From state-of-the-art ventilation to closed loop ventilation

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Abstract

Recent emphasis on energy load delivered during each ventilatory breath has opened a new insight to reduce harmful ventilatory induced lung injury, but no robust clinical evidence of patient benefit produced yet.
Closed loop ventilation is a strategy to adjust respiratory support using physiological feedback data obtained for each delivered cycle of respiratory support. Dependent on the model assumption used, closed loop ventilation aims to identify the ideal combination of tidal volume size, reduced driving pressure or respiratory frequency ultimately reducing the energy loading of the lung.
This review aims to discuss the current state-of-the-art ventilation concepts and their integration in closed loop ventilation.

Keywords: Ventilator Induced lung Injury, Closed loop ventilation, Energy, Power

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Introduction

Mechanical ventilation is generally not considered a treatment for acute respiratory distress but a necessary support modality to enable optimal gas exchange. The clinical challenge includes the adjustment of the ventilator settings to the needs of the patient without inflicting additional harm to the already injured lung.

Mechanical ventilation is a bridge to recovery. The latest guidelines of mechanical ventilation for adult patients with acute respiratory distress syndrome offer ventilation strategies aiming to mitigate ventilator induced lung injury. [1] This includes the use of lower tidal volumes of 4 to 8 mL/kg per breath, lower inspiratory pressures, targeting a plateau pressure<30 cm H_2O for patients with severe ARDS and the use of prone positioning for at least 12 hours per day.

Monitoring and reducing the driving pressure (pressure change to achieve low tidal volumes) and limiting the plateau pressures are additionally accepted strategies. [2-4]

Recent emphasis on energy load delivered during each ventilatory breath has opened a new insight to reduce harmful ventilatory induced lung injury, but no robust clinical evidence of patient benefit produced yet. [5,6]

Closed loop ventilation is a strategy to adjust respiratory support using physiological feedback data obtained for each delivered cycle of respiratory support. Dependent on the model assumption used, closed loop ventilation aims to identify the ideal combination of tidal volume size, reduced driving pressure or respiratory frequency ultimately reducing the energy loading of the lung. [7] This review aims to discuss the current state-of-the-art ventilation concepts and their integration in closed loop ventilation.

Physiological basics of ventilation distribution

For a better understanding of the concept of energy load during each respiratory cycle, the distribution of ventilation in healthy and sick lungs needs to be addressed. In a healthy lung ventilation is determined by a convection dependent (bulk gas flow or tidal flow) and a diffusion dependent gas exchange. The alveolar space is the silent compartment in the healthy lung, where no or hardly any volume change (bulk flow) occurs during tidal breathing. The volume of the alveolar space is maintained anatomically by the fibro-elastic framework in combination with the effect of the surfactant layer inside the alveolus creating an increased surface tension maintaining alveolar volume.

The gas exchange in the alveolar space is determined by diffusion of the relevant gases (Brownian motion of gaseous molecules in a medium) and the direction of diffusion is driven by the concentration gradient of the breathing gases. Tidal volume change (bulk air flow) is distributed in the non-cartilage carrying airways and terminal bronchioli. The convection-diffusion front, the transition from convection (bulk airflow) to diffusion is located in adults between the 16^{th} and 18^{th} generation of airway branching (terminal bronchiole) (Figure 1). [8,9]

In summary, volume change in healthy lungs occurs in the peripheral airways and diffusion occurs in the alveolar space. In the injured lung however, cyclic closure and reopening of alveoli can occur, and hence the convection-diffusion front has moved from the peripheral airways into the alveolar space. This leads to unphysiological strain on the cellular structure of the alveolar space. PEEP titration is used to prevent the cyclic closure of these alveoli. The end expiratory pressure required to prevent alveolar closure can vary between different lung compartments and regions, and hence a single clinically chosen PEEP level will never satisfy optimal alveolar recruitment. [10-12]

Recruitment manoeuvres are used to attempt to recruit as many collapsed alveolar compartments. There is no simple way accurately assessing the aerated lung volume (alveolar space). Inert gas washout techniques have been used for research purpose but have not made it into clinical practice. [13]

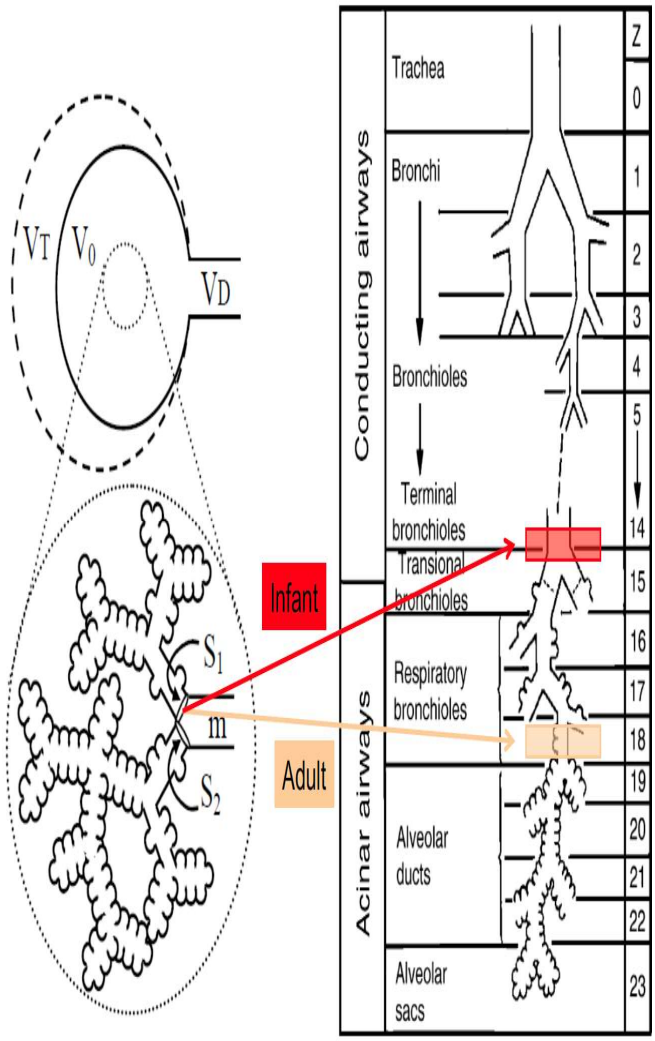

Figure 1 The transition from bulk flow (convection) to diffusion occurs in adults between the 16th and 18th generation of the bronchial branching, whereas this transition occurs in the 14th generation in neonates. VT, volume at end inspiration; V0, volume at end expiration; VD, anatomical dead space.

The costs of dead space ventilation

Even in healthy lungs, a small proportion of ventilation is "wasted" to (anatomical) dead space ventilation, defined as bulk air flow to airways without participating in gas exchange. This dead space can increase with ventilation inhomogeneity (physiological dead space). The greater the physiological dead space in a sick lung, the less efficient the ventilation (greater minute volume required for target end tidal/arterial CO_2) and hence the gas exchange. [14] Mismatched ventilation-perfusion relationship is a major contributor to an increased physiological dead space. [15,16]

State of the Art: the concept of low the tidal volume to reduce VILI

For most patients requiring mechanical ventilation gas exchange can be achieved with moderate ventilatory support and these patients do not develop ventilatory induced lung injury (VILI). In patients with reduced functional residual lung capacity (FRC) however the delivered tidal volume may exceed the physiologically acceptable tidal volume, a concept introduced by Gattinoni with the term "baby lung" (Figure 2). [17]

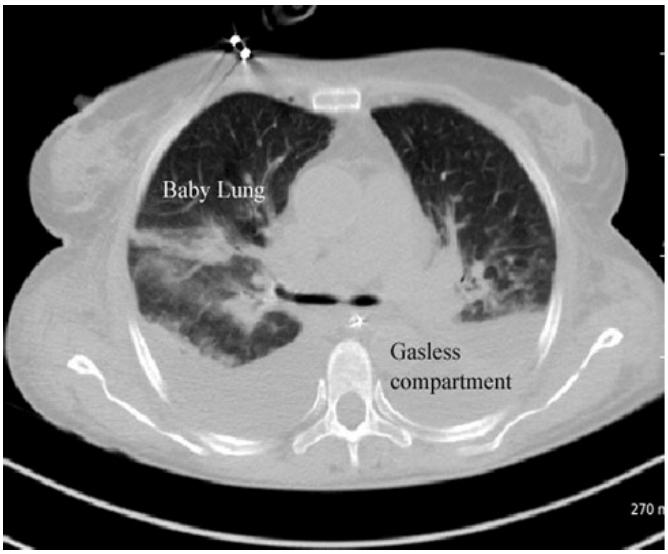

Figure 2 A CT scan of a patient with ARDS and injured lungs in the dependent lung regions leaving only ventilated in the non-dependent part of the lung

The visco-elastic properties, the combination of airway resistance and compliance, determines the ideal size of the tidal volume of the injured lung. The concept of low tidal volumes in patients with acute respiratory distress syndrome (ARDS) has been tested in several high quality randomised controlled trials. [18-23]

The American Thoracic Society recommends the use of tidal volumes between 4 to 8 mL/predicted body weight with plateau pressures < 30 cmH_2O). [24] Low tidal volumes of 4 mL/kg led to an increased respiratory rate and there is a correlation between

cycling lung stretch during mechanical ventilation and VILI. [25-28]

Simply controlling the size of the tidal volume independent of the underlying lung mechanics, may have limited impact. If the physiological dead space is large, the effective alveolar ventilation becomes ineffective to achieve the desired gas exchange and only an increase of the respiratory frequency or tidal volume can overcome this limitation.

Lung protective ventilation using low tidal volumes and limited inspiratory pressures remain the cornerstone of mechanical ventilation in ARDS. Using low tidal volume even if the functional residual capacity (FRC) is normal, has been to be shown safe and may even prevent the development of ARDS.[24] The ARDS network recommendations provide a PEEP and FiO_2 table as a one for all ventilation management strategy with its limitation that a one for all solution may disadvantage some patients.

State of the Art: The concept to reduce driving pressure

Whilst low tidal volumes, lower end-inspiratory (plateau) pressures and higher end-expiratory pressures can improve survival in patients with ARDS, the impact of each of these factors for each individual patient remains uncertain.

The driving pressure in patients without spontaneous breathing effort is defined as the difference between plateau pressure and PEEP (Pplat-PEEP) and can also be expressed as the ratio of the tidal volume divided by the respiratory compliance ($\Delta P = V_T/C_{rs}$). [2,29]

Hence the driving pressure is a parameter that is automatically normalised to FRC. Dependent on lung compliance, a given ΔP may generate a large tidal volume (high compliant lung) or a low tidal volume (low compliance). The driving pressure has been shown to be strongly associated with survival in patients with ARDS and hence changes in ventilator settings aiming to reduce ΔP may lead potentially to reduced mortality in ARDS. [2,30] However this association is not surprising as the sickest lungs will have the lowest compliance and the highest ΔP to achieve acceptable gas exchange.

The concept of reducing the driving pressure to titrate ventilation is currently tested in in a few clinical trials. [31,32] There are a few limitations using this approach. The accurate measurement of the driving pressure requires a sedated and paralysed patient and the measurement of the plateau pressure (obtained by an end inspiratory pause). [33] The difference between the peak pressure and the plateau pressure is result of the additional forces required to overcome inspiratory airway resistance. The importance of this additional resistive force and its impact on lung injury remains unknown.

The effect of reduced ΔP on clinical outcomes in the presence of spontaneous efforts also remains unclear. During spontaneous respiratory efforts, the pleural pressure decreases, creating an increased transpulmonary pressure with increased shear stress to the alveoli. Driving pressure is linked to tidal volume and determined in its efficacy by the same proportion between alveolar minute ventilation and dead space ratio. The measurement of ΔP is performed in the current trials as a once daily assessment and the assumption that the compliance remains unchanged over a 24-hour period is suspect. The attempt to reduce the ΔP results in a reduction in tidal volume and an increase of the respiratory rate to achieve the desired gas exchange for CO_2. [34,35] ΔP is a theoretically more accurate measure of optimal lung mechanics as the resultant tidal volume is driven by the respiratory compliance rather than based on the ideal body weight.

ARDS is a heterogenous lung disease with rapidly changing visco-elastic properties during a single day and therefore targeting a fixed value can be misleading.

The concept of energy load (power)

Lung protective ventilation for ARDS encompasses low tidal volumes, low driving pressures concepts and moderate to high PEEP to avoid high-stress ventilation. [36-38] The low tidal volume and the low driving pressure concept neglect at which respiratory rate the ventilatory support occurs over time.

A recent study analysed the data from several large interventional and observational studies in ARDS and

has shown that a combined new parameter using the respiratory rate and driving pressure (4 x ΔP + RR) is highly predictive for survival in ARDS.[39]

The concept of power, measuring the thermo-dynamic effect of ventilatory support (power input) measured as the energy transfer into the lung, may be indeed more related to VILI. [40] This new concept to reduce high stress ventilation integrates and unifies these previously mentioned lung protective ventilation concepts. High-stress cyclic movement and stretch of any object leads to heat dissipation (heated tyre rubber after driving). This knowledge assists in understanding the potential harm of high-stress ventilation, which leads to inflammation and deformation of cells and extracellular matrix.[41]

During each cycle of breath energy is required to overcome resistive forces of the airways, the elastic forces (both static and dynamic) and turbulent resistive forces.

Energy or work of breathing per breath is the integral (area under the curve) of the applied pressure and the resulting volume change of each single breath (Figure 3). At the start of mechanical ventilation, the lung is inflated to the end-expiratory lung volume using PEEP. This energy is only applied once and stored in the lung and chest wall and hence does not contribute to energy dissipation during respiratory support (elastic static power). During each breath, the inspiratory power is the sum of the tidal dynamic power and resistive power, the equivalent of the energy required to inflate the lung for each breath.

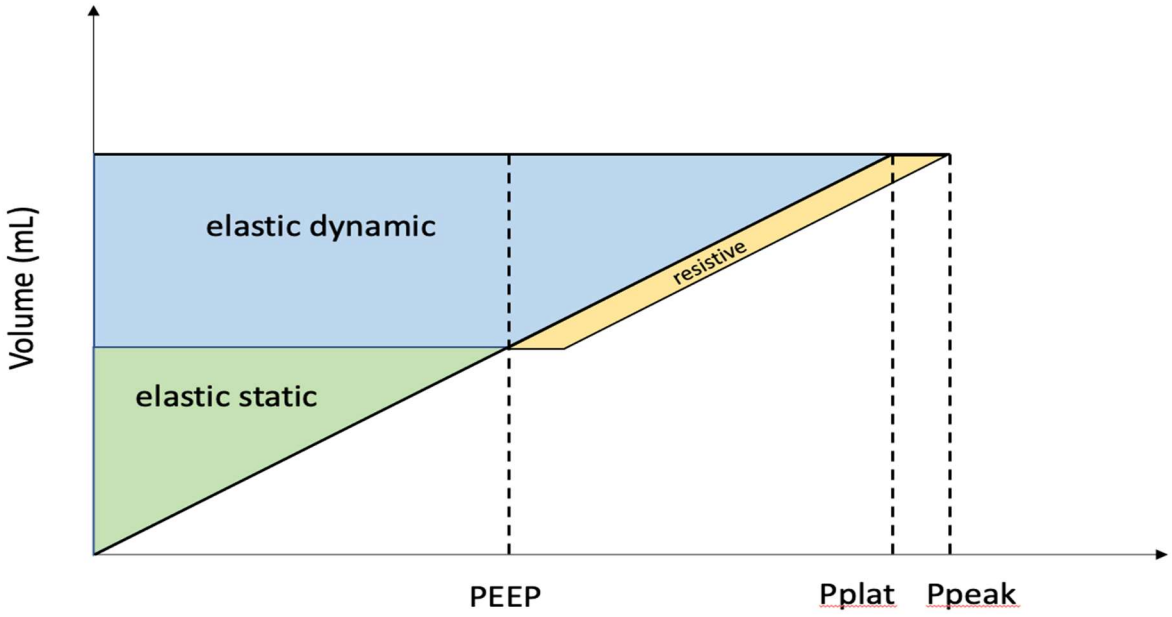

Figure 3 A graphical representation of the work of breathing, which is determined by the dynamic static and the resistive component. PEEP, positive end expiratory pressure, Plat, plateau pressure, Ppeak, peak pressure.

As per figure 3, either a reduction of the tidal volume or the driving pressure will reduce the area under the curve and hence reduces the energy per breath.

The work is then defined as the product of the respiratory frequency (per minute) and the energy required to inflate the lung for each respiratory cycle.

The term power denotes the energy expended over a specific time unit, here over one minute, and is expressed using the units of Joules per minute. Since the power is defined as a product, a multitude of combinations of respiratory frequencies and tidal volumes or ΔP lead to the same result but not all carry the same risk of damage.

Since tidal power includes a resistive and elastic component, it is easy to understand that i.e. excessive inspiratory flow in obstructive lung disease may result in a greater energy delivery per breath due to the greater resistive forces required. Similarly, in restrictive lung disease a larger tidal power is required to achieve the required tidal volume.

The concept of power therefore integrates the pathophysiology of the underlying lung disease with modifiable factors, such as tidal volume, driving pressure and respiratory rate. Thus, any reduction in any component of the cyclic mechanical power should in theory lower the risk of VILI.

In a seminal paper, Gattinoni and colleagues [42]. have shown that this mathematically approach to compute the power based on ventilator settings is highly correlated to the experimentally measured real power applied to patients with normal lungs and patients with ARDS. This finding is important, as newer concepts of ventilation strategies targeting a reduced power may lead to improved outcomes.

There are some important theoretical limitations. Not all lung areas may be subject to the same stress (applied force measured by the transpulmonary pressure) and strain (change of volume relative to FRC). Even if power delivered would be normalised to FRC, this assumption would not necessarily be valid for inhomogeneous lung disease, in which some lung units may be at a higher risk to be exposed to higher power inducing injury.

Marini recently showed that the power delivery changes within each cycle of a breath and is dependent on the flow pattern used. [43] The importance of these flow patterns and their differences and how they deliver power within each breath cycle remains unknown. It is hypothesized that minimizing high flow patterns and power spikes may reduce VILI.

The role of PEEP and power distributed during each breath remains also unclear and the assumption is made that the power used to deliver the tidal volume against PEEP is not stored in the lung/body and would not necessarily contribute to lung injury, an assumption that requires further studies.

Concept of closed loop ventilation

Clinicians adapt ventilator settings based on the patient's physiological condition and requirement for optimal gas exchange using the above mentioned concepts.

The "optimal" combination of ventilator settings in routine practice is difficult to obtain, and an approach of trial and error is required as the visco-elastic properties of the lung may change by the hour. Fine tuning of the ventilator settings ideally should occur in frequent intervals, which is difficult to achieve in a busy intensive care unit and requires a certain level of expertise (clinician control).

The integration of optimal tidal volume, driving pressure, respiratory rate and the most efficient energy loading of the lung can become a daunting task for clinicians. Information on gas exchange (PaO_2, $PaCO_2$, dead space), lung mechanics (restrictive, obstructive or combination of both), progression of disease over time and pathophysiological characteristics (VQ mismatch, reduced pulmonary perfusion or pulmonary hypertension) all impact on optimal gas exchange.

The above discussed concepts of lung protection can be integrated into a mathematical equation that aim to optimise ventilation based on the measurement of the visco-elastic properties of the lung (resistance and compliance).

Adaptive or closed loop ventilation is based on the principle that the ventilator settings (output parameters) are automatically adapted using a feedback loop based on the measured lung function (input parameters). Most of the currently available closed loop modes use a specific mathematical model to automatically optimise the ventilator settings (output) while adhering to lung protective rules.

It is important to note that closed loop ventilation modes have a narrow clinical target, and they only adapt the respiratory support without consideration of many other important patient factors such as underlying cause for respiratory failure, cardiac, renal, neurologic, and metabolic function. Hence closed loop ventilation modes do not replace the clinician at the helm but can make steering easier.

Any closed loop approach is only as good as the implemented basic assumptions of lung protective ventilation (clinical evidence obtained from randomized controlled trials). The author advocates that closed loop ventilation should not replace the bedside practitioner but closed loop ventilation facilitates the ventilatory management using a set of boundaries and assists the clinician in titrating optimal ventilation as any other open (or manual) mode. Human oversight with specific triggers will remain important. It has been shown that there is a substantial difference between what clinician's think they do and what they indeed use in clinical practice and closed loop ventilation may reduce this gap.[44]

The further discussion only includes true closed loop ventilation modes which provide respiratory support in absence or presence of spontaneous and are based on the latest lung protective ventilation approach.

Adaptive Support Ventilation (ASV)

Almost 40 years ago, mandatory minute ventilation (MMV) was implemented with adaptive pressure control. [45] MMV allows the clinician to set a target minute ventilation, the ventilator then applies either volume or pressure-controlled mandatory breaths if the patient generates a lower minute ventilation with spontaneous breaths. The acceptance of this mode is not widespread, possibly due to some limitations: MMV can lead to fast and ineffective breathing and the development of auto-PEEP with high-tidal volumes.

The development of ASV originate from similar principles targeting a pre-set minute volume. [46,47] The goal of ASV is to provide a defined minute volume while achieving a minimal work of breathing. The minute volume is defined by the operator based on the patient's gas exchange requirement and adjusted for the body weight.

The ASV is adjusting the pressure (pressure control ventilation) to achieve a respiratory rate and tidal volume to minimise the work of breathing. Mandatory (pressure control) and spontaneous breaths (pressure support) are supported in presence or absence of spontaneous breathing efforts. The range of possible tidal volume and respiratory rate is defined by a maximum pressure setting selected by the clinician.

The work of breathing is based on the Otis equation. [48] Otis made the assumption that the respiratory control centre of the brain of spontaneously breathing subjects seeks the optimal combination of tidal volume and respiratory rate to minimize the breathing effort. The respiratory muscle effort (P*mus*, pressure generated by inspiratory muscles) can be separated into 3 elements; the pressure generated overcoming the compliance of the lung for a given volume, the pressure overcoming the airway resistance and the pressure for overcoming the turbulent airflow.

Work of breathing equation simplified

$$Pmus(t) = \frac{1}{C} * V(t) + R * V'(t) + R' * V'(t)2$$

Where R is the linear resistance and R' the non-linear (turbulent) resistance, and V' is the flow generated.

Otis then solved the equation to find the optimal frequency at which the minimal effort (power) is required.

ASV measures the expiratory time constant, which is dependent on the patients' airway resistance (R) and lung compliance (C), and adapts the inspiratory:expiratory (I:E) ratio (respiratory frequency) to achieve the target minute volume.

This approach does not consider the goal of lung protective ventilation and may result in rather large tidal volumes. The clinician still needs to adapt PEEP and FiO_2. To avoid excessive peak pressures or large tidal volumes, ASV uses a safety window to operate within pre-set boundaries. The minimal target tidal volume is defined as twice the anatomical dead space estimated by the patient's body weight. The maximal target tidal volume is defined by the maximal peak pressure set by the clinician multiplied by the respiratory compliance. The minimal target respiratory frequency is 5 breaths/min, and the maximal respiratory frequency is defined as the ratio 20/RC.

ASV supports within these boundaries during initiation, maintenance and weaning of mechanical ventilation and hence can operate in all clinical scenarios. [49]

ASV was modified in 2016 to introduce the concept of minimal force of breathing in addition to the minimal work of breathing. [50,51] The minimal force of breathing corresponds to the minimal inspiratory pressure. In the latest development of the ASV mode (INTELiVENT-ASV), the end tidal P_{ETCO2} is measured, and the target minute volume is adjusted to keep P_{ETCO2} within expert-based acceptable range. In addition, the PEEP and FiO_2 is adjusted based on the ARDS network PEEP-FiO_2 tables to maintain a transcutaneous oxygen saturation within an expert-based acceptable range. [52] The PEEP-FiO_2 tables can be adjusted by the bedside clinician.

The advantage of ASV in clinical practice is less ventilator-clinician interactions required and has been shown to reduce in post anaesthesia ICU ventilation the length of mechanical support. [53] The short-term effects of ASV compared to conventional ventilation in acute respiratory failure showed that ASV automatically sets the ventilation parameters to reflect the underlying lung pathophysiology. [54]

In a recent study, Arnal and colleagues investigated INTELiVENT-ASV in 255 ventilated patients with normal lungs (n=98), ARDS (n=129) and COPD (n=28). The study showed that a consistent low driving pressure delivered across all patients of less than 8 cmH_2O, which is associated with reduced incidence of VILI and with a low mortality. [55,56] The tidal volume delivered specifically in patient with ARDS was consistent with the low tidal volume approach.

Limitations of ASV. The main limitation of the ASV mode lays in the Otis equation, which is based on spontaneous and unassisted breathing. Some studies have shown that ASV delivers tidal volumes well beyond accepted lung protection limits. A further limitation is that the clinician needs to adjust the minute volume based on the patient's gas exchange.

From a patient's perspective, ASV does not outperform over standard "manual" techniques and hasn't shown to have an impact on patient centred relevant outcomes such as reduced time spent intubated or survival in acute respiratory failure. ASV mode is only offered on a limited number of ventilator brands making it difficult to assess its role across several health services.

Adaptive Ventilation Mode-2

The new AVM-2 mode is a further advancement of the ASV mode and offers some new interesting approach to optimize ventilation using the concept of minimizing the tidal power delivery to optimize respiratory frequency. [51]

For the purpose of AVM-2, the inspiratory power is the energy the ventilator requires for each breath to overcome elastic and resistive forces. In contrast to the Otis derived power, which is muscle power required for unassisted and spontaneous breathing, the inspiratory power is the force used by the ventilator to generate positive pressure support for a given tidal volume.

The AVM-2 algorithm uses a regular square pressure wave form for pressure-controlled ventilation that minimizes the tidal power to find the optimal frequency for a given minute volume. This approach is a similar to the pressure regulated volume control (PRVC) mode with a pre-set tidal volume (i.e. 6 mL/kg) and the clinician adjusts the respiratory frequency.

The possible advantage of the AVM-2 mode is that the two concepts of low tidal volume and low driving pressure ventilation are integrated to achieve lung protective ventilation. The AVM-2 algorithm is based on a I:E ratio of 1:1 but the uses the RC time constant to adjust I:E ratio with an upper limit of 3 x RC time constant of the lung. This approach has been chosen to maintain oxygenation and to limit intrinsic PEEP.

Resistive and elastic power was defined by Gattinoni. Marini subsequently differentiated elastic power into its components PEEP power and tidal power. The concept of inspiratory power (area inside bolt red line) is the composite of tidal and resistive power. Note, the figure shows work instead of power and power is the result of the product between work and the ventilation frequency.

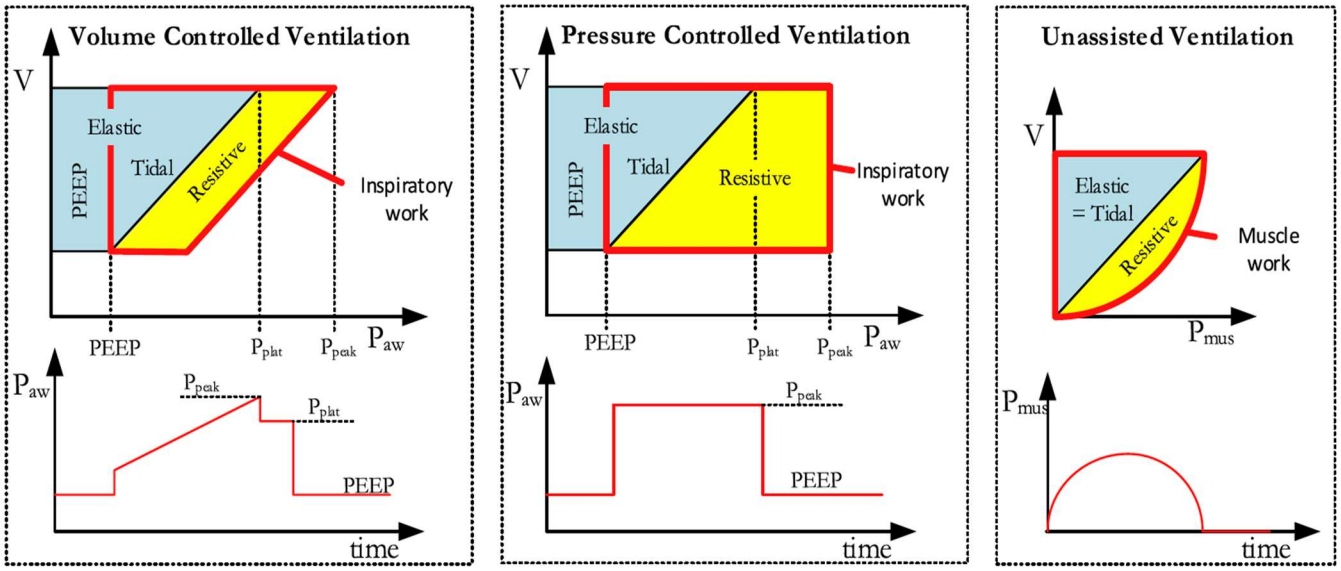

Figure 4 Definition of the different power components of inspiration and expiration. From reference 51 with permission

There are currently no experimental or human data using AVM-2. Van der Staay compared ASV and AVM-2 in lung simulator scenarios using an adult healthy, a COPD and an ARDS model and similarly, a neonatal healthy, a Respiratory Distress (RDS) and a chronic lung disease (CLD) model. [51] The measured outcome parameters were tidal volume, driving pressure and tidal power over various level of alveolar minute volumes. The model used a fixed ratio between tidal volume and anatomical dead space for both modes to guarantee in the scenario a stable end tidal PCO_2. In the healthy adult lung scenario over a wide range of alveolar minute volume (2-6 L/min), the tidal volumes and driving pressures were higher in ASV but the resulting inspiratory power was the same as with AVM-2 mode. In the ARDS scenario, the tidal volume and the driving pressure was higher in the ASV mode, but tidal power was similar in both modes. In the COPD scenario, both ASV and AVM-2 delivered similar tidal volumes, driving pressures and tidal power. In the health neonatal scenario similar to the adults, the tidal volumes and driving pressures were higher in ASV but both, ASV and AVM-2 delivered the same tidal power. In the RDS and CLD model the tidal volumes and driving pressure was again higher in ASV with similar tidal power in both modes. The conclusion was that ASV and AVM-2 perform similar with tidal power as the outcome, but ASV delivers in both, the adult and neonatal lung model higher tidal volumes and greater driving pressure, deviating more away from lung protective ventilation.

What are the next necessary steps?

The author encourages the reader of this article to consider a clinical article written by Marini (How I optimize power to avoid VILI).[40] In this seminal paper a guidance on how to titrate optimal ventilation and attention is given to monitor and carefully optimize the driving pressure, the tidal volume and ultimately the minute volume.

AVM-2 and to some extend ASV automizes this approach to manage a patient with ARDS. Clinical trials using an optimization approach and targeting either tidal volume (current standard approach), driving pressure (less than 15 cmH_2O) and tidal power. Recent data showed that normalised power (power normalised to body weight) is a strong predictor of mortality and hence it can be assumed that tidal power will show the same relationship.[57]

However, in a first step ASV and AVM-2 need to be compared to a mode such as PRVC in a randomised cross over study design. Alternatively, a database containing ventilation parameters using ASV, AVM-2 and standard pressure or volume-controlled modes can be established, and the cumulative data can then be related to relevant clinical outcomes.

In a future step, the measurement of ventilation efficiency needs to be part of the ventilation strategy, and the easiest target can be capnography and measurement of dead space ventilation. A further step is the measurement and consideration of the functional lung size and adapting respiratory support accordingly.

General comment

Many ICUs lack the considerable collective expertise and may encounter significant obstacles when implementing ventilator management protocols and a 24/7 cover of ventilation expertise can't be guaranteed. Closed loop systems may provide a convenient solution to deliver a state-of-the-art ventilation strategy in an environment with lack of expertise or reduced clinical staffing. It is not uncommon that the most junior doctor is making ventilation decisions. Current systems essentially codify evidence-based guidelines to provide partial closed-loop ventilation under carefully controlled conditions. However, the ventilation code is only as good as the assumption implemented. With the current paucity of strong evidence, it remains unclear whether these assumptions should be integrated in an automated system. We currently have a good understanding of predictors of poor outcome in ARDS, but we have less knowledge which ventilator parameter should be optimized.

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