Airway Clearance Techniques for Mechanically Ventilated Patients: Insights for Optimization

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Secretion management in mechanically ventilated patients is a paramount task for clinicians. A better understanding of the mechanisms of flow bias and airway dynamic compression during airway clearance therapy may enable a more effective approach for this population. Ventilator hyperinflation, expiratory rib cage compression, a PEEP-ZEEP maneuver, and mechanical insufflation-exsufflation are examples of techniques that can be optimized according to such mechanisms. In addition, novel technologies, such as electric impedance tomography, may help improve airway clearance therapy by monitoring the consequences of regional secretion displacement on lung aeration and regional lung mechanics. *Key words: airway clearance/secretion management; mechanical ventilation; physiotherapy; physical therapy; sputum; ventilator hyperinflation.* [Respir Care 2020;65(8):1174–1188. © 2020 Daedalus Enterprises]

Introduction

One of the main goals of the physiotherapist and respiratory therapist in the ICU is to prevent and treat respiratory complications in critically ill patients related to pulmonary secretion retention and atelectasis.[1,2] In the mechanically ventilated patient, the primary mechanisms of secretion clearance (ie, mucociliary transport and cough) are impaired. The presence of the artificial airway,[3] poor humidification of inspired gases,[4] and relative immobility[5] are the major causes of pulmonary secretion retention in this population.

Accumulated secretion in the airways, if extensive, starts a self-sustaining cycle of ventilation/perfusion mismatch, gas-exchange impairment, increased work of breathing, and subsequent augmented risk of mechanical ventilation

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dependence, which, in turn, closes a positive loop predisposing to more retention of secretions.[6] In addition, retained secretions are a sequestered growth medium for bacteria, which increases the risk of pneumonia and keeps feeding this cycle.[7,8]

Secretion clearance in patients with artificial airways is mainly performed through endotracheal suctioning.[9] However, this procedure is only able to aspirate secretions located in the large airways up to the third-generation bronchi. Moreover, it has been recommended to apply shallow suctioning instead of deep suctioning, which limits the insertion of the suction catheter to the tip of the artificial airway and further restrains the level of action.[10] Under these factors, it appears reasonable to endorse the performance of maneuvers to mobilize pulmonary secretion from peripheral to central airways.

Several airway clearance techniques have been described, such as manual hyperinflation and ventilator hyperinflation, but these have been mostly associated with short-term effects, in particular improvements in lung compliance and oxygenation, or an increased amount of secretions recovered after the maneuvers.[11] The mechanisms responsible for an effective airway clearance have been elucidated in the last decade, especially regarding the use of flow bias and maneuvers that promote it more efficiently, but there is still room for improvement.

In this paper the role of flow bias and dynamic airway compression during airway clearance therapy is addressed. In addition, we comment and make suggestions on how to apply 4 airway clearance techniques, ventilator hyperinflation, expiratory rib cage compression (ERCC), PEEP-ZEEP, and mechanical insufflation-exsufflation (MI-E), that use these physiological principles to promote secretions removal. Besides their potential to clear pulmonary secretions, these techniques can be easily performed.

Flow Bias and Airways Dynamic Compression During Airway Clearance Therapy

In health, the mechanisms responsible for airway mucus clearance are mucociliary transport and gas–liquid interaction, which includes flow bias and cough.[12] While the mucociliary transport and gas–liquid interaction clear mucus from peripheral and small airways, cough, which is an amplification of the gas–liquid interaction, is the primary method of removing secretions from central airways. However, in the absence of cough, the flow bias becomes an important mechanism of clearing secretions in large airways as well; this is a condition frequently found in mechanically ventilated patients.

Flow Bias

The flow bias is a consequence of the continuous "to and fro" movement of gas in the airways. Averaged over several breaths, the net volume of gas moved in either direction must be equal, but the peak (or mean) flow of the inspiratory and expiratory phases can differ greatly, creating the flow bias.[13] When considering which one is greater, peak inspiratory flow (PIF) or peak expiratory flow (PEF), an inspiratory or expiratory flow bias is established and leads the net movement of mucus in its same direction, that is, toward the lungs or the glottis, respectively. In the normal lung, the narrowing of airways on exhalation increases expiratory air velocity, thus increasing the air–liquid interaction and favoring an expiratory/cephalad mucus flow.[12] However, in mechanically ventilated patients, especially on pressure support ventilation and pressure control continuous mandatory ventilation (CMV), it is usual to find ventilation with PIF that is much higher than the PEF, which creates an inspiratory flow bias and an augmented risk of embedding pulmonary secretion.[14]

The flow bias moves mucus by using the 2-phase gas-liquid transport mechanism and is usually expressed as the ratio (PEF:PIF) or difference (PEF – PIF) between the peak flows. The critical factors that affect mucus transport by this mechanism include inspiratory-expiratory air velocity, viscosity of mucus, and thickness of the mucus layer, which needs to achieve 5–10% of the airway diameter.[15-17] It is worth emphasizing that mucus transport through this mechanism occurs even under tidal volume ventilation; it is not dependent on high flows, and thus does not occur exclusively during cough.[15,17,18]

In the late 1980s, the influence of the flow bias on secretion management in the patient on mechanical ventilation was raised. The first flow bias threshold described in the literature associated with cephalad mucus displacement was a PEF:PIF ratio > 1.11.[18] Since then, this flow bias threshold has been used to infer the efficacy of airway clearance techniques in critical care patients.[19-21] In 2008, Volpe et al,[13] after a series of experiments using a bench bicompartmental model and mucus simulant, demonstrated that the transport of airway secretions by the 2-phase gas–liquid transport mechanism appears to be best explained by the difference between PEF and PIF and not by the PEF:PIF ratio. The authors identified as a critical threshold for mucus displacement toward the glottis a PEF-PIF difference of > 17 L/min, and that the larger this difference, the greater the mucus displacement.[13] Another important finding of this study was that lung mechanical inhomogeneities might determine different regional flow bias; therefore, the flow bias in the airway opening may not represent the flow pattern in all peripheral airways.[13] In 2012, in a study with mechanically ventilated pigs in the semirecumbent position, Li Bassi et al[22] reported that the animal's own mucus was displaced centrally when an average PEF-PIF difference of 33.0 ± 7.6 L/min was obtained, while the average PEF:PIF ratio was 4.3 ± 1.2, well above the in vitro threshold of 1.11.

Comparing the flow bias thresholds described in the literature up to today, the PEF-PIF difference of > 33.0 L/min is probably more clinically relevant to mechanically ventilated patients because this threshold was observed in a in vivo experiment, in which the animal's own mucus was investigated under prolonged mechanical ventilation (from 4 to 72 h), and mucus had to be transported against gravity.[22]

Although body positioning is not within the scope of this review, it is important to comment that the use of a ventilatory strategy with an expiratory flow bias, aimed at improving mucus clearance, was offset when animals were in a semirecumbent position.[23] However, in the Trendelenburg position (head-down tilt of 5°), mucus clearance was preserved and prevented the development of ventilator-associated pneumonia. Another study with sheep and artificial mucus infusion indicated that the expiratory flow bias in a horizontal position resulted in a mucus clearance of 3.1 mL in 10 min, whereas in the head-down position the clearance increased to 11.0 mL in 10 min.[15] These results alert that body positioning (ie, gravity-driven secretion strategies) should be used to facilitate airway clearance therapy.

Airways Dynamic Compression

The airways dynamic compression is also advocated as a valuable way to improve the gas–liquid flow interaction with the premise that expiratory flow is kept constant or higher in narrower airways, resulting in air flow acceleration. This occurs because, according to Bernoulli's principle, gas velocity for the same flow is higher in the narrower airway.[24,25] During maneuvers that increase the pleural pressure, such as manual ERCC, this effect is accentuated because it reduces even further the airway diameter during exhalation. In these situations, as the intrabronchial pressure is progressively lower from the alveoli to the mouth, there will be a point where it equals to the surrounding pleural pressure (ie, the equal pressure point).[25] In the upstream airway segment from the equal pressure point (toward the alveoli), there is no dynamic airway compression, whereas downstream (toward the mouth) pleural pressure exceeds intrabronchial pressure and dynamic compression occurs.[26] The site of the equal pressure point is influenced by the airway stability, the expiratory force, and lung volume. For instance, a higher expiratory force and an exhalation starting from small lung volumes shift the equal pressure point more peripherally.[26,27] On the other hand, an exhalation starting from high lung volumes shift the equal pressure point more centrally. Independent of where equal pressure point is initially located, with an ongoing forced expiration, the equal pressure point gradually moves upstream (toward the alveoli), creating a wave of choke points. In theory, to assist with airway clearance, the equal pressure point needs to be shifted to where the mucus is accumulated to catch mucus in such a choke point and thus expel it toward the glottis by the increased expiratory air flow velocity.[25] These physiological principles are the rational basis for the use of low lung volume to remove secretion from distal airways and high lung volumes from central airways.[12]

However, patients with unstable airways or reduced lung volumes may be susceptible to expiratory flow limitation during compressive or forced expiratory maneuvers, which is believed to be related to the collapsibility of airways.[28,29] If the airways collapse, the downstream flow drops to zero and secretion removal is interrupted.[12,28] In mechanically ventilated patients, expiratory flow limitation is frequently observed in individuals with COPD, obesity, and cardiac failure, and this limitation is influenced by fluid status, the patient's position, bronchoconstriction, and ventilatory conditions.[29] The main consequence of expiratory flow limitation for these individuals is the intrinsic PEEP, whose treatment consists in the application of an external PEEP equivalent to 80–85% of intrinsic PEEP.[29] In this sense, external PEEP has also been recommended as a protective strategy against expiratory flow limitation during forced expiratory maneuvers or ERCC, with the goal of generating a splinting effect.[27]

Airway Clearance Techniques for Mechanically Ventilated Patients

Ventilator hyperinflation, ERCC, PEEP-ZEEP, and MI-E are airway clearance techniques that can be applied in accordance with the mechanisms of flow bias and airway dynamic compression to effectively remove secretions. However, there are some controversies about how they should be applied that require clarification.

Ventilator Hyperinflation

Ventilator hyperinflation can be defined as the use of the ventilator to deliver increased tidal volume aimed at assisting with secretion removal. This technique was introduced as an alternative to manual hyperinflation, which is performed by delivering a large tidal volume with a resuscitation bag, followed by an inspiratory plateau, and a fast release of the bag to provide high expiratory flows.[11] Both ventilator hyperinflation and manual hyperinflation may be applied with a second aim, to open collapsed lung units that are not necessarily associated with airway secretion retention. In this paper, we discuss only the use of ventilator hyperinflation as an airway clearance technique.

The first use of the term "ventilator hyperinflation" took place in 2002[30] and reported that this technique was equivalent to manual hyperinflation in improving secretion removal and static compliance of the respiratory system. Since then, many studies on ventilator hyperinflation have been carried out with general samples of critical care patients.[30-34] These studies confirmed the similarity between ventilator hyperinflation and manual hyperinflation in clearing secretions, improving respiratory mechanics, and gas exchange.[30,32,33] Nevertheless, there is a lack of studies addressing the effects of ventilator hyperinflation or manual hyperinflation on long-term clinically relevant outcomes, such as length of stay, duration of mechanical ventilation, weaning, and incidence of ventilator-associated pneumonia.

Due to the potential advantages of ventilator hyperinflation, we embrace its use instead of manual hyperinflation. When using the ventilator to apply the maneuver, the patient is not disconnected from the mechanical ventilator, which avoids PEEP loss, hypoxemia, and shear stress caused by cyclic opening and closing of small airways. Moreover, different from manual hyperinflation, ventilator hyperinflation makes it possible to monitor and set the parameters of interest for the technique's application.[32,33,35]

Studies on ventilator hyperinflation have used different criteria to determine the inspiratory volume: 50% above the current tidal volume,[34] 130% of the set tidal volume,[32] 15 mL/kg,[33] and volume corresponding to a peak inspiratory pressure of 40 cm H_2O.[30,31,35] Regardless of the criteria chosen, the peak inspiratory pressure was limited to 40 cm H_2O. The main modes used for ventilator hyperinflation were volume control CMV[30,34] and pressure support ventilation.[31] Regarding the inspiratory time or flow settings during ventilator hyperinflation, the following were used: inspiratory time of 3–5 s,[33] inspiratory flow of 20 L/min plus an inspiratory pause of 2 s,[30] or no modification at all.[32] Although using different settings to deliver ventilator hyperinflation, the cited works reported benefits in removing secretions and improving physiological parameters. However, it is plausible to think that there is a combination of settings to achieve the best outcome.

In 2015, Thomas[36] used expiratory flow bias thresholds to compare the effectiveness of different ventilator hyperinflation modes. After 232 trials using a bench lung model circuit, the volume control CMV was more successful than pressure support ventilation and pressure control CMV for delivering ventilator hyperinflation.[36] In 2019, another in vitro study using a mucus simulant and pressure-regulated volume control mode indicated that longer rise times reduced PIF, resulting in favorable expiratory flow bias and increased mucus movement.[37] Also, in 2019, Ribeiro et al compared 6 modes of ventilator hyperinflation in a sample of 30 mechanically ventilated subjects to study flow bias thresholds and lung expansion as dichotomous criteria.[35] They found that volume control CMV with an inspiratory flow of 20 L/min and pressure support ventilation with cycling off of 10% or 25% gave the best results.[35]

For patients presenting with respiratory drive, some ventilatory modes may cause patient–ventilator asynchrony during ventilator hyperinflation, even when the patient is triggering the ventilator. In the study by Ribeiro et al,[35] the authors also reported that volume control CMV with an inspiratory flow of 20 or 50 L/min and pressure control CMV with prolonged inspiratory time (ie, 3 s) were associated with a high incidence of flow and phase asynchronies, respectively.

Another factor to be considered during ventilator hyperinflation is the PEEP adjustment. In a preliminary study from our group (data not published), we investigated the effects of ventilation settings during ventilator hyperinflation on saline secretion displacement, assessed with electrical impedance tomography (EIT) in mechanically ventilated pigs. Ventilator hyperinflation applied in volume control CMV with a high expiratory flow bias (PEF-PIF difference of 40 L/min) and high PEEP resulted in faster lung secretion displacement toward the glottis compared to a maneuver with similar settings but lower inspiratory flow bias (PEF-PIF difference of –12 L/min; Figure 1, A and C). The high PEEP level was set according to a decremental PEEP maneuver monitored with EIT, targeting a compromise of minimum lung collapse and hyperdistention. However, minimum changes in lung impedance were observed when PEEP was lower (ie, equal to high PEEP level minus 5 cm H_2O), despite ventilation with the same expiratory flow bias (Figure 1B). More information about the method used is given in the legend of Figure 1. These results suggest that, in patients with airway or pulmonary collapse, airway clearance techniques require minimum patency of airways to be effective.

Based on the aforementioned studies, we can make recommendations on how to select the ventilator settings to perform an optimized ventilator hyperinflation (Table 1). For patients who present with respiratory discomfort or patient–ventilator asynchronies during ventilator hyperinflation on volume control CMV, we suggest applying ventilator hyperinflation on pressure support ventilation according to the procedure described in Table 2.

Regarding the safety of ventilator hyperinflation, despite the well-known risk of hemodynamic repercussions when using high positive pressures, no significant changes in arterial blood pressure and heart rate during the technique have been reported.[31-33,38] Also, in 2003, Berney and Denehy found no changes in cardiac index and mean arterial oxygen consumption in subjects receiving ventilator hyperinflation with volume control CMV.[38] Concern that ventilator hyperinflation may cause hyperventilation, it seems that, if applied in assisted ventilatory modes or with reduced breathing frequency in controlled ventilation, there is no meaningful change in CO_2 output,[32] P_{aCO_2},[39] or minute ventilation.[35]

Expiratory Rib Cage Compression

ERCC is one of the most commonly applied airway clearance technique in mechanically ventilated patients.[2,40,41]

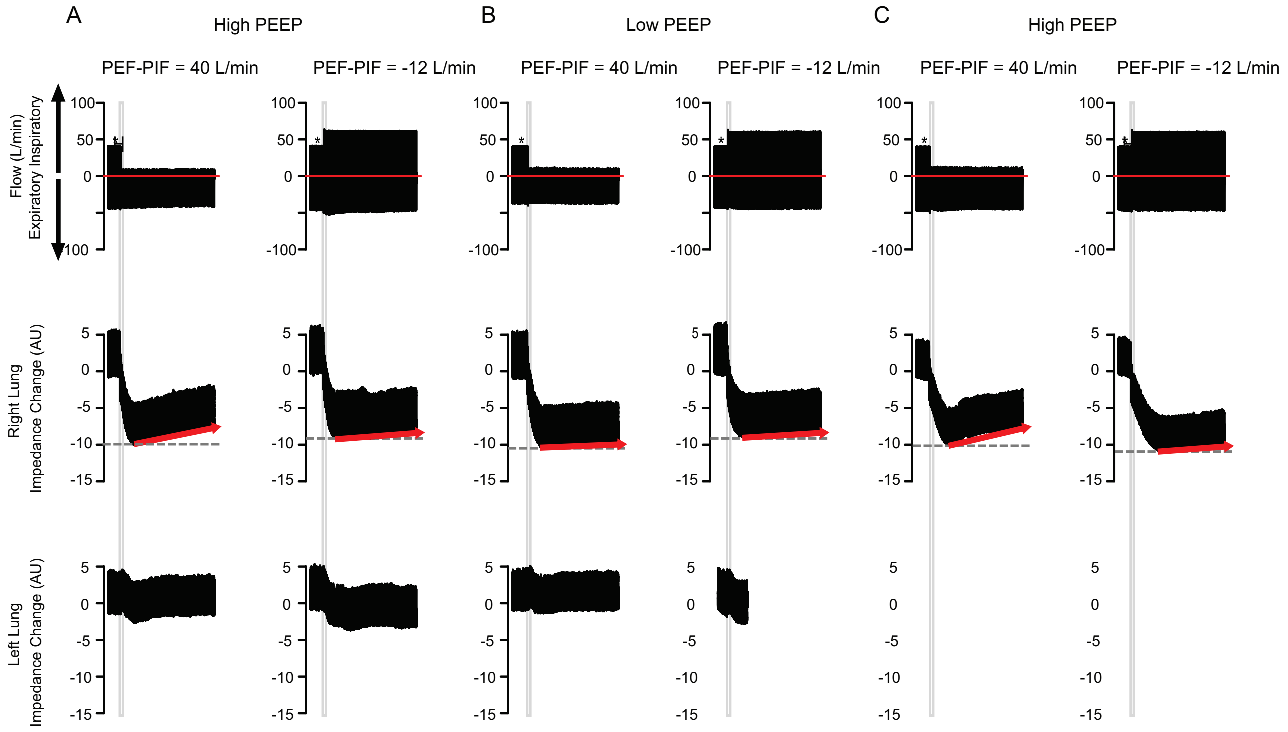

Fig. 1. Representation of lung impedance changes assessed with electrical impedance tomography (EIT) in an animal model of mild lung injury, before and after saline injection (3 mL) in the main right bronchus (indicated by the gray vertical line; the injection lasted for a few seconds). After saline injection, the animal was mechanically ventilated with different expiratory flow bias ventilation and 2 levels of PEEP. High PEEP was set according to a decremental PEEP maneuver targeting minimum levels of alveolar collapse and hyperdistention. Low PEEP was 5 cm H_2O below the high PEEP level. Ventilation after saline injection lasted 30 min. Because the EIT signal is based on the estimation of the resistivity variations within the lung (simplified as impedance changes), the hypertonic saline solution was used as an intrabronchial contrast due to its high conductivity. Note the significant reduction in resistivity measured after saline solution injection into the right lung. (A, C) During high PEEP ventilation and an expiratory flow bias (difference between peak expiratory flow [PEF] and peak inspiratory flow [PIF] = 40 L/min), the right lung plethysmogram had a faster increase (ie, greater slope indicated by the red arrow) than ventilation with an inspiratory flow bias of PEF-PIF difference = –12 L/min. This phenomenon might represent the saline solution with secretion going out from the right lung. (B) Minimal changes were observed in lung resistivity when PEEP was low, indicating that airway collapse prevented saline and secretion removal. Note that there was no change in the left lung plethysmogram. *Standard ventilator settings before saline secretion injection (volume control continuous mechanical ventilation, PEF-PIF difference = 1 L/min). AU = arbitrary units.

Table 1. Suggested Procedure for Ventilator Hyperinflation

Use volume control continuous mandatory ventilation with square wave flow and inspiratory flow of 20–40 L/min.
Increase tidal volume to reach peak inspiratory pressure of 35 cm H_2O and certify that plateau pressure is $\leq$ 30 cm H_2O.*
Set optimal PEEP to maintain airway patency.
Ensure that PEF-PIF difference > 33 L/min; if it is not, consider reducing the inspiratory flow or the rise time.
In patients without respiratory drive, reduce breathing frequency to keep the baseline minute ventilation.
Monitor hemodynamics, oxygen saturation, and ventilator curves throughout the procedure.

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* Because plateau pressure correlates better with barotrauma and ventilator-induced lung injury, it seems important to ensure plateau pressure is $\leq$ 30 cm H_2O.
PEF = peak expiratory flow
PIF = peak inspiratory flow

However, there is great controversy on how this technique should be performed, which is reflected by the several forms of ERCC found in the literature.[42,43] Specific details on how the compression is applied (ie, intensity of the compression, its initiation and duration in relation to the phase of the ventilator cycle, whether performed in association with chest wall vibration, and how chest release is applied at the end of the maneuver) modifies the technique greatly.

To make this topic even more controversial, there is no consensus on terminology used to distinguish the different forms of ERCC.[44] Due to this lack of consistency, comparison among studies that investigated the effects of ERCC requires caution, especially because the technique is not always fully described.

Table 2. Suggested Procedure for Ventilator Hyperinflation*

Use PSV with cycling off of 10% and set the lowest rise time that do not cause flow asynchrony (ie, flow starvation).
Increase PSV to reach peak inspiratory pressure of 30 cm H_2O.
Set optimal PEEP to maintain airway patency.
Certify that the PEF-PIF difference is > 33 L/min; if it is not, consider reducing the rise time.
Monitor hemodynamics, oxygen saturation and ventilator curves throughout the procedure.

* For patients who present flow asynchrony under ventilator hyperinflation on volume control continuous mandatory ventilation.
PSV = pressure support ventilation
PEF = peak expiratory flow
PIF = peak inspiratory flow

Regarding its objectives, ERRC is usually applied either to assist with secretion movement from distal to proximal airways, or to remove secretion from large airways.[45,46] In theory, if ERRC is applied with gradual intensity (from gentle to strong) to prolong exhalation after the onset of the expiratory phase, it removes secretions from distal airways. On the other hand, if ERRC is applied with hard compressions to increase PEF and synchronized with the onset of expiration, it removes secretions from proximal airways. Marti et al[43] named these two techniques soft manual rib cage compression and hard manual rib cage compression, respectively. To facilitate the understanding in this review, we are going to use a similar terminology: soft/long ERCC and hard/brief ERCC.

Chest release during ERCC should be performed slowly to avoid increasing the elastic recoil of the respiratory system and thus prevent the increase in the transpulmonary pressure that could increase the PIF and reduce the expiratory flow bias of the next ventilation cycle.

Marti et al[43] compared these 2 ERCC forms in pigs under prolonged mechanical ventilation, assessing mucus clearance through fluoroscopy tracking of radio-opaque markers. They found that the hard/brief ERCC increased the PEF by ~ 9 L/min and significantly improved mucus clearance in trachea without causing any deleterious effect. On the other hand, the soft/long ERCC did not influence mucus clearance and slightly worsened the static lung elastance and cardiac output. The prolonged chest squeezing probably caused a decrease in the expiratory lung volume and in the venous return, leading to the worsening of respiratory mechanics and hemodynamics, respectively. However, because mucus movement was measured only at the trachea, it is not possible to infer anything about mucus displacement in lung periphery. It is also worth noting that these assessments were measured only prior to and after each technique, without details on how long they lasted.

Others have investigated the use of the soft/long ERCC form, and the results are diverse. In a study with mechanically ventilated rabbits with induced atelectasis by instillation of artificial mucus, Unoki et al[47] reported that the use of this technique followed by suctioning worsened the respiratory compliance and gas exchange compared to the control group submitted only to airway suctioning. However, the rabbits were ventilated with no PEEP, which might have predisposed the animals to airway collapse during ERCC. In another study by the same group, the use of the soft/long ERCC in association with lateral decubitus position in 31 ventilated subjects resulted in no changes in pulmonary mechanics, gas exchange, and secretion clearance.[48] Genc et al[49] also reported that the addition of ERCC to manual hyperinflation did not improve lung compliance and secretion removal in 22 ventilated subjects. On the contrary, a recent study indicated that the use of the soft/long ERCC combined with abdomen compression in 16 subjects with ventilator-associated pneumonia removed more secretion and resulted in a transient improvement in static lung compliance when compared to the control group.[42]

Regarding the hard/brief ERCC form, several studies that investigated this technique in ventilated lung models, animals, and adult subjects reported significant increases in PEF of 8.8 L/min,[50] 8.9 L/min,[43] and 6.7–43.8 L/min,[51-54] respectively. The capacity of the hard/brief ERCC form to increase PEF seems to be mainly determined by the timing of the maneuver application, which should be performed in full synchronization with the onset of expiration.[50] However, other factors, such as properties of the respiratory system, inspired tidal volume, and use of 1 or 2 hands, also influence the resulting PEF.

Avena et al[44] reported that the use of the hard/brief ERCC form followed by airway suctioning in surgical subjects resulted in reduced airway resistance and improved oxygenation, indicating the efficacy of the technique in removing secretion. It is important to note that, in the study by Marti et al,[43] the animals were ventilated with an expiratory flow bias already in the baseline and that the ERCC increased this flow bias, favoring secretion removal. In the study by Avena et al,[44] although the peak flows were not reported, the ERCC probably resulted in an expiratory flow bias because the subjects were ventilated in the volume control CMV mode with a square wave flow and increased inspiratory time. Therefore, in both studies, the efficacy of the hard/brief ERCC form in removing secretion was associated with the presence of an expiratory flow bias.

More recently, Gonçalves et al[55] also reported that the hard/brief ERCC form resulted in greater removal of secretion and improvement of static compliance in 30 mechanically ventilated subjects. In another study with 35 ventilated subjects, the use of the hard/brief ERCC form was optimized (ie, it generated higher PEF (mean difference of 16.5 L/min) and decreased airway resistance) when the technique was applied in association with an increment on PEEP from 5 cm H_2O to 15 cm H_2O and on inspiratory time from 1 s to 2 s.[52] The authors postulated that the higher

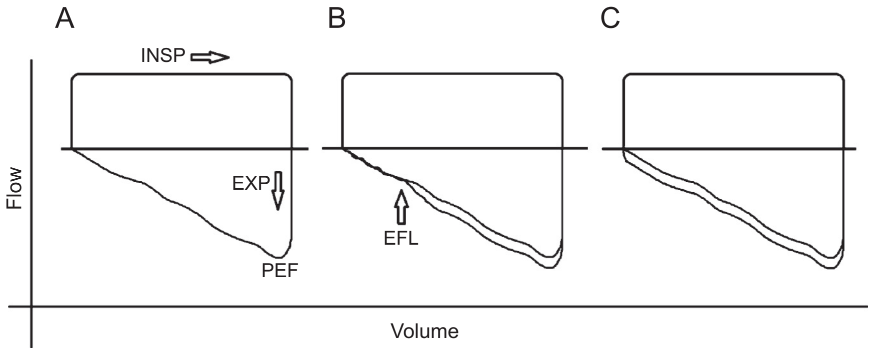

Fig. 2. Suggested use of flow-volume curves to set the PEEP level and compressive force during ERCC. (A) Baseline flow-volume loop. (B) Baseline (internal expiratory curve) and ERCC flow-volume loops (external expiratory curve); the superposition in the terminal part of expiratory flow denotes expiratory flow limitation. (C) Baseline (internal expiratory curve) and ERCC flow-volume loops (external expiratory curve) with a PEEP level set to avoid expiratory flow limitation. Note that the flow is increased until the end of expiration. INSP = inspiration; EXP = expiration; PEF = peak expiratory flow; EFL = expiratory flow limitation; ERCC = expiratory rib cage compression.

PEEP minimized airway collapse during ERCC and thus allowed higher PEF. However, because the subjects were ventilated in the pressure control CMV mode, the increase in the inspiratory time and PEEP could have resulted in higher tidal volume, thus leading to a higher PEF.

Guimaraes et al[53] investigated the application of the hard/long ERCC form in 20 mechanically ventilated subjects with pulmonary infection. The maneuver resulted in an increase in the PEF, in the terminal expiratory flow (which reflects the flow pattern in small airways), and in the amount of removed secretion. However, 6 subjects exhibited expiratory flow limitation during ERCC. This was detected by the superimposition between the baseline (current ventilation) and ERCC flow-volume loops observed on the ventilator display. Because the flow-volume loop is a practical method to detect expiratory flow limitation in ventilated patients,[56,57] the authors suggested that the PEEP level should be increased to stabilize the small airways during ERCC to the point at which there is no superimposition between the baseline and ERCC flow-volume loops (Fig. 2).[53] Moreover, the authors also recommended a hyperinflation maneuver after ERCC to re-inflate the areas collapsed due to the compressive effect.

Considering the methodological limitations of many of the studies mentioned above and the inconsistency in the studies' results, it is not possible to make recommendations regarding the use of the soft/long ERCC form. However, the use of the hard/brief ERCC form appears to be capable of increasing the PEF and thus the expiratory flow bias. Recommendations on how to perform the hard/brief ERCC form are described in Table 3.

Table 3. Suggested Procedure for Hard/Brief ERCC*

Position hands bilaterally on the lower third of the thorax.
Start compression in full synchronization with the onset of expiration; observe the ventilator curves for better performance.
Compression should be hard and fast.
Avoid releasing hands from the chest too quickly to avoid auto-triggering the ventilator and to avoid increasing the transmural pressure, which could increase the PIF of the next cycle.
Monitor the ventilator screen to observe the increment on the PEF caused by ERCC. If there is no increment, the maneuver is not effective.
Monitor hemodynamics, oxygen saturation, and ventilator curves throughout the procedure.

* ERCC indicated to remove secretions from large/central airways.
PIF = peak inspiratory flow
PEF = peak expiratory flow
ERCC = expiratory rib cage compression

PEEP-ZEEP

This technique consists of increasing PEEP to 15 cm H_2O during 5 cycles with peak inspiratory pressure limited to 40 cm H_2O, followed by abrupt reduction of PEEP to 0 cm H_2O.[58,59] By increasing the Δ pressure at the onset of the expiratory phase, this technique increases the PEF and, consequently, the expiratory flow bias. The hard/brief ERRC form can be applied in association with PEEP-ZEEP to augment the expiratory flow bias.

The PEEP-ZEEP technique has been proven to be safe in a general sample of ICU subjects[51] and also in subjects undergoing coronary artery bypass graft surgery.[59] Additional studies have reported that PEEP-ZEEP was equivalent to ERCC[58] and manual hyperinflation[60] at removing secretion and improving pulmonary compliance, respectively. However, the latter two studies did not provide information about the ventilation mode used to apply PEEP-ZEEP and did not describe the peak flows and flow bias achieved. Amaral et al[51] investigated the influence of the ventilation mode (volume control CMV vs pressure control CMV) and the effects of applying the hard/brief ERCC form on the flow bias generated during

PEEP-ZEEP in mechanically ventilated subjects. They reported that the expiratory flow bias was higher in the volume control CMV mode than in the pressure control CMV mode, with a PEF-PIF difference of 39.5 ± 11.5 L/min versus 6.7 ± 5.7 L/min, respectively. This result was caused by a lower PIF in the volume control CMV mode. In addition, in the majority of cycles of PEEP-ZEEP applied in the pressure control CMV mode, an inspiratory flow bias was generated, which might embed mucus (Fig. 3). PEF was 8 L/min higher with ERCC compared to without ERCC, which increased the PEF-PIF difference by the same amount. Another study from the same group also confirmed that combining the hard/brief ERCC with PEEP-ZEEP increased the expiratory flow bias.[46] Figure 4 illustrates the effect of combining ERCC with PEEP-ZEEP.

One limitation of this technique is that using PEEP-ZEEP may induce alveolar collapse in patients with high lung elastance and unstable alveoli. Therefore, it is imperative that PEEP-ZEEP is only applied to carefully selected patients who are not prone to alveolar collapse or acute lung injury.[59] Figure 5 illustrates the effects of the PEEP-ZEEP maneuver on respiratory mechanics in an animal model with healthy lungs (data not published). Regardless of the expiratory pressure gradient (from 30 cm H_2O of inspiratory pressure to PEEP of 10, 5, and 0 cm H_2O), note that the end-expiratory lung volume, assessed with EIT, was restored to similar values previous to all maneuvers. Moreover, no heterogeneities in ventilation distribution were identified with EIT imaging according to the center of ventilation (Fig. 5A). However, observe that the higher the expiratory pressure gradient (Fig. 5B), the higher the PEF (Fig. 5C) and the exhaled volume (Fig. 5A). These preliminary data suggested that an expiratory pressure gradient from 30 cm H_2O to 0 cm H_2O generated the highest expiratory flow bias without inducing alveolar collapse. More studies are necessary to confirm these results.

Mechanical Insufflation-Exsufflation

MI-E is used to simulate cough mechanically by applying positive and negative pressure changes to the airways, either noninvasively via a mask or mouthpiece or invasively via a tracheostomy or endotracheal tube. This therapy was developed in the early 1950s and has been used primarily to assist, noninvasively, airway clearance in patients with neuromuscular weakness.[61-64] However, its use in mechanically ventilated patients has been increasing in the past few years.[65,66]

Only a few studies have investigated the effects of MI-E in critically ill mechanically ventilated subjects.[67-71] The first study was published in 2010 by Bach et al,[67] who reported successful extubation to continuous noninvasive ventilation and MI-E of 155 of 157 subjects with neuromuscular disease considered unweanable after multiple unsuccessful spontaneous breathing trials or extubations. In this first study, the subjects were submitted to MI-E every 20 min while intubated to maintain $S_{pO_2} \geq 95\%$ in ambient air.

In 2012, Gonçalves et al[68] reported that MI-E associated with noninvasive ventilation as part of an extubation protocol reduced re-intubation in an ICU heterogenous population; only 6 subjects in the study group (17%) were reintubated versus 19 subjects in the control group (48%). When considering the subgroup of subjects who used noninvasive ventilation, only 2 subjects (6%) in the study group versus 13 subjects (33%) in the control group were reintubated, suggesting that MI-E improved the efficacy of noninvasive ventilation in subjects who developed respiratory failure after extubation. Moreover, the main reason for re-intubation in the control group was secretion encumbrance associated with severe hypoxemia, indicating that MI-E was effective at clearing secretions and preventing respiratory failure. Subjects in the study group, after passing the spontaneous breathing trial, were submitted to 3 sessions daily of MI-E, which was continued for 48 h after extubation.[68] MI-E treatment consisted of 8 cycles per session, with insufflation and exsufflation pressures set at +40/–40 cm H_2O, with an abdominal thrust applied timed to the exsufflation cycle.

More recently, additional studies have reported that MI-E therapy (ie, 3–4 sessions of 4–10 cycles with pressures set at +40/–40 cm H_2O or +50/–50 cm H_2O) increased secretion removal and pulmonary compliance and reduced airway resistance in a mixed set of subjects ventilated in the ICU.[69,70] On the contrary, one study indicated no benefits of MI-E in terms of respiratory mechanics and secretion removal in 48 mechanically ventilated subjects when compared to isolated airway suctioning.[71] This negative result might be explained by the fact that the included subjects did not have signs or history of difficulty in clearing secretion (such as neuromuscular weakness or being deeply sedated). The only criteria that could indicate secretion retention in their population was mechanical ventilation for > 48 h.[71] It is important to emphasize that, as with any other airway clearance technique, there is no evidence to support the use of MI-E on a routine basis.[72] Recently, MI-E has been recommended for use with ventilated patients with signs of secretion retention and with a weak cough determined by a cough peak flow < 60 L/min to facilitate weaning or to reduce the risk of re-intubation.[73] However, there is still minor evidence endorsing these recommendations.

Regarding MI-E settings (ie, insuffation-exssuflation pressures, rise time or inspiratory flow, and inspiratory-expiratory times), there is no consensus about what settings are optimal for airway clearance. However, adjusting high inspiratory flow might not be indicated in mechanically ventilated patients because it might reduce the expiratory flow bias and, consequently, the efficacy of

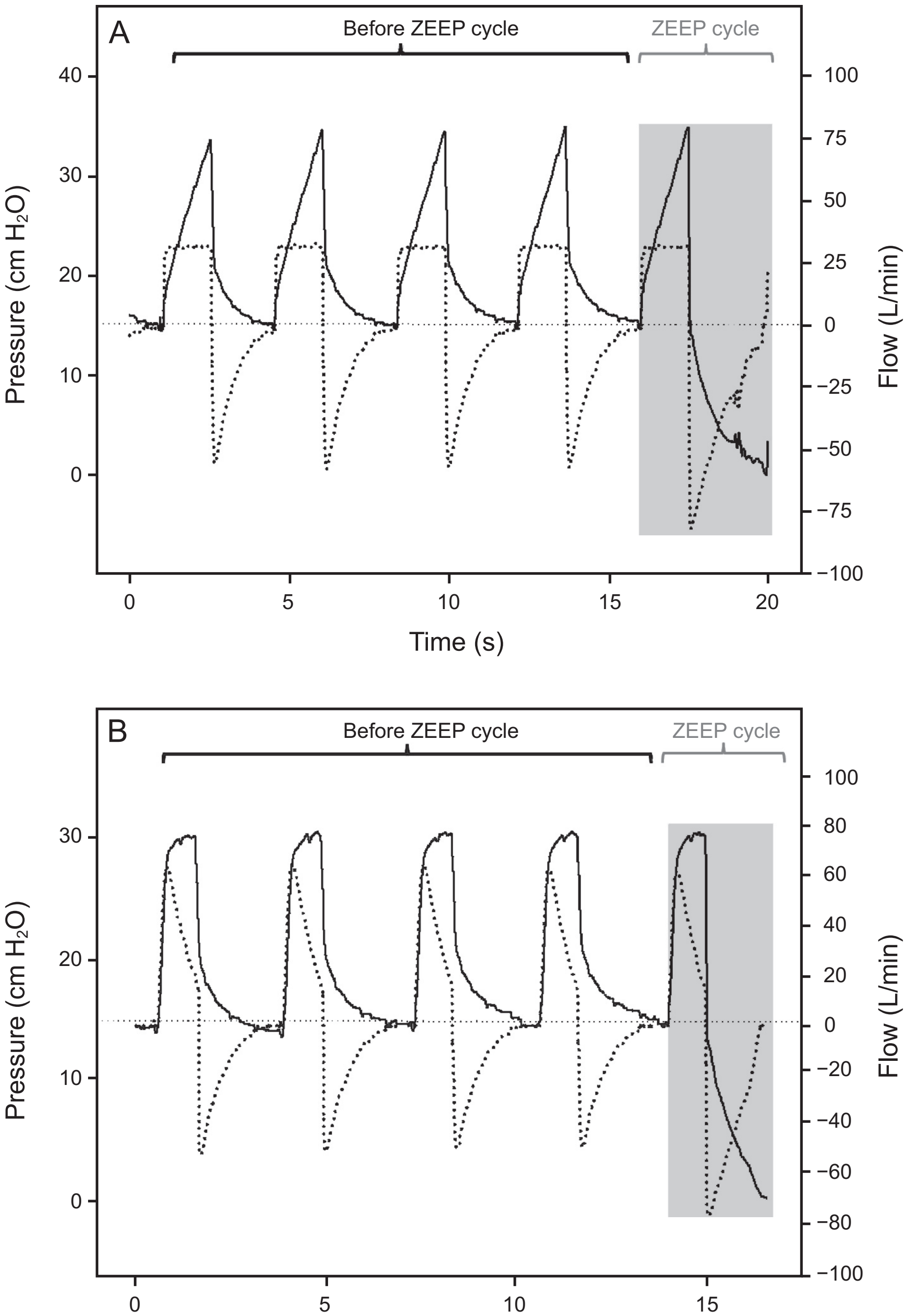

Fig. 3. Airway pressure and air flow curves of the PEEP-ZEEP technique applied in A: the volume-controlled mode and in B: the pressure control mode, without expiratory rib cage compression, for a representative patient. Pressure curve tracings are continuous, and air flow tracings are interrupted. Note the increment in expiratory flow bias (PEF-PIF difference) during the ZEEP cycle during both ventilation modes caused by PEF augmentation. However, in the pressure control mode, the expiratory flow bias (PEF-PIF difference) is 16 L/min, which is enhanced to 50 L/min in the volume control mode. Note also that, during the cycles before ZEEP, there is an inspiratory flow bias (PEF-PIF difference) of −11 L/min in the pressure control mode, whereas there is an expiratory flow bias of 26 L/min in the volume control mode. From Reference 51, with permission.

clearing secretion. This likelihood was demonstrated by Volpe et al[74] in a bench study with a lung model simulating a patient on mechanical ventilation. The authors reported that the MI-E maneuver was optimized by applying slow lung insufflation, which reduced the PIF and, consequently, increased the expiratory flow bias (Fig. 6).

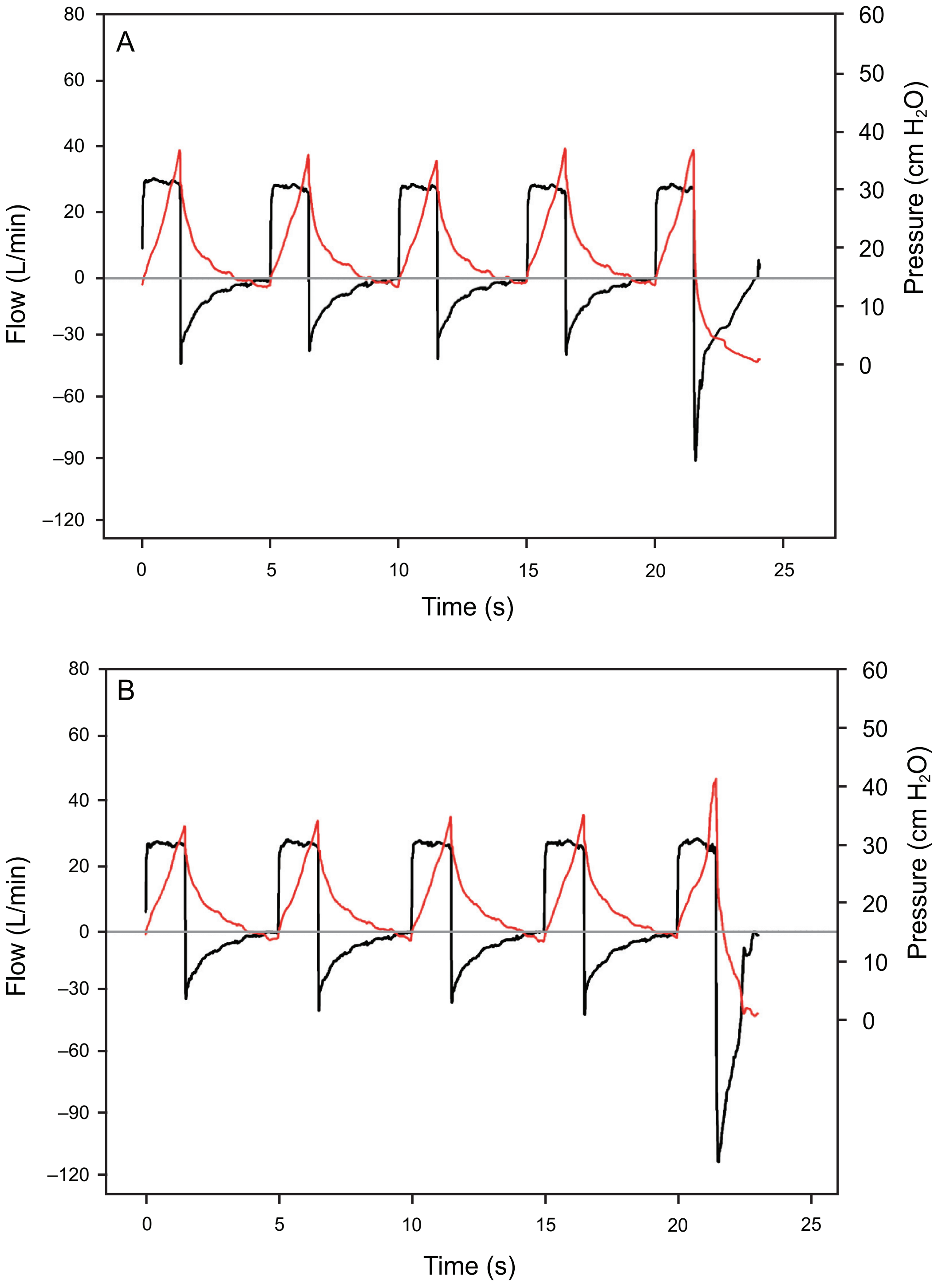

Fig. 4. A: The PEEP-ZEEP maneuver without expiratory rib cage compression and B: the PEEP-ZEEP maneuver with expiratory rib cage compression in a representative subject of the study sample. The expiratory flow bias generated during the ZEEP cycle without expiratory rib cage compression (A) was ~ 60 L/min, whereas, with the addition of expiratory rib cage compression (B), the expiratory flow bias was ~ 83 L/min. From Reference 46, with permission.

As a result, the optimized MI-E maneuver was much more effective at clearing the artificial mucus. Moreover, the authors noted that the expiratory flow bias (PEF – PIF difference) and MI-E pressure gradient were significantly correlated with mucus displacement, whereas the PEF was not.[74] These results indicate that, to optimize airway

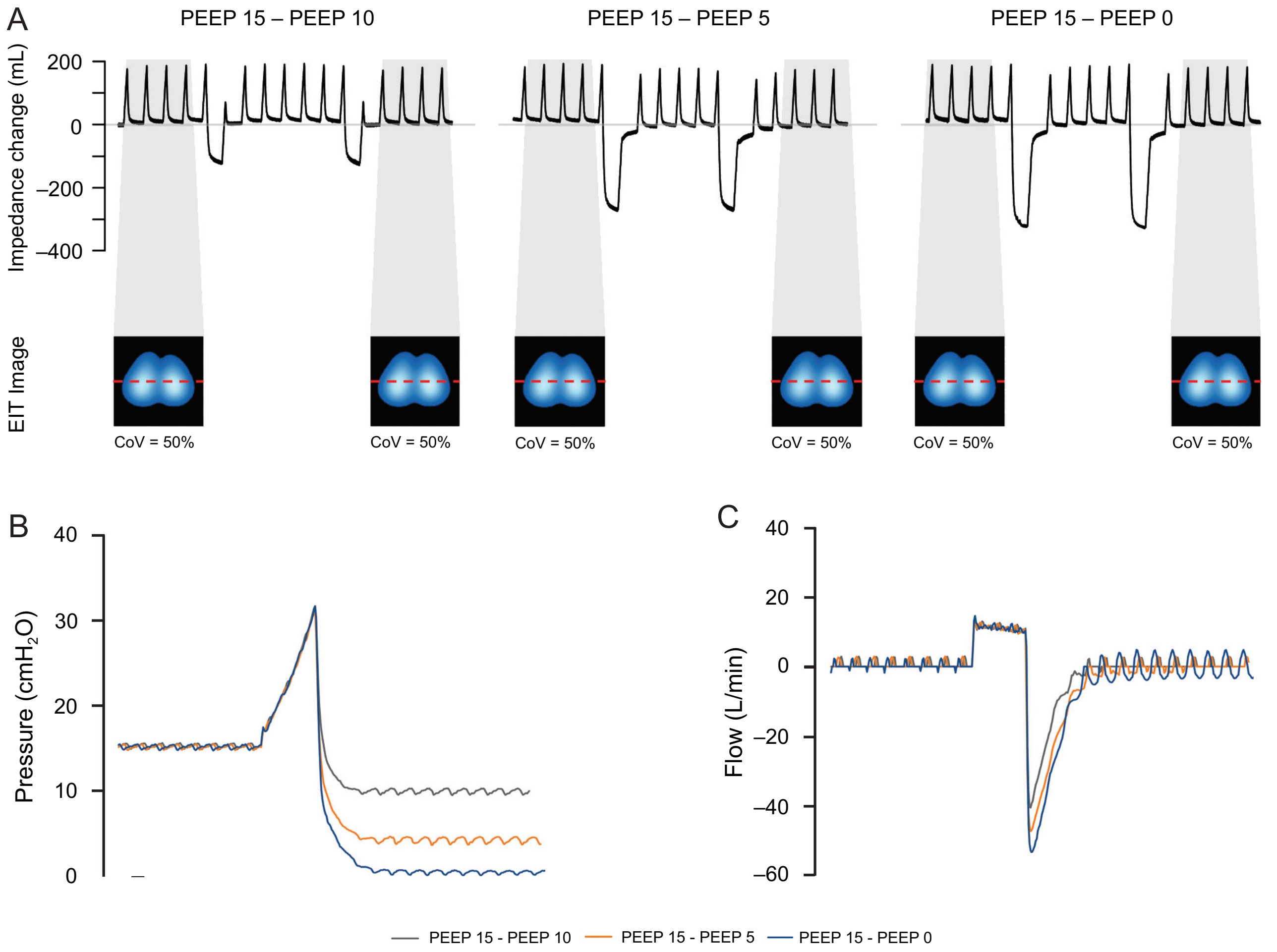

Fig. 5. Representation of the effects of PEEP-ZEEP on respiratory mechanics in an animal model with a healthy lung. A: Global plethysmogram of electrical impedance tomography (EIT) illustrating end-expiratory lung volumes changes before and after the PEEP-ZEEP maneuvers. Functional EIT images (cross section at the fifth intercostal level) show the distributions of regional ventilation based on the center of ventilation method. Ventral is the top and right is the left side of the thorax on each image. The red dotted lines represent the position of the center of ventilation. Note that the ventilation distribution was kept homogeneous after all maneuvers (50% for each region) and end-expiratory lung volumes returned to baseline levels. This complete reversal in the plethysmogram and in the functional image is not common in unstable patients presenting alveolar collapse. B: Expiratory pressure gradient (from 30 cm H_2O of inspiratory pressure to PEEP of 10, 5, and 0 cm H_2O). C: Progressive levels of peak expiratory flow (PEF) reached when PEEP values suddenly decreased from 15 to 10, 5, and 0 cm H_2O. CoV = coefficient of variance.

clearance with MI-E in mechanically ventilated patients, the target should be high PEF-PIF differences, which may be achieved by applying slow insufflation (ie, just the minimum insufflation pressure necessary to guarantee lung expansion) and by setting larger exsufflation pressures, within safe limits, such as +30/–40 cm H_2O and +40/–50 cm H_2O. In agreement with these results, Striegl et al[75] also reported that larger MI-E pressure differentials resulted in a higher PEF when using an infant lung model, which indicated that secretion clearance might be improved by using asymmetric MI-E pressure settings. Interestingly, the use of low inspiratory flow has also been recommended to extubated patients with amyotrophic lateral sclerosis to avoid upper airway collapse and the reduction of pulmonary volume.[76,77]

One concern that has not been investigated properly is whether the of use high exsufflation pressures could reduce the end-expiratory volume leading to hypoxemia and lung injury or, on the contrary, if it causes airway collapse that would prevent this from happening. The use of new technologies, like EIT, should be encouraged to investigate this issue.

Although concerns about the safety of MI-E in mechanically ventilated patients have been mentioned, until now the few published studies did not report complications associated with the use of MI-E in ICU subjects.[66-71] However, MI-E may be deleterious for patients at risk of lung collapse (ie, high PEEP levels) or severe hypoxemia because of the use of negative pressure and the need to disconnect the patient from the mechanical ventilator.[78]

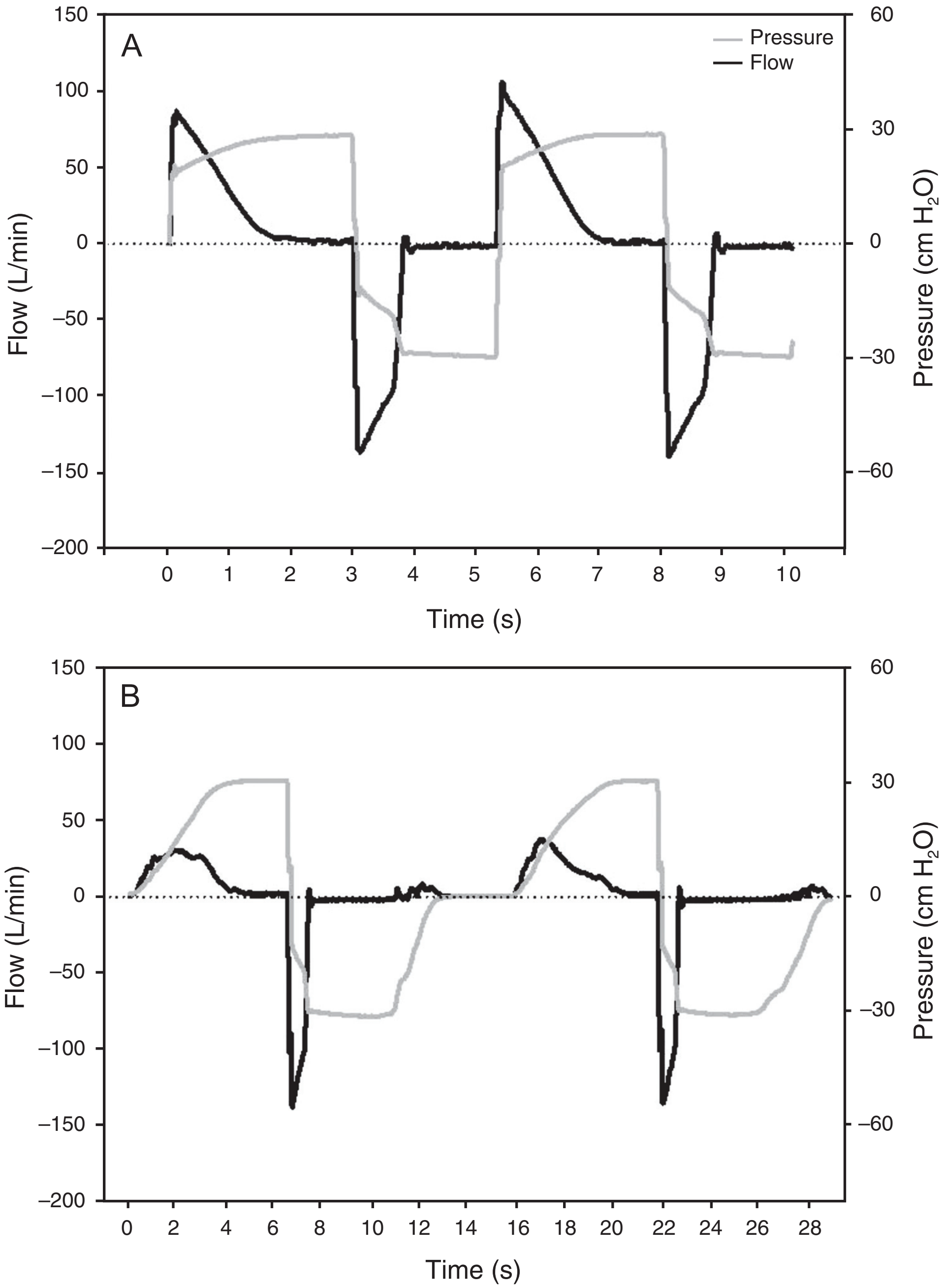

Fig. 6. Pressure and flow curves of two mechanical insufflation-exsufflation cycles performed according to the standard (A) and the optimized maneuvers (B). Note in (B) that the PEF-PIF difference is much higher (ie, ~ 100 L/min), while in (A) the PEF-PIF difference is ~ 45 L/min. From Reference 74.

Summary

Ventilator hyperinflation, the hard/brief ERCC form, PEEP-ZEEP, and MI-E are techniques that have great potential to assist pulmonary secretion clearance in mechanically ventilated patients. These techniques can generate high expiratory flow bias, are easy to apply, and are costless.

A limitation of this review is that the recommendations we made rely on the interpretation of a combination of authors' experiences, preliminary studies, and research. Nevertheless, we have attempted to provide the best available evidence. It is our hope that more reliable evidence on airway clearance techniques will be available in the future.

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