Pulse Pressure Variations in Acute Respiratory Distress Syndrome: "Fifty Shades of Grey"*

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Over the past 15 years, many studies have demonstrated that the fluid responsiveness method for assessing fluid needs in ICU patients is of value and can improve outcomes (1–4). The clinical study by Michard et al (3) was the first to show that pulse pressure variation (PPV) accurately predicts fluid responsiveness—in contrast to pulmonary artery occlusion pressure and central venous pressure, both of which are unable to predict the effect of fluid infusion on septic shock patients. However, PPV has been widely criticized (5). The pathophysiology of PPV is based on the effects of mechanical ventilation, which induces transpulmonary and intrathoracic pressure changes, which in turn have complex effects on the hemodynamics. The magnitude of these effects depends mainly on the transmission of airway pressure variations to the heart and to intrathoracic large vessels and, therefore, is a critical aspect in acute respiratory distress syndrome (ARDS) in which this transmission is impaired. Protective mechanical ventilation (in which a low tidal volume is used to decrease the plateau pressure and driving pressure) is now widely used with ARDS patients (6–8). However, a low tidal volume decreases airway pressure variations and may dramatically decrease the hemodynamic effects of mechanical ventilation. De Backer et al (9) have clearly demonstrated that PPV depends on the tidal volume; the lower the tidal volume, the lower the PPV. Hence, the accuracy of a predefined cutoff value can be questioned in ARDS patients (9). In an attempt to solve this problem, Vallée et al (10) suggested correcting the PPV for the tidal volume. Unfortunately, this approach failed to improve the accuracy of predicting fluid responsiveness. Likewise, the same team failed to demonstrate any improvement in the prediction of fluid responsiveness by adjusting the PPV for airway pressure variations (i.e., the plateau pressure minus the positive end-expiratory pressure) (10). This can be explained by the fact that airway pressure variations induced by the tidal volume are not related to thoracic pressure variations—particularly, in ARDS patients, in whom lung and thoracic elastances are greatly modified (11). Hence, the same tidal volume in different ARDS patients may induce different intrathoracic pressure variations (depending on lung and chest compliance) and thus will have different hemodynamic consequences. This is why Liu et al (12) suggested measuring pleural pressure variations (ΔPpl) as a surrogate of thoracic pressure variations in ARDS patients and then adjusting the PPV accordingly in order to improve prediction and prevent false negatives for fluid responsiveness. A cutoff value of 2 was determined. The authors applied the concept of a "grey zone" approach that has practical value because it allows the determination of three zones: a zone where the analyzed index predicts a positive response to fluid loading, a zone where the index predicts a negative response, and a third zone of uncertainty or "grey zone" (13). In this issue of *Critical Care Medicine*, Liu et al (12) using this "grey zone" approach defined a zone of PPV/ΔPpl between 1.94 and 2.1, which included a very small proportion of the study population (only 3.1%). Therefore, Liu et al concluded that in ARDS patients with a tidal volume less than 8 mL/kg, PPV/ΔPpl appears to be a much more accurate predictor of fluid responsiveness than PPV.

The latter study had a number of limitations. One of the main problems is that the proposed index requires the ARDS patient's esophageal pressure to be measured with a balloon catheter. Esophageal pressure is used as a surrogate of Ppl in many clinical studies. The accuracy of esophageal manometry is subject to debate because many factors may alter the esophageal/Ppl relationship; this includes the esophageal balloon's elastance, the tone of the esophageal wall, heart/lung weight, and the patient's position. But, fortunately, delta esophageal pressure that was used by Liu et al seems to be correlated with ΔPpl (14). Hence, PPV/delta esophageal pressure may be more accurate than PPV to predict fluid responsiveness. However, small number of ICUs routinely assesses esophageal pressure in ARDS patients—even though the approach has been shown to improve outcomes (15).

Another limitation is that during protective ventilation for ARDS patients, the tidal volume (usually around 5 to 6 mL/kg) is lower than the volume of 7 mL/kg in the study by Liu et al; this limitation makes it difficult to extrapolate the findings by Liu et al to patients with a very low tidal volume.

Approximately 14–50% of cases of ARDS are complicated by acute cor pulmonale (16). In this context, it has been clearly demonstrated that many false-positive PPVs occur due to a right ventricular (RV) afterload effect of mechanical ventilation (rather than a preload effect) (17). During mechanical insufflation, intrathoracic pressure and Ppl increase. This decreases venous return, which then decreases RV ejection and (a few seconds later, due to decreased left ventricular

*See also p. 342.

Key Words: acute respiratory distress syndrome; hypovolemia; pulse pressure variations; shock

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[LV] preload) LV ejection—explaining a delta down and PPV only if both the right and left ventricle are working on the steep part of the Frank-Starling curve. In case of acute cor pulmonale, pulmonary arterial pressure is high and the right ventricle is enlarged and working on the flat part of the Frank-Starling relationship; mechanical insufflation increases pulmonary resistance (by increasing transpulmonary pressure, which compresses pulmonary capillaries), increases RV afterload, and decreases RV ejection, LV preload, and LV ejection. Under these circumstances, the PPV does not reflect fluid responsiveness, and fluid infusion may be harmful (17). Hence, RV dilation and/or dysfunction should be ruled out using echocardiography before using PPV as a predictor of fluid responsiveness (17).

The last limitation on the use of PPV (even when corrected for the ΔPpl) is the feasibility of this measurement. To be valid, PPVs should be recorded in mechanically ventilated, well-sedated patients with a sinus rhythm but no spontaneous breathing. In a 1-day point prevalence study performed in 26 ICUs at 22 French hospitals, we found that a very small proportion of ICU patients (14%) satisfied all the validity criteria for the use of PPV (5).

One must bear in mind that other noninvasive methods can be used to assess the fluid responsiveness in ICU patients with ARDS. The passive leg raising (PLR) maneuver using echocardiography (for the measurement of cardiac output) is highly accurate for recognizing fluid responder and can be used, in contrast with PPV, in spontaneously breathing patients and in patients with arrhythmia (18, 19). Given that the PLR maneuver is independent of the tidal volume and heart-lung interactions, it can be used with confidence in ARDS patients with low tidal volume (in combination with or instead of the method by Liu et al) and seems more accurate than PPV (19).

To summarize, despite limitations, the study by Lui et al demonstrates that the PPV/ΔPpl method (based on the pathophysiology of the heart-lung interaction) can be used at the bedside to assess the fluid responsiveness in ARDS patients with low tidal volumes instead PPV. This method seems very accurate and has a small "grey zone" but needs esophageal pressure measurement. If esophageal pressure cannot be measured for some reason, the PLR maneuver with cardiac output measurement using echocardiography can be used.

REFERENCES

1. Perel A, Pizov R, Cotev S: Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology* 1987; 67:498–502
2. Slama M, Masson H, Teboul JL, et al: Respiratory variations of aortic VTI: A new index of hypovolemia and fluid responsiveness. *Am J Physiol Heart Circ Physiol* 2002; 283:H1729–H1733
3. Michard F, Boussat S, Chemla D, et al: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000; 162:134–138
4. Richard JC, Bayle F, Bourdin G, et al: Preload dependence indices to titrate volume expansion during septic shock: A randomized controlled trial. *Crit Care* 2015; 19:5
5. Mahjoub Y, Lejeune V, Muller L, et al: Evaluation of pulse pressure variation validity criteria in critically ill patients: A prospective observational multicentre point-prevalence study. *Br J Anaesth* 2014; 112:681–685
6. Amato MB, Meade MO, Slutsky AS, et al: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; 372:747–755
7. Briel M, Meade M, Mercat A, et al: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA* 2010; 303:865–873
8. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
9. De Backer D, Heenen S, Piagnerelli M, et al: Pulse pressure variations to predict fluid responsiveness: Influence of tidal volume. *Intensive Care Med* 2005; 31:517–523
10. Vallée F, Richard JC, Mari A, et al: Pulse pressure variations adjusted by alveolar driving pressure to assess fluid responsiveness. *Intensive Care Med* 2009; 35:1004–1010
11. Jardin F, Genevray B, Brun-Ney D, et al: Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. *Chest* 1985; 88:653–658
12. Liu Y, Wei L-q, Li G-q, et al: Pulse Pressure Variation Adjusted by Respiratory Changes in Pleural Pressure, Rather Than by Tidal Volume, Reliably Predicts Fluid Responsiveness in Patients With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016; 44:342–351
13. Biais M, Ehrmann S, Mari A, et al; AzuRea Group: Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: The grey zone approach. *Crit Care* 2014; 18:587
14. Chiumello D, Cressoni M, Colombo A, et al: The assessment of transpulmonary pressure in mechanically ventilated ARDS patients. *Intensive Care Med* 2014; 40:1670–1678
15. Talmor D, Sarge T, Malhotra A, et al: Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359:2095–2104
16. Repessé X, Charron C, Vieillard-Baron A: Acute cor pulmonale in ARDS: Rationale for protecting the right ventricle. *Chest* 2015; 147:259–265
17. Mahjoub Y, Pila C, Friggeri A, et al: Assessing fluid responsiveness in critically ill patients: False-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med* 2009; 37:2570–2575
18. Maizel J, Airapetian N, Lorne E, et al: Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Med* 2007; 33:1133–1138
19. Monnet X, Bleibtreu A, Ferré A, et al: Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med* 2012; 40:152–157

Pulse Pressure Variation Adjusted by Respiratory Changes in Pleural Pressure, Rather Than by Tidal Volume, Reliably Predicts Fluid Responsiveness in Patients With Acute Respiratory Distress Syndrome*

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Objectives: 1) To evaluate the ability of pulse pressure variation adjusted by respiratory changes in pleural pressure to predict fluid responsiveness compared with pulse pressure variation alone. 2) To identify factors explaining the poor performance of pulse pressure variation in acute respiratory distress syndrome.

Design: Prospective study.

Setting: Forty-bed university hospital general ICU.

Patients: Ninety-six mechanically ventilated acute respiratory distress syndrome patients requiring fluid challenge.

Interventions: Fluid challenge, 500 mL saline over 20 minutes.

Measurements and Main Results: Before fluid challenge, esophageal pressure was measured at the end-inspiratory and end-expiratory occlusions. Change in pleural pressure was calculated as the difference between esophageal pressure measured at end-inspiratory and end-expiratory occlusions. Hemodynamic measurements were obtained before and after the fluid challenge. Patients were ventilated with tidal volume 7.0 ± 0.8 mL/kg predicted body weight. The fluids increased cardiac output by greater than 15% in 52 patients (responders). Adjusting pulse pressure variation for changes in pleural pressure (area under the receiver operating characteristic curve, 0.94 [0.88–0.98]) and the ratio of chest wall elastance to total respiratory system elastance (area under the receiver operating characteristic curve, 0.93 [0.88–0.98]) predicted fluid responsiveness better than pulse pressure variation (area under the receiver operating characteristic curve, 0.78 [0.69–0.86]; all $p < 0.01$). The gray zone approach identified a range of pulse pressure variation/changes in pleural pressure values (1.94–2.1) in 3.1% of patients for whom fluid responsiveness could not be predicted reliably. On logistic regression analysis, two independent factors affected the correct classification of fluid responsiveness at a 12% pulse pressure variation cutoff: tidal volume (adjusted odds ratio 1.57/50 mL; 95% CI, 1.05–2.34; $p = 0.027$) and chest wall elastance/respiratory system elastance (adjusted odds ratio, 2.035/0.1 unit; 95% CI, 1.36–3.06; $p = 0.001$). In patients with chest wall elastance/respiratory system elastance above the median (0.28), pulse pressure variation area under the receiver operating characteristic curve was 0.94 (95% CI, 0.84–0.99) compared with 0.76 (95% CI, 0.61–0.87) otherwise ($p = 0.02$).

Conclusions: In acute respiratory distress syndrome patients, pulse pressure variation adjusted by changes in pleural pressure is a reliable fluid responsiveness predictor despite the low tidal volume (< 8 mL/kg). The poor predictive ability of pulse pressure variation in acute respiratory distress syndrome patients is more related to low chest wall elastance/respiratory system elastance ratios than to a low tidal volume. (*Crit Care Med* 2016; 44:342–351)

Key Words: chest wall elastance; fluid challenge; gray zone approach; pleural pressure; volume responsiveness

Appropriate fluid management is a crucial issue in patients with acute respiratory distress syndrome (ARDS) (1–3). Pulse pressure variation (ΔPP) has been proposed to predict fluid responsiveness (FR) (4, 5), that is, whether fluid administration will increase cardiac output

*See also p. 452.

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(CO) by greater than 15%. Mechanical ventilation induces cyclic changes in pleural pressure (ΔPpl) that transiently affect ventricular preload, resulting in greater cyclic changes in stroke volume (SV) when the ventricle operates on the steep (responder) rather than on the flat (nonresponder) portion of the Frank-Starling curve (6). These cyclic changes in SV can be evaluated by ΔPP over the respiratory cycle because the pulse pressure is proportional to SV (7).

However, ΔPP is less reliable in ARDS patients, who are often ventilated with a low tidal volume (V_T) (< 8 mL/kg) as part of protective mechanical ventilation (7–10). It is usually hypothesized that the magnitude of ΔPpl could be too small when V_T is low, such that ΔPP is low even in patients exhibiting significant increases in CO after fluid infusion (responders) (false negative [FN]) (11). In an attempt to improve the performance of ΔPP in patients with low V_T, Vallée et al (8) corrected ΔPP by either the driving pressure [ΔPaw = plateau pressure (Pplat) – total positive end-expiratory pressure (PEEPtot)] or V_T and found that neither ΔPP/ΔPaw nor ΔPP/V_T was a better predictor than ΔPP. We believe that these findings were to be expected because the assumption of Vallée et al that ΔPaw is related to the magnitude of ΔPpl is highly unlikely to be fulfilled in ARDS patients, in whom ΔPpl cannot be predicted from either ΔPaw or V_T due to the great variability of the ratio of chest wall elastance (Ecw) to total respiratory system elastance (E_{RS}) (12–14). As recently outlined by da Silva Ramos et al (15), swings in pleural pressure do not necessarily follow ΔPaw (or V_T), given that $\Delta Ppl = \Delta Paw \times Ecw / E_{RS}$ (12).

TABLE 1. Comparison Between Responders and Nonresponders ($n = 96$)

	Responders ($n = 52$)		Nonresponders ($n = 44$)	
Patient Characteristic	**Baseline**	**After Fluids**	**Baseline**	**After Fluids**
Age, yr	56 ± 20		59 ± 14	
Gender, male (%)	37 (71.2)		31 (70.5)	
Acute Physiology and Chronic Health Evaluation II score	25 ± 3.5		25 ± 2.8	
Plateau pressure, cm H_2O	30 ± 4.5		28 ± 4.3[a]	
Tidal volume, mL/kg predicted body weight	7.0 ± 0.8		7.2 ± 0.7	
Respiratory rate, breaths/min	22 ± 6		23 ± 5	
Pao_2:FIo_2 ratio, mm Hg	135 ± 52		138 ± 53	
Respiratory system elastance, cm H_2O/L	35.7 ± 8.2		32.4 ± 8.2	
Chest wall elastance, cm H_2O/L	8 (6.6–11)		10 (7.7–13.0)[a]	
Respiratory changes in pleural pressure, cm H_2O	4.0 (3.0–5.4)		5.0 (4.0–7.0)[a]	
Severe sepsis or septic shock, *n* (%)	31 (59.6)		26 (59.1)	
Heart rate, beats/min	99 ± 17	98 ± 16[b]	94 ± 13	93 ± 12[c]
Mean arterial pressure, mm Hg	70 ± 12	79 ± 10[b]	71 ± 9	75 ± 10[b,d]
central venous pressure, mm Hg	13.4 ± 4.3	16.7 ± 3.4[b]	13.3 ± 4.5	17.0 ± 4.9[b]
Pulse pressure variation, %	14.4 ± 8.5	8.7 ± 5.4[b]	8.2 ± 2.5[e]	7.1 ± 2.4[b,d]
Cardiac index, L/min/m^2	3.4 ± 0.9	4.4 ± 1.0	3.8 ± 0.9[a]	3.8 ± 1.0
Cardiac output, L/min	6.3 ± 1.7	8.0 ± 2.1	7.0 ± 1.9[a]	7.0 ± 2.1
Hemoglobin, g/dL	11 ± 2.6		10 ± 2.5	
Lactate, mEq/L	3.6 ± 1.8		3.5 ± 2.0	
Norepinephrine, *n*; dose(μg/kg/min)	46; 0.8 (0.4–1.1)		40; 0.6 (0.25–1.0)	

FIo_2 = fraction of inspired oxygen, Pao_2 = partial pressure of arterial oxygen.
[a]$p < 0.05$ nonresponders versus responders (at baseline).
[b]$p < 0.001$ versus baseline.
[c]$p < 0.05$ versus baseline
[d]$p < 0.001$ differences in evolution during fluid challenge between responders and nonresponders (analysis of variance).
[e]$p < 0.001$ nonresponders versus responders (at baseline).
Data are mean ± SD or median (25–75% interquartile range). "Responders" refers to patients in whom fluid challenge increased cardiac output by ≥ 15%. "Nonresponders" refers to the other patients.

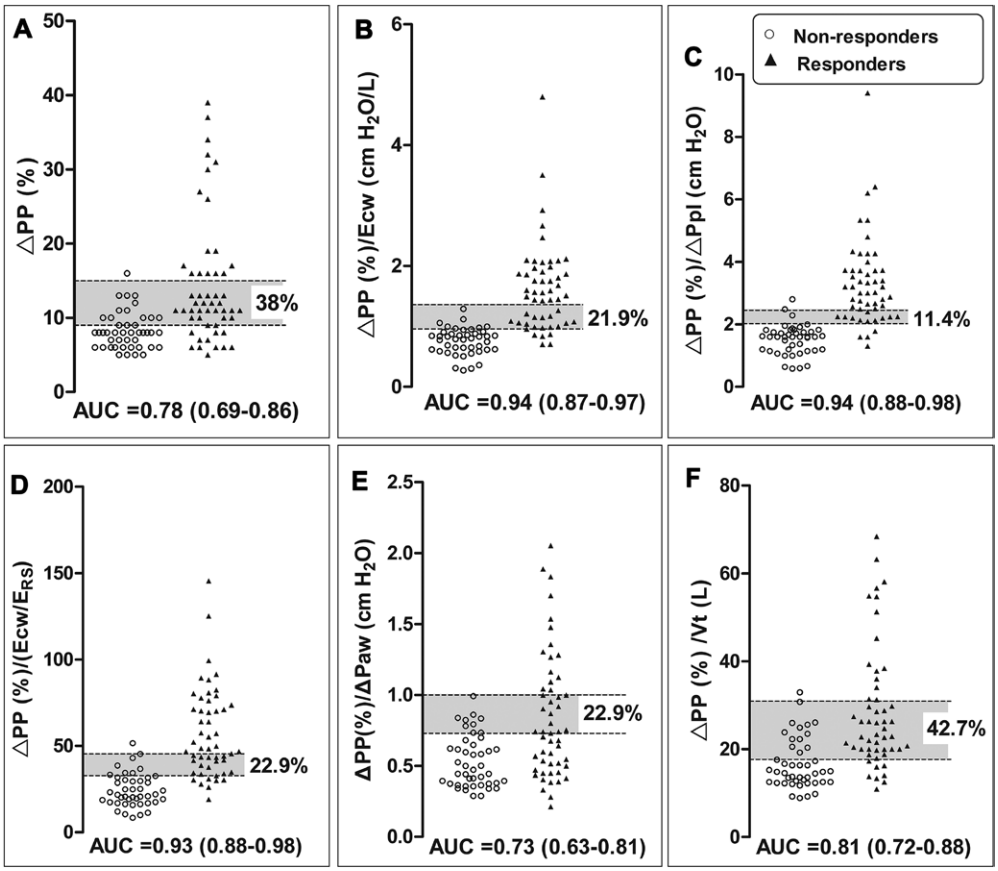

Figure 1. Individual values of baseline pulse pressure variation (ΔPP) and ΔPP corrected for five respiratory variables in responders and nonresponders. The gray zones for "restrictive" fluid strategy (cost ratio = 2), which are represented as *shaded zones*, indicated two cutoffs between which the diagnosis of fluid responsiveness remains uncertain. The percentage in each figure (**A**–**F**) represents the proportion of results inside the gray zone. Responders are defined as patients whose cardiac output increased by at least 15% after a 500-mL saline bolus infusion. Ranges in parentheses represent 95% CIs. AUC = area under the receiver operating characteristic curve, Ecw = chest wall elastance, ERS = respiratory system elastance, ΔPaw = airway driving pressure calculated as the difference between plateau pressure and total positive end-expiratory pressure, ΔPpl = respiratory variations in pleural pressure, VT = tidal volume.

Considering that the small ΔPpl observed in patients with ARDS is the main factor responsible for the low ΔPP values in fluid responders (16), we hypothesized that normalizing ΔPP by ΔPpl could prevent some of the FN results obtained with ΔPP. The first aim of this study was to evaluate the predictive performance of ΔPP/ΔPpl in ARDS patients ventilated with a low VT (< 8 mL/kg). ΔPP/ΔPpl was evaluated using a gray zone approach and a risk-benefit assessment model for fluid administration. The second aim was to investigate the effects of respiratory variables (Pplat, ΔPaw, VT, and Ecw/E_{RS}) on ΔPP performance and to identify the main factors responsible for the poor performance of ΔPP in the ARDS population.

MATERIALS AND METHODS

Setting and Patients

In this prospective observational study, consecutive patients admitted to a 40-bed ICU of a university teaching hospital from July 2013 to July 2014 were assessed. The institutional review board at our hospital approved this study, and written informed consent was obtained from the patients' nearest relatives.

Patients were included if they met all of the following criteria: age older than 18 years; presence of circulatory failure defined as a systolic arterial pressure less than 90 mm Hg (or a > 50 mm Hg decline of systolic arterial pressure in patients known to be hypertensive) with signs of hypoperfusion (urinary flow < 0.5 mL/kg/min for > 2 hr, tachycardia > 100 beats/min, or presence of skin mottling); a diagnosis of ARDS according to the Berlin definition (17); instrumentation with a thermodilution catheter; need for esophageal manometry and fluid challenge, as decided by the attending physician; and absence of cardiac arrhythmia and of spontaneous triggering of the ventilator. Exclusion criteria were uncontrolled hemorrhage, significant valvular disease or intracardiac shunt, and air leakage through chest drains. The study was stopped if the respirator settings were changed or there was respiratory intolerance to volume expansion (a > 5% decrease in pulse oximetry [Spo_2]).

Study Design

Patients were sedated and ventilated with a Viasys Avea ventilator (CareFusion, Yorba Linda, CA) using the volume-controlled mode; VT was adjusted to 5–8 mL/kg based on the patient's predicted body weight (18, 19). The Viasys Avea ventilator can be used to measure esophageal pressure (Pes). An esophageal balloon catheter was passed to a depth of 60 cm from the incisors to measure gastric pressure and then withdrawn to a depth of 40 cm to record Pes during mechanical ventilation. Correct positioning of the balloon was verified as previously described (20). Then, fluid challenge was performed with a 500-mL saline bolus infused over 20 minutes (21). The CO increase induced by fluid challenge was used to classify each patient as a responder (≥ 15% increase in CO) or nonresponder (< 15% increase in CO) (8, 22). FR was also defined as a greater than or equal to 15% increase in SV.

Measurements

Hemodynamic measurements obtained before and after fluid challenge included heart rate (HR), mean arterial pressure (MAP), central venous pressure, SV, ΔPP, and CO. CO was determined by the average of three thermodilution

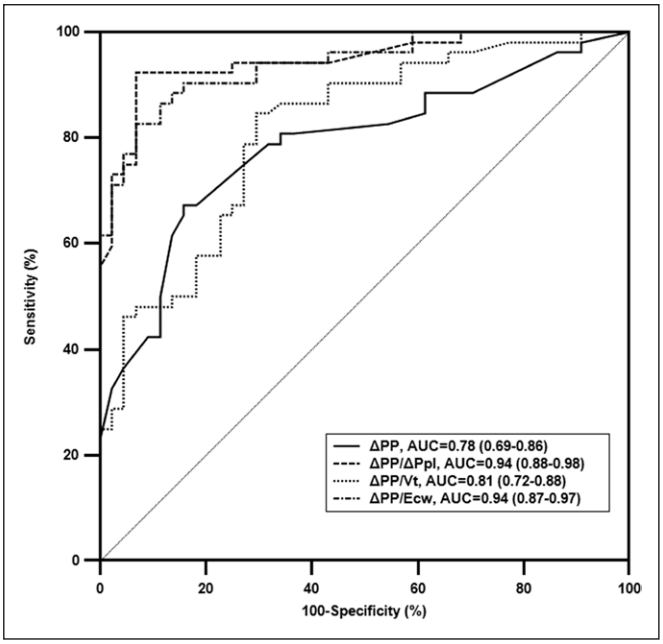

Figure 2. Receiver operating characteristic curves comparing the ability of various indices to detect a fluid-induced increase in cardiac output of > 15% in the whole acute respiratory distress syndrome population ($n = 96$). The area under the receiver operating characteristic curve (AUC) values for pulse pressure variation (ΔPP, %) corrected for respiratory variations in pleural pressure (ΔPpl, cm H_2O) and chest wall elastance (Ecw, cm H_2O/L) were higher than that for ΔPP ($p < 0.001$). AUCs for ΔPP and ΔPP corrected for tidal volume (V_T, L) were not significantly different ($p > 0.05$).

measurements using 15 mL cold saline with the PiCCO system (Pulsion Medical Systems, Munich, Germany). ΔPP was calculated by an observer blinded to the other hemodynamic variables, as previously described (23). Three consecutive measurements were averaged.

Measurements obtained before fluid challenge included the partial pressure of arterial oxygen, PEEPtot, respiratory rate (RR), V_T, Pplat, ΔPaw, Pes measured at end-inspiratory (Pes, eio) and end-expiratory (Pes, eeo) occlusions, E_{RS}, Ecw, and lung elastance (E_L). Pplat was measured during end-inspiratory occlusion and PEEPtot during end-expiratory occlusion. ΔPaw was calculated as Pplat – PEEPtot. ΔPpl was calculated as the difference between Pes, eio and Pes, eeo. E_{RS} was calculated as (Pplat – PEEPtot) / V_T (Eq. *1*). Ecw was calculated as ΔPpl/V_T (Eq. *2*). E_L was estimated as the difference between E_{RS} and Ecw. Rearranging Equations *1* and *2*, it follows that ΔPpl = (Pplat – PEEPtot) × Ecw / E_{RS} (Eq. *3*) and hence ΔPpl = ΔPaw × Ecw / E_{RS} (Eq. *4*). Respiratory system compliance (C_{RS}), which is the reciprocal of E_{RS}, was calculated as V_T / (Pplat – PEEPtot).

Statistical Analysis

Data were expressed as the mean ± SD or the median (25–75% interquartile range) unless otherwise specified. Differences between subgroups at baseline were assessed by Student *t* test or the Mann-Whitney test, as appropriate. Differences between the two groups in the evolution of hemodynamic variables from baseline to the end of fluid challenge were evaluated by repeated-measures analysis of variance.

Correlations between variables were evaluated using linear regression. A multivariate logistic regression model was used to identify factors significantly associated with correct classification (true-positive [TP] and true-negative results) of FR status with a △PP cutoff value of 12%. Given that the percentage of correct classifications at a 12% ΔPP was 63.5% in this study, up to four variables could potentially be included. Adjusted odds ratios (ORs) and 95% CIs were computed for variables independently associated with the event (1 = correct classification of FR).

Receiver operating characteristic (ROC) curves were constructed to evaluate the capacity of each index to predict FR. A result was defined as TP when an index predicted responder status and the patient actually was fluid responsive. Areas under ROC curves (AUCs) were compared using the Hanley-McNeil test (24). In addition, the predictive ability of each index was evaluated using a two-step gray zone approach (25), which indicated two cutoffs between which the diagnosis of FR remained uncertain. The first step comprised the determination of the best threshold in each of the 1,000 bootstrapped populations for each variable. The 95% CI of these 1,000 optimal cutoffs defines a gray zone. A second step defined three classes of response: negative, inconclusive, and positive. We defined inconclusive responses as values with either sensitivity less than 90% or specificity less than 90% (diagnosis tolerance of 10%). Sensitivity and specificity were then plotted on two curves. The gray zone was defined as the largest 95% CI of these two approaches.

Changes in gray zone limits according to the cost ratio (R = cost [false positive (FP)] / cost [FN]) were also evaluated. R less than 1 denotes that not treating an FN result is worse than treating an FP one (which would characterize a "liberal" fluid strategy); R greater than 1 denotes that to treat an FP result is worse than missing an FN one (characterizing "restrictive" fluid management).

Sample Size Estimation

Based on previous results, AUCs for ΔPP were below 0.75 in ARDS patients with low V_T (7, 22), 48% of whom would be expected to exhibit FR (7, 22). Taking into account the finding that ΔPP/ΔPpl was associated with an AUC greater than 0.90 in our pilot measurements, a sample of 34 from the positive group (responders) and 37 from the negative group (nonresponders) would achieve a power of 80% to detect a difference of 0.15 between an AUC of 0.75 and another AUC of 0.90 using a two-sided *z* test at a significance level of 0.05. The analyses were performed using SPSS Version 21.0.0 (IBM, Armonk, NY) and R 3.01 with the pROC package.

RESULTS

Five of the 103 patients (4.9%) meeting the inclusion criteria were excluded because of valvular disease ($n = 1$), intracardiac shunt ($n = 2$), or air leakage through chest drains ($n = 2$). Fluid infusion was interrupted in two patients because of a greater than 5% decrease in Spo_2. Fifty-two of the remaining 96 ARDS patients (54%) were defined as responders because CO increased by greater than or equal to 15% after fluid challenge. The proportion of responders was the same when response was

TABLE 2. Ability of Pulse Pressure Variation and Corrected Pulse Pressure Variation Values to Predict Fluid Responsiveness in 96 Acute Respiratory Distress Syndrome Patients Ventilated With Tidal Volume Less Than 8 mL/kg

Variables	ΔPP	ΔPP/ΔPaw	ΔPP/V_T Predicted Body Weight (kg)	ΔPP × E_{RS}	ΔPP/(HR/RR)	ΔPP Common Cutoff	ΔPP/Ecw	ΔPP/ΔPpl
Area under the receiver operating characteristic curve	0.78 (0.69–0.86)	0.73 (0.6–0.81)	0.81 (0.71–0.88)	0.8 (0.7–0.87)	0.75 (0.65–0.84)	0.78 (0.69–0.86)	0.94 (0.87–0.97)[a]	0.94 (0.88–0.98)[a]
Threshold, %	> 10	> 0.86	> 1.15	> 300	> 2.12	> 12	> 0.996	> 2
Sensitivity, %	67.3 (52.9–79.7)	42.3 (28.7–56.8)	88.5 (76.6–95.6)	75 (61.1–86)	73.1 (58.7–84.0)	42.3 (29.0–56.7)	82.7 (69.7–91.8)	92.3 (81.5–97.9)
Specificity, %	84.0 (69.9–93.4)	97.7 (88.0–99.9)	68.2 (52.4–81.4)	75 (59.7–86.8)	68.2 (52.3–81.0)	88.6 (74.6–95.7)	93.2 (81.3–98.6)	93.2 (81.3–98.6)
Positive likelihood ratio	4.2 (2.1–8.6)	18.6 (2.6–132)	2.8 (1.8–4.3)	3.0 (1.8–5.1)	2.4 (1.4–3.6)	3.7 (1.5–9.0)	12.1 (4.0–36.4)	13.5 (4.5–40.5)
Negative likelihood ratio	0.4 (0.3–0.6)	0.59 (0.5–0.7)	0.17 (0.1–0.4)	0.3 (0.2–0.5)	0.4 (0.2–0.6)	0.65 (0.5–0.8)	0.2 (0.1–0.3)	0.08 (0.03–0.2)
Positive predictive value, %	83.3 (68.0–92.4)	95.6 (76.0–99.7)	76.6 (63.6–86.2)	78 (63.6–88)	73.1 (58.7–84.0)	81.8 (61.3–92.9)	93.4 (81.1–98.3)	94.1 (82.8–98.5)
Negative predictive value, %	68.5 (54.3–80)	58.9 (46.7–70.1)	83.3 (66.5–93.0)	71.7 (56.3–83.5)	68.2 (52.3–81.0)	56.5 (44.1–68.2)	82 (68.1–91.0)	91.1 (77.9–97.2)

ΔPP (%) = pulse pressure variation, ΔPaw (cm H_2O) = airway driving pressure calculated as the difference between plateau pressure and total positive end-expiratory pressure, V_T = tidal volume, E_{RS} (cm H_2O/L) = total respiratory system elastance, HR/RR = heart rate:respiratory rate ratio, Ecw (cm H_2O/L) = chest wall elastance, ΔPpl (cm H_2O) = respiratory changes in pleural pressure.

[a]$p < 0.05$ compared with ΔPP. Ranges in parentheses represent 95% CIs.

defined as a greater than or equal to 15% increase in SV. Comparisons between responders and nonresponders are shown in **Table 1**. In the population as a whole, fluid challenge significantly increased the cardiac index and MAP from 3.6 ± 0.9 to 4.2 ± 1.1 l/min/m^2 ($p < 0.001$) and 70 ± 10 to 78 ± 9.9 mm Hg ($p < 0.001$), respectively, whereas ΔPP was significantly decreased from 11.6 ± 7.1 to 7.9 ± 4.3 ($p < 0.001$). The changes in the MAP and ΔPP were significantly larger in the responders than in the nonresponders (Table 1).

Predictive Performance

Figure 1 shows the individual values of ΔPP and adjusted ΔPP in responders and nonresponders. The abilities of the indices to predict FR were tested by using ROC curve analysis (**Fig. 2**). The areas under the ROC curves for ΔPP values adjusted for ΔPpl, Ecw, and Ecw/E_{RS} were significantly ($p < 0.01$) larger than that for ΔPP alone. Adjusting ΔPP for other variables (Pplat, ΔPaw, V_T, E_{RS}, HR/RR, and E_L) did not improve the predictive performances (all $p > 0.05$) (**Table 2**; and **Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463).The best cutoff values for ΔPP and ΔPP/ΔPpl were 10% (sensitivity = 67.3% and specificity = 84%) and 2% (sensitivity = 92.3% and specificity = 93.2%), respectively. The common ΔPP cutoff of 12% had a sensitivity of 42.3% and specificity of 88.6% (Table 2).

Gray Zones for ΔPP and ΔPP/ΔPpl

For normal fluid policy (cost ratio = 1), the gray zone approach identified a range of ΔPP values, between 7% and 12%, for which FR cannot be reliably predicted. More than 45% of the patients were within this inconclusive zone (**Fig. 3, *A*** and ***B***). By contrast, ΔPP/ΔPpl had a narrow gray zone (1.94–2.1) for normal fluid policy ($R = 1$) that only included 3.1% of the patients (**Fig. 3, *C*** and ***D***). Furthermore, the gray zone limits change according to the cost ratio chosen. When applying "restrictive" fluid management (cost ratio = 2), unnecessary fluid loading is considered to be two times more deleterious than nonoptimal CO maximization (potential risk: organ hypoperfusion); the gray zone for ΔPP/ΔPpl was 2.02–2.45 and included only 11 patients (11.4%) (Figs. 1 and **3*F***; and **Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). All results were the same when responders were defined by a 15% fluid-induced increase in SV.

Factors Influencing Baseline ΔPP Performance

Multivariate logistic regression identified Ecw/E_{RS} (OR, 2.035 per 0.1 unit; 95% CI, 1.36–3.06; $p = 0.001$) and V_T (OR, 1.57 per 50 mL; 95% CI, 1.05–2.34; $p = 0.027$) as the only independent factors associated with correct classification of responsiveness status at a ΔPP cutoff value of 12%, with the former being the major determinant (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463).

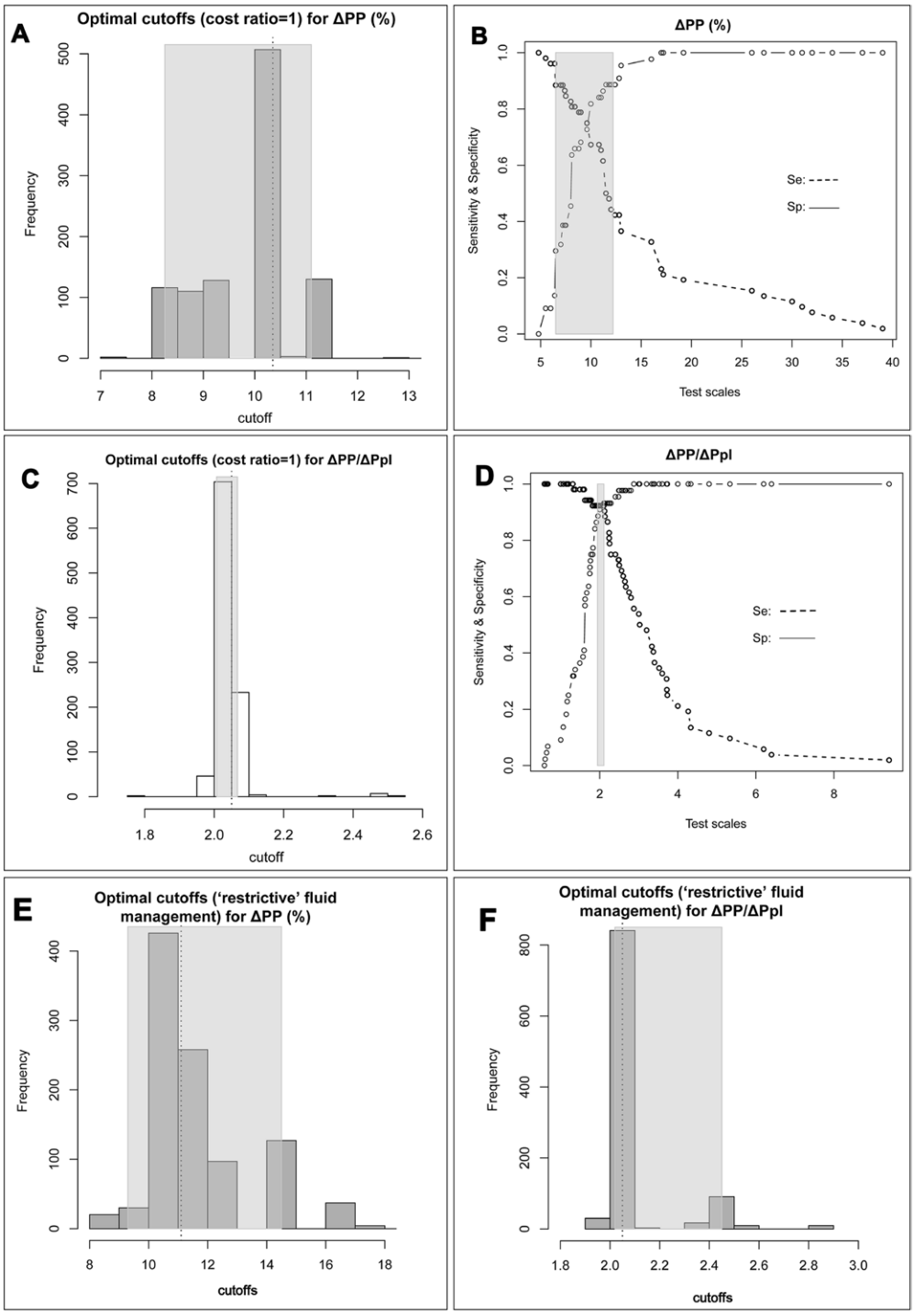

Figure 3. Determination of the gray zones for pulse pressure variation (ΔPP) and ΔPP corrected for respiratory variations in pleural pressure (ΔPpl) according to a normal fluid policy (cost ratio: $R = 1$) or a "restrictive" fluid policy (cost ratio: $R = 2$). The gray zone approach indicated two cutoffs between which the diagnosis of fluid responsiveness remains uncertain. The distribution of the optimal cutoffs for each of the 1,000 resampled population is depicted by histograms (**A**, **C**, **E,** and **F**). The gray zone (95% CI for the optimal cutoffs) is represented as a *shaded zone*. The *vertical dotted lines* indicate the medians of the optimal cutoffs. Two graphs show receiver operating characteristic curves (**B** and **D**) for the sensitivity (Se; *open circle, dashed line*) and specificity (Sp; *open circle, solid line*) of each index (ΔPP [**B**] and ΔPP/ΔPpl [**D**]) according to the value of the cutoff. The inconclusive zone, which is more than 10% of diagnosis tolerance, is represented as a *shaded area*.

To identify any subpopulation in which ΔPP might achieve better results, we performed a subgroup analysis. In the case of Ecw/E_{RS} above the median value (> 0.28), ΔPP was associated with an AUC of 0.94 (95% CI, 0.87–0.99) compared with 0.76 (95% CI, 0.61–0.87) otherwise ($p = 0.02$). The predictive performance of ΔPP differed most between patients with lower and higher values of Ecw/E_{RS} at $Ecw/E_{RS} = 0.38$ (**Fig. 4*C***; and **Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). In addition, ΔPP performed significantly better in patients with V_T above the median value (> 516 mL) than in those with V_T less than 516 mL (**Fig. 4*D***; and **Fig. S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). By contrast, ΔPP performed similarly in subgroups of patients according to the Pplat, ΔPaw, C_{RS}, E_L, and HR/RR ratio (**Fig. 4*B***; and **Fig. S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463).

Among the respiratory variables (Pplat, ΔPaw, V_T, E_{RS}, ΔPpl, and Ecw/E_{RS}), ΔPpl is the most important determinant of ΔPP in both responders ($R^2 = 0.66$; $p < 0.001$) and nonresponders ($R^2 = 0.18$; $p = 0.005$) (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463; and **Fig. S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). Furthermore, ΔPpl is most importantly influenced by Ecw ($R^2 = 0.84$; $p < 0.001$) and Ecw/E_{RS} ($R^2 = 0.69$; $p < 0.001$) and cannot be reliably estimated from V_T, ΔPaw, E_{RS}, and Pplat (**Fig. 5**; and **Table S5**, Supplemental Digital Content 1, http://links.lww.com/CCM/B463).

DISCUSSION

In 96 ARDS patients without arrhythmia or spontaneous respiratory activity, our results confirmed earlier findings (7, 8, 10) that ΔPP is an unreliable predictor of FR. Our study also confirmed a previous hypothesis (11, 26) that ΔPpl is too low at low V_T and,

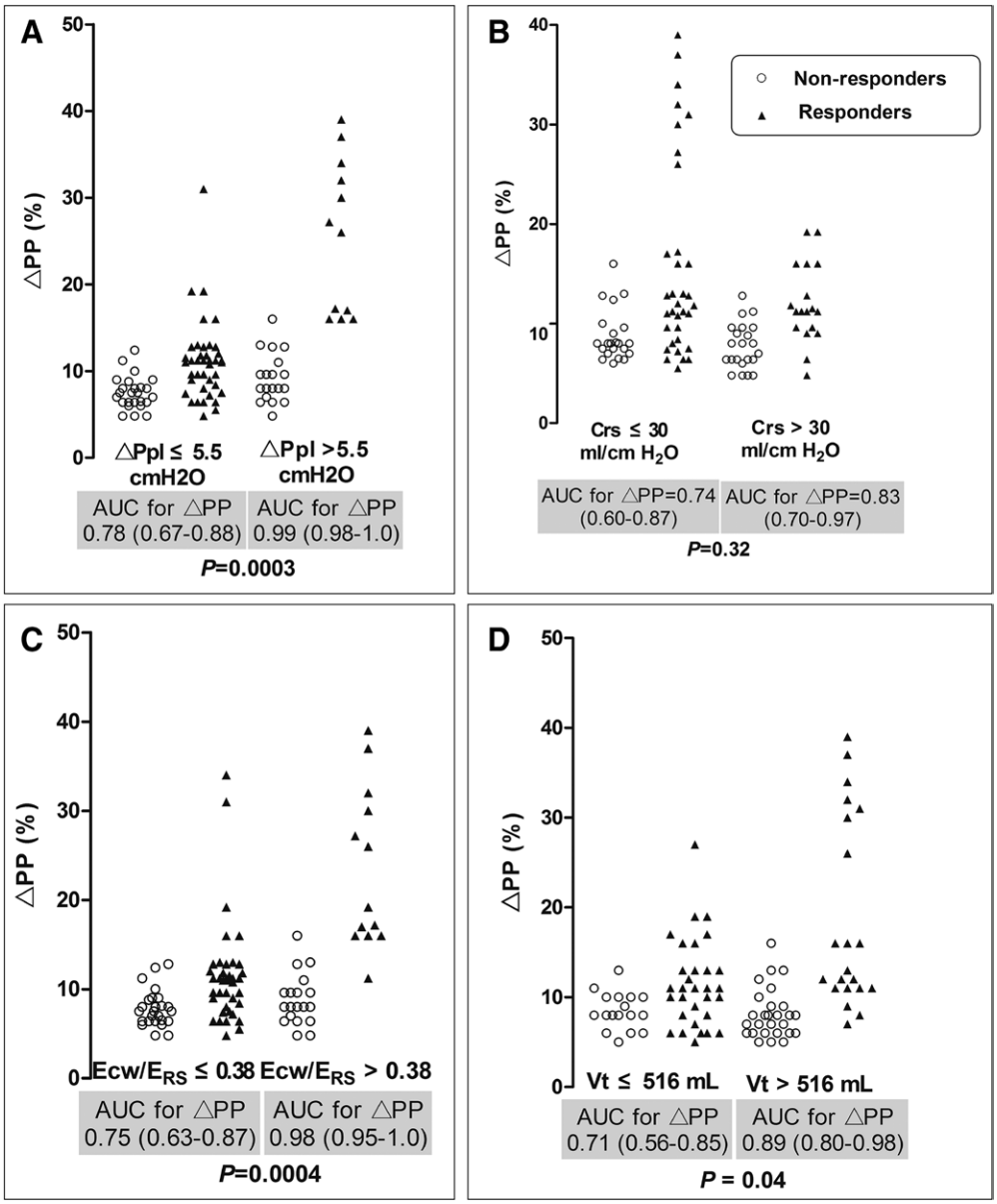

Figure 4. Individual values of baseline pulse pressure variation (ΔPP) according to volume responsiveness status in subgroups of patients analyzed according to respiratory changes in pleural pressure (ΔPpl) higher or lower than 5.5 cm H_2O (**A**), respiratory system compliance (Crs) higher or lower than the median value of 30 mL/cm H_2O (**B**), chest wall elastance/respiratory system elastance ratio (Ecw/Ers) higher or lower than 0.38 (**C**), and tidal volume (Vt) higher or lower than the median value of 516 mL (**D**). AUC = area under the receiver operating characteristic curve.

In previous publications (7, 27), the poor predictive ability of ΔPP was related to low Vt. The present work advances the field by showing that the poor ΔPP performance is related more to a low Ecw/E_{RS} than to the low Vt, such that normalization of ΔPP by Ecw/E_{RS} markedly improved the prediction of FR, whereas ΔPP corrected for Vt did not (Fig. 2 and Table 2). The inability of ΔPP/Vt (or ΔPP/ΔPaw) to improve the prediction of FR in ARDS patients is in line with previous findings (8, 22). Actually, we do believe that a low Vt induces small respiratory variations in pleural pressure (ΔPpl), and consequently low ΔPP values, even in responders (FNs). The issue is that the magnitude of ΔPpl was mostly attenuated by a low Ecw/E_{RS} ratio (R^2 = 0.69), but to a lesser extent by low Vt (R^2 = 0.12) (Fig. 5), emphasizing the prominent role of reduced Ecw/E_{RS} over low Vt in generating the low ΔPP values of responders in the ARDS population (Fig. 4; and Fig. S4, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). Indeed, given that ΔPpl = ΔPaw × Ecw / E_{RS} and ΔPaw = E_{RS} × Vt, the great variability of Ecw/E_{RS} observed in our study (range, 0.07–0.67), similar to the 0.08–0.8 range reported for ICU populations with ARDS in the literature (12, 13, 28, 29), accounts for the inadequacy of ΔPaw or Vt as a determinant of ΔPpl (and of ΔPP) (Fig. 5; and Fig. S4, Supplemental Digital Content 1, http://links.lww.com/CCM/B463) and explains the differences in cutoff values for ΔPP among previous studies (7, 22, 30) (5–12% in ARDS patients).

However, as proposed by Chiumello et al (12), any influence of Ecw/E_{RS} on ΔPpl (and thus on ΔPP) may appear unrealistic in non-ARDS subjects, in whom an Ecw/E_{RS} ratio of 0.5 is expected and for whom the main determinant of ΔPpl would be ΔPaw (11). This could explain why Vallée et al (8) and Muller et al (10) reported that ΔPP performance was largely related to ΔPaw in non-ARDS patients, such that adjusting

therefore, ΔPP can indicate nonresponsiveness in "responders" (FNs). However, the reduced ΔPP can be corrected by low ΔPpl values because ΔPP and ΔPpl are strongly correlated in both responders and nonresponders (Table S4, Supplemental Digital Content 1, http://links.lww.com/CCM/B463; and Fig. S4, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). A ΔPP/ΔPpl greater than 2 predicted FR with a sensitivity of 92.3% and a specificity of 93.2%. We did not investigate the predictive ability of SV variation obtained by the PiCCO device (or by esophageal Doppler monitoring) in ARDS patients. This would be an interesting direction for future studies.

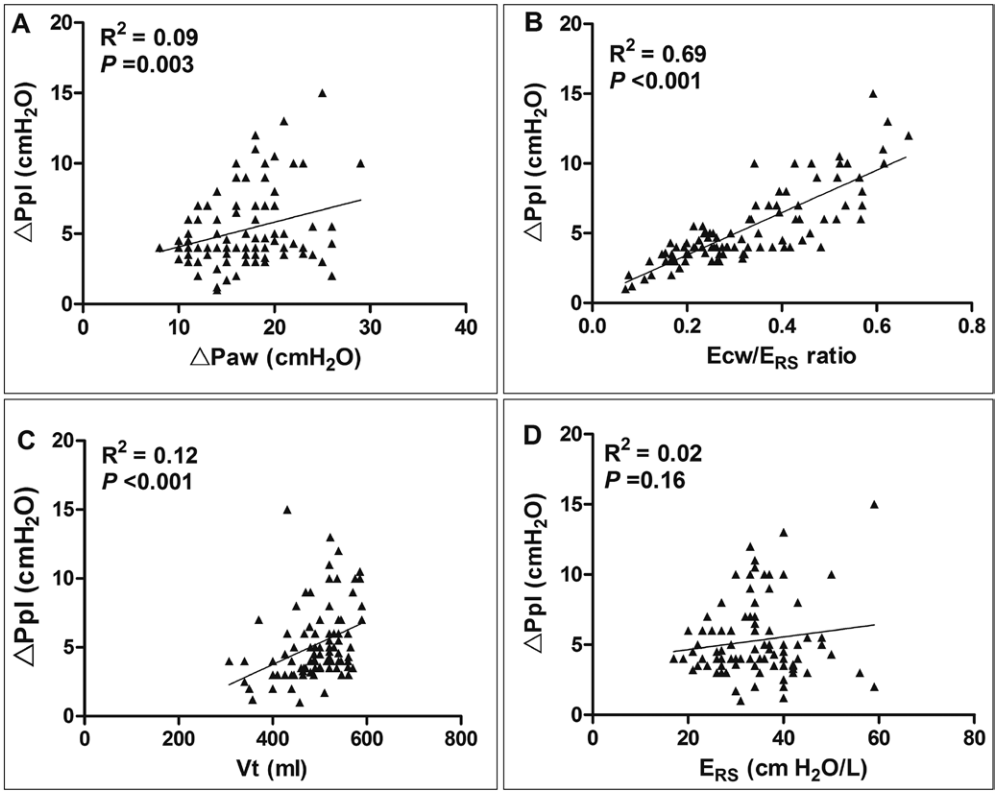

Figure 5. Respiratory changes in pleural pressure (ΔPpl) plotted against four different variables ($n = 96$). According to the physiological equation, airway driving pressure (ΔPaw) and the ratio of chest wall elastance (Ecw) to total respiratory system elastance (Ers) together determine the value of ΔPpl (ΔPpl =ΔPaw × Ecw / Ers). As shown, ΔPpl is strongly correlated with Ecw/Ers (**B**), weakly correlated with ΔPaw (**A**) and tidal volume (Vt) (**C**), and not correlated with Ers (**D**).

ΔPP for ΔPaw increased its performance in patients ventilated with a Vt greater than 8 mL/kg (8).

Although Monnet et al (31) showed that the low ability of ΔPP to predict FR was related to low Crs (= 1 / E_{RS}), others failed to demonstrate any such effect (22, 32). These contradictory findings can be explained by partitioning E_{RS} into its lung and chest wall components. Our study clearly demonstrates that a low Ecw/E_{RS}, rather than a low Crs (or high E_{RS}), induces reduced pleural pressure swings (ΔPpl) and therefore low ΔPP values in responders (FN results). Indeed, the same value of E_{RS} (1 / Crs) can generate dramatically different values of ΔPpl and ΔPP (Fig. 5; and Fig. S4, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). The highly variable relation between E_{RS} and ΔPpl is mainly due to great variations in Ecw (ΔPpl = ΔPaw × Ecw / E_{RS}) and explains why a low Crs is not a key factor accounting for the decreased magnitude of ΔPpl and the consequent low ΔPP values in responders, especially in the case of ARDS, where Ecw varies widely among patients (12, 13).

Despite the high accuracy of ΔPP/ΔPpl in predicting FR, the single cutoff (i.e., ΔPP / ΔPpl > 2) that dichotomizes the population does not enable the clinician to take decisions concerning fluid infusion because there is always an overlap of ΔPP / ΔPpl values between responders and nonresponders (Fig. 1). The gray zone approach provides two cutoffs and appears to be more informative for ICU physicians. One cutoff (the lower limit of the gray zone) is chosen to exclude a fluid challenge with near certainty, whereas the second cutoff (the upper limit of the gray zone) is chosen to initiate a fluid challenge with near certainty. More importantly, the ΔPP/ΔPpl gray zone changes depending on whether the clinician aims at a "restrictive," "normal," or "liberal" fluid policy (Fig. 3; and Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/B463), which is of major clinical importance. A restrictive fluid strategy is highly recommended (3) in ARDS patients for most of the course of treatment. However, the fact that the goal-directed therapy provided at the earliest stages of septic shock has significant short-term and long-term benefits (33) could influence the clinician toward choosing a "liberal" therapy ($R < 1$) for some patients with ARDS and septic shock, at least in the early hours of their illness. When a given value of ΔPP/ΔPpl is in the gray zone (i.e., between 2.02 and 2.45 for a "restrictive" fluid policy), a "minifluid" challenge could be a valuable alternative.

Only some 50% of patients respond to fluid challenge (25, 34), so the poor predictive ability of ΔPP corrected for several respiratory variables (Vt, ΔPaw, and Crs) could be viewed as disappointing because ARDS patients may particularly suffer for unjustified fluid administration (3, 35). Although superior to ΔPP, FR predictions based on ΔPP / (Ecw/E_{RS}) had a relatively low sensitivity and were inconclusive in nearly 25% of patients, potentially limiting their clinical application to ARDS patients (Fig. 1; and Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/B463). One should also bear in mind that Ecw is calculated based on ΔPpl measurements (Eq. *2*). In this study, ΔPP/ΔPpl could detect FR with excellent sensitivity and specificity and a narrow gray zone of uncertainty for each fluid policy. Clinicians should be encouraged to use ΔPP/ΔPpl in an attempt to make more rational and informed decisions on fluid management for ARDS patients in a wide range of circumstances.

In this study, five nonresponders had a ΔPP higher than 12% (FP results). As demonstrated by Vieillard-Baron et al (36), in patients with acute cor pulmonale (ACP), a significant ΔPP may not be the result of a significant change in right ventricular (RV) preload but may be due to a marked increase in RV afterload during insufflation. In a study performed in a series of 35 critically ill and mostly surgical patients, Mahjoub et al (37) reported 34% FP cases of ΔPP. Bouferrache and

Vieillard-Baron (38) commented that FP cases would be more likely to occur in ARDS patients with ACP because the high transpulmonary pressure resulting from the increased E_L (a major determinant of RV afterload) might dramatically increase the ΔPP value through a large increase of RV afterload. However, in the present and other studies (5, 7, 8, 22, 39) of septic or ARDS patients, prevalence of FPs has been lower. The infrequency of FP cases could be explained by the presence of additional factors (low VT ventilation [7, 22], low Ecw/E_{RS} ratio (Fig. 1), high-frequency ventilation [40], and norepinephrine infusion [41]) that tend to reduce, not increase, the amplitude of ΔPP.

Our study has some limitations. First, it was a single-center study, and although our median values for ΔPpl (4.3 cm H_2O) and Ecw/E_{RS} (0.28) are consistent with values reported in the literature for mixed ICU populations with ARDS (19, 28, 42, 43), further studies are needed in other institutions to examine the generalizability of our findings. Second, we did not perform echocardiographic analyses, so we could not illustrate a phenomenon causing FP cases of ΔPP. In some patients, significant ΔPP values may be related to the presence of ACP rather than signifying FR (36, 37). However, as mentioned above, FP cases of ΔPP are expected to be infrequent in ARDS patients. Third, most of the esophageal catheters were designed for research purposes and this technique is underused in clinical settings. Fortunately, with the Pes monitoring incorporated into some ventilators (44), Pes measurements can now be safely and satisfactorily performed at the ICU bedside. Finally, before routine monitoring of Pes can be recommended in patients with ARDS, further studies are needed to determine whether patient outcomes will be improved by using our ΔPP/ΔPpl predictor to guide fluid therapy.

CONCLUSIONS

ΔPP adjusted by ΔPpl improved the prediction of FR by avoiding some of the FNs observed using ΔPP alone. For the restrictive fluid strategy recommended by guidelines for most ARDS patients, we identified a narrow gray zone for ΔPP/ΔPpl (2.02–2.45) that included only 11.4% of all patients, supporting the usefulness of this index for deciding fluid administration in ARDS patients. The low ability of ΔPP to predict FR is related more to a low Ecw/E_{RS} ratio than to a low VT.

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REFERENCES

1. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee Including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637
2. Michard F, Descorps-Declere A, Lopes MR: Using pulse pressure variation in patients with acute respiratory distress syndrome. *Crit Care Med* 2008; 36:2946–2948
3. Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
4. Bendjelid K, Romand JA: Fluid responsiveness in mechanically ventilated patients: A review of indices used in intensive care. *Intensive Care Med* 2003; 29:352–360
5. Michard F, Boussat S, Chemla D, et al: Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000; 162:134–138
6. Michard F, Teboul JL: Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care* 2000; 4:282–289
7. De Backer D, Heenen S, Piagnerelli M, et al: Pulse pressure variations to predict fluid responsiveness: Influence of tidal volume. *Intensive Care Med* 2005; 31:517–523
8. Vallée F, Richard JC, Mari A, et al: Pulse pressure variations adjusted by alveolar driving pressure to assess fluid responsiveness. *Intensive Care Med* 2009; 35:1004–1010
9. Kim HK, Pinsky MR: Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. *Crit Care Med* 2008; 36:2858–2862
10. Muller L, Louart G, Bousquet PJ, et al: The influence of the airway driving pressure on pulsed pressure variation as a predictor of fluid responsiveness. *Intensive Care Med* 2010; 36:496–503
11. Lefrant JY, De Backer D: Can we use pulse pressure variations to predict fluid responsiveness in patients with ARDS? *Intensive Care Med* 2009; 35:966–968
12. Chiumello D, Carlesso E, Cadringher P, et al: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008; 178:346–355
13. Gattinoni L, Carlesso E, Cadringher P, et al: Physical and biological triggers of ventilator-induced lung injury and its prevention. *Eur Respir J Suppl* 2003; 47:15s–25s
14. Gattinoni L, Chiumello D, Carlesso E, et al: Bench-to-bedside review: Chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. *Crit Care* 2004; 8:350–355
15. da Silva Ramos FJ, Costa ELV, Amato MBP: Bedside monitoring of heart-lung interactions. In: Annual Update in Intensive Care and Emergency Medicine 2013. Vincent J-L (Ed). Berlin, Germany, Springer-Verlag, 2013, pp 373–384
16. Michard F: Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005; 103:419–428; quiz 449–455
17. Ferguson ND, Fan E, Camporota L, et al: The Berlin definition of ARDS: An expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38:1573–1582
18. 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* 2000; 342:1301–1308
19. Talmor D, Sarge T, Malhotra A, et al: Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359:2095–2104
20. Baydur A, Behrakis PK, Zin WA, et al: A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Respir Dis* 1982; 126:788–791
21. Freitas FG, Bafi AT, Nascente AP, et al: Predictive value of pulse pressure variation for fluid responsiveness in septic patients using lung-protective ventilation strategies. *Br J Anaesth* 2013; 110:402–408

22. Lakhal K, Ehrmann S, Benzekri-Lefèvre D, et al: Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. *Crit Care* 2011; 15:R85
23. Michard F, Chemla D, Richard C, et al: Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med* 1999; 159:935–939
24. Hanley JA, McNeil BJ: A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983; 148:839–843
25. Cannesson M, Le Manach Y, Hofer CK, et al: Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: A "gray zone" approach. *Anesthesiology* 2011; 115:231–241
26. Teboul JL, Vieillard-Baron A: Clinical value of pulse pressure variations in ARDS. Still an unresolved issue? *Intensive Care Med* 2005; 31:499–500
27. Reuter DA, Bayerlein J, Goepfert MS, et al: Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. *Intensive Care Med* 2003; 29:476–480
28. Gattinoni L, Pelosi P, Suter PM, et al: Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med* 1998; 158:3–11
29. Gattinoni L, Vagginelli F, Chiumello D, et al: Physiologic rationale for ventilator setting in acute lung injury/acute respiratory distress syndrome patients. *Crit Care Med* 2003; 31:S300–S304
30. Huang CC, Fu JY, Hu HC, et al: Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med* 2008; 36:2810–2816
31. Monnet X, Bleibtreu A, Ferré A, et al: Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med* 2012; 40:152–157
32. Biais M, Ehrmann S, Mari A, et al; AzuRea Group: Clinical relevance of pulse pressure variations for predicting fluid responsiveness in mechanically ventilated intensive care unit patients: The grey zone approach. *Crit Care* 2014; 18:587
33. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
34. Michard F, Teboul JL: Predicting fluid responsiveness in ICU patients: A critical analysis of the evidence. *Chest* 2002; 121:2000–2008
35. Rivers EP, Kruse JA, Jacobsen G, et al: The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. *Crit Care Med* 2007; 35:2016–2024
36. Vieillard-Baron A, Chergui K, Rabiller A, et al: Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. *Intensive Care Med* 2004; 30:1734–1739
37. Mahjoub Y, Pila C, Friggeri A, et al: Assessing fluid responsiveness in critically ill patients: False-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med* 2009; 37:2570–2575
38. Bouferrache K, Vieillard-Baron A: Acute respiratory distress syndrome, mechanical ventilation, and right ventricular function. *Curr Opin Crit Care* 2011; 17:30–35
39. Monnet X, Rienzo M, Osman D, et al: Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006; 34:1402–1407
40. De Backer D, Taccone FS, Holsten R, et al: Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology* 2009; 110:1092–1097
41. Nouira S, Elatrous S, Dimassi S, et al: Effects of norepinephrine on static and dynamic preload indicators in experimental hemorrhagic shock. *Crit Care Med* 2005; 33:2339–2343
42. Loring SH, O'Donnell CR, Behazin N, et al: Esophageal pressures in acute lung injury: Do they represent artifact or useful information about transpulmonary pressure, chest wall mechanics, and lung stress? *J Appl Physiol (1985)* 2010; 108:515–522
43. Gulati G, Novero A, Loring SH, et al: Pleural pressure and optimal positive end-expiratory pressure based on esophageal pressure versus chest wall elastance: Incompatible results. *Crit Care Med* 2013; 41:1951–1957
44. Brochard L: Measurement of esophageal pressure at bedside: Pros and cons. *Curr Opin Crit Care* 2014; 20:39–46