Beneficial Hemodynamic Effects of Prone Positioning in Patients with Acute Respiratory Distress Syndrome

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Rationale: **The effects of prone positioning during acute respiratory distress syndrome on all the components of cardiac function have not been investigated under protective ventilation and maximal alveolar recruitment.**

Objectives: **To investigate the hemodynamic effects of prone positioning.**

Methods: **We included 18 patients with acute respiratory distress syndrome ventilated with protective ventilation and an end-expiratory positive pressure titrated to a plateau pressure of 28–30 cm H_2O. Before and within 20 minutes of starting prone positioning, hemodynamic, respiratory, intraabdominal pressure, and echocardiographic data were collected. Before prone positioning, preload reserve was assessed by a passive leg raising test.**

Measurements and Main Results: **In all patients, prone positioning increased the ratio of arterial oxygen partial pressure over inspired oxygen fraction, the intraabdominal pressure, and the right and left cardiac preload. The pulmonary vascular resistance decreased along with the ratio of the right/left ventricular end-diastolic areas suggesting a decrease of the right ventricular afterload. In the nine patients with preload reserve, prone positioning significantly increased cardiac index (3.0 [2.3–3.5] to 3.6 [3.2–4.4] L/min/m^2). In the remaining patients, cardiac index did not change despite a significant decrease in the pulmonary vascular resistance.**

Conclusions: **In patients with acute respiratory distress syndrome under protective ventilation and maximal alveolar recruitment, prone positioning increased the cardiac index only in patients with preload reserve, emphasizing the important role of preload in the hemodynamic effects of prone positioning.**

Keywords: acute respiratory distress syndrome; prone positioning; passive leg raising; pulmonary vascular resistance; intraabdominal pressure

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The effects of prone positioning during acute respiratory distress syndrome on all the components of cardiac function have not been investigated under protective ventilation and maximal alveolar recruitment.

What This Study Adds to the Field

In patients with acute respiratory distress syndrome under protective ventilation and maximal alveolar recruitment, prone positioning increased the cardiac preload, decreased the right ventricular afterload, and increased the left ventricular afterload. These effects resulted in an increase in cardiac index only in patients with preload reserve, emphasizing the important role of preload in the hemodynamic effects of prone positioning.

Prone positioning (PP) reduces mortality in the most severe forms of acute respiratory distress syndrome (ARDS) (1–4). In particular, the PROSEVA study recently reported that early application of prolonged PP sessions in patients with severe ARDS significantly decreased 28- and 90-day mortality (5). PP is now recognized as a potential therapeutic option in the most severe forms of ARDS (6, 7).

In theory, PP might exert different cardiovascular effects that have different effects on cardiac output (Figure 1). By increasing oxygenation and recruiting lung regions, PP might reduce the right ventricular (RV) afterload (8). By increasing the intraabdominal pressure (IAP), it might increase the venous return and the cardiac preload (9–12). This effect might depend on the level of IAP, because a high IAP might collapse the inferior vena cava (11, 12). If cardiac preload increases, the resultant effect on cardiac output might depend on the degree of preload reserve. Finally, by increasing the IAP, PP might increase the left ventricular (LV) afterload. Overall, the resultant effect on cardiac output may vary, depending on the respective weight of these mechanisms. This is what we investigated in the present study.

Some of the results of this study have been previously reported in the form of abstracts (13, 14).

METHODS

The study was conducted in a 15-bed intensive care unit and approved by the Institutional Review Board of our institution.

Patients

We included patients with ARDS (15), monitored by a pulmonary artery catheter and for whom the attending physician decided to perform PP. Exclusion criteria were contraindication to transesophageal echocardiography or PP and known chronic RV failure.

Ventilatory Settings and Respiratory Measurements

Patients were placed in the 45-degree semirecumbent position and ventilated in the volume assist–controlled mode (Evita 4; Dräger Medical, Lübeck, Germany) with protective ventilation (7). The positive end-

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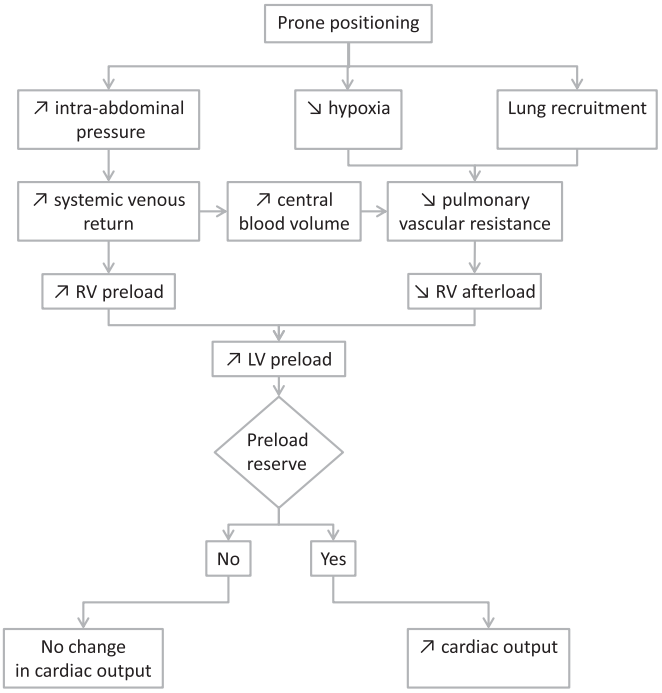

Figure 1. Theoretical hemodynamic effects of prone positioning. The resultant effect of these mechanisms on cardiac output depends on their respective weight. LV = left ventricular; RV = right ventricular.

expiratory pressure (PEEP) level was titrated to obtain a plateau pressure of 28–30 cm H_2O (16, 17). Respiratory rate was adjusted to prevent hypercapnia and to avoid dynamic intrinsic PEEP. Intrinsic PEEP was calculated as the difference between the total PEEP measured during an end-expiratory occlusion and the external PEEP. The fraction of inspired oxygen was adjusted to obtain an oxygen saturation greater than or equal to 90%. The compliance of the respiratory system was calculated as tidal volume / (plateau pressure – total PEEP). In patients receiving nitric oxide, the dose was kept constant during the entire study time. Nitric oxide was not added in any other patient.

Hemodynamic Measurements

Patients were monitored by a pulmonary artery catheter (Edwards LifeSciences, Irvine, CA) and a $PiCCO_2$ device (Pulsion Medical Systems, Munich, Germany). The pressure transducers were pasted on the patient's thorax at the midaxillary line and were kept in this position. The pulmonary vascular resistance (PVR) was calculated as (mean pulmonary artery pressure – pulmonary artery occlusion pressure)/ cardiac index. The ratio of venoarterial carbon dioxide gradient over the arteriovenous oxygen content difference was calculated to estimate anaerobic metabolism (18, 19). The product of the LV end-systolic area times the arterial systolic pressure was calculated and used to estimate the LV afterload.

Echocardiographic Measurements

With transesophageal echocardiography (Envisor Philips B0; Philips Healthcare, Andover, CA) we assessed the anteroposterior and septolateral diameters of the left ventricle, the LV eccentricity index, the LV ejection fraction, and the presence of a paradoxical motion of the interventricular septum in the short-axis cross-sectional view and the end-diastolic area of the right and left ventricles in a long-axis four-chamber view.

IAP Measurements

IAP was estimated from the bladder pressure by injecting 25 ml of saline in the bladder after clamping the urinary drainage bag (AA6118 Folysil; Coloplast, Humlebaek, Denmark) (20). The abdominal pressure transducer was fixed to the patient on the lateral side of the pelvis, 2 cm below the anterior superior iliac spine.

Hemodynamic, respiratory, and the IAP signals were continuously computerized (HEM 4.2; Notocord Systems, Croissy-sur-Seine, France). All measurements were performed at end-expiration.

Study Design

All patients were lying on an air-cushioned bed. Initially, a first set of measurements including hemodynamic, echocardiographic, respiratory, and IAP variables was performed. Then, to assess the preload reserve, a passive leg raising (PLR) test was performed (21, 22). Hemodynamic and IAP measurements were recorded when the maximal effect of PLR on cardiac index was reached (21).

Just before PP, a second set of measurements was performed. PP was performed without any thoracic or pelvic support. In the prone position, one arm was placed over the head and the other was parallel to the rest of the body. Thereafter, PP started. After PP, we measured the plateau pressure and external PEEP was adjusted to obtain a plateau pressure of 28–30 cm H_2O, as in supine position. The abdominal and blood pressure transducers were zeroed versus the atmospheric pressure. After stabilization of all variables (i.e., within 20 min), a third set of measurements was performed. Excepting PEEP, ventilator settings and other treatment were unchanged during the study period.

Statistical Analysis

Variables were summarized as median and interquartile range. Variables before and during PLR and before and after PP were compared by a Wilcoxon test. The presence of preload reserve was defined by a PLR-increase in cardiac index greater than or equal to 10% (21). Patients in whom PP increased cardiac index greater than or equal to 15% were compared with the other ones by a Mann-Whitney *U* test or by a Fisher exact test as appropriate. *P* less than 0.05 was considered statistically significant. Statistical analysis was performed by using MedCalc 11.6.0 software (MedCalc Software, Mariakerke, Belgium).

RESULTS

Study Population

Eighteen patients were included in the study. Their characteristics are summarized in Table 1. Sixteen percent of patients received inhaled nitric oxide.

Changes in Respiratory Data

PP showed a trend toward increased compliance of the respiratory system (Table 2). The ratio of the partial pressure of arterial oxygen over the fraction of inspired oxygen significantly increased. The arterial carbon dioxide partial pressure showed a trend toward decrease during PP (Table 2).

TABLE 1. PATIENTS' CHARACTERISTICS AT BASELINE

Sex, F/M	8/10
Age, yr	72 (48–76)
Cause of ARDS (pulmonary/extrapulmonary)	14/4
Septic shock	15
SAPS II	46 (41–57)
Pa_{O_2}/FI_{O_2}, mm Hg	134 (113–154)
Pa_{O_2}, mm Hg	83 (77–91)
Pa_{CO_2}, mm Hg	34 (30–40)
Lactate, mmol/L	1.8 (1.4–2.5)
Patients receiving norepinephrine	15
Dose of norepinephrine, μg/kg/min	0.53 (0.13–0.72)

Definition of abbreviations: ARDS = acute respiratory distress syndrome; SAPS = simplified acute physiology score.

N = 18; data are expressed as median (interquartile range) or number.

TABLE 2. RESPIRATORY, HEMODYNAMIC, ECHOCARDIOGRAPHIC, AND OXYGEN-DERIVED VARIABLES DURING THE STUDY PROTOCOL ACCORDING TO THE CHANGE IN CARDIAC INDEX DURING PRONE POSITIONING

	Nonsignificant Change in Cardiac Index during Prone Positioning ($n = 9$)		Significant Change in Cardiac Index during Prone Positioning ($n = 9$)	
	Supine Position	Prone Position	Supine Position	Prone Position
Respiratory variables				
Tidal volume, ml/kg of predicted body weight	6.4 (6.0–6.9)	6.4 (6.0–6.9)	6.5 (6.0–7.0)	6.4 (6.0–7.0)
PEEP, cm H_2O	13 (11–15)	15 (11–15)	14 (12–15)	14 (12–15)
Auto PEEP, cm H_2O	1 (0–2)	1 (0–3)	2 (1–2)	2 (1–3)
Plateau pressure, cm H_2O	30 (0–0)	30 (0–0)	30 (0–0)	30 (0–0)
Respiratory rate, cycles/min	35 (30–35)	35 (30–35)	35 (29–35)	35 (29–35)
Respiratory system compliance, ml/cm H_2O	25 (21–27)	26 (22–34)	23 (22–27)	26 (21–30)
Pa_{O_2}/FI_{O_2}, mm Hg	132 (122–200)	218 (169–306)*	137 (79–154)	160 (134–202)*
Pa_{CO_2}, mm Hg	36 (30–43)	37 (27–43)	33 (30–37)	30 (27–37)
Hemodynamic variables				
Cardiac index, L/min/m^2	3.2 (2.8–3.6)	3.3 (2.8–3.9)	3.0 (2.3–3.5)	3.6 (3.2–4.4)*
PLR-induced increase in cardiac index, %	4 (3–6)	—	13 (10–23)†	—
Heart rate, beats/min	104 (78–115)	90 (77–113)	76 (72–96)	89 (67–103)
Stroke volume, ml/m^2	38 (31–44)	36 (32–45)	34 (29–47)	42 (38–58)*
Mean arterial pressure, mm Hg	78 (70–84)	82 (75–91)*	81 (78–90)	90 (88–93)
Right atrial pressure, mm Hg	10 (6–12)	16 (14–18)*	15 (13–18)†	17 (16–23)*
Mean pulmonary artery pressure, mm Hg	34 (31–36)	31 (28–34)	33 (32–45)	33 (27–47)
Pulmonary artery occlusion pressure, mm Hg	17 (12–18)	19 (14–20)*	19 (17–20)	22 (19–26)*
Pulmonary artery mean–occlusion pressure gradient, mm Hg	17 (14–20)	15 (9–16)*	16 (14–23)	11 (9–21)*
Pulmonary vascular resistance, dyn·s/cm^5/m^2	420 (289–559)	284 (226–409)*	514 (333–885)	234 (155–549)*
Intraabdominal pressure, mm Hg	14 (10–15)	17 (13–18)*	16 (12–17)	18 (17–20)*
Tissue oxygenation variables				
Sv_{O_2}, %	71 (63–74)	77 (64–80)	73 (63–75)	75 (69–79)
Oxygen delivery, ml/min/m^2	386 (310–460)	404 (330–511)	355 (273–438)	514 (424–590)*
Oxygen consumption, ml/min/m^2	98 (88–123)	123 (92–144)	65 (42–84)†	113 (101–126)*
Lactate, mmol/L	1.4 (1.2–1.6)	1.3 (1.1–1.6)	2.5 (2.2–10.1)†	2.3 (1.5–9.0)
$P(v\text{-}a)_{CO_2}/C(a\text{-}v)_{O_2}$, mm Hg/ml	1.3 (1.1–1.7)	1.2 (0.9–1.6)	1.4 (1.2–2.2)	1.0 (0.8–1.3)*
Echocardiographic variables				
Left ventricular ejection fraction, %	40 (35–56)	40 (36–49)	57 (50–62)†	60 (53–65)†
Right/left ventricular end-diastolic area ratio	0.65 (0.60–0.75)	0.55 (0.50–0.70)*	0.65 (0.55–0.80)	0.60 (0.50–0.65)*
Left ventricular eccentricity index	1.05 (1.02–1.08)	1.01 (0.99–1.03)*	1.13 (1.02–1.16)	1.00 (0.99–1.06)*
Left ventricular end-systolic area × systolic arterial pressure, cm^2·mm Hg	914 (446–1,231)	1,074 (534–1,587)*	603 (420–895)	946 (765–1,146)*
ICU mortality	5 (56%)		4 (44%)	

Definition of abbreviations: $C(a\text{-}v)_{O_2}$ = arteriovenous oxygen content gradient; ICU = intensive care unit; PEEP = positive end-expiratory pressure; PLR = passive leg raising, $P(v\text{-}a)_{CO_2}$ = venoarterial carbon dioxide tension gradient; Sv_{O_2} = mixed venous oxygen saturation.

N = 18, data are expressed as median (interquartile range) or number (%).

* *P* less than 0.05 prone position versus supine position.

† *P* less than 0.05 patients with versus without significant change in cardiac index during prone positioning.

Changes in Cardiac Index and Oxygen Delivery Induced by PP

In nine patients, PP increased cardiac index by more than 15% (Table 2, Figure 2). In these patients, oxygen delivery and oxygen consumption significantly increased. PP did not modify lactate and significantly decreased the ratio of venoarterial carbon dioxide gradient over the arteriovenous oxygen content difference. The PLR test performed before PP increased cardiac index by more than 10% (Table 2).

In the remaining nine patients, cardiac index did not change significantly during PP (Table 2, Figure 2). Oxygen delivery, oxygen consumption, lactate, and the ratio of venoarterial carbon dioxide gradient over the arteriovenous oxygen content difference ratio were not modified. In this group of patients, the PLR test performed before PP did not increase cardiac index by more than 10% (Table 2).

The LV ejection fraction was significantly higher in patients in whom PP increased cardiac index than in the other patients (Table 2).

Changes in Cardiac Preload and Afterload

PP significantly increased the right atrial pressure and the pulmonary artery occlusion pressure in the overall population regardless of its effects on cardiac index. PVR significantly decreased, as did the difference between the mean pulmonary arterial pressure and the pulmonary artery occlusion pressure (Table 2, Figure 2). The mean arterial pressure increased in patients in whom PP did not increase cardiac index and tended to increase in the other group (Table 2). The product of the LV end-systolic area times the arterial systolic pressure increased in both groups (Table 2).

Changes in the RV Dimensions

In the overall population at baseline, the ratio of the RV/LV end-diastolic areas was above 0.6. We did not observe any acute cor pulmonale at baseline. PP did not induce any new case of acute cor pulmonale. PP significantly reduced the ratio of the RV/LV end-diastolic areas and the eccentricity index (Table 2).

Changes in IAP

At baseline in patients in whom PP increased cardiac index, IAP was between 12 and 15 mm Hg (20) in four patients, between 16 and 20 mm Hg in four patients, between 20 and 25 mm Hg in one patient, and greater than 25 mm Hg in any patient. In the remaining patients, IAP was between 12 and 15 mm Hg in seven patients and between 16 and 20 mm Hg in two patients. In both groups of patients, IAP significantly increased during PP (Table 2).

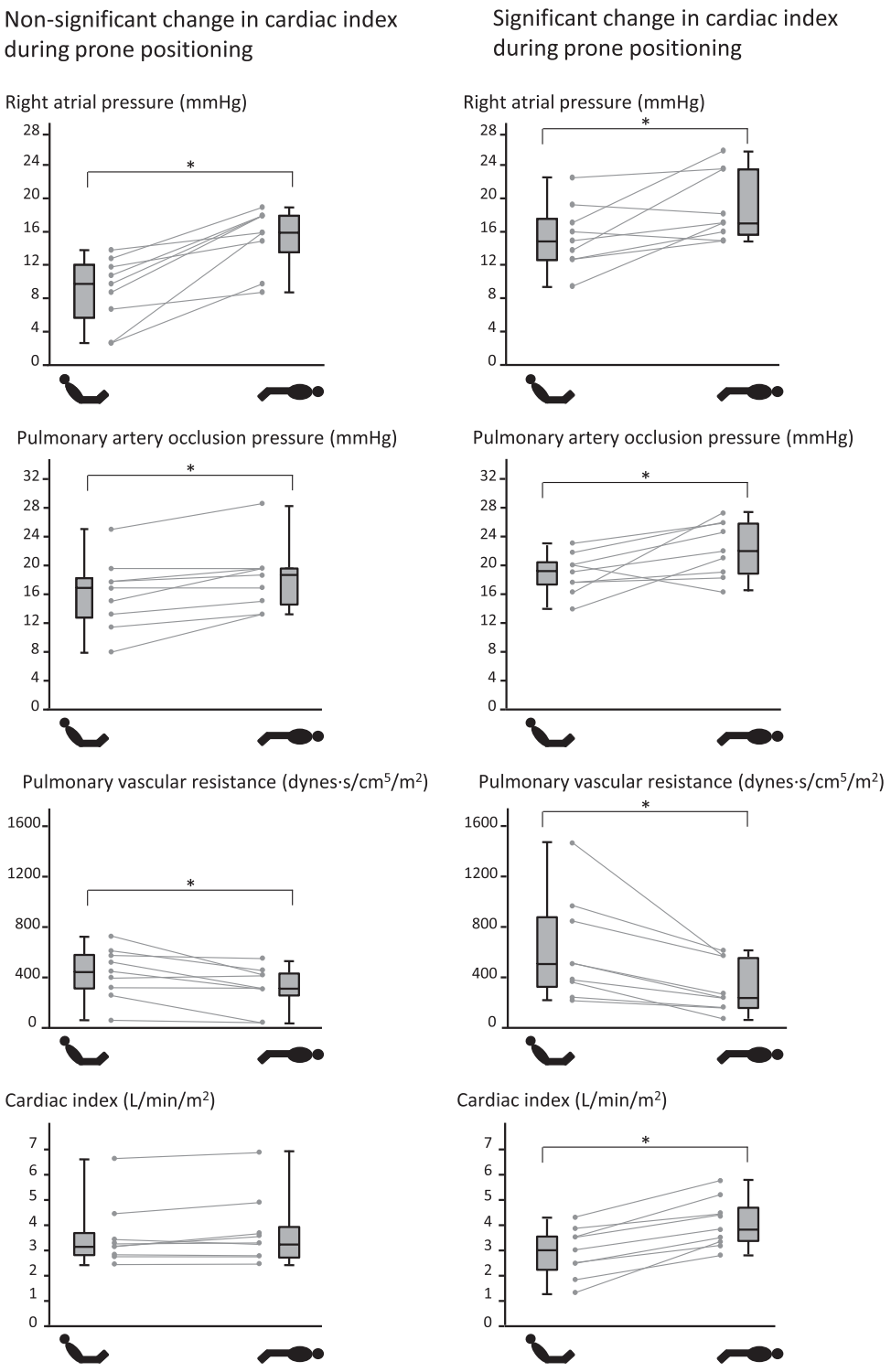

Figure 2. Changes in hemodynamic variables before and during prone positioning in patients with nonsignificant and significant changes in cardiac index induced by prone positioning. In *box and whiskers,* the *median line* corresponds to median, the *lower* and *upper limits* of the *box* to the extremities of the interquartile range, and the *error bars* to the extremities of the 5th–95th percentiles. The *gray lines* correspond to individual data. n = 18. **P* less than 0.05 versus before prone positioning.

DISCUSSION

In patients with ARDS ventilated with protective ventilation and maximal alveolar recruitment, we observed that PP reduced RV afterload and increased cardiac preload. PP increased cardiac index in half of the patients. Significant preload reserve was documented in this group of patients. In the remaining patients, cardiac index did not change with PP and no preload reserve was documented.

Some studies have found that PP had no or minimal hemodynamic effect (23–31) but they have been conducted under different ventilator settings (23, 24, 26, 29–31) and investigated hemodynamics a long time after proning (23, 31). Other studies have shown that PP increased cardiac output (32, 33) but the responsible mechanisms were not fully investigated, in particular because RV afterload was not assessed. Finally, in patients with acute core pulmonale, Vieillard-Baron and coworkers (8) have shown that PP improved RV function and increased cardiac output. Their study was not conducted with protective ventilation and maximal alveolar recruitment (8). Moreover, it described hemodynamic effects 18 hours after PP. Thus, the acute hemodynamic effects induced by PP remained to be documented.

The present study confirms that, in the whole population, PP reduced the RV afterload, as assessed by the decrease in the PVR along with a reduction of difference between mean pulmonary arterial and pulmonary artery occlusion pressures and the ratio of RV/LV end-diastolic areas. It is noteworthy that the true PVR, which is underestimated by the calculated PVR in case of extended zone 2 conditions (Starling resistor effect), might be reduced by the recruitment of pulmonary microvasculature with PP. Indeed, the increase in central blood volume recruits some collapsed pulmonary microvessels (34) and transfers some lung regions from West zone 2 to zone 3 (35). Another explanation for the decrease in PVR and RV afterload might be the potential lung recruitment induced by PP, which possibly increased the lung volume in a way leading to a reduction of PVR (36), as suggested by the improvement of the respiratory system compliance and the ratio of the partial pressure of arterial oxygen over the fraction of inspired oxygen (*see* Table ESM in the online supplement). Finally, we cannot exclude that the improvement in arterial oxygenation was associated with a reduction of the hypoxic pulmonary vasoconstriction in the most hypoxic patients (Figure 1) (37).

PP increased right and left cardiac preload in the whole population. First, this might be caused by the lowering of the trunk from the semirecumbent position, which transfers splanchnic venous blood toward the heart (38). Second, the increase in cardiac preload during PP could also be related to the compression of the splanchnic compartment because of increased IAP (12). The increase in right cardiac preload suggests that this increase in IAP did not collapse the inferior vena cava (i.e., vena cava was in a zone 3 condition) (11, 12). This might be caused by the fact that the IAP was lower than the intramural pressure of the inferior vena cava. Importantly, it is unlikely that the increase in right atrial pressure and pulmonary artery occlusion pressure was simply caused by the transmission of the increased IAP to the thorax (39). Indeed, PEEP was adjusted to keep constant the plateau pressure, maintaining the intrathoracic pressure constant. In this regard, the fact that we did not assess that transmission is a limitation of the study. In the same line, we could not find any clear explanation for the higher right atrial pressure at baseline in patients with preload reserve than in patients without preload reserve. The fact that auto-PEEP and IAP were similar between groups is against the hypothesis that this difference was caused by a higher transmission of IAP or intrathoracic pressure.

Our results also suggest that PP increased the LV afterload in the whole population. This was suggested by the increase in mean arterial pressure (i.e., the main component of hydraulic load) (40) and in the product of the LV end-systolic area times the arterial systolic pressure. We cannot exclude that part of this effect resulted from the transmission of the increase in IAP to the abdominal arterial vasculature (10). This might have increased the intramural pressure of the easily compressible, small abdominal vessels, with essentially unchanged aortic intramural pressure, because the aorta is not easily compressible.

Eventually following PP, cardiac output significantly increased only in the patients with preload reserve. In these patients, both the increase in right cardiac preload and the reduction of RV afterload contributed to an increase in LV preload. Because of preload reserve, this led to an increase in cardiac output (Figure 1).

By contrast, in patients without preload reserve, PP did not change cardiac output. There might be two explanations. First, the reduction in RV afterload resulted in an increase in LV preload (Figure 1). Because of the absence of preload reserve, this did not induce an increase in cardiac output. Interestingly, LV ejection fraction was lower in these patients with no preload reserve than in the other group, consistent with physiology. Second, it is also plausible that the decrease in RV afterload had a small effect on cardiac index because RV dysfunction was not severe in our patients (no cor pulmonale and exclusion of patients with chronic RV failure).

It is noteworthy that LV ejection fraction did not change with PP in both groups. This suggests that the influence of changes in LV afterload on cardiac output was not major.

Our study has some limitations. First, we could not directly assess alveolar recruitment by the quasistatic respiratory system compliance. Second, we did not investigate patients with a very high IAP, in whom PP could collapse the inferior vena cava and decrease cardiac output. Third, our results cannot be extrapolated to PP performed by using thoracic and pelvic supports and with conventional foam mattress, because these factors may affect the effects of PP on the abdominal pressure (41, 42). Fourth, we could not assess preload responsiveness in the prone position. In particular, it was not possible to use pulse pressure and stroke volume respiratory variations for this purpose, because the low tidal volume and/or low lung compliance associated with ARDS preclude to use it for assessing preload dependence (43, 44). Fifth, we did not measure the pleural pressure and we could not assess the transmission of the IAP and the intrathoracic pressure to cardiac pressures. Thus, we could not assess whether the transmural pressures varied to the same extent than the intramural pressures with PP. Finally, the abdominal and cardiac pressures were not measured with the same reference level. However, in a series of 30 other patients, we observed that the difference in height between the two reference levels was 3 cm on average. This corresponds to a hydrostatic pressure gradient of 2.2 mm Hg. Applying this correction to our right atrial pressure values would not significantly change our results, in particular the significant increase in right atrial pressure with PP.

In conclusion, in patients with ARDS with protective ventilation, PP increased cardiac preload and reduced RV afterload. This resulted in an increase in cardiac output only in the patients with preload reserve.

Author disclosures are available with the text of this article at www.atsjournals.org.

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References

1. Mancebo J, Fernández R, Blanch L, Rialp G, Gordo F, Ferrer M, Rodríguez F, Garro P, Ricart P, Vallverdú I, *et al*. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006;173:1233–1239.
2. Gattinoni L, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. *Minerva Anestesiol* 2010; 76:448–454.
3. Abroug F, Ouanes-Besbes L, Dachraoui F, Ouanes I, Brochard L. An updated study-level meta-analysis of randomised controlled trials on proning in ARDS and acute lung injury. *Crit Care* 2011;15:R6.
4. Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Pesenti A, Guérin C, Mancebo J, Curley MA, *et al*. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med* 2010;36:585–599.
5. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
6. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, Brochard L, Brower R, Esteban A, Gattinoni L, *et al*. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012;38:1573–1582.
7. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, *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.
8. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. *Chest* 2007;132:1440–1446.
9. Wauters J, Claus P, Brosens N, McLaughlin M, Hermans G, Malbrain M, Wilmer A. Relationship between abdominal pressure, pulmonary compliance, and cardiac preload in a porcine model. *Crit Care Res Pract* 2012;2012:763181.
10. Bloomfield GL, Ridings PC, Blocher CR, Marmarou A, Sugerman HJ. A proposed relationship between increased intra-abdominal, intrathoracic, and intracranial pressure. *Crit Care Med* 1997;25:496–503.
11. Kitano Y, Takata M, Sasaki N, Zhang Q, Yamamoto S, Miyasaka K. Influence of increased abdominal pressure on steady-state cardiac performance. *J Appl Physiol (1985)* 1999;86:1651–1656.
12. Takata M, Wise RA, Robotham JL. Effects of abdominal pressure on venous return: abdominal vascular zone conditions. *J Appl Physiol (1985)* 1990;69:1961–1972.
13. Jozwiak M, Persichini R, Teboul JL, Silva S, Chemla D, Anguel N, Richard C, Monnet X. Hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome [abstract]. *Intensive Care Med* 2012;38:S165.
14. Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, Richard C, Monnet X. Hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome [abstract]. *Am J Respir Crit Care Med* 2012;185:A4641.
15. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–824.
16. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, *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.
17. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, *et al*.; Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:646–655.
18. Mekontso-Dessap A, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, Teboul JL. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. *Intensive Care Med* 2002;28:272–277.
19. Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, Persichini R, Anguel N, Richard C, Teboul JL. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. *Crit Care Med* 2013;41:1412–1420.
20. Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, Balogh Z, Leppäniemi A, Olvera C, Ivatury R, *et al*. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Med* 2006;32:1722–1732.
21. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 2006;34:1402–1407.
22. Monnet X, Teboul JL. Passive leg raising. *Intensive Care Med* 2008;34:659–663.
23. McAuley DF, Giles S, Fichter H, Perkins GD, Gao F. What is the optimal duration of ventilation in the prone position in acute lung injury and acute respiratory distress syndrome? *Intensive Care Med* 2002;28:414–418.
24. Rialp G, Betbesé AJ, Pérez-Márquez M, Mancebo J. Short-term effects of inhaled nitric oxide and prone position in pulmonary and extrapulmonary acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001;164:243–249.
25. Pelosi P, Bottino N, Chiumello D, Caironi P, Panigada M, Gamberoni C, Colombo G, Bigatello LM, Gattinoni L. Sigh in supine and prone position during acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2003;167:521–527.
26. Chatte G, Sab JM, Dubois JM, Sirodot M, Gaussorgues P, Robert D. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med* 1997;155:473–478.
27. Blanch L, Mancebo J, Perez M, Martinez M, Mas A, Betbese AJ, Joseph D, Ballús J, Lucangelo U, Bak E. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med* 1997;23:1033–1039.
28. Jolliet P, Bulpa P, Chevrolet JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. *Crit Care Med* 1998;26:1977–1985.
29. Matejovic M, Rokyta R Jr, Radermacher P, Krouzecky A, Sramek V, Novak I. Effect of prone position on hepato-splanchnic hemodynamics in acute lung injury. *Intensive Care Med* 2002;28:1750–1755.
30. Borelli M, Lampati L, Vascotto E, Fumagalli R, Pesenti A. Hemodynamic and gas exchange response to inhaled nitric oxide and prone positioning in acute respiratory distress syndrome patients. *Crit Care Med* 2000;28:2707–2712.
31. Papazian L, Bregeon F, Gaillat F, Thirion X, Gainnier M, Gregoire R, Saux P, Gouin F, Jammes Y, Auffray JP. Respective and combined effects of prone position and inhaled nitric oxide in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998;157:580–585.
32. Hering R, Vorwerk R, Wrigge H, Zinserling J, Schröder S, von Spiegel T, Hoeft A, Putensen C. Prone positioning, systemic hemodynamics, hepatic indocyanine green kinetics, and gastric intramucosal energy balance in patients with acute lung injury. *Intensive Care Med* 2002;28:53–58.
33. Hering R, Wrigge H, Vorwerk R, Brensing KA, Schröder S, Zinserling J, Hoeft A, Spiegel TV, Putensen C. The effects of prone positioning on intraabdominal pressure and cardiovascular and renal function in patients with acute lung injury. *Anesth Analg* 2001;92:1226–1231.
34. Fougères E, Teboul JL, Richard C, Osman D, Chemla D, Monnet X. Hemodynamic impact of a positive end-expiratory pressure setting in acute respiratory distress syndrome: importance of the volume status. *Crit Care Med* 2010;38:802–807.
35. West JB. State of the art: ventilation-perfusion relationships. *Am Rev Respir Dis* 1977;116:919–943.
36. Whittenberger JL, McGregor M, Berglund E, Borst HG. Influence of state of inflation of the lung on pulmonary vascular resistance. *J Appl Physiol* 1960;15:878–882.
37. Orchard CH, Sanchez de Leon R, Sykes MK. The relationship between hypoxic pulmonary vasoconstriction and arterial oxygen tension in the intact dog. *J Physiol* 1983;338:61–74.
38. Jabot J, Teboul JL, Richard C, Monnet X. Passive leg raising for predicting fluid responsiveness: importance of the postural change. *Intensive Care Med* 2009;35:85–90.
39. Valenza F, Chevallard G, Porro GA, Gattinoni L. Static and dynamic components of esophageal and central venous pressure during intra-abdominal hypertension. *Crit Care Med* 2007;35:1575–1581.
40. Chemla D, Nitenberg A. Systolic duration, preload, and afterload: Is a new paradigm needed? *Intensive Care Med* 2006;32:1454–1455; author reply 1456–1457.
41. Michelet P, Roch A, Gainnier M, Sainty JM, Auffray JP, Papazian L. Influence of support on intra-abdominal pressure, hepatic kinetics of indocyanine green and extravascular lung water during prone positioning in patients with ARDS: a randomized crossover study. *Crit Care* 2005;9:R251–R257.
42. Chiumello D, Cressoni M, Racagni M, Landi L, Li Bassi G, Polli F, Carlesso E, Gattinoni L. Effects of thoraco-pelvic supports during prone position in patients with acute lung injury/acute respiratory distress syndrome: a physiological study. *Crit Care* 2006;10:R87.
43. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005;31:517–523.
44. Monnet X, Bleibtreu A, Ferré A, Dres M, Gharbi R, Richard C, Teboul JL. 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.

the definition of primary graft dysfunction after lung transplantation. *J Heart Lung Transplant* 2010;29:1231–1239.
9. Keshavjee S, Davis RD, Zamora MR, de Perrot M, Patterson GA. A randomized, placebo-controlled trial of complement inhibition in ischemia-reperfusion injury after lung transplantation in human beings. *J Thorac Cardiovasc Surg* 2005;129:423–428.
10. Peng Q, Li K, Sacks SH, Zhou W. The role of anaphylatoxins C3a and C5a in regulating innate and adaptive immune responses. *Inflamm Allergy Drug Targets* 2009;8:236–246.
11. Pratt JR, Basheer SA, Sacks SH. Local synthesis of complement component C3 regulates acute renal transplant rejection. *Nat Med* 2002;8:582–587.
12. Suzuki H, Lasbury ME, Fan L, Vittal R, Mickler EA, Benson HL, Shilling R, Wu Q, Weber DJ, Wagner SR, *et al*. Role of complement activation in obliterative bronchiolitis post-lung transplantation. *J Immunol* 2013;191:4431–4439.

The Hemodynamic Effects of Prone Positioning in Patients with Acute Respiratory Distress Syndrome Remain to Be Defined

To the Editor:

We have a number of concerns regarding the results and conclusions of the study by Jozwiak and colleagues (1) and the accompanying editorial by Magder (2).

Jozwiak and colleagues' Table 2 indicates that the hemodynamic data were obtained with patients in the supine and prone positions, but the Methods section implies that the "supine" measurements were made with patients in the 45° upright posture. We would like clarification as to which posture was used as the "control." Zero reference pressures, central vascular filling pressures, and bladder pressure will change when moving from a 45° upright to 0° supine or prone. Accordingly, the changes the authors and editorialist attribute to prone positioning could have been due to taking patients out of the 45° upright position rather than to turning them prone *per se*. The effect of passive leg raising will also be affected by whether the patients were supine or in the 45° upright posture.

The level of positive end-expiratory pressure was changed between the hemodynamic measurements obtained in the two postures. Although the mean change was only 2 cm H_2O, even such a small difference can affect venous return, left- and right-sided transmural pressures, mean systemic venous pressure, and, to some extent, transpulmonary pressure.

Sixteen of the 18 patients were receiving inhaled NO. Although the dose was kept constant during the study, regional ventilation most definitely changes with prone positioning, and this will increase the number of vessels that might be exposed to NO, thereby altering global pulmonary vascular resistance.

Patients whose cardiac index did not change with prone positioning had a mean cardiac index (interquartile range) measured in the supine position (or 45° upright?) of 3.2 (2.8, 3.6) L/min/m^2, yet the average heart rate of patients in this group was reported as being 104 beats/min and the average stroke volume as 38 ml/m^2. Based on these two measurements, the average cardiac index should have approximated 3.95 L/min/m^2. This discrepancy is neither noted nor explained, and is particularly important in light of the reported increase in the mixed venous oxygen saturation (from 71 to 77%) that occurred in this group of patients on turning to the prone position. How could this occur if cardiac index did not change?

Although a number of clinical and laboratory studies have shown that prone positioning rarely, if ever, has adverse hemodynamic effects, we suggest that problems with the methodology used by Jozwiak and colleagues (1), and the results they present, do not allow us to conclude that prone positioning benefits hemodynamics to any meaningful extent or to accurately assess the effects of preload as they describe. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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References

1. Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, Richard C, Monnet X. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013;188:1428–1433.
2. Magder S. Is all on the level? Hemodynamics during supine versus prone ventilation [editorial]. *Am J Respir Crit Care Med* 2013;188:1390–1391.

Reply: Prone Positioning Actually Exerts Benefits on Hemodynamics!

From the Authors:

We read with interest the comments of Drs. Albert and Hubmayr about our study (1). Concerning the first of their comments, patients were in the 45° semirecumbent position at baseline (2) as stated in the Methods. We agree that the hemodynamic effects of prone positioning should result from the addition of lowering the trunk to the horizontal position and prone positioning from the supine position, as we have previously reported (3) and noted in the Discussion. The postural change we used in the present study is recommended for clinical practice and was the method used in recent trials (4) (i.e., starting from the semirecumbent position).

Pressure transducers were fixed directly on the patient's thorax and were not moved from this position during the postural changes. Pressure transducers were carefully zeroed against atmospheric pressure after each postural change. Finally, we agree that the hemodynamic effects of passive leg raising are influenced by the starting position of the patient, as we have also previously reported (3). This is particularly relevant to our study, in which prone positioning also started from the semirecumbent position (2).

The adjustment of positive end-expiratory pressure after prone positioning resulted only in a 2-cm H_2O (1.5 mm Hg) increase.

Given the low level of transmission of the intraalveolar pressure to the intrathoracic pressure and hence to the intramural pressure during acute respiratory distress syndrome with low lung compliance, this 1.5-mm Hg increase in alveolar pressure should only minimally affect the intramural pressures, in particular the backpressure to venous return. The median compliance of the respiratory system in our study was around 24 ml/cm H_2O, consistent with an airway pressure transmission of approximately 30% (5).

As for the assertion that the use of inhaled nitric oxide (iNO) was an important confounder, please note that it was not 16 of the 18 patients but rather 16% of the patients (i.e., 3 patients) who received iNO. Thus, it is very unlikely that iNO played a pivotal role in the decrease of the pulmonary vascular resistance observed after prone positioning.

All data were reported as median (interquartile range) as noted in our report and not as mean (interquartile range). The product of the median values of stroke volume index and heart rate is expected to be mathematically different from the median of the individual products of stroke volume index and heart rate. This probably accounts for the "discrepancy" pointed out by Albert and Hubmayr. Concerning mixed venous oxygen saturation in patients without increases in cardiac index with prone positioning, the difference between median values in supine and prone positions was not statistically significant ($P = 0.3$).

We thank Albert and Hubmayr for the opportunity to add additional clarity to our report, and we strongly believe that our methodology was appropriate and our conclusions sound. Based on our results showing a potential increase in cardiac output with prone positioning, we share with Albert and Hubmayr the opinion that prone positioning does not exert harmful hemodynamic effects. ■

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References

1. Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, Richard C, Monnet X. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013;188:1428–1433.
2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, *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. *Intensive Care Med* 2013;39:165–228.
3. Jabot J, Teboul JL, Richard C, Monnet X. Passive leg raising for predicting fluid responsiveness: importance of the postural change. *Intensive Care Med* 2009;35:85–90.
4. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
5. Teboul JL, Pinsky MR, Mercat A, Anguel N, Bernardin G, Achard JM, Boulain T, Richard C. Estimating cardiac filling pressure in mechanically ventilated patients with hyperinflation. *Crit Care Med* 2000;28:3631–3636.

Reply

From the Editorialist:

Albert and Hubmayr point out that the initial hemodynamic measurements in the study by Jozwiak and colleagues (1) were made with subjects in the 45° upright posture and not flat. I had missed this point, but it only adds quantitatively and not qualitatively to my comments in the accompanying editorial (2) and brings up some further important measurement issues.

The advantage of making measurements based on 5 cm below the sternal angle is that the center of the right atrium remains at a relatively constant vertical distance from this level because the right atrium is a round and anterior structure. Thus, pressures measured at this level are comparable whether lying flat or at 45°. This is not true for measurements made relative to the midaxillary position. When that level is used, measurements cannot be compared easily in different positions. It is likely that deviations of measured values from the midatrial value with the change to the prone position were even larger than I suggested, and, as such, the increase in the gradient for venous return was even larger.

The key point for me in this study is not whether the hemodynamics were improved in the prone position, for that is not easy to assess. Rather, what is important are the changes in oxygenation in relation to the changes in cardiac output. Because subjects started with the thorax at 45°, the increase in the pressure gradient for venous return likely was even greater than I suggested. This strengthens my point that the smaller increase in oxygenation in subjects who were fluid responsive was likely because in the prone position the increased gradient for venous return transferred volume from the venous reservoir to the thoracic compartment. This reduced the benefit to oxygenation that came from being in the prone position. In contrast, those who were not volume responsive, and thus right-side limited, were "protected" from the fluid shift. Again, this suggests that more aggressive diuresis would have been helpful. Regarding the small increase in positive end-expiratory pressure noted by Albert and Hubmayr, this, if anything, would have helped the volume responsive patients by preventing some of the volume shift. I would argue that the volume-responsive subjects required an even larger increase in positive end-expiratory pressure to protect their lungs! Finally, this study emphasizes the importance of proper leveling of transducers and stating in papers how this was done. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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