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Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation*

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Abstract

Objective—To reevaluate the clinical impact of external positive end-expiratory pressure (external-PEEP) application in patients with severe airway obstruction during controlled mechanical ventilation. The controversial occurrence of a paradoxic lung deflation promoted by PEEP was scrutinized.

Design—External-PEEP was applied stepwise (2 cm H_2O, 5-min steps) from zero-PEEP to 150% of intrinsic-PEEP in patients already submitted to ventilatory settings minimizing overinflation. Two commonly used frequencies during permissive hypercapnia (6 and 9/min), combined with two different tidal volumes (V_T: 6 and 9 mL/kg), were tested.

Setting—A hospital intensive care unit.

Patients—Eight patients were enrolled after confirmation of an obstructive lung disease (inspiratory resistance, >20 cm H_2O/L per sec) and the presence of intrinsic-PEEP (≥5 cm H_2O) despite the use of very low minute ventilation.

Interventions—All patients were continuously monitored for intra-arterial blood gas values, cardiac output, lung mechanics, and lung volume with plethysmography.

Measurements and Main Results—Three different responses to external-PEEP were observed, which were independent of ventilatory settings. In the biphasic response, isovolume-expiratory flows and lung volumes remained constant during progressive PEEP steps until a threshold, beyond which overinflation ensued. In the classic overinflation response, any increment of external-PEEP caused a decrease in isovolume-expiratory flows, with evident overinflation. In the paradoxic response, a drop in functional residual capacity during external-PEEP application (when compared to zero-external-PEEP) was commonly accompanied by decreased plateau pressures and total-PEEP, with increased isovolume-expiratory flows. The paradoxic response was observed in five of the eight patients (three with asthma and two with chronic obstructive pulmonary disease) during at least one ventilator pattern.

Conclusions—External-PEEP application may relieve overinflation in selected patients with airway obstruction during controlled mechanical ventilation. No *a priori* information about disease, mechanics, or ventilatory settings was predictive of the response. An empirical PEEP trial investigating plateau pressure response in these patients appears to be a reasonable strategy with minimal side effects.

*See also p. 1652.

The authors have no financial interest to disclose.

Keywords

intrinsic positive end-expiratory pressure; applied positive end-expiratory pressure; mechanical ventilation; obstructive pulmonary disease; waterfall effect; negative effort dependence

Many patients with obstructive pulmonary disease require ventilatory assistance during acute exacerbations. During this critical period, dynamic overinflation and air trapping are major challenges for clinicians (1–12). Besides the associated hemodynamic impairment, patients with obstructive pulmonary disease frequently experience dyssynchrony during assisted ventilation and difficulty triggering mechanical breaths (2–4,6,9,10,13,14). This difficulty is caused by the large difference between alveolar and upstream pressures at end-expiration (intrinsic positive end-expiratory pressure, or intrinsic-PEEP), imposing an increased load on inspiratory muscles.

Under such conditions, external-PEEP application minimizes pressure differences across obstructed airways, reducing the effort to trigger the ventilator (2–4,9,10). Provided that external-PEEP is set below intrinsic-PEEP, chances of overinflation are low (6,8). The explanation for this response is based on the dynamic flow-limitation theory and its hydraulic analogue: the waterfall model (15–17). Contrary to these recognized benefits of external-PEEP during assisted ventilation, there are only anecdotal data suggesting benefit from external-PEEP during controlled mechanical ventilation of patients with obstructive lung disease (10, 11,18,19). Qvist et al. (18) reported two patients with severe asthma in whom external-PEEP levels of 17–25 cm H_2O during controlled ventilation resulted in reduced peak airway pressures, improvement of blood pressure, and returning of the diaphragm to normal position These effects were interpreted as paradoxic lung deflation promoted by PEEP. Reporting less impressive benefits, two other investigators detected increments in expiratory flow during external-PEEP application with controlled mechanical ventilation (10,19).

According to the waterfall analogy, one can explain how external-PEEP does not impair an expiratory flow that is already limited (16,17,20). However, it is impossible, through this analogy, to explain how it could increase expiratory flow in response to a decreased driving pressure. This traditional concept has agreed with findings in the majority of studies in this field: with the exception of the few reports mentioned above, external-PEEP application during controlled ventilation has repeatedly produced negligible effects on gas exchange (21) or overinflation (22) but never a deflation (“paradoxic response”).

We designed the present study to reevaluate this controversy, investigating whether the paradoxic response associated with PEEP could be convincingly demonstrated and characterized at the bedside. To assess its clinical consequences, we intensively monitored patients with severe airway obstruction under controlled mechanical ventilation, submitting them to a stepwise protocol of external-PEEP application.

METHODS

The Institutional Human Subjects Committee at the Hospital das Clínicas, São Paulo, Brazil, approved this study. Informed consent was obtained from the next of kin. Patients with a history of chronic obstructive pulmonary disease or asthma who were intubated and mechanically ventilated and met the following entry criterion were studied: inspiratory resistance of >20 cm H_2O/L per sec and intrinsic-PEEP of ≥5 cm H_2O when tidal volumes (V_T) were set at 6 mL/kg and respiratory rate (RR) at 6 breaths/min. Exclusion criteria were hemodynamic instability and contraindications for sedation, paralysis, or hypercapnia. The patients who met our inclusion criteria were enrolled consecutively. All patients underwent standard medical

therapy, including systemic glucocorticoids and nebulized bronchodilators plus suctioning as needed. Bronchodilators and suctioning were provided before and after but not during the experimental protocol. A blinded clinician assessed the patients' status throughout the experimental protocol to ensure the ongoing safety of the study.

Instrumentation

Patients were ventilated with a BEAR 1000 ventilator (VIASYS Healthcare, Conshohocken, PA). Flow was measured by a heated pneumotachometer (0–160 L/min; Hans Rudolph, Kansas City, MO) connected to a differential pressure transducer (± 2 cm H_2O; MP-45, Validyne, Northridge, CA). Volume was determined by digital integration of the flow signal. Differential pressure transducers (Validyne MP-45; ± 100 cm H_2O) measured airway opening pressure. Arterial blood gas and pH values were monitored with a continuous intravascular system (Paratrend-7, Diametrics Medical, Roseville, MN). Mixed venous oxygen saturation and cardiac index were continuously monitored with special pulmonary artery catheters (Baxter-Vigilance CCO/SVO_2 monitor). Changes in end-expiratory lung volume were continuously assessed by inductive plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY).

Calibration

Pressure transducers were calibrated with a water column. Flow signal was iteratively calibrated by forcing the digitally integrated flow signal to match a reference volume (1 L) provided by a supersyringe, within 1% of the nominal value.

Proper positioning of the esophageal catheter was assessed during spontaneous breaths against an occluded airway (23). The catheter was repositioned to achieve esophageal pressure swings equivalent to proximal airway pressure swings.

Calibration of plethysmography was performed in two steps. In the first step, which corresponded with the least-squares method proposed by Chadha et al. (24), we obtained the calibration factors for rib cage (RC) and abdominal (Ab) sensors, k1 and k2, respectively. Subsequently, we tested the linearity of the **SUM** of both calibrated signals (representing total volume changes detected by plethysmograph) against a reference volume provided by a supersyringe connected to the endotracheal tube. Coordinate pairs representing the **SUM** signal versus supersyringe volume were plotted and a linear regression line was fitted. After checking a coefficient of determination above 0.95, the slope of the regression line was used as a fine-tuning calibration factor (K3), according to this equation: calibrated-**SUM** = K3. (k1. $\mathbf{V}_{RC}$ + k2. $\mathbf{V}_{Ab}$). The oscillator of the plethysmograph was warmed up for at least 1 hr before the measurements to ensure that drifts in plethysmograph signal were negligible during the experiment. In a side *in vitro* experiment, we observed that our device presented a maximum drift of 2.0 mL/min when warmed beforehand.

Experimental Protocol

All patients were studied in supine position after sedation with fentanyl citrate and diazepam and paralyzation with pancuronium bromide. Criteria for interrupting the protocol were as follows: cardiac output of ≤2 L/min per m^2; mixed venous saturation of ≤70%; mean arterial blood pressure of <60 mm Hg; and cardiac arrhythmias.

After stabilization, baseline intrinsic-PEEP was assessed by end-expiratory double occlusion (5 secs) under the following conditions: controlled mechanical ventilation, zero external-PEEP, V_T = 6 mL/kg, RR = 6 breaths/min, and inspiratory flow = 40 L/min. Progressive levels of external-PEEP were applied stepwise in increments of 2 cm H_2O, every 5 mins, from zero to a value matching 150% of baseline intrinsic-PEEP. The same PEEP titration procedure was repeated with the four different combinations of V_T and RR selected in random order (Table

1). The combinations covered recommended settings for minimizing lung overinflation during severe airway obstruction (25,26). The baseline intrinsic-PEEP was measured at the beginning of each ventilatory pattern and subsequently was used as a reference to adjust external-PEEP for that particular combination of V_T and RR. At the end of each 5-min trial period, an end-expiratory airway occlusion (5 secs) was performed, immediately followed by an end-inspiratory airway occlusion (5 secs). Whenever a certain external-PEEP was applied, the end-expiratory equilibrium pressure after occlusion was called total-PEEP. Other hemodynamic and respiratory variables were collected at the end of each 5-min trial period, just before occlusion maneuvers.

Analysis

After digital conversion, three direct signals (proximal pressure, flow, and esophageal pressure) and two indirect signals (integrated volume from the pneumotachometer and calibrated-**SUM**) were collected continuously and analyzed with specially developed software. By tracking flow signal, the start of inspiration was automatically identified, and five synchronous waveform segments (one for each signal) were generated for each respiratory cycle. A representative mean-cycle for each signal was then obtained by point-by-point averaging of five to eight consecutive cycles during each external-PEEP step, just before occlusion maneuvers. Subsequently, we obtained functional residual capacity (FRC; calibrated-**SUM** at end-expiration), peak pressures, external-PEEP, and flow-volume loops (by plotting all data points for flow measured at the pneumotachometer against the **SUM** signal from the plethysmograph, within a respiratory cycle).

Isovolume pressure-flow curves were obtained in a sequential procedure. First, an appropriate isovolume was chosen, by analyzing all flow-volume loops across incremental external-PEEP steps, plotted on the same coordinates. By drawing an imaginary vertical line crossing the **SUM** axis, we identified a convenient **SUM** value at which this vertical line intersected concomitantly the x-axis, the loop at zero external-PEEP, and a maximum number of loops at different external-PEEP levels. By doing so, we ensured that we had information about the patient's instantaneous expiratory flow across different external-PEEP levels, *at the same known lung volume*. Second, we identified both the corresponding proximal pressure and the predicted alveolar pressure at this specific lung volume (assuming relaxation conditions). The predicted alveolar pressure was calculated after obtaining a static pressure volume (P-V) curve of the respiratory system. To obtain this curve, coordinate pairs, representing airway pressures measured at end-inspiratory occlusion versus calibrated-**SUM**, were extracted at the end of each external-PEEP step. After obtaining one coordinate pair for each PEEP step, an exponential curve was fitted across all data points:

$$(V = V_o + a(1 - e^{-b.\,Pprox})) \quad [1]$$

where V is volume above FRC, measured during inspiratory pause (extracted from calibrated-**SUM**), V_o equals the estimated FRC at zero external-PEEP, and P_{PROX} is airway pressure measured during inspiratory pause.

The coefficients V_0, a, and b were estimated, and predicted alveolar pressure was calculated by substituting the coefficients and the corresponding isovolume (V) in the formula. Finally, driving pressure was calculated as the difference between the predicted alveolar pressure and the proximal airway pressure detected when the isovolume condition was achieved. Similarly, the instantaneous expiratory flow at isovolume condition was also identified across the PEEP steps and plotted against its corresponding driving pressure.

Inspiratory resistance was calculated by dividing the difference between peak and plateau pressures (end-inspiratory occlusion = 5 secs) by the value of inspiratory flow immediately before occlusion.

Averaged isovolume resistance was calculated according to the method of Frank and Mead (27,28), assuming negligible hysteresis during tidal ventilation and equal elastic forces during inspiration and exhalation, at equivalent lung volumes. By choosing specific time points at inspiration and exhalation where lung volume is the same (isovolume time points), we assumed resistance to be the difference in proximal pressures at these isovolume time points (inspiration minus exhalation), divided by the sum of absolute flow values during inspiration and expiration, at the same isovolume time points. Our software automatically detected 100 pairs of matched isovolume time points, calculating 100 values of resistance along tidal volume. We then displayed the average of these 100 resistance values.

Statistics

Data are presented as mean ± SD. Repeated-measures analysis of variance was used to test the significance of trends in respiratory and hemodynamic variables across incremental external-PEEP steps and across ventilatory settings. Using cardiac-index and arterial PCO_2 as dependent variables, we performed multiple linear regression to assess their association with ventilatory parameters or with the presence/absence of paradoxic response.

RESULTS

Eight patients meeting all inclusion criteria and none of the exclusion criterion completed the protocol (Table 2). Patients were studied during their first to tenth day of mechanical ventilation. Three patients were excluded because of hemodynamic instability (2) or improvement in airway obstruction (1) before protocol start, reaching intrinsic-PEEP levels <5 cm H_2O (measured under RR = 6 breaths/min and V_T = 6 mL/kg).

The mean values for total-PEEP, FRC, plateau pressure, and peak airway pressures are presented in Figures 1 and 2. These data, averaged across patients, demonstrated an apparently consistent response with external-PEEP application, exhibiting a two-phase response in most situations. There were slight changes or no changes in these averaged parameters below 80% to 100% of baseline intrinsic-PEEP, followed by a sharp increase above 100% of baseline intrinsic-PEEP. However, the pooled responses in Figures 1 and 2 were very different from the response of individual patients. Figure 3 illustrates the changes in FRC for every patient during each V_T and RR setting. There was considerable variability among patients and within a single patient as the ventilatory pattern changed. On a few occasions we observed a deflation response to external-PEEP levels exceeding 100% of baseline intrinsic-PEEP.

Figures 4 and 5 illustrate the three distinct patterns of response to the application of external-PEEP.

The paradoxic response (patient 4) involved a decrease in FRC, total PEEP, and plateau pressures, with an increase in isovolume expiratory flows as external-PEEP increased.

In the biphasic response (patient 7), the FRC, plateau pressure, and isovolume expiratory flows remained constant with the incremental application of external-PEEP until it exceeded a critical pressure. Beyond this level, FRC and plateau pressures markedly increased and expiratory flow decreased.

In the classic overinflation response (patient 5), any application of external-PEEP promoted an increase in FRC and plateau pressures, with decreased isovolume expiratory flows.

In five of the eight patients (three with asthma and two with chronic obstructive pulmonary disease), at least one ventilatory pattern resulted in a paradoxic response. Only four patients (two with asthma and two with chronic obstructive pulmonary disease) demonstrated a clear biphasic response during at least one ventilatory pattern, and six patients (three with asthma and three with chronic obstructive pulmonary disease) presented a classic overinflation response during at least one ventilatory pattern. We could not find any relationship between baseline resistance, intrinsic-PEEP, and ventilator settings and the ensuing response.

Table 3 illustrates the effect of applied external-PEEP on static compliance and airway resistance. Whereas compliance was not affected by the application of external-PEEP, airway resistance decreased as external-PEEP increased, whatever the method of resistance calculation. Hemodynamic and blood gas responses to the application of external-PEEP are listed in Table 4. The application of external-PEEP did not affect cardiac index, venous oxygen saturation, or arterial PO_2, but it was associated with an increased arterial PCO_2.

Multiple linear regression demonstrated a positive correlation (r) between cardiac index and arterial PCO_2 ($p < .0001$; partial $r = .56$) and a negative correlation between FRC changes and cardiac index ($p < .0001$; partial $r = -.47$). There was a marginally significant association between the presence of paradoxic response and an increased cardiac index during external-PEEP rise ($p = .05$), but the same was not true for arterial $PaCO_2$ ($p = .7$).

DISCUSSION

The major findings in this study can be summarized as follows. First, we could convincingly demonstrate the occurrence of “paradoxic responses” to external-PEEP application during controlled mechanical ventilation, occurring in a significant proportion of patients with obstructive pulmonary disease (five of eight). Second, we observed three specific responses during stepwise PEEP application: a) paradoxic response (an increased isovolume expiratory flow with a decrease in FRC, plateau pressures, and total-PEEP while external-PEEP was applied); b) biphasic response (no deleterious effect on expiratory-flow, FRC, plateau pressures, or total-PEEP until external-PEEP exceeded a specific level); and c) classic overinflation (any application of external-PEEP resulted in evident lung overinflation). Finally, we observed a variable behavior (deflation vs. inflation) depending on tidal volume, respiratory rate, and external-PEEP settings, which could not be related to baseline disease or mechanics.

We believe that our observations are of relevance to clinicians involved in the care of patients with obstructive lung disease. In the spontaneously breathing patient, the application of external-PEEP can be useful to reduce the effort required for triggering the ventilator (2). This phenomenon is well known and currently used by most intensivists. However, for patients being passively ventilated, the application of external-PEEP is not generally believed to have important effects. The observations of the current study suggest that, at least in some hyperinflated patients, a deflation response may be observed, carrying eventual benefits in situations where more traditional measures were already attempted such as the optimization of frequency/tidal-volume combinations (25,26). In one of our patients (Fig. 3C), external-PEEP application resulted in a 450-mL reduction in FRC, with 7 cm H_2O reduction in plateau pressures.

Our results imply that a therapeutic trial with external-PEEP must be applied to determine the response in a given patient and for each particular set of ventilatory conditions. Although there has been some debate about the prevalence of flow limitation in asthma vs. chronic obstructive pulmonary disease, theoretically with different implications concerning external-PEEP application, we did not find any typical behavior discriminating these two diseases. Unfortunately, our sample size was too small for us to draw definite conclusions.

We could not demonstrate any large benefit of the paradoxic response in terms of blood gas values or hemodynamics, except for a marginal increment in cardiac output. We believe that our particular study design was responsible for such inconsistency. Although the 5-min period at each external-PEEP step was long enough to stabilize end-expiratory lung volume (as could be assessed from plethysmographic signals), it was insufficient to stabilize blood gases. Because the time constant for CO_2 distribution across body compartments is approximately three times the length of studied steps (29), our blood gases were probably contaminated by carryover effects. Multivariate analysis indicated that $Paco_2$ levels and cardiac output were directly related; as a result, the beneficial effect of decreased lung volume may have been offset by an increase in cardiac output. A more complete evaluation of the full impact of external-PEEP in such patients would require a much longer study period.

The occurrence of a paradoxic deflation seems somewhat counterintuitive on the basis of traditional teaching in respiratory physiology. The classic waterfall theory of flow limitation suggests that expiratory flow is determined by pressure gradients up to the choke point and that conditions downstream from choke point have no influence on expiratory flow (15,16). By analogy, the level of the lake downstream from a waterfall is said to have no influence on the water flow falling into it (provided that the lake level does not exceed the waterfall's edge). The water flow would be determined basically by the difference in level between the headspring and the edge of the waterfall. Since external-PEEP represents the level of the downstream lake in such an analogy, it follows that external-PEEP application either should have no influence on expiratory flow or should only impair it when intrinsic-PEEP is approached.

However, a review of the literature in this area suggests some alternative mechanisms through which paradoxic responses could occur (30). The waterfall theory is based on a one-compartment model, which is useful to explain some clinical observations but overly simplistic for explaining phenomena such as those observed here. By considering regional imbalances in lung mechanics, with parallel heterogeneity in time constants and airway stiffness (31), we could offer some alternative hypotheses for the paradoxic deflation response.

The application of external positive end-expiratory pressure in patients with obstructive pulmonary disease during controlled ventilation and low-minute ventilation conditions results in a variable and unpredictable response, affected by the ventilatory pattern.

For instance, one could argue that a hyperinflated lung unit might experience sticky airway closure during exhalation against too low expiratory pressures, trapping some highly pressurized air behind. Step application of external-PEEP—associated with transiently high end-inspiratory pressures—might reopen such a disconnected lung unit and then, because of airway hysteresis, this external-PEEP might be enough to prevent expiratory airway recollapse in the next breaths, promoting progressive deflation.

Second, intraparenchymal tethering forces could extend the consequences of the inflation of one lung unit to its vicinity, as already demonstrated (32,33). For example, if one lung unit without flow limitation is adjacent to a hyperinflated lung unit with flow limitation, it is possible that hyperinflation of the non-flow-limited lung unit could exert a distending influence on the flow-limited airway, increasing radial tensions over obstructed airways and allowing deflation of the flow-limited unit. That is to say, an increase in lung volume in one lung unit may be more than counterbalanced by the deflation of an adjacent lung unit.

Third, according to the wave speed theory, the maximal expiratory flow through a collapsible tube is a function of the cross-sectional area of the tube, the density of the gas, and the rigidity of the tube (31,34). One could conceive that the application of external-PEEP could indirectly promote changes in the rigidity of the tubes upstream or in the vicinity of the choke point.

Either via longitudinal traction or radial traction of the upstream segment, stiffening of such an airway could yield a higher maximal flow rate, thus promoting regional deflation (35,36).

Finally, with consideration of the Bernoulli principle, it is possible that external-PEEP just acted as an expiratory retarder (19), limiting air flow velocity in areas of constriction and consequently minimizing intraluminal pressure drop—with eventual collapse—secondary to air flow acceleration.

Limitations

We did not prove the presence of flow limitation in our patients by using the traditional negative expiratory pressure technique (37–39). However, we used plethysmography during varied external-PEEP levels, superposing flow-volume loops at each external-PEEP level. Because we had a reference volume (measured at zero external-PEEP), we could use both the absence of leftward shift in the flow-volume loops during external-PEEP increments and the observation of an unchanged expiratory flow at isovolume conditions as good indicators of flow limitation (this was precisely what characterized the biphasic response). In fact, the logic of the maneuver is very similar: instead of proving that an increased driving pressure (promoted by the negative expiratory pressure maneuver) cannot increase expiratory flow, we proved that a decreased driving pressure (produced by external-PEEP application) cannot change expiratory flow at isovolume conditions (40–42).

Despite the somewhat imprecise measurement of lung volume provided by inductance plethysmography (43,44), drift errors in our device were previously assessed (±2 mL/min) and were shown to be negligible in comparison with the changes in FRC reported here. Furthermore, every time we observed a deflation response in the plethysmograph, there was a concomitant fall in plateau pressures and eventually in the intrinsic-PEEP, suggesting coherency in the data.

CONCLUSION

The application of external-PEEP in patients with obstructive pulmonary disease during controlled ventilation and low-minute ventilation conditions results in a variable and unpredictable response, affected by the ventilatory pattern. In some settings, external-PEEP causes overinflation; in others, FRC and intrinsic-PEEP are decreased, and in still others no response to PEEP is observed until external-PEEP exceeds baseline intrinsic-PEEP. Our results suggest that an external-PEEP trial to determine the level resulting in the minimum plateau pressure might be a useful bedside approach, with acceptable drawbacks.

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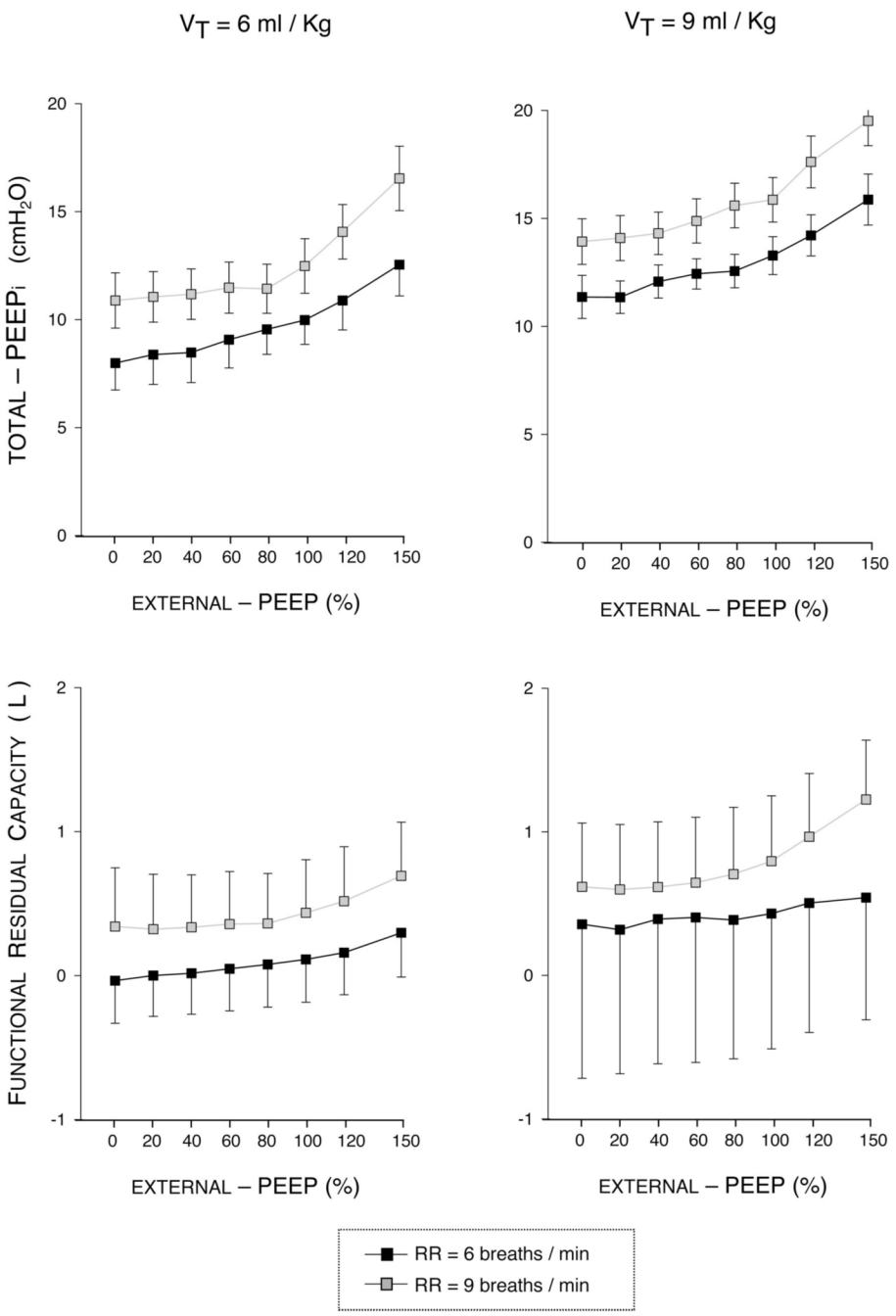

Figure 1.

Changes in total intrinsic positive end-expiratory pressure (*PEEP$_i$*) and functional residual capacity (FRC) with increments in external-PEEP (mean ± SEM across patients). External-PEEP is shown as a percentage of external-PEEP$_i$ measured at zero external-PEEP. The FRC measured at zero external-PEEP was considered as the reference. *Gray squares* represent a respiratory rate (*RR*) of 9 breaths/min and *black squares*, an RR of 6 breaths/min. The graphs at *left* represent trials with a small tidal volume (*V_T*; 6 mL/kg), and those at *right* represent trials with a high V_T (9 mL/kg).

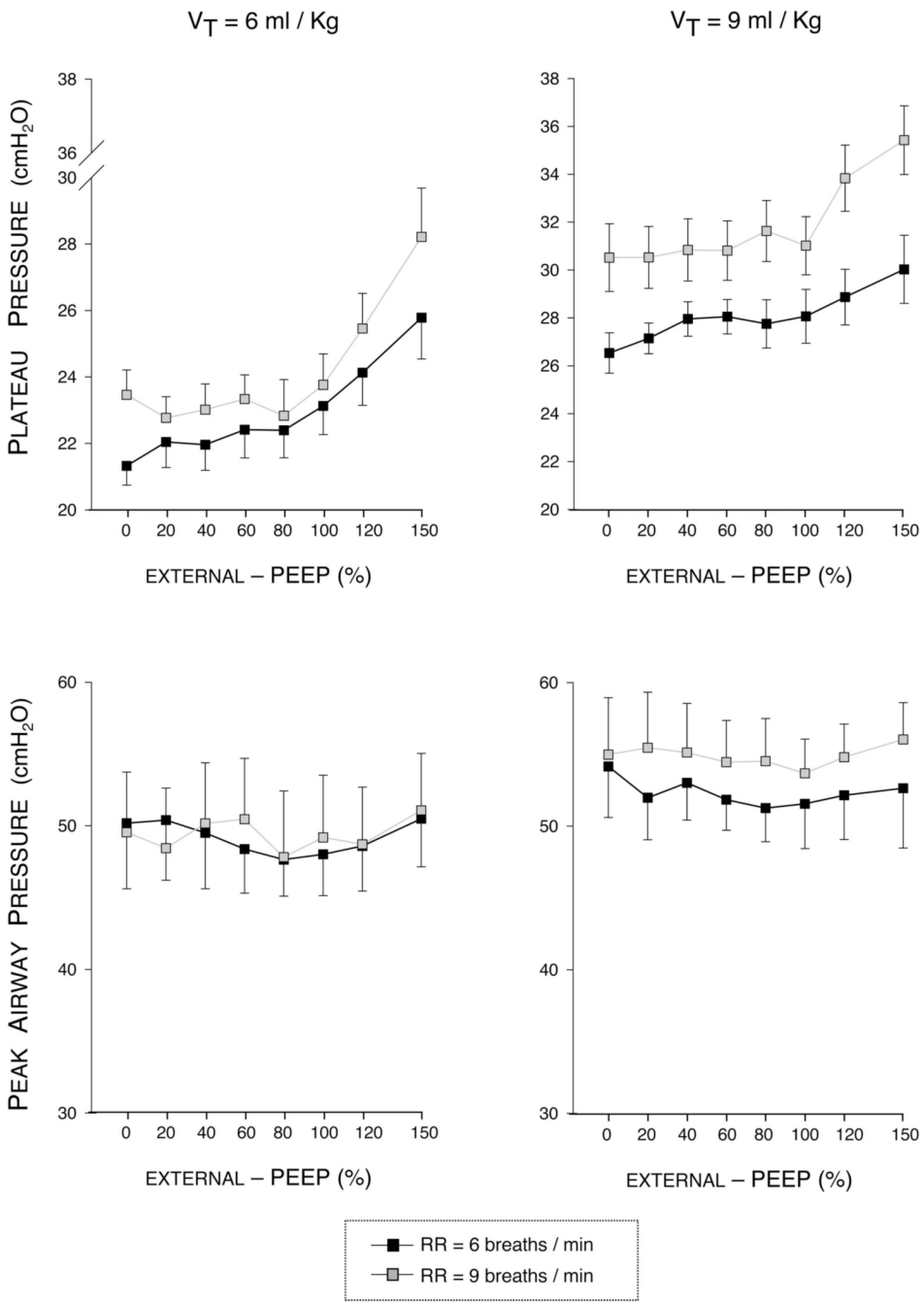

Figure 2.

Plateau pressures and peak airway pressures with increments in external positive end-expiratory pressure (*PEEP*; mean ± SEM across patients). External-PEEP is shown as a percentage of intrinsic-PEEP measured at zero external-PEEP. The *gray squares* represent a respiratory rate (*RR*) of 9 breaths/min and *black squares*, an RR of 6 breaths/min. The graphs at *left* represent trials with a small tidal volume (V_T; 6 mL/kg), and those at *right* represent trials with a high V_T (9 mL/kg).

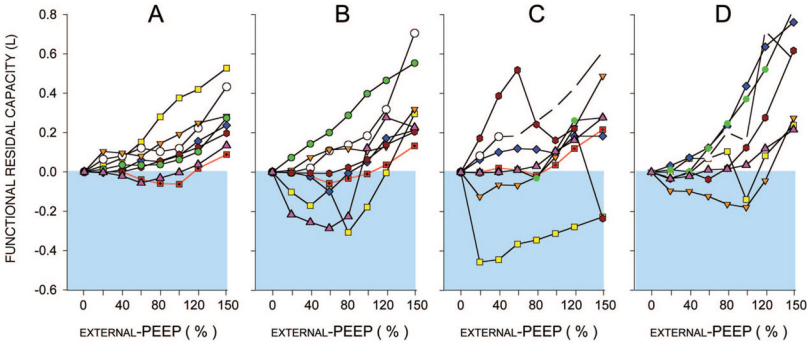

Figure 3.

Changes in functional residual capacity (FRC) assessed by inductive plethysmography. Individual responses along the incremental external positive end-expiratory pressure (*PEEP*) steps, from zero external-PEEP (reference) to a value matching 150% of intrinsic-PEEP measured at zero external-PEEP conditions. *A*, tidal volume (V_T) = 6 mL/kg, respiratory rate (RR) = 6 breaths/min; *B*, V_T = 6 mL/kg, RR = 9 breaths/min; *C*, V_T = 9 mL/kg, RR = 6 breaths/min; *D*, V_T = 9 mL/kg, RR = 9 breaths/min. The FRC measured at zero external-PEEP was considered as the reference. *Points inside the gray zone* indicate the occurrence of a paradoxic response.

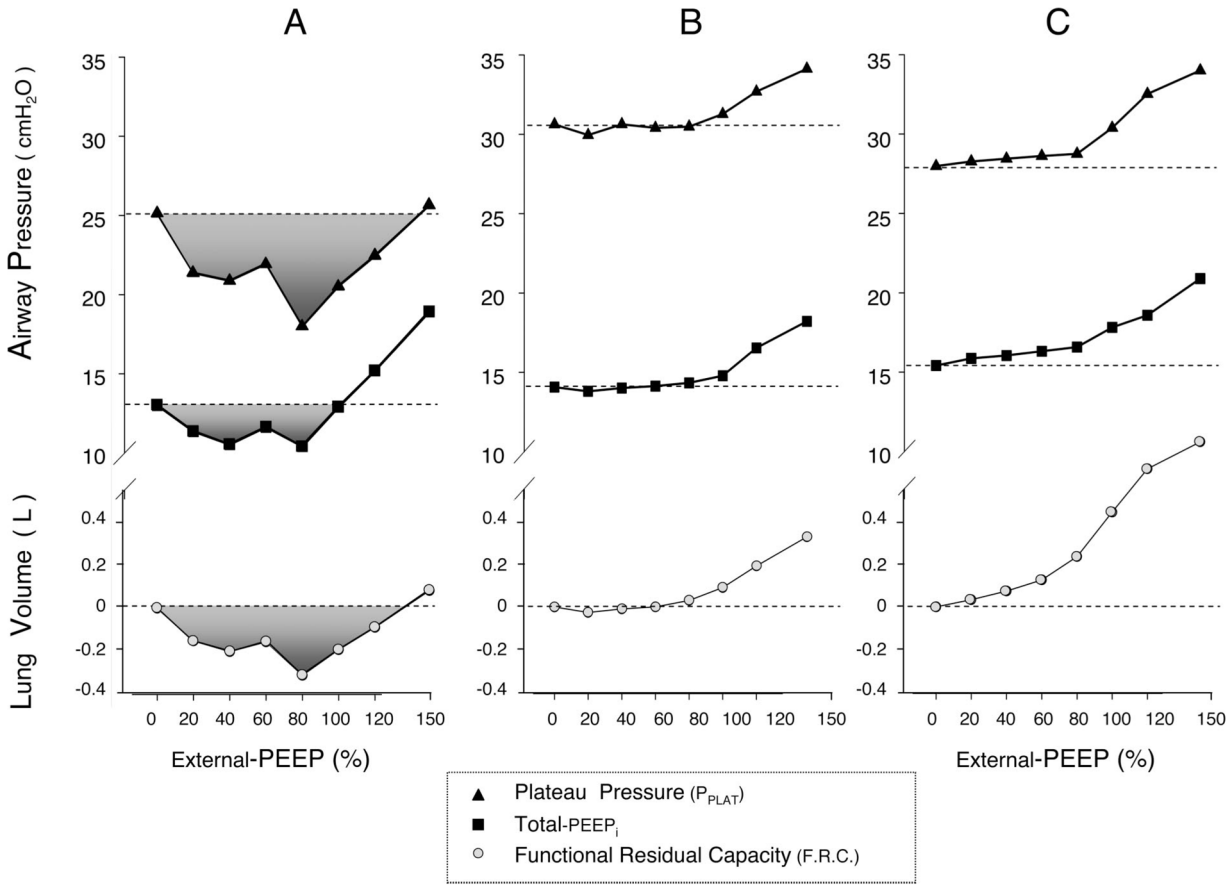

Figure 4.

Three of the possible responses observed in plateau pressure (P_{PLAT}), total intrinsic positive end-expiratory pressure ($PEEP_i$), and functional residual capacity (*F.R.C.*) with the application of external-PEEP (represented as percentage of $PEEP_i$ measured at zero external-PEEP). The FRC measured at zero external-PEEP was considered as the reference. *A*, paradoxic response (patient 4), observed with a tidal volume (V_T) of 6 mL/kg and respiratory rate (RR) of 9 breaths/min; *B*, biphasic response (patient 7), observed with V_T of 9 mL/kg and RR of 6 breaths/min; *C*, classic overinflation response (patient 5), observed with a V_T of 9 mL/kg and RR of 9 breaths/min.

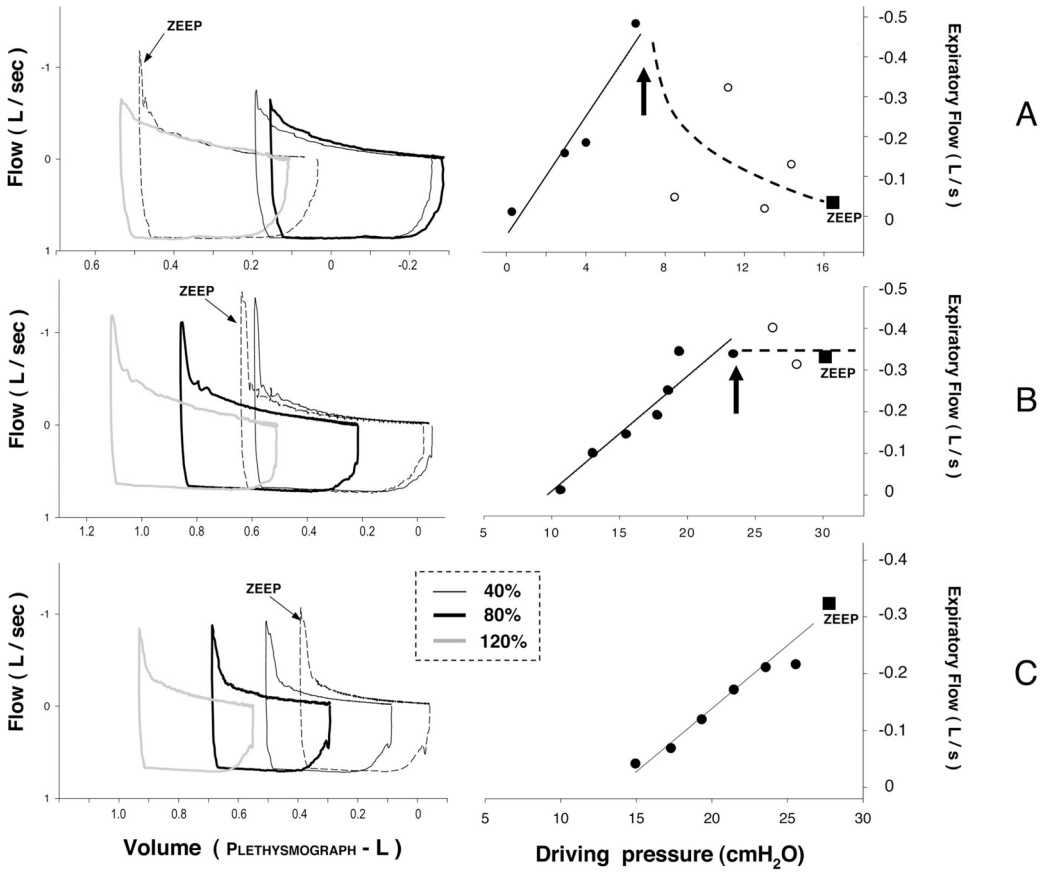

Figure 5.

On the *left*, examples of flow-volume (F-V) loops, and on the *right*, driving pressure vs. expiratory flow relationships at isovolume conditions (from the same patients whose data are illustrated in Figure 4). *A*, paradoxic response, characterized by a rightward shift of the F-V loops at low external-PEEP followed by a leftward shift with high external-PEEP. The decrease in driving pressure resulted in a paradoxic increase in expiratory flow up to a critical pressure, beyond which expiratory flow decreased. *B*, biphasic response, characterized by nearly superimposed F-V loops at low external-PEEP levels, followed by a leftward shift at higher external-PEEP levels. *C*, classic overinflation response, characterized by a leftward shift of F-V loops with any external-PEEP increment; correspondingly, there was a quasilinear relationship between expiratory flow and driving pressures measured at isovolume conditions. Different loops represent data points collected when the external-PEEP was matching 40%, 80%, and 120% of baseline intrinsic-PEEP measure at zero end-expiratory pressure (*ZEEP*).

Table 1

Ventilator settings during the application of external peak end-expiratory pressure (PEEP)

Setting	V_T, mL/kg	V, L/min	RR, breaths/min
1	6	40	6
2	6	40	9
3	9	40	6
4	9	40	9

V_T, tidal volume; $\dot{V}$, inspiratory flow; RR, respiratory rate.

Table 2

Characteristics of patients

Patient No.	Age, Yrs	Sex	Baseline Disease	APACHE II Score	Cause of AVF	Intrinsic PEEP at ZEEP (V_T = 6/RR = 6)
1	80	F	Asthma	19	Bronchopneumonia	5.2
2	71	F	Asthma	18	Asthma exacerbation	7.7
3	85	F	COPD	28	Bronchopneumonia	11.4
4	71	M	COPD	22	Bronchopneumonia	13.5
5	72	M	Asthma	20	Bronchopneumonia	7.9
6	25	M	Asthma	19	Asthma exacerbation	5.0
7	55	M	COPD	15	COPD exacerbation	5.2
8	62	M	COPD	19	Bronchopneumonia	5.9

APACHE, Acute Physiology and Chronic Health Evaluation; AVF, acute ventilatory failure; PEEP, positive end-expiratory pressure (measured during long expiratory pause); ZEEP, zero end-expiratory pressure; V_T, tidal volume; RR, respiratory rate; COPD, chronic obstructive pulmonary disease.

Table 3

Pulmonary mechanics (respiratory system)

	External-PEEP Applied (% of Baseline Intrinsic-PEEP)								
	0	**20**	**40**	**60**	**80**	**100**	**120**	**150**	***p* Value**
Compliance, mL/cm H_2O	46.0 (±1.3)[a]	46.3 (±1.3)	45.8 (±1.4)	46.1 (±1.3)	46.1 (±1.4)	46.0 (±1.5)	44.8 (±1.6)	43.9 (±1.7)	.51
Resistance, inspiratory, cm H_2O/L per sec	34.7 (±1.3)	33.5 (±1.1)	33.2 (±1.0)	32.3 (±1.0)	30.3 (±0.9)	29.5 (±0.7)	27.9 (±0.8)	29.6 (±0.9)	<.0001
Resistance, total: cm H_2O/L per sec	47.5 (±2.1)	44.5 (±2.0)	42.5 (±1.8)	39.9 (±1.6)	36.7 (±1.6)	34.0 (±1.5)	30.7 (±1.5)	28.7 (±1.6)	<.0001

Compliance, static compliance measured during expiratory and inspiratory occlusion maneuver, averaged across the four combinations of tidal volume (V_T) and respiratory rate (RR); resistance, inspiratory, resistance measured after an end-inspiratory occlusion maneuver, averaged across the four combinations of V_T and RR; resistance, total, resistance measured by the isovolume method proposed by Frank and Mead (27,28), using 100 isovolume data points during inspiration and expiration, averaged across the four combinations of V_T and RR.

[a]Values are mean (±SEM) across all ventilatory settings.

Table 4

Hemodynamics and gas exchange

	External-PEEP Applied: % of Baseline Intrinsic-PEEP								
	0	**20**	**40**	**60**	**80**	**100**	**120**	**150**	***p* (ANOVA)**
CI	3.7 (±0.4)[a]	3.8 (±0.4)	3.8 (±0.4)	3.8 (±0.4)	3.8 (±0.4)	3.7 (±0.4)	3.7 (±0.4)	3.7 (±0.4)	.56
Svo_2	78.7 (±1.0)	79.2 (±1.1)	79.6 (±1.1)	79.4 (±1.0)	79.4 (±1.2)	79.4 (±1.1)	79.5 (±1.3)	80.8 (±1.5)	.20
Pco_2	61.0 (±4.5)	62.1 (±4.3)	62.8 (±4.5)	63.4 (±4.6)	64.2 (±4.6)	65.8 (±4.7)	65.8 (±4.5)	65.5 (±4.5)	.007
Po_2	128.8 (±10.8)	130.4 (±10.5)	128.8 (±9.2)	133.1 (±9.0)	133.2 (±9.3)	133.3 (±8.8)	133.1 (±8.3)	132.7 (±7.9)	.38

PEEP, positive end-expiratory pressure; baseline intrinsic-PEEP, intrinsic-PEEP measured during the application of zero external-PEEP; ANOVA, analysis of variance; CI, cardiac index; SvO_2, mixed venous saturation measured at the tip of the Swan-Ganz catheter.

[a]Values are mean (±SEM) for all trials (averaged across the four combinations of tidal volume and respiratory rate).