1–2 cm H_2O, so that the ventilator does most of the work of inflating the lungs and the contribution required from the patient's respiratory muscles is negligible. However, Marini et al. [39, 40] have shown that the patient's inspiratory muscles can perform a significant amount of work, which can equal, in some conditions, the work performed during unassisted ventilation. This situation may be even worse in the presence of $PEEP_i$. Indeed, $PEEP_i$ adds to the triggering pressure and the total amount of the effort required by the patient's respiratory muscles to produce the pressure boost may be seriously increased. With high levels of $PEEP_i$ (Fig. 3), the patient's inspiratory muscles continue to contract under load, even during ventilatory assistence, and cannot recover from fatigue, so that weaning may be delayed or become impossible [60].

Because of its important clinical implications [61], measurement of $PEEP_i$ should be a mandatory part of the routine assessment of respiratory function in critically ill patients.

Measurement

First of all, $PEEP_i$ must be suspected from the shape of the expired flow versus time (Fig. 2) or volume (Fig. 4) relationship, whenever low flow, the final portion of the expiration, is suddenly cut by the onset of inspiration. We believe that continuous and adequate display of flow and pressure versus time records should be an essential monitoring facility in modern microprocessor-equipped ventilators.

In general, measurement of $PEEP_i$ and DPH is much easier during controlled ventilation than during assisted ventilation and weaning, since respiratory muscles are more active in the latter conditions. When the respiratory muscles are relaxed and sufficient time for equilibration between regional units with different time constants has been allowed, the pressure at the airway opening during airway occlusion reflects mean alveolar pressure for the definition of still fluid (Pascal's law). Simple and commonly available equipment such as a pneumotachograph for measuring flow, and a differential pressure transducer for sampling airway pressure can be used to measure $PEEP_i$, DPH and respiratory system mechanics [62, 63]. Since measurement of $PEEP_i$ may present more problems during assisted ventilation and weaning than during CV, the two modes of ventilation will be discussed separately.

Controlled ventilation

During CV, $PEEP_i$ can be easily measured either by end-expiratory airway occlusion (EEO) [2, 10, 23] (Fig. 1) or by simultaneous recording of flow ($\dot{V}_i$) and pressure at the airway opening (P_{ao}) (Fig. 2) [3]. Although in one study [3] the two methods yielded similar results, a more

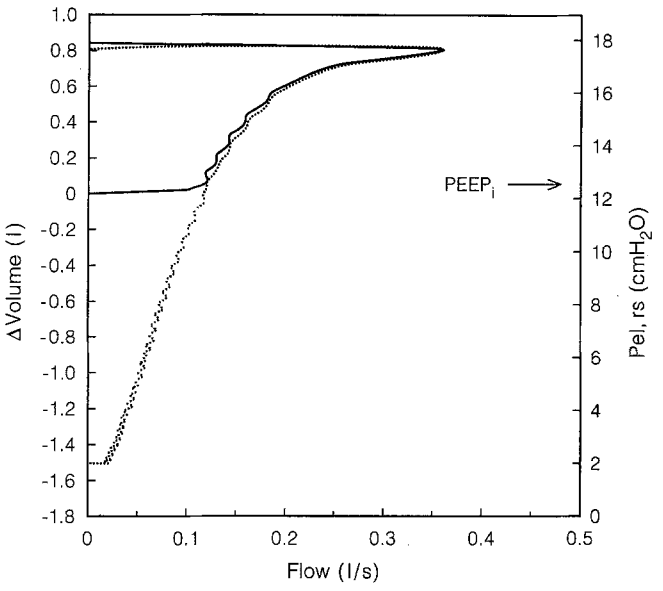

Fig. 4 Relaxed expiratory volume-flow curves in a mechanically ventilated patient with acute exacerbation of COPD during controlled ventilation. The *continuous line* represents tidal expiration, whereas the *dashed line* represents the attempt of complete expiration to the relaxation volume, which, however, was not achieved. At the end of the tidal expiration, flow is suddenly cut by the next mechanical lung inflation, indicating DPH. The volume axis (extrapolated to zero) was transformed into a pressure axis (right *y* axis) by dividing volume by respiratory compliance according to the formula: $P_{el,rs}$ = Volume/C_{rs}, where $P_{el,rs}$ is the elastic recoil pressure of the respiratory system, and C_{rs} is the respiratory compliance calculated by the interrupter technique (Fig. 5). Dynamic hyperinflation, i.e. the difference between the relaxed volume and the tidal expired volume, amounted to >1.5 l with a corresponding $PEEP_i$ amounting to >12 cmH_2O

recent report revealed that $PEEP_i$ measured by EEO was markedly greater than $PEEP_i$ measured by simultaneous $\dot{V}_i$ of flow and P_{ao} recording [64]. $PEEP_i$ measured by EEO actually reflects the end-expiratory elastic recoil of the respiratory system under static conditions, whereas $PEEP_i$ measured from the change in P_{ao} preceding $\dot{V}_i$ reflects the minimum "dynamic" $PEEP_i$. Since the lung units time constants are unequal, a well-recognised phenomenon in patients with airway and lung parenchyma diseases [10, 20, 25, 65, 66], $PEEP_i$ cannot be distributed homogeneously in the lungs, but will be greater in units with long time constants and a slow rate of emptying than in units with short time constants and rapid expiration. During EEO, there is time for equilibration (*Pendelluft*) of lung units with different regional $PEEP_i$ such that $PEEP_i$ measured as the plateau pressure at airway opening during occlusion (Fig. 1) reflects the mean value after equilibration. In contrast, $PEEP_i$ measured from the change in P_{ao} preceding inspiratory flow (Fig. 2) is the minimum $PEEP_i$. With incomplete expiration, the units with long time constants are still emptying while those with fast time constants start filling such that the change in P_{ao} preceding flow reflects the amount of pressure required to counterbalance $PEEP_i$ in the fast time constant units, i.e. the lowest $PEEP_i$, to start inspiratory flow. $PEEP_i$ obtained from continuous recording of P_{ao} and $\dot{V}_i$ is referred to herein after dynamic $PEEP_i$ ($PEEP_{i,dyn}$).

End-expiratory airway occlusion

End-expiratory airway occlusion can be performed manually at the expiratory port of the ventilator during the last 0.5 s of an expiration [1, 67]. Alternatively, a pneumatic valve can be used for rapid occlusion at the airway opening [3, 16, 25]. The second technique has the advantage of excluding the compliance of gas compression in the ventilator tubing (around 0.7 ml/cmH_2O [20]), though some variability may be due to occlusion timing. However, near the end of expiration the volume expelled per unit of time is very small due to extreme airway compression, so that small changes in TE would not be expected to affect the magnitude of $PEEP_i$ substantially, at least for TE around 3 s [3, 67]. With shorter TE, the difference is not negligible and $PEEP_i$ can increase significantly with decreasing TE [3]. $PEEP_i$ can be measured with ventilators which are already equipped with the end-expiratory occlusion hold, i.e., a button for the rapid occlusion of the expiratory port exactly at the end of the tidal expiration (e.g. Servo 900C, Siemens). With other ventilators, which do not include this option, airway occlusion can be achieved by means of manually operated valves [68, 69].

In our experience (Table 2), a plateau in airway pressure was constantly observed within 1.0 s from the onset of occlusion. However, D'Angelo et al. [9] observed that a longer time was required for equilibration (up to 5 s) even in normal anaesthetised subjects during airway occlusion at different lung volumes so as to observe a plateau in airway pressure. Since airway occlusion lasting a few seconds does not create any discomfort to the patient, occlusion longer than 1 s (up to 5 s) may also be used in clinical practice. With EEO, $PEEP_i$ can also be directly read on the ventilator's analog pressure display when recording facilities are not available. However, a significant advantage of recording signals on paper or screen is the possibility of observing the plateau in airway pressure, thus providing direct evidence of respiratory muscle relaxation and the absence of leaks in the circuit as well as equilibration between alveolar and airway opening pressure. With the airway pressure analogic signal recorded either on paper or on screen $PEEP_i$ is measured as the difference between the value of plateau pressure during airway occlusion and atmosphere, as illustrated in Fig. 1. If PEEP was set by the ventilator, $PEEP_i$ is measured as the difference between end-expiratory plateau pressure, which represents total PEEP ($PEEP_t$) and the pre-interruption level, which reflects the level of PEEP set by the

ventilator. Although this technique can lead to slight underestimation of $PEEP_i$ and overestimation of PEEP because of a small amount of resistive pressure dur to end-expiratory flow, the error is likely to be negligible. This may be particularly useful in calculating changes in $PEEP_i$ during a stepwise application of external PEEP.

$PEEP_i$ measured by EEO reflects the end-expiratory elastic recoil of the total respiratory system ($PEEP_{i,rs}$). We recently divided $PEEP_{i,rs}$ into its lung ($PEEP_{i,l}$) and chest wall component ($PEEP_{i,w}$) using EEO together with the oesophageal balloon technique [10, 19, 70]. In our COPD and ARDS patients, $PEEP_{i,rs}$ substantially reflected $PEEP_{i,l}$, with a small chest wall contribution (about 16%, on average).

$PEEP_i$ can be divided not only between the lung and the chest wall, but also between the two lungs. In some instances, $PEEP_i$ is unevenly distributed between the two lungs. For example, $PEEP_i$ measured during differential lung ventilation amounted to 12 cmH_2O in the more severely diseased lung, whereas 4 cmH_2O of $PEEP_i$ was found in the other lung [71]. In certain patients, such as those with coexisting chronic airway obstruction and fibrotic lung process, unilateral pulmonary hyperinflation and unilateral $PEEP_i$ up to 15 cmH_2O can be observed [72].

Interrupter technique

The interrupter technique consists of multiple brief airway occlusions performed during relaxed expiration and has been described in detail elsewhere [16, 20]. As illustrated in Fig. 5, the interrupter technique enables both *dynamic hyperinflation,* as the difference between V_r (intercept on the volume axis) and the $\Delta V = 0$, which represents end-expiratory lung volume during tidal ventilation, and $PEEP_i$, as the value of airway pressure at $\Delta V = 0$, to be measured. *Total respiratory system compliance* can be obtained from the slope of the regression line calculated from the points through the central (linear) portion of the VP relationship.

Static pressure-volume curve

$PEEP_i$ was recently measured on the static pressure-volume curve obtained by means of the supersyringe technique [73] which also enables respiratory compliance to be determined and the "inflection point" to be detected in patients with ARDS [74]. For measurement of $PEEP_i$, complete expiration to V_r is not possible. Instead, the airway is occluded at the end of the tidal expiration and $PEEP_i$ is measured as the amount of pressure which has to be applied with the supersyringe before the respiratory system starts inflating [73]. Fernandez et al. [73] found an excellent correlation between $PEEP_i$ measured by EEO and $PEEP_i$ measured using the supersyringe in 16 patients ($r = 0.96$, slope close to 1). A new computer-controlled occlusion method (SCASS = static compliance by automated single steps) has been recently proposed for the determination of $PEEP_i$ in mechanically ventilated patients [75].

Continuous recording of flow and pressure at airway opening

As illustrated in Fig. 2, this is an indirect method for measuring $PEEP_i$. On the basis of the equation of motion (Eq. 3), it assumes that the change in P_{ao} preceding inspiratory flow reflects the amount of pressure required to counterbalance $PEEP_i$. This technique provides the value of $PEEP_{i,dyn}$ and is of particular value for continuous monitoring of $PEEP_i$, for example during changes in the ventilator setting or to follow the effects of bronchodilator therapy. Provided that the difference between EEO-$PEEP_i$ and $PEEP_{i,dyn}$ is kept in mind, this technique has the advantage of avoiding any manoeuvre in ventilator setting, allowing monitoring of $PEEP_i$

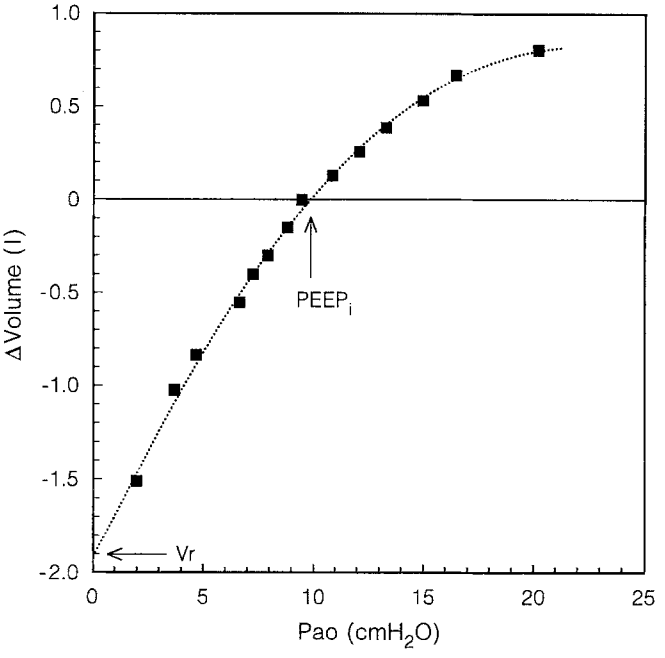

Fig. 5 Volume-pressure relationship in a mechanically ventilated patient with acute exacerbation of COPD during controlled ventilation. Pressure was measured at the airway opening (P_{ao}). The interrupter technique was used throughout a complete relaxed expiration. Dots are measurements from multiple interruptions. Complete expiration went well below the tidal expiration and the elastic equilibrium volume of the respiratory system (V_r) is represented by the intercept on the Y axis: the difference between V_r and ΔVolume = 0 provides the amount of DPH (> 1.5 l in this patient). The value for P_{ao} at ΔVolume = 0 reflects the amount of the PEEP (about 10 cmH_2O in this patient)

breath-by-breath. Moreover, with some ventilators that do not have the end-expiratory occlusion button, continuous recording of V_I and P_{ao} can be the only means of assessing rapid changes in $PEEP_i$. A modification of this approach has been suggested by Braschi et al. [76].

To summarise, during CV, measurement of $PEEP_i$ is important, particularly in patients with obstructive airway disease and also easy to perform with simple, non-invasive, bedside techniques.

Assisted modes of mechanical ventilation and weaning

Because of its implications in terms of respiratory muscle function and energetics of breathing, measurement of DPH and $PEEP_i$ should routinely be performed in the course of the assessment of respiratory function before weaning is attempted, particularly in patients recovering from acute exacerbation of COPD. EEO should be attempted first. However, since the respiratory muscles are active in patients during assisted ventilation and weaning, techniques requiring respiratory muscle relaxation, such as EEO and the interrupter technique, may be unsuccessful, at least in common clinical practice. Nevertheless, some investigators have also obtained reasonable plateaux during assisted ventilation [67] and continuous positive airway pressure (CPAP) [18]. Since expiration is mostly relaxed during assisted ventilation, the interrupter technique could also be used, as is the case in experimental animals [77] and in both anaesthetised [78] and awake normal subjects [79]; however, this has yet to be attempted in critically ill patients with ventilator modes other than CV. Hoffmann et al. recently suggested the use of respiratory inductive plethysmography (RIP) to measure $PEEP_i$ during assisted ventilation [80]. Using the RIP technique, the magnitude of $PEEP_i$ is calculated from the amount of external PEEP which can be applied without changes in the end-expiratory thoracic volume. The technique has the advantage of being non-invasive, but still poses a few problems; for example, the patient has to be relaxed, at least during the procedure, in the same way as during satisfactory end-expiratory airway occlusion. In addition, the value of $PEEP_i$ obtained with the RIP technique is lower than the true $PEEP_i$ since application of PEEP equal to the initial $PEEP_i$ induces a moderate increase in thoracic volume [81]; only values of PEEP between 75% [18] and 85% [19] of the initial $PEEP_i$ do not significantly increase the end-expiratory volume. Finally, the RIP calibration procedure may not be easy or straightforward at the bedside.

Oesophageal balloon

Although it represents an additional invasive procedure in the crowded atmosphere surrounding the patients in the intensive care unit, the oesophageal balloon technique to measure changes in P_{pl} remains, in most cases, the only means of measuring $PEEP_i$ and pulmonary mechanics in actively breathing patients. As illustrated in Fig. 3, $PEEP_i$ is measured from the change in ΔP_{pl} preceding flow. $PEEP_i$ measured in this way represents dynamic $PEEP_i$, as is the case for $PEEP_i$ obtained from continuous recording of V_I and P_{ao} (Fig. 2), and it is significantly lower, compared with static $PEEP_i$ [18].

This method of measuring $PEEP_{i,dyn}$, which has been used in both acutely ill [18, 67, 82, 83] and stable [26–28] COPD patients, is valid provided that the expiratory muscles are relaxed at the end of expiration. If the expiratory muscles actively contract during expiration, the decrease in P_{pl} in early inspiration could be due to expiratory muscle relaxation rather than to inspiratory muscle contraction [29, 45]. However, in acutely ill COPD patients the gastric component of $PEEP_i$ did not exceed a few centimetres of water becoming negligible at the highest values of $PEEP_i$ (Fig. 6).

Pleural pressure can be measured by a balloon-catheter system incorporated in a nasogastric tube used for nutrition thus rendering the process less invasive [84].

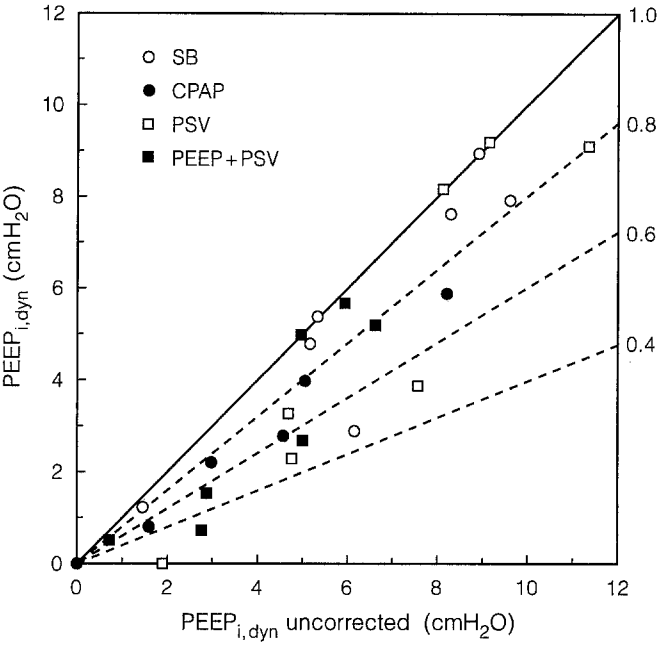

Fig. 6 Relationship between values of $PEEP_{i,dyn}$ corrected (*$PEEP_{i,dyn}$*) and uncorrected (*$PEEP_{i,dyn}$ uncorrected*) for expiratory muscle relaxation in seven patients with COPD and ARF. The *symbols* are data from each patient during different ventilatory modes with (*closed symbols*) and without (*open symbols*) application of CPAP or PEEP. *Solid line* is the line of identity. *Dashed lines* indicate different ratios of corrected to uncorrected $PEEP_{i,dyn}$

Treatment

The problem of reducing DPH and $PEEP_i$ has a major clinical impact for the treatment of patients with acute exacerbation of COPD and asthma. In such patients, DPH and $PEEP_i$ are systematically present reaching excessive values. This can lead to impaired cardiac function, enhanced risk of barotrauma, reduced inspiratory muscle pressure-generating capacity and abnormally increased energy cost of breathing. Although some levels of $PEEP_i$ have also been observed in patients without chronic airway disease [23, 25], the reduction of $PEEP_i$ in these patients is likely to be less relevant in the clinical picture and easy to accomplish with small changes in T_E. Therefore this section of the article will concentrate mainly on the treatment of $PEEP_i$ in patients with acute exacerbation of COPD and asthma. Basically, there are four methods for reducing $PEEP_i$: (1) changes in ventilator setting; (2) reduction in patient ventilatory demand; (3) bronchodilators; and (4) application of external PEEP. Clearly, the latter does not reduce DPH. All methods are suitable for simple application in the clinical setting and can be used in synergy.

Changes in ventilator setting and apparatus

The ventilatory pattern should be set so as to provide the longest expiratory phase compatible with the patient's comfort and adequate gas exchange. This can be achieved during controlled ventilation by decreasing ventilatory frequency (e.g. from 15 to 12–10 breaths/min) and the inspiratory time (T_I), or increasing inspiratory flow rate (V_I). At any given level of minute ventilation (VE) a rise in V_I will reduce T_I and increase T_E; reducing the T_I/T_{TOT} or the I:E ratio. High values of peak cycling pressure (P_{peak}) associated with high inspiratory flow should not be noticeable. The high P_{peak} can in fact be due to the resistive pressure required to push inspiratory flow through the endotracheal tube and the conducting airway, and will not affect alveolar pressure. The use of high inspiratory flow to lengthen the expiratory duration, although useful, may not be sufficient. In mechanically ventilated patients with severe airflow obstruction, a complete expiration can require more than 20 s [20, 21]. Such a long T_E cannot be used in clinical ventilator setting. In addition, a T_E slightly longer than 3 s may give rise to only a small reduction in $PEEP_i$ due to the extremely low expiratory flow rate.

Tidal volume can be also reduced so as to decrease the amount of air to be exhaled and hence DPH and $PEEP_i$. However, reduction in V_T will decrease alveolar ventilation and hence determine a rise in P_aCO_2. Traditionally, a P_aCO_2 higher than 45 mmHg has been perceived as an adverse event in mechanically ventilated patients. This traditional view has been challenged by Darioli and Perret [85], who used "controlled hypoventilation" to improve the clinical outcome in patients with status asthmaticus, and also by Hickling et al. [86] in ARDS patients. Tuxen et al. [56] showed that the magnitude of pulmonary hyperinflation is a major problem in patients with status asthmaticus, and that the reduction of pulmonary hyperinflation can be associated with a better clinical outcome [55]. In order to improve expiratory flow, the ETT should have the largest possible internal diameter compatible with the patient's characteristics; cleaning of the tube by frequent suctioning is also extremely important in prevening an abnormal increase in flow resistance due to the accumulation of secretions in the lumen.

Reduction of ventilatory demand

During assisted ventilation techniques such as ACV, SIMV and PSV, and weaning, it is more difficult to control the ventilator setting than during CV, because it depends, at least in part, upon the patient's ventilatory demand and pattern. In such circumstances, it can be important to reduce the patient's ventilatory demand and minute ventilation. For example, overfeeding and/or excessive carbohydrate feeding unduly increase CO_2 production. Correct nutritional support will reduce CO_2 and hence the ventilatory drive. It is also important to reduce the dead space as possible by keeping the proximal tip of the ETT as close as possible to the Y-piece of the ventilatory tubing. Changes in ventilatory mode may also decrease $PEEP_i$; for example, Conti et al. [49] reduced $PEEP_i$ from 17 cmH_2O to 7 cmH_2O in a mechanically ventilated COPD patient by switching the ventilatory mode from SIMV to PSV: the respiratory frequency decreased from 31 to 13 breaths/m, and cardiac complications due to excessive pulmonary hyperinflation disappeared.

Bronchodilators

It has been shown that commonly used bronchodilators such as methylxanthines (doxofylline) and β_2-adrenergic agonists (e.g. fenoterol and albuterol) are also active in mechanically ventilated patients with acute exacerbation of COPD [87–91]. Both groups of drugs significantly reduce airway resistance because of their relaxant effect on bronchial smooth muscle. The improved rate of lung emptying decreases DPH and $PEEP_i$. Bernasconi et al. [88] showed that β_2-adrenergic agonists could determine a significant, albeit brief, bronchodilatation in patients already receiving a continuous infusion of aminophylline. Manthous et al. [91] recently showed that the decrease in resistive pressure was greater with nebulised albuterol than with equal doses delivered by metered dose inhalers. The delivery system may be as important as the drug itself in determing the therapeutic response [92].

It has been shown in stable COPD patients that the decrease in lung volume determined by bronchodilators can increase inspiratory muscle strength by improving the operational length of diaphragmatic fibres in their length-tension relationship [26]. This effect, associated with a reduction in $PEEP_i$ and in work of breathing [93] can be very important for weaning.

There is little evidence of the effect of steroids in mechanically ventilated COPD patients. It could be predicted that steroids improve airway patency by reducing the amount of secretions in the bronchial lumen as well as the inflammatory process in the bronchial wall. Nava et al. [94] showed that parenteral steroids can reduce DPH and $PEEP_i$ in mechanically ventilated COPD patients.

A special condition requiring aggressive measures in order to reduce airway resistance is a life-threatening asthma attack [95]; for example, adrenaline can determine an important reduction in both $PEEP_i$ and DPH (Fig. 7). However, in some cases, the failure of conventional bronchodilators to reverse the severe airflow obstruction and DPH can be observed. In some patients, supplemental bronchodilatation can be obtained by deep sedation reaching anaesthetic levels, considering that profound sedation can have per se a bronchial smooth muscle relaxant effect [96]. In addition, some volatile and/or intravenous anaesthetics have a bronchodilating action, such as ketamine and, particularly, halothane, a volatile general anaesthetic that is a popular "last resort" powerful bronchodilator [96].

Application of PEEP

Contrary to the traditional notion and taking some controversy into account [29, 97], it seems acceptable that moderate (judicious) levels of PEEP can be of benefit in patients with acute exacerbation of COPD during assisted ventilation and weaning [22, 83]. As mentioned above, $PEEP_i$ is an inspiratory threshold load which has to be counterbalanced by the patient's inspiratory muscles either beginning inspiration or triggering the mechanical breath. Provided that tidal expiration is flow limited, application of PEEP will partly replace $PEEP_i$, without adding to it and hence without increasing lung volume, until a critical value somewhat lower than $PEEP_i$ has been exceeded [17, 83]. In line with the cascade theory of expiratory flow limitation [98, 99], these results were obtained in several clinical studies [17–19, 47, 80, 100]. Figure 8 shows that application of PEEP lower than $PEEP_i$ in a COPD patient during controlled ventilation did not increase peak cycling pressure.

During assisted ventilation and weaning, application of PEEP can unload the patient's inspiratory muscles.

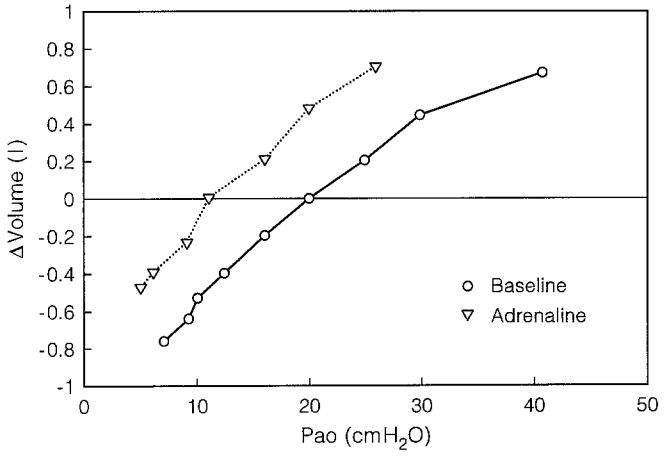

Fig. 7 Static volume-pressure relationship in a mechanically ventilated patient with acute severe asthma. As in Fig. 5, *experimental points* were obtained by the interrupter technique. *Stars* and *empty triangles* are interrupter measurements before and after 0.1 mg adrenaline. The relaxant effect of adrenaline on bronchial smooth muscle decreased both the amount of DPH and $PEEP_i$, without changes in the slope of the volume-pressure relationship, i.e. respiratory compliance. Though the patients were allowed 30 s for breathing out, expiration was still not completed because of the externe flow resistance and maybe expiratory flow limitation. Measurement of DPH and $PEEP_i$ was performed as illustrated in Fig. 5

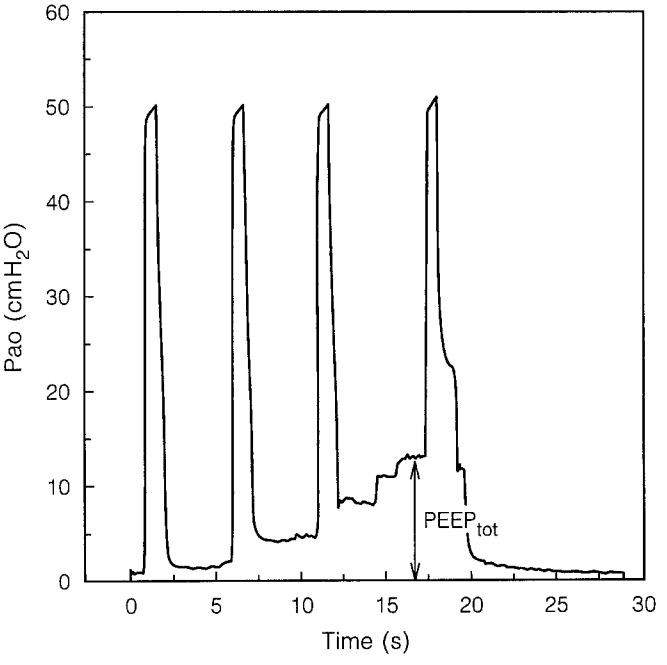

Fig. 8 Pressure at the airway opening (P_{ao}) versus time during controlled ventilation in a given patient with acute exacerbation of COPD. $PEEP_i$ was measured by EEO. From the first mechanical inflation, PEEP was set by the ventilator at 5 cmH_2O (second inflation) and at 10 cmH_2O (third inflation). Then the total PEEP (i.e. PEEPtot = PEEP + $PEEP_i$) was measured again by EEO. Since PEEP partly replaced $PEEP_i$, without adding to it, because of flow limitation, the peak cycling pressure did not change despite increasing PEEP set by the ventilator. This figure illustrates a simple way to assess the effect of PEEP set by the ventilator in patients with $PEEP_i$ at least during CV

The initial value of $PEEP_i$ should not be exceeded [97], and individual differences should also be taken into account [101]. Moreover, the presence of expiratory flow limitation should also be assessed, for example following the procedure illustrated in Fig. 4. It has been shown by Tuxen, that application of PEEP in patients without evidence of expiratory flow limitation, can further increase pulmonary hyperinflation and its adverse consequences [97]. In this context, it should be noted that, while there is evidence of expiratory flow limitation in mechanically ventilated COPD patients, it is still not known whether expiratory flow limitation exists in mechanically ventilated patients with status asthmaticus. In such circumstances, the rationale for application of PEEP in asthma remains uncertain and further investigation is required. High levels of PEEP, up to 25 cmH_2O, have been used with the purpose of opening closed airways [102]. An unusual case was recently published [103] concerning a 51-year-old woman with pulmonary oedema and bronchospasm, who managed to produce "auto PEEP" by holding her head out of the window while her husband was driving to the hospital at 80 mph; it was calculated that the effect of the above corresponded to 8 cmH_2O PEEP. Apparently, this was needed to keep the patient out of a coma [103].

Although no controlled, randomised clinical trials have shown that weaning of COPD patients is significantly improved by the use of PEEP (or CPAP), clinical and physiological studies have documented that application of PEEP or CPAP nearly up to the level of initial $PEEP_i$, in COPD patients, being of benefit during assisted ventilation [67], pressure support ventilation [100] and weaning [18]. As shown by Fernandez et al. [42], moderate levels of PEEP can be adapted to ventilated patients with $PEEP_i$, who were thought to be fighting the ventilator. Low levels of PEEP and CPAP (about 5 cmH_2O) were used for mask (non-invasive) ventilatory support in patients with acute exacerbation of COPD [47]. CPAP was also applied to asthmatic patients with acute asthma [104] and respiratory failure [105] in the emergency room.

Although it is generally agreed that the initial level of $PEEP_i$ should not be exceeded, some controversy still remains as to the best level of PEEP to be set. Ranieri et al. [19] suggested a level of external PEEP amounting to 85% of the initial $PEEP_i$. Georgopoulos et al. [101] recently concluded that the individual patient response to PEEP is still unpredictable. Fernandez et al. [81] observed that levels of PEEP equal to initial $PEEP_i$ caused a moderate but detectable increase in end-expiratory volume, which was more marked in patients with high pulmonary compliance. During mask ventilatory support, Appendini et al. [47] used a level of CPAP and PEEP amounting to 90% of the initial $PEEP_i$ and did not observe significant changes in end-expiratory volume.

Table 3 Treatment of $PEEP_i$

Changes in ventilator setting
- Increase expiratory duration
- Decrease ventilatory frequency
- Decrease tidal volume

Reduction in the ventilatory demand
- Decrease carbohydrate intake
- Reduce dead space
- Reduce anxiety, pain, fever, shivering

Reduction of total flow resistance
- Use of large bore endotracheal tubes
- Frequent suctioning
- Bronchodilators

Application of external PEEP nearly up to the level of initial $PEEP_i$

In our practice, the minimum and maximum level of PEEP are represented by $PEEP_{i,\,dyn}$ and $PEEP_i$, respectively, measured during end-expiratory airway occlusion. If $PEEP_{i,dyn}$ is not measured, a level of PEEP amounting to 85% of EEO-$PEEP_i$ appears safe [19, 47]. Application of moderate levels of PEEP, i.e. lower than $PEEP_i$ measured by end-expiratory airway occlusion, should be started almost simultaneously with the institution of assisted modes of ventilation to decrease the ventilatory load [106]. Whether or not CPAP is a choice technique for weaning has yet to be established [107]. Methods for the management of $PEEP_i$ are listed in Table 3.

Conclusion

In this review we have examined the physiological basis, the clinical implications, the measurement techniques and the treatment of $PEEP_i$ in critically ill patients during mechanical ventilation and weaning. $PEEP_i$ actually occurs much more frequently in the intensive care setting than was originally thought. However, all the published studies address mainly the physiological aspects and concern a small number of patients. More complete, long-term, randomised clinical trials are needed in the near future to investigate the clinical impact of $PEEP_i$ as well as the advantage of applying PEEP, and CPAP.

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