

Protective ventilation booklet

Frank Ralfs

Important notes

Medical knowledge is subject to constant change due to research and clinical experience. The authors of this publication have taken utmost care to ensure that all information provided, in particular concerning applications and effects, is current at the time of publication. This does not, however, absolve readers of the obligation to take clinical measures on their own responsibility. Liability claims against the authors or the editor which are based upon material or hypothetical damages caused by the use or non-use of information provided are excluded.

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations.

Drägerwerk AG & Co. KGaA reserves all rights, especially the right of reproduction and distribution. No part of this publication may be reproduced or stored in any form by mechanical, electronic or photographic means without the prior written permission of Drägerwerk AG & Co. KGaA.

Protective ventilation booklet

Frank Ralfs

Editor

Drägerwerk AG & Co. KGaA

Moislinger Allee 53–55

23558 Lübeck, Germany

www.draeger.com

CONTENTS

Foreword	06
Introduction	08
Adverse effects of mechanical ventilation	09
The concept of protective ventilation	12
Optimization of tidal volume and PEEP	22
Conclusions about protective ventilation	33
Tools for lung protective ventilation	34
Conclusion and outlook	46
References	48

D-944-2010



Lluís Blanch MD
 Critical Care Center, Hospital de Sabadell.
 Insitut Universitari Parc Tauli.
 Universitat Autònoma de Barcelona. Spain
 CIBER de Enfermedades Respiratorias.
 Instituto de Salud Carlos III. Spain.
 Email: lblanch@tauli.cat

1. Foreword

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

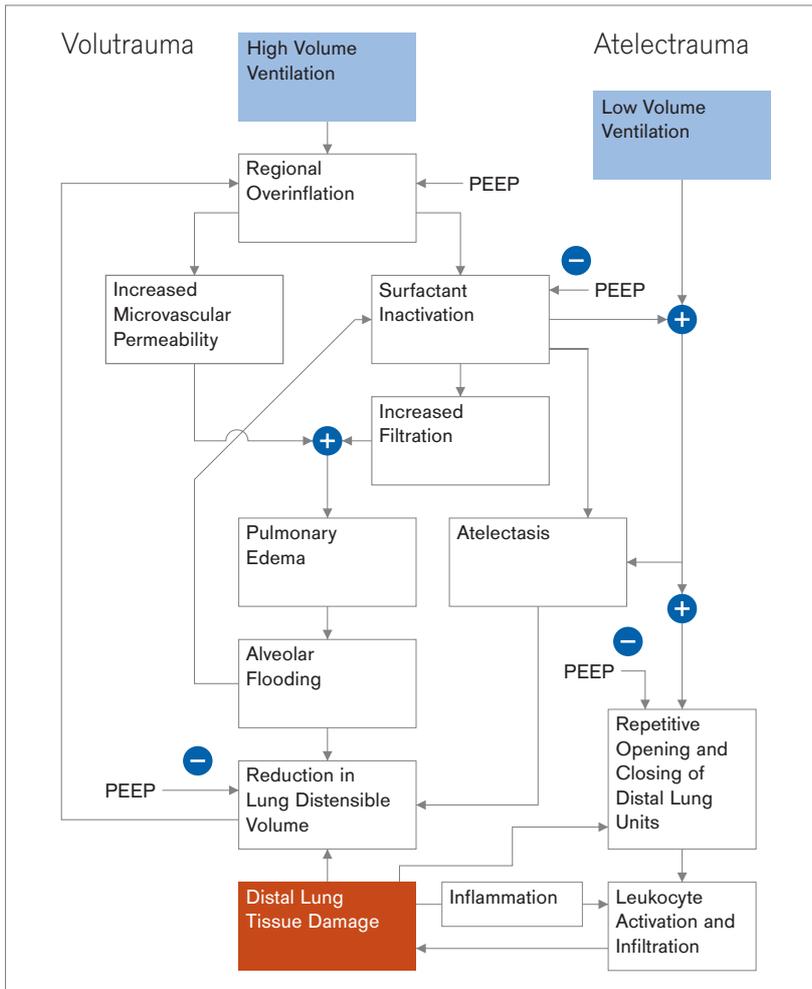


Figure 1: Contributors to mechanical ventilation-induced lung injury. PEEP (Positive endexpiratory pressure) generally opposes injury or edema formation (minus sign) except when it contributes to overinflation (plus sign) [7].

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-aerated 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 (CO₂ 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 CO₂ 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?

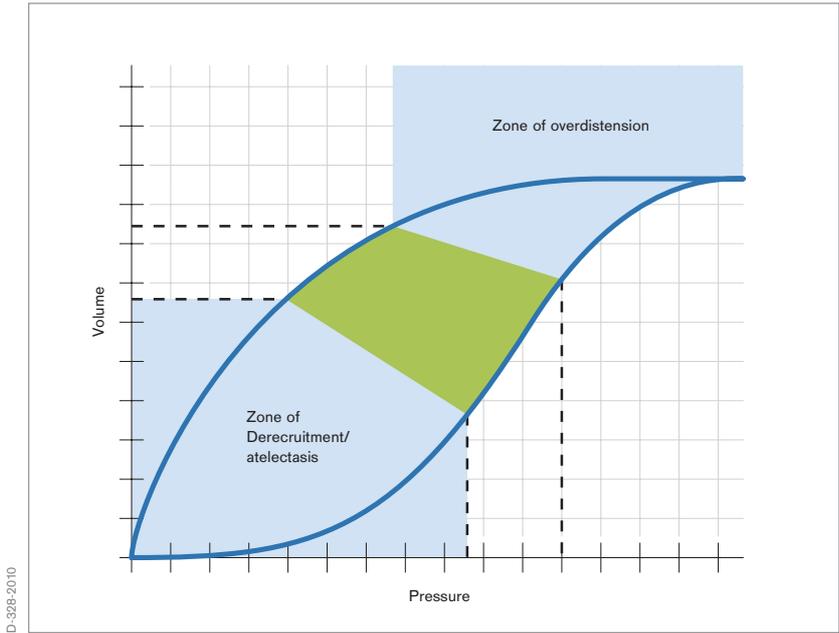


Figure 2: Theoretical "safe zone" in a static pressure volume loop between tidal derecruitment/recruitment and overdistension.

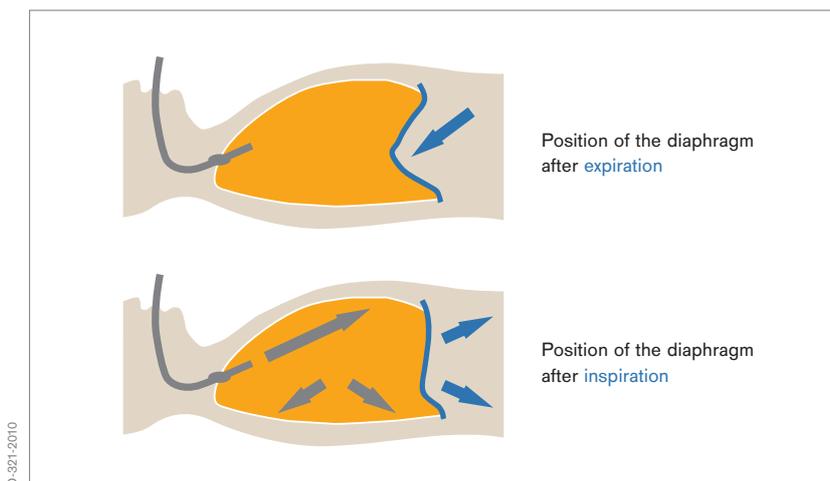


Figure 3: Diaphragmatic activity during spontaneous breathing favors redistribution of gas to dependent, well perfused areas.

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, dependent 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 leads 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].

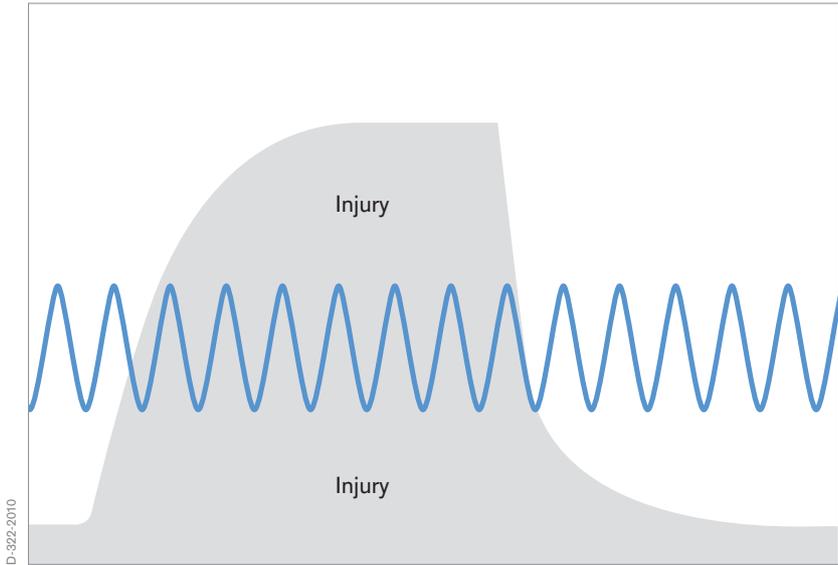
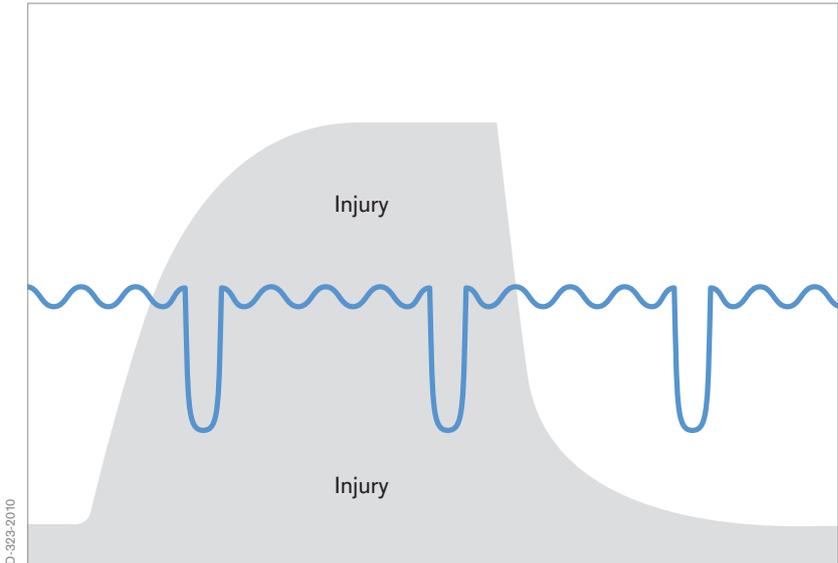


Figure 4: Protective ventilation with high frequency oscillation: very low tidal volume ventilation with high continuous distending pressures maintains lung volume while efficiently removing CO₂.

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 CO₂ removal is mediated by different mechanisms, frequently using tidal volumes which are



D-323-2010

Figure 5: Balancing adequate end-expiratory lung volume and hyperinflation with APRV. A high continuous airway pressure maintains lung volume, intermittent releases contribute to CO₂ 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 hemorrhage (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 CO₂ removal. Brief pressure releases facilitate gas exchange and

eliminate CO₂ 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

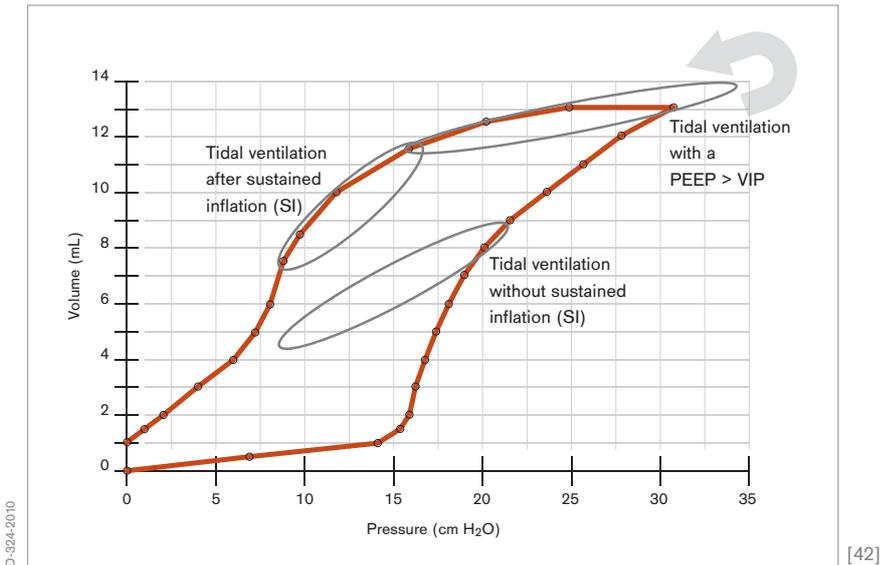


Figure 6: Recruitment maneuvers (sustained inflations) allowed ventilation with an increased end-expiratory lung volume with moderate PEEP levels in an experimental lung model of ALI [42].

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 H₂O [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 H₂O 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 cmH₂O 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 H₂O for 30 seconds and a pressure controlled recruitment maneuver comprising a PEEP of 20 and an inspiratory pressure of 40 cm H₂O 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 H₂O 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

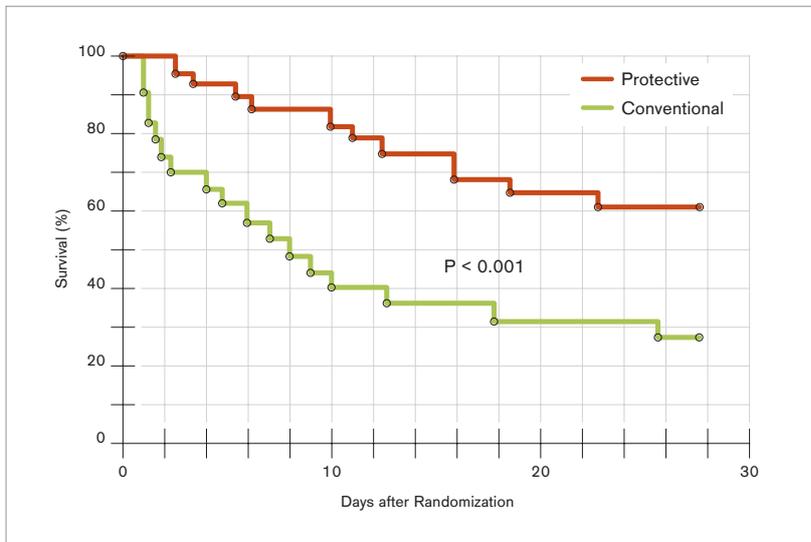


Figure 7: Protective versus conventional ventilation: 28-day survival among 53 patients with ARDS assigned to protective or conventional mechanical ventilation [60].

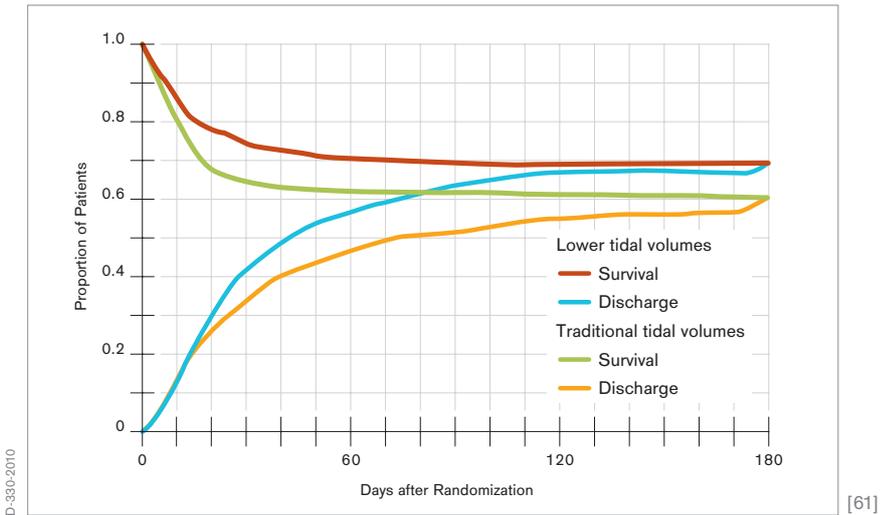


Figure 8: Low tidal volumes versus traditional tidal volumes: Probability of survival and of being discharged home and breathing without assistance during the first 180 days. Patients treated with lower tidal volumes showed a better survival and a better chance of being discharged and without assistance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

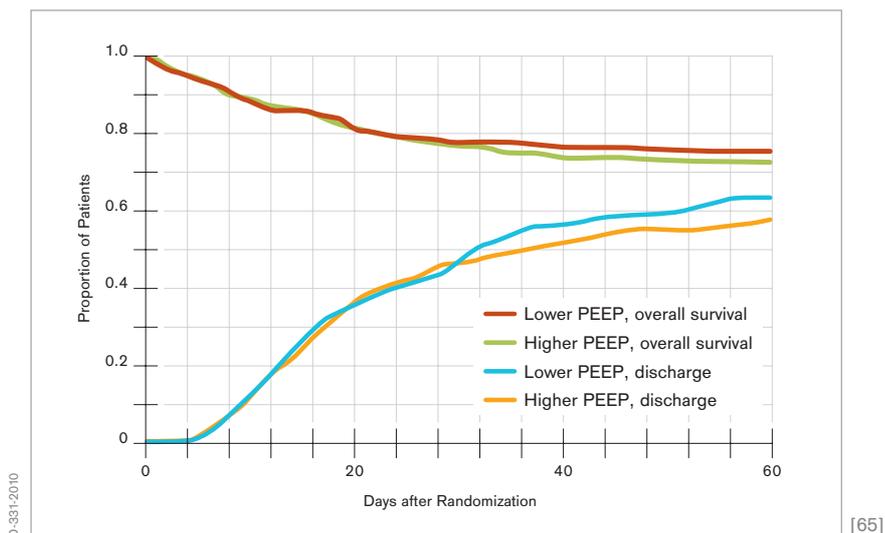


Figure 9: High PEEP versus low PEEP: probabilities of survival and of discharge home while breathing without assistance. There was no significant difference between the high PEEP and the low PEEP group [65].

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 H₂O 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 H₂O) with low tidal volume strategy with a level of PEEP set to achieve a plateau pressure of 28 to 30 cm H₂O (initial average of 15,8 cm H₂O). 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 measure 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].

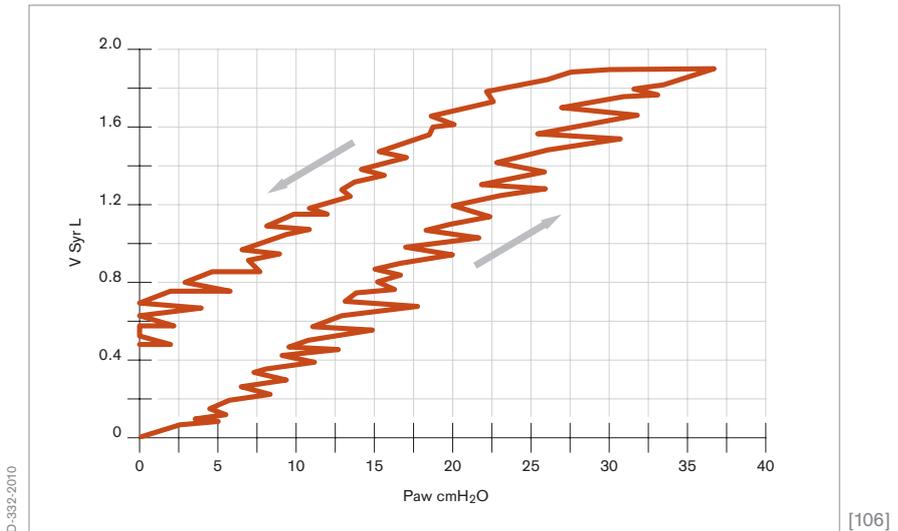


Figure 10: PV loop constructed with the super syringe method [106].

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.

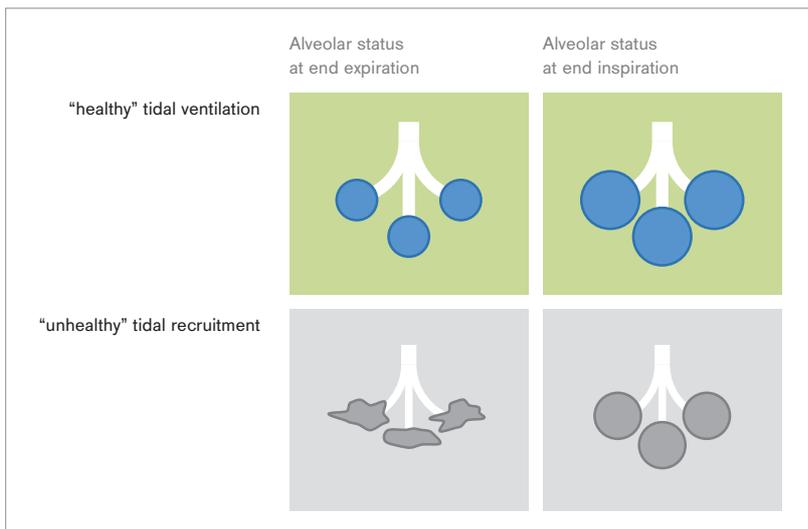
As airflow ceases in between the individual “tidal steps”, there is no resistive pressure involved and the measured pressures only represent the elastic recoil of the respiratory system during inspiration and expiration. Characteristic points on this pressure volume loop can be used to individually optimize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



D-3266-2010

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 H₂O [60, 90].

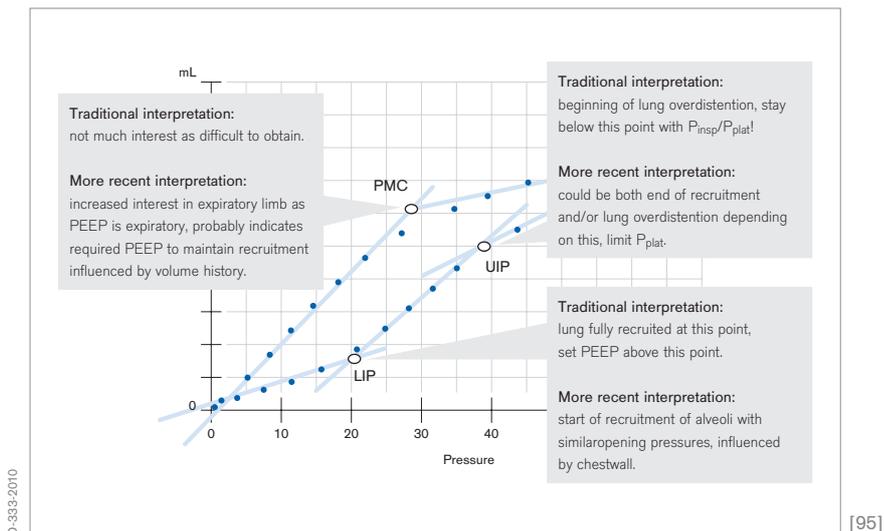


Figure 12: Characteristic points on a PV loop and their interpretation [95].

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.

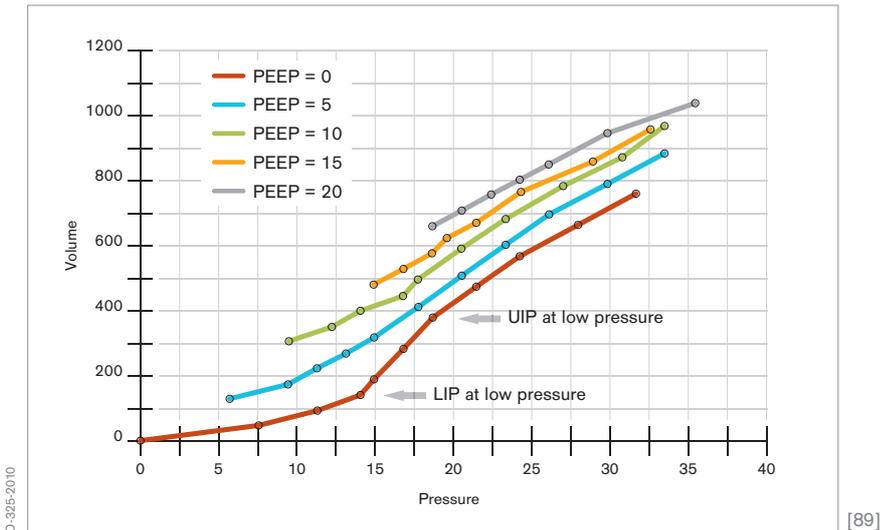


Figure 13: PV loops started from lower PEEP levels at baseline are more likely to exhibit inflection points [89].

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

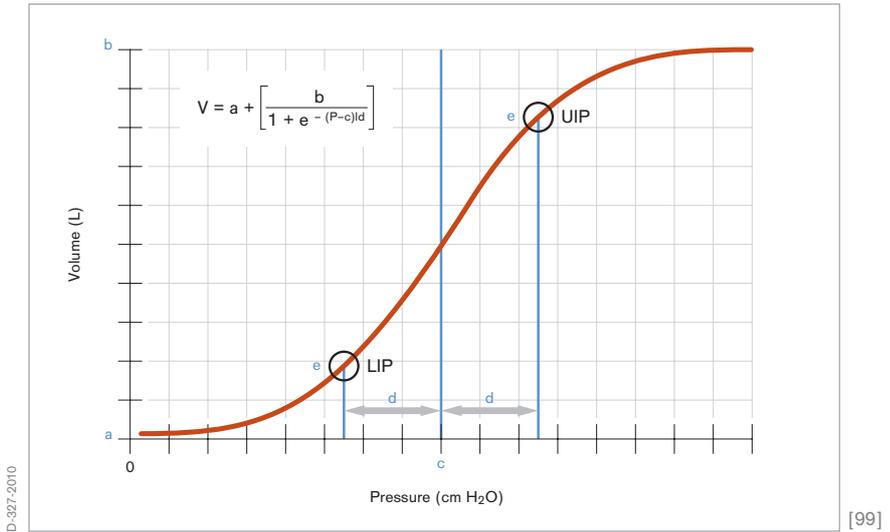


Figure 14: Sigmoidal equation to objectively quantify pressure volume loops [99].

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 too 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-aerated 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.

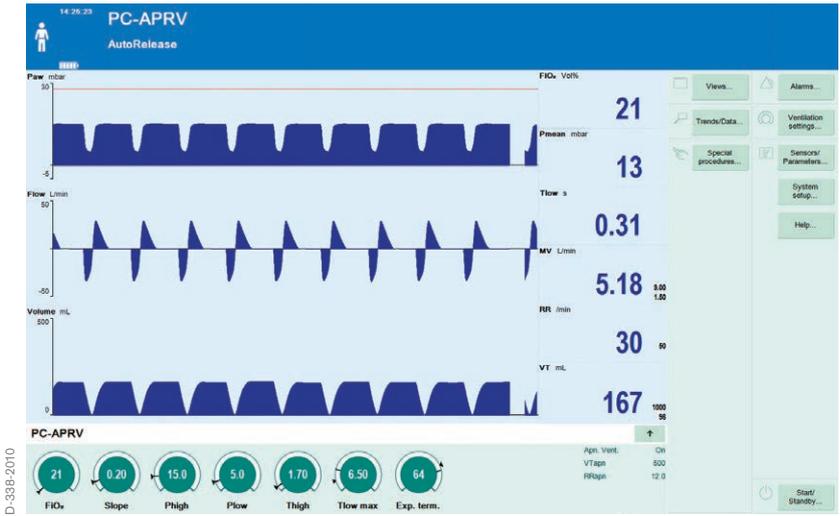
7. Tools for lung protective ventilation

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 CO₂ through spontaneous breathing and intermittent pressure releases.

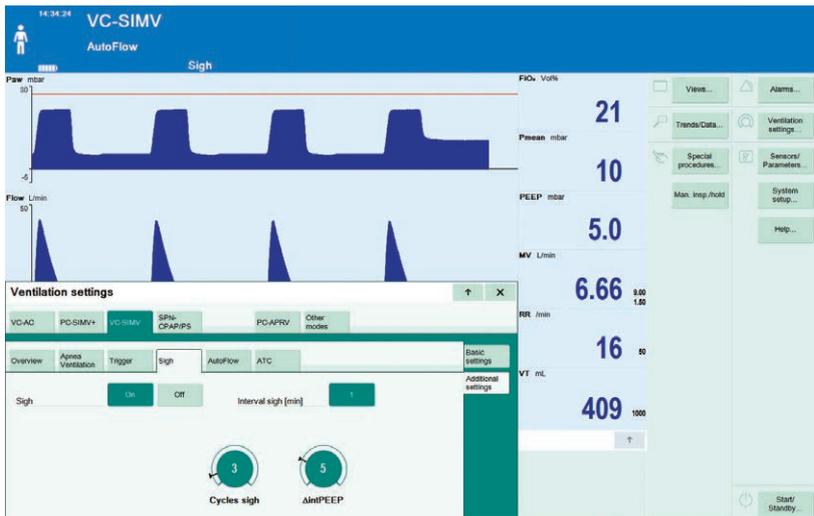
When the underlying pulmonary condition is restrictive and hypoxic in nature, fewer and shorter releases should be scheduled to avoid de-recruitment and maintain end-expiratory lung volume. When hypercapnia is an issue, more and longer releases will be required to assure sufficient ventilation. Typical settings of APRV are a P_{low} pressure of 0 to encourage a very high initial expiratory flow but a T_{low} 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 CO₂ removal and maintenance of end-expiratory lung volume for oxygenation.



D-338-2010

Figure 15: APRV AutoRelease in Evita Infinity V500.



D-3-01-2010

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.

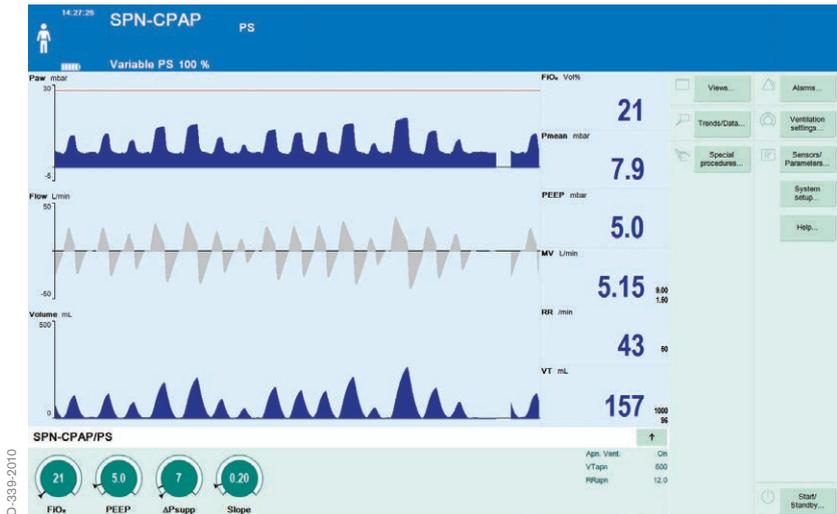


Figure 17: Variable PS in Evita Infinity V500.

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 H₂O, a variability of 100% means that the actual delta PS fluctuates from 0 to 20 cm H₂O. The sequence of PS breaths follows a random function according to a Gaussian distribution. If resulting values come within 5 cm H₂O of the airway pressure high alarm limit, another value will be generated and applied.

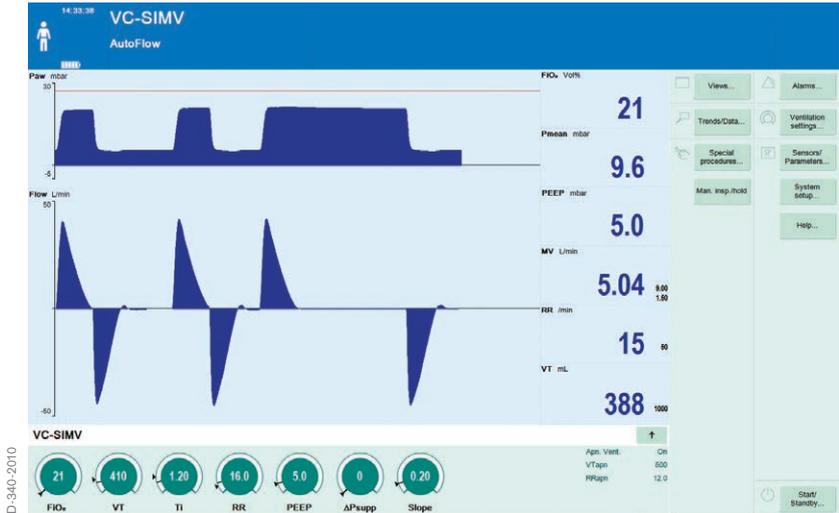


Figure 18: Inspiration hold in Evita Infinity V500.

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 $VT_{spn\ mean}$ 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.

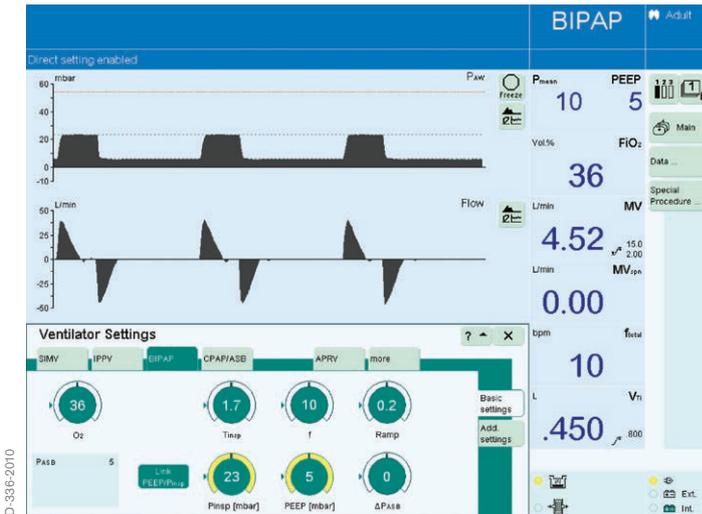


Figure 19: QuickSet and PressureLink function in the Evita XL.

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.

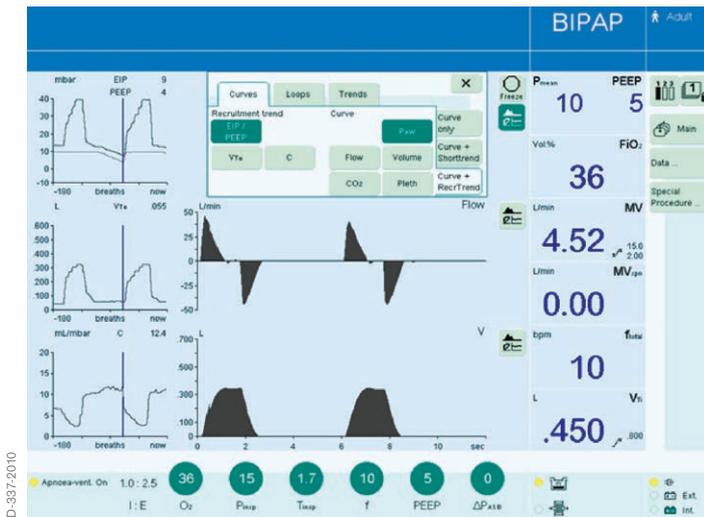


Figure 20: Recruitment trends in Evita XL.

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

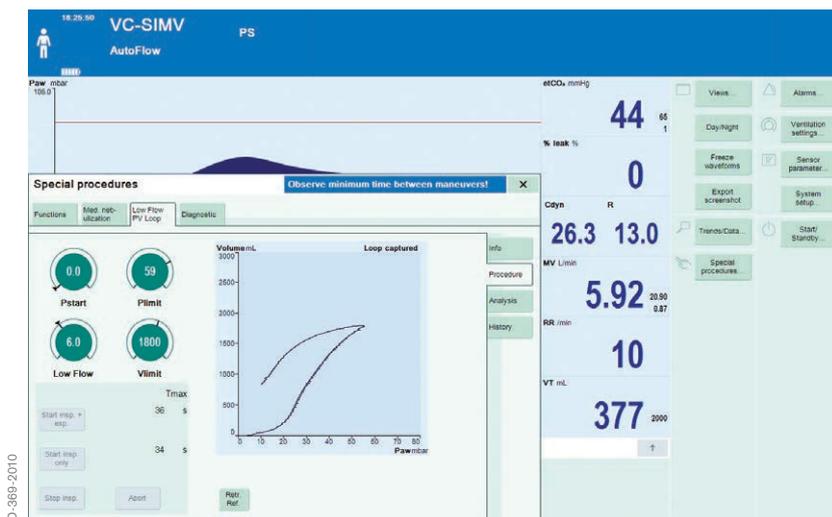


Figure 21: Low flow PV loop maneuver - procedure in the Evita Infinity V500.

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 necessary 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 or 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.

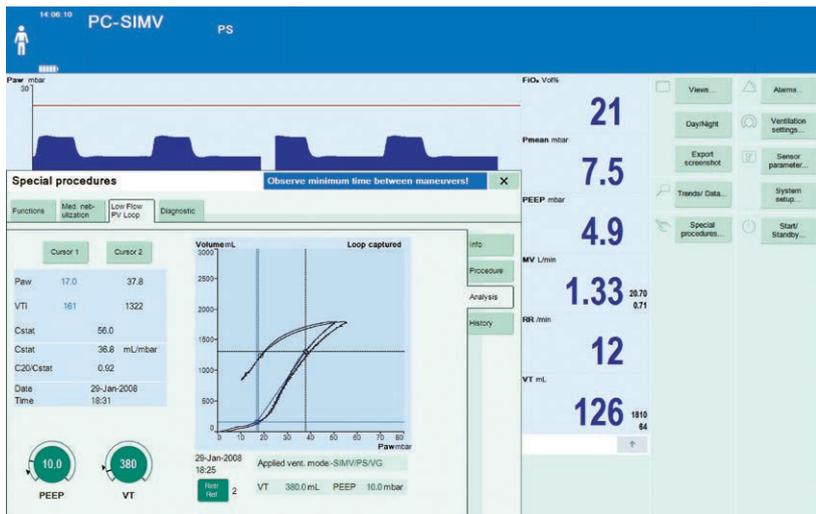


Figure 22: Low flow PV loop maneuver - analysis in the Evita Infinity V500.

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 refer 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.

References

- [1] Somerson SJ, Sicilia MR. Historical perspectives on the development and use of mechanical ventilation. *J Am Assoc Nurse Anesth* 1992; 60: 83-94.
- [2] Lewandowski K. Extracorporeal membrane oxygenation for severe acute respiratory failure. *Crit Care*. 2000;4(3):156-68. Epub 2000 Apr 12. Review.
- [3] Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson ND. Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med*. 2009 Feb 1;179(3):220-7. Epub 2008 Nov 14. Review.
- [4] Slutsky AS, Tremblay LN: Multiple System Organ Failure. Is Mechanical Ventilation a Contributing Factor? *Am J Respir Crit Care Med* Vol 157. pp 1721–1725, 1998
- [5] Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998;129:433–440
- [6] Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med* Vol. 171.pp 388-416, 2005
- [7] Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med*. 1998 Jan;157(1): 294-323.

- [8] Ricard JD, Dreyfuss D, Saumon G. Ventilator-induced lung injury. *European Respiratory Journal*, 1 August 2003, vol. 22, no. Supplement 42, pp. 2S-9S
- [9] Slutsky AS. Lung injury caused by mechanical ventilation. *Chest*. 1999 Jul;116(1 Suppl):9S-15S.
- [10] Chu EK, Whitehead T, Slutsky AS. Effects of cyclic opening and closing at low- and high-volume ventilation on bronchoalveolar lavage cytokines. *Crit Care Med*. 2004 Jan;32(1):168-74.
- [11] Beale R, Grover ER, Smithies M, Bihari D. Acute respiratory distress syndrome ("ARDS"): no more than a severe acute lung injury? *BMJ*. 1993 Nov 20;307(6915):1335-9. Review.
- [12] Marini JJ, Gattinoni L. Ventilatory management of acute respiratory distress syndrome: a consensus of two. *Crit Care Med*. 2004 Jan;32(1):250-5.
- [13] Gattinoni L, Carlesso E, Cadringer P, Valenza F, Vagginelli F, Chiumello D. Physical and biological triggers of ventilator-induced lung injury and its prevention. *Eur Respir J Suppl*. 2003 Nov;47:15s-25s.
- [14] Murphy DB, Cregg N, Tremblay L, Engelberts D, Laffey JG, Slutsky AS, Romaschin A, Kavanagh BP. Adverse Ventilatory Strategy Causes Pulmonary-to-Systemic Translocation of Endotoxin. *Am J Respir Crit Care Med* Vol 162. pp 27-33, 2000
- [15] Terragni PP, Rosboch G, Tealdi A, Corno E, Menaldo E, Davini O, Gandini G, Herrmann P, Mascia L, Quintel M, Slutsky AS, Gattinoni L, Ranieri VM. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2007 Jan 15;175(2):160-6. Epub 2006 Oct 12.

- [16] Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis.* 1987 Sep;136(3):730-6
- [17] Bidani A, Tzouanakis AE, Cardenas VJ Jr, Zwischenberger JB. Permissive hypercapnia in acute respiratory failure. *JAMA*1994, 272:957-962.
- [18] Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 1994, 22:1568-1578.
- [19] Putensen C, Mutz N, Putensen-Himmer G, Zinserling J. Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;159:1241-1248.
- [20] Neumann P, Wrigge H, Zinserling J, Hinz J, Maripuu E, Andersson LG, Putensen C, Hedenstierna G. Spontaneous breathing affects the spatial ventilation and perfusion distribution during mechanical ventilatory support. *Crit Care Med.* 2005 May;33(5):1090-5.
- [21] Wrigge H, Zinserling J, Neumann P, Muders T, Magnusson A, Putensen C, Hedenstierna G. Spontaneous breathing with airway pressure release ventilation favors ventilation in dependent lung regions and counters cyclic alveolar collapse in oleic-acid-induced lung injury: a randomized controlled computed tomography trial. *Crit Care.* 2005;9(6):R780-9. Epub 2005 Nov 16.
- [22] Putensen C, Hering R, Muders T, Wrigge H. Assisted breathing is better in acute respiratory failure. *Curr Opin Crit Care.* 2005 Feb;11(1):63-8. Review.

- [23] Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J* 2001; 16: 1374-1450.
- [24] Wysocki M, Cracco C, Teixeira A, Mercat A, Diehl JL, Lefort Y, Derenne JP, Similowski T. Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation. *Crit Care Med*. 2006 Aug;34(8):2076-83.
- [25] Funk DJ, Graham MR, Girling LG, Thliveris JA, McManus BM, Walker EK, Rector ES, Hillier C, Scott JE, Mutch WA. A comparison of biologically variable ventilation to recruitment maneuvers in a porcine model of acute lung injury. *Respir Res*. 2004 Nov 24;5:22.
- [26] McMullen MC, Girling LG, Graham MR, Mutch WA. Biologically variable ventilation improves oxygenation and respiratory mechanics during one-lung ventilation. *Anesthesiology* 2006; 105:91-7
- [27] Arold SP, Mora R, Lutchen KR, Ingenito EP, Suki B. Variable tidal volume ventilation improves lung mechanics and gas exchange in a rodent model of acute lung injury. *Am J Respir Crit Care Med* 2002; 165:366-71
- [28] Mutch WA, Harms S, Ruth Graham M, Kowalski SE, Girling LG, Lefevre GR. Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung. *Am J Respir Crit Care Med*. 2000 Jul; 162(1):319-23.
- [29] Gama de Abreu M, Spieth PM, Pelosi P, Carvalho AR, Walter C, Schreiber-Ferstl A, Aikele P, Neykova B, Hübler M, Koch T. Noisy pressure support ventilation: A pilot study on a new assisted ventilation mode in experimental lung injury. *Crit Care Med* 2008; 36:818-27

- [30] Spieth PM, Carvalho AR, Pelosi P, Hoehn C, Meissner C, Kasper M, Hübler M, von Neindorff M, Dassow C, Barrenschee M, Uhlig S, Koch T, de Abreu MG. Variable tidal volumes improve lung protective ventilation strategies in experimental lung injury. *Am J Respir Crit Care Med.* 2009 Apr 15;179(8):684-93. Epub 2009 Jan 16.
- [31] Spieth PM, Carvalho AR, Güldner A, Pelosi P, Kirichuk O, Koch T, de Abreu MG. Effects of different levels of pressure support variability in experimental lung injury. *Anesthesiology.* 2009 Feb;110(2):342-50.
- [32] Suki B, Alencar AM, Sujeer MK, Lutchen KR, Collins JJ, Andrade JS, Ingenito EP, Zapperi S, Stanley HE. Life-support system benefits from noise. *Nature* 1998; 393:127-8
- [33] Mutch WA, Graham MR, Girling LG, Brewster JF. Fractal ventilation enhances respiratory sinus arrhythmia. *Respir Res.* 2005 May 9;6:41.
- [34] Chang HK. Mechanisms of gas transport during ventilation by high-frequency oscillation. *J Appl Physiol.* 1984 Mar;56(3):553-63. Review.
- [35] Ferguson ND, Slutsky AS. Point. High-frequency ventilation is the optimal physiological approach to ventilate ARDS patients. *J Appl Physiol.* 2008 Apr;104(4):1230-1. Epub 2007 Nov 29. Links
- [36] Putensen, Zech, Wrigge. Longterm effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit CareMed* 2001; 164:43-49
- [37] Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. *Crit Care Med.* 2005 Mar;33 (3 Suppl):S228-40. Review.

- [38] Putensen, Zech, Wrigge. Longterm effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med* 2001; 164:43–49
- [39] Froese AB, Kinsella JP. High-frequency oscillatory ventilation: lessons from the neonatal/pediatric experience. *Crit Care Med*. 2005 Mar;33 (3 Suppl):S115-21.
- [40] Keszler M, Durand DJ. Neonatal high-frequency ventilation. Past, present, and future. *Clin Perinatol*. 2001 Sep;28(3):579-607.[Links](#)
- [41] Lapinsky SE, Mehta S. Bench-to-bedside review: Recruitment and recruiting maneuvers. *Crit Care*. 2005 Feb;9(1):60-5. Epub 2004 Aug 18.
- [42] Rimensberger PC, Pristine G, Mullen BM, Cox PN, Slutsky AS. Lung recruitment during small tidal volume ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. *Crit Care Med*. 1999 Sep;27(9):1940-5.
- [43] Rimensberger PC, Cox PN, Frndova H, Bryan AC. The open lung during small tidal volume ventilation: concepts of recruitment and “optimal” positive end-expiratory pressure. *Crit Care Med*. 1999 Sep;27(9):1946-52.
- [44] Carvalho AR, Jandre FC, Pino AV, Bozza FA, Salluh JI, Rodrigues R, Ascoli FO, Giannella-Neto A. Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. *Crit Care* 2007, 11:R86

- [45] Nielsen J, Nilsson M, Fredén F, Hultman J, Alström U, Kjaergaard J, Hedenstierna G, Larsson A. Central hemodynamics during lung recruitment maneuvers at hypovolemia, normovolemia and hypervolemia. A study by echocardiography and continuous pulmonary artery flow measurements in lung-injured pigs. *Intensive Care Med.* 2006 Apr;32(4):585-94. Epub 2006 Mar 7.
- [46] Odenstedt H, Lindgren S, Olegård C, Erlandsson K, Lethvall S, Aneman A, Stenqvist O, Lundin S. Slow moderate pressure recruitment maneuver minimizes negative circulatory and lung mechanic side effects: evaluation of recruitment maneuvers using electric impedance tomography. *Intensive Care Med.* 2005 Dec;31(12):1706-14. Epub 2005 Sep 22.
- [47] Villagrà A, Ochagavía A, Vatua S, Murias G, Del Mar Fernández M, Lopez Aguilar J, Fernández R, Blanch L. Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2002 Jan 15;165(2):165-70.
- [48] Musch G, Harris RS, Vidal Melo MF, O'Neill KR, Layfield JD, Winkler T, Venegas JG. Mechanism by which a sustained inflation can worsen oxygenation in acute lung injury. *Anesthesiology.* 2004 Feb;100(2):323-30. Erratum in: *Anesthesiology.* 2004 May;100(5):1336.
- [49] Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology.* 2002 Apr;96(4):795-802.
- [50] Riva DR, Oliveira MB, Rzezinski AF, Rangel G, Capelozzi VL, Zin WA, Morales MM, Pelosi P, Rocco PR. Recruitment maneuver in pulmonary and extrapulmonary experimental acute lung injury. *Crit Care Med.* 2008 Jun;36(6):1900-8.

- [51] Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: Different syndromes? *Am J Respir Crit Care Med* 1998; 158:3-11
- [52] Thille AW, Richard JC, Maggiore SM, Ranieri VM, Brochard L. Alveolar recruitment in pulmonary and extrapulmonary acute respiratory distress syndrome: comparison using pressure-volume curve or static compliance. *Anesthesiology*. 2007 Feb;106(2):212-7.
- [53] Brower RG, Morris A, MacIntyre N, Matthay MA, Hayden D, Thompson T, Clemmer T, Lanken PN, Schoenfeld D. ARDS Clinical Trials Network, National Heart, Lung, and Blood Institute, National Institutes of Health. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med*. 2003 Nov;31(11):2592-7. Erratum in: *Crit Care Med*. 2004 Mar;32(3):907.
- [54] Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, Souza CE, Victorino JA, Kacmarek RM, Barbas CS, Carvalho CR, Amato MB. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2006 Aug 1;174(3):268-78. Epub 2006 May 11.
- [55] Kacmarek RM. Strategies to optimize alveolar recruitment. *Curr Opin Crit Care*. 2001 Feb;7(1):15-20.
- [56] Bugeo G, Bruhn A, Hernandez G, Rojas G, Varela C, Tapia JC, Castillo L. Lung computed tomography during a lung recruitment maneuver in patients with acute lung injury. *Intensive Care Med*. 2003 Feb;29(2):218-25. Epub 2003 Jan 18.

- [57] Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology*. 2002 Apr;96(4):795-802.
- [58] Odenstedt H, Lindgren S, Olegård C, Erlandsson K, Lethvall S, Aneman A, Stenqvist O, Lundin S. Slow moderate pressure recruitment maneuver minimizes negative circulatory and lung mechanic side effects: evaluation of recruitment maneuvers using electric impedance tomography. *Intensive Care Med*. 2005 Dec;31(12):1706-14. Epub 2005 Sep 22.
- [59] Patroniti N, Foti G, Cortinovis B, Maggioni E, Bigatello LM, Cereda M, Pesenti A. Sigh improves gas exchange and lung volume in patients with acute respiratory distress syndrome undergoing pressure support ventilation. *Anesthesiology*. 2002 Apr;96(4):788-94.
- [60] Amato, Barbas, Medeiros et al. Effect of a protective ventilation strategy on mortality in the ARDS. *New England Journal of Medicine* 1998; 338:347-354.
- [61] Brower RG, Matthay MA, Morris A, Schoenfeld D, Taylor Thompson B, Wheeler A. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000 May 4;342(18):1301-8.
- [62] Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *N Engl J Med*. 1998 Feb 5;338(6):355-61.

- [63] Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondéjar E, Clémenti E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med.* 1998 Dec;158(6):1831-8.
- [64] Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med.* 1999 Aug;27(8):1492-8.
- [65] Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004;351(4):327-336.
- [66] Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE. Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008 Feb 13;299(6):637-45.
- [67] Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L. Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008 Feb 13;299(6):646-55.

- [68] Vieillard-Baron A, Charron C, Jardin F. Lung “recruitment” or lung overinflation maneuvers? *Intensive Care Med.* 2006 Jan;32(1):177-8. Epub 2005 Nov 11.
- [69] Lim CM, Soon Lee S, Seoung Lee J, Koh Y, Sun Shim T, Do Lee S, Sung Kim W, Kim DS, Dong Kim W. Morphometric effects of the recruitment maneuver on saline-lavaged canine lungs. A computed tomographic analysis. *Anesthesiology.* 2003 Jul;99(1):71-80.
- [70] Caramenz MP, Kacmarek RM, Helmy M, Miyoshi E, Malhotra A, Amato MB, Harris RS. A comparison of methods to identify open-lung PEEP. *Intensive Care Med.* 2009 Apr;35(4):740-7. Epub 2009 Jan 31.
- [71] Carvalho AR, Jandre FC, Pino AV, Bozza FA, Salluh JI, Rodrigues R, Ascoli FO, Giannella-Neto A. Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. *Crit Care* 2007, 11:R86.
- [72] Schreiter D, Reske A, Stichert B, Seiwerts M, Bohm SH, Kloepfel R, Josten C. Alveolar recruitment in combination with sufficient positive end-expiratory pressure increases oxygenation and lung aeration in patients with severe chest trauma. *Crit Care Med.* 2004 Apr;32(4):968-75.
- [73] Badet M, Bayle F, Richard JC, Guérin C. Comparison of optimal positive end-expiratory pressure and recruitment maneuvers during lung-protective mechanical ventilation in patients with acute lung injury/acute respiratory distress syndrome. *Respir Care.* 2009 Jul;54(7):847-54.

- [74] Hickling KG. Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. *Am J Respir Crit Care Med.* 2001 Jan;163(1):69-78
- [75] Toth I, Leiner T, Mikor A, Szakmany T, Bogar L, Molnar Z. Hemodynamic and respiratory changes during lung recruitment and descending optimal positive end-expiratory pressure titration in patients with acute respiratory distress syndrome. *Crit Care Med.* 2007 Mar;35(3):787-93.
- [76] Albaiceta GM, Piacentini E, Villagra A, Lopez-Aguilar J, Taboada F, Blanch L. Application of continuous positive airway pressure to trace static pressure-volume curves of the respiratory system. *Crit Care Med.* 2003 Oct;31(10):2514-9.
- [77] Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975;292(6):284-289.
- [78] Brochard L. What is a pressure-volume curve? *Crit Care.* 2006;10(4):156. Review.
- [79] Albaiceta GM, Luyando LH, Parra D, Menendez R, Calvo J, Pedreira PR, Taboada F. Inspiratory vs. expiratory pressure-volume curves to set end-expiratory pressure in acute lung injury. *Intensive Care Med.* 2005 Oct;31(10):1370-8. Epub 2005 Aug 10.
- [80] Mankikian B, Lemaire F, Benito S, Brun-Buisson C, Harf A, Maillot JP, Becker J. A new device for measurement of pulmonary pressure-volume curves in patients on mechanical ventilation. *Crit Care Med.* 1983 Nov; 11(11): 897-901.

- [81] Blanc Q, Sab JM, Philit F, Langevin B, Thouret JM, Noel P, Robert D, Guerin C. Inspiratory pressure-volume curves obtained using automated low constant flow inflation and automated occlusion methods in ARDS patients with a new device. *Intensive Care Med.* 2002 Jul;28(7):990-4. Epub 2002 Jun 12.
- [82] Gama AM, Meyer EC, Gaudencio AM, Grunauer MA, Amato MB, de Carvalho CR, Barbas CS. Different low constant flows can equally determine the lower inflection point in acute respiratory distress syndrome patients. *Artif Organs.* 2001 Nov; 25(11): 882-9.
- [83] Servillo G, Svantesson C, Beydon L, Roupie E, Brochard L, Lemaire F, Jonson B. Pressure-volume curves in acute respiratory failure: automated low flow inflation versus occlusion. *Am J Respir Crit Care Med.* 1997 May;155(5):1629-36.
- [84] Lu Q, Vieira SRR, Richecoeur J, Puybasset L, Kalfon P, Coriat P, Rouby JJ. A simple automated method for measuring pressure-volume curves during mechanical ventilation. *Am J Respir Crit Care Med* 1999;159:275-282.
- [85] Piacentini E, Wysocki M, Blanch L. A new automated method versus continuous positive airway pressure method for measuring pressure-volume curves in patients with acute lung injury. *Intensive Care Med.* 2009 Mar;35(3):565-70. Epub 2008 Oct 14.
- [86] Artigas A, Bernard GB, Carlet J, et al. The American-European Consensus Conference on ARDS, part 2. Ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. *Am J Respir Crit Care Med* 1998; 157: 1332± 1347.

- [87] Matamis D, Lemaire F, Harf A, et al. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest* 1984; 86: 58± 66.
- [88] Jonson B, Richard JC, Straus C, Mancebo J, Lemaire F, Brochard L. Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. *Am J Respir Crit Care Med*. 1999 Apr; 159(4 Pt 1): 1172-8.
- [89] Hickling KG. The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med*. 1998 Jul;158(1):194-202.
- [90] Takeuchi M, Goddon S, Dolhnikoff M, Shimaoka M, Hess D, Amato MB, Kacmarek RM. Set positive end-expiratory pressure during protective ventilation affects lung injury. *Anesthesiology*. 2002 Sep;97(3):682-92.
- [91] Kallet RH. Pressure-volume curves in the management of acute respiratory distress syndrome. *Respir Care Clin N Am*. 2003 Sep; 9(3): 321-41.
- [92] Creamer KM, McCloud LL, Fisher LE, Ehrhart IC. Closing pressure rather than opening pressure determines optimal positive end-expiratory pressure and avoids overdistention. *Chest*. 1999 Jul;116 (1 Suppl):26S-27S.
- [93] Rimensberger PC, Cox PN, Frndova H, Bryan AC. The open lung during small tidal volume ventilation: concepts of recruitment and “optimal” positive end-expiratory pressure. *Crit Care Med*. 1999 Sep;27(9):1946-52.

- [94] Hickling KG. Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. *Am J Respir Crit Care Med.* 2001 Jan;163(1):69-78
- [95] Nishida T, Suchodolski K, Schettino GP, Sedeek K, Takeuch M, Kacmarek RM. Peak volume history and peak pressure-volume curve pressures independently affect the shape of the pressure-volume curve of the respiratory system. *Crit Care Med.* 2004 Jun;32(6):1358-64.
- [96] Takeuchi M, Sedeek KA, Schettino GP, Suchodolski K, Kacmarek RM. Peak pressure during volume history and pressure-volume curve measurement affects analysis. *Am J Respir Crit Care Med.* 2001 Oct 1;164(7):1225-30.
- [97] Hickling KG. The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs *Am J Respir Crit Care Med.* 1998 Jul;158(1):194-202
- [98] Mehta S, Stewart TE, MacDonald R, Hallett D, Banayan D, Lapinsky S, Slutsky A. Temporal change, reproducibility, and interobserver variability in pressure-volume curves in adults with acute lung injury and acute respiratory distress syndrome. *Crit Care Med.* 2003 Aug; 31(8): 2118-25.
- [99] Harris RS, Hess DR, Venegas JG. An objective analysis of the pressure-volume curve in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000, 161:432-9.
- [100] Venegas JG, Harris RS, Simon BA. A comprehensive equation for the pulmonary pressure-volume curve. *J Appl Physiol.* 1998 Jan; 84(1): 389-95.

- [101] Heller H, Brandt S, Schuster KD. Development of an algorithm for improving the description of the pulmonary pressure-volume curve. *J Appl Physiol* 2002, 92:1770.
- [102] Henzler D, Orfao S, Rossaint R, Kuhlen R. Modification of a sigmoidal equation for the pulmonary pressure-volume curve for asymmetric data. *J Appl Physiol* 2003, 95:2183-4. author reply 2184
- [103] Albaiceta GM, Garcia E, Taboada F. Comparative study of four sigmoid models of pressure-volume curve in acute lung injury. *Biomed Eng Online*. 2007 Feb 14;6:7.
- [104] Nielsen J, Ostergaard M, Kjaergaard J, et al. Lung recruitment maneuver depresses central haemodynamics in patients following cardiac surgery. *Intensive Care Med* 2005; 31:1189-1194
- [105] Nielsen J, Nilsson M, Fredén F, Hultman J, Alström U, Kjaergaard J, Hedenstierna G, Larsson A. Central hemodynamics during lung recruitment maneuvers at hypovolemia, normovolemia and hypervolemia. A study by echocardiography and continuous pulmonary artery flow measurements in lung-injured pigs. *Intensive Care Med*. 2006 Apr;32(4):585-94. Epub 2006 Mar 7.
- [106] Dall'ava-Santucci J, Armaganidis A, Brunet F, Dhainaut JF, Chelucci GL, Monsallier JF, Lockhart A. Causes of error of respiratory pressure-volume curves in paralyzed subjects. *J Appl Physiol*. 1998 Jan;64(1):42-9
- [107] Henzler D, Mahnken A, Dembinski R, Waskowiak B, Rossaint R, Kuhlen R. Repeated generation of the pulmonary pressure-volume curve may lead to derecruitment in experimental lung injury. *Intensive Care Med*. 2005 Feb;31(2):302-10. Epub 2004 Dec 9.

CORPORATE HEADQUARTERS

Drägerwerk AG & Co. KGaA
Moislinger Allee 53–55
23558 Lübeck, Germany

www.draeger.com

Manufacturer:

Drägerwerk AG & Co. KGaA
Moislinger Allee 53–55
23558 Lübeck, Germany

Locate your Regional Sales
Representative at:
www.draeger.com/contact



REGION EUROPE CENTRAL AND EUROPE NORTH

Drägerwerk AG & Co. KGaA
Moislinger Allee 53–55
23558 Lübeck, Germany
Tel +49 451 882 0
Fax +49 451 882 2080
info@draeger.com

REGION EUROPE SOUTH

Dräger Médical S.A.S.
Parc de Haute Technologie d'Antony 2
25, rue Georges Besse
92182 Antony Cedex, France
Tel +33 1 46 11 56 00
Fax +33 1 40 96 97 20
dlimfr-contact@draeger.com

REGION MIDDLE EAST, AFRICA

Drägerwerk AG & Co. KGaA
Branch Office
P.O. Box 505108
Dubai, United Arab Emirates
Tel +971 4 4294 600
Fax +971 4 4294 699
contactuae@draeger.com

REGION ASIA / PACIFIC

Dräger Medical
South East Asia Pte Ltd.
25 International Business Park
#04-27/29 German Centre
Singapore 609916, Singapore
Tel +65 6572 4388
Fax +65 6572 4399
asia.pacific@draeger.com

REGION NORTH AMERICA

Dräger Medical, Inc.
3135 Quarry Road
Telford, PA 18969-1042, USA
Tel +1 215 721 5400
Toll-free+1 800 437 2437
Fax +1 215 723 5935
info.usa@draeger.com

REGION CENTRAL

AND SOUTH AMERICA
Dräger Panama Comercial
S. de R.L.
Complejo Business Park,
V tower, 10th floor
Panama City
Tel +507 377 9100
Fax +507 377 9130
contactcsa@draeger.com