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Variable positive end-expiratory pressure can maintain oxygenation in experimental acute respiratory distress syndrome induced by oleic acid in dogs

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Abstract

The use of positive end-expiratory pressure (PEEP) or lung recruitment maneuvers (RM) to improve oxygenation in acute respiratory distress syndrome (ARDS) is used but it may reduce cardiac output (CO). Intermittent PEEP may avoid these complications. Our objective was to determine if variable PEEP compared with constant PEEP is capable of maintaining arterial oxygenation and minimizing hemodynamic alterations with or without RM. Eighteen dogs with ARDS induced by oleic acid were randomized into three equal groups: group 1, low variable PEEP; group 2, high variable PEEP, and group 3, RM + high variable PEEP. All groups were submitted to constant PEEP, followed by variable PEEP (PEEP was increased from 5 to 10 cmH_2O in group 1, and from 5 to 18 cmH_2O in the other two groups). PaO_2 was higher in group 3 (356.2 ± 65.4 mmHg) than in group 1 (92.7 ± 29.7 mmHg) and group 2 (228.5 ± 72.4 mmHg), $P < 0.05$. PaO_2 was maintained during variable PEEP except in group 2 (318.5 ± 82.9 at constant PEEP to 228.5 ± 72.4 at variable PEEP). There was a reduction in CO in group 3 after RM (3.9 ± 1.1 before to 2.7 ± 0.5 $L \cdot min^{-1} \cdot (m^2)^{-1}$ after; $P < 0.05$), but there was not any difference between constant and variable PEEP periods (2.7 ± 0.5 and 2.4 ± 0.7 $L \cdot min^{-1} \cdot (m^2)^{-1}$; $P > 0.05$. Variable PEEP is able to maintain PaO_2 when performed in combination with RM in dogs with ARDS. After RM, CO was reduced and there was no relevant difference between the variable and constant PEEP periods.

Key words: Acute respiratory distress syndrome (ARDS); PEEP; Mechanical ventilation; Oleic acid

Introduction

Acute respiratory distress syndrome (ARDS) is a severe lung disease caused by a variety of direct and indirect injuries. It is characterized by a decrease in pulmonary static compliance and arterial hypoxemia secondary to pulmonary edema and atelectasis (1). The use of mechanical ventilation to treat ARDS has been described since its definition in 1967 by Ashbaugh et al. (2). In the 1970's, high tidal volume and high pressures of mechanical ventilation were the rule to treat these patients, but in the 1980's ventilator-induced lung injury was described as a side effect of this form of mechanical ventilation (3-5).

Positive end-expiratory pressure (PEEP) has been used to avoid hypoxemia because it maintains lung end-expiratory inflation and prevent intratidal collapse and decollapse (5,6). It is known that tidal over-distension caused by mechanical ventilation contributes to severe lung injury (4-6) and that gentle lung ventilation is the most efficient way to prevent hypoxemia and reduce lung injury (7,8). Lung protection strategy generally requires the use of high PEEP to keep the alveoli open without cyclic distension, or the best PEEP to keep the oxygenation over 92% (8,9). But the use of high PEEP levels may result in severe complications such as

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volutrauma, barotrauma and mainly hemodynamic alterations, which can be associated with high tidal inflation or over-distention (1,10-12).

Therefore, the application of variable PEEP becomes an interesting alternative to the use of high levels of PEEP during mechanical ventilation because it recruits closed alveoli and avoids over-distention, and also hemodynamic complications. However, there are reports in the literature of lung injury induced by mechanical ventilator (10-13).

Variable PEEP consists of the application of PEEP alternating high and low pressure levels at the end of expiration (14-16). The use of variable PEEP in ARDS may assist pulmonary gas exchange (16,17). The use of a lower PEEP should theoretically be associated with the prevention of hemodynamic alterations and pulmonary hyperinflation (14,15). Sighs were later used in order to increase PEEP or tidal volume once or twice per minute during mechanical ventilation with the same objective in patients with lung injury, so as to restore oxygenation without complications of positive pressure (17).

The efficiency of recruitment maneuvers has been studied by several researchers, but for which length of time and how to carry out this procedure in patients with ARDS is controversial (18-23). We considered that if recruitment maneuvers maintain the lungs open avoiding recruitment and de-recruitment of the lung units, the associated use of variable PEEP should also yield better results.

The objective of the present study was to evaluate the effects of variable compared to constant (conventional) PEEP in dogs with ARDS induced by oleic acid, and to determine changes in gasometry and ventilatory mechanics (including hemodynamic alterations) at different pressure levels in the presence and absence of an alveolar recruitment maneuver.

Material and Methods

For the experiment, male mongrel dogs were anesthetized with sodium pentobarbital and paralysis was maintained by pancuronium bromide in *iv* boluses. The animals were submitted to orotracheal intubation using a number 8 Rush® cannula (Germany) and placed under mechanical ventilation (Bird® 6400 ventilator, Sti model, USA) in the supine position, with the following initial values: 100% FiO_2, tidal volume of 6 to 8 mL/kg, respiratory rate of 25 to 35 bpm to keep $PaCO_2$ between 35 and 45 mmHg, and an inspiratory flow rate that would maintain the inspiratory/expiratory ratio at 1:3. These settings were maintained during the entire experiment, with a PEEP of 5 cmH_2O.

For arterial gasometry and measurement of mean arterial pressure (MAP) we used the femoral artery, while the femoral vein was used for hydration with 0.9% physiological saline (15 mL/kg during the procedures) and for oleic acid administration (an additional volume of 15 mL/kg 0.9% physiological saline was used after oleic acid administration). A Swan-Ganz catheter was inserted for hemodynamic measurements.

MAP had to be over 80 mmHg at the beginning of the procedures in all groups.

Protocol

The study was approved by the Ethics Committee of the Federal University of São Paulo. After a stabilization period of 30 min using mechanical ventilation, the dogs were randomized into three groups of 6 animals each. Group 1, low variable PEEP; group 2, high variable PEEP; group 3, alveolar recruitment maneuver + high variable PEEP.

The study consisted of the following five experimental 30-min periods: i) Pre-lesion period. Introduction of catheters and mechanical ventilation using the initial parameters. During this period, dogs showing a PaO_2 of over 400 mmHg and an MAP over 80 mmHg were included in the experiment; ii) Lesion period. ARDS was induced by the intravenous administration of 0.08 mg/kg body weight of oleic acid. ARDS was defined as a PaO_2/FiO_2 ratio lower than 150 mmHg. When this value was not obtained within 60 min, the animal was excluded from the study. When the pH values fell below 7.25, sodium bicarbonate was administered; iii) Constant PEEP period 1 (PEEP 1). Constant PEEP was applied; iv) Variable PEEP period (PEEP). Variable PEEP was applied as described below; v) Constant PEEP period 2 (PEEP 2). Constant PEEP was applied (Figure 1).

Variable PEEP

During variable and constant PEEP periods, a specific PEEP value was established for each group: for group 1,

				Group 1	10 cmH_2O	→	5-10 cmH_2O	→	10 cmH_2O
Pre-lesion	→	Lesion	→	**Group 2**	18 cmH_2O	→	5-18 cmH_2O	→	18 cmH_2O
				Group 3	RM + 18 cmH_2O	→	5-18 cmH_2O	→	18 cmH_2O
					C PEEP 1	→	**V PEEP**	→	**C PEEP 2**
					30 min		**30 min**		**30 min**

Figure 1. Protocol of the 5 experimental 30-min periods. PEEP = positive end-expiratory pressure; group 1 = low variable PEEP; group 2 = high variable PEEP; group 3 = alveolar recruitment maneuver (RM) + high variable PEEP; C PEEP 1 = constant PEEP period 1; V PEEP = variable PEEP; C PEEP 2 = constant PEEP period 2.

PEEP was kept at 10 cmH_2O during constant periods and changed from 5 to 10 cmH_2O every 20 s during variable periods. For group 2, PEEP was kept at 18 cmH_2O during constant periods and increased from 5 to 18 cmH_2O every 20 s during variable periods. For group 3, an alveolar recruitment maneuver was performed (elevation of PEEP up to a peak pressure of 50 cmH_2O, repeated three times within one minute), followed by a constant period of PEEP, which was kept at 18 cmH_2O; during variable periods, PEEP was changed from 5 to 18 cmH_2O every 20 s.

Measurements

All measurements were made at the end of each 30-min experimental period: pre-lesion, lesion, constant PEEP 1, variable PEEP, and constant PEEP 2 periods. During the variable periods, measurements were made at 15 and 30 min to evaluate the changes. Mean values were used for statistical analysis. During variable PEEP periods, arterial blood samples, hemodynamic variables and respiratory mechanics were collected at a PEEP of 5 cmH_2O.

Hemodynamic measurements. Cardiac output (CO) was measured by the thermodilution method using the Dixtal® model DX 2010 measuring system (Brazil, with a fluid temperature of 0 to 3°C, and the mean of three measurements was recorded. Pulmonary capillary wedge pressure and pulmonary arterial pressure were also measured using a Swan-Ganz catheter. Mean systemic arterial pressure was monitored with the intravenous catheter in the femoral artery.

Respiratory measurements. Ventilatory levels: static compliance and plateau pressure were measured using a Ventcare-Takaoka® monitor (Brazil) and a pressure transducer. Inspiratory and expiratory flows were determined with a pneumotachograph installed between the Y connection of the ventilator and the endotracheal tube. We performed one occlusion using the hold button of the mechanical ventilator for at least 3 s and maintained plateau pressure, tidal volume and PEEP, to calculate static compliance. To calculate static compliance during variable PEEP periods, this occlusion was performed when PEEP was 5 cmH_2O. Arterial blood samples were collected from the femoral artery using a radiometer model ABL 330 (Uruguay) to measure pH, PaO_2, $PaCO_2$, HCO_3, and base excess. Oxygen delivery to tissue (DO_2) was calculated with the equation: DO_2 = CaO_2 cc / dL x (CO L / min) x 10, where CaO_2 is arterial oxygen content = (Hb) x 1.38 x SaO_2 + (0.003 x PaO_2), Hb = hemoglobin, SaO_2 = arterial oxygen saturation, PaO_2 = arterial oxygen pressure, CO = cardiac output, and 10 is the factor used to convert L to dL.

The protocol time from the beginning of the procedure, and stabilization time until data collection was less than 4 h for each dog.

Statistical analysis

Data are reported as means ± SD because they were found to have a normal distribution. Analysis consisted of five assessment periods within each group (dependent variables). Data were compared by analysis of variance for repeated measures (ANOVA) and complemented with the Tukey-Kramer test in case of statistical significance. In all analyses, statistical significance was accepted when $P < 0.05$.

Results

Eighteen dogs were studied, and no animal died or was excluded before the end of the experiment. Animal mean weight was 19.8 ± 1.5 kg. Table 1 shows the initial characteristics of all groups, that did not differ between groups.

Gas exchange. There was a statistically significant decrease in PaO_2 after lung injury in all groups (Table 2). The introduction of PEEP-improved oxygenation was more evident when a higher PEEP was applied, i.e., in groups 2 and 3, and a lower PaO_2 were observed in group 1. In group 3, PaO_2 increased further due to the recruitment maneuver. PaO_2 was not maintained during the variable PEEP period in group 2 (P = 0.5261; Table 2). There was a significant increase in $PaCO_2$ after lung injury during the constant PEEP 1 and PEEP 2 periods in all groups (P = 0.01; Table 2). DO_2 was lower in group 3 compared with groups 1 and 2 after the lesion period (P = 0.001), but there was no difference between the constant and variable PEEP periods within any group (P = 0.6705; Table 2).

Ventilatory measurements. No improvement in static

Table 1. Initial characteristics of the animals studied.

	RR (rpm)	Vt (mL)	PaO_2/FiO_2	Cst (cmH_2O)	CO ($L \cdot min^{-1} \cdot (m^2)^{-1}$)
Group 1	30.6 ± 2.4	126.6 ± 41.7	523.1 ± 28.7	28.4 ± 7.1	7.8 ± 3.2
Group 2	29.4 ± 1.9	138.5 ± 32.7	533.1 ± 18.5	24.3 ± 6.0	6.8 ± 2.9
Group 3	30.6 ± 1.6	120.0 ± 20.0	517.4 ± 23.3	21.8 ± 4.2	5.4 ± 3.1

Data are reported as means ± SD for 6 dogs in each group. RR = respiratory rate; rpm = respirations per minute; Vt = tidal volume; PaO_2 = arterial oxygen pressure; FiO_2 = inspiratory oxygen fraction; Cst = static compliance; CO = cardiac output. See Figure 1 for explanation of groups. There were no statistical differences between groups (P > 0.05, Tukey-Kramer test).

Table 2. Gas exchange in groups studied in all phases of the protocol.

	Pre-lesion	Lesion	Constant PEEP 1	Variable PEEP	Constant PEEP 2
Group 1					
PaO_2 (mmHg)	523.1 ± 28.7	69.8 ± 16.4*	112.3 ± 43.5&	92.7 ± 29.7	105.9 ± 42.4
$PaCO_2$ (mmHg)	38.2 ± 4.4	40.5 ± 6.6#	48.2 ± 2.0	47.7 ± 1.9	50.6 ± 5.2
DO_2 (mL O_2/min)	1480.7 ± 173.2	813.0 ± 42.9*	876.7 ± 65.7	837.2 ± 54.3	822.5 ± 46.2
Group 2					
PaO_2 (mmHg)	533.1 ± 18.5	72.3 ± 14.8*	318.5 ± 82.9&	228.5 ± 72.4$	280.7 ± 70.2
$PaCO_2$ (mmHg)	38.2 ± 4.4	41.1 ± 7.5#	53.8 ± 8.7	49.7 ± 9.9	53.6 ± 5.7
DO_2 (mL O_2/min)	1619.2 ± 50.3	849.3 ± 41.5*	888.7 ± 41.0	797.4 ± 60.7	880.0 ± 22.3
Group 3					
PaO_2 (mmHg)	517.4 ± 23.3	78.6 ± 17.8*	395.9 ± 41.5&	356.2 ± 65.4	363.7 ± 101.9
$PaCO_2$ (mmHg)	38.2 ± 4.1	46.2 ± 9.5#	56.2 ± 7.0	47.6 ± 6.2	56.7 ± 8.7
DO_2 (mL O_2/min)	1456.1 ± 85.8	719.1 ± 92.3*	584.8 ± 55.0	524.2 ± 50.4	563.4 ± 67.3

Data are reported as means ± SD for 6 dogs in each group. PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide pressure; DO_2 = oxygen delivery to tissues. See Figure 1 for explanation of groups. *P < 0.001 *vs* pre-lesion; &P < 0.05 *vs* lesion; $P < 0.05 *vs* constant PEEP 1; #P < 0.05 *vs* constant PEEP 1 and constant PEEP 2 (Tukey-Kramer test).

Table 3. Effect of intermittent PEEP on respiratory and hemodynamic parameters of dogs with acute respiratory distress syndrome.

	Pre-lesion	Lesion	Constant PEEP 1	Variable PEEP	Constant PEEP 2
Group 1					
PPl (cmH_2O)	11.0 ± 1.4	15.3 ± 2.4	18.8 ± 5.2+	14.3 ± 4.4	21.3 ± 2.7+
Cst (mL/cmH_2O)	28.4 ± 7.1	17.0 ± 5.8	17.3 ± 6.4	17.6 ± 6.9	16.2 ± 4.4
Group 2					
PPl (cmH_2O)	10.1 ± 2.4	15.6 ± 2.2	29.0 ± 3.2+	16.0 ± 3.2#	28.8 ± 3.5+
Cst (mL/cmH_2O)	24.3 ± 6.0	17.0 ± 5.2	16.9 ± 2.5	17.0 ± 6.8	17.8 ± 4.7
Group 3					
PPl (cmH_2O)	12.0 ± 1.2	17.5 ± 1.5	30.8 ± 3.8+	17.6 ± 1.9#	30.5 ± 2.5+
Cst (mL/cmH_2O)	21.8 ± 4.2	12.3 ± 1.7	13.4 ± 3.9	12.8 ± 2.6	13.2 ± 2.4

Data are reported as means ± SD for 6 dogs in each group. PPl = plateau pressure; Cst = static compliance. See Figure 1 for explanation of groups. +P < 0.05 vs pre-lesion; #P < 0.05 *vs* constant PEEP 1 and constant PEEP 2 (Tukey-Kramer test).

compliance and no changes in plateau pressure (P = 0.2450) were observed in any of the groups during the constant or variable PEEP periods. There was a decrease in plateau pressure during variable PEEP in groups 2 and 3 (P = 0.002; Table 3).

Hemodynamic measurements. Significant hemodynamic repercussions were observed in group 3, with a significant decline in CO after the alveolar recruitment maneuver (P = 0.001), but there were no alterations between variable and constant PEEP (P = 0.2401; Figure 2). During the pre-lesion period, pulmonary capillary wedge pressure was below 12 mmHg in all groups, and pulmonary arterial pressure was below 20 mmHg. There was no change in MAP (P = 0.5238). All dogs maintained an MAP of more than 70 mmHg during the experiment (Figure 3).

Discussion

Analysis of dogs with ARDS induced by oleic acid administration showed that the use of variable PEEP is able to maintain DO_2 when compared with constant PEEP, but PaO_2 dropped when highly variable PEEP was used without

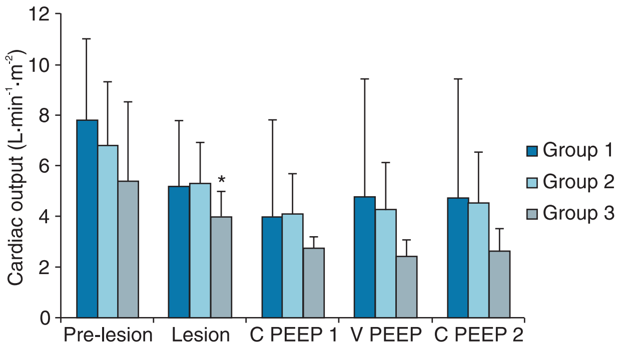

Figure 2. Cardiac output is reported as means ± SD for all groups. See Figure 1 for explanation of abbreviations. *P < 0.05 *vs* C PEEP 1, V PEEP and C PEEP 2 (Tukey-Kramer test).

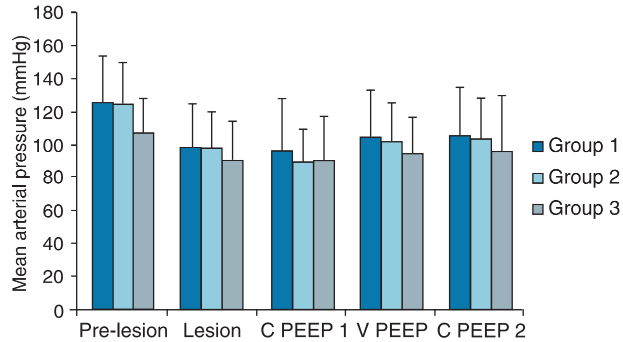

Figure 3. Mean arterial pressure is reported as means ± SD for all groups. See Figure 1 for explanation of abbreviations. P > 0.05 (Tukey-Kramer test)

recruitment maneuvers.

When the recruitment maneuver was applied in the present study, there was a PaO_2 increase, which was sustained during variable PEEP in group 3. Thus, further collapsed areas were opened before we started the variation. The application of the recruitment maneuver (23,24) has been standardized by Lachmann (19) according to "the open-lung concept". There is no doubt that initial lung recruitment rapidly improves oxygenation, which will only be maintained when using high PEEP levels (25-29). These observations were also made in ARDS patients with increased functional residual capacity and end-expiratory lung volume after the utilization of lung inflation or with sighs associated with PEEP (16,30,31). It is known that low PEEP in ARDS patients cannot improve oxygenation (1,6-9). This fact was also observed in our study in group 1 when PaO_2 was kept lower than 150 mmHg throughout the study.

Some studies have shown that a fluctuating PEEP in animals with lung injury is more effective for gas exchange than with constant PEEP (14,16). Others have shown that the use of periodic PEEP can maintain adequate oxygenation in ARDS patients, but constant PEEP could improve these levels (17). In our study, we found an increase in PaO_2 only in the group that underwent the recruitment maneuver, but in group 2 there was a decrease in PaO_2. We did not change any other parameter (such as tidal volume or peak pressure) of mechanical ventilation as done in other studies (16,32-34). Except for PEEP during variable PEEP, this fact did not contribute to increased PaO_2 in group 1 or to PaO_2 maintenance in group 2. In terms of oxygen delivery to tissue, we observed maintenance of DO_2 in all groups during variable PEEP, but there were lower values in group 3 when compared to the other two groups, reflecting the decrease of CO after recruitment maneuvers. Despite the fact that PaO_2 was the lowest in group 1, the DO_2 maintained normal values because there was no decrease in CO during variable PEEP.

Regarding alterations in $PaCO_2$ caused by oleic acid-induced lung injury, we observed an elevation during constant PEEP periods, but not during variable PEEP periods. These findings can be explained by the changes in lung volume during oscillation of PEEP but have not been observed in other studies with variable PEEP (16,17).

In patients with ARDS, the use of high PEEP might result in overdistension and higher inspiratory peak pressure because of a heterogeneous injury to the lung, which means that some areas can be overinflated whereas others are collapsed, resulting in a reduction in gas exchange and compliance. On the other hand, a decrease in PEEP may cause alveolar de-recruitment and lung injury caused by mechanical ventilation. However, as shown by Suh et al. (13), there is lung de-recruitment when lower PEEP is used, an event related to PaO_2, indicating that, the lower the PaO_2, the worse the de-recruitment (1,4,6). In the present study, we did not perform histological analysis of the lung, but we observed the maintenance of PaO_2 after recruitment maneuvers in group 3, and therefore we believe that, lung de-recruitment occurred, it did not disturb the oxygenation.

As expected, we observed reduction in compliance after the lesion period, but we did not observe any difference in periodic or variable PEEP, possibly because complete expansion of the lungs was not used in this protocol.

We observed a change in hemodynamics only in group 3, a fact possibly due to the higher intrapulmonary pressure used in this group. A fall in CO was observed after oleic acid-induced injury, as expected for the model used (25) and reduction of CO was also observed after the installation of PEEP; however, this decrease was only significant in group 3. Normally, hemodynamic repercussions in ARDS are influenced by the PEEP level applied (1). However, in the present study, despite a decline in CO, no difference between the periods of variable and constant PEEP was observed in any group. We did not introduce vasoactive drugs because MAP was always over 70 mmHg in all groups, but the animals received 0.9% physiological saline solution

(15 mL/kg) twice, i.e., during the procedure and after oleic acid administration. Even with numeric differences between phases in MAP there was not statistical difference probably because the standard deviation was high. Similar results were reported in a study of oleic acid-induced lung injury by Uchida et al. (15,16). However, in a study of unilateral lung injury, Sato et al. (14) observed improved CO when fluctuating PEEP was used. Another explanation for the lack of changes in CO observed here is the fact that all measurements made during the variable PEEP period were performed at a pressure of 5 cmH_2O.

The use of variable PEEP in our study was chosen because in previous tests in our laboratory we found that oscillation of PEEP of less than three times a minute, every 20 s, made it difficult to maintain oxygenation, because positive end-expiratory pressure in ARDS is necessary for adequate oxygenation. The lower value of PEEP (5 cmH_2O) was chosen because it is the lowest value regularly used during mechanical ventilation. PEEP of 18 cmH_2O was used because in previous pilot studies in our laboratory the second point of the pressure x volume curve was around 16 in dogs with ARDS. Thus, we decided to increase 2 cmH_2O to use PEEP value between the first and the second inflexion point in pressure x volume curve. And finally, the PEEP of 10 cmH_2O was chosen arbitrarily because it was close to the other two values.

In the present study, PEEP was changed to a period of 30 min and therefore we do not know whether a longer period or different intervals would be able to maintain oxygenation or would lead to hemodynamic alterations, since some studies have demonstrated that the beneficial effects of recruitment may only be maintained for short periods of time (20,21). We chose on this period because we believe it is sufficient to evaluate variations in the respiratory system. We did not study a variable PEEP of 10 cmH_2O in combination with a recruitment maneuver since previous experience from our laboratory demonstrated that this PEEP level is unable to maintain the oxygenation gain obtained with previous alveolar recruitment. Different types of variable PEEP in terms of the number of elevations per minute and pressure values might alter the results.

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