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EXPERIMENTAL

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Acute hemodynamic changes during lung recruitment in lavage and endotoxin-induced ALI

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Abstract *Objective:* To assess acute cardiorespiratory effects of recruitment manoeuvres in experimental acute lung injury. *Design:* Experimental study in animal models of acute lung injury. *Setting:* Experimental laboratory at a University Medical Centre. *Animals:* Ten pigs with bronchoalveolar lavage and eight pigs with endotoxin-induced ALI. *Interventions:* Two kinds of recruitment manoeuvres during 1 min; a) vital capacity manoeuvres (ViCM) consisting in a sustained inflation at 30 cmH_2O and 40 cmH_2O; b) manoeuvres obtained during ongoing pressure-controlled ventilation (PCRM) with peak airway pressure 30 cmH_2O, positive end-expiratory pressure (PEEP) 15 and peak airway pressure 40, PEEP 20. Recruitment manoeuvres were repeated after volume expansion (dextran 8 ml/kg). Oxygenation, mean arterial, and pulmonary artery pressures, aortic, mesenteric, and renal blood flow were monitored. *Measurements and results:* Lower pressure recruitment manoeuvres (ViCM30 and PCRM30/15) did not significantly improve oxygenation. With ViCM and PCRM at peak airway pressure 40 cmH_2O, PaO_2 increased to similar levels in both lavage and endotoxin groups. Aortic blood flow was reduced from baseline during PCRM40/20 and ViCM40 by 57±3% and 61±6% in the lavage group and by 57±8% and 82±7% ($P<0.05$ vs PCRM40/20) in endotoxin group. The decrease in blood pressure was less pronounced. Prior volume expansion attenuated circulatory impairment. After cessation of recruitment hemodynamic parameters were restored within 3 min. *Conclusion:* Effective recruitment resulted in systemic hypotension, pulmonary hypertension, and decrease in aortic blood flow especially in endotoxinemic animals. Circulatory depression may be attenuated using recruitment manoeuvres during ongoing pressure-controlled ventilation and by prior volume expansion.

Keywords Acute lung injury · Lung recruitment · Bronchoalveolar lavage · Endotoxin · Hemodynamics · Oxygen delivery

Introduction

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are accompanied by atelectasis formation, increasing venous admixture, and arterial hypoxemia [1, 2]. Different recruitment manoeuvres (RMs), as proposed by the "open lung concept", have been used to expand lung volume and to improve gas exchange [3]. Application of a vital capacity manoeuvre, where the lungs are inflated to 40 cmH_2O during 15 s in healthy anesthetised subjects [4] and for 40 s in ARDS patients [5] has been used. RMs have also been performed in pressure-controlled ventilation using PEEP levels of 15–25 cmH_2O and increasing peak airway pressures (PAP) up

to 45–60 cmH_2O [6]. The optimal way of performing RMs is, however, still debated.

It is known that increased airway pressure and PEEP may have pronounced extrapulmonary effects [7]. The application of PEEP decreases cardiac output by reducing right ventricular preload and by increasing right ventricular afterload [8, 9]. The splanchnic organs are sensitive to the effects of increased PEEP due to decreased cardiac output, increased venous outflow pressure, pooling of blood, and organ compression [8, 10, 11, 12]. PEEP is known to influence renal function [13] by reduced renal blood flow, elevated renal venous pressure [14, 15], and hormonal responses [16, 17, 18]. In this study the acute effects of different RMs on arterial oxygenation, aortic, mesenteric and renal blood flow, and oxygen delivery were assessed in two experimental ALI models. In one group ALI was achieved by repeated bronchoalveolar lavage (BAL) with isotonic saline causing a lung injury with surfactant depletion [19, 20]. In the other group ALI was induced by infusion of endotoxin (ET) [21]. Two RMs were studied; a vital capacity manoeuvre (ViCM) with a sustained inflation and an RM during ongoing pressure-controlled ventilation (PCRM). Effects of RMs were studied in normovolemic animals and repeated after volume expansion.

Material and methods

The study was approved by the Committee for Ethical Review of Animal Experiments at Göteborg University and performed in accordance with NIH guidelines. Ten pigs (24–26 kg) were included in the BAL group and eight animals (28–33 kg) in the ET group.

Anaesthesia

Induction was performed using ketamine (Ketalar, Park-Davis, Sweden) 30 mg/kg and azaperon (Stresnil, Janssen-Cilag, Pharma, Austria) 80 mg intramuscularly. Anaesthesia was maintained by infusion of pentobarbitalnatrium (Apoteksbolaget, Sweden) 6 mg·kg·h and fentanyl (Fentanyl Pharmalink, Pharmalink, Sweden) 0.2 mg/h. Muscle relaxation was achieved by a bolus of pancuronium (Pavulon, Organon, Sweden) 0.1 mg/kg, followed by infusion 0.3 mg·kg·h. The pigs were tracheotomised and mechanically ventilated through an 8-mm endotracheal tube using a Servo 300 or 900C ventilator (Siemens-Elema, Sweden), volume-controlled ventilation (VC), tidal volume (TV) 8 ml/kg, respiratory rate (RR) 20/min, positive end-expiratory pressure (PEEP) 5 cmH_2O, inspiration-to-expiration ratio (I:E) 1:2 and FiO_2 0.5. Normovolemia was maintained by infusion of Ringer's solution with 2.5% glucose, 10 ml·kg·h, increased to 20 ml·kg·h after laparotomy. Anticoagulation was achieved by 2500 IE heparin (Heparin Leo, Leo Pharma, Sweden) intravenously, repeated after 4 h.

Preparation

Arterial and central venous lines were surgically placed and a pulmonary artery catheter (CCOmbo/SVO_2, Edwards Life Sciences, California, USA) inserted via the right internal jugular vein. Heart rate (HR), central venous pressure (CVP), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and mixed venous oxygen saturation (SvO_2) were monitored. Oxygen saturation (SpO_2) was recorded from the tail of the pig. A femoral artery and vein were cannulated and connected using silicon tubings. An on-line PaO_2 monitor (Polytrode pO_2 sensor, Polystan, Denmark, response time 20 s) was inserted in the circuit. Descending aortic blood flow (ABF) was determined using a transoesophageal echo-Doppler (Dynemo 3000, Sometec, France) positioned in the oesophagus. Ultrasonic flowmeter probes (Transsonic Systems, N.Y., USA) were placed around the portal vein and a renal artery to monitor mesenteric blood flow (QPV) and renal artery blood flow (QRA). The animals were placed in supine position. Respiratory rate, volumes, and pressures were measured using side stream spirometry. Inspiratory and expiratory fractions of oxygen and carbon dioxide (FiO_2, $FETO_2$, $FiCO_2$, $FETCO_2$) were measured with paramagnetic and infrared technology respectively (AS/3, Datex-Ohmeda, Finland).

Experimental procedure for BAL animals

After preparation the ventilator was set at VC 8 ml/kg, RR 20/min, I:E 1:2, PEEP 10 cmH_2O, FiO_2 1.0 and repeated BAL with saline (total amount 9–15 l) was performed to establish ALI [19, 20]. The procedure was finished when there were no visual signs of surfactant in the fluid exchange and PaO_2 was less than 10 kPa at FiO_2 1.0. The animals were allowed to stabilise for 1 h with PEEP set at 5–10 cmH_2O to avoid severe hypoxemia. The experimental protocol started with an RM to expand the lungs initially followed by derecruitment with reduction of PEEP to 0 cmH_2O and then resuming the initial ventilatory settings in each animal, PEEP kept at 5–10 cmH_2O. Four RM, each preceded by derecruitment, were used in random order. Two ViCMs were performed with sustained inflation at 30 cmH_2O and 40 cmH_2O (ViCM30 and ViCM40) for 1 min using CPAP mode and two PCRMs performed in pressure-controlled mode, RR 40, I:E 1:1 and PAP 30 cmH_2O and PEEP 15 (PCRM30/15) or PAP 40 and PEEP 20 (PCRM40/20) for 1 min.

MAP, MPAP, QPV, QRA, SvO_2, SpO_2, PaO_2, and ABF were recorded every 15 s during the RMs. The animals were volume loaded using dextran 70 (Macrodex®, Pharmalink AB, Sweden), 8 ml/kg over 30 min followed by RMs repeated in the same order as before. Following cessation of RMs, hemodynamics were followed for 3 min. After the experiment the animal was killed during deepened anaesthesia.

Experimental procedure for endotoxin animals

Anaesthesia and preparation was carried out as described above. *E. coli* lipopolysaccharide endotoxin, serotype 0111:B4, (Sigma, St. Louis, USA) was dissolved in saline and heated to 37 °C. The infusion was started at a rate of 2.5 g·kg·h and increased stepwise during 30 min to a rate of 20 g·kg·h kept for 2.5 h. During the last 30 min the animals were volume resuscitated using hetastarch solution (Heas-steril, Meda, Sweden) to baseline cardiac output. The study protocol then followed the BAL-animal protocol but using only the high airway pressure (PAP 40 cmH_2O) RMs i.e., ViCM40 and PCRM40/20 in random order, each for 1 min before and after volume expansion with dextran solution 8 ml/kg.

Calculations and statistics

Respiratory, hemodynamic and shunt calculations were made using standard formulae. Global oxygen delivery (DO_2global) was calculated from values for descending aortic blood flow and mesen-

teric (DO_2mes) and renal (DO_2ren) oxygen delivery from portal venous and renal artery blood flows respectively.

$$DO_2\text{global} = ABF \times ((1.34 \times Hb \times SaO_2) + (0.225 \times PaO_2)) \quad (1)$$

$$DO_2\text{mes} = QPV \times ((1.34 \times Hb \times SaO_2) + (0.225 \times PaO_2)) \quad (2)$$

$$DO_2\text{ren} = QRA \times ((1.34 \times Hb \times SaO_2) + (0.225 \times PaO_2)) \quad (3)$$

Values are presented as mean±SEM unless stated otherwise. Analysis of variance (ANOVA) for repeated measures were performed followed by Fisher's PLSD and if significant, paired *t*-test was used to evaluate changes from baseline to 1 min. Comparisons of pulmonary shunt at baseline and 1 min were made using paired *t*-test. The change in ABF and shunt during RMs was calculated using linear regression analysis. A *P*-value <0.05 was considered statistically significant.

Results

BAL animals, low and high pressure RMs

The hemodynamic and respiratory parameters for the BAL group during the low pressure RMs (PAP 30 cmH_2O) at baseline and at 1 min of recruitment are presented in Table 1 and corresponding data for the high pressure RMs

Table 1 Baseline data and values at 1 minute of recruitment in the BAL-group using low pressure recruitment manoeuvres presented as mean ± SEM. (ViCM30; vital capacity manoeuvre with sustained inflation with 30 cm H_2O and PCRM30/15; recruitment manoeuvre in pressure controlled ventilation with peak airway pressure 30 cm H_2O, PEEP 15, RR 40/min and I:E 1:1).

	Recruitment manoeuvre	Volume status	Bronchoalveolar lavage group	
			Baseline	1 min
PaO_2 (kPa)	ViCM 30	Normovolemia	6.7±0.6	14.1±5.0
		Volume expansion	7.1±0.5	10.9±2.4
	PCRM 30/15	Normovolemia	6.9±0.7	13.7±3.5
		Volume expansion	7.1±0.6	14.8±3.7
SvO_2 (%)	ViCM 30	Normovolemia	50±4	44±5
		Volume expansion	53±4	51±2[b]
	PCRM 30/15	Normovolemia	51±4	54±5[c]
		Volume expansion	54±4	59±3
Shunt (%)	ViCM 30	Normovolemia	64±4	50±6[a]
		Volume expansion	65±4	54±7
	PCRM 30/15	Normovolemia	66±6	43±6[a]
		volume expansion	65±4	45±6[a,c]
Mean arterial pressure (mmHg)	ViCM 30	Normovolemia	110±5	95±7[a]
		Volume expansion	112±4	100±7
	PCRM 30/15	Normovolemia	108±6	90±8[a]
		Volume expansion	118±7	105±9[a,b]
Mean pulm artery pressure (mmHg)	ViCM 30	Normovolemia	30±1.7	38±1.7[a]
		Volume expansion	36±1.3	43±1.0[a,b]
	PCRM 30/15	Normovolemia	29±1.7	31±2.0[a,c]
		Volume expansion	35±1.5	36±1.8[b,c]
Aortic blood flow (l/min)	ViCM 30	Normovolemia	3.6±0.2	2.4±0.3[a]
		Volume expansion	3.8±0.3	3.1±0.3[a,b]
	PCRM 30/15	Normovolemia	3.6±0.2	2.5±0.2[a]
		Volume expansion	4.2±0.4	3.5±0.5 [a,b,c]
Portal venous blood flow (ml/min)	ViCM 30	Normovolemia	1277±166	857±116[a]
		Volume expansion	1413±179	1082±160[a,b]
	PCRM 30/15	Normovolemia	1358±194	1091±171[a,c]
		Volume expansion	1420±212	1157±157[a]
Renal artery blood flow (ml/min)	ViCM 30	Normovolemia	184±28	165±28[a]
		Volume expansion	230±22	196±25[a,b]
	PCRM 30/15	Normovolemia	193±29	176±26[a]
		Volume expansion	211±28	194±27[a]
Global oxygen delivery (ml/min)	ViCM 30	Normovolemia	338±21	220±18[a]
		Volume expansion	336±33	306±39[b]
	PCRM 30/20	normovolemia	330±29	273±15[a,c]
		Volume expansion	369±27	350±30[b,c]
Mesenteric oxygen delivery (ml/min)	ViCM 30	Normovolemia	125±21	88±15[a]
		Volume expansion	130±23	98±15[a]
	PCRM 30/15	Normovolemia	132±28	126±26
		Volume expansion	132±29	118±21
Renal oxygen delivery (ml/min)	ViCM 30	Normovolemia	17.1±2.3	16.8±2.7
		Volume expansion	18.7±2.7	18.4±2.5
	PCRM 30/15	Normovolemia	18.4±3.1	20.4±3.2
		Volume expansion	18.6±3.0	19.9±3.1

[a] *P*<0.05 compared to baseline values
[b] *P*<0.05 compared to normovolemia
[c] *P*<0.05 compared to ViCM30

Table 2 Baseline data and values at 1 minute of recruitment presented as mean ± SEM for the bronchoalveolar lavage group and the endotoxin group. (ViCM40, vital capacity recruitment manoeuvre with a sustained inflation with 40 cm H_2O and PCRM40/20, recruitment manoeuvre in pressure control ventilation with peak

	Recruitment manoeuvre	Volume status	Bronchoalveolar lavage group		Endotoxin group	
			Baseline	1 min	Baseline	1 min
PaO_2 (kPa)	ViCM 40	Normovolemia	6.7±0.7	29±8[a]	23±6	39±10
		Volume expansion	6.8±0.6	48±6[a,b]	19±7	47±9[a]
	PCRM 40/20	Normovolemia	6.9±0.6	49±8[a,c]	22±6	53±6[a]
		Volume expansion	7.0±0.6	57±6[a]	20±6	53±10[a]
SvO_2 (%)	ViCM 40	Normovolemia	49±5	51±5	61±5	57±6[a]
		Volume expansion	48±4	62±2[a,b]	63±4	58±7
	PCRM 40/20	Normovolemia	52±4	60±4[a,c]	63±5	57±7[a]
		Volume expansion	52±4	66±4[a]	67±2	64±5
Shunt (%)	ViCM 40	Normovolemia	66±5	35±8[a]	32±7	20±6[a]
		Volume expansion	64±5	22±3[a]	36±5	20±5[a]
	PCRM 40/20	Normovolemia	67±4	24±6[a,c]	31±5	14±4[a]
		Volume expansion	66±4	23±6[a]	39±5	19±3[a,b]
Mean arterial pressure (mmHg)	ViCM 40	Normovolemia	110±6	73±7[a]	67±8	39±9[a]
		Volume expansion	112±4	80±5[a,b]	76±9	50±8[a,b]
	PCRM 40/20	Normovolemia	107±5	69±6[a]	70±7	47±7[a]
		Volume expansion	116±7	84±7[a,b]	76±10	60±7[a,b]
Mean pulm artery pressure (mmHg)	ViCM 40	Normovolemia	29±1.8	43±1.1[a]	35±1.9	41±2.8
		Volume expansion	37±1.7	48±1.1[a,b]	41±2.0	47±2.3[a,b]
	PCRM 40/20	Normovolemia	29±1.5	34±1.5[a,c]	36±2.1	37±2.5[c]
		Volume expansion	36±1.9	38±1.5[a,b,c]	42±1.2	42±1.7[b,c]
Aortic blood flow (l/min)	ViCM 40	Normovolemia	3.6±0.2	1.5±0.3[a]	3.3±0.5	0.6±0.3[a]
		Volume expansion	4.0±0.3	2.0±0.2[a,b]	4.3±0.5	1.6±0.5[a,b]
	PCRM 40/20	Normovolemia	3.9±0.2	1.6±0.1[a]	3.1±0.6	1.2±0.3[a]
		Volume expansion	4.0±0.2	2.5±0.2[a,b]	4.3±0.5	2.4±0.5[a,b,c]
Portal venous blood flow (ml/min)	ViCM 40	Normovolemia	1288±201	638±139[a]	755±61	203±83[a]
		Volume expansion	1280±161	769±150[a]	1010±106	397±73[a,b]
	PCRM 40/20	Normovolemia	1530±214	776±143[a,c]	775±76	360±85[a,c]
		Volume expansion	1510±194	924±139[a,c]	1103±90	608±60[a,b,c]
Renal artery blood flow (ml/min)	ViCM 40	Normovolemia	209±31	156±32[a]	128±45	67±57[a]
		Volume expansion	230±22	195±20[b]	149±35	75±39[a]
	PCRM 40/20	Normovolemia	210±35	139±23[a]	154±47	89±54[a]
		Volume expansion	226±31	193±26[b]	159±36	117±43[a]
Global oxygen delivery (ml/min)	ViCM 40	Normovolemia	329±28	157±22[a]	416±66	91±42[a]
		Volume expansion	334±29	262±23[a,b]	491±61	211±66[a,b]
	PCRM 40/20	Normovolemia	370±33	212±17[a,c]	405±72	141±48[a]
		Volume expansion	352±33	297±29[b]	481±50	301±61[a,b]
Mesenteric oxygen delivery (ml/min)	ViCM 40	Normovolemia	134±28	83±17[a]	96±6	30±13[a]
		Volume expansion	124±25	102±19	112±8	51±11[a,b]
	PCRM 40/20	Normovolemia	152±27	101±17[a]	101±10	40±14[a,c]
		Volume expansion	136±27	108±16	123±8	76±9[a,b,c]
Renal oxygen delivery (ml/min)	ViCM 40	Normovolemia	19±3	18±4	16±6	9.4±8[a]
		Volume expansion	19±2	22±2	17±4	10±6[a]
	PCRM 40/20	Normovolemia	20±3	18±2	20±6	11±8[a]
		Volume expansion	19±3	23±3[a]	18±4	15±6

[a] $P<0.05$ compared to baseline values
[b] $P<0.05$ compared to normovolemia
[c] $P<0.05$ compared to ViCM40

(PAP 40 cmH_2O) in Table 2. Relative changes from baseline during high pressure RMs are shown in Fig. 1 and Fig. 2. Significantly greater improvement in oxygenation was achieved during recruitment with higher airway pressure levels (40 cmH_2O vs 30 cmH_2O, $P<0.01$) where PCRM40/20 was superior to ViCM40 ($P<0.01$). Recruitment with the higher pressure levels also caused significantly more negative circulatory effects with more pronounced decreases in MAP ($P<0.01$ both ViCM and PCRM) and ABF ($P<0.01$ and $P<0.05$ for ViCM and PCRM, respectively) than the lower airway pressure level. MPAP increased significantly during recruitment, especially during ViCM ($P<0.01$ vs PCRM, both pressure levels).

Volume expansion (dextran solution, 8 ml/kg) resulted in an increase in CVP from 5±1 mm Hg to 9±1 mm Hg

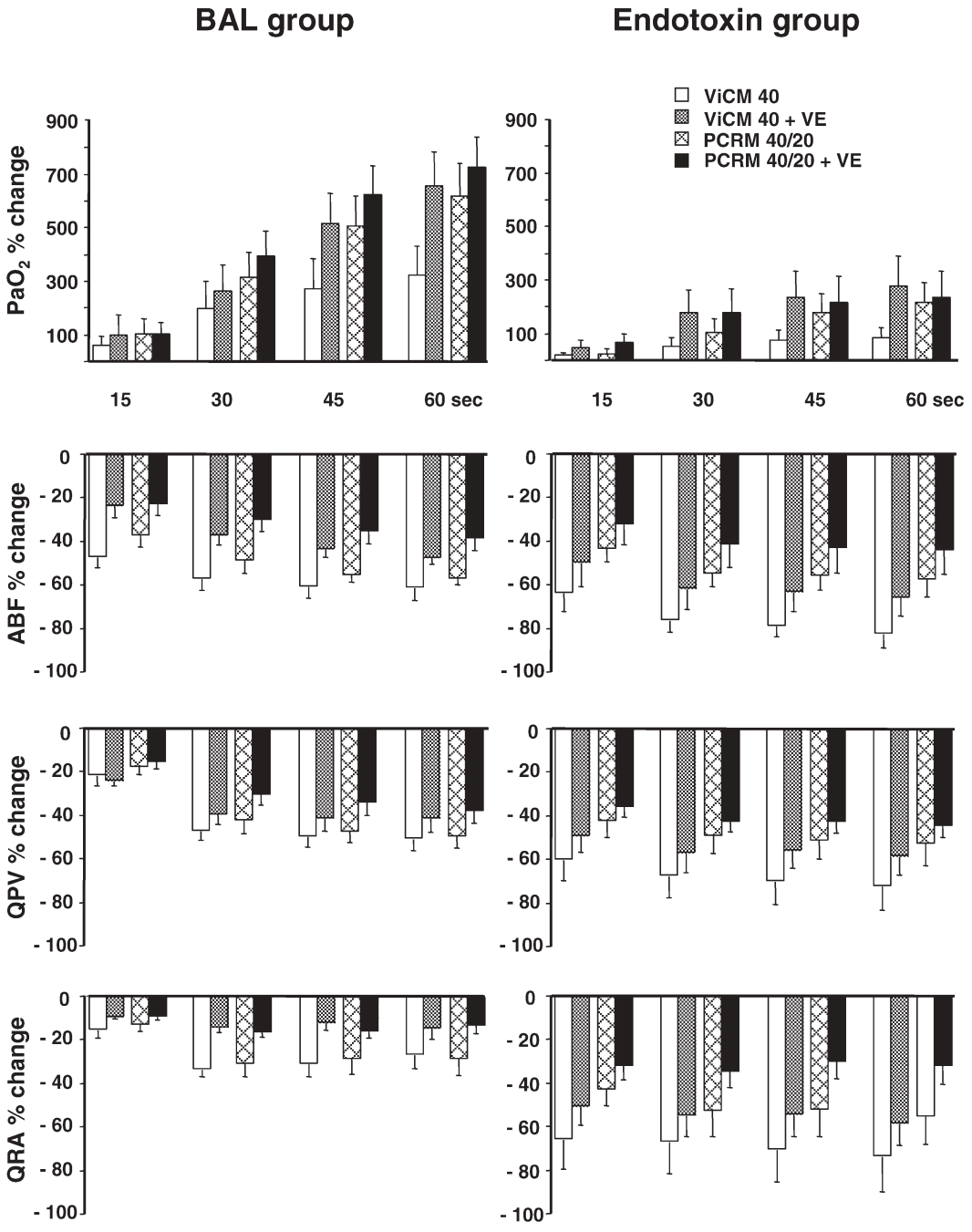

Fig. 1 Improvement in arterial oxygenation (PaO_2) and reductions in aortic blood flow (ABF), mesenteric blood flow (QPV), and renal artery blood flow (QRA) presented as relative changes from baseline at 15 s, 30 s, 45 s, and 60 s of recruitment using either vital capacity manoeuvre (ViCM40) or pressure-controlled recruitment manoeuvre (PCRM40/20) in bronchoalveolar lavage (BAL) and endotoxin-induced ALI. Bars grouped together indicate the same recruitment manoeuvre before and after volume expansion (VE).

(P<0.05), but had only minor effect on ABF at baseline (see Table 1 and Table 2). Volume expansion attenuated the decrease in ABF induced by the two RMs (P<0.01 both ViCM and PCRM, low- and high-pressure RMs). Despite a marked effect on arterial oxygenation, there was a significant decrease in the combined effect of recruitment on circulation and blood oxygenation, i.e., global DO_2 during the recruitment procedures due to the negative effect on ABF. The decrease in global DO_2 was greater during the ViCM compared to the PCRM (P<0.05,

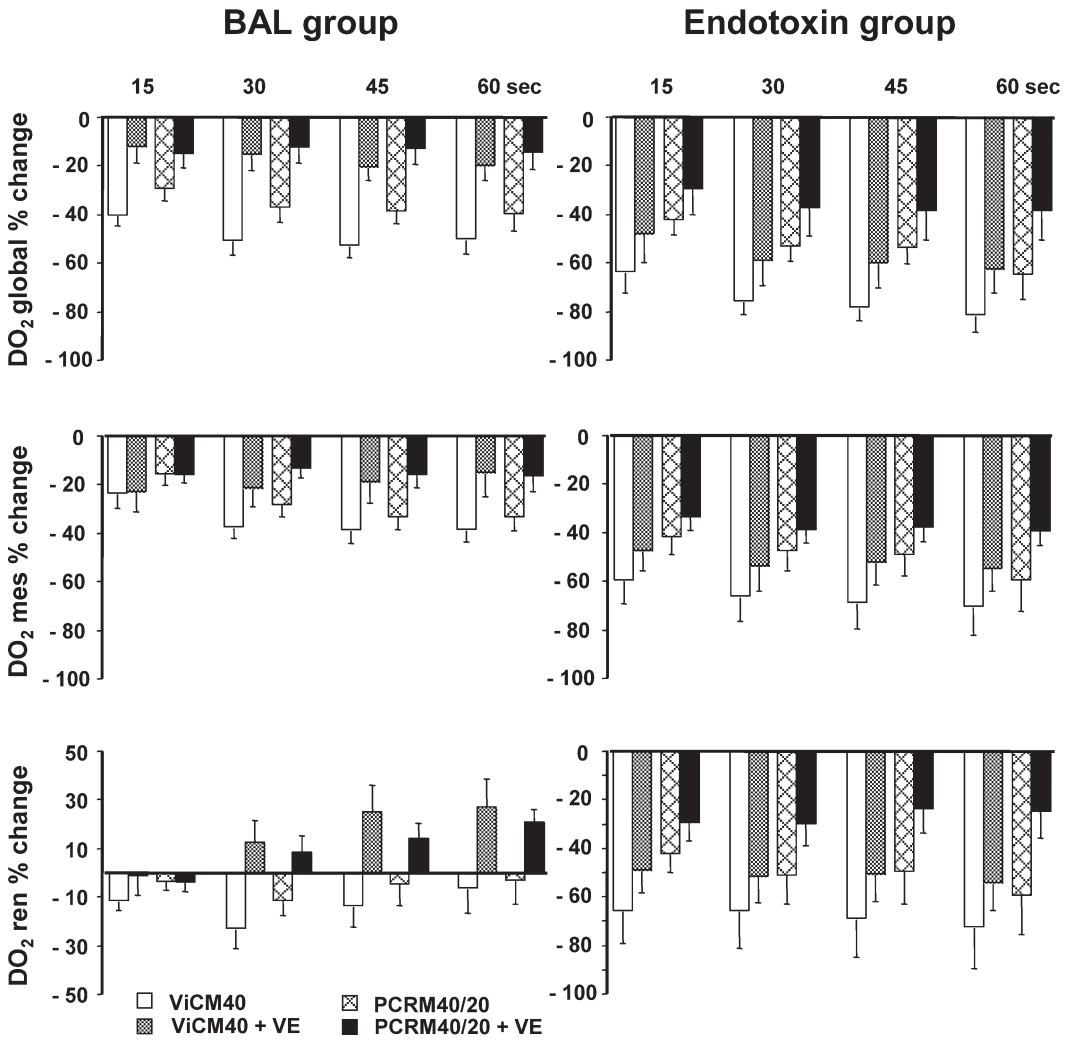

Fig. 2 The effect on global (DO_2global), mesenteric (DO_2mes), and renal (DO_2ren) oxygen delivery as relative changes from baseline at 15 s, 30 s, 45 s, and 60 s of recruitment using either vital capacity manoeuvre (ViCM40) or pressure-controlled recruitment manoeuvre (PCRM40/20) in bronchoalveolar lavage (BAL) and endotoxin-induced ALI. Bars grouped together indicate the same recruitment manoeuvre before and after volume expansion (VE).

both pressure levels). Volume expansion prior to recruitment attenuated the decrease in global DO_2, but the decrease was not statistically significant during PCRM40/20 or during lower pressure RMs.

The reduction in QPV and mesenteric DO_2 paralleled the reduction in ABF and global DO_2 during RM but were not significantly improved by volume expansion.

Renal blood flow and renal DO_2 were not significantly changed during recruitment in normovolemic animals. Following volume expansion there was an increase in renal DO_2 during a PCRM40/20 ($P<0.05$).

After cessation of RMs hemodynamic parameters gradually returned towards baseline, ABF being 86% (mean, range 27–124%) of baseline at 1 min and 96% (range 62–139%) of baseline at 3 min.

Endotoxin animals, high-pressure RMs

Data from six of the eight animals subjected to endotoxin infusion is presented in Table 1 and Fig. 1 and Fig. 2. Two pigs did not complete the protocol as they died in circulatory failure following endotoxin infusion. Endotoxin infusion lowered MAP and ABF with PaO_2 at baseline being around 20 kPa at FiO_2 1.0, corresponding to a shunt around 30%. During recruitment PaO_2 increased to levels similar to that observed during recruitment in the BAL-group (see Table 2). RMs induced severe circulatory depression with marked decrease in ABF, QPV, and QRA as well as in global, mesenteric, and renal oxygen delivery. The reduction in QPV and DO_2mes were significantly

more pronounced during a ViCM compared to a PCRM ($P<0.05$ both).

Endotoxin animals responded to volume expansion (dextran solution, 8 ml/kg) with increase in CVP from 7±1 mmHg to 10±1 mmHg ($P<0.05$). Volume expansion also attenuated circulatory effects of RMs in the ET-group.

The relative changes in global and regional hemodynamics for the BAL- and ET-groups are shown in Fig. 1 and Fig. 2. Generally, greater decreases in ABF, QPV and QRA and in corresponding oxygen delivery were observed during RMs in the ET-group compared to the BAL-group and particularly during ViCMs.

After cessation of RMs in the ET-group ABF had returned to 81% (mean, range 40–119%) of baseline at 1 min and 103% (range 89–129%) at 3 min. Within 1–3 min after RMs, MAP, MPAP, QPV, and QRA all had returned to baseline levels.

Discussion

The main findings of this study were that: (1) RMs with high inspiratory pressure levels (40 cmH_2O vs 30 cmH_2O) were needed to achieve rapid and pronounced improvement in oxygenation in BAL-induced ALI in animals; (2) high-pressure RMs were associated with more negative hemodynamic effects which were generally more severe if performed as vital capacity manoeuvres compared to RMs performed by ongoing pressure-controlled ventilation; (3) despite improved oxygenation during RMs, a significant reduction in global oxygen delivery was observed; (4) in the BAL-induced ALI, RMs was associated with generally more pronounced reduction in mesenteric versus renal blood flow and oxygen delivery; (5) RMs performed in an endotoxin model of ALI was associated with greater negative circulatory effects than those performed in a BAL-model of ALI; and (6) prior volume expansion could partially attenuate circulatory depression induced by RMs.

Animal models of ALI

Recent clinical studies have pointed out subgroups of patients with ALI/ARDS based on the aetiology and duration of lung injury [22, 23, 24, 25]. It is logical that different experimental models of ALI should be used to mimic the heterogeneity of ALI/ARDS. In the present study we used a BAL-model in which repeated bronchoalveolar lavage was performed to achieve a reproducible and pronounced decrease in oxygenation and a model with endotoxin-induced lung injury where deterioration in gas exchange was more variable between animals and less pronounced than in the BAL-model.

In both models, however, RMs induced pronounced improvement in oxygenation to similar levels (although from different baselines). It has been suggested that the improvement in oxygenation in this situation could be due to several factors. In a study in ARDS-patients, Dantzker et al. observed that PEEP and high tidal volume ventilation resulted in parallel decrease in shunt and cardiac output together with an improvement in arterial oxygenation [26]. In the present study, RMs resulted in substantial decrease in aortic blood flow as well as shunt reduction and improvement in oxygenation. In contrast to the study by Dantzker et al we found no correlation ($r=0.1$) between the degree of reduction in ABF and the reduction in pulmonary shunt fraction. Furthermore, when the decrease in ABF during RMs was attenuated by prior volume expansion reduction in pulmonary shunt still occurred to a similar extent. This indicates that the decrease in ABF is not a prerequisite for the shunt reduction and improvement in oxygenation observed in this study during RMs.

In this as well as in previous studies [19, 20] we did observe that the BAL-model exhibited a prominent alveolar collapse and is responsive to different RMs if sufficient pressure is applied. This model is more responsive to RMs than other experimental models of ALI [22, 23] and could correspond to surfactant depletion in the early stage of ALI. In contrast, endotoxin infusion damaged pulmonary endothelial cells leading to increased permeability and interstitial oedema [21, 23]. Extrapulmonary effects of endotoxin infusion are more pronounced than in BAL-animals. Thus, hemodynamics were generally more unstable in the ET-group which also was reflected by two pigs dying from circulatory failure before the recruitment protocol was implemented.

Circulatory effects of RMs

The safety and efficacy of RMs are still not clear. In previous studies most investigators have used ViCMs using airway pressures of 30–60 cmH_2O for 15–40 s [5, 22, 27, 28]. Fujino et al. [29] studied effects of RMs in a sheep model with lavage-induced ARDS where hemodynamic measurements were performed at the end of the RMs using bolus thermodilution. Only modest changes in cardiac output were observed. In the present animal study, and in a study performed in ARDS patients [5], more pronounced effects of RMs was observed using continuous Doppler monitoring of aortic blood flow. It is possible that in order to detect shortlasting but important effects during RMs on-line monitoring of central hemodynamics may be valuable [5, 22, 28, 29, 30].

In the present study, using a BAL-model of ALI/ARDS ViCM with pressure levels of 30 cmH_2O was not sufficient to achieve more than a moderate (n.s.) increase in oxygenation during a 60-s manoeuvre. A more effec-

tive RM using a ViCM with a pressure level of 40 cmH_2O was associated with pronounced circulatory side effects with a decrease in ABF of 61±6%. Generally, we observed using continuous monitoring that the relative reduction in ABF was much more pronounced than the decrease in MAP (34±5% during ViCM40 in BAL animals). Monitoring of changes in arterial pressure thus underestimates true effects of RMs which can be detected by continuous blood flow monitoring.

Circulatory effects using RMs during ongoing pressure control ventilation are less documented. In this study we observed less pronounced circulatory effects of this RM as compared to the ViCM especially in the ET-group although PCRMs produced a comparable improvement in oxygenation. This is probably a consequence of intermittent lowering of peak airway pressures from 40 cmH_2O with each breath, resulting in a lower mean intrathoracic pressure and improved venous return compared to a sustained ViCM at 40 cmH_2O. Performing RMs during ongoing ventilation may also be preferable to a ViCM to avoid further hypercapnia and decrease in pH which might increase pulmonary artery pressures and right ventricular afterload [31, 32].

A number of factors may determine the degree of hemodynamic effects of RMs. In this study we observed that RMs in endotoxin-induced ALI was associated with more marked circulatory effects than in BAL-induced ALI. This may mimic the clinical situation in patients with sepsis-induced ALI and unstable circulation which may then be especially vulnerable to recruitment with ViCM. Another factor is volume status. We observed that volume expansion by dextran solution only had minor effects on aortic blood flow at baseline in the BAL-group. Still, it did attenuate the hemodynamic effect induced by RMs indicating that volume expansion could be used to counteract circulatory side effects of RMs although maintenance of fluid balance in ALI/ARDS may limit this option. We also noted that volume expansion resulted in significant better improvement in oxygenation during ViCM40 in the BAL-group. This could be due to the high oxygen extraction during this manoeuvre as a consequence of pronounced circulatory depression. In endotoxin-induced ALI volume expansion was even more beneficial, improving ABF at baseline prior to recruitment as well as attenuating parts of the dramatic effects of RMs. Again, this emphasises the importance of individually evaluating volume status prior to RMs.

Following cessation of the RMs, ABF and MAP returned to baseline levels during the first 3 min in agreement with previous observations [5]. It may be argued that these shortlasting hemodynamic alterations can be acceptable in terms of patient safety. One problem is, however, that the degree of hemodynamic impairment with a combination of pulmonary hypertension, systemic hypotension, and decrease in aortic blood flow/cardiac output may be variable in animals/humans and possibly life-threatening in a hypovolemic patient with sepsis as suggested by the profound hemodynamic alterations observed in the endotoxin group in our study.

During the last decade the open lung concept and the use of RMs has been advocated with the use of airway pressure up to 60 cmH_2O to fully open up the lungs [3, 6]. This, and other studies, indicates that these recommendations may need to be modified and that before RM are advocated as routine procedures their safety and efficacy should be evaluated in controlled clinical trials.

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