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EXPERIMENTAL

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Ventilation with biphasic positive airway pressure in experimental lung injury

Influence of transpulmonary pressure on gas exchange and haemodynamics

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Abstract *Objective:* We investigated whether improvement in ventilation perfusion ($\dot{V}_A/\dot{Q}$) distribution during mechanical ventilation using biphasic positive airway pressure (BIPAP) with spontaneous breathing may be attributed to an effectively increased transpulmonary pressure (P_{TP}) and can also be achieved by increasing P_{TP} during controlled ventilation. *Design:* In 12 pigs with saline lavage-induced lung injury we compared the effects of BIPAP to pressure-controlled ventilation with equal airway pressure (PCV_{AW}) or equal transpulmonary pressure (PCV_{TP}) on $\dot{V}_A/\dot{Q}$ distribution assessed by the multiple inert gas elimination technique (MIGET). *Setting:* Animal laboratory study. *Measurements and results:* Intrapulmonary shunt was 33±11% during BIPAP, 36±10% during PCV_{AW} and 33±15% during PCV_{TP} (p= n.s.). BIPAP resulted in higher PaO_2 than PCV_{AW} (188±83 versus 147±82 mmHg, p<0.05), but not than PCV_{TP} (187±139 mmHg). Oxygen delivery was significantly higher during BIPAP (530±109 ml/min) versus 374±113 ml/min during PCV_{AW} and 353±93 ml/min during PCV_{TP} (p<0.005). Tidal volume with PCV_{TP} increased to 11.9±2.3 ml/kg, compared to 8.5±0.8 with BIPAP and 7.6±1.4 with PCV_{AW} (p<0.001) and cardiac output decreased to 3.5±0.6 l/min (BIPAP 4.9±0.8 and PCV_{AW} 3.9±0.8, p<0.006). *Conclusions:* In experimental lung injury, BIPAP with preserved spontaneous breathing was effective in increasing regional P_{TP}, since pressure-controlled ventilation with the same P_{TP} resulted in similar gas exchange effects. However, PCV_{TP} caused increased airway pressures and tidal volumes, whereby, with BIPAP, less depression of oxygen delivery and cardiac output were observed. BIPAP could be useful in maintaining pulmonary gas exchange and slightly improving oxygenation without interfering with circulation as strongly as PCV does.

Keywords Ventilation-perfusion ratio · Respiratory distress syndrome, adult · Positive-pressure respiration · Positive-pressure breathing

Introduction

Severe impairment of oxygenation in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is caused by inhomogeneous ventilation-perfusion ($\dot{V}_A/\dot{Q}$) distribution and an increased shunt fraction. The supine position and mechanical ventilation have been shown to aggravate $\dot{V}_A/\dot{Q}$ mismatch further by redirection of blood flow to poorly (low $\dot{V}_A/\dot{Q}$) or non-ventilated areas (intrapulmonary shunt, $\dot{Q}_S/\dot{Q}_T$) [1, 2, 3]. Therapeutic strategies during mechanical ventilation aim to re-open collapsed alveolar areas, leading to shunt reduction and a more homogeneous $\dot{V}_A/\dot{Q}$ distribution. Active movement of the diaphragm during spontaneous breathing has been proposed to promote recruitment of dorsal atelectasis in experimental forms of ALI [4] as well as in ARDS

patients [5]. Putensen et al. [4] observed improvements in $\dot{V}_A/\dot{Q}$ distributions during unsynchronised spontaneous breathing with biphasic positive airway pressure (BIPAP) as compared to pressure-controlled ventilation (PCV) using equal minute ventilation or airway pressures, respectively. In contrast, pressure-support ventilation (PSV) did not improve $\dot{V}_A/\dot{Q}$ distributions [2, 6, 7]. Recruitment is determined by regional transpulmonary pressure (P_{TP}), which needs to be much higher in the dependent lung regions to keep alveoli open [8]. P_{TP} is defined as the difference between airway opening pressure (P_{AW}) and pleural pressure (P_{PL}), the latter being positive during positive pressure inspiration and negative in spontaneous respiratory effort. We therefore hypothesised that improvements in $\dot{V}_A/\dot{Q}$ distributions with unsynchronised spontaneous breathing during BIPAP are attributable to an effectively increased regional P_{TP} in dependent lung regions, which can also be achieved by increasing P_{AW} during PCV.

Materials and methods

The study protocol was approved by the administrative Animal Care Committee and conducted according to the NIH convention. In 14 pre-medicated female German-bred pigs, weighing 29±2.1 kg, anaesthesia was induced intravenously with thiopentone 5 mg/kg, followed by a continuous infusion of 5–8 mg/kg per h thiopentone, remifentanyl 0.05–0.1 μg/kg per min and ketamine 5–8 mg/kg per h. The animals were endotracheally intubated and ventilated according to the study protocol. A 16-gauge catheter (Vygon, Ecouen, France) was inserted into the femoral artery and a 8.5 Fr venous sheath (Arrow Deutschland, Erding, Germany) into the femoral vein. A pulmonary artery catheter (SP5107, 7.5F, Becton Dickinson, Heidelberg, Germany) was positioned under transduced pressure guidance. Since the animals were fasted, a bolus of 500 ml hydroxyethyl starch 200/0.5 was given and a continuous infusion of Ringer's solution was started at 5 ml/kg per h. Urine output was measured via a transurethral catheter. Temperature was maintained at 37.3±0.4°C during the experiment using an active warming air flow blanket (WarmTouch, Mallinckrodt).

Cardiovascular and ventilatory measurements

Systolic (SAP) and mean arterial pressures (MAP), central venous (CVP), mean pulmonary artery (MPAP) and pulmonary capillary wedge pressures (PCWP) were directly measured and recorded, with the reference point set at mid-chest level. Cardiac output (CO) was determined by thermal dilution as the mean of three measurements taken at end-expiration (Datex-Ohmeda AS/3, Duisburg, Germany).

Gas flow was measured between the tracheal tube and the Y-piece of the ventilator circuit by a differential pressure transducer (CP100, Bicore, Irvine, CA, USA). Tidal volume (V_T) was derived from the integrated flow signal. Spontaneous breathing during BIPAP was estimated from the flow-volume curves recorded. Airway pressure (P_{AW}) was measured at the proximal end of the tracheal tube. Oesophageal pressure (P_{ES}) was measured with a balloon catheter (SmartCath, Bicore). Correct placement was verified using the occlusion technique [9]. The change in oesophageal pressure, calculated as ΔP_{ES} by the Bicore monitor, was used to set inspiratory pressures (P_{INSP}). When calculating transpulmonary pressure (P_{TP}): since $P_{TP} = P_{AW} - P_{PL}$, ΔP_{ES} must add to P_{TP}, if unsynchronised spontaneous breathing efforts are present, thus the calculated $P_{TP} = P_{AW} + \Delta P_{ES}$ (Fig. 1).

Hypoxic pulmonary vasoconstriction (HPV), as an important modulator of oxygenation [10], was analysed in respect to its stimulants, PAO_2 and $P\bar{v}O_2$. PVR, calculated as (MPAP – PCWP)/CO was considered to represent HPV adequately, since pulmonary vascular tone could not be measured at constant flow conditions [11].

Gas analysis

Arterial and mixed venous blood samples were collected simultaneously and analysed immediately for blood gases (Abl 510, Radiometer, Copenhagen, Denmark). Oxygen-saturated haemoglobin ($HbaO_2$ and $Hb\bar{v}O_2$) was measured with a species-adjusted co-oximeter (OSM3, Radiometer).

Determination of $\dot{V}_A/\dot{Q}$ distribution was done by multiple inert gas elimination technique (MIGET, [12]), which has been described in detail before [4, 7, 13]. Intrapulmonary shunt, dead space and low and high $\dot{V}_A/Q$ ratios were calculated from these. Briefly, six inert gases with different solubility in blood (sulphur hexafluoride, ethane, cyclopropane, enflurane, ether and acetone) dissolved in saline solution are constantly infused to steady state elimination from the lung. Analysis of simultaneously drawn arterial and mixed venous blood samples together with expiratory-collected gaseous samples using a gas chromatograph (GC 14 B, Shimadzu, Duisburg, Germany) enables the mathematical construction of a 50-compartment model of different $\dot{V}_A/\dot{Q}$ distributions against blood flow or ventilation, respectively. The fraction of blood flow ($\dot{Q}_T$) through essentially not ventilated alveoli ($\dot{V}_A/\dot{Q}$ <0.005) is called

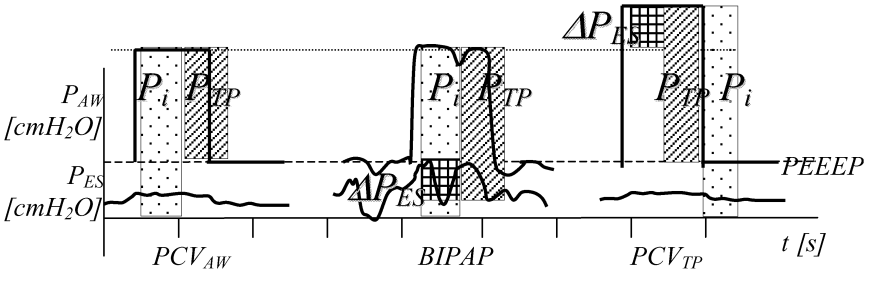

Fig. 1 Experimental protocol. Measurements and parameters used to set inspiratory pressures. *PCV_{AW}* pressure-controlled ventilation (*PCV*) with airway pressure equal to that of BIPAP, *PCV_{TP}* PCV with transpulmonary pressure equal to that of BIPAP, *P_i* set inspiratory pressure, *ΔP_{ES}* change in oesophageal pressure, *P_{TP}* calculated transpulmonary pressure

shunt, regions with poor ventilation in relation to their perfusions are called low $\dot{V}_A/\dot{Q}$ (0.005–0.1). Non-perfused, ventilated areas (dead space, $\dot{V}_A/\dot{Q}$ >100) can be differentiated from high $\dot{V}_A/\dot{Q}$ regions, with poor perfusion (10< $\dot{V}_A/\dot{Q}$<100). From the fractions of shunt and blood flow through ventilated regions, the absolute values of pulmonary shunt flow and pulmonary non-shunt flow were calculated by multiplying with CO. The standard deviation of the logarithmic distribution of perfusion (log$SD\dot{Q}$) and ventilation (log$SD\dot{V}_E$), as well as the mean $\dot{V}_A/\dot{Q}$ ratio of perfusion and ventilation, were calculated as measurements of mismatch of blood flow and ventilation against $\dot{V}_A/\dot{Q}$. The exactness of the mathematical modelling was tested by calculating the residual sum of squares (RSS).

Experimental protocol

Experimental ALI was induced by surfactant depletion achieved through repeated lung lavage [14]. ALI was considered stable when there was a constant PaO_2/FIO_2 ratio below 100 mmHg for at least 60 min (ALI measurement). The FIO_2 was kept at 1.0 throughout the protocol. Animals were then ventilated with an EVITA IV ventilator (Draeger Medical, Lübeck, Germany):

BIPAP	The low pressure level was set at 5 cmH_2O and the high level to achieve a tidal volume (V_T) of 8 ml/kg. Sedation and respiratory rate (RR) were adjusted to allow spontaneous breathing. A spontaneous portion (V_{SPONT}) of total ventilation (V_E) was targeted at 20%. Inspiratory/expiratory (I:E) ratio was maintained at 1:1.
PCV_{AW} (equal P_{AW})	Pressure-controlled ventilation with PEEP at 5 cmH_2O. The animals were sedated to apnoea. Inspiratory pressure (P_{INSP}) was set to be equal to that in BIPAP or to reach a V_T of 8 ml/kg.
PCV_{TP} (equal P_{TP})	P_{INSP} was set according to $P_{INSP,BIPAP}$ + $\Delta P_{ES,BIPAP}$ (Fig. 1) and PEEP at 5 cmH_2O. A subsequent increase in tidal volume was anticipated. RR and inspiration time were adjusted to reach comparable values for V_E and I:E ratios. The absence of spontaneous breathing during pressure-controlled modes was verified by the P_{ES} trace.

For the setting of equal P_{TP}, PCV_{TP} had always to be preceded by BIPAP, thus three different orders were possible, to which animals were randomly assigned. A 60 min equilibration interval was allowed between measurements, no recruitment manoeuvres were undertaken during the study period. After finishing the experiment, the animals were killed with a thiopentone overdose.

Statistical analysis

The data are expressed as means ± standard deviation. If non-parametric, Friedman's test for dependent groups showed significant values, for comparison between ventilator modes Wilcoxon's signed ranks test was performed with p values less than 0.05 considered as statistically significant. Correlations between PVR, CO and shunt were analysed using Pearson's coefficient (SPSSWIN 10.0, SPSS, Chicago, USA).

Results

Of the 14 animals, 2 died from massive increase of pulmonary pressure and persistent right heart failure before completing the protocol. No difference in baseline physiological characteristics could be observed between these and the animals completing the study period. All basic physiological conditions were comparable among the groups, except sedation, which was less during BIPAP (Table 1).

Haemodynamic and respiratory parameters

The haemodynamic data are presented in Table 2. CO was significantly higher during BIPAP. The protocol requirements regarding equality of airway or transpulmonary pressures were fully met, since the peak pressures (PIP) measured in PVC_{AW} and BIPAP as well as the P_{TP} calculated in PCV_{TP} and BIPAP were almost identical (Table 3). PIP was significantly higher in PCV_{TP} as compared to the other modes. Spontaneous ventilation (V_{SPONT}) during BIPAP accounted for 17% of total ventilation (V_E). As expected, V_T increased during PCV_{TP} (p=0.003).

Gas exchange parameters

After partial recovery from the initial lung injury, changes in oxygenation were inconsistent. Four animals, which had received BIPAP as the first ventilatory mode, had considerable improvements in oxygenation, which did not

Table 1 Fluid management and sedation

	ALI[a]	BIPAP	PCV_{AW}	PCV_{TP}
Total fluid (ml/kg per h)	13.2±4.2	14.8±2.9	15.2±2.8	15.6±2.8
Urine output (ml/kg per h)	9.1±5.0	9.2±4.7	8.9±3.9	9.1±4.0
Thiopentone (mg/kg per h)	4.0±1.9	2.2±1.1	5.6±1.8[b]	5.7±1.8[b]
Ketamine (mg/kg per h)	5.9±2.0	5.3±1.3	6.9±1.3	7.2±1.4
Remifentanyl (μg/kg per min)	0.17±0.1	0.02±0.04	0.21±0.12[b]	0.21±0.11[b]

Measurement times according to protocol: *ALI* induction of acute lung injury (for comparison only), *BIPAP* biphasic positive airway pressure ventilation, *PCV_{AW}* pressure-controlled ventilation with same airway pressure as in BIPAP, *PCV_{TP}* same transpulmonary pressure as in BIPAP
Data expressed as means ± SD
[a] ALI not included in analysis
[b] p<0.001 versus BIPAP

Table 2 Haemodynamic data

	ALI[a]	BIPAP	PCV_{AW}	PCV_{TP}
HR (min)	89±16	101±16[b]	85±14	80±12
MAP (mmHg)	108±13	97±10	102±14	94±10
CVP (mmHg)	7.0±2.6	5.9±1.6	6.9±2.1	6.6±1.8
MPAP (mmHg)	26.1±3.4	22.3±3.7	27.8±4.6[b]	25.8±5.7
PCWP (mmHg)	7.3±1.4	5.9±1.6	7.1±1.5	6.7±2.4
SVR (dyn.sec.cm^{-5})	1802±377	1540±366[c,d]	2084±583	2029±408
PVR (dyn.sec.cm^{-5})	341±114	282±108[c,d]	452±132	452±200
CO (l/min)	4.7±0.9	4.9±0.8[c,d]	3.9±1.1	3.5±0.6
SV (ml)	52.3±9.0	49.2±7.9[e]	45.5±7.8	45.1±8.0
DO_2 (ml/min)	421±111	530±109[c,d]	374±113	353±93
VO_2 (ml/min)	129±19	144±16	135±19	137±20

Measurement times according to protocol: *ALI* baseline measurement after induction of acute lung injury (for comparison only, not included in analysis), *BIPAP* biphasic positive airway pressure ventilation, PCV_{AW} pressure controlled ventilation with same airway pressure as in BIPAP, PCV_{TP} same transpulmonary pressure as in BIPAP
HR heart rate, *MAP* and *CVP* mean arterial and central venous pressures, *PCWP* pulmonary capillary wedge pressure, *MPAP* mean pulmonary artery pressure, *SVR* and *PVR* systemic and pulmonary vessel resistances, *CO* cardiac output, *SV* stroke volume, DO_2 oxygen delivery, VO_2 oxygen consumption
Data expressed as means ± SD
[a] ALI not included in analysis
[b] $p<0.02$ versus others
[c] $p<0.01$ versus PCV_{TP}
[d] $p<0.01$ versus PCV_{AW}
[e] $p<0.05$ versus others

Table 3 Respiratory measurements

	ALI[a]	BIPAP	PCV_{AW}	PCV_{TP}
$V_{T\ mech}$ (ml/kg)	7.8±0.8	8.4±0.8	7.6±1.5	11.9±2.3[b]
$V_{E,tot}$ (l/min)	6.3±1.5	7.6±0.9	6.1±1.7[b]	7.5±2.2
V_{SPONT} (l/min)	0	1.3±0.7[c]	0	0
RR_{mech} (min)	28±4	26±3[d]	28±4	22±4[e]
RR_{SPONT} (min)	0	20±9[c]	0	0
$T_{i/tot}$	0.51±0.03	0.51±0.03	0.49±0.05	0.43±0.05[d]
PIP (cmH_2O)	28.3±3.6	23.9±3.4	23.7±3.6	30.2±4.4[b]
MIP (cmH_2O)	11.8±1.1	13.5±1.7	13.9±2.5	15.5±2.1[d]
ΔP_{ES} (cmH_2O)	0.8±0.7	6.2±1.3[c]	0.8±0.5	0.8±0.4
P_{TP} (cmH_2O)	24.1±3.7	25.2±3.5	19.4±3.6[c]	26.0±4.4

Measurement times according to protocol: *ALI* baseline measurement after induction of acute lung injury (for comparison only, not included in analysis), *BIPAP* biphasic positive airway pressure ventilation, PCV_{AW} same airway pressure as in BIPAP, PCV_{TP} same transpulmonary pressure as in BIPAP
$V_{T\ mech}$ mechanical tidal volume, $V_{E,tot}$ total minute ventilation, V_{SPONT} spontaneous portion of V_E, RR_{mech} set ventilatory rate, RR_{SPONT} spontaneous RR, $T_{i/tot}$ inspiratory/total time ratio, *PIP* peak inspiratory pressure, *MIP* mean inspiratory pressure, ΔP_{ES} changes in oesophageal pressure, P_{TP} transpulmonary pressure
Values are means ± SD
[a] ALI not included in analysis
[b] $p<0.01$ versus others
[c] $p<0.0001$ versus others
[d] $p<0.05$ versus others
[e] $p<0.01$ versus PCV_{AW}

change further in the course of the experiment. PaO_2 was significantly increased during BIPAP (p=0.041) as compared to PCV_{AW}. There were no differences between BIPAP and PCV_{TP} (Fig. 2, Table 4). $PaCO_2$ decreased significantly during PCV_{TP}, even though V_E between BIPAP and PCV_{TP} remained unchanged and was less during PCV_{AW} (p=0.013). The highest oxygen delivery (DO_2) could be observed during BIPAP ($p<0.0001$, Fig. 3), while there was no significant change in oxygen consumption (VO_2). This resulted in a significantly lower oxygen extraction ratio during BIPAP (28%; PCV_{AW} 38%; PCV_{TP} 42%; $p<0.05$).

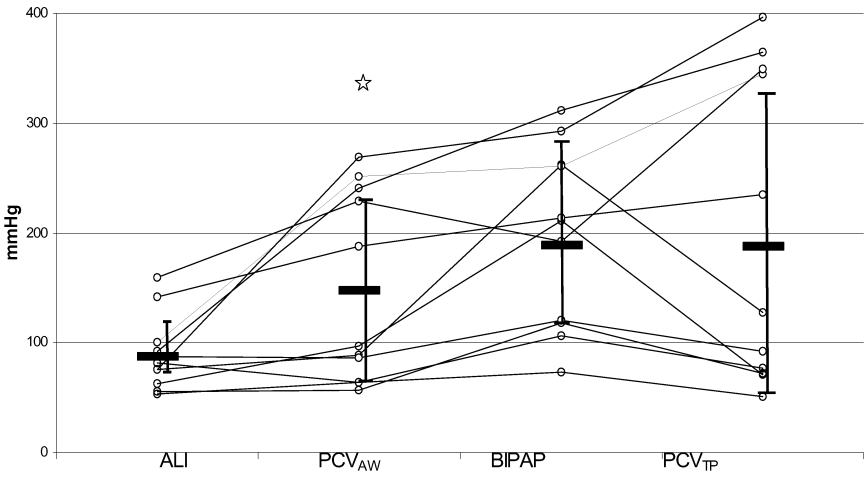

Fig. 2 Arterial partial oxygen pressure (PaO_2). *Solid lines* individuals, *dashes* means ± 1SD. Measurement times: *ALI* lung injury after induction (not included in analysis), PCV_{AW} PCV with airway pressure equal to that of BIPAP, PCV_{TP} PCV with transpulmonary pressure equal to that of BIPAP. *p<0.05 BIPAP versus PCV_{AW}

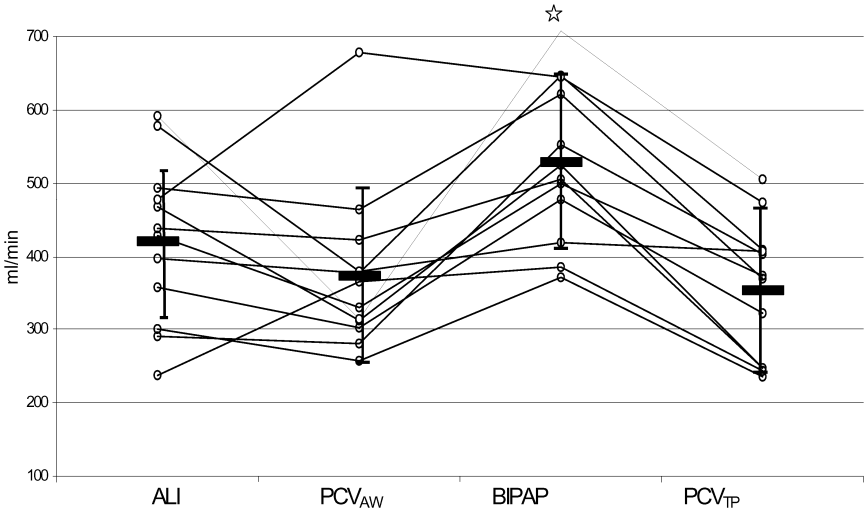

Fig. 3 Oxygen delivery (DO_2). *Solid lines* individuals, *dashes* means ± 1SD. Measurement times: *ALI* lung injury after induction (not included in analysis), PCV_{AW} PCV with airway pressure equal to that of BIPAP, PCV_{TP} PCV with transpulmonary pressure equal to that of BIPAP. *p<0.05 versus others

Multiple inert gas elimination technique measurements

The complete data are presented in Table 4. $\dot{Q}_S/\dot{Q}_T$ was the same during BIPAP and PCV_{TP} and tended to be higher during PCV_{AW}, but did not reach statistical significance. Low $\dot{V}_A/\dot{Q}$ fraction reacted in an inverse manner, suggesting a redirection of blood flow from low $\dot{V}_A/\dot{Q}$ to shunt regions during PCV_{AW}. There was a high degree of $\dot{V}_A/\dot{Q}$ dispersion, as represented by increased log$SD\dot{Q}$, but there were no differences between modes. Overall, we could not observe differences between modes in comparing fractions of blood flow to regions with high and normal $\dot{V}_A/\dot{Q}$ to regions with low $\dot{V}_A/\dot{Q}$ and shunt. However, if absolute values of blood flow through shunt regions (pulmonary shunt flow) and ventilated regions (pulmonary non-shunt flow) are calculated depending on CO, both were significantly higher during BIPAP (p<0.005).

Ventilation was most evenly distributed during PCV_{TP} with approximately 71% of the ventilation going to ideal V_A/Q regions, and dead space was significantly lowest during PCV_{TP} as compared to BIPAP and PCV_{AW} (p<0.005). The quality of MIGET measurements was good as the residual sums of squares (RSS) were less than 3.5 in 58.7% and less than 10 in 91.6% with no differences between modes.

Discussion

We did not find significant differences in pulmonary oxygenation between BIPAP ventilation, allowing up to 20% spontaneous breathing, and PCV, if applied at comparable transpulmonary pressures. An increase in dead space ventilation was observed during BIPAP. Even though there were no differences in oxygenation indices if P_{TP} was kept the same, differences in haemodynamics

Table 4 Gas exchange and multiple inert gas elimination technique (MIGET) data

	ALI	BIPAP	PCV_{AW}	PCV_{TP}
pHa	7.39±0.06	7.36±0.06	7.36±0.09	7.44±0.11
PaO_2 (mmHg)	86.7±33	188±83[a]	147±82	187±138
$PaCO_2$ (mmHg)	43±7	44±8	45±11	36±11[b]
$P\bar{v}O_2$ (mmHg)	42±5	52±6[c,d]	43±8	39±6
$HbaO_2$ (%)	90.7±6.4	95.8±4.6[b]	91.7±7.4	91.8±9.3
$\dot{Q}$ Shunt ($\dot{V}_A/\dot{Q}<0.005$) (% of $\dot{Q}_T$)	46.9±7.8	32.8±1.8	35.5±10.4	33.4±14.5
$\dot{Q}$ Low ($0.005< \dot{V}_A/\dot{Q}<0.1$) (% of $\dot{Q}_T$)	3.2±4.3	8.3±7.8	6.1±7.0	7.9±6.0
$\dot{Q}$ Normal ($0.1< \dot{V}_A/\dot{Q}<10$) (% of $\dot{Q}_T$)	48.1±7.0	58.2±11.8	58.3±13.1	57.8±17.5
$\dot{Q}$ High ($10< \dot{V}_A/\dot{Q}<100$) (% of $\dot{Q}_T$)	1.9±6.4	0.6±2.1	0.1±0.2	0.9±1.9
$\dot{V}$ Dead space ($\dot{V}_A/\dot{Q}>100$) (% of $\dot{V}_E$)	40.6±13.4	44.9±9.0[c,d]	36.4±8.2[d]	26.0±9.4
$\dot{V}$ Normal ($10> \dot{V}_A/\dot{Q}>0.1$) (% of $\dot{V}_E$)	56.2±13.7	53.2±7.8[d]	62.8±8.8[d]	70.7±11.0
logSD $\dot{Q}$	1.2±0.6	1.64±0.75	1.49±0.66	1.78±0.83
logSD $\dot{V}$	0.5±0.1	0.62±0.14	0.66±0.22	0.59±0.13
RSS	7.9±6.9	4.4±4.3	4.5±3.0	5.2±3.7
Pulmonary shunt flow (l/min)	2.18±0.59	1.59±0.53[b]	1.37±0.49	1.17±0.57
Pulmonary non-shunt flow (l/min)	2.46±0.56	3.30±0.81[c,d]	2.51±0.84	2.37±0.70

ALI baseline measurement after induction of lung injury (for comparison only, not included in analysis), *BIPAP* biphasic positive airway pressure ventilation, PCV_{AW} same airway pressure as in BIPAP, PCV_{TP} same transpulmonary pressure as in BIPAP, $HbaO_2$ oxygen saturated haemoglobin
Values are means ± SD
[a] $p<0.05$ versus PCV_{AW}
[b] $p<0.05$ versus others
[c] $p<0.005$ versus PCV_{AW}
[d] $p<0.005$ versus PCV_{TP}

showed a clear increase in DO_2 due to higher CO during BIPAP.

Validity of oesophageal pressure for calculation of transpulmonary pressure

Lung recruitment depends on the distribution of P_{TP}, which has been shown to correlate inversely to a vertical gradient from non-dependent to dependent lung regions [15]. We recognise that measuring oesophageal pressure (P_{ES}) instead of pleural pressure (P_{PL}) is a simplification, since there are regional differences in lung and chest wall mechanics. Pelosi et al. [8] have shown, in a lung injury model, that P_{PL} follows a vertical gradient, which itself decreases with increasing P_{AW}. Comparing the measurements of P_{PL} and P_{ES}, there was some bias in dependent and non-dependent regions, and good agreement only in the middle lung. However, the correlation between P_{PL} and P_{ES} was always good and they concluded that the changes in P_{ES} (ΔP_{ES}) were representative for P_{PL} changes in the same direction. Our study design was not targeted at absolute values for P_{TP}, but at comparable values between ventilator modes, and any systematic bias would be the same for each group and can be neglected for the purpose of our study.

Stability of lung injury model

The model of surfactant washout predominately causes atelectasis formation, at least in the short term. It has the advantage of being specific for changes in pulmonary function and recruitment without being affected by additional vascular or infectious injury. With the experience of over 100 experiments [7, 16, 17, 18, 19] and comparative studies showing equal effects of lung lavage and oleic acid induced lung injury [20], we think the observed effects would also be reproducible with other models. However, one limitation of the model is the dependency on successful recruitment. In those animals receiving BIPAP as the first intervention, obviously some effective, persistent recruitment took place. It cannot be clarified post hoc, if a derecruitment strategy implemented between the ventilation modes would have produced different behaviour.

Influence of sedation

Avoiding neuromuscular blocking agents, we sedated animals to apnoea for PCV modes. The haemodynamic data must be interpreted in view of the possibility that the improved haemodynamics during BIPAP were merely associated with lighter sedation. However, CO during BIPAP was comparable to the baseline measurements after induction of ALI (Table 2), where deeper sedation levels were present as well. The increase of DO_2 during BIPAP was also caused by a significant increase of its determinants ($HbaO_2$, PaO_2, Table 4) independently of mere sedation effects.

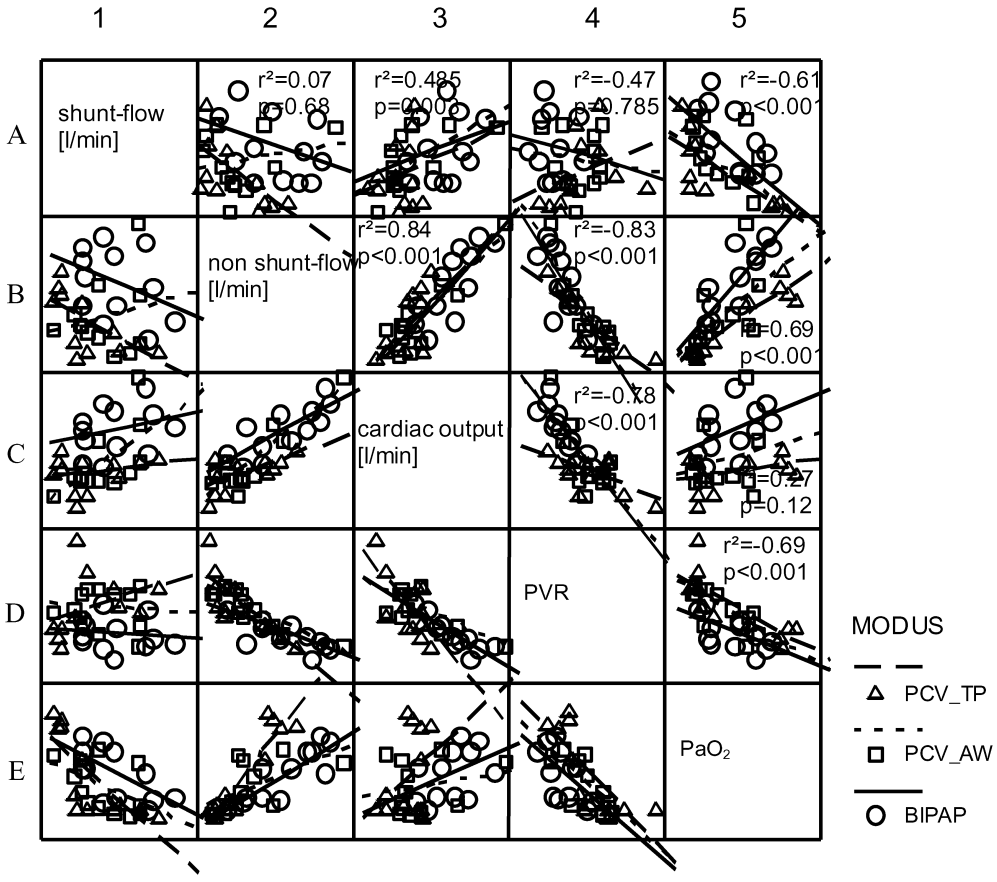

Fig. 4 Correlations between cardiac output (*CO*), pulmonary blood flow through shunted and non-shunted regions, pulmonary vascular resistance (*PVR*) and oxygenation. r^2 Pearson's correlation coefficient. PaO_2 did not correlate with CO (C5), but with PVR (D5), non-shunt flow (B5) and inversely with shunt flow (A5). CO modulated PVR (C4) and non-shunt flow (B3). Increased PVR significantly decreased non-shunt flow (B4), but not shunt flow (A4). Therefore, PVR was not effective in preserving oxygenation, but increased with decreasing PaO_2 (E4). No significant differences in correlations were found between breathing modes

Interpretation of shunt

The most surprising finding of our study was that, in contrast to previous findings, oxygenation was not directly correlated with $\dot{Q}_S/\dot{Q}_T$. The importance of hypoxic pulmonary vasoconstriction (HPV) has been impressively shown [10]. The main determinant of HPV ($P\bar{v}O_2$) is modulated by CO via DO_2 and hypoxemia per se. CO correlated positively [21, 22, 23] with shunt fraction under otherwise stable conditions. Even though CO and $P\bar{v}O_2$ increased with BIPAP, $\dot{Q}_S/\dot{Q}_T$ did not. Notably, no correlations were found between CO and oxygenation in any mode (Fig. 4, cell C5). Matrix correlation analysis revealed a highly significant correlation between PaO_2 and PVR (cell D5), shunt flow (A5) and non-shunt flow (B5). Only in PCV_{AW} mode there was a weak correlation between PaO_2 and shunt flow (r^2=–0.525, p=0.08). PVR correlated inversely with non-shunt flow (B4), but not with shunt flow (A4), whereby some mathematical coupling seems possible. In conclusion, in PCV_{AW} the HPV response to lowered $P\bar{v}O_2$ reduced non-shunt flow but did not influence shunt flow. In BIPAP, genuine alveolar recruitment and improved $\dot{V}_A/\dot{Q}$ matching might have been counterbalanced by $P\bar{v}O_2$-mediated attenuation of HPV, but still might have lead to improvements in oxygenation. During PCV with equal P_{TP}, oxygenation was not different from BIPAP, but CO was significantly depressed and PVR higher. This can be explained by an increase of HPV, but an increased alveolar ventilation is also possible.

In a clinical setting, Rossaint et al. could not demonstrate a positive correlation of $P\bar{v}O_2$ with $\dot{Q}_s/\dot{Q}_T$ in ARDS patients [23]. They concluded that decreased pulmonary vascular reactivity blunted HPV in ARDS patients. Interestingly, we also found only weak correlations between $P\bar{v}O_2$ and $\dot{Q}_s/\dot{Q}_T$ (r^2= –0.4, p=0.012 overall, insignificant within groups), but a good correlation between $P\bar{v}O_2$ and PVR (–0.69, p<0.001).

Effects of ventilation

Spontaneous breathing efforts seem to have a positive effect on oxygenation, but the mechanism is still discussed. Mechanical ventilation without diaphragm movement was demonstrated to produce atelectasis and increased shunt [24], and recruitment of dorsobasal atelectasis through active diaphragm movement has proved possible [1]. Work by Santak [25] suggested no change in $\dot{V}_A/\dot{Q}$ distribution if pressure support were combined with

SIMV and compared to controlled ventilation. Putensen et al. [4] demonstrated a reduction of pulmonary shunt, dead space ventilation and improved oxygenation, if spontaneous breathing were allowed using BIPAP, but not with PSV [6, 7], which is a breath-by-breath support of patient-triggered inspiratory efforts. In comparing BIPAP to PCV with equal P_{TP} our results could not reproduce the reduction of intrapulmonary shunt previously reported, which has been in the range of 7–16% [2, 4]. There are some methodological differences between our study and previous findings: in the study comparing BIPAP with and without spontaneous breathing giving equal V_E [2], P_{INSP} was not increased as much (4 cmH_2O as compared to 7 cmH_2O mean difference in our study), therefore probably not generating an equal P_{TP}. Also, V_T in our study necessarily increased to 12 ml/kg in PCV_{TP}. It could not have been equalled without changes in mean airway pressure or I:E ratio. As a result, a tidal recruitment during PCV_{TP} per se [8] cannot be ruled out completely.

Consistent with other findings [25, 26], dead space ventilation during BIPAP was increased, probably caused by an ineffectively high spontaneous respiratory rate with tidal volumes below or close to anatomic dead space. Also, there is no collateral ventilation in pigs, in contrast to dogs and humans [27, 28], which might be the reason for this lack of a protective mechanism in near-collapsed areas. This is in contrast to some previous results [2, 6], where redirection of blood flow through previously non-perfused dead space was speculated to be the mechanism. This effect, however, is limited and can be counteracted by a massive increase in anatomic dead space ventilation. In these studies [2, 6] $V_{E,SPONT}$ accounted only for variable amounts, 10–13% of total V_E, but it was 17% in our study. To date the optimum portion of spontaneous breathing remains unclear. Still, gas exchange was effective enough for an unchanged $PaCO_2$ and respiratory rates (in terms of diaphragm movements) even as high as 50 min^{-1} can be tolerated from a clinical point of view, if there are no signs of patient distress.

In conclusion, the data presented suggest that improvements in oxygenation during BIPAP are attributable to favourable hemodynamic stability and an effectively increased transpulmonary pressure in the dependent lung, since we could demonstrate equal effects on gas exchange if inspiratory pressures were increased to yield the same transpulmonary pressure during controlled ventilation. However, this resulted in increased airway pressures and tidal volumes, which are associated with worse outcome in ARDS patients [29, 30] and impairment of venous return [31, 32]. The effect of preserved diaphragm activity on the recruitment of previously atelectatic lung regions and a more homogeneous distribution of blood flow with redirection to normal $\dot{V}_A/\dot{Q}$ areas could not be demonstrated in our model. On the contrary, we conclude that, in evaluating different ventilation modes, the determination of the capacity of the pulmonary gas exchanger is inadequately represented by sole calculation of shunt fractions. More complex regulation mechanisms in an in-vivo system, e.g. HPV, have to be taken into account.

From this point of view, BIPAP could be useful in maintaining pulmonary gas exchange and slightly improving oxygenation without interfering with circulation as strongly as PCV does. These results contribute to the understanding of the physiological mechanisms during mechanical ventilation with preserved spontaneous breathing. Further studies need to assess the effect of spontaneous breathing activity on ventilator-associated lung injury and clinical outcomes in ALI patients.

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