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BRIEF REPORT

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Spontaneous breathing during airway pressure release ventilation in experimental lung injury: effects on hepatic blood flow

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Abstract *Objective:* Positive pressure ventilation can affect systemic haemodynamics and regional blood flow distribution with negative effects on hepatic blood flow. We hypothesized that spontaneous breathing (SB) with airway pressure release ventilation (APRV) provides better systemic and hepatic blood flow than APRV without SB. *Design:* Animal study with a randomized cross-over design. *Setting:* Animal laboratory of Bonn University Hospital. *Subjects:* Twelve pigs with oleic-acid-induced lung injury. *Interventions:* APRV with or without SB in random order. Without SB, either the upper airway pressure limit or the ventilator rate was increased to maintain constant pH and $PaCO_2$. *Measurements and results:* Systemic haemodynamics were determined by double-indicator dilution, organ blood flow by coloured microspheres. Systemic blood flow was best during APRV with SB. During APRV with SB blood flow (ml g^{-1} min^{-1}) was 0.91 ± 0.26 (hepatic arterial), 0.29 ± 0.05 (stomach), 0.64 ± 0.08 (duodenum), 0.62 ± 0.10 (jejunum), 0.53 ± 0.07 (ileum), 0.53 ± 0.07 (colon), 0.46 ± 0.09 (pancreas) and 3.59 ± 0.55 (spleen). During APRV without SB applying high P_{aw} it decreased to 0.13 ± 0.01 (stomach), 0.37 ± 0.03 (duodenum), 0.29 ± 0.03 (jejunum), 0.31 ± 0.05 (ileum), 0.32 ± 0.03 (colon) and 0.23 ± 0.04 (pancreas) $p < 0.01$, respectively. During APRV without SB applying same P_{aw} limits it decreased to 0.18 ± 0.03 (stomach, $p < 0.01$), 0.47 ± 0.06 (duodenum, $p < 0.05$), 0.38 ± 0.05 (jejunum, $p < 0.01$), 0.36 ± 0.03 (ileum, $p < 0.05$), 0.39 ± 0.05 (colon, $p < 0.05$), and 0.27 ± 0.04 (pancreas, $p < 0.01$). Arterial liver blood flow did not change significantly when SB was abolished (0.55 ± 0.11 and 0.63 ± 0.11, respectively). *Conclusions:* Maintaining SB during APRV was associated with better systemic and pre-portal organ blood flow. Improvement in hepatic arterial blood flow was not significant.

Keywords Acute respiratory distress syndrome · Acute lung injury · Mechanical ventilation · Hepatic blood flow · Microspheres

Introduction

Hepato-splanchnic hypoperfusion and dysfunction have been demonstrated to contribute substantially to increased mortality of critically ill patients [1]. Positive-pressure ventilation has been shown to decrease systemic [2] and hepato-splanchnic blood flow and performance [3, 4]; therefore, ventilatory strategies should be applied that improve gas exchange and minimally affect hepatic blood flow.

Airway pressure release ventilation (APRV) provides mechanical assistance by time-cycled switching between two levels of continuous positive airway pressure while allowing spontaneous breathing throughout the ventilatory

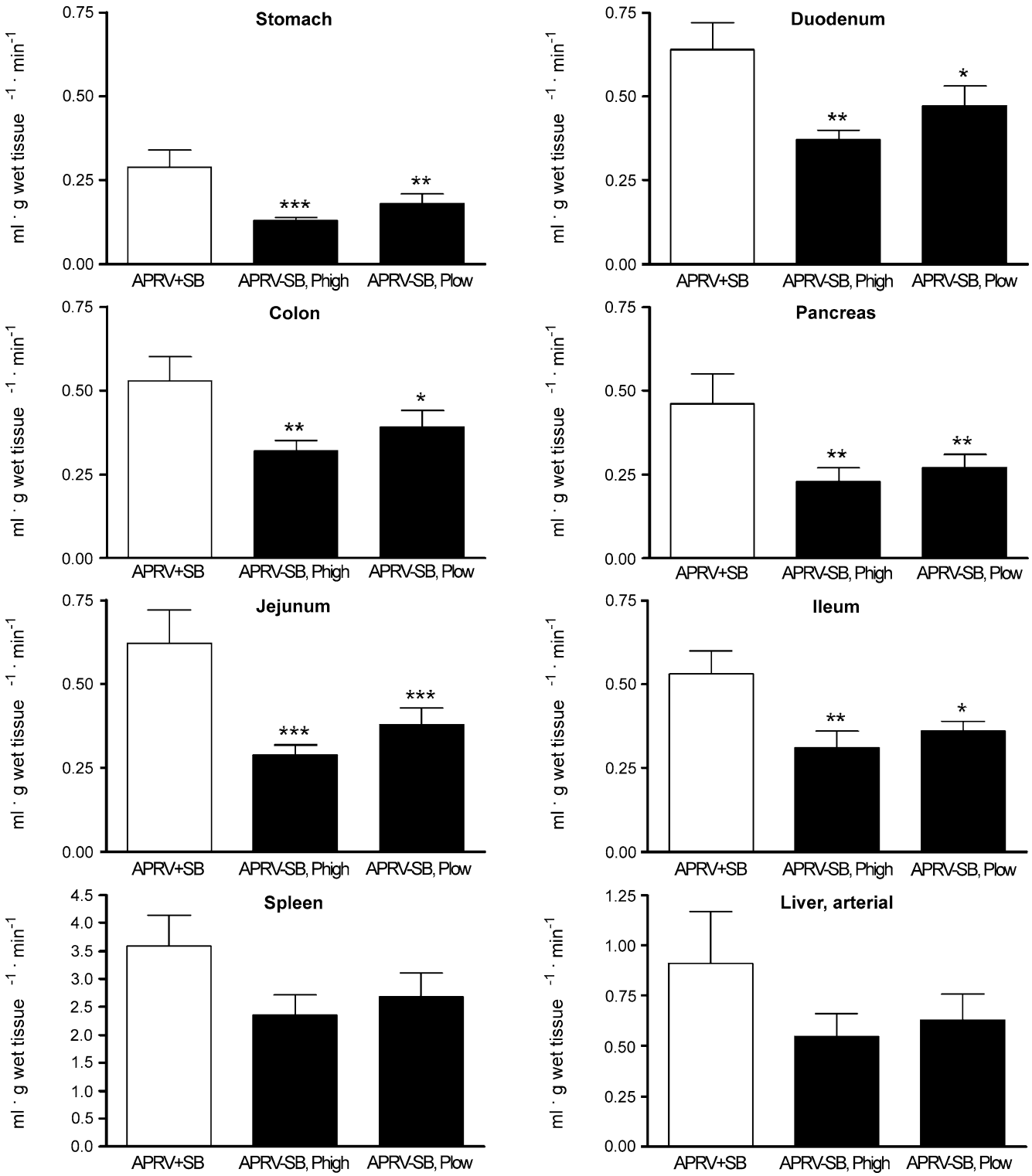

Fig. 1 Hepato-splanchnic blood flow (ml g wet tissue^{-1} min^{-1}). *APRV+SB*, airway pressure release ventilation with spontaneous breathing; *APRV-SB, Phigh* airway pressure release ventilation without spontaneous breathing and high airway pressure level to maintain minute volume; *APRV-SB, Plow*, airway pressure release ventilation without spontaneous breathing and low tidal volume with increased respiratory frequency to keep minute volume constant. All modes were applied in random order. *Asterisks* reflect p-value compared with APRV with spontaneous breathing: $*p<0.05$; $**p<0.01$; $***p<0.001$. Note the differing scales for spleen and liver

cycle [5]. In critically ill patients spontaneous breathing during APRV has been shown to improve systemic blood flow and regional perfusion to kidneys [6]. In an animal model with oleic-acid-induced lung injury we demonstrated that spontaneous breathing during APRV also provides better intestinal blood flow as determined by the coloured microspheres technique [7]. In this paper we present data derived from these experiments demonstrating the effects of APRV with and without spontaneous breathing on hepatic blood flow.

Materials and methods

The study was conducted in accordance with the Principles of Laboratory Animal Care [8] and approved by the Laboratory Animal Care and Use Committee of the District of Cologne, Germany. We used 12 pigs with oleic-acid-induced acute lung injury being tracheotomized and ventilated using the APRV mode of a standard ventilator (EVITA, Dräger, Lübeck, Germany). APRV with spontaneous breathing, and two periods of APRV without spontaneous breathing, were applied in random order. During absence of spontaneous breathing the same $paCO_2$ and pH levels were maintained either by increasing the upper airway pressure level or the respiratory rate. While analgosedation (sodium pentobarbital 2 mg/kg h^{-1} and ketamine 2 mg/kg h^{-1}) was kept constant throughout the study, neuromuscular blockade was induced with boli of 0.05 mg/kg intravenous cis-atracurium (Nimbex, GlaxoSmithKline, Munich, Germany) during the periods without spontaneous breathing. Absence of spontaneous breathing was monitored by online registration of oesophageal pressure [7]. The amount of spontaneous breathing during APRV was quantified by measuring minute volumes before and after neuromuscular blockade. After the ventilatory modality was changed, 30 min of equilibration were allowed before measurements.

Measurements included the transpulmonary double-indicator dilution technique (COLD-Z-021, Pulsion Medical Systems, Munich, Germany) to determine systemic haemodynamics and the coloured microspheres technique to measure hepatic arterial, and preportal (intestinal, pancreatic, splenic) tissue blood flow [9]. A comprehensive description of the instrumentation of the animals and measurements is provided in our previous paper [7]. In brief, after killing the animals at the end of the experiments, small pieces of the respective tissues were removed and the numbers of captured microspheres determined by spectrophotometric analysis. Tissue blood flow could be derived by relating the amount of microspheres harvested from the tissue samples to the number of microspheres harvested from an adequate aortic blood flow reference.

Statistical analysis

Results are expressed as mean ± standard error of the mean. Data were evaluated for normal distribution with the

Table 1 Ventilatory and gas exchange variables. *APRV*, airway pressure release ventilation; P_{aw}, mean airway pressure; F_iO_2, inspired oxygen fraction; P_{low}, low airway pressure level; P_{high}, high airway pressure level; $P_{oesophageal}$, oesophageal pressure; *RR*, respiratory rate; V_T, tidal volume; V_E, minute volume; P_aO_2, arterial oxygen tension; P_aCO_2, arterial carbon dioxide tension; $pH_{arterial}$, arterial pH; $V_{E\,spontaneous}$, proportion of spontaneous breathing of total minute ventilation

	APRV with spontaneous breathing[a]	APRV without spontaneous breathing, high P^a_{aw}	APRV without spontaneous breathing, low P^a_{aw}
F_iO_2 (%)	35 ± 2	35 ± 2	35 ± 2
P_{low} (cmH_2O)	5 ± 0	5 ± 0	5 ± 0
P_{high} (cmH_2O)	14 ± 1	22 ± 1[b]	15 ± 1[e]
P_{aw} (cmH_2O)	11.3 ± 0.5	15.7 ± 0.6[b]	12.2 ± 0.4[e]
$P_{oesophageal}$ (cmH_2O)	8.7 ± 1.3	10.5 ± 1.3[b]	9.4 ± 1.3[c,e]
RR (min^{-1})	40 ± 3	18 ± 2[b]	52 ± 3[d,e]
V_T($ml\,kg^{-1}$)	7.2 ± 0.4	11.3 ± 0.9[b]	5.6 ± 0.5[e]
V_E ($l\,min^{-1}$)	4.1 ± 0.2	3.5 ± 0.3[c]	4.6 ± 0.3[f]
$V_{E\,spontaneous}$ (%)	54 ± 3	0 ± 0[b]	0 ± 0[b]
P_aO_2/FiO_2 (mmHg)	332 ± 29	269 ± 24[c]	269 ± 24[c]
P_aCO_2 (mmHg)	56 ± 3	55 ± 3	58 ± 3
$pH_{arterial}$	7.36 ± 0.02	7.36 ± 0.02	7.35 ± 0.03
Lactate ($mmol\,l^{-1}$)	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.3

Values are mean ± SEM
[a] Randomized order of ventilatory settings
[b] $p < 0.001$ compared with APRV with spontaneous breathing
[c] $p < 0.05$ compared with APRV with spontaneous breathing
[d] $p < 0.01$ compared with APRV with spontaneous breathing
[e] $p < 0.001$ compared with APRV without spontaneous breathing and high P_{aw}
[f] $p < 0.05$ compared with APRV without spontaneous breathing and high P_{aw}

Shapiro–Wilks W-test. Data obtained during the different ventilatory modes were compared using one-way analysis of variance. When a significant F ratio was obtained, differences between the means were examined with the Newman–Keuls test. Differences were considered to be statistically significant if p was less than 0.05.

Results

Spontaneous breathing accounted for $54 \pm 3\%$ of the total minute volume and improved arterial oxygenation as compared with full ventilatory support ($p < 0.05$; Table 1). To keep P_aCO_2 and arterial pH constant during neuromuscular blockade, either the upper airway pressure limit had to be increased resulting in a higher V_T and mean P_{aw} ($p < 0.001$) or, at an unchanged mean P_{aw}, the ventilator rate had to be increased ($p < 0.01$). Spontaneous breathing resulted in the lowest mean oesophageal pressure ($p < 0.05$, Table 1).

Cardiac output (141 ± 8 ml kg^{-1} min^{-1} APRV+SB, 110 ± 3 APRV-SB, high P_{aw}, 127 ± 5 ml kg^{-1} min^{-1} APRV-SB, low P_{aw}), intrathoracic blood volume (23 ± 1 ml kg^{-1} APRV+SB, 19 ± 1 ml kg^{-1} APRV-SB, high P_{aw}, 21 ± 1 ml kg^{-1} APRV-SB, low P_{aw}), stroke volume (1.1 ± 0.08 ml kg^{-1} beat^{-1} APRV+SB, 0.8 ± 0.03 ml kg^{-1} beat^{-1} APRV-SB, high P_{aw}, 0.9 ± 0.08 ml kg^{-1} beat^{-1} APRV-SB, low P_{aw}) and oxygen delivery (18.5 ± 1.3 ml kg^{-1} min^{-1} APRV+SB, 14.1 ± 0.5 APRV-SB, high P_{aw}, 15.6 ± 0.4 ml kg^{-1} min^{-1} APRV-SB, low P_{aw}) increased with spontaneous breathing and were lowest during full ventilatory support at increased upper P_{aw} ($p < 0.01$). In parallel with systemic blood flow, gastric ($p < 0.01$), intestinal ($p < 0.05$) and pancreatic perfusion ($p < 0.01$) increased during APRV with spontaneous breathing (Fig. 1). Hepatic arterial and splenic blood flow were not significantly altered but also tended to improve when spontaneous breathing was maintained.

Discussion

The intention of this brief report is to demonstrate the effects of spontaneous breathing during APRV on the dual circulation of the liver in experimental acute lung injury. Blood flow to most of the preportal organs draining blood into the portal circulation improved with spontaneous breathing, whereas the effects of the ventilatory modality on the hepatic arterial circulation were less prominent.

We used APRV that provides a constant degree of ventilatory support by time-cycled switching between two CPAP levels, allowing spontaneous breathing in any phase of the ventilator cycle [5]. If spontaneous breathing is abolished, APRV is not different from pressure-controlled ventilation. The results of the present study should essentially reflect the effect of spontaneous breathing during APRV on hepatic blood flow, because in the absence of spontaneous breathing, either the ventilator rate or the upper P_{aw} limits were increased to compensate for the decrease in alveolar ventilation and to maintain constant $PaCO_2$ and pH. In addition, the level of analgosedation was maintained constant at the different steps of the protocol.

The liver receives approximately 25–30% of systemic blood flow [10]. One-third of total liver blood flow originates from the systemic circulation via the hepatic artery and two-thirds from the portal circulation. We used the microspheres technique because it lacks the need for any surgical manipulation, such as laparotomy, that per se may have impact on tissue perfusion [11]. The 15-μm diameter microspheres that we used show negligible shunting from arterial to portal venous circulation [12]. By this technique, it was possible to distinguish between arterial and portal perfusion. Microspheres harvested from the liver tissue originated solely from the hepatic arterial blood flow, while portal blood flow could be derived indirectly from perfusion measurements of multiple tissue samples of the stomach, intestines, pancreas and spleen.

Hepato-splanchnic perfusion has been shown to deteriorate with an increase in ventilatory support [3, 4, 13]. In these studies, the impairment of hepato-splanchnic perfusion paralleled the decrease in cardiac output. We found that APRV with spontaneous breathing increased pre-portal blood flows in excess of systemic blood flow and intrathoracic blood volume as compared with full ventilatory support. This is of additional interest, because even after restoration of adequate systemic haemodynamics, intestinal perfusion may be insufficient during mechanical ventilation [14].

Changes in hepatic arterial and splenic blood flow showed similar patterns but were not statistically significant, which may be attributed to a larger dispersion of the data. In addition, hepatic arterial blood flow may have been, in part, counter-regulated by an intrinsic hepatic mechanism: the hepatic arterial buffer response (HABR) [15]. A decrease in portal blood flow triggers an increase in hepatic arterial perfusion to maintain overall liver perfusion, and vice versa. This mechanism may be regulated by intrahepatic adenosine production and may be mediated by opening of intrahepatic arterio-venous shunts [16]. The HABR can compensate for reductions of portal blood flow up to 20–30% [15, 17, 18]; however, in our experiments, we did not find any increase in hepatic arterial blood flow. This may be explained by an exhausted HABR, since previous studies showed that the compensatory capacity of the HABR can be weakened during positive pressure ventilation in the presence of impaired systemic blood flow, hypoxaemia or endotoxaemia [13, 19].

Conclusion

Our results add further information to previous findings that spontaneous breathing during APRV improves blood flow to splanchnic organs, such as intestines and pancreas. Changes in hepatic arterial blood flow showed similar patterns but were not as prominent as those of pre-portal blood flow. Because the liver plays a key role in the pathogenesis of multiple organ failure, further studies are needed to evaluate the effects of spontaneous breathing using APRV and other modalities of partial ventilatory support on the hepatic circulation in critically ill patients.

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