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SCIENTIFIC ARTICLE

Effects of the positive end-expiratory pressure increase on sublingual microcirculation in patients with acute respiratory distress syndrome

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KEYWORDS
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Abstract
Objective: The aim of this study was to evaluate the impact of increased positive end-expiratory pressure on the sublingual microcirculation.
Methods: Adult patients who were sedated, under mechanical ventilation, and had a diagnosis of circulatory shock and acute respiratory distress syndrome were included. The positive end-expiratory pressure level was settled to obtain a plateau pressure of 30 cm H_2O and then maintained at this level for 20 minutes. Microcirculatory (obtained by videomicroscopy) and hemodynamic variables were collected at baseline and compared with those at the end of 20 min.
Results: Twelve patients were enrolled. Overall, the microcirculation parameters did not significantly change after increasing the positive end-expiratory pressure. However, there was considerable interindividual variability. There was a negative, moderate correlation between the changes in the De Backer score ($r = -0.58$, $p = 0.048$), total vessel density ($r = -0.60$, $p = 0.039$) and baseline values. The changes in total vessel density ($r = 0.54$, $p = 0.07$) and perfused vessel density ($r = 0.52$, $p = 0.08$) trended toward correlating with the changes in the mean arterial pressure.
Conclusion: Overall, the microcirculation parameters did not significantly change after increasing the positive end-expiratory pressure. However, at individual level, such response was heterogeneous. The changes in the microcirculation parameters could be correlated with the baseline values and changes in the mean arterial pressure.

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PALAVRAS-CHAVE
Síndrome do desconforto respiratório do adulto;
Pressão positiva expiratória final;
Microcirculação;
Hemodinâmica;
Choque;
Ventiladores mecânicos

Efeitos do aumento de pressão positiva ao final da expiração sobre a microcirculação sublingual em pacientes com síndrome do desconforto respiratório agudo

Resumo
Objetivo: O objetivo deste estudo foi avaliar o impacto do aumento de pressão positiva expiratória final (PEEP) sobre a microcirculação sublingual.
Métodos: Os pacientes adultos que foram sedados, sob ventilação mecânica, com diagnóstico de choque circulatório e síndrome do desconforto respiratório agudo foram incluídos. O nível da PEEP estabelecido para obter uma pressão de platô de 30 cm H_2O e depois mantida nesse nível por 20 minutos. As variáveis microcirculatória (obtida por microscopia de vídeo) e hemodinâmica foram registradas na fase basal e comparadas com aquelas ao final de 20min.
Resultados: Doze pacientes foram incluídos. Em geral, os parâmetros da microcirculação não apresentaram alterações significativas após o aumento da PEEP. Porém, houve considerável variabilidade interindividual. Houve uma correlação negativa, moderada, entre as alterações no escore de De Backer (r = -0,58, p = 0,048), na densidade total do vaso (r = -0,60, p = 0,039) e nos valores basais. As alterações na densidade total do vaso (r = 0,54, p = 0,07) e na densidade do vaso perfundido (r = 0,52, p = 0,08) apresentaram tendência de correlação com as alterações na pressão arterial média.
Conclusão: Em geral, os parâmetros da microcirculação não apresentaram alterações significativas após o aumento da PEEP. No entanto, individualmente, essa resposta foi heterogênea. As alterações nos parâmetros da microcirculação puderam ser correlacionadas com os valores basais e alterações na pressão arterial média.

Introduction

In patients with moderate or severe acute respiratory distress syndrome (ARDS), a ventilator strategy based on higher rather than lower levels of positive end-expiratory pressure (PEEP) is recommended.[1,2] The PEEP results in alveolar recruitment, reduced shunting, and increased partial pressure of oxygen (PaO_2).[2] However, the extrapulmonary effects of high PEEP can limit this approach. The effects on the hemodynamics and regional blood flow are the main concerns.[3]

The ultimate goal of respiratory and hemodynamic interventions is to restore effective tissue perfusion and oxygen delivery to maintain cellular metabolism. Therefore, the assessment of the microcirculation might improve our understanding of the effects of therapies beyond restoring systemic hemodynamics.[4] Alterations in microvascular blood flow are underlying mechanisms that are implicated in the development of multiple organ dysfunction and, ultimately, death.[5] Several studies have shown that severe and persistent microcirculatory alterations are strong predictors of the outcome.[6–9] Microcirculatory alterations can still be present even when the global hemodynamics are optimized.[10] These findings suggest that targeting the microcirculation is a logical approach for interventions that aim to improve tissue perfusion.[4]

Clinical studies exploring the regional perfusion alterations induced by the PEEP using different tools have focused on the splanchnic area and shown conflicting results.[11–13] As the microcirculatory effects of the PEEP have not been established, the aim of this study was to evaluate the impact of increasing the PEEP levels in the sublingual microcirculation parameters using videomicroscopy.

Methods

This study was conducted in a 35 bed mixed Intensive Care Unit (ICU) in a university hospital from July 2011 to October 2012. The local ethics committee approved the study, and the patients' closest relatives signed informed consent forms to allow for data collection.

We included adult patients with ARDS who were mechanically ventilated with a plateau pressure $\leq$ 25 cm H_2O and PEEP $\leq$ 10 cm H_2O as well as an indication of an increase in the PEEP by the attending physician. All patients were receiving sedation with a Ramsay scale of 6, had circulatory shock with the need for vasopressor and hemodynamic monitoring with a pulmonary artery catheter and an arterial catheter. ARDS was defined according to the Consensus conference.[14] The exclusion criteria were pregnancy, intracranial hypertension, abdominal compartment syndrome and oral injuries. We also excluded patients in whom the primary cause of circulatory shock was active bleeding (suspected or confirmed) or cardiogenic shock, which was defined as a cardiac index (CI) < 1.8 $L \cdot min^{-1} \cdot m^{-2}$ without support and pulmonary artery occlusion pressure $\geq$ 18 mmHg.

Interventions

The selected patients were mechanically ventilated (Vela, Viasys, Palm Springs, CA, USA) using the volume-controlled mode. The tidal volume was adjusted to 6 $mL \cdot kg^{-1}$ (based on the patient's predicted body weight) and there were no changes in the other ventilatory parameters. The static compliance of the respiratory system was calculated after an end-inspiratory pause of 2 s. Each patient was observed for 10 min before the PEEP changes to ensure that there

were no significant variations in the hemodynamic and ventilator parameters. The PEEP level was then increased to obtain a plateau pressure of 30 cm H_2O (measured after an end-inspiratory pause of 2 s). The PEEP was maintained at these levels for 20 min. Throughout the study period, the doses of the sedative, inotropic and vasopressor medications remained constant. If the mean arterial pressure (MAP) decreased below 65 mmHg, the CI decreased more than 50% or pulse oximetry decreased below 90% during this period of observation, the intervention was interrupted. After the protocol, the attending physician adjusted the PEEP level.

We measured the hemodynamic, ventilatory and microcirculatory parameters at baseline (T0) and immediately after the 20 min period (T1). The CI was measured using a semi-continuous thermodilution technique that considered the mean value of four consecutive measurements from the STAT mode screen of the Vigilance® monitor (Edwards Lifesciences, Irvine, CA, USA). All pressures were determined at the end-expiration with the zero reference level settled at the 4th to 5th intercostal space along the mid-axillary line.

We assessed the sublingual microvascular network using Sidestream Dark Field (SDF) imaging (Microscan; MicroVision Medical, Amsterdam, Netherlands). Briefly, the Microscan is a hand-held video microscope system that illuminates a tissue of interest with stroboscopic green (530 nm) light emitting diodes. Hemoglobin absorbs the 530 nm wavelength light, which in turn is captured via the imaging probe's light guide and a charge-coupled device camera. Clear images of flowing RBCs are depicted as dark moving globules in the lumen of blood vessels against a white/grayish background. The recommended techniques for ensuring high image quality were adopted.[15] After removing saliva and oral secretions, the probe was applied over the mucosa. At each time point, three videos were recorded in different sites at the base of the tongue, at least 10 s per site. Special care was taken to avoid pressure artifacts, which was verified by checking ongoing flow in larger microvessels. All of these videos were obtained using the AVA 3.0® software (Microvision Medical, Amsterdam, Netherlands) considering for analyses vessels with a diameter less than 20 μm (small vessels). The entire sequence was used to characterize the semi-quantitative characteristics of microvascular blood flow, particularly the presence of stopped or intermittent flow. It distinguishes between no flow (0), intermittent flow (1), sluggish flow (2), and continuous flow (3). A value was assigned to each individual vessel. After stabilization of the images using the AVA 3.0 software, we determined the microcirculatory flow index (MFI), total vessel density (TVD), proportion of perfused vessels (PPV), De Backer score, and perfused vessel density (PVD) as previously described.[15] Blinded investigators (ATB and NFN) analyzed all images in a random order.

Statistical analysis

We hypothesized a mean decrease of 0.5 and a standard deviation of the difference of 0.5 in the MFI after an increased in the PEEP to calculate the sample size required for comparing two paired samples (significance level of 0.05 and power of 80%). The required sample size was 10 patients; to correct for the potential non-parametric distribution of the variable, we adjusted this required sample size to 12 patients.

Data are expressed as numbers (%) or medians and interquartile ranges (25th to 75th percentile). Nonparametric tests were used because of the small sample size. The hemodynamic, respiratory, and microcirculatory variables were compared at T0 and T1 using the Wilcoxon paired test. Additional analyses were conducted to test the linear correlation between the baseline microcirculatory variables and their changes after the PEEP increase (ΔMFI, ΔTVD, ΔPPV, ΔPVD and ΔDe Backer score) using the Spearman correlation test.

We used SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The results with p-values < 0.05 were considered significant. For the sample size calculation, we used MedCalc software 14.12.0 (MedCalc Software bvba, Belgium).

Table 1 Patient characteristics.

Variables	(n = 12)
Age, y	68.0 (50.2–76.5)
Gender (male)	7 (58.3)
SOFA inclusion	15 (13–17)
APACHE II score	27 (20–34)
Admission category	
Postoperative shock	4 (33.3)
Septic shock	8 (66.7)
Infection site	
Pneumonia	3 (25.0)
Intraabdominal infection	3 (25.0)
Urinary tract infection	2 (16.6)
Catheter-related infection	1 (8.3)
Vasoactive drugs	
Norepinephrine	12 (100)
Dobutamine	5 (41.6)
Epinephrine	2 (16.6)
Body mass index, kg m^{-2}	23.0 (21.8–24.8)
Hospital mortality	8 (66.7)

SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiological Chronic Health Evaluation. Results are expressed as the number (%) or median (25%–75%).

Results

We enrolled 12 patients with ARDS and circulatory shock with a median age of 68.0 (50.25–76.50) years. Septic shock was the most common reason for ICU admission. The main clinical data are shown in Table 1.

The median increase in the PEEP levels to achieve a plateau pressure of 30 cm H_2O was 7.5 (6.0–10.0) cm H_2O. After an increase in the PEEP, ten patients had a decreased CI and nine had a decreased MAP. Increasing the PEEP levels led to a significant increase in the PaO_2 (p = 0.05); however, there was a significant decrease in the oxygen delivery (p = 0.01). The hemodynamic and respiratory variables are given in Table 2.

Table 2 Changes in the hemodynamic, respiratory and metabolic variables after a change in the PEEP.

Variables	Baseline	After PEEP	*p*-value
HR, bpm	100.50 (92.50–111.25)	98.50 (91.50–114.50)	0.710
CI, $L \cdot min^{-1} \cdot m^{-2}$	3.71 (3.45–5.00)	3.45 (2.65–4.52)	0.005
MAP, mmHg	78.50 (75.25–86.00)	77.00 (68.25–85.00)	0.100
CVP, mmHg	12.00 (7.25–13.75)	13.00 (9.75–16.00)	0.004
mPAP, mmHg	24.00 (18.50–37.75)	26.50 (23.25–35.50)	0.110
PAOP, mmHg	9.90 (8.15–13.50)	13.90 (12.92–16.25)	0.008
ΔPP, %	3.75 (2.37–7.35)	6.50 (3.20–13.00)	0.009
PaO_2/FiO_2 ratio	163.50 (126.42–228.66)	205.00 (154.13–238.57)	0.070
PaO_2, mmHg	88.00 (80.50–108.50)	101.50 (89.05–119.00)	0.050
Tidal volume, mL	467.50 (438.75–557.50)	467.50 (438.75–557.50)	1.000
PEEP, cm H_2O	7.00 (5.00–9.50)	15.00 (14.25–19.00)	0.002
SvO_2, %	75.50 (64.40–81.22)	75.60 (62.62–83.12)	0.630
Lactate, $mg \cdot dL^{-1}$	30.00 (26.25–49.25)	28.00 (17.50–44.25)	0.640
DO_2, $mL \cdot min^{-1}$	855.53 (532.81–1044.77)	781.39 (504.55–970.11)	0.010
VO_2, $mL \cdot min^{-1}$	192.83 (161.60–231.00)	180.65 (151.73–202.72)	0.230
Compliance, $mL \cdot cm^{-1}$ H_2O	35.89 (24.31–44.16)	35.85 (24.31–44.64)	0.480

HR, hearth rate; CI, cardiac index; MAP, mean arterial pressure; CVP, central venous pressure; mPAP, pulmonary artery pressure; PAOP, pulmonary artery occluded pressure; ΔPP, pulse pressure variation; PaO_2, oxygen partial pressure; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SvO_2, oxygen mixed venous saturation; DO_2, oxygen delivery; and VO_2, oxygen consumption. Data are expressed as the median (25%–75%). Wilcoxon paired test.

Table 3 Changes in the microcirculatory variables after a change in the PEEP.

Variable	Baseline	After PEEP	*p*-value
TVD, $mm \cdot mm^{-2}$	13.51 (12.64–15.24)	14.95 (11.80–15.63)	0.875
PVD, $mm \cdot mm^{-2}$	11.25 (10.06–14.24)	11.87 (10.26–13.09)	0.583
PPV, %	83.14 (77.72–91.48)	81.02 (77.25–87.26)	0.695
De Backer, $n \cdot mm^{-2}$	9.50 (8.73–10.24)	9.60 (8.09–10.40)	0.875
MFI	2.62 (2.28–2.75)	2.55 (2.28–2.75)	0.799

PEEP, positive end-expiratory pressure; TVD, total vessel density; PPV, proportion of perfused vessels; PVD, perfused vessel density; and MFI, microcirculatory flow index. Data are expressed as the median (25%–75%). Wilcoxon paired test.

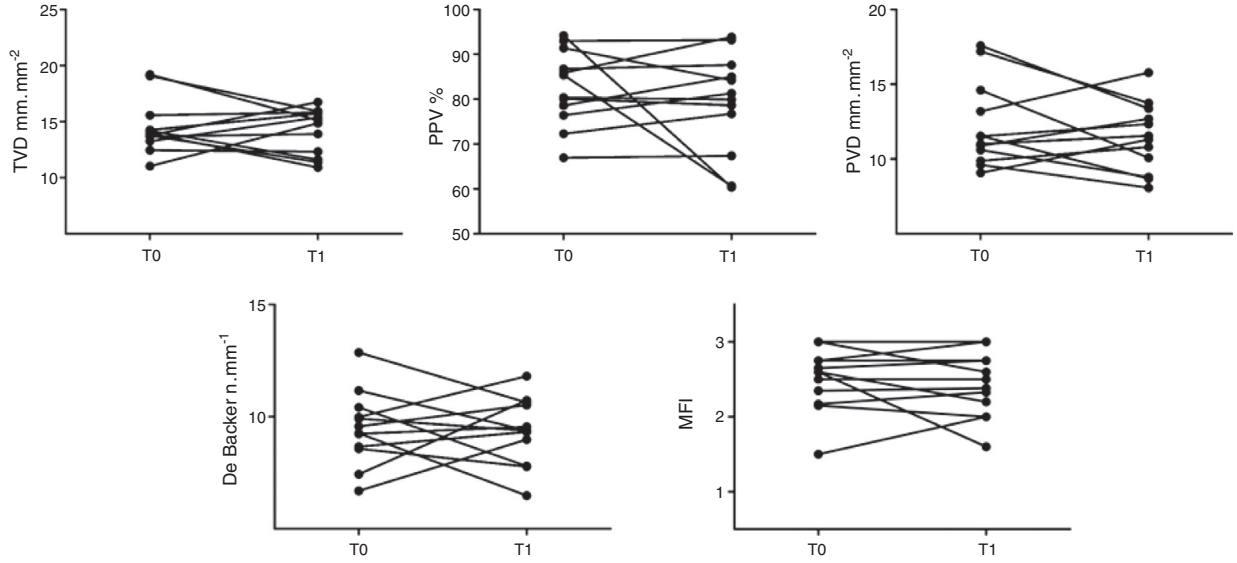

Figure 1 Individual behavior of the sublingual microvascular parameters (T0, baseline; T1, after PEEP increase; MFI, microcirculatory flow index; TVD, total vessel density; PPV, proportion of perfused vessels; and PVD, perfused vessel density).

Overall, the microcirculation parameters did not vary significantly after an increase in the PEEP (Table 3). However, there was considerable interindividual variability. The individual changes in the microcirculatory parameters are shown in Fig. 1. In two patients, there were dramatic falls in the PPV. These patients had important decrease in the CI and MAP.

There was a negative, moderate correlation between the ΔDe Backer ($r = -0.58$, $p = 0.048$) and ΔTVD ($r = -0.60$, $p = 0.039$) and their baseline values. This was not the case for the ΔMFI ($r = -0.29$, $p = 0.36$) or ΔPPV ($r = -0.48$, $p = 0.12$). There was a trend negative correlation between ΔPVD ($r = -0.57$, $p = 0.05$) and baseline value. Interestingly, ΔTVD ($r = 0.54$, $p = 0.07$) and ΔPVD ($r = 0.52$, $p = 0.08$) had a trend of correlating with the changes in the MAP. No other correlation was found between the changes in microcirculatory parameters and changes in the systemic hemodynamics or changes in the PEEP levels.

Discussion

We found that there was considerable variation in the individual sublingual microcirculatory responses to increases in the PEEP, although there were no overall changes. The PEEP-induced alterations in the microcirculatory parameters correlated with the baseline values in the TVD and De Backer scores. Moreover, there was a trend of a correlation between changes in the MAP and changes in the PVD and TVD.

Overall, the microcirculation parameters did not significantly change after increasing the PEEP. However, the considerable interindividual variability suggests the need for further studies aiming at understanding the factors that influence the individual variations of response. The mechanisms involved in microcirculation alterations after a PEEP increase probably included factors other than systemic hemodynamics. The role of intra-abdominal pressure,[16] neurohumoral activity,[17] oxygen-dependent metabolic signals,[18] the potential effect of increased PEEP levels on central venous pressure,[19] and changes in the organ blow flow induced by sepsis cannot be neglected.[20] Microcirculation blood flow control is a very complex phenomenon and the highly heterogeneous responses at a patient-level in our study could be explained by the interactions of multiple factors.[21]

Our study was the first to evaluate the sublingual microcirculatory responses to increases in the PEEP. However, previous studies have examined the effects of the PEEP on regional perfusion using other tools. Bruhn et al. showed that a PEEP of 10–20 cm H_2O did not affect the gastric mucosal perfusion measured by gastric tonometry, and it was hemodynamically tolerated in most of the ARDS patients included in the study.[12] Kiefer et al. reported that a PEEP increase of 5 cm H_2O did not have a consistent effect on the splanchnic blood flow and metabolism when the cardiac index is stable.[13] By contrary, in another study, increasing the PEEP levels from 5 to 15 cm H_2O induced a decrease in the CO with a concomitant drop in the hepatic vein O_2 saturation and hepatic glucose production.[11] Data from experimental studies suggest that the effect of the PEEP on splanchnic blood is dose-dependent and can usually be reversed with the maintenance of systemic hemodynamics.[3,22]

Unfortunately, our small sample size precludes advanced statistical analyses to determine the microcirculatory behavior in the subgroup of patients with hemodynamic impairment. However, we observed a trend in the correlation between the changes in the MAP and sublingual microcirculation; patients with a decrease in the MAP after a PEEP increase had decreased microvascular perfusion. The vast majority of the studies with videomicroscopy to evaluate therapeutic interventions have indicated that the sublingual microcirculatory effects were relatively independent of the systemic effects.[8,23,24] However, there is some evidence suggesting that the microcirculation is not completely dissociated from the systemic hemodynamics, and changes in the microcirculation perfusion could parallel changes in the MAP.[23,25–27] Of note, we did not find any correlation between changes in the CI and changes in the microcirculatory variables.

We cannot rule out the possibility that the changes between measurements could be random variations associated with SDF technique or statistical phenomenon.[28] However, the negative correlation between the microcirculatory variables and their baseline values was significant for TVD and De Backer score and trended to be significant for PVD. Interestingly, some studies have indicated that these changes could be correlated with the baseline values. In sepsis, the response of the microcirculation to noradrenaline depends on the baseline microcirculatory state; the perfused capillary density improved in patients who had an altered sublingual perfusion at baseline.[23] The increase in the microcirculatory blood flow was inversely correlated with the baseline levels in septic shock patients after 12 hours of high volume hemofiltration.[29] The change in the capillary perfusion after red blood cell transfusion was correlated with the baseline capillary perfusion, and it improved in patients with altered capillary perfusion at baseline.[30] Our results are in agreement with these studies and suggest that the microcirculatory blood flow improved in patients with a lower sublingual perfusion at baseline, while it decreased in patients with higher microvascular blood flow. These results need to be confirmed by additional studies.

Our study has several limitations other than the small sample size. The study period was short, and we only evaluated the sublingual microcirculation at one time point after the PEEP increases. Therefore, the results cannot be extrapolated to prolonged changes in the PEEP. We also lacked a control group. Finally, we did not evaluate the impact of stepwise PEEP elevation, and we used a variable PEEP value.

Conclusion

In conclusion, there was considerable variation in the individual sublingual microcirculatory responses to an increase in the PEEP, although there were no overall changes in the sublingual microcirculatory parameters. However, alterations in the microcirculatory perfusion could be correlated to baseline values and changes in the MAP.

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Conflicts of interest

The authors declare no conflicts of interests.

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