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Application of Mid-Frequency Ventilation in an Animal Model of Lung Injury: A Pilot Study

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BACKGROUND: Mid-frequency ventilation (MFV) is a mode of pressure control ventilation based on an optimal targeting scheme that maximizes alveolar ventilation and minimizes tidal volume (V_T). This study was designed to compare the effects of conventional mechanical ventilation using a lung-protective strategy with MFV in a porcine model of lung injury. Our hypothesis was that MFV can maximize ventilation at higher frequencies without adverse consequences. We compared ventilation and hemodynamic outcomes between conventional ventilation and MFV. METHODS: This was a prospective study of 6 live Yorkshire pigs (10 ± 0.5 kg). The animals were subjected to lung injury induced by saline lavage and injurious conventional mechanical ventilation. Baseline conventional pressure control continuous mandatory ventilation was applied with V_T = 6 mL/kg and PEEP determined using a decremental PEEP trial. A manual decision support algorithm was used to implement MFV using the same conventional ventilator. We measured P_{aCO_2}, P_{aO_2}, end-tidal carbon dioxide, cardiac output, arterial and venous blood oxygen saturation, pulmonary and systemic vascular pressures, and lactic acid. RESULTS: The MFV algorithm produced the same minute ventilation as conventional ventilation but with lower V_T (−1 ± 0.7 mL/kg) and higher frequency (32.1 ± 6.8 vs 55.7 ± 15.8 breaths/min, $P < .002$). There were no differences between conventional ventilation and MFV for mean airway pressures (16.1 ± 1.3 vs 16.4 ± 2 cm H_2O, $P = .75$) even when auto-PEEP was higher (0.6 ± 0.9 vs 2.4 ± 1.1 cm H_2O, $P = .02$). There were no significant differences in any hemodynamic measurements, although heart rate was higher during MFV. CONCLUSIONS: In this pilot study, we demonstrate that MFV allows the use of higher breathing frequencies and lower V_T than conventional ventilation to maximize alveolar ventilation. We describe the ventilatory or hemodynamic effects of MFV. We also demonstrate that the application of a decision support algorithm to manage MFV is feasible. *Key words: mechanical ventilation; lung injury; auto-PEEP; hemodynamic; algorithms; pulmonary gas exchange; decision support; ventilation protocol; optimum ventilation; targeting scheme.* [Respir Care 2014;59(11):1–•. © 2014 Daedalus Enterprises]

Introduction

Mid-frequency ventilation (MFV) is a new mode of ventilation based on a unique form of optimal targeting scheme[1] that maximizes alveolar ventilation and minimizes tidal volume (V_T) while being responsive to changes in lung mechanics.[2,3] MFV capitalizes on the properties of a pressure control breath and its response to changes in ven-

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tilatory frequency. The theoretical basis of MFV has been explained in detail elsewhere.[3] It is classified as a form of pressure control continuous mandatory ventilation (CMV) with set-point targeting. Briefly, during ventilation of a passive subject with pressure control breaths, V_T is a function of set inspiratory pressure (above PEEP), set inspiratory and expiratory times, and both inspiratory and expiratory time constants.[4,5] If frequency is increased while keeping inspiratory pressure and inspiratory-expiratory ratio (I:E) constant, the V_T will decrease due to a shortened inspiratory time and the development of a low level of auto-PEEP. However, the decrease in V_T is offset by the increase in frequency such that the minute ventilation rises asymptotically (ie, beyond a certain point, a further increase in frequency produces no meaningful increase in minute ventilation).[5] However, alveolar minute ventilation behaves differently. Alveolar ventilation is a function of V_T and dead space. If dead space remains relatively constant,[6,7] then as frequency increases and V_T decreases, the alveolar minute ventilation will increase and then decrease,[3] thus showing a local maximum value. We termed the frequency at which alveolar ventilation is maximal the optimum frequency.

In our preliminary studies, the optimum frequency was higher and resulted in lower V_T than conventional modes for the same level of ventilation. However, the optimum frequency was not as high as that produced by specialized high-frequency ventilators (high-frequency jet ventilators and high-frequency oscillatory ventilators); hence, we named this new mode mid-frequency ventilation. Moreover, because this is a pressure control mode at a constant I:E, the peak inspiratory pressure and mean airway pressure remain constant as frequency changes.[3,5,8,9] These findings are of particular clinical relevance, as the current practice is to limit ventilatory frequency to prevent the ill effects of auto-PEEP on hemodynamics and gas exchange.[10,11] However, mathematical models and physical lung simulators do not reflect the complex mechanics of real lung-ventilator systems, nor do they reflect the effects of mechanical ventilation on hemodynamics. Therefore, this study was designed to compare the effects of conventional mechanical ventilation using a lung-protective strategy with MFV in a porcine model. Our hypothesis was that MFV results in the benefits predicted by our previous studies without adverse consequences. Specifically, we sought to compare ventilatory parameters, hemodynamic parameters, and blood gas values between conventional ventilation and MFV.

QUICK LOOK

Current knowledge

Mid-frequency ventilation (MFV) is a pressure control method of mechanical ventilation that allows the delivery of small tidal volumes (V_T) and rapid breathing frequencies with conventional mechanical ventilators. No animal or human trials have been accomplished to date.

What this paper contributes to our knowledge

In a paralyzed porcine pediatric model of acute respiratory failure, MFV allowed the use of higher breathing frequencies and lower V_T than conventional ventilation to maximize alveolar ventilation over a short period of observation. Hemodynamic consequences were similar, although animals treated with MFV experienced a 40% increase in heart rate.

Methods

The Institutional Animal Care and Use Committee of the Arkansas Children's Hospital Research Institute approved this study. All research was conducted at the Applied Respiratory Physiology Laboratory, Arkansas Children's Hospital, and the University of Arkansas for Medical Sciences, Little Rock, Arkansas. The study was designed to demonstrate that maximizing alveolar ventilation and minimizing V_T are achievable in a model of acute lung injury using a MFV algorithm to identify optimum settings. We compared conventional lung-protective ventilation at stable baseline settings to MFV at optimum settings.

Animal Model Preparation

Two-week-old male Yorkshire pigs had constant intravenous anesthesia, analgesia, and neuromuscular blockade with fentanyl (5 μg/kg/h), propofol (3 mg/kg/h), and vecuronium (0.3–0.7 mg/kg/h). A lactated Ringer solution (10 mL/kg bolus, repeated twice if needed to stabilize vital signs) was given at initiation of the study, followed by a maintenance infusion of 4 mL/kg/h. The left internal jugular was cannulated with a 5 French triple-lumen catheter

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(Cook Medical, Bloomington, Indiana). The left carotid was cannulated with a 4–5 French single-lumen catheter (Cook Medical). The pulmonary artery was cannulated via the right internal jugular with a pulmonary artery catheter (4 French thermodilution balloon catheter, Arrow International, Reading, Pennsylvania). Animals were intubated with a cuffed endotracheal tube (5.0–6.0-mm inner diameter). The cuff was inflated to a minimum occlusion pressure.[12] Mechanical ventilation was delivered with a Servo-i ventilator (Maquet, Wayne, New Jersey) with a heated wire circuit (RS240, Fisher & Paykel Healthcare, Auckland, New Zealand) and a heated humidifier (MR290 humidification system, Fisher & Paykel Healthcare). An expiratory carbon dioxide monitor used to measure end-tidal carbon dioxide (Maquet) was placed at the proximal end of the endotracheal tube.

Experimental Protocol

Lung Injury. After the pig had stabilized, the lungs were lavaged in the supine and alternating lateral decubitus positions with 3 aliquots (30 mL/kg) of isotonic saline at 38°C. Injurious ventilatory settings (V_T = 20 mL/kg and zero PEEP) were maintained for 30-min intervals until lung compliance (after a recruitment maneuver) was ~50% from baseline.

Baseline Conventional Ventilation. All animals were ventilated with pressure control CMV. Inspiratory rise time was set at 0 ms. The inspiratory pressure above PEEP was set to deliver a V_T of 6 mL/kg. The I:E was 1:1. The baseline ventilatory frequency was adjusted to achieve a P_{aCO_2} of 40 ± 5 mm Hg, but was kept below 35 breaths/min. Set PEEP was based on the trend of volumetric carbon dioxide and dynamic characteristic using the Open Lung Tool function of the Servo-i ventilator.[13] The maneuver to set PEEP was a recruitment phase, followed by a decremental PEEP phase. The recruitment phase started with a stepwise increase of PEEP to 12–14 cm H_2O (increments of 2 cm H_2O) and increasing inspiratory pressure (above PEEP) in steps of 2 cm H_2O while monitoring volumetric tidal carbon dioxide elimination and dynamic characteristic in a graphic display. The point where the volumetric carbon dioxide elimination peaked or reached a plateau was considered to be the point of maximum recruitment. Then, the V_T was decreased to baseline (6 mL/kg) by decreasing the inspiratory pressure. We proceeded to the decremental PEEP phase, where PEEP was lowered by 1 cm H_2O every 4–6 breaths until dynamic characteristic decreased (interpreted as alveolar collapse). At that point, a recruitment phase was repeated, and the PEEP level was set at 2 cm H_2O above the previously identified point of alveolar collapse. This maneuver was repeated after each ventilator disconnection or de-recruitment event.

The settings were maintained for 20 min before obtaining measurements and proceeding to the next study phase. The F_{IO_2} was 1.0 and was not changed through the experiment. Once hemodynamic stability was achieved, the settings were maintained for 60 min before obtaining measurements and proceeding to MFV.

MFV Ventilation Using a Decision Support Algorithm. MFV was managed with an explicit algorithm (Fig. 1). MFV was implemented as pressure control CMV with a conventional ventilator (Servo-i). The algorithm advises manual adjustment of ventilatory frequency, I:E, inspiratory pressure, and PEEP following the MFV strategy. Each step in the algorithm was dictated by the response in alveolar ventilation (assessed in terms of P_{aCO_2}) to a ventilatory change. The target P_{aCO_2} was 40 ± 2 mm Hg. Arterial blood gases were drawn 10 min after each ventilatory change, and this dictated the next change in settings. Optimum settings were reached when a step repeated itself in the algorithm (same instruction after a change). This resulted in a set of frequency, I:E, and airway pressures that were considered to be optimized. The optimum settings were then continued for 60 min. Measurements were obtained at the end of the 60 min on optimum MFV settings.

Measurements. The respiratory system characteristics (resistance and compliance) were obtained by quasi-static pressure-volume curves and the forced oscillation technique (flexiVent, Scireq, Montreal, Canada) before and after lung injury.[14]

The ventilatory output (V_T, airway pressures relative to atmospheric pressure, breathing frequency, resistance and compliance calculations, and end-tidal carbon dioxide) was continuously recorded and downloaded to a removable memory card in the Servo-i. End-expiratory airway pressure was continuously measured and recorded. The level of auto-PEEP was measured after a 2-s expiratory pause and recorded from the monitor.

Hemodynamic measurements, including heart rate, systemic, venous and pulmonary artery pressures, pulse rate, and core temperature (pulmonary artery catheter), were continuously recorded via a physiologic monitor (SC 9000X, Siemens, Berlin, Germany). Cardiac output was determined by averaging 3 measurements obtained after the injection of 3 mL of iced isotonic solution through the proximal port of the pulmonary artery catheter. Arterial blood gases were obtained with a minimum blood draw technique and analyzed with an i-STAT analyzer (Abbot, Princeton Point of Care, New Jersey).

Statistical Analysis

Summary statistics (eg, mean ± SD) at postinjury baseline were estimated for ventilation, hemodynamic, and

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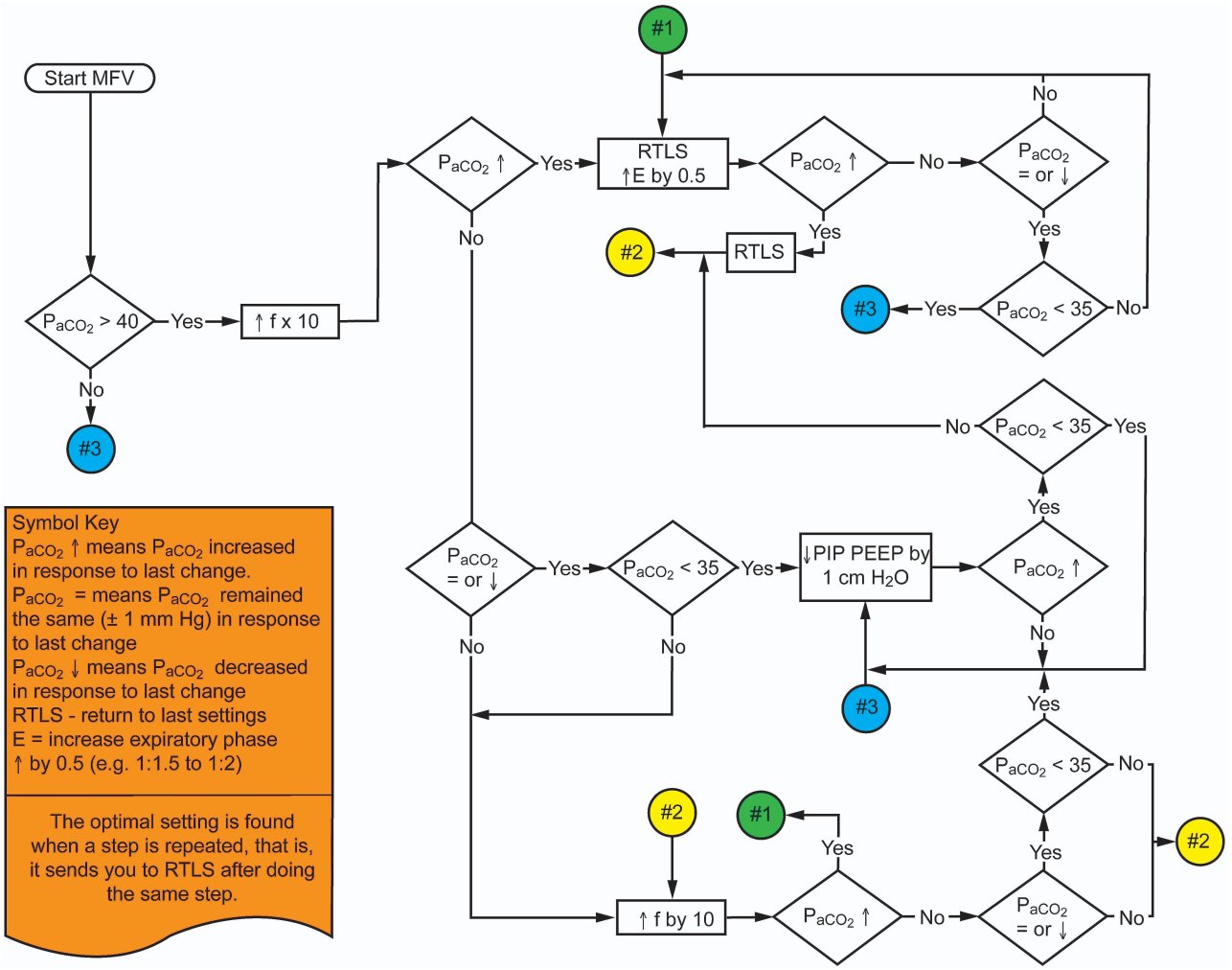

Fig. 1. Mid-frequency ventilation (MFV) representative management algorithm. The process starts with increasing frequency. The response assessed for each step is the change in P_{aCO_2}. The change in P_{aCO_2} dictates the next step. Predefined goals for each step are followed. The optimum setting is found once a step is repeated, ie, one reaches return to last setting (RTLS) after repeating a step. ↑ E = increase in expiratory phase by 0.5; PIP = peak inspiratory pressure; f = frequency (breaths/min).

blood gas values. Change was calculated for each variable as values at optimum frequency minus values at baseline. Significant change was evaluated using Wilcoxon signed-rank tests for paired observations, or a regression model adjusting for baseline measures was used to determine whether a statistically significant change existed between ventilation groups. Additionally, a repeated-measures analysis was conducted to assess change over time in ventilation, hemodynamic, and blood gas values between MFV and conventional mechanical ventilation groups. Regression models assessed change in outcomes between groups accounting for time elapsed (in min) since the postinjury baseline as well as repeated measures on each animal. All analysis was completed using Stata 12.0 (StataCorp, College Station, Texas).

Results

Six 2-week-old male Yorkshire pigs (mean weight 10 ± 0.5 kg) were studied. After induction of lung injury, the lung static compliance dropped from 21.4 ± 2.9 to 12.9 ± 3.7 mL/cm H_2O.

Table 1 presents a representative progression of a study animal through the protocol. During CMV, the inspiratory pressure had to be adjusted to maintain a V_T of 6 mL/kg. At the initiation of MFV (ie, end of 1 h of CMV), the P_{aCO_2} was elevated to 50.2 ± 8.5 mm Hg. The rate was adjusted (to a maximum rate of 35 bpm) before initiation of the MFV protocol to achieve the target P_{aCO_2}. It took an average of 6.8 (range 3−10) steps (Table 1, values indicated by §) in the MFV algorithm to achieve the optimum MFV

Table 1. Representative Progression of a Study Animal Through the MFV Protocol

Time From Last Step*	Study Phase	Ventilatory Settings					Ventilatory Outcomes				
		Breathing Frequency (breaths/min)	I:E	T_I (s)	Set PIP (cm H_2O)	Set PEEP (cm H_2O)	V_T (mL/kg)	P_{aCO_2} (mm Hg)	ET_{CO_2} (mm Hg)	MV (L/min)	Mean Airway Pressure (cm H_2O)
0 min	Healthy baseline†	25	1:1	1.18	11	5	6.5	42.5	55	1.58	8
60 min	Baseline after lung injury	20	1:1	1.47	16	10	6.3	41.7	41	1.24	14
60 min	CV after 1 h	20	1:1	1.47	17–22‡	10	5.7	63.5	59	1.1	15
20 min	MFV at start	35	1:1	0.86	22	10	5.7	46.9	47	1.9	15
14 min	MFV algorithm step	45§	1:1	0.67	22	10	6.1	38.8	38	2.6	15
14 min	MFV algorithm step	55§	1:1	0.55	22	10	5.6	36.9	37	3.1	15
14 min	MFV algorithm step	65§	1:1	0.47	22	10	5.3	35.2	36	3.31	15
14 min	MFV algorithm step	75§	1:1	0.4	22	10¶	4¶	46.5	45	2.79	16
14 min	MFV algorithm step	65§	1:1.5§	0.37	22	11	4.8	41	37	3.1	16
14 min	MFV algorithm step	65	1:2§	0.31	23	11	5	40.9	37	3.1	15
14 min	MFV algorithm step	65‖	1:2.5§	0.26‖	22‖	11‖	4.6‖	38.2‖	37‖	3.09‖	14‖
14 min	MFV algorithm step	65	1:3§	0.23	22	11	4.5	42.9	40	2.76	14
14 min	MFV algorithm step	75§	1:2.5§	0.23	22	11	3.9	44.5	43	3	14
NA	Start of Optimum settings	65	1:2.5	0.26	22	11	NA	NA	NA	NA	NA
60 min	1 h after optimum MFV	65	1:2.5	0.26	22	11	4.3	49.2	44	2.44	14

Pig weight was 9.2 kg.
* Approximate times
† Ventilator settings before lung injury were PEEP 5 cm H_2O and F_{IO_2} 0.3.
‡ Inspiratory pressure was adjusted during conventional ventilation to maintain the tidal volume (V_T) at target.
§ Changes in ventilatory settings according to the algorithm in response to P_{aCO_2} levels.
‖ Optimum settings for mid-frequency ventilation (MFV) protocol.
¶ Rate-related de-recruitment
I:E = inspiratory-expiratory ratio
T_I = inspiratory time
PIP = peak inspiratory pressure above atmospheric pressure
ET_{CO_2} = end-tidal carbon dioxide
MV = minute ventilation (exhaled)
CV = conventional ventilation
NA = not applicable

settings (values indicated by ‖). The ¶ symbols highlight events where, after a frequency increase, there is a sudden drop in V_T (beyond what was expected). We termed these events rate-related de-recruitment. They happened mainly at higher than optimum rates. From our previous experience, these are controlled with a recruitment maneuver and an increase of PEEP (see the rise of 1 cm H_2O on the set PEEP in Table 1).

Table 2 summarizes the ventilation and hemodynamic outcomes. The optimum frequency was 24 breaths/min above conventional lung-protective ventilation (55.7 vs 32.1 breaths/min, $P = .035$), which resulted in a 1 mL/kg reduction in V_T, and the P_{aCO_2} was lower than at baseline. After 1 h of ventilation with the optimum MFV settings (where no changes were made), the P_{aCO_2} was higher than baseline conventional ventilation, but the difference was not statistically significant. The mean and peak airway pressures remained constant, whereas the total PEEP increased. The auto-PEEP measured after an expiratory pause was 1.4 cm H_2O higher on MFV (0.6 vs 2.4, $P = .02$). There was an increase in airway PEEP of ~1 cm H_2O due to the decrease in expiratory time. There was no statistically significant hemodynamic change when comparing MFV and conventional lung-protective ventilation. However, the heart rate was higher upon achieving the optimum MFV settings, and, although it decreased, it remained higher after 1 h of MFV.

We evaluated the change in hemodynamic and ventilation variables between the beginning of optimum MFV settings and after 1 h (see Table 3). There was a nonsignificant reduction in V_T; associated with a nonsignificant increase in P_{aCO_2}. Lactate values decreased by 0.2 mg/dL.

Discussion

The main finding of our study is that MFV allows the use of a higher breathing frequency and lower V_T than conventional lung-protective ventilation. These results are consistent with our previous theoretical work.[2,3] We demonstrated that a simple manual algorithm allowed implementation of MFV with a conventional ventilator.

MFV allows the delivery of ventilation at a range of frequencies that are above what clinicians typically use. Conventional practice limits frequency due to concerns

Table 2. Differences of Ventilation and Hemodynamic Outcomes Between Conventional Ventilation and Optimum Settings Using the MFV Algorithm

	Conventional Ventilation (mean ± SD)	Optimum MFV (mean ± SD)*	Change (mean ± SD)	P†
Ventilation				
Ventilatory frequency (breaths/min)	32.1 ± 6.8	55.7 ± 15.8	23.7 ± 17.6	.035
V_T (mL/kg)	6.1 ± 0.5	5.2 ± 0.8	−1.0 ± 0.7	.046
MV (L/min)	1.9 ± 0.4	2.8 ± 1.0	0.9 ± 1.1	.17
PIP (cm H_2O)	23.1 ± 2.0	25.8 ± 4.8	2.7 ± 3.7	.17
$\bar{P}_{aw}$ (cm H_2O)	16.1 ± 1.3	16.4 ± 2.0	0.2 ± 1.6	.75
Auto-PEEP (cm H_2O)	0.6 ± 0.9	2.4 ± 1.1	1.8 ± 0.5	.02
PEEP (cm H_2O)	9.2 ± 0.5	10.6 ± 1.2	1.5 ± 1.3	.03
Hemodynamics				P†
Heart rate (beats/min)	112.6 ± 37.1	158.9 ± 55.2	46.3 ± 62.8	.34
Mean arterial pressure (mm Hg)	88.9 ± 10.7	86.9 ± 30.7	−2.0 ± 24.7	.76
Mean pulmonary artery pressure (mm Hg)	29.3 ± 6.6	29.7 ± 6.8	0.4 ± 7.5	.28
Central venous pressure (mm Hg)	5.8 ± 3.2	5.2 ± 2.6	−0.6 ± 1.3	.03
Pulmonary artery occlusion pressure (mm Hg)	6.0 ± 2.9	5.2 ± 3.3	−0.8 ± 0.4	.80
Cardiac output (L/min)	1.4 ± 0.7	1.5 ± 0.4	0.1 ± 0.5	.65
Blood analysis				
pH	7.33 ± 0.05	7.32 ± 0.11	0.00 ± 0.13	.24
P_{aCO_2} (mm Hg)	50.2 ± 8.5	51.7 ± 17.4	1.6 ± 16.4	.47
P_{aO_2} (mm Hg)	398.3 ± 117.4	404.2 ± 85.9	5.8 ± 130.7	.35
HCO_3 (mEq/L)	26.1 ± 4.9	25.7 ± 2.7	−0.5 ± 4.7	.64
Lactate (mg/dL)	0.9 ± 0.6	0.5 ± 0.2	−0.4 ± 0.6	.20
$S_{\bar{v}O_2}$ (%)	78.7 ± 8.9	78.7 ± 7.2	0.0 ± 8.0	.45
Hemoglobin (g/dL)	7.8 ± 1.0	7.4 ± 0.8	−0.2 ± 1.4	.59

* Results after 1 h of mid-frequency ventilation (MFV).
† Results for ventilation outcomes from Wilcoxon signed-rank test for paired observations; results for hemodynamics and blood analysis from regression adjusting for baseline.
V_T = tidal volume
MV = minute ventilation
PIP = peak inspiratory pressure (above atmospheric pressure)
$\bar{P}_{aw}$ = mean airway pressure
$S_{\bar{v}O_2}$ = mixed venous oxygen saturation

about the development of auto-PEEP and its adverse hemodynamic effects.[10,15,16] However, MFV is different from conventional CMV with regard to the development of frequency-related auto-PEEP. In conventional ventilation, when keeping all variables constant and increasing frequency, auto-PEEP rises exponentially to very high values, but only slightly in MFV. In a similar fashion, mean airway pressure rises exponentially to very high values for conventional ventilation, but does not change with frequency for MFV (Fig. 2, unpublished simulator data). This is why conventional ventilation is limited to relatively low frequencies (due to the hemodynamic consequences of auto-PEEP and mean airway pressure), whereas MFV can use a wider range of frequencies.

In this context, MFV allows the exploration of all ranges of ventilatory frequencies. The current paradigm limits ventilation to frequencies below 35 breaths/min in adults and 60 breaths/min in infants using conventional modes.[11,17-21] Indeed, this recommendation makes sense when maintaining a relatively constant V_T.[15,22] However, our study demonstrates that the MFV strategy allows the clinician to provide higher frequencies. More importantly, our data are in keeping with data generated from neonatal studies in which conventional ventilation applied at higher breathing frequencies with pressure control ventilation (similar to MFV) led to improved ventilation outcomes.[23,24]

Our study demonstrated an increase in heart rate during the application of MFV, which, although not statistically significant, raises the concern for a decrease in stroke volume. Given the lower central venous pressure, stable airway, and pulmonary pressures, we suspect the cause was hypovolemia (decreasing central venous pressure through the study). Nonetheless, it is possible that the hemodynamic monitoring did not detect or was not capable of detecting a difference.

Our study also adds a description of the rate-related de-recruitment. This event develops mainly at higher ventilatory frequencies, although it can happen at lower frequencies (but still > 35 breaths/min) in the presence of lung injury. We speculate the rate-related de-recruitment is

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Table 3. Differences of Ventilation and Hemodynamic Outcomes Between Mid-Frequency Ventilation at Optimal Settings and After 1 h

	Initial Optimal Settings (mean ± SD)	After 1 h (mean ± SD)	Change (mean ± SD)	P*
Ventilation				
V_T (mL/kg)	5.5 ± 0.7	5.2 ± 0.8	0.4 ± 0.7	.17
MV (L/min)	3.0 ± 0.7	2.8 ± 1.0	0.2 ± 0.4	.25
PIP (cm H_2O)	26.0 ± 4.8	25.8 ± 4.8	0.2 ± 1.1	.35
$\bar{P}_{aw}$ (cm H_2O)	16.2 ± 2.2	16.4 ± 2.0	−0.1 ± 0.5	.60
PEEP (cm H_2O)	10.7 ± 1.3	10.6 ± 1.2	0.0 ± 0.5	.60
Hemodynamics				
Heart rate (beats/min)	176.5 ± 55.3	158.9 ± 55.2	17.6 ± 26.6	.25
Mean arterial pressure (mm Hg)	86.2 ± 11.5	86.9 ± 30.7	−0.7 ± 21.1	.60
Mean pulmonary artery pressure (mm Hg)	29.0 ± 5.0	29.7 ± 6.8	−0.7 ± 2.9	.46
Central venous pressure (mm Hg)	5.6 ± 3.2	5.2 ± 2.6	0.3 ± 1.5	> .99
Blood analysis				
pH	7.38 ± 0.05	7.32 ± 0.11	0.05 ± 0.07	.12
P_{CO_2} (mm Hg)	46.2 ± 7.8	51.7 ± 17.4	−5.6 ± 11.0	.17
P_{O_2} (mm Hg)	426.2 ± 81.2	404.2 ± 85.9	22.0 ± 67.7	.35
HCO_3 (mEq/L)	27.0 ± 2.6	25.7 ± 2.7	1.3 ± 2.7	.35
Lactate (mg/dL)	0.7 ± 0.2	0.5 ± 0.2	0.2 ± 0.2	.046

* Results from Wilcoxon signed-rank test for paired observations.
V_T = tidal volume
MV = minute ventilation
PIP = peak inspiratory pressure (above atmospheric pressure)
$\bar{P}_{aw}$ = mean airway pressure.

a manifestation of inappropriate PEEP and cyclic recruitment by V_T. During a tidal breath (more so with an inappropriately low PEEP), lung recruitment occurs throughout the inspiratory time.[25-27] In MFV, as frequency increases, inspiratory time and V_T decrease. Thus, ongoing cyclic recruitment may be lost despite an unchanging mean airway pressure and the presence of auto-PEEP. At some point, the gradual de-recruitment reaches a threshold below which a cascade of lung collapse occurs. The sudden de-recruitment further decreases V_T, leading to more lung collapse. The concept is similar to what may happen with high-frequency oscillatory ventilation, where a de-recruitment event manifests as loss in ventilation.[28] Recruitment and PEEP always lead to its resolution. Perhaps at higher frequencies, there needs to be a prophylactic increase in PEEP. However, this is only a hypothesis, which requires further testing.

A concern regarding ventilation at higher frequencies is the potential increase in lung injury due to repeated exposure to injurious ventilatory cycles. This has been examined in several studies[29-31] most recently by Vaporidi et al.[32] They demonstrated a correlation with lung injury in a mouse model. However and most importantly, they also concluded that the injury was prevented with a concomitant decrease in V_T.[29,30] In support of this, Conrad et al[30] found that, at a normal V_T (5 mL/kg) versus a high (20 mL/kg) V_T, the cyclic stretch did not induce injury across a range of breathing frequencies.

Our study has several limitations. Our pig model of lung injury may not be a clinical representation of lung injury. Furthermore, it is a known model, which may improve with time.[33] However, V_T and lung compliance remained stable through the study, suggesting no improvement in the lung conditions. Although the P_{aO_2}/F_{IO_2} argues against the presence of lung injury, we did postmortem histological evaluation of the lungs (for control), and all had evidence of lung injury. Further studies should focus on evaluation of cytokines, comparative histological damage, and effect of time on MFV. Furthermore, the V_T in pigs required for lung protection is not necessarily the 6 mL/kg/ideal body weight we use in humans.[34] However, we wanted to replicate the conditions seen in current practice and evaluate the effects of MFV on hemodynamics and ventilation rather than on lung injury. Another limitation (or rather aberration) is that our pigs demonstrated higher than expected pulmonary pressures.[35,36] We repeatedly revised the systems and calibrated the system before each study. We found that the pulmonary artery catheter flush system caused a rise in pressure due to the constant flow of flush solution and the small diameter of the catheter lumen. We believe that this did not affect our results, as the artifact was present throughout the experiment, and the waveforms changed appropriately with clinical condition. Finally, the algorithm used P_{aCO_2} to direct management of MFV. Although this may not seem clinically feasible, this was a pilot trial. We envision that MFV would

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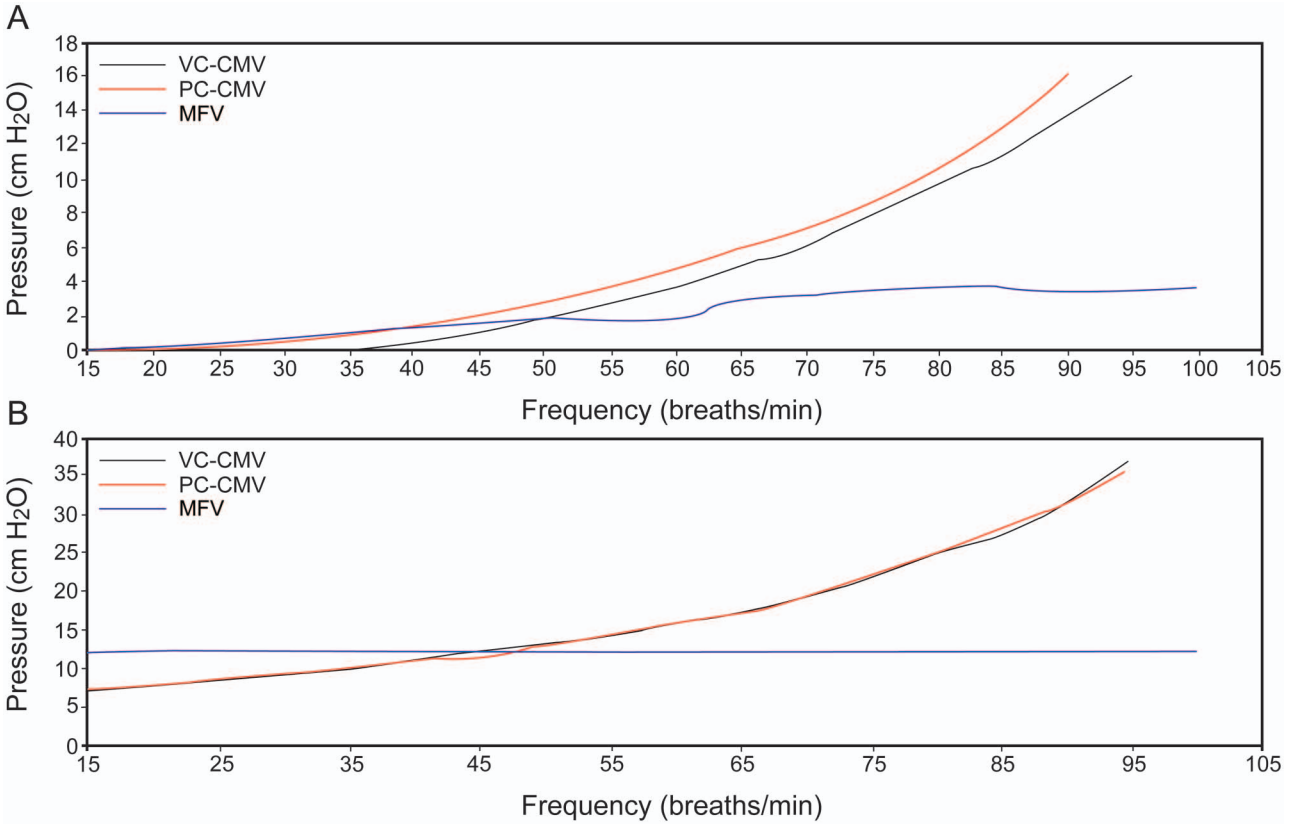

Fig. 2. Difference between mid-frequency ventilation (MFV), volume control continuous mandatory ventilation (VC-CMV), and pressure control CMV (PC-CMV) when frequency is increased. The figure shows a graphical representation of the results of a physical lung simulator (ASL 5000, IngMar Medical, Pittsburgh, Pennsylvania) ventilated at increasing frequency with volume control CMV, pressure control CMV, and MFV. For all modes, the frequency was increased (with all other settings held constant) from 15 to 90 breaths/min. A: auto-PEEP. B: mean airway pressure.

be programmed into the ventilator to drive an optimal targeting scheme.[1] Other signals, such as end-tidal carbon dioxide or transcutaneous signals, could be used to give feedback on minute ventilation. From the practical standpoint, all this can be accomplished within the current constraint imposed by the Food and Drug Administration of maximum conventional ventilatory frequency of 150 breaths/min. MFV opens a range of capabilities for current critical care ventilators without the need for specialized equipment.

Our results must be interpreted with caution. The development of a mode of mechanical ventilation needs to move from the theoretical background to animal application to technological development and clinical application. These steps are essential for understanding what the mode does. We have developed the theoretical background in other studies; the goal of this study was to assess feasibility and hemodynamic effects in vivo. There are several other areas to assess. We have not evaluated the application of MFV in the presence of spontaneous breathing. As this is a pressure control mode, spontaneous breaths could cause larger V_T, asynchrony, and higher auto-PEEP. We need to assess other algorithms, feedback loops, and effects on lung injury. Further research needs to be performed on MFV as a ventilatory mode before it can be applied clinically.

Conclusions

In this pilot study, we demonstrated that MFV allows the use of higher breathing frequencies and lower V_T than conventional ventilation. We described the effects on gas exchange, airway pressures, and potential issues with derecruitment. We also demonstrated the feasibility of a decision support algorithm to manage MFV.

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