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Effects of spontaneous breathing during airway pressure release ventilation on renal perfusion and function in patients with acute lung injury

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Abstract *Objective:* Controlled mechanical ventilation can impair systemic and renal blood flow and function, which may be aggravated by respiratory acidosis. We hypothesized that partial ventilatory support using airway pressure release ventilation (APRV) with spontaneous breathing provides better cardiopulmonary and renal function than full ventilatory support using APRV without spontaneous breathing. *Design:* Prospective randomized study. *Setting:* Intensive care unit of a university hospital. *Patients:* Twelve patients with acute lung injury (ALI). *Interventions:* Airway pressure release ventilation with and without spontaneous breathing, maintaining either the same minute ventilation (V_E) or the same airway pressure (Paw) limits. *Measurements:* Systemic hemodynamics were estimated by double-indicator dilution, effective renal blood flow (ERBF) by para-aminohippurate, and glomerular filtration rate (GFR) by inulin clearance. *Results:* Compared to APRV with spontaneous breathing, cardiac index (CI) was decreased when the upper Paw limit was increased to provide the same V_E (4.26±1.21 l min^{-1} m^{-2} vs 3.72±0.99 l min^{-1} m^{-2}; $p<0.05$) while CI was increased when Paw limits were held constant (4.91±1.41 l min^{-1} m^{-2}; $p<0.05$). Effective renal blood flow and GFR were higher during APRV with spontaneous breathing (858±388 ml min^{-1} m^{-2} and 94±47 ml min^{-1} m^{-2}) than during APRV without spontaneous breathing and the same V_E (714±236 ml min^{-1} m^{-2} and 82±35 ml min^{-1} m^{-2}) or the same Paw (675±287 ml min^{-1} m^{-2} and 80±41 ml min^{-1} m^{-2};$p<0.05$). Urine volume did not change. *Conclusions:* Spontaneous breathing during APRV was associated with better renal perfusion and function than APRV without spontaneous breathing applying either the same V_E or the same Paw limits. Maintaining spontaneous breathing during ventilatory support may, therefore, be advantageous in preventing deterioration of renal function in patients with ALI.

Keywords Mechanical ventilation · Spontaneous breathing · Hemodynamics · Renal function · Lung injury

Introduction

Mechanical ventilation is commonly applied during acute lung injury (ALI) to improve gas exchange. However, patients with ALI rarely die of hypoxia and/or hypercarbia but commonly develop multiple organ system dysfunction syndrome, including renal failure, which is a cause of increased mortality [1, 2].

Positive pressure ventilation has been shown to worsen renal excretory function, resulting in retention of water and sodium [3]. Increased airway and intrathoracic pressures associated with mechanical ventilation not only

compromise systemic [4], but also renal, hemodynamics and subsequently may lead to renal dysfunction [5, 6]. However, ventilatory strategies limiting peak inspiratory pressure can result in hypercapnia and respiratory acidosis [7, 8, 9], which may also worsen renal function [10].

Facilitation of renal perfusion and function has been documented during intermittent mandatory ventilation, which adds mechanical cycles to unsupported spontaneous breathing [5]. In patients with ALI, partial ventilatory support is increasingly used even in the early course of the disease [11, 12, 13]. Spontaneous breathing with airway pressure release ventilation (APRV), which provides mechanical assistance by time-cycled switching between two levels of continuous positive airway pressure (CPAP) [14], has been shown in experimental and clinical studies to improve systemic hemodynamics and gas exchange [15, 16]. In these patients an improvement in systemic perfusion has been considered an advantage of partial ventilatory support compared to controlled mechanical ventilation [16], presumably because a fall in intrathoracic pressure during spontaneous inspiration improves venous return and cardiac index (CI). However, it is not known whether spontaneous breathing with APRV is associated with better renal blood flow and function in patients with ALI.

We hypothesized that spontaneous breathing during APRV will improve cardiopulmonary and renal function in patients with ALI. To test this hypothesis we investigated the cardiorespiratory and renal function during APRV with and without spontaneous breathing using either the same minute ventilation (V_E) or the same airway pressure (Paw) limits on a random basis.

Materials and methods

Patients

After approval by the Bonn university ethics committee and written informed consent obtained from the next of kin, 12 mechanically ventilated patients with ALI were studied. The criteria of the American-European Consensus Conference were used to define ALI [17]. Patients receiving catecholaminergic or dopaminergic drugs and diuretics, and those with renal transplants or renal replacement therapy were excluded, as were patients with cerebral injury. Organ Failure Score [18], Simplified Acute Physiology Score II [19] and duration of ventilatory support before the study were recorded at a patient's inclusion in the study (Table 1).

Routine clinical management of the patients included the use of a central venous and a thermistor-tipped fiberoptic artery catheter (Pulsiocath PV2024–4F, Pulsion Medical Systems, Munich, Germany) advanced via the femoral artery into the aorta.

Ventilatory measurements

Gas flow was measured at the proximal end of the tracheal tube with a heated pneumotachograph (No.2; Fleisch, Lausanne, Switzerland) connected to a differential pressure transducer (Huba Control, Würenlos, Switzerland). Tidal volume (V_T) and V_E were derived from the integrated gas flow signal. Airway pressure was measured at the same position with another differential pressure transducer (SMT, Munich, Germany). Esophageal pressure (Pes) was measured with a balloon catheter (International Medical, Zutphen, Netherlands) connected to a differential pressure transducer (SMT, Munich, Germany) as described by Brunner and Wolff [20].

Cardiovascular measurements

Heart rate (HR) was obtained from the electrocardiogram. Mean arterial blood pressure (MAP) and central venous pressure (CVP) were transduced (Combitrans, Braun, Melsungen, Germany) and recorded (CS/3, Datex-Engström, Helsinki, Finland). The transpulmonary double-indicator dilution method was used to estimate cardiac output and intrathoracic blood volume as described previously [21]. Indocyanine green dye (ICG) (Becton Dickinson, Cockeysville, Md., USA), 25 mg dissolved in 15 ml iced 5% glucose solution, was used as double-indicator and injected into the right atrium via the central venous line. Simultaneously dilution curves for dye and temperature were recorded in the aorta with the thermistor-tipped fiberoptic artery catheter. From these curves a computer (COLD-Z-021, Pulsion Medical Systems, Munich, Germany) estimated cardiac output with the dye-dilution method and determined the mean transit time of the first pass of the dye indicator (mtt_{ICG}) for calculating intrathoracic blood volume [21]. An

Table 1 Demographic data and clinical characteristics (*SAPS II* Simplified Acute Physiology Score II [19]; *MOF score* Multiple Organ Failure score [18])

Patient	Sex	Age	Cause of acute lung injury	Time from onset*	SAPS II score	MOF score	Outcome
1	m	74	Sepsis	34	28	5	Died
2	m	53	Sepsis	5	23	2	Survived
3	f	57	Multiple trauma, lung contusion	5	14	2	Survived
4	f	58	Sepsis	13	28	5	Survived
5	m	75	Hemorrhagic shock	8	27	4	Survived
6	m	24	Multiple trauma, lung contusion	5	20	3	Survived
7	m	58	Pneumonia	4	20	5	Survived
8	m	57	Multiple trauma, flail chest	11	27	3	Survived
9	m	62	Aortocoronary bypass, pneumonia	8	18	4	Survived
10	m	61	Peritonitis, sepsis	11	26	3	Survived
11	f	31	Hemorrhagic shock	7	14	4	Survived
12	m	34	Pneumonia	13	34	2	Died

* Days on mechanical ventilation before the study

average of three measurements were performed at random moments during the ventilatory cycle.

Blood gas analysis

Arterial blood gases and pH were determined immediately after sampling in duplicate with standard blood gas electrodes (ABL 510, Radiometer, Copenhagen, Denmark). In each sample hemoglobin and oxygen saturation (SO_2) were analyzed using spectrophotometry (OSM 3, Radiometer, Copenhagen, Denmark).

Renal measurements

Urine was collected at 60min intervals after air-washout of the urinary bladder using a Foley catheter. Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were determined by the steady-state clearance technique of para-aminohippuric acid (PAH) (Merck, West Point, USA) and inulin (Laevosan, Linz, Austria) [22]. Urine and plasma samples were analyzed for PAH and inulin (DU-40, Beckman Instruments, Brea, Calif., USA) sodium, creatinine (Synchron CX 7, Beckman Instruments, Brea, Calif., USA) and osmolality (semi-micro osmometer, Knauer, Berlin, Germany).

Data analysis

Tidal volume was indexed for predicted body weight (V_{Tpbw}) which was calculated as equal to 50+0.91 (centimeters of height –152.4) in male and 45.5+0.91 (centimeters of height –152.4) in female patients [11]. Mean changes in Pes (ΔPes) for each measuring period were derived from the amplitudes of Pes swings; transmural central venous pressure (CVP_{tm}) was derived by subtracting averaged Pes from CVP. Standard formulas were used to calculate cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI) and oxygen delivery index (DO_2I). Intrathoracic blood volume index (ITBVI) was calculated as CI × mtt_{ICG} [21]. Effective renal plasma flow and GFR were determined using the standard clearance formula and corrected to body surface area. Effective renal blood flow (ERBF) was calculated as ERPF × (1–hematocrit)$^{-1}$ [22], renal fraction of cardiac output (RF) as ERBFI × CI, renal vascular resistance index (RVRI) as MAP × ERBF^{-1} × 80,000, and filtration fraction (FF) as GFR × ERBF^{-1} [22]. Fractional sodium excretion (FE_{Na}), and osmolar clearance (C_{osm}) were calculated using standard formulas [22].

Protocol

After inclusion in the study, patients were positioned supine and received a continuous infusion of sufentanil (42±16 μg h^{-1}) and midazolam (9±4 mg h^{-1}) to achieve a Ramsay sedation score of 4 [23]. Only crystalloid fluids were given and fluid replacement and infusion of all drugs remained unchanged throughout the study except for cis-atracurium, which was given during the periods of full ventilatory support to suppress spontaneous breathing efforts.

Pressure-limited ventilatory support was provided with a demand valve CPAP circuit of a standard ventilator (Evita 4, Dräger, Lübeck, Germany). The low pressure level was titrated corresponding to the highest PaO_2/FIO_2 and the high pressure level was adjusted to produce a V_T of approximately 6 ml kg^{-1} predicted body weight during transient neuromuscular blockade (1 mg kg^{-1} intravenous succinylcholine). After recovery of spontaneous breathing, the ventilator rate was set to maintain $PaCO_2$ between 45 and 55 mmHg and FIO_2 to maintain PaO_2 above 80 mmHg. All patients resumed spontaneous breathing during ventilatory support with the settings described above. After a 60min equilibration period on APRV with spontaneous breathing, baseline ventilatory data were recorded.

Then all patients received APRV with or without spontaneous breathing in random order, using either identical low and high airway pressure levels or the same V_E. To maintain V_E constant without spontaneous breathing, the high airway pressure level was increased. To guarantee the absence of spontaneous breathing during the periods without spontaneous breathing, neuromuscular blockade was induced with intravenous cis-atracurium (bolus 11±4 mg followed by 8±4 mg h^{-1} as a continuous infusion). Train-of-four stimulation was used to monitor muscle relaxation (N-NMT monitor, Datex-Engström, Helsinki, Finland). The neuromuscular blockade was considered sufficient with the disappearance of the twitch response to a train-of-four supramaximal ulnar nerve stimulation at 2.0 Hz for 1.5 s every 2 min. The absence of spontaneous breathing was verified by online registration of the Pes tracings.

A 60min equilibration period followed each intervention before measurements. Prior to each intervention, at least 30 min were allowed for cardiopulmonary variables to return to baseline values (±10%) and the patients' lungs were inflated manually twice to an airway pressure of 40 cmH_2O for 20 s to restore lung history.

Statistical analysis

At least 12 patients have to be studied to detect differences in CI, renal blood flow and GFR between two levels of the three ventilatory settings with the Tukey HSD test in the given cross-over design at a significance level of 5% (α=0.05) with a probability of 79.8% (β=0.798) based on a detectable contrast of 1.405 for a within-patient SD of 1.0 and a residual SD of 0.5.

The results are expressed as means ± standard deviation (SD). The data were evaluated for normal distribution with Shapiro-Wilk's W test. Data obtained during the different ventilatory modes were compared using the one-way ANOVA test followed by the Tukey HSD test. Differences were considered to be statistically significant if p was less than 0.05.

Results

Ventilatory variables, lung mechanics and gas exchange variables are shown in Table 2. During APRV, spontaneous breathing accounted for more than 30% of the total V_E. Spontaneous breathing during APRV was associated with an increase in PaO_2 (p<0.05) when compared to full ventilatory support. When airway pressure limits were held constant in the absence of spontaneous breathing, as compared to APRV with spontaneous breathing, V_E and pH_a were lowest and $PaCO_2$ highest (p<0.05). To maintain V_E at the same level when spontaneous breathing was abolished, the high Paw level had to be elevated, resulting in an increase in V_T and mean Paw (p<0.05) and no change in $PaCO_2$. Mean Pes was lowest and ΔPes highest during APRV with spontaneous breathing (p<0.05).

Changes in gas exchange and cardiovascular variables are shown in Table 3. In the absence of spontaneous breathing at the same Paw limits, HR and CI increased (p<0.05) and SVRI decreased (p<0.05) with hypercapnia and respiratory acidosis. Intrathoracic blood volume, CVP_{tm}, CI, SVI and DO_2I were lowest when spontaneous breathing was abolished and the high airway pres-

Table 2 Ventilation, lung mechanic and gas exchange variables (*APRV* airway pressure release ventilation, V_E minute ventilation, *Paw* airway pressure, FIO_2 fractional inspired oxygen, *PEEP* positive end-expiratory pressure, *PIP* peak inspiratory pressure, *RR* respiratory rate, V_T tidal volume, V_{Tpbw} tidal volume indexed for predicted body weight, $V_{Espontan}$ minute ventilation during spontaneous breathing, *Pes* esophageal pressure, *ΔPes* mean changes in esophageal pressure, PaO_2 arterial partial pressure of oxygen, $PaCO_2$ arterial partial pressure of carbon dioxide)

	APRV with spontaneous breathing[a]	APRV without spontaneous breathing, same V_E[a]	APRV without spontaneous breathing, same Paw[a]
FIO_2 (%)	0.48±0.1	0.48±0.1	0.48±0.1
PEEP (cmH_2O)	16±2	16±2	16±2
PIP (cmH_2O)	24±3	29±4	24±3
RR (min^{-1})	21±6	14±3[b]	14±3[b]
V_T (ml)	432±192	632±160[b]	418±112[c]
V_{Tpbw} (ml kg^{-1})	6±2	9±2[b]	6±1[c]
V_E (l min^{-1})	9.38±0.86	8.92±0.29	5.71±1.13[b,c]
$V_{Espontan}$ (l min^{-1})	3.67±1.52	0	0
$V_{Espontan}$ (%)	38±15	0	0
Mean Paw (cmH_2O)	19±2	23±2[b]	19±2[c]
Mean Pes (cmH_2O)	12±4	15±4[b]	13±3[c]
ΔPes (cmH_2O)	9±3	4±2[b]	3±2[b]
$PaCO_2/FIO_2$ (mmHg)	294±58	265±74[b]	254±62[b]
Pa_{CO2} (mmHg)	52±11	50±9	72±30[b,c]
pH	7.36±0.06	7.37±0.06	7.24±0.14[b,c]

Values are mean ± SD
[a] Tested on a randomized basis
[b] $p<0.05$ compared with APRV with spontaneous breathing
[c] $p<0.05$ compared with APRV without spontaneous breathing, same V_E

Table 3 Cardiovascular variables (*APRV* airway pressure release ventilation, V_E minute ventilation, *Paw* airway pressure, *HR* heart rate, *MAP* mean arterial pressure, CVP_{tm} transmural central venous pressure, *ITBVI* intrathoracic blood volume index, *CI* cardiac index, *SVI* stroke volume index, *SVRI* systemic vascular resistance index, DO_2I oxygen delivery index)

	APRV with spontaneous breathing[a]	APRV without spontaneous breathing, same V_E[a]	APRV without spontaneous breathing, same Paw[a]
HR (min^{-1})	97±22	95±22	110±24[b,c]
MAP (mmHg)	81±8	79±6	85±12
CVP_{tm} (mmHg)	5±4	2±4[b]	4±3[c]
ITBVI (ml m^{-2})	891±238	802±270[b]	912±238[c]
CI (l min^{-1} m^{-2})	4.26±1.21	3.72±0.99b	4.91±1.41[b,c]
SVI (l $beat^{-1}$ m^{-2})	45±13	41±13[b]	46±13[c]
SVRI (dyne s cm^{-5} m^2)	1434±523	1559±537	1292±509[b,c]
Hemoglobin (g dl^{-1})	10.8±1.4	10.8±1.4	10.8±1.5
$D_{O2}I$ (ml min^{-1} m^{-2})	629±143	544±121[b]	709±160[b,c]

Values are mean ± SD
[a] Tested on a randomized basis
[b] $p<0.05$ compared with APRV with spontaneous breathing
[c] $p<0.05$ compared with APRV without spontaneous breathing, same V_E

sure level was elevated to keep V_E constant ($p<0.05$). Arterial Hb and MAP remained unchanged for all conditions tested.

The variables reflecting renal perfusion and function are given in Table 4. Effective renal blood flow, GFR and C_{osm} were highest in the presence of spontaneous breathing ($p<0.05$). Suppression of spontaneous breathing at the same Paw limits was associated with a significant reduction in RF and an increase in RVRI ($p<0.05$). Urine output, FF and FE_{Na} remained unchanged throughout the study.

Discussion

This study was designed to evaluate the effects of spontaneous breathing during APRV on renal perfusion and function in patients with ALI. We found that spontaneous breathing with APRV was associated with an improvement in renal hemodynamics and function. In the presence of spontaneous breathing the concomitant increase in systemic blood flow and arterial oxygenation improved oxygen delivery as compared to full ventilatory support with increased upper Paw limits to maintain V_E constant. In contrast, full ventilatory support without spontaneous breathing at the same Paw limits resulted in hypercapnia, which was associated with higher CI and

Table 4 Renal function variables (*APRV* airway pressure release ventilation, V_E minute ventilation, *Paw* airway pressure, U_{vol} urine volume, *ERBF* effective renal blood flow, *RF* renal fraction of cardiac output, *RVRI* renal vascular resistance index, *GFR* glomerular filtration rate, *FF* filtration fraction, FE_{Na} fractional excretion of sodium, C_{osm} osmolar clearance)

	APRV with spontaneous breathing*	APRV without spontaneous breathing, same VE[a]	APRV without spontaneous breathing, same Paw[a]
U_{vol} (ml h^{-1})	143±54	130±34	132±84
ERBF (ml min^{-1} m^{-2})	858±388	714±236[b]	675±287[b]
RF (%)	20.8±9.0	19.4±6.0	14.5±6.6[b,c]
RVRI (dyne s cm^{-5} m^2)	9379±4895	10002±3918	12853±8942[b,c]
GFR (ml min^{-1} m^{-2})	94±47	82±35[b]	80±41[b]
FF (%)	19.1±15.6	19±13.1	21.6±18.6
FE_{Na} (%)	1.85±1.71	2.17±1.93	2.12±2.67
C_{osm} (ml min^{-1})	3.36±1.04	3.27±1.1	3.17±2.23[b]

Values are mean ± SD
[a] Tested on a randomized basis
[b] $p<0.05$ compared with APRV with spontaneous breathing
[c] $p<0.05$ compared with APRV without spontaneous breathing, same V_E

oxygen delivery. However, renal perfusion and function consistently did not improve during mechanical ventilation in the absence of spontaneous breathing.

Partial ventilatory support is used increasingly, not only to separate patients from mechanical ventilation but to provide stable ventilatory assistance of a desired degree during ventilatory failure [11, 12, 13, 16]. 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 mechanical ventilator cycle [14]. When spontaneous breathing is abolished, APRV is no different from pressure-controlled ventilation [14]. In the present study V_T was 6±2 ml kg^{-1} predicted body weight during APRV with spontaneous breathing and APRV without spontaneous breathing at the same Paw limits. Because the ventilatory rate remained unchanged during APRV, the absence of spontaneous breathing while maintaining Paw limits constant resulted in lower alveolar ventilation with a marked increase in $PaCO_2$. The upper Paw limit had to be significantly increased in our patients to deliver the same V_E during APRV without spontaneous breathing at an unchanged ventilatory rate; this resulted in V_T of 9 ml kg^{-1} predicted body weight. A recent multicenter trial in 861 patients with ALI observed 25% improvement in outcome by reduction in V_T from 12 to 6 ml kg^{-1} predicted body weight at moderate PEEP levels while avoiding hypercapnia and respiratory acidosis by allowing ventilatory rates to increase up to 35 min^{-1} during assist-controlled mechanical ventilation or administration of intravenous bicarbonate [11].

A previous study by Hickling et al. [24], in 53 patients with ALI, suggested improved outcome during ventilation with low V_T and toleration of permissive hypercapnia. In contrast, several randomized clinical trials in patients with ALI could not demonstrate any advantage or even improved outcome when low V_T ranging between 4 and 6 ml kg^{-1} body weight was used during positive pressure inflation and toleration of hypercapnia and respiratory acidosis [7, 8, 9]. Although it was not the purpose of our study to investigate the effects of different lung protective ventilatory strategies on renal function, it is noteworthy that V_T and acid base balance during APRV with spontaneous breathing were quite similar to the target values proposed by the ARDS network study [11].

In our patients controlled mechanical ventilation with higher Paw limits to keep V_E constant was associated with an increase of mean Pes, as a surrogate for intrathoracic pressure, and a decrease in ITBVI, CVP_{tm}, SVI and CI. The higher cardiac preload and systemic blood flow found with spontaneous breathing during APRV, when compared to APRV without spontaneous breathing and the same V_E, may be attributed to the periodic fall in intrathoracic pressure during spontaneous inspiration, which may improve venous return and cardiac output [16]. Consistent with our findings, an increase of right ventricular end-diastolic volume, right ventricular ejection fraction and CI has been demonstrated recently during APRV with spontaneous breathing in patients with ALI [16]. A marked increase in HR and CI at unchanged SVI, ITBVI and CVP_{tm}, found during APRV without spontaneous breathing at the same Paw limits when compared to APRV with spontaneous breathing, may be attributed to hypercapnia and respiratory acidosis [25, 26, 27, 28, 29]. Compatible with these investigations [25, 26, 27, 28, 29], an increase in CI during permissive hypercapnia was associated with decreased systemic vascular resistance, reflecting systemic vasodilation, which effected no change in MAP in our patients.

Spontaneous breathing during APRV consistently improved arterial oxygenation. This observation is in agreement with the experimental [15] and clinical [12, 13, 16] findings that spontaneous breathing with APRV improves arterial oxygenation by decreasing intrapulmonary shunting. Changes in CI caused by mechanical ventilation have been reported to correlate positively with intrapulmonary shunting [26]. However, the increase in CI associated

with respiratory acidosis did not essentially affect arterial blood oxygenation in our patients, when compared to mechanical ventilation with higher Paw and normal acid base balance. This may be explained by the physiologic concept that, during permissive hypercapnia, the higher CI decreases the arteriovenous O_2 content difference, thereby offsetting the effects of the higher intrapulmonary shunt on arterial oxygenation [26]. In contrast, during spontaneous breathing with APRV the increased CI was associated with an increased PaO_2 and a higher DO_2I. This supports previous findings that, during spontaneous breathing with APRV, an increase in CI and PaO_2 contributes to the higher DO_2I [16]. However, the increase in DO_2I was highest during permissive hypercapnia.

Despite the highest CI and DO_2I, APRV without spontaneous breathing resulting in hypercapnia was associated with essentially unchanged ERBF and GFR, while RVRI markedly increased and RF decreased when compared to APRV without spontaneous breathing at higher Paw limits. Our findings are in agreement with observations of impaired renal blood flow and function in patients with hypercapnic respiratory failure [10, 30, 31]. In patients with ALI, hypercapnia and respiratory acidosis have been suggested to be responsible for the higher incidence of renal failure requiring dialysis during mechanical ventilation with low V_T [9]. Compatible with our observations, recent findings indicate that hypercapnia reduces renal functional reserve [32] and increases renal vascular resistance which cannot be reversed by hyperoxemia or dopaminergic stimulation [30, 31]. Acute hypercapnia has been shown directly to induce renal vasoconstriction [33] and to stimulate sympathetic response pathways more than acidosis alone [34]. When compared to APRV without spontaneous breathing at higher Paw levels, the unchanged renal function during permissive hypercapnia in the presence of renal vasoconstriction can only be explained by the maintenance of the same level of renal blood flow due to the increase in systemic blood flow.

Despite the smaller increase in CI and DO_2I, APRV with spontaneous breathing was associated with an increase in ERBF and GFR. Several studies observed a decrease in cardiac output, renal blood flow, GFR, sodium excretion and urinary flow when increasing ventilatory support [3, 5, 6, 35, 36, 37]. In contrast to our patients breathing spontaneously with APRV, previous investigations have compared either unsupported spontaneous breathing with positive pressure ventilation [3, 5, 35] or spontaneous breathing at different CPAP levels [6, 36]. Our results are in agreement with those of Steinhoff and coworkers [5, 35], who observed improvement in renal function following switching from mechanical ventilation to spontaneous breathing with intermittent mandatory ventilation. Based on these findings, it was suggested that improved renal function is associated with the periodic decrease in intrathoracic pressure due to inspiratory efforts between the mandatory cycles [5, 35]. However, it is difficult to evaluate the effect of different ventilatory support modalities on renal function on the basis of previous non-randomized trials, because the degree of mechanical lung inflation or ventilatory support was altered considerably during the course of these investigations. In our patients APRV with and without spontaneous breathing was provided with the same V_E or Paw limits. Therefore, our results should reflect essentially the effect of unassisted spontaneous breathing during ventilatory support on cardiovascular and renal function.

Arterial pH in the absence of spontaneous breathing averaged 7.24 in our study. This is well above the pH values proposed as a buffering threshold by several recent multicenter study groups investigating lung protective mechanical ventilation [7, 8, 9]. We therefore saw no need to buffer our patients. However, we can not completely rule out that avoiding respiratory acidosis in the absence of spontaneous breathing during APRV, by increasing the ventilator rate, may have improved renal perfusion and function to the same extent as observed with spontaneous breathing. Despite an improvement in GFR at unchanged excretion of sodium, urine output did not increase in our patients with spontaneous breathing during APRV. These results may be explained by too short observation periods and by the fact that changes in GFR and renal excretion of sodium and water are not necessarily associated. Renal excretion is mainly determined by tubular, i.e. GFR-independent, processes unless GFR is extremely low.

Patients with acute renal failure receiving dopaminergic and diuretic drugs were excluded from the study to eliminate any confounding effects of those drugs. Thus, the results presented may not be applicable to patients with pre-existing renal dysfunction. However, since patients with ALI are at risk of developing acute renal failure, which is associated with an increase in mortality [1, 2], any intervention that prevents a worsening of renal perfusion and function may be of clinical relevance.

The results of this study demonstrate that spontaneous breathing with APRV provides better arterial blood oxygenation and systemic blood flow and, thereby, contributes to improved renal perfusion and function. Maintaining spontaneous breathing during partial ventilatory support may therefore be of advantage in preventing a deterioration of renal perfusion and function in patients with ALI. Further studies are warranted to test our results obtained during APRV, using other modalities of partial ventilatory support and in patients with impaired renal function.

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References

1. Montgomery AB, Stager MA, Carrico CJ, Hudson (1985) Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 132:485–489
2. De Mendoca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F (2000) Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 26:915–921
3. Sladen A, Laver MB, Pontoppidan H (1968) Pulmonary complications and water retention in prolonged mechanical ventilation. N Engl J Med 279:448–453
4. Pinsky MR (1997) The hemodynamic consequences of mechanical ventilation: an evolving story (see comments). Intensive Care Med 23:493–503
5. Steinhoff HH, Kohlhoff RJ, Falke KJ (1984) Facilitation of renal function by intermittent mandatory ventilation. Intensive Care Med 10:59–65
6. Annat G, Viale JP, Bui XB, Hadj AO, Benzoni D, Vincent M, Gharib C, Motin J (1983) Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins. Anesthesiology 58:136–141
7. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White PJ, Wiener CM, Teeter JG, Dodd, Almog Y, Piantadosi S (1999) Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients (see comments). Crit Care Med 27:1492–1498
8. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clementi E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume Reduction in ARDS. Am J Respir Crit Care Med 158:1831–1838
9. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS (1998) Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group (see comments). N Engl J Med 338:355–361
10. Howes TQ, Deane CR, Levin GE, Baudouin SV, Moxham J (1995) The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. Am J Respir Crit Care Med 151:378–383
11. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network (see comments). N Engl J Med 342:1301–1308
12. Sydow M, Burchardi H, Ephraim E, Zielmann S, Croizier TA (1994) Long-term effects of two different ventilatory modes on oxygenation in acute lung injury. Comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med 149:1550–1556
13. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, Mutz N (2001) Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 164:43–49
14. Stock MC, Downs JB, Frolicher DA (1987) Airway pressure release ventilation. Crit Care Med 15:462–466
15. Putensen C, Rasanen J, Lopez FA, Downs JB (1994) Effect of interfacing between spontaneous breathing and mechanical cycles on the ventilation-perfusion distribution in canine lung injury. Anesthesiology 81:921–930
16. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J (1999) Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 159:1241–1248
17. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R (1994) Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med 20:225–232
18. Goris RJ, Te BT, Nuytinck JK, Gimbrere JS (1985) Multiple-organ failure. Generalized autodestructive inflammation? Arch Surg 120:1109–1115
19. Le Gall J, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
20. Brunner JX, Wolff G (1988) Measuring esophageal pressure with an esophageal balloon, pulmonary function indices in critical care patients. Springer, Berlin Heidelberg New York, pp 118–121
21. Hoeft A (1995) Transpulmonary indicator dilution: an alternative approach for hemodynamic monitoring. In: Vincent JL (ed) Yearbook of Intensive Care and Emergency Medicine. Springer, Berlin Heidelberg New York, pp 593–605
22. Duarte CG, Preuss HG (1993) Assessment of renal function – glomerular and tubular. Clin Lab Med 13:33–52
23. Ramsay MA, Savege TM, Simpson BR, Goodwin R (1974) Controlled sedation with alphaxalone-alphadolone. BMJ 2:656–659
24. Hickling KG, Walsh J, Henderson S, Jackson R (1994) Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 22:1568–1578
25. Feihl F, Eckert P, Brimioulle S, Jacobs O, Schaller MD, Melot C, Naeije R (2000) Permissive hypercapnia impairs pulmonary gas exchange in the acute respiratory distress syndrome. Am J Respir Crit Care Med 162:209–215
26. Weber T, Tschernich H, Sitzwohl C, Ullrich R, Germann P, Zimpfer M, Sladen RN, Huemer G (2000) Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 162:1361–1365
27. Carvalho CR, Barbas CS, Medeiros DM, Magaldi RB, Lorenzi FG, Kairalla RA, Deheinzelin D, Munhoz C, Kaufmann M, Ferreira M, Takagaki TY, Amato MB (1997) Temporal hemodynamic effects of permissive hypercapnia associated with ideal PEEP in ARDS. Am J Respir Crit Care Med 156:1458–1466
28. Thorens JB, Jolliet P, Ritz M, Chevrolet JC (1996) Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome (see comments). Intensive Care Med 22:182–191

29. Puybasset L, Stewart T, Rouby JJ, Cluzel P, Mourgeon E, Belin MF, Arthaud M, Landault C, Viars P (1994) Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome (see comments). Anesthesiology 80:1254–1267
30. Sharkey RA, Mulloy EM, O'Neill SJ (1998) Acute effects of hypoxaemia, hyperoxaemia and hypercapnia on renal blood flow in normal and renal transplant subjects. Eur Respir J 12:653–657
31. Sharkey RA, Mulloy EM, O'Neill SJ (1999) The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. Chest 115:1588–1592
32. Sharkey RA, Mulloy EM, Kilgallen IA, O'Neill SJ (1997) Renal functional reserve in patients with severe chronic obstructive pulmonary disease (see comments). Thorax 52:411–415
33. Hall JE (1982) Regulation of renal hemodynamics. Cardiovascular physiology IV (Vol 26). In: Guyton A (ed) International review of physiology. University Park Press, Baltimore, pp 243–321
34. Offner B, Czachurski J, Konig SA, Seller H (1994) Different effects of respiratory and metabolic acidosis on preganglionic sympathetic nerve activity. J Appl Physiol 77:173–178
35. Steinhoff H, Falke K, Schwarzhoff W (1982) Enhanced renal function associated with intermittent mandatory ventilation in acute respiratory failure. Intensive Care Med 8:69–74
36. Jarnberg PO, De Villota ED, Eklund J, Granberg PO (1978) Effects of positive end-expiratory pressure on renal function. Acta Anaesthesiol Scand 22:508–514
37. Rossaint R, Jorres D, Nienhaus M, Oduah K, Falke K, Kaczmarczyk G (1992) Positive end-expiratory pressure reduces renal excretion without hormonal activation after volume expansion in dogs. Anesthesiology 77:700–708