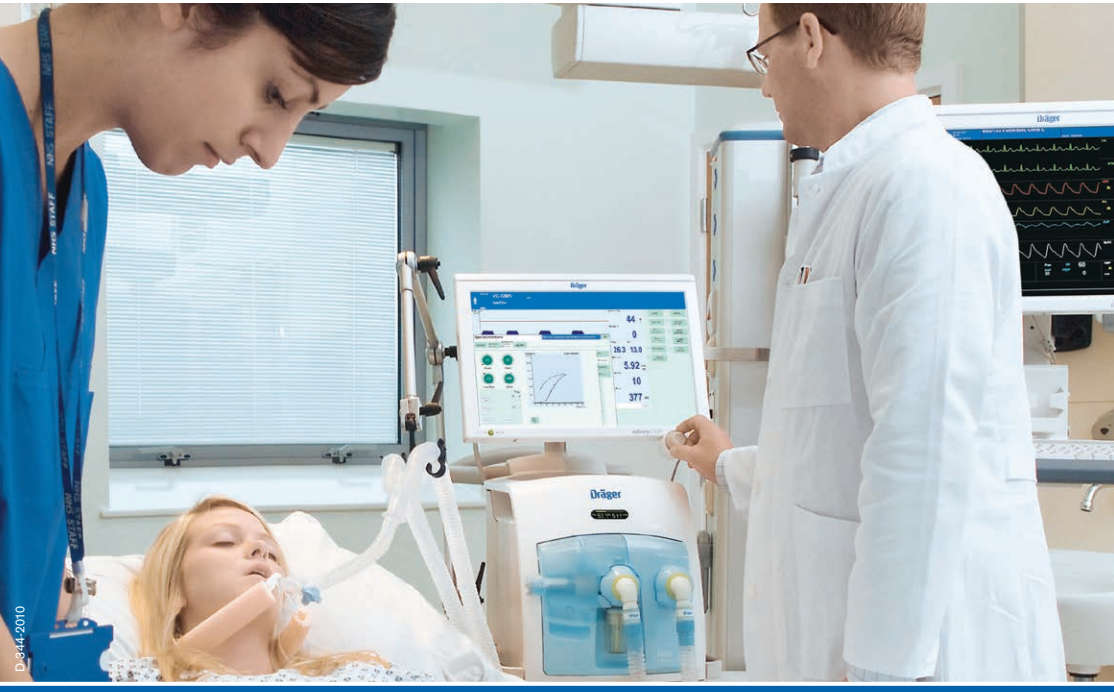

D344-2010

Protective ventilation booklet

Frank Ralfs

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1. Foreword

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Mechanical ventilation is life saving in patients with acute respiratory distress syndrome (ARDS) although it can inadvertently promote or increase previous lung damage when inappropriate intrathoracic pressures or high tidal volumes (VT) are used. In the early stages of ARDS, collapsed units can be stabilized by applying sufficient levels of positive end-expiratory pressure (PEEP). However, although PEEP has been in use for more than 40 years, the appropriate levels of positive pressure at end-expiration are still under debate. Limiting VT and plateau pressure decreases mortality in ARDS. The ARDSnet trial on VT demonstrated that, in terms of overall survival, using a VT of 6 ml/kg is better than using a VT of 12 ml/kg at a similar level of PEEP, i.e. similar lung volume at end-expiration. In patients with acute lung injury (ALI)/ARDS, lung deformation above similar resting lung volume and the propensity to injury is much lower during ventilation with lower VT.

Cyclic opening and closing of unstable lung units may cause shear stress at the epithelium of the alveolar walls and further aggravate lung damage. A number of experimental models of ARDS have shown that ventilation with high PEEP attenuates lung injury by reducing the number of atelectatic or edematous alveoli at end-expiration. Furthermore, short-term application of unusually elevated inspiratory (to open up lung units) and expiratory (to maintain the units open) airway pressures have proven beneficial in improving oxygenation and lung mechanics, in restoring near normal lung volume at end-expiration, and in attenuating histologic lesions in several animal models of lung injury. However, after initial enthusiasm, a number of questions about optimal lung recruitment or non-conventional options for mechanical ventilation remain unanswered. Many different methods of performing alveolar recruitment at the bedside have been proposed, but the best rationale of use, frequency, and duration have not been established and no conclusive results on clinical outcomes have been reached.

New modes of mechanical ventilation have been designed in an attempt to improve the quality of patient-ventilator synchrony with fewer clinical interventions and thus decrease human workload. Beyond the classic volume control assisted ventilation, pressure control assisted ventilation, and pressure support ventilation modes, modern ventilators provide a myriad of alternative built-in modes of total, partial, or adaptive breath-by-breath or within-the breath ventilator support, some of which are difficult for clinicians or caregivers to understand because it is so difficult to predict how individual patients are going to react. Moreover, no randomized controlled trial has clearly shown that one conventional ventilation mode leads to better outcomes than another mode, with the exception of pressure support ventilation compared with synchronized intermittent mandatory ventilation to wean patients from mechanical ventilation.

An understanding of the pathophysiology of ALI and the control of breathing driven by the patient's complex brain centers to fulfill the patient's needs is mandatory at the bedside. Regardless of the mode employed, the ventilator must be set up based on the aforementioned principles and continuously monitored. In other words, clinicians should not force patients to be ventilated according to the brain of the individual who operated the ventilator. This is a key principle for professionals caring for patients receiving mechanical ventilation.

In summary, this booklet provides a comprehensive overview of common problems encountered when caring for mechanically ventilated patients with ALI as well as practical solutions and alternatives. I would like to congratulate the author and the company for undertaking this initiative. The clear and concise descriptions they provide in this complex field will help practitioners involved in providing respiratory care and utilizing its associated technology. The booklet should be considered an essential reference manual in pulmonary critical care.

2. Introduction

Breathing contributes to the physiological status quo called homeostasis which is the precondition for every cell of the human body to live and function. Patients who, for various reasons, fail to maintain their gas exchange themselves, need to be treated with artificial positive pressure ventilation.

Negative pressure ventilation was in widespread use with the iron lung during the polio epidemics in the 1950's. Clinical application and also mortality turned out to be much better with positive pressure ventilation which is why it is today without therapeutic alternative for the treatment of patients with respiratory failure. Negative pressure ventilation is rarely used nowadays apart from marginal adjunctive assistance for some patients [1]. Extracorporeal membrane oxygenation (ECMO) provides an additional option to supplement positive pressure ventilation in cases where conventional or high frequency positive pressure ventilation fails to succeed. However, this method is invasive and associated with side effects such as bleeding, infection and additional organ failure [2].

Positive pressure mechanical ventilation has side effects as well. Though life supporting, it may paradoxically contribute to the high mortality still seen in patients with acute respiratory distress syndrome and acute lung injury (ARDS, ALI) [3, 4]. This is particularly the case when treatment regimes are used which do not consider side effects of mechanical ventilation. So the question remains: What is now considered to be state of the art?

The objective of this booklet is to provide an overview of various approaches to more protective mechanical ventilation. It describes tools which may help make their application easier, safer and more efficient. The objective of this booklet is not to advise caregiver to follow or advocate any particular method of protective respiratory care.

3. Adverse effects of mechanical ventilation

During the last several decades, awareness of the potentially adverse effects of mechanical ventilation has grown. Circumventing the natural defense mechanisms of the upper airway in intubated patients and suppression of cough reflexes can lead to ventilator associated pneumonia (VAP) [5]. Because of this, it has a high priority to begin weaning the patient off the ventilator as quickly as possible. It has been shown that non-invasive ventilation can reduce the incidence of VAP [6].

Mechanical ventilation, particularly in patients with ARDS/ALI may also lead to ventilator associated lung injury (VALI), also referred to as ventilator induced lung injury (VILI) [7, 8]. Cyclic collapse and reopening of alveoli may damage the lung tissue and is consequently referred to as “atelectrauma” [9]. This may damage structures, particularly in restrictive lung diseases where the lung tends to collapse without adequate positive end-expiratory pressure (PEEP) and may reopen during tidal ventilation [10].

Mechanical ventilation using high volumes (“volutrauma”) may likewise damage the lung by overdistending lung tissue [9]. Unfortunately, due to their mechanical properties, healthier alveoli with a greater compliance are particularly prone to this type of injury.

Ventilation with high intra-pulmonary pressures in itself, formerly referred to as “barotrauma” seems not to damage the lung, unless a pressure is exerted “across” the lung, thus, a high trans-pulmonary pressure prevails [11].

In a concept borrowed from mechanical engineering, the terms strain and stress have been established in lung physiology to describe the impact of mechanical ventilation on pulmonary structures. The term “stress” describes the condition of a trans-pulmonary pressure exerted “across” the lung. The term “strain” describes the condition of a tidal volume delivered

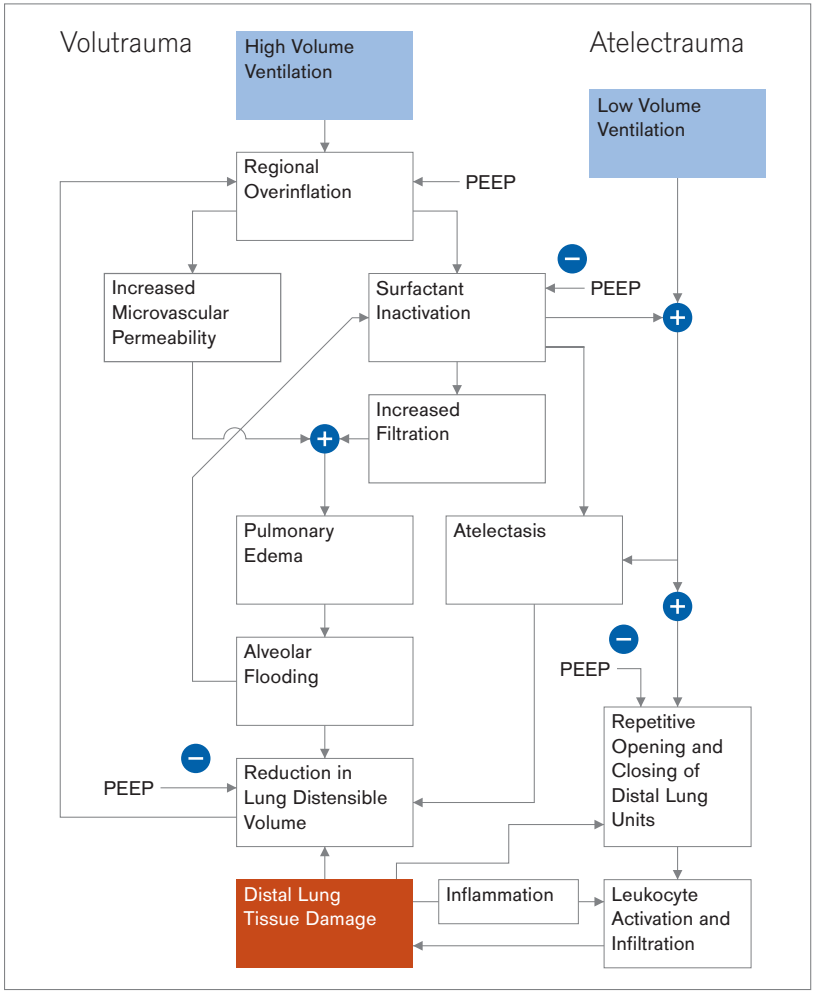

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Figure 1: Contributors to mechanical ventilation-induced lung injury. PEEP (Positive endexspiratory pressure) generally opposes injury or edema formation (minus sign) except when it contributes to overinflation (plus sign) [7].

to a lung in relation to the end-expiratory lung volume [13]. Taking into account the “baby-lung concept” (in ARDS, the lung is “small” rather than “stiff”) [16], looking at the “strain” provides a different way to judge the amount of tidal volume delivered to a lung: rather than relating it to predicted body weight, which may underestimate the injurious effect of even small tidal volumes in patients with large non-areated lung compartments [15].

Both non-physiological strain and stress may initiate a “biotrauma” in which biophysical and biochemical injuries lead to increased alveolar-capillary permeability, surfactant inactivation and the release of inflammatory mediators [12, 13].

The transmission of pulmonary infection, bacterial translocation and release of mediators into the systemic circulation with subsequent systemic inflammation may be one cause of multi organ system failure and high mortality rates encountered in patients with ARDS and high mortality rates [4, 14].

4. The concept of protective ventilation

Taking into account the aforementioned concept to explain adverse effects of mechanical ventilation, optimizing ventilator settings to avoid cyclic atelectasis and overdistension of alveoli should translate into improved outcomes in patients with acute lung injury [9].

This translates into a challenge of balancing different objectives; oxygenation and ventilation (CO_2 elimination) targets, the influence on the circulation and the search for the "safest" window for gas exchange with different choices of pressures, volumes - and timing.

High PEEP may help to avoid atelectasis and, if set appropriately, reduce pulmonary resistance [68]. This, however, also shifts the tidal ventilation towards higher end-inspiratory lung volumes. Small tidal volumes may avoid the development of "volutrauma" but may lead to an increased dead space fraction and hypercapnia. High plateau pressures resulting from high end-expiratory pressures and the tidal volumes necessary to control hypercapnia may cause barotrauma, overdistention and can impair cardiac function and circulation.

Many respiratory disorders result in very inhomogeneous pulmonary conditions. As maintaining stable blood gases is the predominant goal, even the most protective ventilation settings may not be able to avoid inducing VILI in some regions of such a lung [15]. The acceptance of elevated CO_2 levels in favor of a "safer" zone for ventilation ("permissive hypercapnia") [17, 18] has been discussed however, the question remains: What is the best overall strategy to apply mechanical ventilation in patients with severe ARDS?

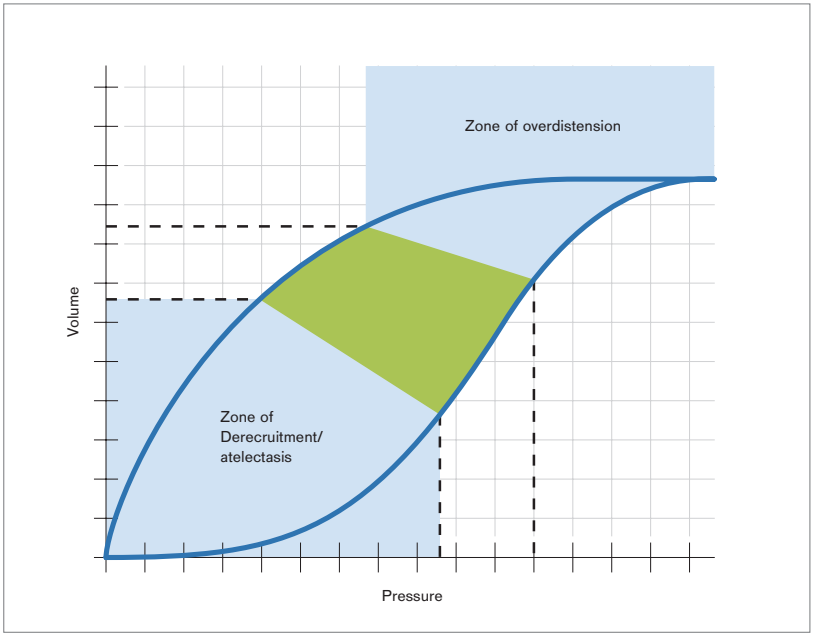

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Figure 2: Theoretical “safe zone” in a static pressure volume loop between tidal derecruitment/recruitment and overdistension.

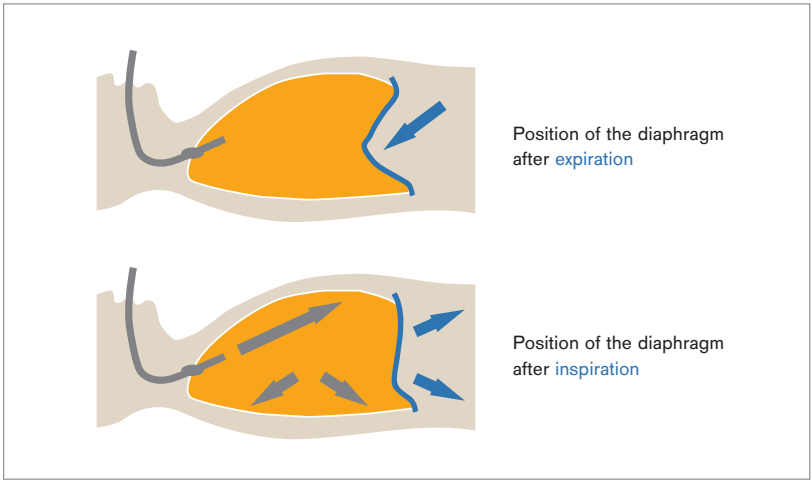

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Figure 3: Diaphragmatic activity during spontaneous breathing favors redistribution of gas to dependent, well perfused areas.

1. SPONTANEOUS BREATHING

Patients breathing spontaneously during mechanical ventilation have an improved pulmonary compliance and can thus maintain their end-expiratory lung volumes more easily. Atelectrauma secondary to cyclic collapse and tidal recruitment seems to be reduced [21]. Spontaneous breathing and a reduction in sedation levels lead to a shorter duration of respiratory support and ICU stay [22].

Patients in a supine position, actively using their diaphragm demonstrate improved ventilation of their dorsal lung regions. Ventilation is increasingly directed to the well perfused, dependend lung regions, improving V/Q matching. It has long been recommended to allow spontaneous breathing not only during weaning but particularly in the phase of acute respiratory failure in order to avoid or alleviate ventilator induced lung injury by aforementioned mechanisms [22].

2. VARIABLE VENTILATION

Healthy biological systems show a physiological variability which lends to them a greater flexibility and more robust function as compared to biological systems under conditions of disease. The latter tend to lose their variability and exhibit a greater monotony in physiologic variables. A reduced heart rate variability is considered a marker for myocardial infarction and congestive heart failure [23].

A non-variable breathing pattern may be observed in patients who failed to wean from mechanical ventilation [24]. Accordingly, it has been proposed to reintroduce variability to mechanical ventilation to provide a more physiological respiratory pattern and to improve outcome. Variable ventilation in controlled ventilation has been associated with improved oxygenation, a reduction of mean peak airway and airway pressures as well as improved pulmonary function in animal models [25, 26, 27, 28]. Similar results were found in experimental studies on variable pressure support ventilation [29, 30]. Interestingly, the externally induced tidal volume variability of 100 % of the adjusted delta pressure support which yielded the best results in this study in terms of oxygenation and intrapulmonary shunt was similar to the variability that can be found in healthy subjects [31].

Mechanisms explaining the observed improvement in respiratory function include lung recruitment, surfactant release and improved V/Q matching as a consequence of the redistribution of pulmonary blood flow [29, 30].
A positive influence on respiratory sinus arrhythmia (RSA), associated with lower shunt fraction and lower dead space ventilation has also been found [33]. In a lung model study, Suki et al. referred to as stochastic resonance of biological systems which, if stimulated, led to improved responses of such a system [32].

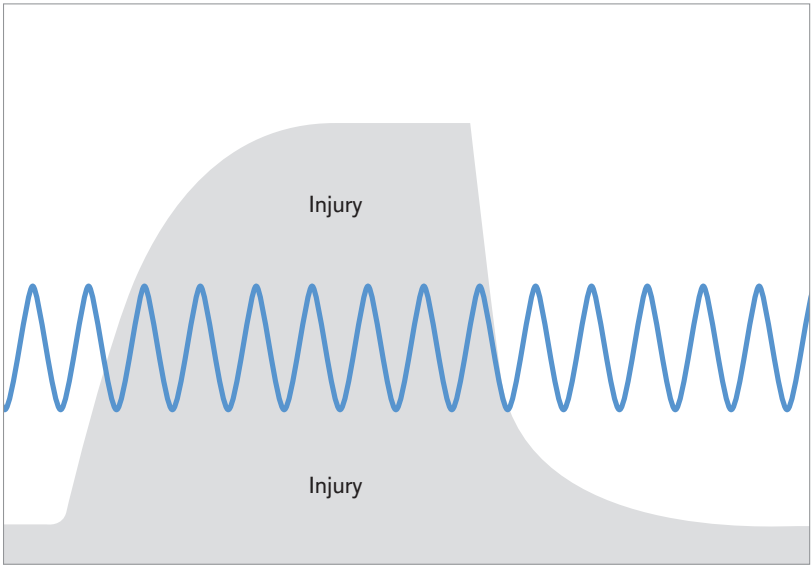

Figure 4: Protective ventilation with high frequency oscillation: very low tidal volume ventilation with high continous distending pressures maintains lung volume while efficiently removing CO_2.

3. APRV / HFO

The hypothesis of the protective nature of both high frequency ventilation and airway pressure release ventilation draws on the assumption that both achieve the gas exchange in the “safe zone” of the pressure volume curve. A relatively high mean airway pressure (referred to as continuous distending pressure in HFO (High Frequency Oscillation) or P_{high} in APRV (Airway Pressure Release Ventilation), which is required to maintain a “healthy” end-expiratory lung volume and to assure proper oxygenation in restrictive lung diseases, is used in both approaches. At the same time, there is little movement “upwards” and “downwards” on the pressure volume curve.

During HFO, the patient usually requires sedation and CO_2 removal is mediated by different mechanisms, frequently using tidal volumes which are

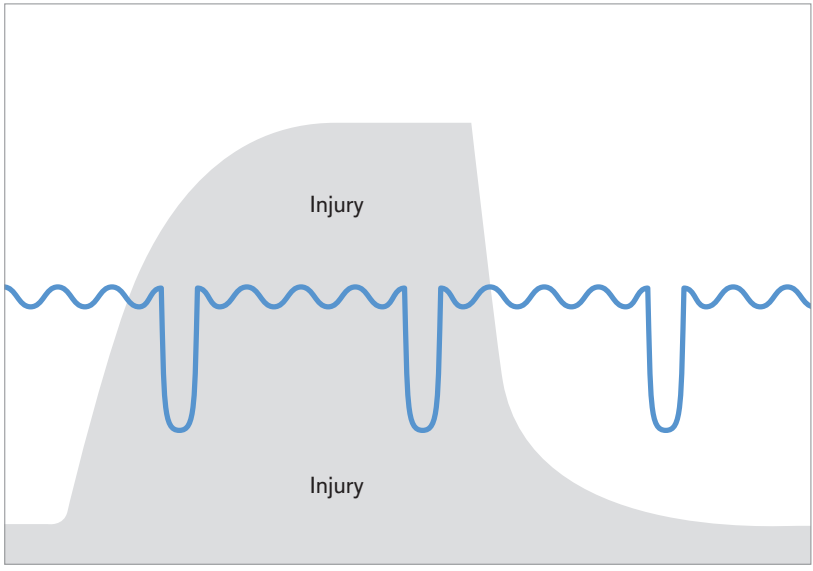

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Figure 5: Balancing adequate end-expiratory lung volume and hyperinflation with APRV.
A high continuous airway pressure maintains lung volume, intermittent releases contribute to CO_2 elimination.

smaller than the dead space. Gas exchange mechanisms include convection (bulk flow), asymmetrical velocity profiles, Taylor dispersion, molecular diffusion, pendelluft or cardiogenic mixing [34]. The majority of studies on HFO were carried out in neonatal patients with an overall small reduction in chronic lung disease (CLD) but a small increase of intracranial hemorrage (ICH) and periventricular leukomalacia (PVC) [40]. More recent experimental studies comparing high frequency oscillation with conventional protective ventilation indicate promising physiological and inflammatory results [35].

During APRV, the patient does not necessarily need to be sedated and should be breathing spontaneously on the P_{high} level, which accounts for a portion of the CO_2 removal. Brief pressure releases facilitate gas exchange and

eliminate CO_2 but they must be kept short in order to maintain appropriate end-expiratory lung volumes and avoid de-recruitment. In hypercapnic respiratory disorders, there should be more or longer releases, whereas hypoxic or restrictive disorders require fewer and shorter releases [36]. APRV seems to be associated with improved V/Q matching, less sedation and reduced peak airway pressures, as spontaneous breathing is encouraged and ventilation is turned "upside down" [37, 38].

Both HFO and APRV promote alveolar recruitment due to the continuously elevated pressure exerted during an extended period of time. As alveolar recruitment not only depends on the pressure or volume applied but also on the duration [36]: This temporal aspect plays an important role in recruitment with APRV and HFO. In addition to this, it might "be easier to stay in the safe zone of lung expansion" [39].

4. RECRUITMENT MANEUVERS

Different types of recruitment maneuvers and their application have been discussed controversially during the past decade.

Recruitment maneuvers have been shown to improve oxygenation and pulmonary mechanics [41]. Proponents of recruitment maneuvers point out that the tidal cycle is shifted towards the deflation portion of the pressure volume loop, where supposedly less cyclic de-recruitment and recruitment ("atelectrauma") takes place during the respiratory cycle [42]. This assumes that the PEEP is set above the "closing pressure" of the lung, or at least for a majority of the alveoli, the point at which the lung begins to collapse during exhalation [43]. The part of the delta pressure that can be spent as elastic pressure can be used exclusively for tidal ventilation in stable alveoli – not for tidal recruitment.

On the other hand, there is evidence that recruitment maneuvers may overinflate parts of the lung, particularly in inhomogeneous pulmonary diseases [44, 68]. Recruitment maneuvers temporarily reduce arterial

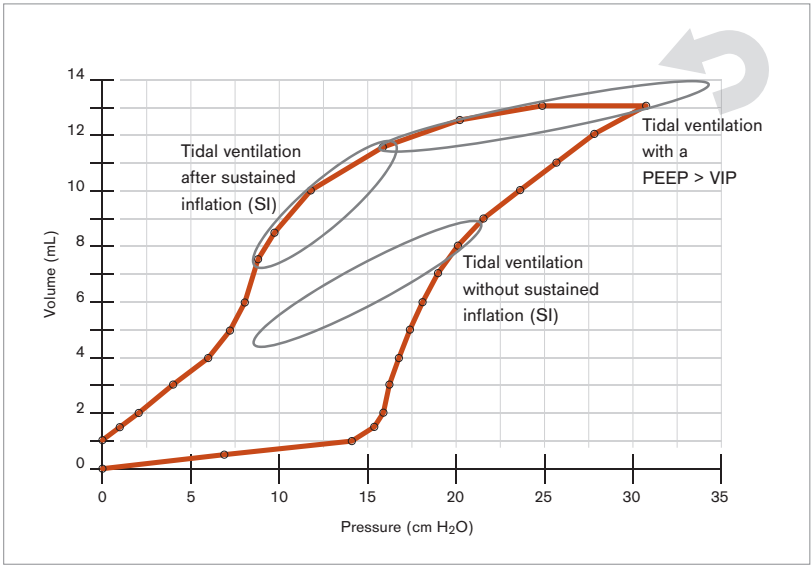

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Figure 6: Recruitment maneuvers (sustained inflations) allowed ventilation with an increased end-expiratory lung volume with moderate PEEP levels in an experimental lung model of ALI [42].

pressure and cardiac output, with the extent and duration depending on the fluid status of the patient and the maneuver used [45, 46]. Recruitment maneuvers seem to be less effective if the applied ventilation settings have previously been optimized [47]. Opponents of recruitment maneuvers underscore the risk of induced over-inflation and hemodynamic impairment [48, 69].

Both the timing and the type of underlying disease seem to influence the efficacy of recruitment maneuvers. Early on in the course of disease, it appears more likely that atelectasis is reversible and that the lung can be reopened without any negative side effects [49]. The hypothesis that recruitment maneuvers are more successful in ARDS of extrapulmonary

origin (e.g. increased chest wall elastance or increased abdominal pressure) than of intrapulmonary origin [50, 51] has been recently questioned [52].

In the ALVEOLI trial conducted by the National Heart Lung and Blood Institute's ARDS Clinical Trials Network, the first 80 patients randomized to the higher PEEP arm of the study were subjected to recruitment maneuvers and compared to patients who did not receive recruitment maneuvers. The results show only a short-lived improvement in oxygenation and compliance [53]. A possible conclusion is that ventilation had been optimized prior to the maneuver, or that the PEEP setting was not optimized after the maneuver, which is recommended to maintain the effect.

Different types of recruitment maneuvers have been studied clinically, with inspiratory pressures between 30 and 60 cm H_2O [54]: sustained inflations for up to 40 seconds, intermittent sighs with larger pressures or volumes and periodic increases in end-expiratory pressure, inspiratory pressure or both maneuvers in multiple patterns [55].

Bugedo et al. found improved oxygenation and lung compliance with limited over-inflation using a stepwise increase of PEEP and inspiratory pressure [56]. This study encompassing ten patients employed dynamic CT monitoring to assess alveolar recruitment and potential hyperinflation.

Amato et al. used sustained inflations with pressures of 35 to 40 cm H_2O for 30 to 40 seconds which may have contributed to the improved survival at 28 days, better weaning and reduced clinical barotrauma when compared to the control group [60].

Grasso et al. investigated 22 patients with ARDS using recruitment maneuvers with an inspiratory pressure of 40 cmH_2O for 40 seconds and found an improved oxygenation primarily in patients with early ARDS and without reduced chest wall compliance [57].

Odenstedt et al. compared three different types of recruitment maneuvers with regard to circulatory and lung mechanics side effects in an animal study using continuous monitoring with electrical impedance tomography (EIT). The slow, low-pressure recruitment maneuver (PEEP at 15, VT of 10ml/kg and occasional prolonged inspirations) reduced pulmonary shunting and resulted in improved oxygenation and compliance when compared to sustained inflation with a pressure of 40 cm H_2O for 30 seconds and a pressure controlled recruitment maneuver comprising a PEEP of 20 and an inspiratory pressure of 40 cm H_2O for 30 seconds. Also, circulatory depression was less pronounced using this more subtle recruitment method [58].

Patroniti et al. studied pressure support ventilation with intermittent sighs once per minute. The sighs consisted of pressure controlled inspirations at either 35 cm H_2O or the PS level + 20% (whichever was higher) applied for 3-5 seconds. Results pointed towards improved oxygenation and respiratory mechanics [59].

5. Optimization of tidal volume and PEEP

1. GENERAL APPROACHES

Lower tidal volume

In an attempt to evaluate outcome improvements due to small tidal volume ventilation as opposed to larger tidal volumes, several studies were conducted in the late 1990's. Two of those studies showed a significant improvement in mortality; Amato et al. compared tidal volumes of 6 ml/kg predicted body-weight and a PEEP set according to the lower inflection point on a static PV curve in the protective ventilation group with 12 ml/kg predicted bodyweight and a low PEEP strategy in the control group in 53 patients [60]. In a study of 861 patients, the ARDS Clinical Trials Network also found significantly

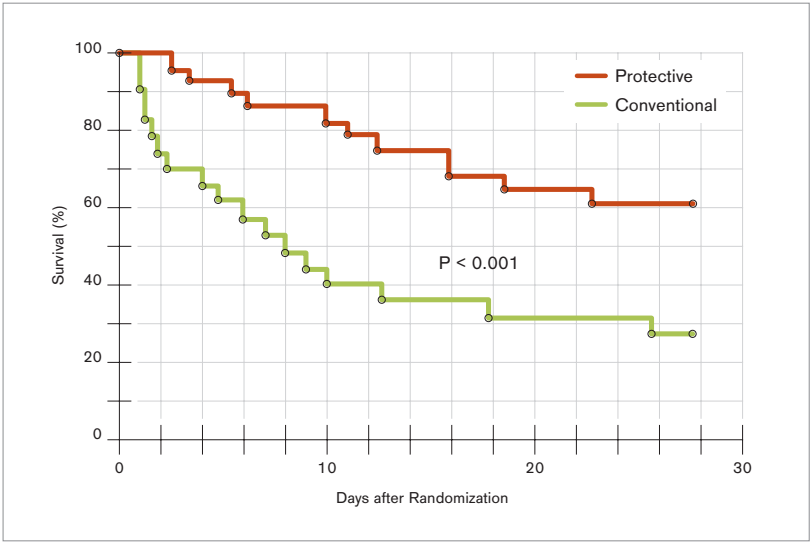

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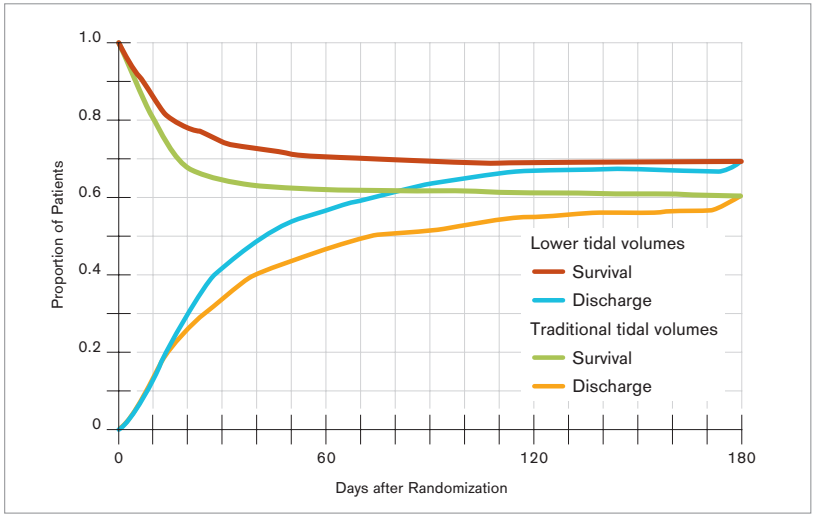
Figure 7: Protective versus conventional ventilation: 28-day survival among 53 patients with ARDS assigned to protective or conventional mechanical ventilation [60].



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[61]

Figure 8: Low tidal volumes versus traditional tidal volumes: Probability of survival and of being discharged home and breathing without assistance during the first 180 days. Patients treated with lower tidal volumes showed a better survival and a better chance of being discharged and without assistance during the first 180 days [61].

improved mortality (31.0 percent vs. 39.8 percent) in patients ventilated with a tidal volume of 6 ml/kg predicted body weight versus a tidal volume of 12 ml/kg [61]. PEEP levels were equal in both study arms. The three other controlled studies compared weight-based tidal volumes of smaller differences in protective ventilation and used smaller plateau pressures in the control group. They were not able to show the same results [62] [63] [64].

Higher PEEP

In the ALVEOLI trial, the ARDS Clinical Trials Network encompassing 549 patients, a tidal volume of 6 ml/kg predicted body weight was applied using either a higher or lower positive end-expiratory pressure (PEEP). The PEEP setting was guided by two different FiO_2/PEEP tables which determined the combination of both parameters to be used in order to achieve a target

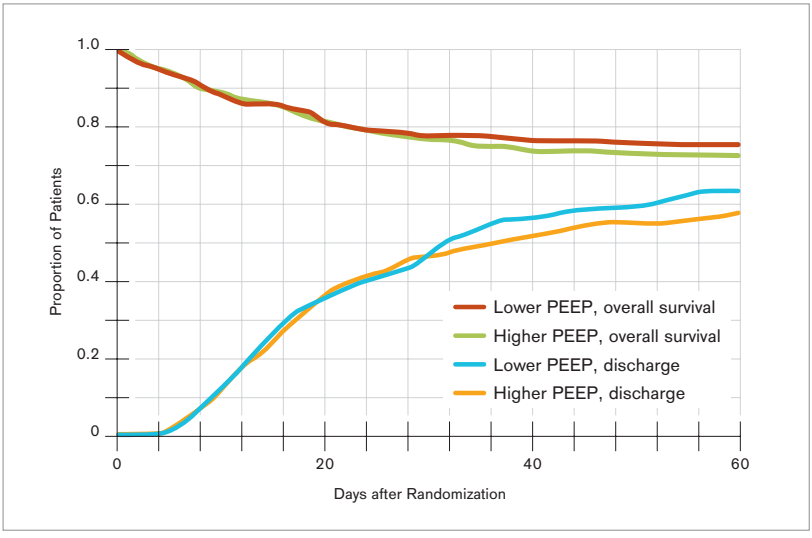

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Figure 9: High PEEP versus low PEEP: probabilities of survival and of discharge home while breathing without assistance. There was no significant difference between the high PEEP and the low PEEP group [65].

oxygenation level. Although oxygenation was improved in the high PEEP group, there were no significant differences found in clinical outcomes such as in-hospital mortality or duration of mechanical ventilation [65].
More recently, two further studies investigated the effects of higher versus lower PEEP levels. The “Open Lung Ventilation Study” investigators compared a low tidal volume strategy with conventional PEEP levels in the control group with a low tidal volume strategy with higher PEEP levels, recruitment maneuvers and a plateau pressure limit at 40 cm H_2O in the open lung group. Apart from an improvement in oxygenation, there was a trend towards lower mortality in the high PEEP group, but no statistically significant difference [66].

The “EXPRESS Study” group compared a low tidal volume strategy (close to 6 ml/predicted body weight) with moderate PEEP levels in the control group

(initial average of 8.4 cm H_2O) with low tidal volume strategy with a level of PEEP set to achieve a plateau pressure of 28 to 30 cm H_2O (initial average of 15,8 cm H_2O). Some patients subjected to higher PEEP exhibited significantly increased fluid requirements, probably secondary to a poor tolerance of the high PEEP levels. As in the open lung study, there were indicators for improved mortality, but no significant differences [67].

2. PATIENT TAILORED APPROACHES

Breath-by-breath approaches

Shifting PEEP and inspiratory pressure levels upwards and downwards breath by breath can be used to assess the respiratory mechanics of a patient and tailor ventilation settings accordingly. If the delta pressure in PEEP and inspiratory pressure is kept constant while doing this, the dynamic compliance provides an indication of the "steepness" of the PV curve at these pressure levels. Trended in time, the combination of PEEP and inspiratory pressure can retrospectively be optimized to best fit the mechanical properties of the lung [70]. When analyzing various monitored parameters measured during such an incremental or decremental PEEP trial, dynamic compliance and elastance correlated well with evidence gained from CT scans [71]. The ability to continuously measured arterial oxygenation is currently not commercially available and therefore remains limited to experimental settings [72].

As PEEP maintains end-expiratory lung volume, it has been recommended to begin from a level of high PEEP and inspiratory pressures at which adequate alveolar recruitment can be assumed and slowly decrease both PEEP and inspiratory pressure step by step. At the point where both tidal volumes begin to drop, de-recruitment probably starts to take place and oxygenation starts to fall. The required PEEP setting from the "pulmonary perspective" is likely to be within or above this range [73, 74]. However, as PEEP influences circulation, hemodynamic considerations must be taken into account [75].

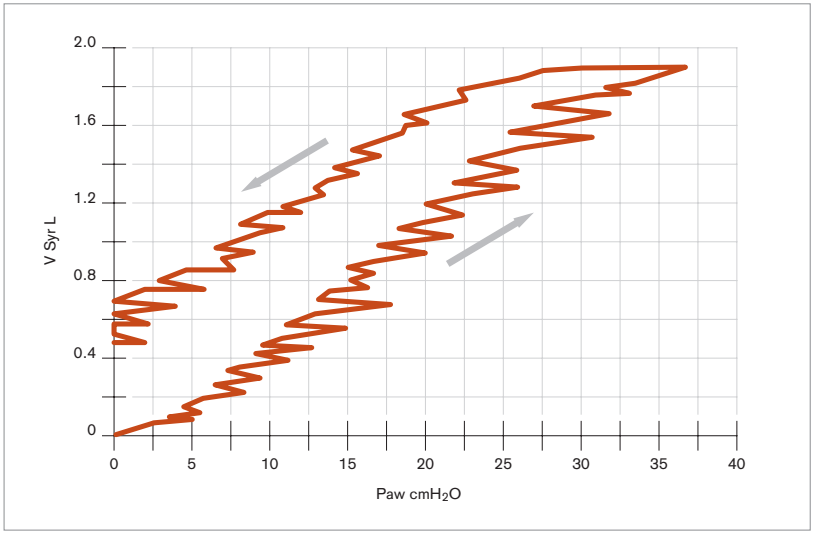

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Figure 10: PV loop constructed with the super syringe method [106].

The advantage of a breath-by-breath method lies in the fact it can be easily performed with standard equipment [76] and that tidal ventilation continues even while the maneuver is performed. Recent data [71] supports the idea that the PEEP at the best respiratory compliance provides the best compromise between recruitment and hyperinflation, as was demonstrated by Peter Suter et al. earlier [77].

Intra-tidal approaches

The golden standard of respiratory mechanics is the super syringe method, where the lung is filled and emptied in a stepwise manner, allowing equilibration in between the small tidal volume steps [78]. The resulting measurement points which are combined to form a static pressure volume loop exclusively representing the elastic properties of the lung.

As airflow ceases in between the individual “tidal steps”, there is no resistive pressure involved and the measured pressures only represent the elastic recoil of the respiratory system during inspiration and expiration. Characteristic points on this pressure volume loop can be used to individually optimize ventilation settings such as PEEP and tidal volume [79].

Bedside application of the super syringe method is clinically cumbersome as it requires detachment of the patient from the ventilator, potentially leading to a loss of end-expiratory lung volume [76]. Furthermore, the super syringe method results in a significant period of “apnea”.

A similar maneuver using slow and constant flow during inspiration and expiration has also been suggested [80]. Here, although flow does not cease completely, it can be neglected if it is small enough. A constant flow below 10 l/min has been found to yield identical results when compared to the super syringe method, this is because the pressure drop associated with such a flow is very small compared to the elastic pressure of the respiratory system [81, 82, 83].

Constant flow is preferable, as this merely shifts the elastic pressure volume loop slightly to the right, toward higher pressures [84], but does not change the shape of the PV loop. If flow is not constant, a resistive pressure, changing over time during inflation and deflation, could alter the shape of the pressure volume loop and complicate both the determination and the interpretation of points on the loop. Both variability and extent of flow contribute to an undesired influence of the resistive pressure on the PV loop [85].

Earlier research was priliminary focused on the lower and upper inflection points on the inflation limb of a low-flow PV curve. As these points embrace the steepest part of the pressure volume loop with the highest compliance (at least in ideal PV loops), it was traditionally recommended to ventilate the patient between the lower and upper inflection points (UIP) in order to achieve the highest tidal volume with the smallest pressure gradient [86]. If ventilation occurred below the lower inflection point (LIP), it was assumed that the lung would collapse [87]. Ventilation above the upper inflection point was assumed to cause the overdistention of the lung.

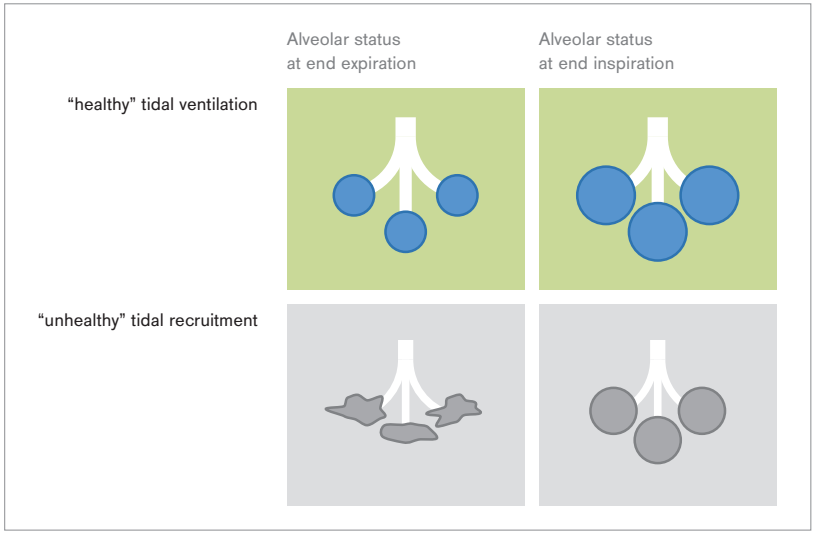
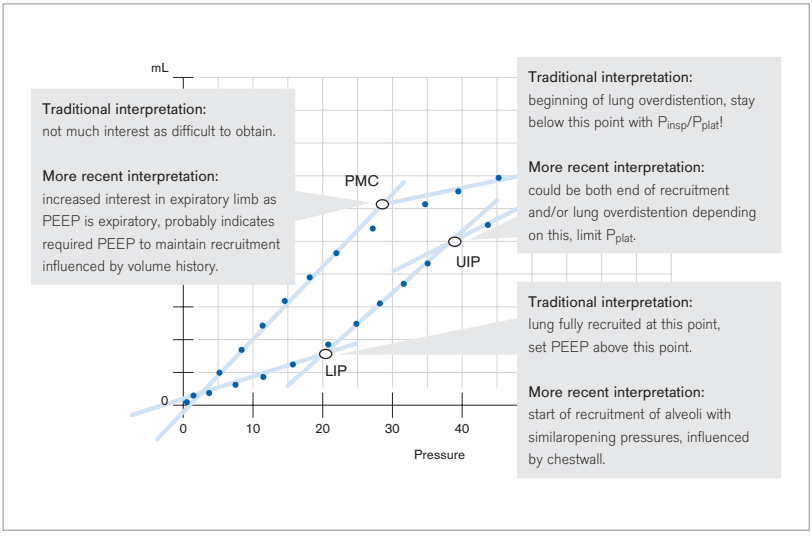


Figure 11: Repeated tidal recruitment and de-recruitment may lead to VILI (lower pictures). If alveoli are stabilized by sufficient PEEP at end-expiration, tidal ventilation is less likely to induce any negative side effects (upper pictures).

A steep portion in the inspiratory pressure volume loop may, however, indicate both “healthy” tidal ventilation as well as “unhealthy” intra-tidal recruitment. More recent theoretical and clinical studies have found evidence of alveolar recruitment above the upper inflection point [88, 89]. It was shown that it was possible to shift the upper inflection point farther upwards, suggesting that the UIP does not necessarily signify the beginning of hyperinflation but may instead hold recruitment potential [88].

Both phenomena may occur at the same time in different lung regions, partly masking each other, making therapeutic conclusions difficult. Nonetheless, both experimental and clinical studies demonstrated good results with PEEP settings of LIP + 2 cm H_2O [60, 90].

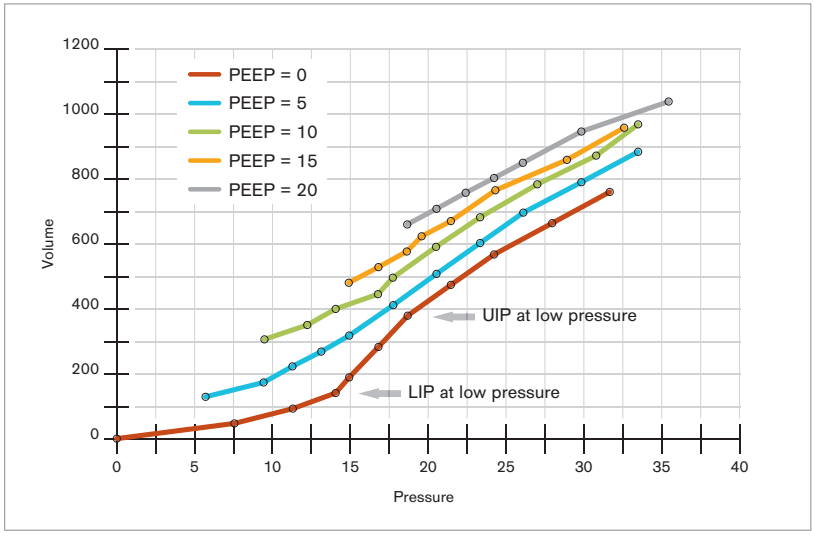


[95]

Figure 12: Characteristic points on a PV loop and their interpretation [95].

More recently, interest has shifted towards the point of maximum curvature (PMC) on the expiratory limb of the pressure volume loop. As PEEP is used to prevent loss of end-expiratory volume during exhalation, it may make sense to identify a loss of volume while slowly deflating the lung. While in some patients, the PMC corresponded well with the LIP, many times it does not [91]; this may suggest that observing deflation rather than inflation could be beneficial [92, 93, 94].

It has been theoretically and experimentally shown that the shape of the PV curve in general, is influenced by the ventilation regime applied prior to its measurement [95, 97]. In other words, the “volume history” determines the shape of the PV loop. Ventilation with lower PEEP levels prior to measuring a PV loop more frequently reveals a lower inflection point [96]. This may be explained by additional alveolar recruitment during regular ventilation.



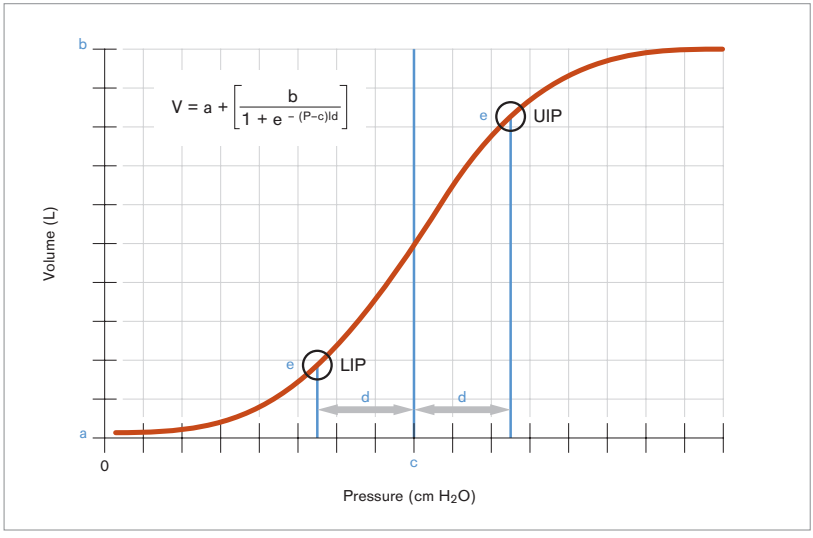
[89]

Figure 13: PV loops started from lower PEEP levels at baseline are more likely to exhibit inflection points [89].

When comparing static PV loops measured at different points in time the individual settings preceding these measurements need therefore to be taken into account.

Another important question with regard to both clinical studies and practice is to determine just how reliably and reproducibly clinicians are able to detect characteristic points on a pressure volume loop [98]. To avoid interpretation error in the determination of ideal settings derived from a static pressure volume curve a variety of sigmoidal equations have been suggested [99, 100, 101, 102, 103] for automatic detection of LIP, UIP and PMC.

During a low flow or recruitment maneuvers an elevated pressure is exerted on the lung and the chest for a prolonged period. This can have



[99]

Figure 14: Sigmoidal equation to objectively quantify pressure volume loops [99].

transient hemodynamic implications such as reduced cardiac output, arterial pressure or shunting of pulmonary blood flow to less aerated regions [48, 104, 105]. Patients subjected to such maneuvers must be able to tolerate the applied pressures and volumes over the time of the maneuver and should be vigilantly monitored [75].

6. Conclusions about protective ventilation

To date, the use of lower tidal volumes and limited plateau pressures in the management of patients with ALI and ARDS is the only approach to protective ventilation that has proven to reduce mortality. Many trials of other approaches showed trends towards improvements of certain variables, but, so far, do not allow unambiguous conclusions with regard to the question how to ideally adjust mechanical ventilation. There could be different reasons for this: There might be too few studies with too few patients enrolled in randomized controlled trials that have the ability to show significant improvements clearly attributable to the treatment strategy under investigation. Type and course of disease may differ among patients to such an extent that general recommendations could be to far from the optimum for individual patients. Even a low VT strategy was shown to be associated with tidal hyperinflation in patients with large non-areated lung compartments [15]. Individual adaptations of ventilator settings, however, depend on the monitoring tools by which they can be guided. Today, there are more and more such tools available in modern ventilators.

7. Tools for lung protective ventilation

APRV AUTORELEASE (EVITA INFINITY V500)

The objective of APRV is to balance oxygenation and ventilation by maintaining an adequate end-expiratory lung volume while eliminating enough CO_2 through spontaneous breathing and intermittent pressure releases.

When the underlying pulmonary condition is restrictive and hypoxic in nature, fewer and shorter releases should be scheduled to avoid de-recruitment and maintain end-expiratory lung volume. When hypercapnia is an issue, more and longer releases will be required to assure sufficient ventilation. Typical settings of APRV are a P_{low} pressure of 0 to encourage a very high initial expiratory flow but a Tlow time of down to 0.1 seconds to limit the actual pressure drop in the lung. The set P_{low} pressure of 0 is therefore never reached. Changes in respiratory mechanics, however, require manual readjustment of T_{low} to achieve the same balance of ventilation and maintenance of end-expiratory lung volume. If compliance or resistance increases, the time constant of the respiratory system also increases, requiring longer T_{low} times. If compliance or resistance drop, the time constant decreases, and shorter T_{low} times are required.

With the AutoRelease function of the Evita Infinity V500, a percentage of the peak expiratory flow can be set at which APRV cycles back to the high pressure level P_{high}. This assures that the T_{low} time will be automatically and continuously optimized to achieve the desired balance between necessary CO_2 removal and maintenance of end-expiratory lung volume for oxygenation.

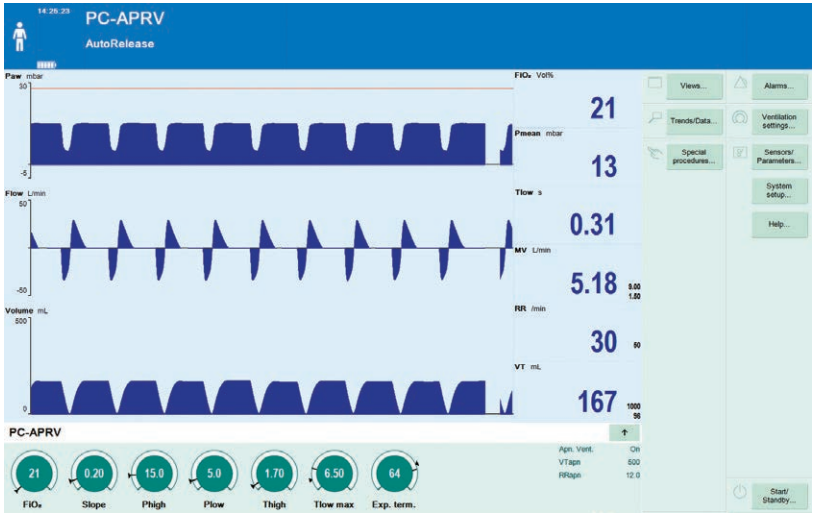


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Figure 15: APRV AutoRelease in Evita Infinity V500.

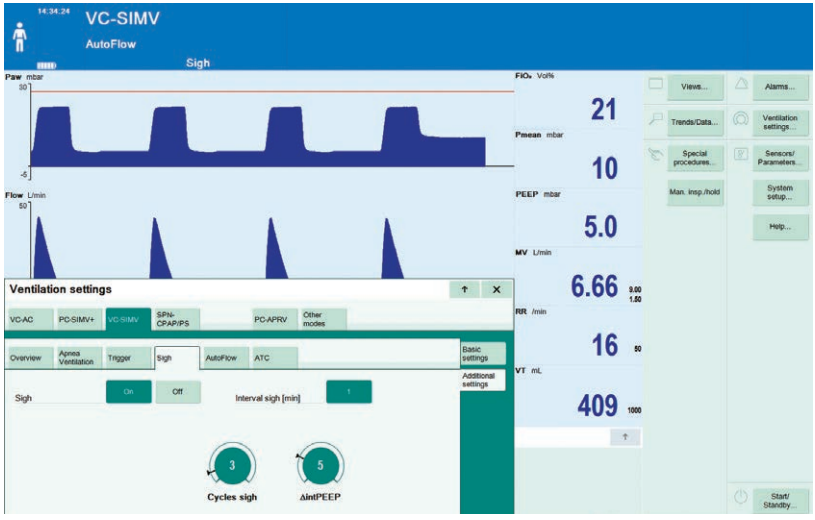

Figure 16: Sigh function in Evita Infinity V500.

SIGH FUNCTION (EVITA INFINITY V500, EVITA XL)

With the introduction of low tidal volume ventilation it was argued that intermittent sighs to counterbalance progressive de-recruitment due to smaller tidal volumes might experience a renaissance.

The sigh function of the Evita Infinity V500 can be used in both volume controlled and pressure controlled ventilation. By programming an increased PEEP for a given number of respiratory cycles at predetermined intervals, ventilation is shifted up the pressure volume curve for a limited time. In pressure controlled ventilation, the inspiratory pressure is increased by the same amount as the PEEP, while the driving pressure remains the same. Also, in volume controlled ventilation, the same target volume at higher PEEP levels leads to higher plateau pressures. The sigh function works accordingly on both the inspiratory and expiratory sides during the preset number of respiratory cycles.

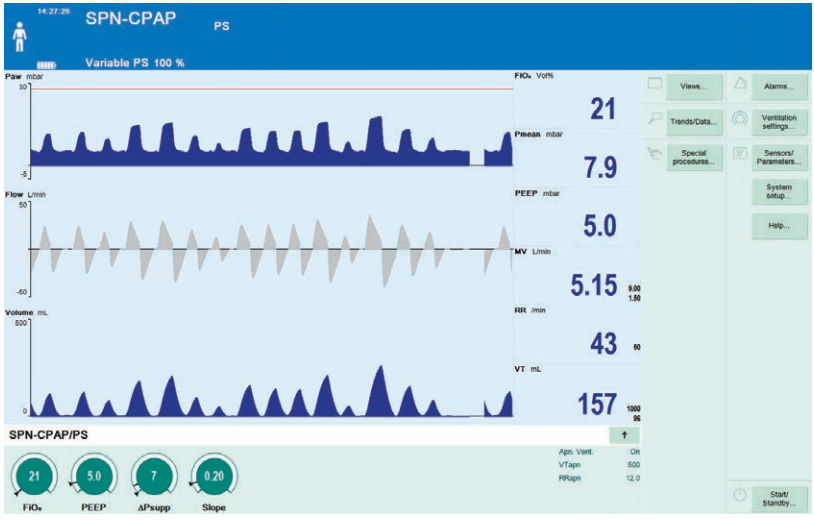

Figure 17: Variable PS in Evita Infinity V500.

VARIABLE PS (EVITA INFINITY V500)

Biologically variable ventilation or "noisy pressure support" seems to improve oxygenation and lung function [32]. According to Suki et al., there is an optimal variability at which biological systems perform best [32]. Abreu et al. investigated various degrees of variability during spontaneous breathing and discovered that the variability which yielded the most positive results was close to the variability found during spontaneous breathing in healthy subjects [31]. In the Evita Infinity V500, the function "variable PS" can be activated as an adjunct to the SPN-CPAP/PS mode. The caregiver can adjust the degree of variability from 0 to 100%. With a delta PS of 10 cm H_2O, a variability of 100% means that the actual delta PS fluctuates from 0 to 20 cm H_2O. The sequence of PS breaths follows a random function according to a Gaussian distribution. If resulting values come within 5 cm H_2O of the airway pressure high alarm limit, another value will be generated and applied.

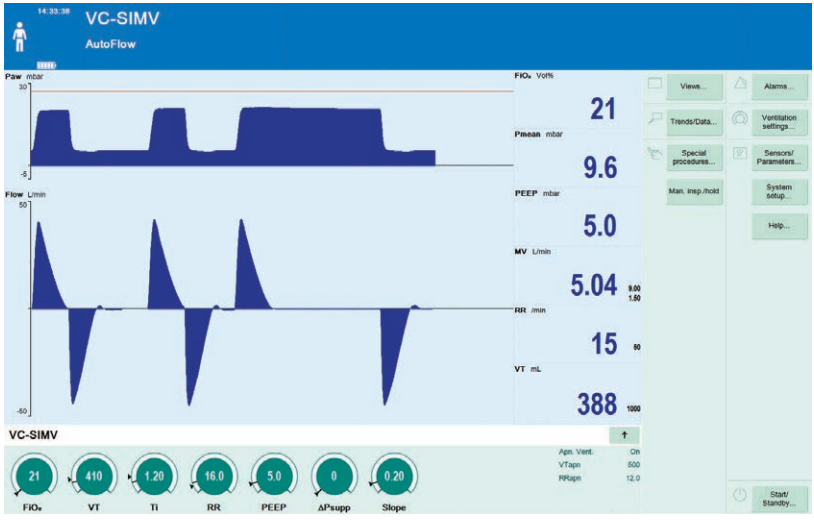

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Figure 18: Inspiration hold in Evita Infinity V500.

The mean pressure support equals the set PS in the SPN-CPAP/PS mode. However, during the averaging period, the mean PS may be slightly higher or lower than the set PS. To allow an assessment of this, the additional measured values $P_{supp\ mean}$ and $VT_{spon\ mean}$ averaged over 10 breaths are provided.

INSPIRATORY HOLD (EVITA XL AND EVITA INFINITY V500)

Sustained inflations can be applied using the manual insp hold button, which can be placed as a configurable button in the main menu area. Touching this button initiates a breath and if it is held down, the inspiration is prolonged until either the button is released or a time of 40 seconds has elapsed. This function therefore enables recruitment maneuvers of a predetermined pressure for up to 40 seconds.

It requires the interaction of the caregiver to hold the button down and will still provide an alarm if the minute ventilation alarm threshold is violated.

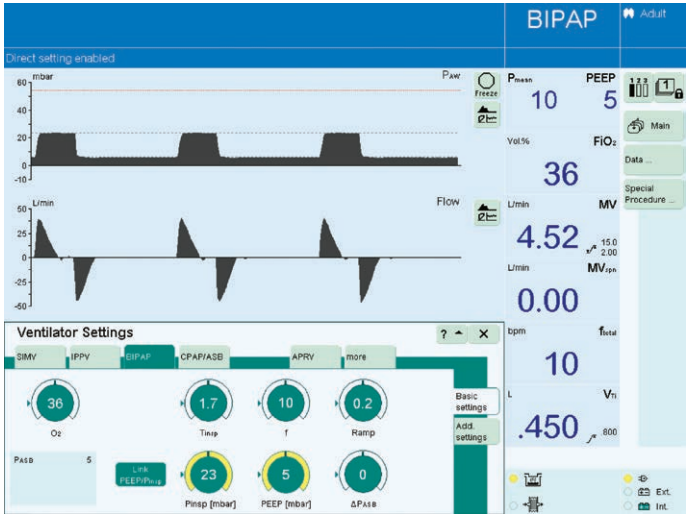

Figure 19: QuickSet and PressureLink function in the Evita XL.

If used for long, sustained inflations, it is recommended to adjust the apnea alarm suitably to avoid activating apnea ventilation while the maneuver is carried out. Sustained inflation maneuvers have been shown to transiently reduce venous return, cardiac output and arterial pressure [48, 58]. Patients must therefore be hemodynamically stable enough to tolerate such maneuvers and be monitored closely.

QUICKSET AND PRESSURELINK (EVITA XL AND EVITA INFINITY V500)

Both incremental and decremental pressure maneuvers can be performed conveniently with the QuickSet and PressureLink function.

If the rotary knob is held down while setting of PEEP or inspiratory pressure, the parameters are put in place in real time. Respective therapy control knobs turn dark green with a yellow rim indicating that the parameter is adjustable although continuously confirmed and active.

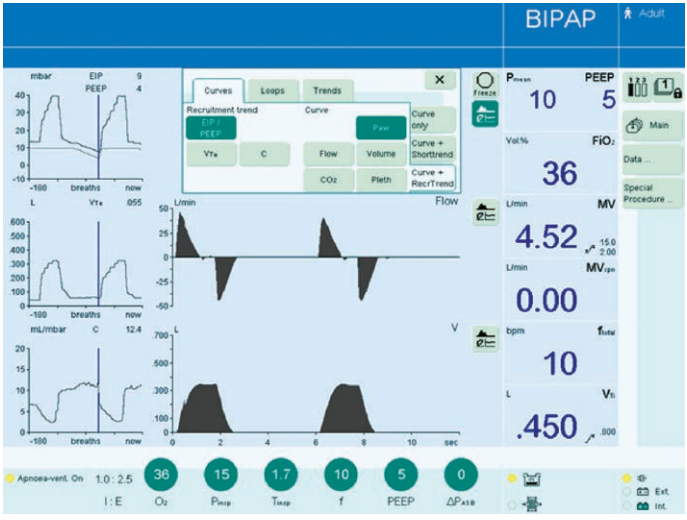

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Figure 20: Recruitment trends in Evita XL.

In this QuickSet mode, it is not necessary to preselect, adjust and then confirm. This helps to quickly shift pressures up and down within the span of a few breaths and directly monitor the influence on the patient.

To assess the effect of recruitment maneuvers or decremental PEEP trials by means of the compliance or elastance of the respiratory system, it can be advantageous to keep the delta pressure between PEEP and inspiratory pressure constant during the procedure. With the PressureLink function, caregivers can first select one therapy control knob and then touch the Link button to simultaneously preselect both PEEP and inspiratory pressure settings. Any adjustment will now affect both parameters, and the delta pressure will remain the same.

QuickSet and PressureLink can also be combined to facilitate convenient breath-by- breath adjustments of PEEP and inspiratory pressure with a

constant delta pressure. First, one therapy control knob is preselected, a second is then added by touching the link button. If the rotary knob is held down for approximately 3 seconds, QuickSet is activated for both parameters and a constant delta pressure can be shifted upwards or downwards to assess respiratory mechanics at different points on the pressure volume curve.

RECRUITMENT TRENDS (EVITA XL)

Breath-by-breath trending of tidal volume, dynamic compliance, PEEP and end-inspiratory pressure provides the caregiver with information about changes in respiratory mechanics at different ventilator settings. Used during a recruitment maneuver or decremental PEEP trial, breath-by-breath changes in compliance or tidal volume may indicate the point of best compliance, the starting point of de-recruitment or overdistention as judged by decreasing compliance. Retrospective analysis of the PEEP and end-inspiratory pressure that were in place at the same time may provide valuable information with regard to the optimization of settings.

LOW FLOW PV LOOP (EVITA XL AND EVITA INFINITY V500)

With the Low Flow PV loop maneuver, a quasi-static PV loop can be recorded during inspiration and expiration. The operator can choose between inspiration-only low-flow inflation and a maneuver which comprises both inflation and deflation. As this maneuver requires appropriate sedation of the patient, it is not possible to initiate it in spontaneous ventilation modes. Leakages should be avoided, since a representative PV loop cannot be recorded in the presence of leaks. Care should be taken to set the type of humidification correctly, as the accuracy of the flow measurement depends on this.

By setting the flow that is delivered during the inflation and also controlled during the deflation at a sufficiently low level, the resistive pressure component can be neglected and virtually only the elastic properties are recorded. The initial pressure of the maneuver can be set between the current PEEP setting and zero. Although some de-recruitment may have to

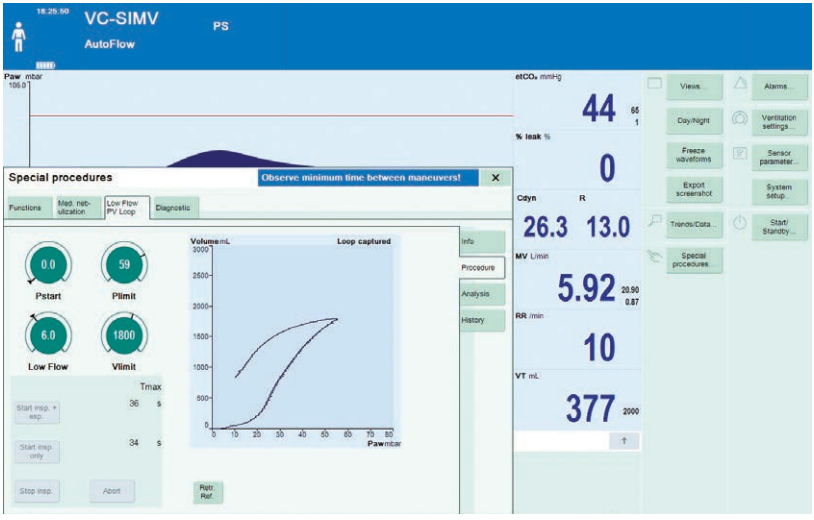

Figure 21: Low flow PV loop maneuver - procedure in the Evita Infinity V500.

be accepted in order to find opening or closing pressures, reducing the PEEP level drastically for such a maneuver in patients with severe lung disease may have detrimental effects [107].

If a pressure between PEEP and zero is selected, the maneuver ends at the set PEEP level, which means that the loop will not be “closed”. Because the low-flow PV loop also acts as a lung recruitment maneuver, in order to maintain the positive effect of such recruitment, it is neccessary to apply at least the PEEP level that prevailed prior to the maneuver. If the caregiver decides on a low-flow deflation down to lower pressures, the PEEP level must be reduced prior to the maneuver.

Limits for both pressure and volume can be set for the maneuver. As soon as either the set pressure of volume limit is reached, the maneuver is either discontinued (inspiration) or cycled into low-flow deflation.

The maximum duration of the maneuver is defined by the adjusted volume limit and the low-flow setting and is displayed on the maneuver start page. If the pressure limit is reached before the volume limit is reached, the maneuver time is shortened accordingly.

There are two possibilities to end a low-flow PV loop: The abort button abruptly ends the maneuver and releases the pressure to the PEEP level, as might be required in face of a severe hemodynamic impairment. The abort button must be preselected and confirmed, as a sudden release of pressure may cause a dramatic increased venous return which can potentially cause cardiac distension. The second possibility is to gently end the low-flow inflation and cycle into low-flow deflation (or a predetermined pressure reduction when performing inspiration-only maneuver) by touching the stop inspiration button. This function does not need to be preselected and is activated as soon as the button is touched. The recorded loop is still considered valid and displayed. If the maneuver is aborted, the loop is discarded.

Following completion of a low-flow PV loop maneuver, it is not possible to start another maneuver for 60 seconds in order to avoid potential adverse hemodynamic consequences which could result. The start buttons are “greyed out” during this time.

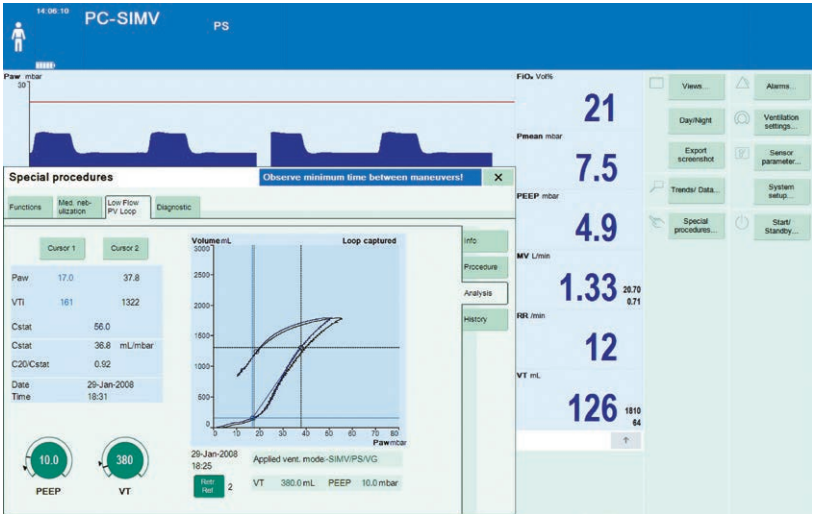

Figure 22: Low flow PV loop maneuver - analysis in the Evita Infinity V500.

Once the maneuver is completed, the loop will be displayed on the analysis page. If inflection points or the point of maximum curvature on the expiratory limb can be identified in the Evita Infinity V500, those points will be indicated with small circles. Cursors will then be placed on these points in order to provide respective measurement of pressures and volumes.

If the PV loop cannot be used to determine these points using the underlying model, none will be displayed in the loop. In such a case, the cursors will be placed at the left and the right end of the loop.

To assist with understanding the volume history of the lung, the ventilation mode, the PEEP setting and the inspiratory pressure or tidal volume setting at the start of the maneuver are recorded and displayed together with the loop. PV loops initiated from higher PEEP levels with high inspiratory pressures look different from PV loops initiated from lower PEEP levels or

smaller inspiratory pressures. This needs to be taken into account when comparing low-flow PV loops which have been recorded at different times.

Up to ten low-flow PV loops can be stored for reference and future assessment. On the analysis page, one low-flow PV loop can be called up as a reference for the most recent PV loop. It is displayed in black as opposed to blue and no inflection point or point of maximum curvature is displayed. Cursors only refere to the current low-flow PV loop and not to the reference. On the history page, each stored low-flow PV loop can be called up, measured with the two cursors. Inflection points or the point of maximum curvature are displayed.

To facilitate graphical optimization of ventilation settings, two therapy control knobs can be found directly on the analysis page. Depending on the ventilation mode in use, PEEP, inspiratory pressure and the tidal volume can be adjusted directly from the analysis page. As soon as these therapy control knobs are preselected or adjusted, a help line is displayed on the PV loop in order to visualize the change in therapy.

Conclusion and outlook

While tools to optimize ventilator settings for individual patients and treatment phases have become more widely available in modern ventilators, there is one limitation they all have in common: They are global in nature and treat the lung as if it was one organ (which it is) with a disease with evenly distributed symptoms (which it is not). Unfortunately, in the most challenging cases in respiratory therapy, the contrary is true. Instead of relating the tidal volume to predicted or ideal body weight, it has been suggested to relate it to the end-expiratory lung volume, as in an ARDS “baby lung”, there might be plenty of non-aerated lung tissue [16]. Whereas the first determines what the patient’s gas exchange requires, the latter may better indicate what can still be considered lung protective. Even this would still be global, as end-expiratory lung volume in many cases is by far not evenly distributed across the lung.

To balance stress and strain, atelectrauma and hyperinflation for individual patients in individual situations, regional information of gas distribution is needed. Continuous assessment of the regional development of end-expiratory lung volume and extent and regional distribution of ventilation would allow caregivers to optimize settings based on what happens in different parts of the lung. With the help of a new respiratory monitoring based on electrical impedance tomography, this could be possible in the near future.

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