Intensive Care Med (2016) 42:1206–1213
DOI 10.1007/s00134-016-4403-7

ORIGINAL

Mortality and pulmonary mechanics in relation to respiratory system and transpulmonary driving pressures in ARDS

Elias Baedorf Kassis[1*], Stephen H. Loring[2] and Daniel Talmor[2]

Abstract

Purpose: The driving pressure of the respiratory system has been shown to strongly correlate with mortality in a recent large retrospective ARDSnet study. Respiratory system driving pressure [plateau pressure—positive end-expiratory pressure (PEEP)] does not account for variable chest wall compliance. Esophageal manometry can be utilized to determine transpulmonary driving pressure. We have examined the relationships between respiratory system and transpulmonary driving pressure, pulmonary mechanics and 28-day mortality.

Methods: Fifty-six patients from a previous study were analyzed to compare PEEP titration to maintain positive transpulmonary end-expiratory pressure to a control protocol. Respiratory system and transpulmonary driving pressures and pulmonary mechanics were examined at baseline, 5 min and 24 h. Analysis of variance and linear regression were used to compare 28 day survivors versus non-survivors and the intervention group versus the control group, respectively.

Results: At baseline and 5 min there was no difference in respiratory system or transpulmonary driving pressure. By 24 h, survivors had lower respiratory system and transpulmonary driving pressures. Similarly, by 24 h the intervention group had lower transpulmonary driving pressure. This decrease was explained by improved elastance and increased PEEP.

Conclusions: The results suggest that utilizing PEEP titration to target positive transpulmonary pressure via esophageal manometry causes both improved elastance and driving pressures. Treatment strategies leading to decreased respiratory system and transpulmonary driving pressure at 24 h may be associated with improved 28 day mortality. Studies to clarify the role of respiratory system and transpulmonary driving pressures as a prognosticator and bedside ventilator target are warranted.

Keywords: ARDS, Driving pressure, Esophageal manometry, Transpulmonary driving pressure, Respiratory system driving pressure, Mortality

*Correspondence: ekassis@partners.org; ekassis@gmail.com
[1] Division of Pulmonary and Critical Care, Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Bulfinch 108, Boston, MA 02114, USA
Full author information is available at the end of the article

Take-home message: Strategies titrating PEEP to target positive transpulmonary pressure in ARDS result in lower respiratory system and transpulmonary driving pressure secondary to improved elastance. Decreased respiratory system and transpulmonary driving pressures at 24 h were associated with improved 28 day morality, and changes in driving pressure with inventions were not seen immediately.

Introduction

Acute respiratory distress syndrome (ARDS) [1, 2] carries a high morbidity and mortality and remains a very common clinical problem [3, 4]. The backbone of current treatment is the use of "lung protective" ventilation, i.e. limiting tidal volumes (V_T) and keeping end-inspiratory plateau pressures low while maintaining sufficiently high positive end-expiratory pressure (PEEP) [5–9]. Lung protective ventilation strategies are thought to reduce

mechanical stress by maintaining alveolar aeration (limiting repetitive opening and closing) while preventing overexpansion of the lung, thereby decreasing ventilator-induced lung injury [10–12]. These strategies have been shown to reduce mortality, demonstrating the importance of respiratory mechanics in determining outcomes in patients with ARDS [5–8].

Results from a recent study using data from nine randomized trials suggest that the driving pressure (DP) of the respiratory system (DP_{RS}), which is easily measured at the bedside (DP_{RS} = plateau pressure − PEEP), may be a superior marker for the severity of lung injury, providing improved prognostication and correlation with mortality [13]. The authors of this study reported that higher DP_{RS} correlated with increased mortality even in patients already receiving low-volume lung protective ventilation [13]; however, they did not account for the effects of the chest wall in their analysis [14]. This latter parameter can be obtained using the transpulmonary DP (DP_L = end-inspiratory transpulmonary pressure−end-expiratory transpulmonary pressure), which is the pressure actually applied to the lungs. Using DP_L for monitoring and prognostication of ARDS eliminates the variable effects of the chest wall on the respiratory system. In addition, because chest wall compliance and pleural pressure vary widely between patients [15], measuring DP_L instead of DP_{RS} may be the more appropriate measure.

Esophageal manometry provides a useful estimate of pleural pressure and can be used to determine separate contributions of lung and chest wall in determining respiratory system mechanics [15–17]. In the EPVent trial, our group tested the use of esophageal manometry for managing mechanical ventilation in patients with ARDS [15]. We found that maintenance of positive transpulmonary pressures resulted in significantly higher PEEP, improved oxygenation (P/F ratio) and improved respiratory system compliance [15]. Maintenance of positive transpulmonary pressures is in accordance with the concept of personalization and "a la carte" ventilatory management in ARDS [18]. In the study reported here, we used esophageal pressure measurements from EPVent to follow changes in DP_{RS} and DP_L over time in the two treatment groups.

Methods

Study cohort

The EPvent study was approved by the institutional review board at the Beth Israel Deaconess Medical Center in Boston, and written consent was obtained from each patient or surrogate [15]. Patients were included in the study if they had acute lung injury or ARDS as defined by the American–European Consensus Conference [2]. Of the original 61 subjects, 56 had sufficient data at baseline and 24 h to calculate DP_{RS} and DP_L for further analysis. Of the five patients excluded, three were from the intervention group (1 in the 3 died), and two were from the control group (both died). The full results of the EPVent trial have been published elsewhere [15].

Physiologic measurements

Subjects were monitored while supine with the head of the bed elevated to 30°. An esophageal balloon-catheter was placed, and measurements were obtained to estimate intrathoracic pressures. Airway pressure, tidal volume and air flow were recorded during tidal ventilation and during end-expiratory holds and end-inspiratory holds (plateau) (Fig. 1). Between baseline and 5 min, every patient underwent a recruitment maneuver with an airway pressure increase to 40 cmH_2O for 30 s and V_T set at 6 cc/kg ideal body weight. Patients in the intervention group had PEEP levels adjusted to achieve a positive transpulmonary pressure of 0–10 cm H_2O at end-expiration according to a sliding scale based on the fraction of inspired oxygen (see Fig. 1 in EPvent [15]). The control group had PEEP titrated as per the standard low PEEP ARDSnet tables [5]. Measured variables included total PEEP (measured at end-expiratory hold), plateau pressure, end-expiratory esophageal pressure, end-inspiratory esophageal pressure and V_T; all other variables in our study were calculated from these values (Fig. 1). Transpulmonary pressure was calculated as airway pressure minus esophageal pressure (a surrogate for intrathoracic pressure) (Fig. 1). DP_{RS} was calculated as the plateau pressure minus total PEEP (Fig. 1). DP_L was calculated from the transpulmonary pressures at the same times (Fig. 1). Elastance of the respiratory system (E_{RS}) was calculated as the change in airway pressure from end-expiratory hold to plateau divided by V_T, and lung elastance (E_L) was calculated as the change in transpulmonary pressure at the same times. The 28 day mortality was also recorded. Data were analyzed at baseline, at 5 min (after the recruitment maneuver and adjustment of tidal volume and PEEP to protocol settings) and at 24 h.

Statistical analysis

Continuous variables with a normal distribution were analyzed via analysis of variance (ANOVA) and linear regression. We compared DP_{RS} and DP_L between 28 day survivors and 28 day non-survivors, and compared DP_{RS}, DP_L, E_{RS}, E_L and PEEP between the control and intervention groups at baseline, 5 min and 24 h. Changes in these variables (DP_{RS}, DP_L, etc.) over time between the control and intervention groups and between survivors and non-survivors were assessed by ANOVA repeated measures analysis with the interaction terms (time × physiological

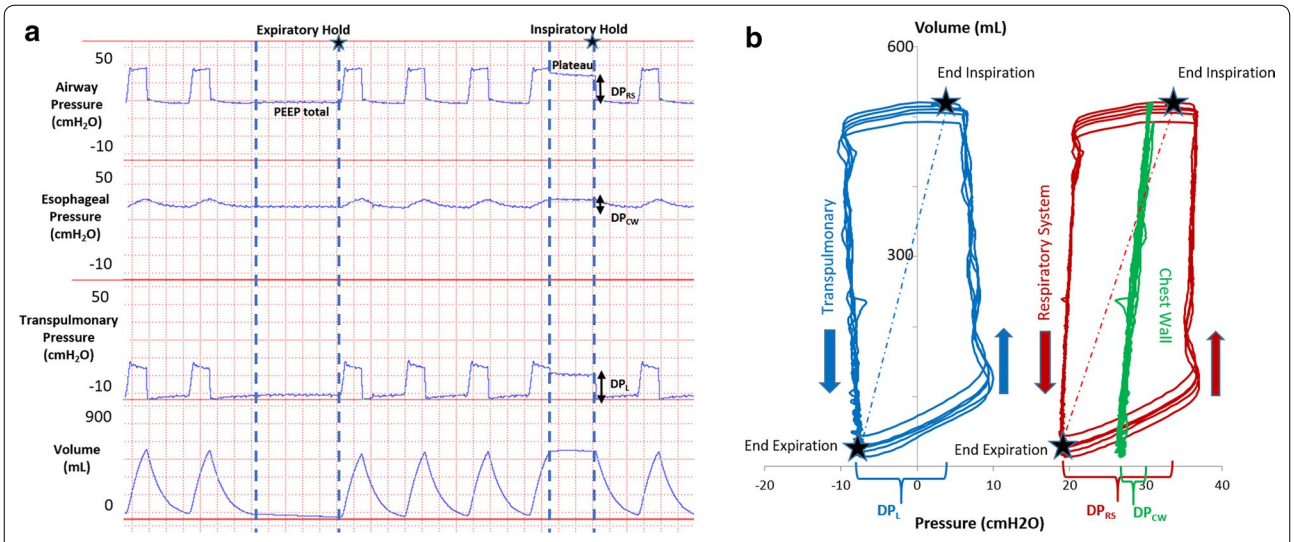

Fig. 1 Pressure and volume tracings from a study patient. **a** Time tracings show the pressure and volume change during tidal breathing with expiratory and inspiratory holds. Airway pressure (P_{ao}) is the total respiratory system pressure, esophageal pressure (P_{es}) is an estimate of the pleural and trans-chest wall pressure and transpulmonary pressure (P_L) is calculated as P_{ao} minus P_{es}. DP_{RS} Respiratory system driving pressure [plateau pressure—total positive end-expiratory pressure (*PEEP*)], DP_{CW} chest wall driving pressure (P_{es} at end-inspiratory hold—P_{es} at end-expiratory hold), DP_L transpulmonary driving pressure (P_L at the end-inspiratory hold—P_L at end-expiratory hold). **b** Pressure–volume (P–V) curves during tidal breathing following respiratory system pressures (P_{ao}), transpulmonary pressures (P_L) and chest wall pressures (P_{es}). *Dotted lines* represent the static compliance of the respiratory system and lung as measured by the slope between end-inspiratory holds and end-expiratory holds (*stars*), *arrows* indicate the direction of the inspiration and expiration

measurement) added into the analysis. We used LOWESS (locally weighted scatterplot smoothing) to compare individual values of DP_{RS} and DP_L in order to determine if DP_{RS} is predictive of DP_L in a given patient and if variation of ΔDP_{RS} resulting from a change in PEEP setting is predictive of the variation of ΔDP_L. Dichotomous and nominal variables were compared using chi-square analysis with Fisher's exact test.

Results

Data from 29 patients in the control group and 27 patients in the intervention group were analyzed. The cohorts were well matched by age, sex, race, Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission, primary physiologic injury, baseline organ failure, gas exchange (pH, PaO_2, pCO_2), lactate and hemodynamics (Table 1). There were 42 survivors and 14 non-survivors at 28 days. Compared with non-survivors, survivors had a significantly lower APACHE II score (24.7 vs. 31.5; $p < 0.0001$), higher pH (7.35 vs. 7.27, $p < 0.001$), lower lactate level (2.1 vs. 5.8, $p < 0.0001$), but they were otherwise similar in race, gender, age, heart rate and blood pressure at baseline.

To evaluate the correlation between driving pressure and survival we compared 28 day survivors and non-survivors. There was no difference between these groups in baseline DP_{RS} (13.6 vs. 15.5 cmH_2O; $p = 0.08$), baseline DP_L (10.1 vs. 10.4 cmH_2O; $p = 0.75$), 5 min DP_{RS} (12.3 vs. 14.7 cmH_2O; $p = 0.054$) or 5 min DP_L (8.5 vs. 10.6 cmH_2O; $p = 0.09$), although mean DP_L and DP_{RS} were higher in non-survivors at all time points (Fig. 2a, b). At 24 h, survivors had a significantly lower DP_{RS} (10.5 vs. 14.7 cmH_2O; $p < 0.0001$) and DP_L (7.8 vs. 10.1 cmH_2O; $p = 0.03$) (Fig. 2a, b). From baseline to 24 h, survivors showed a significant decrease in both DP_{RS} (ΔDP_{RS} −3.29 vs. −0.81 cmH_2O; $p = 0.03$) and DP_L (ΔDP_L −2.3 vs. −0.3 cmH_2O; $p = 0.04$) compared with non-survivors. Similarly, E_{RS} and E_L were lower at baseline in survivors (E_{RS} 28.1 vs. 35.3 cmH_2O/L, $p = 0.02$; E_L 21.1 vs. 24.3 cmH_2O/L, $p = 0.3$) and decreased over 24 h (E_{RS} 25.2 vs. 34.6 cmH_2O/L, $p = 0.001$; E_L 18.6 vs 24.4 cmH_2O/L, $p = 0.05$). In both survivors and non-survivors there was no interaction with time (DP_{RS}, $p = 0.12$; DP_L, $p = 0.59$). Notably, ten of 29 (34.5 %) patients in the control group and four of 27 (14.8 %) patients in the intervention group died by 28 days ($p = 0.085$).

To evaluate the effects of PEEP adjustment targeting positive transpulmonary pressure on changes in driving pressure, we compared the control and intervention groups. There was no difference between groups in baseline DP_{RS} (14.0 vs. 14.1 cmH_2O; $p = 0.97$), baseline DP_L (10.1 vs. 10.3 cmH_2O; $p = 0.80$), 5 min DP_{RS} (12.2 vs. 13.6 cmH_2O; $p = 0.22$) or 5 min DP_L (8.5 vs. 9.5 cmH_2O; $p = 0.35$). At 24 h there was no difference

Table 1 Baseline group characteristics

Characteristics	Control ($n = 29$)	Intervention ($n = 27$)	p value
Male sex	15 (52)	18 (67)	0.29
Age (years)	52 ± 23	54 ± 17	0.68
White race	25 (86)	23 (85)	0.64
Predicted body weight (kg)	62 ± 11	68 ± 9	0.053
APACHE II score	27 ± 7	27 ± 7	0.89
Primary physiologic injury			0.72
Pulmonary	5 (17)	5 (19)	
Abdominal	11 (38)	13 (48)	
Trauma	9 (31)	6 (22)	
Sepsis	1 (3)	2 (7)	
Other	3 (10)	1 (4)	
Organ failure at baseline			
Cardiac	10 (35)	8 (30)	0.70
Renal	14 (48)	17 (63)	0.27
Neurologic	11 (38)	11 (41)	0.83
Hepatic	8 (28)	10 (37)	0.45
Hematologic	3 (10)	7 (26)	0.12
Arterial blood gas			
pH	7.33 ± 0.08	7.34 ± 0.09	0.43
$PaCO_2$ (mmHg)	40 ± 8	42 ± 8	0.22
PaO_2 (mmHg)	107 ± 45	90 ± 24	0.10
P/F ratio (mmHg)	143 ± 56	142 ± 52	0.96
Hemodynamic variable			
Lactate (mg/dL)	3.2 ± 3.3	3.0 ± 3.6	0.86
Heart rate (beats/min)	99 ± 19	99 ± 25	0.99
Systolic blood pressure (mmHg)	108 ± 18	109 ± 19	0.81
Diastolic blood pressure (mmHg)	55 ± 11	59 ± 11	0.26

Data are presented as the number with the percentage in parenthesis or as the mean ± standard deviation (SD)

APACHE II Acute Physiology and Chronic Health Evaluation II, *$PaCO_2$*, (*PaO_2*) partial pressure of carbon dioxide (oxygen) in arterial blood

in DP_{RS} between groups (12.0 vs. 11.1 cmH_2O; $p = 0.31$), while DP_L was significantly lower in the intervention group (9.4 vs. 7.2 cmH_2O; $p = 0.02$) (Table 2; Fig. 2c, d). In terms of changes between baseline and 24 h, the intervention group showed a non-significant change in DP_{RS} (ΔDP_{RS} −2.39 vs. −2.97 cmH_2O, $p = 0.57$) and a significant decrease in DP_L (ΔDP_L −0.65 vs. −3.07 cmH_2O, $p = 0.004$). There was a strong interaction between time and DP_{RS} ($p = 0.015$) and DP_L ($p < 0.001$), respectively. The relationship between DP_{RS} and DP_L at any given time point and the relationship between the ΔDP_{RS} and ΔDP_L (baseline to 5 min and baseline to 24 h) were assessed by LOWESS, revealing a strong linear relationship, but significant variation in DP_L and ΔDP_L for any given DP_{RS} or ΔDP_{RS}, respectively (Electronic Supplemental Material figure). There was no difference in DP_{CW} at any time point compared by intervention or mortality, and there was wide variability among all patients in both groups (Table 2).

To evaluate the causes of driving pressure changes within individual subjects, changes in elastance, PEEP and V_T were examined concurrently. The decrease in DP_L at 24 h was explained by a similar decrease in E_L over the same period. There was no difference between control and intervention groups in baseline E_{RS} (29.9 vs 29.9 cmH_2O/L, $p = 0.99$), baseline E_L (21.7 vs 22.1 cmH_2O/L, $p = 0.86$), 5 min E_{RS} (29.9 vs 32.2 cmH_2O/L, $p = 0.48$) or 5 min E_L (21.1 vs 22.9 cmH_2O/L, $p = 0.58$) (Fig. 3). At 24 h the intervention group had a slight decrease in E_{RS} that did not reach statistical significance (29.8 vs 25.2 cmH_2O/L, $p = 0.07$) and significantly lower E_L (23.4 vs 16.5 cmH_2O/L, $p = 0.007$) (Table 2; Fig. 3) and greater change from baseline (ΔE_{RS} −0.09 vs −4.75 cmH_2O/L, $p = 0.01$, ΔE_L 1.69 vs −5.66 cmH_2O/L, $p = 0.0002$) relative to the control group. There was a strong correlation between baseline-to-24 h ΔDP_{RS} and ΔE_{RS} ($r^2 = 0.36$, $p < 0.0001$) and even stronger correlation between ΔDP_L and ΔE_L ($r^2 = 0.65$, $p < 0.0001$, Fig. 4). In contrast, the improved DP at 24 h did not appear to be related to differences in V_T between groups (Table 2).

As PEEP was the only adjusted variable between groups, any differences in DP and elastance should be secondary to differences in PEEP between the control and intervention groups. At baseline, PEEP was the same between the control group and intervention group prior to initiating the protocol (13.0 vs. 12.7 cmH_2O; $p = 0.79$). Targeting positive end-expiratory transpulmonary pressure in the intervention group resulted in increased PEEP at 5 min (12.9 vs. 20.0 cmH_2O; $p < 0.0001$) and 24 h (11.0 vs. 19.3 cmH_2O, $p < 0.0001$) (Table 2; Fig. 3.)

Discussion

The data from our study suggest that utilizing PEEP titration to target positive transpulmonary pressure via esophageal manometry results in both improved elastance and driving pressures. These findings suggest that strategies leading to decreased DP and elastance could be associated with improved 28 day mortality.

Determinations of driving pressure change

The relationship between DP and its determining variables (elastance and V_T) was illustrated in our study, with changes in DP_L in the intervention group strongly correlating with improvement in lung elastance. This improvement was seen despite a small increase in mean

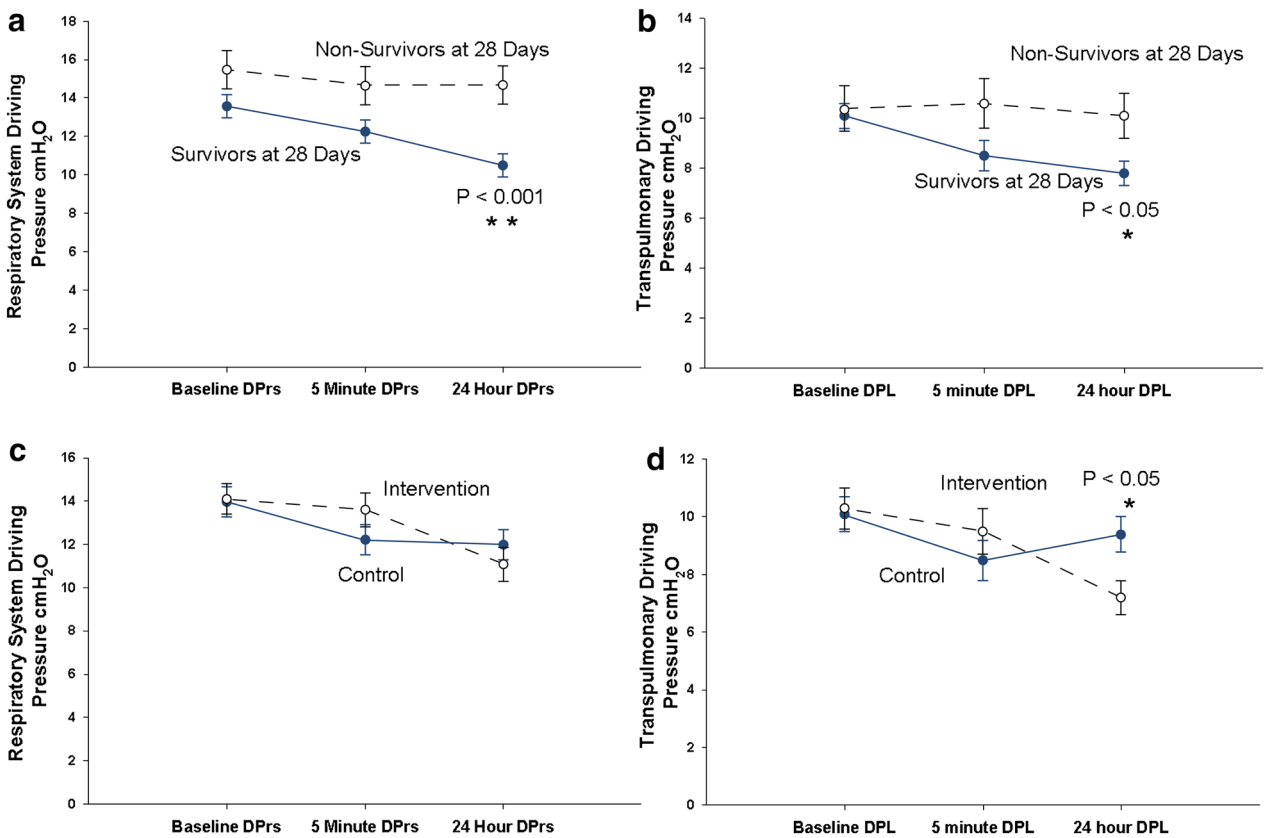

Fig. 2 **a**, **b** Respiratory system and transpulmonary driving pressures in survivors ($n = 42$) and non-survivors ($n = 14$) at 28 days. **c**, **d** Respiratory system and transpulmonary driving pressures in the control group ($n = 29$) and the intervention group ($n = 27$). Data points are means with standard errors at baseline, 5 min and 24 h. *p* values were assessed by analysis of variance (ANOVA)

Table 2 Mechanics at baseline, 5 min and 24 h

Measurement	Baseline			5 min			24 h		
	Control	Intervention	*p* value	Control	Intervention	*p* value	Control	Intervention	*p* value
Driving pressure (cmH_2O)									
Respiratory system	14.0 ± 3.5	14.1 ± 3.5	1.0	12.2 ± 3.3	13.6 ± 4.7	0.2	12.0 ± 3.6	11.1 ± 3.4	0.3
Transpulmonary	10.1 ± 3.3	10.3 ± 3.6	0.8	8.5 ± 3.1	9.5 ± 4.4	0.8	9.4 ± 3.6	7.2 ± 3.0	0.02
Chest wall	3.9 ± 2.4	3.8 ± 0.7	0.7	3.6 ± 0.4	3.8 ± 0.4	0.7	2.7 ± 0.6	3.9 ± 0.6	0.1
Elastance (cmH_2O/L)									
Respiratory system	29.9 ± 10.7	29.9 ± 10.1	1.0	29.9 ± 8.8	32.2 ± 15.3	0.5	29.8 ± 10	25.2 ± 8.8	0.07
Pulmonary	21.7 ± 10.2	22.1 ± 10.1	0.9	21.1 ± 8.9	22.9 ± 14.7	0.6	23.4 ± 10.5	16.5 ± 7.6	0.007
Chest wall	8.2 ± 4.5	7.8 ± 3.7	0.7	8.7 ± 4.1	8.7 ± 5.1	1.0	6.4 ± 5.9	8.7 ± 6.6	0.2
$PEEP_{total}$ (cmH_2O)	14.8 ± 3.6	14.5 ± 4.8	0.8	15.0 ± 3.3	21.9 ± 5.1	<0.0001	13.1 ± 3.4	20.6 ± 4.9	<0.0001
Tidal volume (ml)	490 ± 108	488 ± 103	1.0	415 ± 73	441 ± 82	0.2	416 ± 68	448 ± 64	0.07

Data are presented as the mean ± SD

V_T in the intervention group relative to the control group by 24 h. These results clearly suggest that adjusting PEEP via esophageal manometry to maintain positive transpulmonary pressures resulted in decreases in both elastance and in DP_L. Several studies have suggested possible improved outcomes using higher PEEP strategies

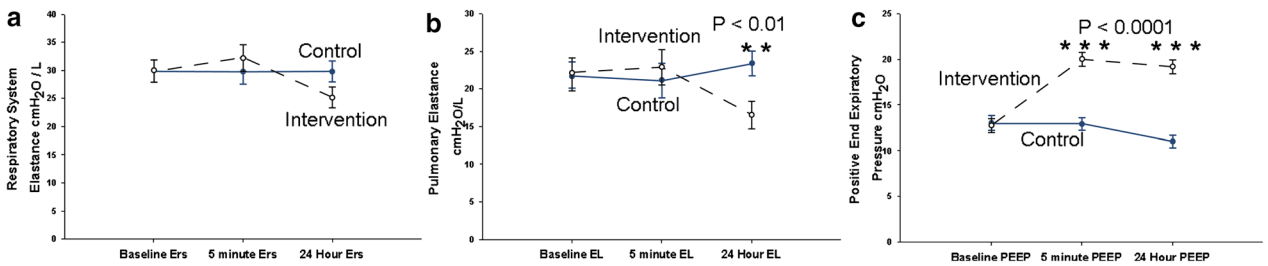

Fig. 3 Control group ($n = 29$) vs. intervention group ($n = 27$) at baseline, 5 min and 24 h. Means and standard errors are shown for elastance of the respiratory system (**a**), pulmonary elastance (**b**), PEEP (**c**). *p* values were assessed by ANOVA

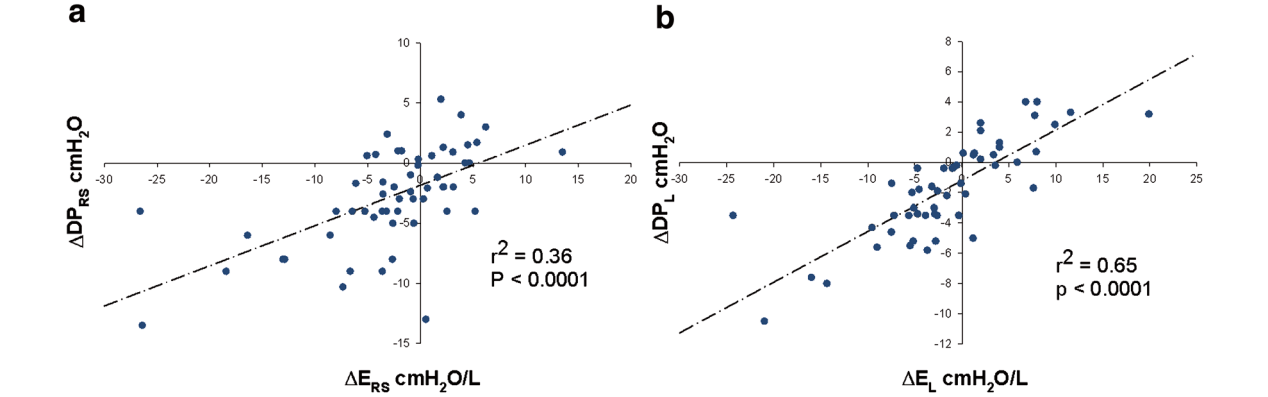

Fig. 4 **a** Change in driving pressure of the respiratory system (ΔDP_{RS}) vs. change in respiratory system elastance (ΔR_{SE}) between baseline and 24 h. **b** Change in transpulmonary driving pressure (ΔDP_L) vs. change in pulmonary elastance (ΔEL) between baseline and 24 h. R^2 was calculated by the linear fit model and *p* was calculated by ANOVA

in patients with ARDS [7, 19–22]. Recruitment leading to increased size of the "baby lung" with subsequent improved compliance [23–25] might be the dominant reason for this finding. However, high PEEP alone is unlikely to be beneficial in all patients. Inappropriate PEEP may in fact cause hemodynamic compromise [26], increased dead space fraction [27] and direct barotrauma with lung over-distension and worsened compliance [27–29].

Our data illustrate that a more targeted approach utilizing esophageal pressure measurements to account for chest wall dynamics may better characterize a "best PEEP" for an individual patient. Although esophageal manometry represents mid-thorax pleural pressures, the net effect of this PEEP optimization appears to improve overall elastance and DP. Finding this "best PEEP" may optimize alveolar recruitment, increasing the size of the "baby lung" and reducing repetitive alveolar opening and closing (atelectrauma), while limiting over-distension and lung injury. Although mean PEEP increased in the intervention group, PEEP was not increased in all cases and the benefit from esophageal pressure monitoring appears to be more nuanced than simply attributing the improved DP_L to the observed increase in PEEP.

Respiratory system versus transpulmonary monitoring

Amato et al. suggested that DP_{RS} would be a reasonable surrogate for DP_L in their analysis [13]; however, the results of our study may question this assessment. Although the majority of the respiratory system driving pressure was accounted for by the lungs, a significant portion (roughly 33 % on average) was secondary to the influence of the chest wall. Despite the LOWESS plots reflecting the expected linear relationship between DP_{RS} and DP_L, these plots illustrate the challenge to estimate the DP_L for any given patient based upon the measured DP_{RS}, with significant variability in chest wall elastance likely secondary to abdominal distension, obesity or chest wall edema which might contribute noise to the DP_{RS} signal, not reflecting underlying lung properties. In theory, by excluding chest wall effects, DP_L may be superior to DP_{RS} as the more accurate marker of lung distending pressures, and utilizing esophageal manometry to estimate and remove the chest wall component may be superior to standard respiratory system measurements using airway pressures. Interestingly, we did not see a significant decrease in DP_{RS} at 24 h in the intervention group despite the statistically significant

decrease in DP_L. While the current study lacks the statistical power to test the hypothesis that DP_L is superior to DP_{RS}, the observations in our study support further tests of this hypothesis. As DP_{RS} appeared to be at least equal to DP_L in terms of mortality correlation, it currently remains unclear if either measurement is superior.

Mortality prediction

With respect to the use of DP as an outcome predictor, Amato et al. proposed that scaling V_T to body weight and "normalizing" to lung size was insufficient as functional lung size in ARDS is markedly decreased [13]. These authors hypothesized that this "baby lung" [24] is manifested as lower respiratory system compliance (C_{RS}) and that "normalizing V_T to C_{RS} and using the ratio as an index of the "functional' size of the lung" would be superior to V_T alone and provide a better predictor of outcomes [13]. This "normalization" the authors refer to is the measured DP_{RS}, which they found to be the strongest predictor of mortality in patients with ARDS. In our study, DP_{RS} and DP_L both decreased by 24 h in the 28 day survivor group, suggesting its possible use for prognostication. As elastance was similarly lower in survivors, it is unclear if DP is independently prognostic, and DP_{RS}, E_{RS}, DP_L and E_L could be further tested in a larger sample size. Ultimately it remains unclear from our data if DP might be useful for prognostication or if higher DP is simply another marker for poorly compliant lungs.

Driving pressure manipulation

It has also been suggested that manipulation of DP could be used for ventilator management at the bedside [13]. Theoretically, DP could be adjusted by changing the V_T (low V_T would similarly lower DP) and by adjusting the PEEP (to optimize compliance). The effects of PEEP adjustment on DP in our study were not seen at the 5 min time point. If there is a delayed response, titration of interventions designed to influence DP in real-time might be challenging. Given that we had data only at 5 min and 24 h, future studies will be needed to clarify the optimal time to determine these changes.

Limitations

There are several significant limitations to this study that will need to be addressed in future investigations. The small sample size and the unequal number of subjects in the survivor and non-survivor groups makes meaningful interpretation of the data challenging, as do the small (but equal) numbers when comparing by intervention. These small numbers do not allow for multivariate analysis to determine if DP might emerge as an independent predictor of mortality and limit our direct comparison of DP_{RS} and DP_L. Furthermore, the retrospective nature of this analysis weakens the interpretation as driving pressure was not a pre-specified endpoint in the initial study.

Conclusions

To our knowledge this is the first study to evaluate DP_L via esophageal manometry as a tool to optimize ventilatory settings in ARDS patients. Although DP_L appeared to be the superior to DP_{RS} for monitoring changes in pulmonary mechanics, further investigation is needed to determine if DP_L or DP_{RS} is better for following mechanics and predicting mortality. These data lend support for future studies on interventions designed to improve driving pressure to determine if DP_L or DP_{RS} can be directly targeted at the bedside to improve outcomes.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4403-7) contains supplementary material, which is available to authorized users.

Author details

[1] Division of Pulmonary and Critical Care, Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Bulfinch 108, Boston, MA 02114, USA. [2] Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, USA.

Acknowledgments

The authors acknowledge Robert Gerber for assistance in making the figures and Victor Novak for assistance with statistical analysis. There was no separate funding source for this study, however the original EPVent study was funded under Stephen Lorings RO1 Grant HL-52586.

Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflicts of interest.

Received: 9 February 2016 Accepted: 23 May 2016
Published online: 18 June 2016

References

1. Bernard GR, Artigas A (2016) The definition of ARDS revisited: 20 years later. Intensive Care Med 42:640–642. doi:10.1007/s00134-016-4281-z
2. Bernard GR, Artigas A, Brigham KL (1994) The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824. doi:10.1164/ajrccm.149.3.7509706
3. Wang CY, Calfee CS, Paul DW et al (2014) One-year mortality and predictors of death among hospital survivors of acute respiratory distress syndrome. Intensive Care Med 40:388–396. doi:10.1007/s00134-013-3186-3
4. Villar J, Blanco J, Kacmarek RM (2016) Current incidence and outcome of the acute respiratory distress syndrome. Curr Opin Crit Care 22(1):1–6. doi:10.1097/MCC.0000000000000266
5. Anonymous (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The acute respiratory distress syndrome network. N Engl J Med 342:1301–1308. doi:10.1056/NEJM200005043421801
6. Amato MB, Barbas CS, Medeiros DM et al (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354. doi:10.1056/NEJM199802053380602
7. Briel M, Meade M, Mercat A et al (2010) Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute

respiratory distress syndrome: systematic review and meta-analysis. JAMA 303:865–873. doi:10.1001/jama.2010.218
8. Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A (2006) A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med 34:1311–1318. doi:10.1097/01.CCM.0000215598.84885.01
9. Gattinoni L, Quintel M (2016) Is mechanical ventilation a cure for ARDS? Intensive Care Med 42:916–917. doi:10.1007/s00134-016-4266-y
10. Dreyfuss D, Hubmayr R (2016) What the concept of VILI has taught us about ARDS management. Intensive Care Med 42:811–813. doi:10.1007/s00134-016-4287-6
11. Slutsky AS (1999) Lung injury caused by mechanical ventilation. Chest J 116:9S–15S
12. Slutsky AS, Ranieri VM (2013) Ventilator-induced lung injury. N Engl J Med 369:2126–2136. doi:10.1056/NEJMra1208707
13. Amato MB, Meade MO, Slutsky AS et al (2015) Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 372:747–755. doi:10.1056/NEJMsa1410639
14. Loring SH, Malhotra A (2015) Driving pressure and respiratory mechanics in ARDS. N Engl J Med 372:776–777. doi:10.1056/NEJMe1414218
15. Talmor D, Sarge T, Malhotra A et al (2008) Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 359:2095–2104. doi:10.1056/NEJMoa0708638
16. Talmor D, Sarge T, O'Donnell CR, Ritz R, Malhotra A, Lisbon A, Loring SH (2006) Esophageal and transpulmonary pressures in acute respiratory failure. Crit Care Med 34:1389–1394. doi:10.1097/01.CCM.0000215515.49001.A2
17. Akoumianaki E, Maggiore SM, Valenza F et al (2014) The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med 189:520–531. doi:10.1164/rccm.201312-2193CI
18. Beitler JR, Goligher EC, Schmidt M et al (2016) Personalized medicine for ARDS: the 2035 research agenda. Intensive Care Med 42:756–767. doi:10.1007/s00134-016-4331-6
19. Brower RG, Lanken PN, MacIntyre N et al (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327–336. doi:10.1056/NEJMoa032193
20. Grasso S, Fanelli V, Cafarelli A, Anaclerio R, Amabile M, Ancona G, Fiore T (2005) Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med 171:1002–1008 (**200407-940OC [pii]**)
21. Meade MO, Cook DJ, Guyatt GH et al (2008) Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 299:637–645. doi:10.1001/jama.299.6.637
22. Mercat A, Richard JC, Vielle B et al (2008) Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 299:646–655. doi:10.1001/jama.299.6.646
23. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. Am Rev Respir Dis 136:730–736. doi:10.1164/ajrccm/136.3.730
24. Gattinoni L, Pesenti A (2005) The concept of "baby lung". Intensive Care Med 31:776–784. doi:10.1007/s00134-005-2627-z
25. Gattinoni L, Marini JJ, Pesenti A, Quintel M, Mancebo J, Brochard L (2016) The "baby lung" became an adult. Intensive Care Med 42:663–673. doi:10.1007/s00134-015-4200-8
26. Luecke T, Pelosi P (2005) Clinical review: positive end-expiratory pressure and cardiac output. Crit Care 9:607–621 (**cc3877 [pii]**)
27. Suter PM, Fairley B, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284–289. doi:10.1056/NEJM197502062920604
28. Gattinoni L, Caironi P, Cressoni M et al (2006) Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 354:1775–1786
29. Eisner MD, Thompson BT, Schoenfeld D, Anzueto A, Matthay MA, Network Acute Respiratory Distress Syndrome (2002) Airway pressures and early barotrauma in patients with acute lung injury and acute respiratory distress syndrome. Am J Respir Crit Care Med 165:978–982. doi:10.1164/ajrccm.165.7.2109059