Airway pressure and transpulmonary pressure during high-frequency oscillation for acute respiratory distress syndrome

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BACKGROUND: High-frequency oscillation (HFO) is used for the treatment of refractory hypoxic respiratory failure.
OBJECTIVE: To demonstrate that the mean transpulmonary pressure (P_L) cannot be inferred from mean airway pressure (mPaw).
METHODS: In seven patients already undergoing HFO for refractory acute respiratory distress syndrome, esophageal pressure (Pes) was measured using an esophageal balloon catheter. Pleural pressure (Ppl) and P_L were calculated from Pes.
MAIN RESULTS: In the seven patients (mean [± SD] age 59±9 years) treated with HFO at 5±1 Hz and amplitude 75±10 cmH_2O, the mPaw was 27±6 cmH_2O, Ppl was 9±6 cmH_2O and P_L was 18±11 cmH_2O. Successful catheter placement and measurement of Pes occurred in 100% of subjects. There was no correlation between P_L and mPaw. The majority of subjects required hemodynamic support during the use of HFO; the frequency and degree of support during the study period was no different than that before the study.
CONCLUSION: The present report is the first to describe measuring Pes and calculating Ppl during HFO for acute respiratory distress syndrome. While both current guidelines and recent trials have titrated treatment based on mPaw and oxygenation, there is wide variability in P_L during HFO and P_L cannot be predicted from mPaw.

Key words: *Adult; Critical care; High-frequency oscillation; Lung; Mechanical ventilation; Pneumonia*

La pression des voies aériennes et la pression transpulmonaire pendant l'oscillation à haute fréquence pour soigner le syndrome de détresse respiratoire aiguë

HISTORIQUE : L'oscillation à haute fréquence (OHF) est utilisée pour traiter l'insuffisance respiratoire hypoxique réfractaire.
OBJECTIF : Démontrer qu'on ne peut pas inférer la pression transpulmonaire moyenne (Pm) à partir la pression moyenne des voies aériennes (Pmva).
MÉTHODOLOGIE : Chez sept patients qui subissent déjà une OHF en raison d'un syndrome de détresse respiratoire aiguë réfractaire, la pression œsophagienne (Pœ) a été mesurée à l'aide d'un cathéter à ballonnet œsophagien. La pression pleurale (Ppl) et la Pm ont été calculées à partir de la Pœ.
PRINCIPAUX RÉSULTATS : Chez les sept patients (moyenne [±ÉT] de 59±9 ans)traités par OHF à 5±1 Hz et à une amplitude de 75±10 cm d'eau, la Pmva s'élevait à 27±6 cm d'eau, la Pplà 9±6 cm d'eau et la TP à 18±11 cm d'eau. On a pu installer le cathéter et mesurer la Pœ chez 100 % des sujets. Il n'y avait pas de corrélation entre la Pmet la Pmva. La majorité des sujets avaient besoin d'un soutien hémodynamique pendant l'utilisation de l'OHF. La fréquence et le degré de soutien pendant la période de l'étude ne différaient pas d'avant l'étude.
CONCLUSION : Le présent rapport est le premier à décrire la mesure de la Pœ et le calcul de la Ppl pendant une OHF pour soigner un syndrome de détresse respiratoire aiguë. Bien que, selon les lignes directrices actuelles et dans les récents essais, le traitement était titré d'après la Pmva et l'oxygénation, on constate une grande variabilité de la Pm pendant l'OHF, et on ne peut prédire la Pm à partir de la Pmva.

Hypoxic respiratory failure and acute respiratory distress syndrome (ARDS) are common reasons for mechanical ventilation in critically ill patients. Although causation varies, ARDS is currently defined as severe hypoxia (partial pressure of oxygen [PaO_2]/fraction of inspired oxygen [FiO_2] ratio <300) within one week of a known clinical insult, new or worsening hypoxia not due to left heart failure, and bilateral opacifications on chest x-ray (1).

Recent advances in clinical practice have focused on minimizing ventilator-induced lung injury (VILI) by minimizing tidal volume (V_T) and alveolar pressure (P_A). The ARDS Network trial of low V_T ventilation demonstrated that V_T <6 mL/kg and end-inspiratory plateau airway pressure (Pplat) <30 cmH_2O may decrease absolute mortality by almost 9% (2).

High-frequency oscillation (HFO) is a novel form of ventilation that is increasingly used for the treatment of refractory hypoxic respiratory failure resulting from acute lung injury or ARDS, and provides many of the benefits of lung-protective ventilation gained with a low V_T strategy (3). HFO delivers V_T as little as 23 mL to 225 mL (often smaller than dead space) using higher mean airway pressure (mPaw) than conventional mechanical ventilation (CMV) and frequencies from 3 Hz to 10 Hz (4). Although some investigators have attempted to infer appropriate mPaw during HFO from analysis of pressure-volume curves (5), this analysis rarely occurs in clinical practice. Rather, mPaw is determined empirically, usually by setting it at 3 cmH_2O to 5 cmH_2O higher than the mPaw generated during CMV. Despite the known lack of relationship between airway pressure (Paw) and transpulmonary pressure (P_L) during CMV, no attempts have been made to determine P_L during HFO. In fact, current guidelines and two recent large clinical trials of HFO titrate ventilator management to mPaw rather than P_L (6-8). The goal of the present study was to demonstrate the feasibility of esophageal manometer placement during HFO and to obtain measurements of esophageal pressure (Pes), thereby estimating pleural pressure (Ppl) and P_L. Based on the known lack of relationship between mPaw and P_L during CMV, we hypothesized that P_L could not be predicted from mPaw during HFO.

METHODS

Subjects

All experimental procedures and protocols were approved by the Clinical Research Ethics Board at the University of British Columbia and Vancouver General Hospital (Vancouver, British Columbia). The trial was prospectively registered at ClinicalTrials.gov as NCT01321398.

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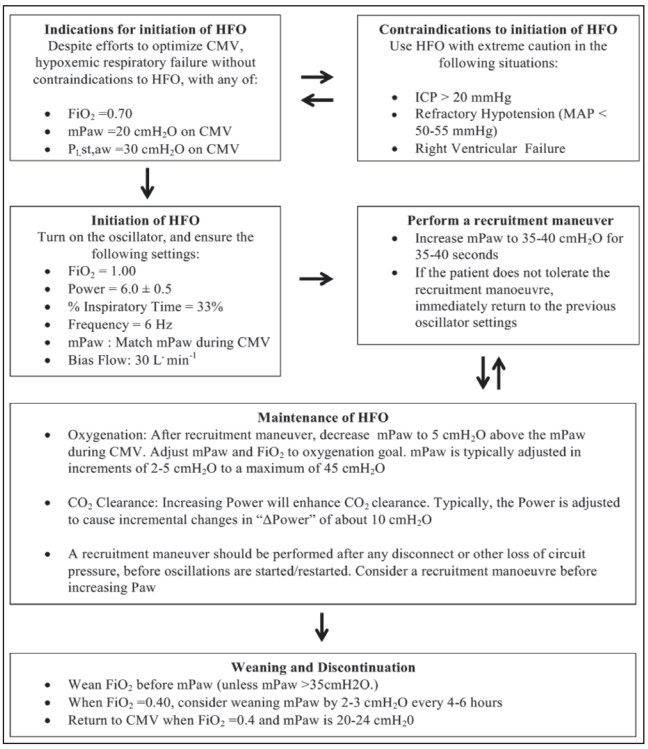

Figure 1) *Clinical practice algorithm used to initiate and manage high-frequency oscillation (HFO) during observational period. CMV Conventional mechanical ventilation; ICP Intracranial pressure; FiO_2 Fraction of inspired oxygen; MAP Mean arterial pressure; mPaw Mean airway pressure; P_L Transpulmonary pressure*

Patients were considered for the clinical use of HFO if they exhibited hypoxia, high mPaw or high Pplat refractory to optimized CMV and had no contraindications to HFO. Clinical management of HFO followed an explicit algorithm that prescribed mPaw adjustments, FiO_2 adjustments and recruitment manoeuvres (Figure 1). All patients undergoing HFO between October 2010 and July 2011 were considered for the study and were included (n=7) if they were receiving HFO for severe hypoxic respiratory failure or ARDS and were ≥19 years of age. Patients receiving HFO were excluded from the present observational study if they had esophageal lesions, or had undergone esophageal surgery within the previous six months or experienced unstable cervical spine or cervical spinal cord injury. Informed written consent was obtained from the surrogate decision makers of all patients before the investigations. On average, the experimental data were recorded six days after the initiation of mechanical ventilation and two days after the initiation of HFO. Demographic and clinical information including age, cause of the acute lung injury, Acute Physiology and Chronic Health Evaluation (APACHE) II score, mean arterial blood pressure, central venous pressure, vasopressor dosing and pulmonary variables relevant to HFO such as bias flow, frequency, pressure amplitude as well as measured pressures (mPaw, Pes, Ppl and P_L), were recorded.

Experimental protocol

All patients were ventilated using an adult HFO ventilator (Model 3100B, SensorMedics, USA). Patients were evaluated while supine. In all patients, an esophageal balloon catheter (No. 47-9005, Ackrad Laboratory, USA) was placed through the mouth into the esophagus to measure Pes. Catheter placement was performed by a study physician according to an adaptation of a previously detailed method (9) and was confirmed using a bedside chest radiograph. Positioning could not be assessed by traditional methods due to the ventilator mode and the patients' need for sedation. Positioning was considered to be correct when the tip of the catheter was visualized in the middle one-third

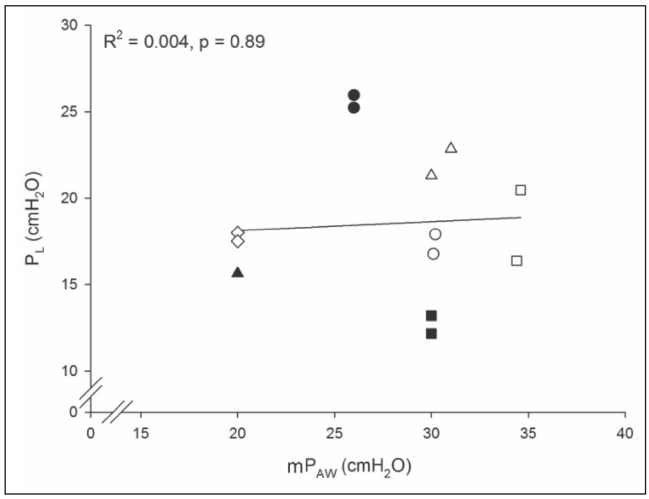

Figure 2) *Relationship between transpulmonary pressure (P_L) and mean airway pressure (mPaw). Hollow and solid circles, squares, diamonds and triangles are the observed pressures for individual patients at two time points. The single black triangle represents measurements at the two times points with identical values. The hollow diamonds represent the patient with hypoxia after lung transplantation. The solid line represents the values predicted by linear regression analysis. R^2 is the percent of variation of P_L that is predicted by mPaw*

of the distance from the thoracic inlet to the diaphragm. After placement was confirmed, air was evacuated from the balloon with a syringe and 1 mL of air was injected to partially inflate the balloon. Paw was obtained using a port at the side of the endotracheal tube connected to a differential transducer. Both pressures were measured using a calibrated piezoelectric pressure transducer (Raytech Instruments, Canada). All data were recorded continuously at 1000 Hz using a 16-channel analogue-to-digital data acquisition system (PowerLab/16SP model ML 795, ADI, USA) and stored on a computer for subsequent analysis (LabChart version 7.1.3, ADInstruments, USA). Both Paw measurements and Ppl estimates were recorded for 30 s after 1 min without spontaneous breathing or patient care-related movement. The arithmetic mean value of Paw and Ppl values for this 30 s period were used in the calculations. These measurements were repeated on the same day, 5 min after the original measurements. Pes was assumed to overestimate Ppl by 5 cmH_2O based on previously published estimates (10). The P_L was calculated as the difference between mean Ppl and mPaw.

Data analysis

Data analysis was performed using Stata release 10 (StataCorp, USA). Linear regression was used to model the association between P_L and mPaw (Figure 2), as well as the association of P_L with central venous pressure and vasopressor dose. To account for the within-subject correlation, linear regression was performed on the mean P_L and mPaw measurements. Statistical significance was defined at $P \leq 0.05$.

RESULTS

The seven patients included in the study had ARDS secondary to pneumonia (n=6) or acute complications of lung transplantation (n=1) (Table 1). Two patients were co-enrolled in the Oscillation for ARDS Treated Early (OSCILLATE) trial (7). Before the study, the mean duration of HFO was one-half the mean duration of mechanical ventilation (Table 1). Severity of respiratory failure was confirmed with arterial blood gas values (Table 1). Two patients died in the intensive care unit and five patients survived to discharge from hospital. During the assessment period, the average mean arterial pressure was 79±10.6 mmHg, the average central venous pressure was 12±3.6 cmH_2O and four subjects required blood pressure support with intravenous

norepinephrine (average dose 11.3±8.9 μg/min). Esophageal balloon placement and measurements of Pes were achieved without complication in all seven patients. No patients underwent chemical paralysis immediately before or during the measurement period. The measurements provided mean values of Paw, Pes, estimated Ppl and calculated P_L (Table 1). P_L ranged from 12.2 cmH_2O to 25.2 cmH_2O and Ppl from 0.8 cmH_2O to 17.8 cmH_2O. Linear regression showed no relationship between P_L and mPaw (β=0.05 [95% CI −0.82 to 0.92]; P=0.89) (Figure 2). Neither central venous pressure nor vasopressor dose displayed a significant relationship with P_L (P=0.073 and P=0.97, respectively).

DISCUSSION

While the use of esophageal manometry has been advocated for the estimation of Ppl during CMV for ARDS, we are the first to report on its use during HFO for adult ARDS. We have demonstrated that Pes can be measured by readily available methods during HFO, and our derived measurements support our hypothesis that P_L cannot be predicted from mPaw. Collectively, our findings have meaningful implications for clinical care because P_L has potentially competing effects in the management of ARDS. Specifically, appropriate P_L is a key determinant of adequate oxygenation during mechanical ventilation (11); however, alveolar overdistension (due to high P_L) may be a primary factor in the generation of VILI (12,13). Therefore, the accurate assessment of Ppl and P_L may allow clinicians to maximize the beneficial effects of mechanical ventilation while minimizing iatrogenic harm.

Both Ppl and P_L depend on the relationships between the elastance of the chest wall (Ew), the lung (E_L) and the total respiratory system (Ers, which is the sum of Ew and E_L), such that Ppl = Paw × Ew/Ers (14). In healthy individuals, Ew and E_L are approximately equal, such that the Ew/Ers ratio has a value of approximately 0.5. This ratio remains constant; therefore, it is reasonable to make assumptions about the value of Ppl based on Paw in healthy subjects. However, in ARDS, both Ew and E_L may vary considerably (both between subjects and within a subject if measured at different times during their illness), such that the ratio of Ew to Ers may vary from 0.2 to 0.8 (14,15). The predominant cause of alterations in Ew during ARDS is abnormal abdominal pressure due to ascites, bowel distension or intra-abdominal blood (15). Additionally, pleural effusions, obesity and patient positioning may alter Ew (16,17). Due to these causes of variation in Ew, P_L may vary fourfold for a given Paw and it is exceedingly difficult to assume that P_L may be inferred from Paw. While this is widely known during CMV, we are the first to demonstrate this during HFO in adult ARDS. During HFO, Ppl may vary with pleural fluid viscosity changes due to frequency-dependent oscillatory effects in excised dog lungs (18). While this phenomenon may occur in intact humans with lung injury, the impact of frequency-dependent pleural viscosity changes on Pes measurement and Ppl estimation in this situation is unclear.

Two recently published randomized clinical studies have compared best CMV versus HFO in adult patients with ARDS (7,8). With a combined total of 1343 patients enrolled, the OSCILLATE and High-Frequency Oscillation for Acute Respiratory Distress Syndrome (OSCAR) trials found harm and equivalence, respectively, when HFO was compared with best practice CMV. Consistent with current guidelines (6), these two well-conducted trials initiated HFO with either a standard mPaw of 30 cmH_2O (OSCILLATE) or an mPaw of 5 cmH_2O above Pplat during CMV (OSCAR). Both studies titrated mPaw to arterial blood gases and neither estimated Ppl or P_L.

While the results of the OSCILLATE and OSCAR studies may reflect a true lack of benefit of HFO over CMV in ARDS, there are several points related to the underlying respiratory mechanics that should be considered when interpreting these data. Neither OSCILLATE nor OSCAR assessed Ew, Ppl or P_L and were, therefore, unable to titrate mPaw and lung distension to any individual patient's respiratory mechanics. This raises the possibility that some patients (those with high Ppl and Ew) may have received lower distending pressures than necessary to prevent VILI and, thus, may have experienced relative hypoxia and atelectasis. Conversely, patients with very low Ppl and Ew could conceivably have received injuriously high levels of P_L. Either of these 'P_L-Paw mismatches' could have led to poorer outcomes than might have been apparent if P_L have been assessed and mPaw titrated to individual patients' physiology. Ideally, these assessments of Ppl and Ew should be performed continuously or in a repeated fashion because Ew and P_L may vary over time in the same patient.

TABLE 1
Patient characteristics, ventilator settings and pressures in patients treated with high-frequency oscillation for acute respiratory distress syndrome

Age, years	59±9
Patients, men/women, n/n	5/2
Weight, kg	80±40
APACHE II score	25±7
Duration of mechanical ventilation before study, days	4±3
Duration of high-frequency oscillation before study, days	2±1
Arterial blood gas values	
$PaCO_2$, mmHg	50±7
PaO_2, mmHg	80±10
FiO_2	0.5±0.1
HCO_3^-, mEq/L	27±5
PaO_2/FiO_2 ratio	160±40
High-frequency oscillation variables	
Bias flow, L	30±1
Frequency, Hz	5±1
Amplitude, cmH_2O	75±10
Measured and estimated pressures, cmH_2O	
mPaw	27±5
Pes	14±7
Ppl	9±7
P_L	18±4

Data presented as mean ± SD unless otherwise indicated. APACHE Acute Physiology and Chronic Health Evaluation; FiO_2 Fraction of inspired oxygen; HCO_3^- Bicarbonate; *mPAW Mean airway pressure; $PaCO_2$ Partial pressure of carbon dioxide; Pes Esophageal pressure; Ppl Pleural pressure; P_L Transpulmonary mean airway pressure*

In the present study, the mean P_L was <19 cmH_2O (Table 1), and the difference between the lowest and the highest value (12.2 cmH_2O and 25.2 cmH_2O) was >100%. This raises the possibility that some of our patients safely tolerated higher mPaw, which may contribute to improved oxygenation and clinical outcomes. It is unknown whether similar P_L values occurred in previous human HFO trials; however, this possibility may help to explain the negative mortality results demonstrated to date.

We estimated Ppl values during HFO to be from 0.8 cmH_2O to 17.8 cmH_2O (derived from Pes of 5.8 cmH_2O to 22.8 cmH_2O), values similar to those found in previous measurements during CMV of ARDS patients (19). If known to treating clinicians, these values may prompt a change in mean airway settings during HFO. Additionally, the present study shows that P_L cannot be estimated from mPaw during HFO.

Limitations

The present study had several limitations that must be recognized when considering the use of esophageal manometry and P_L calculation during HFO. First, accurate measurement of Pes and estimation of Ppl is dependent on correct manometer placement. Due to patients' requirements for sedation, we were unable to perform voluntary 'sniff' testing of manometer placement. Similarly, we were precluded from performing passive occlusion tests because this would have required clamping of the endotracheal tube. Given the severe hypoxia that our patients experienced, this was believed to be an unreasonable

intervention. We believe that chest x-ray verification of placement provides a reasonable alternative strategy in this situation, and has been used in similar studies when conventional methods were not adequate (10).

Second, the validity of esophageal manometry in critically ill patients has been questioned: lung expansion in ARDS is heterogeneous and measured pressures may reflect local conditions present only in the tissue adjacent to the measurement site rather than whole lung conditions (20). Furthermore, the practice of subtracting 5 cmH_2O pressure from Pes to estimate Ppl may not be valid in all patients. Alternative methods include subtracting 2 cmH_2O to 3 cmH_2O (21) after measuring Pes following an end-expiratory occlusion or measuring Pes after a period of patient disconnection from the ventilator (22,23). While we considered these latter two methods, in our opinion, they presented an unwarranted risk to the subjects. Despite the variability in Pes measurements introduced by these uncertainties, estimation of Ppl using esophageal manometry appears to be clinically useful (10,19). In fact, a recent randomized trial showed an improvement in PaO_2/FiO_2 ratio of 88 mmHg in a treatment group guided by Pes than in a control group.

Third, our study may be limited by the assumption that P_A and Paw are equivalent during HFO, which may not be valid regionally or globally. Some investigators have demonstrated that P_A may be lower or similar to mPaw and others have suggested that P_A may exceed mPaw in some circumstances because of variations in ventilator settings, patient position, and variation between inspiratory and expiratory impedance (24-28). However, measuring P_A directly is invasive and risky in patients with severe ARDS. Fourth, the small sample size in the present observational series may result in the study being underpowered.

Fourth, all patients enrolled in our study had ARDS due to a pulmonary cause as opposed to ARDS due to an 'extrapulmonary' cause (29). While our data are unable to clarify this issue, differences in lung recruitability and in the role of chest wall and lung elastances in pulmonary versus extrapulmonary ARDS may have altered the relationship between mPAW and P_L if our patients had extrapulmonary causes of ARDS.

Finally, even if estimates of Ppl during HFO are accurate and reliable, it is unknown what the optimal P_L should be. Although recommendations exist for limits of pressures measured at the airway (such as Pplat) during CMV, no similar guidelines are available for P_L limits during either CMV or HFO. Due to the uncertainties of measurement, and the lack of evidence-based guidelines, we urge extreme caution in the use of Ppl and P_L for the management of mPaw during HFO.

CONCLUSIONS

The current study was the first to demonstrate that P_L may be measured during HFO for adult ARDS and that it cannot be inferred from mPaw. The fact that P_L could not be estimated from mPaw raises the possibility that poor outcomes in both clinical practice and trials of HFO may be due to individual differences in P_L at the same mPaw. Further study may confirm whether this supposition is correct and whether estimation of P_L during HFO in adults would improve outcomes. While it is clear that mPaw is a poor surrogate for P_L, we caution clinicians in the use of Ppl to estimate P_L during HFO until further investigations have been performed.

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