The Spontaneous Breathing Pattern and Work of Breathing of Patients With Acute Respiratory Distress Syndrome and Acute Lung Injury

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BACKGROUND: The spontaneous breathing pattern and its relationship to compliance, resistance, and work of breathing (WOB) has not been examined in patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). Clinically, the ratio of respiratory frequency to tidal volume (f/V_T) during spontaneous breathing may reflect adaptation to altered compliance, resistance, and increased WOB. We examined the relationship between f/V_T, WOB, and respiratory system mechanics in patients with ARDS/ALI. METHODS: Data from spontaneous breathing trials were collected from 33 patients (20 with ARDS, 13 with ALI) at various points in their disease course. WOB and respiratory system mechanics were measured with a pulmonary mechanics monitor that incorporates Campbell diagram software. Differences between the patients with ARDS and ALI were assessed with 2-sided unpaired *t* tests. Multivariate linear regression models were constructed to assess the relationship between f/V_T and other pulmonary-related variables. RESULTS: Patients with ARDS had significantly lower compliance than those with ALI (24 ± 6 mL/cm H_2O vs 40 ± 13 mL/cm H_2O, respectively, $p < 0.001$), but this did not translate into significant differences in either WOB (1.70 ± 0.59 J/L vs 1.43 ± 0.90 J/L, respectively, $p = 0.30$) or f/V_T (137 ± 82 vs 107 ± 49, respectively, $p = 0.23$). Multivariate linear regression modeling revealed that peak negative esophageal pressure, central respiratory drive, duration of ARDS/ALI, minute ventilation deficit between mechanical ventilation and spontaneous breathing, and female gender were the strongest predictors of f/V_T. CONCLUSION: The characteristic rapid shallow breathing pattern in patients with ARDS/ALI occurs in the context of markedly diminished compliance, elevated respiratory drive, and increased WOB. That f/V_T had a strong, inverse relationship to peak negative esophageal pressure also may reflect the influence of muscle weakness. *Key words: acute lung injury, acute respiratory distress syndrome, breathing pattern, frequency-to-tidal volume ratio, lung compliance, minute ventilation, rapid shallow breathing index, work of breathing, inspiratory time.*
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Introduction

Although tachypnea and dyspnea are hallmarks of acute respiratory distress syndrome (ARDS),[1–4] the spontaneous breathing pattern adopted by patients with ARDS or acute lung injury (ALI) has not been examined in regard to either respiratory system mechanics (compliance and resistance) or work of breathing (WOB). ARDS/ALI is char-

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acterized by decreased lung compliance (C_L) and, in many patients, decreased chest wall compliance (C_{CW}).[5] Decreased compliance in ARDS/ALI is associated with tachypnea and implies that elastic WOB is elevated. This assumption is based on the theory of minimal work,[6] which posits that the respiratory frequency (f) adopted by a patient to achieve a target alveolar ventilation represents a strategy to minimize inspiratory effort and maximize muscular efficiency by balancing the elastic and resistive components of WOB. Therefore, to minimize elastic WOB during spontaneous breathing, patients with ARDS/ALI should maintain minute ventilation ($\dot{V}_E$) with a relatively rapid f and small tidal volume (V_T). However, lung resistance is increased in ARDS/ALI[5] and with the additional resistance of the artificial airway may influence the spontaneous breathing pattern.

When elevated, the f/V_T ratio adopted by a patient during a brief trial of spontaneous breathing is an accurate predictor of subsequent weaning failure.[7] Thus, it may be an indirect marker of excessive inspiratory muscle work load, impending muscle fatigue, or simply reflects muscle weakness. It is unknown whether the f/V_T exhibited by patients with ARDS/ALI is significantly influenced by elastic WOB, or if it represents a more generalized strategy to accommodate the interplay between respiratory system mechanics, inspiratory muscle strength, and breathing effort. Furthermore, it is unknown whether the severity of lung injury (ARDS vs ALI) and the associated differences in respiratory system mechanics[5] also affect f/V_T. Using data collected from previous WOB studies,[8–10] we describe the spontaneous breathing pattern and WOB of patients with ARDS/ALI. In addition, we inquire whether elastic or resistive WOB, other measures of inspiratory muscle function, or respiratory system mechanics are independent predictors of f/V_T.

Methods

Subjects

Data were collected between 1995 and 2004, from 33 patients, 20 of whom were initially diagnosed with ARDS, and 13 with ALI, using the American-European Consensus Conference definition.[11] These patients had been enrolled into prospective clinical trials that compared WOB between mechanical ventilation modes[8,9] or triggering systems.[10] Enrollment into these studies represented nonconsecutive patients and was based upon meeting ARDS or ALI criteria, along with the ability to actively trigger breaths during mechanical ventilation. Patients were judged to be clinically stable so as to safely allow WOB measurements. However, patients differed in regard to their disease course: some were studied in the acute phase of ARDS/ALI, whereas most were studied in the chronic phase of lung injury. Overall, patients were studied at a mean of 14 days into their course of ARDS/ALI (95% confidence interval [CI] 7–21 d).

Over the 10-year period that patients were enrolled into these studies, mechanical ventilation practices changed. All patients enrolled into the first 2 studies[8,10] were managed on either volume or pressure assist-control ventilation at a mean ± SD V_T of 10 ± 2 mL/kg predicted body weight. On the day of the study these patients required a positive end-expiratory pressure (PEEP) of 6.6 ± 2.7 cm H_2O, an inspired oxygen fraction (F_{IO_2}) of 0.46 ± 0.08, had a $\dot{V}_E$ demand of 12.4 ± 2.9 L/min, and their P_{aO_2}/F_{IO_2} was 215 ± 52 mm Hg. During the third study,[9] all patients were managed with lung-protective ventilation on volume or pressure assist-control, or pressure-regulated volume control, at a mean V_T of 6.7 ± 1.1 mL/kg. On the day of study these patients required a PEEP of 7.5 ± 2.9 cm H_2O, an F_{IO_2} of 0.46 ± 0.12; had a $\dot{V}_E$ demand of 11.0 ± 2.8 L/min, and a P_{aO_2}/F_{IO_2} of 209 ± 64 mm Hg.

As part of these experimental protocols,[8–10] patients underwent a brief (1–2-min) trial of spontaneous breathing on continuous positive airway pressure (CPAP) at a mean pressure of 5.8 ± 3.3 cm H_2O. CPAP was delivered using either a high continuous-flow system through a modified Jackson-Reese circuit,[8,10] or through the demand-flow system of a ventilator (E-2, Dräger, Telford, Pennsylvania), with a non-bias flow trigger level of 3 L/min.[9]

These spontaneous breathing trials (SBTs) were executed solely to evaluate each patient's ability to generate a spontaneous V_T, inspiratory flow rate ($\dot{V}_I$), and inspiratory time (T_I), with which to compare to the corresponding settings during mechanical ventilation. SBTs were not done in relation to any clinical evaluation for weaning readiness. Each SBT was performed only by a member of the research team. Some variables collected from the SBT, such as V_T, peak $\dot{V}_I$, T_I, f/V_T, and WOB, were reported in one of the previous studies.[8]

Procedures

Upon enrollment, a nasogastric tube (SmartCath, Viasys Healthcare, Palm Springs, California) with an esophageal balloon was placed in the lower third of the esophagus. The balloon position was manipulated while inspecting the synchrony between the peak esophageal pressure (P_{es}) and airway pressure deflections. When cardiac artifact was minimized, an occlusion test was performed for position confirmation, using the method described by Baydur et al.[12] All patients were studied in the semi-recumbent position. Maximal inspiratory pressure (MIP) was measured using "method 1" described by Marini et al,[13] whereby the airway was occluded at end-expiration, which allows no movement of air in either an inspiratory or expiratory direction.

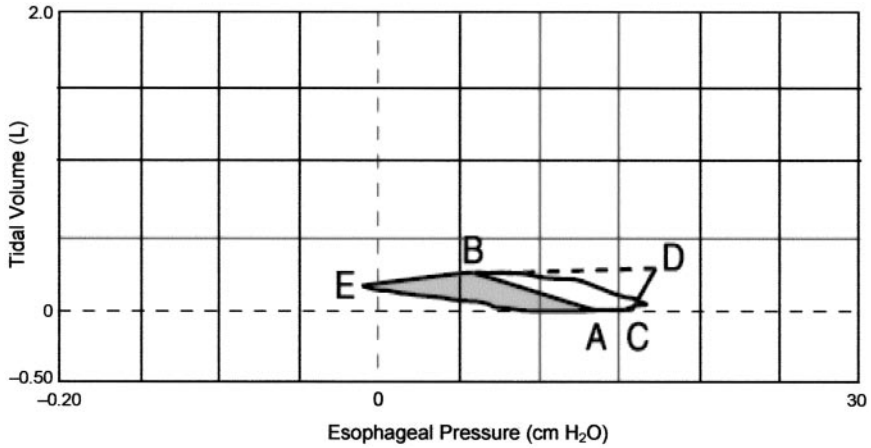

Fig. 1. Campbell diagram of work of breathing (WOB) in a patient with acute respiratory distress syndrome from necrotizing fasciitis and sepsis, with a respiratory system compliance of 26 mL/cm H_2O and a chest wall compliance of 164 mL/cm H_2O. Line CD represents the chest wall compliance curve obtained under conditions of passive ventilation, and is placed by the pulmonary mechanics monitor at the end-expiratory baseline pressure. Line AB represents the lung compliance; point A represents the onset of inspiratory flow, and point B represents the point of maximum tidal volume. Point E represents the maximum negative esophageal pressure. The shaded area AEBA represents the resistive WOB. Area CABDC represents the elastic WOB done on both the lung and the chest wall.

Prior to data collection, respiratory system mechanics were measured during a brief period of passive ventilation that was achieved by additional sedation with propofol or fentanyl, and transient hyperventilation to suppress spontaneous ventilatory activity. Quasi-static respiratory-system compliance (C_{RS}) was calculated as V_T divided by the difference between the end-inspiratory plateau pressure (measured during a 1-s pause) and applied PEEP. C_{CW} curves were constructed from the average of 2–5 esophageal pressure-volume tracings characterized by a counterclockwise movement, a narrow loop, and a rightward rotation of the axis.[8] C_L was calculated by first converting both C_{RS} and C_{CW} to elastance units (E), which is the linear expression of serial compliance relationships. Lung elastance was derived as $E_L = E_{RS} - E_{CW}$, and then was transformed back into compliance units ($1/E_L = C_L$).[5] As stated previously,[8,9] all measurements of patient WOB were taken only after central respiratory drive had returned to the baseline value, following sedation for measurement of passive respiratory system mechanics. All SBTs occurred only after measurements were made during patient-triggered mechanical ventilation.

Measurements

Ventilation variables were measured with a pulmonary mechanics monitor that incorporates Campbell diagram software (Bicore CP-100, Viasys Healthcare, Palm Springs, California). The precision and accuracy of this monitor has been validated previously.[14,15] The monitor and transducers were calibrated prior to each study. An airway pressure/flow transducer (Var-Flex, Viasys Healthcare, Palm Springs, California) was placed at the patient Y-adapter.

Data collection during SBTs included standard measurements of f, V_T, and peak inspiratory flow. Other measurements included: (1) pressure-time product (PTP), which was determined with the method of Sassoon et al,[16] as the integral of the negative change in P_{es} over inspiratory time (T_I); (2) inspiratory change in esophageal pressure (ΔP_{es}), which was determined as the maximum negative change in P_{es} from the end-expiratory plateau; (3) esophageal pressure measured at 100 ms after the onset of inspiratory effort ($P_{0.1}$), which is a mechanical correlate of central respiratory drive; and (4) intrinsic PEEP, which was measured dynamically as the difference in P_{es} between the end-expiratory plateau and the pressure measured at the onset of inspiratory flow, minus the lowest airway pressure change from baseline at the onset of flow.[8] In addition, Campbell diagram software was used to measure total inspiratory WOB and to divide WOB into its elastic and resistive subcomponents (Fig. 1).[14]

A 40-breath printed report containing all data points, except the Campbell diagram measurements of WOB, was generated during each CPAP trial. From that report, 20 randomly selected breaths were used for data analysis. During this same time period, WOB data obtained from 10 individual Campbell diagram plots were recorded.

Calculations of f/V_T were made from 20 discreet measurements of f, divided by the corresponding V_T. $\dot{V}_E$ during spontaneous breathing was calculated as the product of V_T and f. In addition the $\dot{V}_E$ measured during mechanical ventilation just prior to the SBT was used to calculate differences in $\dot{V}_E$ between the 2 conditions ($\Delta\dot{V}_{E(MV-SB)}$). The power output of the inspiratory muscles ($\dot{W}$) was calculated as the product of the total inspiratory WOB and $\dot{V}_E$

during spontaneous breathing. Lung injury score was calculated with the method described by Murray et al.[17]

Data Analysis

Descriptive data are reported as mean and 95% CI. When assessed with the Kolmogorov-Smirnov test, the data were consistent with a normal distribution. Therefore, comparisons between patients with ARDS and ALI are expressed as mean ± SD, and differences between the groups were assessed by 2-sided unpaired *t* tests. Multivariate linear regression was used to model f/V_T in terms of other measurements. Best subsets selection was used to select the best 2 predictors when used together, the best 3, the best 4, and the best 5. Models with more than 5 predictors were not examined, because of the limited size of the data set. Examination of quadratic terms suggested that linearity assumptions were acceptable for the chosen predictors. Basic statistical analyses were done with statistics software (InStat 3.0, GraphPad Software, San Diego, California). Univariate, bivariate, and multivariate modeling were done with another statistics software package (SAS, SAS Institute, Cary, North Carolina). Differences were considered significant when $p < 0.05$.

Results

The spontaneous breathing pattern of our patients with ARDS/ALI was characterized by tachypnea, decreased V_T, and elevated f/V_T. This occurred with abnormally low measurements of C_{RS}, C_{CW}, and C_L (Table 1). Central respiratory drive ($P_{0.1}$) was increased and occurred with increased ΔP_{es}, PTP, WOB, and $\dot{W}$, whereas inspiratory muscle strength (MIP) was markedly decreased. Low to moderate levels of intrinsic PEEP were detected in 18 (55%) patients.

Compared to patients with ALI, those with ARDS had significantly higher lung injury score, significantly lower C_{RS} and C_L, and exhibited a trend toward a lower V_T and higher f/V_T (Table 2). However, this did not translate into a higher WOB compared to patients with ALI. In addition, the relative contribution of elastic and resistive components to total inspiratory WOB was the same for patients with ARDS and ALI. We were unable to analyze the data in terms of pulmonary versus extrapulmonary source of lung injury, because of an imbalance in distribution of both lung injury severity and etiology: only 10 of 33 patients had a pulmonary source of lung injury, and 6 of these patients had ALI.

In the univariate linear regression, peak $\dot{V}_I$, MIP, and C_L were significant predictors of f/V_T, whereas ΔP_{es}, $\Delta\dot{V}_{E(MV\text{-}SB)}$, C_{RS}, duration of lung injury prior to study, and PTP approached statistical significance (Table 3). In the multivariate linear regression, the best predictive model of f/V_T consisted of ΔP_{es}, $P_{0.1}$, $\Delta\dot{V}_{E(MV\text{-}SB)}$, duration of lung injury, and female sex (Table 4).

Other variables that were significant predictors of f/V_T were an initial diagnosis of ARDS (estimated increase of 55.15, 95% CI 16.45–93.85, $p = 0.0069$) and elastic WOB (estimated increase of 68.11 per J/L, 95% CI 11.6–124.6, $p = 0.0199$) when controlled for ΔP_{es} and $P_{0.1}$ in the best 4-predictor model. C_L appeared to be predictive of f/V_T (estimated decrease of 1.45 per unit increase in C_L, 95% CI 0.47–2.44, $p = 0.0052$) when controlled for ΔP_{es}

Table 1. Spontaneous Breathing Pattern, Respiratory Drive-Related Variables, Pulmonary Mechanics, and Work-Related Variables of Patients With Acute Respiratory Distress Syndrome and Acute Lung Injury

Variable	Mean	95% CI
f/V_τ	125	100–151
V_T (mL)	289	243–335
V_T (mL/Kg)	4.4	3.8–5.1
f (breaths/min)	30	27–32
$\dot{V}_{E\text{-}SB}$ (L/min)	8.59	7.01–10.16
$\dot{V}_{E\text{-}MV}$ (L/min)	13.09	11.99–14.56
$\Delta\dot{V}_{E(MV\text{-}SB)}$ (L/min)	4.69	3.37–6.01
Peak $\dot{V}_I$ (L/min)	36	32–41
T_I (s)	0.80	0.73–0.87
T_I/T_{tot}	0.38	0.35–0.42
$P_{0.1}$ (cm H_2O)	5.8	4.9–6.6
ΔP_{es} (cm H_2O)	16.5	14.3–18.7
PTP (cm H_2O/s/min)	296	252–340
WOB total (J/L)	1.60	1.34–1.85
WOB elastic (J/L)	0.92	0.76–1.08
WOB resistive (J/L)	0.68	0.56–0.80
WOB elastic/total	0.57	0.54–0.61
WOB resistive/total	0.43	0.39–0.46
$\dot{W}$ (J/min)	12.80	10.0–15.7
MIP (cm H_2O)	50	44–57
PEEPi (cm H_2O)	3.6	2.0–5.0
C_{RS} (mL/cm H_2O)	30	26–35
C_{CW} (mL/cm H_2O)	125	105–146
C_L (mL/cm H_2O)	43	36–50

CI = confidence interval
f = respiratory frequency
V_T = tidal volume
$\dot{V}_{E\text{-}SB}$ = minute ventilation capability during spontaneous breathing
$\dot{V}_{E\text{-}MV}$ = minute ventilation demand during mechanical ventilation
$\Delta\dot{V}_{E(MV\text{-}SB)}$ = minute ventilation difference between mechanical ventilation and spontaneous breathing
$\dot{V}_I$ = inspiratory flow rate
T_I = inspiratory time
T_I/T_{tot} = ratio of inspiratory time to total breathing cycle time
$P_{0.1}$ = esophageal pressure 100 ms after beginning of inspiration
ΔP_{es} = peak negative esophageal pressure
PTP = pressure-time product
WOB = work of breathing
$\dot{W}$ = power output of the inspiratory muscles
MIP = maximum inspiratory pressure
PEEPi = intrinsic positive end-expiratory pressure
C_{RS} = respiratory system compliance
C_{CW} = chest wall compliance
C_L = lung compliance

Table 2. Comparison of Breathing Pattern, Pulmonary Mechanics, and Work-Related Characteristics Between Patients With Acute Respiratory Distress Syndrome and Patients With Acute Lung Injury During Spontaneous Breathing

	ARDS	ALI	p
n	20	13	NA
Age (y)	43.8 ± 14.9	54.5 ± 14.3	0.05
Lung injury score	2.46 ± 0.60	1.67 ± 0.52	< 0.001
f/V_T	137 ± 82	107 ± 49	0.23
V_T (mL)	261 ± 113	333 ± 145	0.12
V_T (mL/Kg)	4.2 ± 2.0	4.8 ± 1.8	0.36
f (breaths/min)	29 ± 8	30 ± 8	0.81
$\dot{V}_{E\text{-}SB}$ (L/min)	7.83 ± 4.51	9.75 ± 4.24	0.23
$\dot{V}_{E\text{-}MV}$ (L/min)	13.09 ± 4.28	13.56 ± 2.44	0.38
$\Delta\dot{V}_{E(MV\text{-}SB)}$ (L/min)	5.26 ± 4.14	3.82 ± 2.93	0.35
Peak $\dot{V}_I$ (L/min)	36 ± 14	38 ± 14	0.73
T_I (s)	0.78 ± 0.18	0.83 ± 0.20	0.49
T_I/T_{tot}	0.37 ± 0.10	0.40 ± 0.10	0.37
$P_{0.1}$ (cm H_2O)	5.9 ± 1.9	5.6 ± 2.9	0.72
ΔP_{es} (cm H_2O)	17.6 ± 6.2	14.8 ± 6.3	0.22
PTP (cm H_2O/s/min)	292 ± 126	302 ± 129	0.83
$\dot{W}$ (J/min)	12.8 ± 8.6	12.8 ± 7.3	0.99
C_{RS} (mL/cm H_2O)	24 ± 6.2	40 ± 13	< 0.001
C_{CW} (mL/cm H_2O)	112 ± 49	146 ± 66	0.10
C_L (mL/cm H_2O)	33 ± 10	55 ± 27	0.0015
WOB total (J/L)	1.70 ± 0.59	1.43 ± 0.90	0.30
WOB elastic (J/L)	0.97 ± 0.37	0.84 ± 0.55	0.44
WOB resistive (J/L)	0.74 ± 0.30	0.59 ± 0.38	0.21
WOB elastic/total	0.57 ± 0.09	0.58 ± 0.10	0.72
WOB resistive/total	0.43 ± 0.09	0.42 ± 0.10	0.62
MIP (cm H_2O)	50 ± 19	51 ± 19	0.90
PEEPi (cm H_2O)	3.8 ± 3.0	3.3 ± 3.4	0.77
CPAP (cm H_2O)	6.7 ± 3.6	4.5 ± 2.3	0.06
ETT inner diameter (mm)	7.5 ± 0.4	7.5 ± 0.5	0.99

ARDS = acute respiratory distress syndrome
ALI = acute lung injury
NA = not applicable
f = respiratory frequency
V_T = tidal volume
$\dot{V}_{E\text{-}SB}$ = minute ventilation capability during spontaneous breathing
$\dot{V}_{E\text{-}MV}$ = minute ventilation demand during mechanical ventilation
$\Delta\dot{V}_{E(MV\text{-}SB)}$ = minute ventilation difference between mechanical ventilation and spontaneous breathing
$\dot{V}_I$ = inspiratory flow rate
T_I = inspiratory time
T_I/T_{tot} = ratio of inspiratory time to total breathing cycle time
$P_{0.1}$ = esophageal pressure 100 ms after beginning of inspiration
ΔP_{es} = peak negative esophageal pressure
PTP = pressure-time product
$\dot{W}$ = power output of the inspiratory muscles
C_{RS} = respiratory system compliance
C_{CW} = chest wall compliance
C_L = lung compliance
WOB_T = work of breathing
MIP = maximum inspiratory pressure
PEEPi = intrinsic positive end-expiratory pressure
CPAP = continuous positive airway pressure
ETT = endotracheal tube

Table 3. Univariate Linear Regression Analysis of Pulmonary Mechanics Variables That Predict f/V_T During a Brief Spontaneous Breathing Trial

Predictor	Estimate	95% CI	p
Peak $\dot{V}_I$ (L/min)	−2.21	−3.90 to −0.51	0.013
MIP (cm H_2O)	−1.35	−2.59 to −0.11	0.034
C_L (mL/cm H_2O)	−1.18	−2.35 to −0.02	0.047
ΔP_{es} (cm H_2O)	−3.79	−7.70 to 0.12	0.057
$\Delta\dot{V}_{E(MV\text{-}UAB)}$ (L/min)	6.38	−0.23 to 13.0	0.058
C_{RS} (mL/cm H_2O)	−1.79	−3.67 to 0.08	0.060
Duration of lung injury (d)	1.14	−0.12 to 2.39	0.074
PTP (cm H_2O/s/m)	−0.17	−0.37 to 0.03	0.090

f = respiratory frequency (breaths/min)
V_T = tidal volume
CI = confidence interval
$\dot{V}_I$ = inspiratory flow rate
MIP = maximum inspiratory pressure
C_L = lung compliance
ΔP_{es} = peak negative esophageal pressure
$\Delta\dot{V}_{E(MV\text{-}UAB)}$ = minute ventilation difference between patient-triggered mechanical ventilation and unassisted breathing
C_{RS} = respiratory system compliance
PTP = pressure-time product

Table 4. Multivariate Linear Regression Model of Pulmonary Mechanics Variables That Predict f/V_T

Predictor	Estimate	95% CI	p
ΔP_{es} (cm H_2O)	−10.93	−15.61 to −6.25	< 0.001
$P_{0.1}$ (cm H_2O)	19.73	7.49 to 31.97	0.003
Duration of lung injury (d)	1.63	0.67 to 2.59	0.002
$\Delta\dot{V}_E$ (L/min)	6.74	1.78 to 11.70	0.01
Female (%)	45.98	5.86 to 86.11	0.03

CI = confidence interval
ΔP_{es} = peak negative esophageal pressure
$P_{0.1}$ = esophageal pressure 100 ms after beginning of inspiration
$\Delta\dot{V}_E$ = minute ventilation difference between patient-triggered mechanical ventilation and unassisted breathing

and $P_{0.1}$ in the best 3-predictor model. Despite some evidence of non-normal residuals from the model ($p = 0.048$), the results were similar when bias-corrected, accelerated bootstrapping was used to obtain confidence intervals.[18]

Discussion

The spontaneous breathing pattern of our patients with ARDS/ALI was consistent with the theory of minimal work: that the f adopted by a patient to achieve a target $\dot{V}_E$ represents a strategy to minimize inspiratory effort. In the presence of reduced C_{RS} and elevated elastic WOB, the body's attempt to minimize effort and maximize efficiency should manifest as a rapid shallow breathing pattern. Accordingly, we found that f/V_T was directly related to elastic WOB and inversely related to ΔP_{es}.

It should be emphasized that the negative relationship between effort (ΔP_{es} and PTP) and f/V_T also occurred in the context of both prolonged illness and diminished inspiratory muscle strength. On average, our patients were studied 14 days into their course of ARDS/ALI and had a MIP that was 45–70% of normal range values (72–110 cm H_2O).[19] The strong inverse relationship between respiratory muscle strength (MIP) and f/V_T also suggests that rapid shallow breathing in ARDS/ALI may indicate either inspiratory muscle weakness or impending fatigue in the face of an overwhelming work load. This interpretation is supported by the direct relationship between both f/V_T with $\Delta \dot{V}_{E(MV\text{-}SB)}$ and with the duration of ARDS/ALI in the multivariate analysis. That peak $\dot{V}_I$ was the best single predictor of f/V_T in the univariate analysis may signify that the capacity to generate a high peak $\dot{V}_I$ is intimately related to V_T size. In fact, peak inspiratory flow as a predictor of V_T achieved an r^2 of 0.42 ($p < 0.001$).

In their theory of minimal work, Otis et al[6] framed the f response according to the magnitude and distribution of elastic and resistive loads in terms of target alveolar ventilation. Our results suggest that Otis's prediction extends to conditions of severe pathology. During spontaneous breathing, our patients seemingly could not achieve their target alveolar ventilation, as they accrued a $\dot{V}_E$ deficit of 3.5–6 L/min that, in turn, was a significant predictor of f/V_T.

Otis et al also cautioned that their theory did not account for the effects of gas exchange abnormalities, such as severe ventilation-perfusion mismatch and increased dead-space fraction,[6] which are both prominent features of ARDS.[20,21] Although an initial diagnosis of ARDS was a particularly strong predictor of f/V_T, P_{aO_2}/F_{IO_2} measured on the day of study was not (estimate −0.20, 95% CI −0.66 to 0.27, $p = 0.40$). Yet our study focused on respiratory system mechanics and was not designed to address the potential influence of gas exchange abnormalities on breathing pattern.

Since the first descriptions of ARDS,[1,2] the implication has been that rapid shallow breathing reflects lung "stiffness," and the inverse correlation between f/V_T and compliance found in this study support that observation. That C_L was a stronger predictor of f/V_T than C_{RS} may be explained by the fact that the average C_L of our patients was 35–60% of normal range values (70–122 mL/cm H_2O), whereas C_{CW} at worst was 69% of normal range values (118–179 mL/cm H_2O).[5]

In contrast to patients with ARDS, those with ALI had less severe injury, as measured by the lung injury score, and significantly higher C_{RS} and C_L. However, this did not translate into a significantly lower elastic WOB, which may be explained by the fact that patients with ALI also breathed at a higher V_T. The relative contributions of elastic and resistive WOB to the total inspiratory WOB were 57% and 43%, respectively, and were not different between patients with ARDS and those with ALI. Otis et al[6] found that in normal subjects the elastic work of inspiration accounted for 63% of the total WOB, whereas 29% was expended overcoming resistive forces, and 8% in overcoming the viscoelastic resistance to tissue deformation. Interestingly, the proportion of work distribution in ARDS/ALI was similar to that found in normal subjects. We were surprised by this finding, and we speculate that the abnormally low C_{RS} may have been balanced by increased resistance from the artificial airway, along with increased airway and tissue resistance often found in patients with ARDS.[5]

We also were intrigued by the influence of gender on f/V_T in patients with ARDS/ALI. Gender-based comparisons of breathing pattern, work, strength and mechanics-related variables revealed no statistically significant differences. However, there was a trend toward lower C_L in women, compared to men (36.6 ± 9.5 mL/cm H_2O vs 48.6 ± 25.0 mL/cm H_2O, respectively, $p = 0.11$), which in the univariate and 3-predictor multivariate models was a strong predictor of f/V_T. In a small sample size of 20 men and 13 women, a 25% lower C_L may have influenced the f/V_T of our women patients.

There were 2 technical limitations in our measurements that require comment. First, our equipment did not allow for scalar display of P_{es}, so that C_{CW} was measured dynamically (which is the standard method for determining total WOB). Therefore, our measurements of C_{CW} systematically underestimated true static C_{CW}, as they included the viscoelastic resistance associated with chest wall deformation. This caused a systematic overestimation of C_L in our patients. Yet chest wall viscoelastance in ARDS is relatively small (1.4–1.8 cm H_2O/L/s),[22] so that the error in our results is probably minor.

Second, $P_{0.1}$ reflects central respiratory drive and typically is measured as the change in *airway pressure* under static conditions, so that neither lung mechanics nor the force-velocity characteristics of the inspiratory muscles influence the measured pressure.[23] Any appreciable volume change that occurs during the measurement dissipates pressure and causes a systematic underestimation of true $P_{0.1}$. Our $P_{0.1}$ measurement used P_{es}, which would tend to negate the effects of lung mechanics. Also, C_L was markedly reduced in our patients, which may have blunted pressure transmission across the lung parenchyma. Furthermore, over half of our patients had intrinsic PEEP. Both factors may contribute to a lag time[24] between the beginning of inspiratory effort and any subsequent volume change during the first 100 ms. Linear regression revealed a modest positive relationship between $P_{0.1}$ and WOB ($r^2 = 0.31$, $p < 0.001$), which is consistent with other studies.[25] Despite these limitations, our $P_{0.1}$ measurements represented the magnitude of negative P_{es} development

within 100 ms of inspiratory effort. These values were both highly elevated and predictive of f/V_T in the multivariate linear regression model. Whether this reflects inspiratory muscle force-velocity relationships more than central respiratory drive cannot be determined.

An additional limitation is that, for patient safety reasons, data from the SBTs were collected over a brief time period of 1–2 min. Therefore, the data generated from these trials may not represent a stabilized spontaneous breathing pattern. In the more severely ill patients breathing with a fatiguing work load, it is quite possible that the spontaneous breathing pattern would not become stable. Moreover, these measurements were made in patients with various causes and severity of lung injury, at various time points in the disease process. Nevertheless, this study provides a preliminary, if limited, description of the spontaneous breathing characteristics of patients with ALI/ARDS.

Conclusions

The rapid shallow breathing pattern of our patients with ARDS/ALI was associated with markedly diminished C_{RS} and elevated elastic WOB. Multivariate logistic regression modeling of f/V_T was consistent with Otis's theory of minimal work. However, the models also suggest that, in addition to both respiratory system mechanics and effort, muscle strength, duration of ALI, and sex may influence f/V_T.

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