Review Article

Mid-frequency ventilation: A potential strategy for lung protective neonatal mechanical ventilation

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Abstract. Mid-frequency ventilation (MFV) is a mode of mechanical ventilation where pressure controlled breaths are delivered at higher than usual respiratory rates with a conventional ventilator. The use of higher than normal frequencies has been used in clinical practice for the last 30 yr. However, MFV is based in the mathematical modeling of a pressure control breath; were as ventilator frequency increases, at a constant inspiratory to expiratory time ratio, alveolar ventilation demonstrates a peak (maximized). This peak is typically found at higher than usual respiratory rates (optimal frequency) and lower tidal volume (V_T). The clinical consequence is that for a given alveolar ventilation target, MFV provides optimal inspiratory pressure and respiratory frequency with the least V_T . MFV is a strategy where peak alveolar ventilation is identified and results in lower V_T at the same ventilation pressures. Current ventilators are able to deliver higher rates and thus can optimize the delivery of mechanical ventilation. Current clinical practice of mechanical ventilation utilizes a low V_T approach as a protective lung strategy to prevent further ventilator induced lung injury and thus potentially reduce mortality. Further, neonatal and pediatric patients who fail a conventional low V_T protective lung strategy are transitioned to either high frequency ventilation, which delivers small V_T at fast respiratory rates, or more invasive and expensive support such as extracorporeal membrane oxygenation. MFV may offer an alternative to deliver a protective lung strategy without the need for advanced equipment.

Keywords: Mechanical ventilation, mid-frequency ventilation, lung injury, pressure control, acute respiratory distress syndrome

1. The respiratory rate and mechanical ventilation

There are multiple factors that determine the spontaneous respiratory rate [1]. Perhaps, the one that best describes the resting respiratory rate is the work of Otis et al. [2]. They described the relation between work

of breathing and respiratory rate, where for constant minute ventilation the respiratory rate corresponds to the lowest work of breathing. That is, for given minute ventilation, the respiratory rate is a result of a series of signals that aim to minimize inspiratory effort and maximize muscle efficiency. The spontaneous respiratory rate is faster during illness and responds to changes in the respiratory system characteristics (resistance and compliance) [3].

The spontaneous respiratory frequency during the neonatal period is higher than during infancy and

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early childhood [4]. Spontaneous respiratory frequency decreases progressively until it reaches that of adults. The faster baseline respiratory frequency of neonates is the result of lower lung and chest wall compliance, a higher metabolic rate, a pliable rib cage, which distorts easily with large pleural pressure swings, and a lower functional residual capacity [5]. These factors tend to make increasing breathing frequency more efficient than increasing tidal volume (V_T).

In contrast, when a patient is on mechanical ventilation, the physiologic signals that control the patient's respiratory frequency are often over-ridden by settings on the machine. It is the clinician at the bedside who decides the respiratory frequency, not the patient's physiology. Although in theory, the selection of ventilator breath frequency is determined by the patient's basal respiratory frequency, anticipated ventilator needs, diagnosis, physiology, synchrony and measurements of gas exchange [6]; in practice, the rate is set to keep the level of carbon dioxide and pH within acceptable limits. Clinical observation usually moves towards no action when the pH is within the physiologically normal range and the settings/measurements are "appropriate". There are situations where titration of respiratory frequency obeys other knowledge. In obstructive lung disease, respiratory frequency is tailored to avoid auto-positive end-expiratory pressure (auto-PEEP) and tolerate hypercapnia [7]. In lung injury and acute respiratory distress syndrome, lower V_T and faster respiratory frequencies are utilized [8]. However, attempts to increase the respiratory frequencies with conventional modes (particularly using volume control) can lead to rapid development of air trapping, auto-PEEP and hemodynamic compromise [9–11]. Common clinical practice limits respiratory frequencies to 60 bpm for neonates and allows the tolerance of a lower pH or higher arterial carbon dioxide tension.

An alternative to clinician-selected respiratory frequencies is computer control of mechanical ventilation. A "closed-loop" control adjust the ventilatory pattern based on feedback signals of various types. There are different closed-loop methods to control respiratory frequency and/or minute ventilation. One method is to adjust the inspiratory pressure to encourage a spontaneous breath frequency target set by the operator (Mandatory Rate Ventilation, Taema-Horus). Another example is an expert based algorithm (SmartCare/PS, Dräger) that automatically adjusts the level of ventilatory support based on the spontaneous breath frequency, end tidal carbon dioxide and V_T [12]. These modes are only effective in patients capable of spontaneous

breathing, which limits their application. In absence or intermittent presence of spontaneous breaths, an option is to set a target for minimum minute ventilation. One example is the mode called "mandatory minute volume ventilation" (Dräger Evita XL ventilator). The operator sets a value for mandatory breaths, but these breaths are suppressed as long as the minute ventilation due to spontaneous breaths exceeds the set target, thus providing a mode that serves both comfort (i.e., patient-ventilator synchrony) and safety (guaranteed minimum minute ventilation) [13]. An advanced form of mandatory minute ventilation, adaptive support ventilation (ASV) (Hamilton Medical G5 ventilator) allows the machine to determine the backup mandatory breath frequency. ASV uses a closed-loop control algorithm to calculate the target breath frequency based on the Otis equation for minimizing work of breathing. Despite their theoretical appeal, none of these modes is used in neonatology.

In summary, the current paradigm of how to set the respiratory frequency in conventional mechanical ventilation is to attempt to keep the frequencies at or below 60 bpm for neonates [14]. No guideline or mode has aimed at optimizing the frequency or minute ventilation in the neonate. On the other hand, modes that use higher than normal breathing frequencies, including high frequency jet ventilation and high frequency oscillatory ventilation were first developed commercially for neonates [15].

2. Theory of mid-frequency ventilation

In 2008, we described mid-frequency ventilation (MFV) [16]. The term "mid-frequency" was coined to highlight the use of ventilatory frequencies above those used in normal clinical practice but below those used with specially designed high frequency ventilators. Using a mathematical model for pressure controlled ventilation [17,18], we demonstrated that for a given set of respiratory system characteristics and ventilating pressures there is a specific frequency where alveolar ventilation is maximal [16]. The clinical consequence is that for a given alveolar ventilation target, MFV provides optimal inspiratory pressure and respiratory frequency with the least V_T . This is the first mode that aims at optimizing minute alveolar ventilation. MFV is based on the properties of a pressure control breath, where for a given inspiratory pressure, the resultant V_T is dependent on the characteristics of the respiratory

Fig. 1. Illustrated above is a mid-frequency ventilation interactive spreadsheet shot. The upper graph is minute ventilation that is a function of frequency. Thus, alveolar minute ventilation becomes a function of the respiratory rate and dead space. In this example, we use values simulating the neonatal respiratory characteristics. The peak alveolar ventilation is achieved at 150 bpm. In the lower graph, the mean alveolar pressure and auto PEEP are demonstrated as a function of frequency. PEEP = Positive end-expiratory pressure.

system (airway resistance, compliance), total positive end-expiratory pressure (PEEP) and the inspiratory and expiratory times [19]. If the inspiratory pressure and inspiratory to expiratory time (I:E) ratio are kept constant while increasing the respiratory frequency, the minute ventilation curve will rise asymptotically (reach a plateau). This plateau would be the consequence of decreasing inspiratory time and increasing auto-PEEP leading to smaller V_T . However, if dead space (V_D) remains relatively constant, the alveolar ventilation ($f \times [V_T - V_D]$) will increase to a maximum before decreasing (as V_D ventilation becomes predominant). We termed the frequency where the peak alveolar ventilation was reached the “optimal frequency”. For most patients (except premature infants) a plot of minute alveolar ventilation against frequency shows a clear maximum value (i.e. the curve is concave downward) at the “optimum” frequency. When the inflation pressure is adjusted so that the peak of this curve matches the desired target minute alveolar ventilation, V_T will be minimized. The MFV “optimization”

of ventilator settings often results in lower V_T at higher than usual respiratory frequencies [20]. This approach is illustrated in Fig. 1.

3. Mid-frequency ventilation versus volume control ventilation versus regular pressure control ventilation

There are clear differences between MFV versus conventional ventilation using either volume or pressure control. Table 1 summarizes the difference between modes if we assume a model with constant respiratory system characteristics (V_D , compliance and resistance) where conventional ventilation keeps V_T and inspiratory time constant. In volume control, the increase in frequency will increase minute ventilation and minute alveolar ventilation linearly. Because the inspiratory time is constant, the expiratory time shortens, and auto-PEEP increases rapidly resulting in increasing peak inspiratory pressures and mean airway pressure.

Table 1
Comparison of ventilation outcomes between modes as respiratory frequency is increased

Parameters	Pressure-controlled mechanical ventilation	Volume controlled-continuous mandatory ventilation	Mid-frequency ventilation
Tidal volume	Constant	Constant	Decreases
Minute ventilation	Linear increases	Linear increases	Asymptotic
Alveolar ventilation	Linear increases	Linear increases	Peaks
Inspiratory pressure	Increases	Increases	Constant
Peak airway pressure	Increases	Increases	Constant
Mean airway pressure	Increases	Increases	Constant
Auto-positive and-expiratory pressure	Increases	Increases	Increases

In pressure control ventilation, assuming the aim is to keep the V_T constant, inspiratory pressure would need to increase to overcome the effect of auto-PEEP (which decreases the effective driving pressure and thus decreases the V_T). The result is a linear increase in minute and alveolar ventilation. The airway pressures, mean, peak and auto-PEEP all increase.

In contrast, with MFV, I:E, inspiratory pressure and mean airway pressure remain constant as frequency is increased. As a result, the V_T decreases, while the minute ventilation plateaus, and the minute alveolar ventilation reaches a peak at the optimum frequency. As with other modes, auto-PEEP increases with MFV, but at lower levels for any given frequency. The development of auto-PEEP is a function of V_T and the expiratory time [18]. If V_T increases or expiratory time shortens, auto-PEEP must increase. In MFV, the tendency to develop auto-PEEP due to decreasing expiratory time is attenuated by the concurrent decrease in V_T resulting from the decrease in inspiratory time. As a result, auto-PEEP is lower at any frequency than would occur by increasing frequency in conventional modes of ventilation.

4. Historical higher frequencies in neonates

Higher than normal respiratory frequencies, have been used in clinical practice for the last 30 yr. There are reports and randomized control trials on animal models, neonates and adults. It was the neonatal population where its implementation was better researched. In the late 1960's, faster ventilator frequencies were applied following the rationale that they mimicked the infants' higher spontaneous frequency. This led to the observation that faster frequencies led to less asynchrony [15,21]. Several trials [21–27] were done in neonates leading to two randomized multicenter trials

[26,27]. The conclusion of this experience was that ventilation at faster frequencies was more synchronous, with less air leak, and it provided efficient gas exchange [28]. Most of these studies used pressure control ventilation with a fixed I:E ratio and a fixed frequency. The inspiratory pressures were adjusted to achieve the target ventilation, and set PEEP either was absent or kept low and constant. Most studies were focused on clinical outcomes (death, air leak or pneumothorax) and only some reported measurements of airway pressures and hemodynamics [21–23]. An interesting observation from some of these studies was that frequencies higher than 60 bpm seemed to be better in terms of tolerance, ventilation and air leak [22,24,25,27]. A major limitation was the ventilator's performance at rapid ventilatory frequencies [29–31]. During the same time, specialized ventilators were developed which could also deliver ventilation at faster frequencies [32,33]. The literature is plagued with confusing terminology at that time, which refers to faster than usual respiratory frequencies as high frequency positive pressure ventilation. However, the reader is cautioned that some of these trials were done with specialized [34,35], or makeshift ventilators [36]. The study that was closest in application to MFV was done by Greenough et al. [24] who studied three different ventilatory frequencies (30, 60 and 120 bpm) in 32 preterm infants with respiratory distress syndrome (RDS). They kept mean airway pressure, I:E, fraction of inspired oxygen and inspiratory pressures constant while respiratory frequencies were varied. Significant improvement in oxygenation was observed at a ventilatory frequency of 120 bpm in non-paralyzed infants. These non-paralyzed infants achieved synchronous respirations at a faster ventilator frequency leading to an improvement in oxygenation. Again, the authors clearly noted the effect of ventilator performance on patient outcomes, those ventilated with a particular ventilator could not achieve

the same ventilation goals as the other group. Note that in all of these studies, the ventilator frequency was adjusted arbitrarily, as opposed to MFV wherein frequency is adjusted according to a mathematical model that predicts an optimum value.

5. Delivery of mid-frequency ventilation

Most current conventional ventilators reach a frequency of up to 150 bpm, the maximum allowed by the Federal Drug Administration. The pneumatic performance of the ventilator has improved through time, an essential requirement for safe and appropriate ventilation at fast frequencies [19,30,31]. A key feature is the rate of pressurization of the circuit, as any variation from ideal will affect the airway pressures and delivered V_T . For example, Greenough and Greenall [31] found a reduction in the delivered V_T as the ventilator frequency increased. Her study had second-generation ventilators and required increases in the flow at rapid ventilatory frequencies to maintain the mean airway pressure constant. Current ventilators are better at pressurization of the system and maintaining the target pressure [17]. Even small differences in the ability of the ventilator to deliver and maintain a perfect square pressure waveform can degrade on performance using MFV [19]. We also found that the equations that correct for the circuit compliance do not take into account frequency and impedance [37], and thus the use of a flow sensor at the circuit wye improves volume delivered accuracy [38]. This factor becomes crucial when dealing with neonates and pediatric patients, where small differences in performance will have large impact on the volume delivered.

6. Mid-frequency ventilation in different pathologies

The main determinant of V_T delivered for a preset inspiratory pressure waveform in a static respiratory system is the time constant of the respiratory system. The time constant (in seconds) represents a measure of time necessary for achieving 63% change in the airway pressure. The time constant is calculated as the product of resistance and compliance of the respiratory system. We have evaluated the behavior of MFV in different lung physiologies (normal, restrictive and obstructive) using a lung model [16]. We found that the equations used for MFV choose ventilator settings (V_T , frequency and inspiratory pressure) in concordance with clinical practice and lung physiology. In a follow up study, we

evaluated the differences between clinicians' choices and MFV in terms of ventilation outcomes [20]. We created five hypothetical clinical scenarios of paralyzed patients with healthy lungs, acute respiratory distress syndrome, morbid obesity, emphysema and severe asthma. A survey asked clinicians at an academic center for ventilator settings on each scenario. The survey results were used to determine the clinicians' ventilator settings. The calculated alveolar minute ventilation goal chosen by the clinicians was used as the goal for MFV. A lung simulator was programmed and ventilated with the clinical scenarios' respiratory system characteristics with the clinician-selected settings and MFV. In the normal lung, MFV reduced the V_T by 54% (3.5 vs. 7.6 mL/kg), which in turn, resulted in a decrease in 30% end inspiratory volume (a surrogate marker of volutrauma). In the restrictive scenarios, MFV used V_T 30% lower (4.2 mL/kg vs. 6.1 mL/kg) which resulted in 11% less end inspiratory volume. A major concern while delivering mechanical ventilation to patients with obstructive physiology (i.e. asthma) is the development of air trapping. High respiratory frequency is one of the causes of air trapping. For a given expiratory time constant, auto-PEEP is a function of expiratory time and delta pressure. With conventional ventilation, as frequency increases, expiratory time decreases and delta pressure is kept constant or increased. With MFV and constant I:E, as frequency increases, delta pressure decreases offsetting the decrease in expiratory time. Interestingly, MFV is sensible to obstruction and uses lower respiratory frequencies. The result of using MFV for obstructive disease needs further investigation.

In general, MFV achieved the same alveolar minute ventilation with less volume and inspiratory pressure (compared to humans). MFV uses higher minute ventilation to offset the effects of V_D volume on smaller V_T . A remarkable finding with MFV was higher end-expiratory volumes and lower end inspiratory volumes when compared to clinician's choices or ASV [39]. End inspiratory volume, represents the total volume the lung is exposed to during a ventilation strategy, a key factor in lung injury. End expiratory volume is a manifestation of PEEP and auto-PEEP. Although auto-PEEP was associated with a slightly higher mean airway pressure (1–3 cmH₂O), it was expected and predicted by the MFV calculations. The auto-PEEP generated by higher ventilator frequencies may achieve equal recruitment when compared to set PEEP but with less hemodynamic compromise [40]. We found 6 to 26% higher end-expiratory volume in MFV, which correlated with development of auto-PEEP.

7. Mid-frequency ventilation in neonates

The time constant in RDS has been calculated to be as short as 0.05 sec [41]. In MFV, the lower the time constant, the higher the optimal frequency. In a neonate, if we use the values reported for RDS (resistance = 125 cmH₂O/L/s, compliance = 0.0005 L/cmH₂O, $V_D/V_T = 0.45$) [42], we found that optimum MFV frequency was higher (around 100 bpm) and optimum V_T lower (4.4 mL/kg) than the upper limit (6 mL/kg) of current recommendations for neonates with RDS (60/min and 6 mL/kg, respectively) [43]. Optimum V_T during MFV can be lower than actual values in recent controlled studies [42].

In view of the prior experience, lung physiology and experience with synchrony at faster frequencies, in theory, the use of MFV in neonates may have the most applicability.

In conclusions, current clinical practice of mechanical ventilation utilizes a low V_T approach as a protective lung strategy to prevent further ventilator induced lung injury and thus potentially reduce mortality. Further, neonatal and pediatric patients who fail a conventional low V_T protective lung strategy are transitioned to either high frequency ventilation (HFV), which delivers small V_T at fast respiratory rates or more invasive and expensive support such as extracorporeal membrane oxygenation. Due to the specialized ventilator required to administer HFV, the ability to monitor potential lung over distension is limited, as well as the ability to transport within the institution for diagnostic services or to other institutions for specialized care. High frequency ventilators are an expensive limited resource, and availability would be severely limited in epidemics causing respiratory failure. The ability to use a conventional ventilator to perform lung recruitment without causing ventilator induced lung injury in patients who fail a traditional lung protective strategy would expand availability of resources and improve versatility of care in place of HFV.

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