Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome.

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Abstract

Purpose

To evaluate the effects of acute hypercapnia induced by positive end-expiratory pressure (PEEP) variations at constant plateau pressure (Pplat) in patients with severe acute respiratory distress syndrome (ARDS) on right (R) and left ventricular (LV) function.

Methods

Prospective observational study in two academic intensive care units enrolling 11 adults with severe ARDS (PaO_2/FiO_2 <150 mm Hg at PEEP >5 cm H_2O). We compared three ventilatory strategies, each used for 1 hour, with Pplat at 22 [20 –25] cm H_2O: low PEEP (5.4 cm H_2O) or high PEEP (11.0 cm H_2O) with compensation of the tidal volume reduction by either a high respiratory rate (high PEEP/high rate) or instrumental dead space decrease (high PEEP/low rate). We assessed RV function (transesophageal echocardiography), alveolar dead space (expired CO_2), and alveolar recruitment (pressure-volume curves).

Results

Compared to low PEEP, PaO_2/FiO_2 ratio and alveolar recruitment were increased with high PEEP. Alveolar dead space remained unchanged. Both high-PEEP strategies induced higher $PaCO_2$ levels (71 [60–94] and 75 [53–84], vs. 52 [43–68] mm Hg) and lower pH values (7.17 [7.12–7.23] and 7.20 [7.16–7.25] vs. 7.30 [7.24–7.35]), as well as a significant decrease in cardiac index, RV dilatation and LV deformation. The decrease in stroke index tended to be negatively correlated to the increase in alveolar recruitment with high PEEP.

Conclusions

Acidosis and hypercapnia induced by tidal volume reduction and increase in PEEP at constant Pplat was associated with impaired RV function and hemodynamics despite a positive effect on oxygenation and alveolar recruitment.

MESH Keywords Acidosis, Respiratory ; etiology ; Acute Disease ; Aged ; Analysis of Variance ; Echocardiography, Transesophageal ; Female ; Humans ; Hypercapnia ; diagnosis ; etiology ; Intensive Care ; methods ; Linear Models ; Male ; Middle Aged ; Positive-Pressure Respiration ; adverse effects ; methods ; Prospective Studies ; Respiratory Dead Space ; Respiratory Distress Syndrome, Adult ; complications ; metabolism ; physiopathology ; therapy ; Respiratory Rate ; Severity of Illness Index ; Statistics, Nonparametric ; Tidal Volume ; Ventricular Dysfunction, Right ; diagnosis ; etiology

Author Keywords lung injury ; acidosis ; right heart ; alveolar recruitment ; alveolar dead space

INTRODUCTION

At present, a consensus emerges concerning the need for limiting plateau pressure (Pplat) values during ventilation of patients with acute respiratory distress syndrome (ARDS) [1 , 2], but the optimal level of positive end expiratory pressure (PEEP) remains contentious in a given patient. Although many studies have demonstrated that increasing PEEP has beneficial effects on alveolar recruitment, oxygenation and duration of mechanical ventilation [3 , 4], augmented airway pressures levels have also been shown to be deleterious on right ventricular (RV) systolic function and hemodynamics [5 , 6]. At present, it is not clear whether these noxious effects are specifically related to PEEP level or Pplat level, since the studies were completed while modifying both PEEP and Pplat [5 , 6].

In addition, respiratory acidosis is a common feature in patients ventilated for severe ARDS according to a lung recruitment strategy, with tidal volume (V_T) limitation and augmented PEEP. Although some studies suggest that hypercapnic acidosis per se may contribute to the benefits of lung-protective ventilation [7 , 8], experimental and clinical data also suggest that hypercapnia may impair hemodynamic

function, despite the cardiac-index increase due to tachycardia and peripheral vasodilatation [9 –11]. In particular, it has been found that hypercapnia may induce vasoconstriction of the pulmonary vascular bed [11] leading to RV systolic overload [10]. Therefore, a ventilatory strategy resulting in augmented partial pressure of arterial carbon dioxide ($PaCO_2$) levels might be deleterious in patients who have severe ARDS, especially if induced abruptly.

The goal of this prospective two-center physiological study was to evaluate the relative roles of acute permissive hypercapnia and PEEP variations at constant Pplat, i.e., at variable V_T, on hemodynamics and RV function evaluated by transesophageal echocardiography in patients with severe ARDS. We characterized the properties of the respiratory system by measuring dead space (using expired CO_2) and alveolar recruitment (using pressure-volume curves). Our hypothesis was that hypercapnia and PEEP variations may alter RV function and hemodynamics in patients with severe ARDS.

PATIENTS AND METHODS

Patients

Patients diagnosed with ARDS (defined according to the criteria of the American–European Consensus Conference) [12] within the last 2 days were included prospectively if their PaO_2/FiO_2 ratio was less than 150 mm Hg at PEEP greater than 5 cm H_2O. Noninclusion criteria were contraindications to transesophageal echocardiography, chronic obstructive pulmonary disease, pneumothorax, intracranial hypertension, profound hypoxemia (PaO_2/FiO_2 ratio <50 mm Hg), and hemodynamic instability (defined as a need for epinephrine or norepinephrine in doses greater than 2 mg/hour, fluid bolus, or catecholamine dosage escalation within the last 2 hours). The protocol was approved by our institutional review board (N° P040202), and informed consent was obtained from each patient's next of kin. Sedation (midazolam, Sanofi-Aventis, France) and neuromuscular blockade (cisatracurium, or atracurium, GlaxoSmithKline, France) were used in all patients. The Simplified Acute Physiologic Score (SAPS II) and Lung Injury Score (LIS) were computed as previously described [13 , 14]. The patients did not present pre-existing myocardial or pulmonary diseases except for one patient with a history of tuberculosis and another one with a history of coronary heart disease.

Tested ventilatory strategies

The ventilator was a Servo 900C (Siemens-Elema AB, Solna, Sweden) or a Servo-i (Maquet SA, Ardon, France). Three ventilatory strategies were evaluated in each patient, using volume-controlled ventilation (Figure 1). In the low-PEEP strategy, PEEP was increased by steps of 1 cm H_2O to counterbalance intrinsic PEEP, as previously explained [15]. In patients without intrinsic PEEP, PEEP was set at 5 cm H_2O. Respiratory rate was set at 15/min. If pH was less than 7.30, the respiratory rate was increased to 20/min in order to obtain a pH of at least 7.30 without inducing intrinsic PEEP, if possible. V_T was set close to 8 ml/kg of predicted body weight [16]. If Pplat was 30 cm H_2O or more, V_T was lowered by steps of 1 ml/kg until Pplat was less than 30 cm H_2O or V_T was 4 ml/kg. The second strategy combined a lung-protective ventilation and the same Pplat, using a high PEEP and a high respiratory rate (high PEEP/high rate strategy). PEEP was twice as high as in the low PEEP strategy, whereas V_T was lower in order to keep Pplat constant. To counterbalance the effect of V_T reduction on alveolar ventilation, the respiratory rate was increased to the highest rate that did not induce intrinsic PEEP. In the third strategy, PEEP was high and the respiratory rate was low (high PEEP/low rate strategy). The only difference with the high PEEP/high rate strategy was that the effect of V_T reduction was counterbalanced by decreasing the instrumental dead space, instead of by increasing the respiratory rate. The dead space decrease was achieved by substituting a heated humidifier for the heat-and-moisture exchanger. Thus, we were able to evaluate the effect of PEEP and $PaCO_2$ variations at constant Pplat (low PEEP vs. high PEEP/high rate and low PEEP vs. high PEEP/low rate), while controlling for possible effects of respiratory rate variations (high PEEP/high rate vs. high PEEP/low rate) [17].

The low PEEP strategy was used first, to determine the target Pplat. The order of the other two strategies was then determined by random allocation using the sealed-envelope method. During the study, treatment changes that might influence the ventilatory or hemodynamic conditions (e.g., fluid bolus or changes in the dosages of catecholamines, sedatives, or neuromuscular blockers) were avoided unless clinically urgent. Each ventilatory strategy was used for 1 hour, at the end of which the following were recorded: arterial pressure, Pplat, PEEPtot, arterial blood gases, expired CO_2, pressure-volume curves, and transesophageal echocardiography. Pplat was recorded after a 0.5-sec end-inspiratory pause, and PEEPtot was the pressure value recorded after a 2-sec end-expiratory pause. Static compliance of the respiratory system was calculated as $V_T/(Pplat-PEEPtot)$. Mean airway pressure (Paw) was calculated as Paw = [(Pplat × inspiratory time) + (PEEPtot × expiratory time)]/respiratory cycle time. Blood gases were analysed using a RAPID Lab 1265 System (Siemens Healthcare, Deerfield, IL, USA) or a GEM Premier 3000 Analyser (Instrumentation Laboratory, Lexington, MA, USA).

Echocardiographic study

Transesophageal echo-Doppler studies were performed using a Sequoia C 256 (Siemens, Malvern, PA) or Envisor (Philips Ultrasound, Bothell, WA) machine equipped with a multiplane 5-MHz transesophageal echocardiographic transducer. Using the signal from the ventilator, airway pressure was displayed on the screen of the echo-Doppler machine, ensuring accurate determination of the timing of cardiac events relative to the respiratory cycle. Echocardiographic images were recorded on videotape, and a computer-assisted

quantitative evaluation was performed by a single trained investigator who was unaware of the ventilatory strategy being used. Echocardiographic variables were measured at end-expiration and averaged over five respiratory cycles in the 2 patients who had atrial fibrillation.

The collapsibility index of the superior vena cava, i.e., the inspiratory decrease in superior vena cava diameter, was determined as previously described [18] and used as an index of RV preload dependency. Patients who had evidence of hypovolemia received fluid bolus therapy before the study. With the ultrasonic beam parallel to the long axis of the pulmonary artery, pulmonary artery flow was assessed using pulsed Doppler spectrum recordings at a high speed of 5 cm/sec. By tracing the pulmonary flow envelope, the velocity-time integral was automatically processed. RV stroke index was computed as the product of the velocity-time integral by the pulmonary area (which was calculated from the systolic pulmonary diameter) normalized for body surface area. Cardiac index was calculated as the product of stroke index by heart rate. Left ventricular (LV) areas at end-systole and end-diastole were measured from the four-chamber view of the cardiac chambers. The long axis of the LV was measured at end-systole and end-diastole as the distance from the apex to the midpoint of the mitral valve ring. The volumes of the LV at end-systole and end-diastole and the LV ejection fraction were computed using the single-plane, area-length method. On the same view, RV end-diastolic area was measured, and the end-diastolic RV/LV area ratio was computed as previously described [19]. LV maximum systolic elastance, a measure of LV systolic contractility, was computed as the systolic artery pressure divided by the LVES volume [20]. Left ventricular end-systolic area (LVESA) and left ventricular end-diastolic area (LVEDA) were measured on a short-axis cross-sectional view of the LV at the midpapillary muscle level, and LV fractional area contraction was computed as (LVEDA-LVESA)/LVEDA. Two diameters were measured on the same view: D_1 bisecting and perpendicular to the plane of the interventricular septum, and D_2 perpendicular to D_1 and therefore parallel to the interventricular septum. The end-systolic eccentricity index, reflecting RV systolic overload, was computed as D_2/D_1, as proposed by Ryan et al [21].

Pressure-volume curves

At the end of each ventilatory strategy, elastic pressure-volume curves were recorded and analyzed using a constant [22] or sinusoidal low-flow inflation technique [23]. The PEEP-induced increase in end-expiratory lung volume was calculated by recording the expiratory volume during PEEP removal [3]. The volume recruited by PEEP was measured by superimposing the curves [24].

Dead space

Expiratory CO_2 recordings were used to assess end-tidal CO_2, and the alveolar dead space fraction (expressed as the percent of V_T) was calculated using the Bohr equation [25]. In addition, total dead space fraction and its partitions were calculated (as percents of V_T), using the single breath test for CO_2 and a CO_2 Analyzer 930 (Siemens-Elema, Solna, Sweden), as previously described [26]. The latest evaluation was impossible in 4 patients because of the unavailability of the CO_2 analyzer during the protocol.

Statistical analysis

Data were analyzed using the SPSS Base 10.0 statistical software package (SPSS Inc, Chicago, IL). Continuous data were expressed as median [interquartile range] and compared using nonparametric analysis of variance (Friedman test) and the Wilcoxon paired test. In order to better scrutinize the relationship between hemodynamic changes and respiratory parameters, we pooled the results of the three respiratory strategies and explored the correlations between respiratory parameters (V_T, PEEP, mean airway pressure, respiratory frequency, $PaCO_2$ and arterial pH) on the one hand and hemodynamic variables (RV stroke index and end-systolic eccentricity index) on the other hand. In addition, to evaluate independent respiratory factors associated with RV stroke index and end systolic eccentricity index, significant or marginally significant ($p \leq 0.20$) univariate factors were examined in a multivariate fashion using a backward stepwise multiple linear regression. Two-tailed P values less than 0.05 were considered significant. Correlations were tested using the Spearman's or Pearson's method. In one patient who could not tolerate the last experimental condition, the latest data recorded before end of protocol where considered for analysis and unavailable data (pressure volume curves) were considered as missing values.

RESULTS

Patients

We included 11 patients (8 men and 3 women), with severe ARDS. Age was 74 [57–79] years, SAPSII was 50 [32–63], and predicted body weight was 59 [51–65] kg. LIS was 2.8 [2.5–3.0], PaO_2/FiO_2 was <150 mm Hg (110 [80–130] mm Hg), and respiratory system compliance was 30 [24–35] ml/cm H_2O. Causes of ARDS included pneumonia (n=6), aspiration (n=3), alveolar hemorrhage (n=1), and massive blood transfusion (n=1).

Respiratory variables (Table 1)

Pplat was similar with all three strategies. $PaCO_2$, PEEP, and V_T were similar with the high PEEP/high rate and high PEEP/low rate strategies. Respiratory rate was similar with the low PEEP and high PEEP/low rate strategies. With the two high PEEP strategies,

hypercapnia and acidosis were more pronounced, and the PaO_2/FiO_2 ratio was significantly improved, compared to the low PEEP strategy. Alveolar recruitment was also significantly superior with the high PEEP strategies than with the low PEEP strategy. Instrumental and total dead space fractions were significantly higher with high PEEP/high rate than with the two other strategies. Alveolar dead space fraction was similar with the three strategies when evaluated using the single breath test for CO_2 (Table 1) or the Bohr equation (29 [24–37] % with low PEEP, 30 [27–39] % with high PEEP/high rate, and 30 [24–38] % with high PEEP/low rate, p=0.42).

Hemodynamics (Table 2)

Nine of 11 included patients received norepinephrine (dose range from 0.8 mg/hour to 2.0 mg/hour) and the 2 others did not receive any catecholamine. Vasopressor drug doses were kept constant throughout the study in all but one patient, in whom an arterial pressure drop when changing from low PEEP to high PEEP/high rate required an increase in the norepinephrine dose and premature end of the study. Heart rate was faster with the two HP strategies than with the low PEEP strategy. Systolic and mean arterial pressures were lower with high PEEP/high rate than with low PEEP strategy. The base excess was more negative with the two high PEEP strategies than with the low PEEP strategy.

Echocardiography (Table 3)

LV systolic function was not affected by changes in ventilation: LV ejection fraction, LV fractional area contraction, and LV systolic maximal elastance were similar with the three ventilation strategies. The superior vena cava collapsibility index did not change. In contrast, high PEEP was associated with deterioration in RV function, as indicated by the significantly higher end-diastolic RV/LV area ratio and end-systolic eccentricity index with the two high PEEP strategies compared to the low PEEP strategy. RV stroke index and cardiac index were significantly lower with the two high PEEP strategies than with the low PEEP strategy.

Correlates between respiratory and hemodynamic variables

There was a trend towards a negative correlation between the decrease in stroke index and the increase in alveolar recruitment when shifting ventilatory settings from low PEEP to high PEEP ($r = -0.50$, p=0.06, figure 2). When pooling the results of the three strategies, we found by univariate analysis that RV stroke index was significantly correlated to arterial pH whereas end-systolic eccentricity index was significantly correlated to PEEPtot, V_T , and arterial pH (Table 4). Multivariate regression analysis identified arterial pH as the sole independent correlate of RV stroke index and end-systolic eccentricity index (Table 4).

DISCUSSION

The main results of this study were that increasing PEEP at constant Pplat in patients with severe ARDS induced acute respiratory acidosis, which resulted in RV dysfunction and decreased RV stroke index.

This RV dysfunction was not related to PEEP-induced impairment of venous return, as shown by the absence of variations in the superior vena cava collapsibility index and the increase in RV end diastolic area; in addition, patients who had evidence of hypovolemia received fluid bolus therapy before the study. RV dysfunction was related to systolic overload, as evidenced by an increase in RV size (higher end-diastolic RV/LV area ratio) associated with LV deformation (higher end-systolic eccentricity index).

In our study, RV systolic overload could be due to augmented PEEP per se or to acute hypercapnia. Deleterious effects of high PEEP levels on RV systolic function have been reported previously, but both PEEP and Pplat were modified in these studies, precluding a separate assessment of the role for each factor [5 , 6]. Other arguments do not support the hypothesis of PEEP induced RV systolic overload in our patients. First, the so-called high-PEEP level used in our study (10–11 cm H_2O) was lower than the levels shown in previous studies to impair RV systolic function [5 , 27]. Second, respiratory acidosis but not PEEP was associated with RV stroke index and end-systolic eccentricity index by multivariate analysis.

Acute permissive hypercapnia has been reported to induce a hyperdynamic state in patients with ARDS [28 , 29]. However, hypercapnia can exacerbate hypoxic vasoconstriction [30 , 31] and can also directly induce vasoconstriction of the pulmonary vasculature, as shown in experimental animals [32], young healthy volunteers [33], brain-dead patients subjected to apnea tests [34], cardiac-surgery patients [35], and patients with ARDS [11 , 36]. In an animal model of progressive balloon occlusion of the RV outflow tract, acute hypercapnic acidosis had no effect on RV function when the outflow tract was normal but significantly impaired RV performance when the RV afterload was increased, leading to a greater rise in RV end-diastolic pressure compared to normocapnic controls [10]. Interestingly, our patients had substantial RV systolic overload related to severe ARDS, with an end-diastolic RV/LV area ratio greater than 0.6 in more than 60% of patients with low PEEP strategy.

Although RV dilatation, as assessed using the end-diastolic RV/LV area ratio, was more marked with both high PEEP strategies than with the low PEEP strategy, it was also slightly more marked with high PEEP/low rate than with high PEEP/high rate. Given that the echocardiographic measurements were performed at end-expiration, the greater increases in pleural (and pericardial) pressure with the high

PEEP/high rate strategy related to the higher PEEPtot value might affect RV effective elastance [6 , 37], thereby limiting RV dilatation compared to the high PEEP/low rate strategy. Indeed, whereas an increase in RV outflow impedance tends to reduce the ejection volume and to increase the end-diastolic volume, an increase in RV diastolic elastance reduces the end-diastolic volume, and the net result of these opposite effects on RV size depends on which factor predominates [6]. Hemodynamic impairments in our study were not more severe with high PEEP/high rate compared to high PEEP/low rate, indicating that the higher respiratory rate had no specific effect on the RV afterload increase.

We found no evidence that hypercapnia impaired LV contractility. LV ejection fraction, LV fractional area contraction, and LV maximal systolic elastance were similar with the three ventilatory strategies in our study. Although LV ejection fraction and LV fractional area contraction are of limited value for precisely estimating LV contractility, in particular because they vary with loading conditions, LV maximal systolic elastance is theoretically less dependent on loading. Contrary to previous reports [9], the lack of impairment of LV contractility in our study suggests that respiratory acidosis was not associated with a decrease in the developed force of the cardiac muscle per se. Conversely, respiratory acidosis induced RV systolic overload through afterload increase.

Our results are in accordance with a previous study who established that increasing PEEP improves alveolar recruitment, even when Pplat is kept constant [3]. We found a trend ($p=0.06$) towards a negative correlation between the decrease in stroke index and the increase in alveolar recruitment when shifting ventilatory settings from low PEEP to high PEEP. This is an interesting finding since lung recruitability varies widely among patients with ARDS [38]. The amount of recruited lung with PEEP may positively influence the hemodynamic response to ventilatory settings. Poor recruitment capabilities may be associated with a poorer hemodynamic response to PEEP in severe ARDS patients.

Our study has some limitations. It is a physiological protocol and we included a relatively small number of selected patients with severe ARDS (PaO_2 /FiO_2 ratio < 150 mm Hg) and continuous neuromuscular blockade. This may limit the interpretation of our data. Moreover, the very short study period of one hour per ventilation strategy might not be enough to reflect the consequences for the patients with ARDS, who are ventilated for several days or even weeks. Although our results suggest caution when implementing acute hypercapnia in such patients with severe ARDS, these data do not formally contradict previous studies reporting a benefic role for hypercapnia in less severe patients. Recent randomized clinical trials aimed at testing strategies for setting PEEP in large cohorts of patients with ALI/ARDS did not individually find any difference in mortality [4 , 39 , 40], but evidenced an improvement in lung function [4 , 40] and a reduced duration of mechanical ventilation and organ failure with higher levels of PEEP [4].

CONCLUSIONS

Increasing PEEP at constant Pplat during severe ARDS induces acute hypercapnia that may impair RV function and decrease cardiac index. Because hypercapnia is frequently considered as benign or even beneficial during mechanical ventilation, these findings may have important clinical implications. In case of impaired RV function, lung protective ventilation should be gradually adapted to limit hypercapnia and RV overload.

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Footnotes:

This study was performed at the Henri Mondor Teaching Hospital, Créteil, France; and at the Ambroise Paré Teaching Hospital, Boulogne-Billancourt, France.

DISCLOSURES No potential conflict of interest to disclose.

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Figure 1

Tested ventilatory strategies. HME, heat-and-moisture exchanger; HH, heated humidifier; RR, respiratory rate; Pplat, plateau pressure; PEEP, positive end-expiratory pressure; LP, low PEEP; HP/HR, high PEEP and high respiratory rate; HP/LR, high PEEP and low respiratory rate.

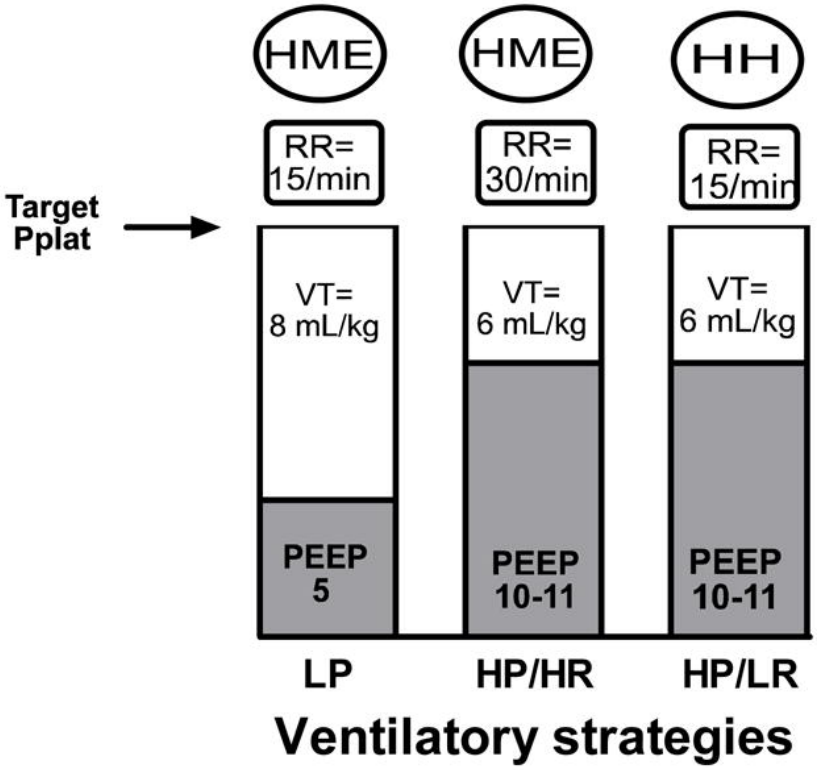

Figure 2

Correlation between decrease in stroke index (fractional percent change) and increase in alveolar recruitment (fractional percent change) when changing ventilatory settings from low PEEP to high PEEP/high rate. (r= −0.50, p=0.06).

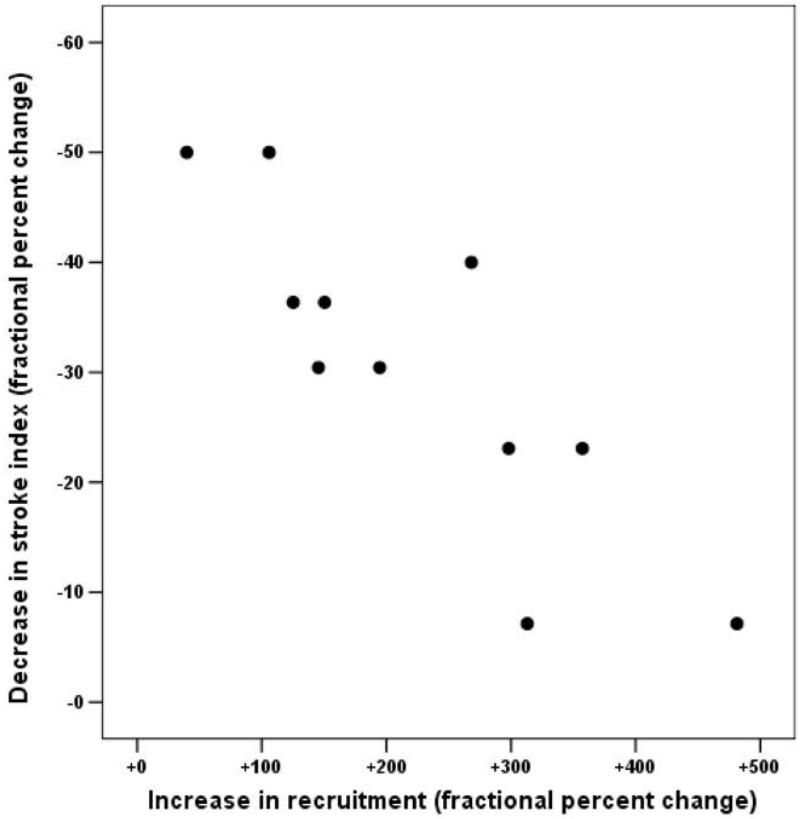

Table 1
Respiratory variables

	LP strategy	HP/HR strategy	HP/LR strategy
Pplat, cm H_2O	22.1 [18.9–27.0]	23.0 [20.1–28.0]	22.0 [19.5–26.2]
PEEPtot, cm H_2O	5.4 [5.0–6.0]	11.0 [10.0–12.0]*	10.0 [10.0–12.0]*
Paw, cm H_2O	11.8 [10.8–12.7]	15.5 [14.8–16.9]*	15.5 [13.8–16.7]*
V_T, mL	548 [468–605]	336 [260–360]*	356 [281–398]*
V_T, mL/kg	8.5 [8.3–8.9]	5.3 [4.5–6.1]*	5.8 [4.5–7.4]*
Respiratory rate, bpm	15 [15–20]	26 [25–30]*	15 [15–20]#
Minute ventilation, L/min	8.3 [7.2–9.8]	8.4 [7.1–8.8]	5.3 [4.6–7.5]*#
$PaCO_2$, mm Hg	52 [43–68]	71 [60–94]*	75 [53–84]*
pH	7.30 [7.24–7.35]	7.17 [7.12–7.23]*	7.20 [7.16–7.25]*
PaO_2/FiO_2 ratio, mm Hg	88 [60–110]	103 [74–138]*	101 [81–137]*
Alveolar recruitment at elastic distending pressure of:			
15 cm H_2O (mL) ¶	64 [40–89]	151 [77–245]*	133 [67–197]*
17.5 cm H_2O (mL) ¶	42 [36–65]	117 [50–184]*	116 [44–146]*
PEEP-induced increase in end-expiratory lung volume, mL	215 [110–269]*	520 [310–614]*	547 [392–561]*
Dead space fraction, % of V_T (n=7)¶¶			
Total dead space	72 [60–77]	88 [73–90]*	72 [55–80]#
Airway dead space	35 [31–47]	61 [46–67]*	42 [29–50]#
Alveolar dead space	25 [23–29]	20 [14–23]	25 [16–31]

LP, low positive end-expiratory pressure; HP, high positive end-expiratory pressure; HR, high respiratory rate; LR, low respiratory rate; Pplat, plateau pressure; PEEPtot, total positive end-expiratory pressure; V_T, tidal volume; Paw, mean airway pressure. Data are medians [interquartile range]. n=11 patients unless otherwise stated.

¶ In one patient who could not tolerate the last experimental condition, unavailable data (pressure volume curves) were considered as missing values.

¶¶ In seven patients, total dead space fraction and its partitions were calculated (as percents of V_T), using the single breath test for CO_2 and a CO_2 Analyzer 930 (Siemens-Elema, Solna, Sweden).

* P <0.05 compared to the low PEEP strategy and

# P <0.05 compared to the high PEEP/high rate strategy.

Table 2
Hemodynamic variables

	LP strategy	HP/HR strategy	HP/LR strategy
Heart rate, bpm	108 [81–114]	113 [105–119]*	114 [103–124]*
Systolic arterial pressure, mm Hg	117 [108–137]	103 [91–117]*	110 [100–118]
Mean arterial pressure, mm Hg	70 [65–80]	65 [60–73]*	70 [62–75]
Base excess, mmol/L	0.00 [−5.4 to 1.00]	−3.70 [−6.45 to 0.30]*	−2.75 [−6.43 to 0.73]*

LP, low positive end-expiratory pressure; HP, high positive end-expiratory pressure; HR, high respiratory rate; LR, low respiratory rate. Data are medians [interquartile range];
* P <0.05 compared to the LP strategy.

Table 3
Echocardiographic variables.

	LP strategy	HP/HR strategy	HP/LR strategy
LV ejection fraction, %	62 [57–71]	64 [49–67]	59 [53–66]
LV fractional area contraction, %	58 [55–65]	57 [53–70]	62 [54–65]
LV maximal systolic elastance, mmHg/mL	5.5 [3.9–6.3]	5.2 [4.1–6.6]	5.4 [4.3–7.2]
Superior vena cava collapsibility index, %	0 [0–26]	0 [0–8]	0 [0–23]
RV stroke index, cm^3/m^2	22 [20–32]	17 [10–26]*	16 [11–27]*
Cardiac index, $L/min/m^2$	2.60 [1.53–3.54]	1.87 [1.16–2.98]*	1.89 [1.38–3.35]*
End-systolic eccentricity index	1.10 [1.02–1.25]	1.19 [1.07–1.54]*	1.28 [1.00–1.52]*
End-diastolic RV/LV area ratio	0.64 [0.56–0.77]	0.85 [0.62–1.10]*	1.0 [0.69–1.20]*#
End-diastolic RV/LV area ratio > 0.6	7 (64%)	9 (82%)	9 (82%)

LP, low positive end-expiratory pressure; HP, high positive end-expiratory pressure; HR, high respiratory rate; LR, low respiratory rate; LV, left ventricle; RV, right ventricle; see text for definitions.
Data are medians [interquartile range]
* P <0.05 compared to the LP strategy and
# P <0.05 compared to the HP/HR strategy

Table 4

Correlates between hemodynamic variables (right ventricle stroke index and end-systolic eccentricity index) and respiratory variables.

	Univariate analysis	Multivariate analysis
	rho (p value)	p value
Correlation with right ventricle stroke index		
PEEPtot	−0.29 (0.13)	0.70
Paw	−0.30 (0.13)	0.72
V_T	0.10 (0.78)	-
Respiratory rate	− 0.19 (0.32)	-
$PaCO_2$	− 0.16 (0.42)	-
pH	0.41 (0.03)	0.04
Correlation with end-systolic eccentricity index		
PEEPtot	0.39 (0.03)	0.87
Paw	0.19 (0.31)	0.53
V_T	−0.39 (0.03)	0.32
Respiratory rate	0.11 (0.55)	-
$PaCO_2$	0.34 (0.05)	0.10
pH	−0.54 (<0.01)	<0.01

Pplat, plateau pressure; PEEPtot, total positive end-expiratory pressure; V_T, tidal volume; Paw, mean airway pressure.