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Hemodynamics and Renal Function During Low Frequency Positive Pressure Ventilation with Extracorporeal CO_2 Removal *

A Comparison with Continuous Positive Pressure Ventilation

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Abstract. Six lambs were anesthetized and connected in venovenous mode to a Membrane Lung for Extracorporeal CO_2 removal. The animals underwent several hours periods of continuous positive pressure ventilation (CPPV), at 5 cmH_2O positive end expiratory pressure (PEEP), alternated with several hours periods of low frequency positive pressure ventilation (5 cmH_2O PEEP, 2 b.p.m.) with extracorporeal CO_2 removal (LFPPV-$ECCO_2R$). During LFPPV-$ECCO_2R$ compared with CPPV, cardiac output increased by 26%, pulmonary vascular resistances and systemic vascular resistances decreased by 28% and 22% respectively. The renal funtion improved significantly during LFPPV-$ECCO_2R$ compared with CPPV, i.e. urinary flow, creatinine clearance and osmolar clearance increased by 50%, 37% and 52% respectively. In these experiments LFPPV-$ECCO_2R$, a form of completely artificial ventilation, seems to prevent hemodynamic and renal complications of CPPV.

Key words: artificial ventilation, lung and end positive pressure ventilation, apnea, hemodynamic, renal function, membrane lung, extracorporeal circulation.

Introduction

Both hemodynamic [29, 18] and hepato-renal [20, 31, 19] derangements have been reported during continuous positive pressure ventilation (CPPV). Such alterations have been attributed in part to positive end expiratory pressure (PEEP). However, during intermittent mandatory ventilation (IMV) at low mechanical respiratory rate (RR), hemodynamics are substantially less affected [6]. Recently we have described a new form of respiratory management, low-frequency positive pressure ventilation with extracorporeal CO_2 removal (LFPPV-$ECCO_2R$) [10].

In this way the lungs are kept continuously inflated with positive pressure and are ventilated once or twice per minute, some oxygen is supplied by diffusion and mass movement into the natural lungs, and the great bulk of total carbon dioxide produced is removed by a carbon dioxide membrane lung (CDML) [25].

We have suggested that this form of pulmonary ventilation could reduce or prevent barotrauma of CPPV and avoid its systemic and regional complications [10]

The aim of this work was to compare hemodynamic changes and hepato-renal function during LFPPV-$ECCO_2R$ and during CPPV at the same level of PEEP (5 cmH_2O).

Material and Methods

Surgical Preparation

Six sheep, weighing between 24 and 28 kg, were anesthetized with thiopental and paralyzed with Tubocurarine. The animals were tracheostomized and cystostomized. Wire reinforced polyurethane catheters were advanced through the external jugular vein into the inferior vena cava for blood drainage and into the superior vena cava for blood return. The distal part of both jugular veins was cannulated to prevent cerebral oedema. A thermodilution Swan Ganz catheter was positioned in the pulmonary artery

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and a polyvinyl catheter was inserted into a common carotid artery. After surgery the animals were allowed to fully recover (30 – 60 min), and were then placed in a cage maintained at 30°C. The sheep were then slightly sedated, paralyzed and connected to the extracorporeal circuit (ECC) for venovenous bypass.

Extracorporeal Circuit

Blood was pumped through a Kolobow SciMed membrane lung (2.5 m^2 surface area) at a blood flow ranging between 600 and 1000 ml min^{-1}. The perfusion circuit was first flushed with carbon dioxide, and was then primed with heparinized (8 U ml^{-1}) Ringer's lactate [23]; after priming, the Ringer's lactate was replaced with fresh heparinized sheep blood to avoid hemodilution. The extracorporeal blood flow was monitored with an extracorporeal blood flow meter (Biotronix flow meter, model 615). The hemoglobin oxygen saturation of blood entering the membrane lung was monitored continuously with an "on line" oxymeter (Optisat) [36]. The membrane lung was ventilated with humified room air at flows ranging between 5 and 8 l min^{-1}, at 10 cmH_2O pressure, measured with a Collins spirometer. The CO_2 concentration of gas effluent from the membrane lung was measured with a Beckman CO_2 Analyzer model LB2.

Animal Monitoring

Pulmonary Function: Both in CPPV and in LFPPV the animals were ventilated with a servo ventilator mod. 900B at 5 cmH_2O positive end expiratory pressure (PEEP). The inspiration/expiration ratio was 1:2 and inspiratory pause was 33% of the total cycle. Ventilatory flow rate and tracheal pressure (EMT transducer) were recorded on mingograf 34 ink recorder. A small teflon catheter was placed through the tracheostomy tube, advanced to the level of the carina through which in LFPPV-ECCO$_2$R 100% oxygen flowed during end expiratory pause at a rate of 200 ml min^{-1}, at 5 cmH_2O pressure.

A water valve was positioned between a calibrated oxygen source and the teflon tube. The oxygen not consumed by the natural lung during end expiratory pause was vented through the water valve, as previously shown during apnoeic oxygenation with ECCO$_2$R [24].

The functional residual capacity (FRC) was measured by helium dilution technique at atmospheric pressure (Heliometer Collins). Total static compliance was computed from tracheal pressure readings after insufflation with 100 ml of room air. The expired gas was collected in a Collins Spirometer and analyzed for oxygen and carbon dioxide with a Beckman mod. OM11 and LB2. In CPPV periods, using standard formulas, we computed alveolar $PO_2(PAO_2)$, oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$). During LFPPV-ECCO$_2$R periods the above parameters were measured as follows: $\dot{V}CO_2$ equalled the CO_2 removed through the CDML, the amount of CO_2 removed through the lung ventilation being negligible. The O_2 consumption was measured by keeping the animals in apnea over a period of 2 – 3 minutes: the volume of continuously added oxygen through the teflon tube required to maintain 5 cmH_2O pressure in the natural lungs (no bubbling in the water valve), plus oxygen transport across the CDML equalled metabolic consumption [24]. The O_2 transferred by the membrane lung (in v-v mode) was about 15% total $\dot{V}O_2$, the rest being provided by diffusion through the natural lungs.

The alveolar gases were measured by direct sampling from the trachea inlet at a constant rate of 8 ml sec^{-1} and analyzed with Beckman analyzer OM11 and LB2. Alveolar gas was presumed to be present when the PCO_2 plateau in the pulmonary gas equalled the PCO_2 in arterial blood.

Blood Gases: Blood gases were measured in an ABL1 radiometer. The hemoglobin and oxygen hemoglobin saturation was measured with a micro blood analyzer (MBA Carlo Erba). The venous admixture ($\dot{Q}_{va}/\dot{Q}$) was calculated by the following equation

$$\dot{Q}_{va}/\dot{Q} = \frac{C_cO_2 - C_aO_2}{C_cO_2 - C_{\bar{v}}O_2}$$

where CaO_2 was Hb × 1.39 × arterial hemoglobin saturation + (PaO_2 × 0.003), $C\bar{v}O_2$ = Hb × 1.39 × mixed venous blood oxygen saturation + ($P\bar{v}O_2$ × 0.003), and CcO_2 was Hb × ideal hemoglobin oxygen saturation at PAO_2 + (PAO_2 × 0.003). The ideal oxygen hemoglobin saturation was computed using a nomogram for sheep blood at the prevailing PAO_2 [30].

Hemodynamics: Pulmonary and systemic artery pressures were measured with Elema Schönander EMT 34 transducers and recorded on mingograf 34 ink recorder.

Cardiac output (CO) was computed according to the Fick equation, i.e.

$$CO = \frac{\dot{V}O_2 \text{ of natural lungs}}{C_aO_2 - C_{\bar{v}}O_2}$$

Renal and Liver Function: The creatinine clearance, the osmolar output (Osmometer, Knauer) and the osmolar clearance were computed hourly according to standard equations. Bilirubin, SGPT, SGOT, and alkaline phosphatase were measured hourly.

Coagulation: Heparin at 300 units kg^{-1} was given just before cannulation and then was given by continuous infusion to maintain the activated clotting time (ACT) [14, 4] between 240 and 400 seconds; the actual dose of heparin ranged about 100 units kg^{-1}hr^{-1}. Blood hematocrit was measured by the microcentrifuge method. Platelet count was determined by phase microscopy. Fibrinogen was measured by enzymatic methods [35]. These tests were all determined in duplicate before surgery, at the time of cannulation, and 15, 30 and 60 minutes later. After bypass was begun, the blood tests were performed every four hours. All blood samples were taken from the arterial line.

Experimental Procedure

After starting the ECC the animals were ventilated for 2–3 hours until the hemodynamic parameters were completely stabilized. The ventilatory pattern was as follows: FIO_2 0.30, tidal volume (TV) 12 ml kg^{-1} and RR 16 min^{-1}. During this time there was no gas exchange through the extracorporeal apparatus (zero gas flow in the membrane lung). Following this, we compared two different modes of ventilation:

A) CPPV: FIO_2 = 0.30: TV = 12 ml kg^{-1}: RR = 16 b.p.m.: PEEP = 5 cmH_2O while on extracorporeal bypass without gas exchange across the membrane lung (zero gas flow).

B) LFPPV-ECCO$_2$R: FIO_2 = 0.30: TV = 12 ml kg^{-1}: RR = 2 b.p.m.: PEEP = 5 cmH_2O while on extracorporeal bypass with gas exchange across the membrane lung (gas flow on).

Both CPPV and LFPPV-ECCO$_2$R periods were for one hour and were randomly repeated in each animal for a total of up to 24 to 48 hours. Each animal had an average of 18 periods in CPPV and 18 periods in LFPPV-ECCO$_2$R. Measurements were made at the end of each hourly period in five out of the six animals studied. In one animal, the hemodynamic and urinary output were measured every five minutes and each study period in CPPV and LFPPV-ECCO$_2$R lasted 20 minutes, for a total of 6 hours. The fluid intake was kept constant at 10 ml kg^{-1}hr^{-1} during the first 2–3 hours, and successively at 6 ml kg^{-1}hr^{-1}. All animals survived the experimental procedure. The variance analysis of the collected data was performed according to Armitage [1].

Results

Throughout the study periods there was no change in metabolic activity ($\dot{V}O_2$ = 4.95 ml min^{-1} ± 0.80 (SE) in CPPV, and 4.9 ml min^{-1} ± 0.80 (SE) during LFPPV), and no change in base excess.

Pulmonary Function: The FRC was not affected when lowering the ventilation frequency from 16 b.p.m. to 2 b.p.m., while the total static compliance was significantly higher during CPPV then in LFPPV-ECCO$_2$R (Fig. 1.).

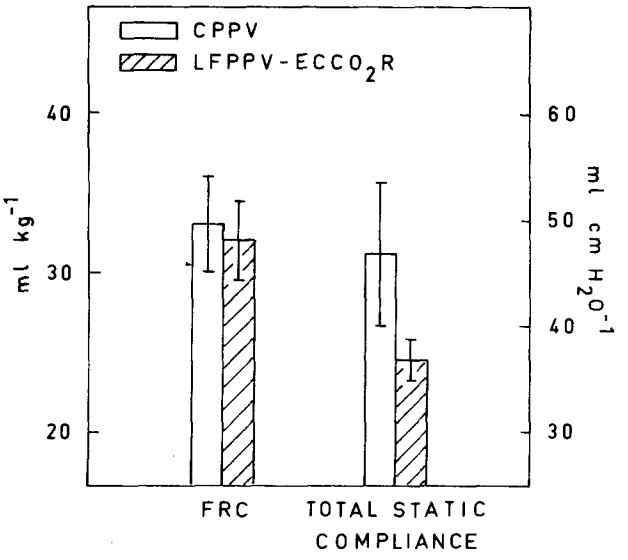

Fig. 1. Functional residual capacity (FRC) and total static compliance during Continuous Positive Pressure Ventilation (CPPV) and Low Frequency Positive Pressure Ventilation with Extracorporeal CO_2 Removal (LFPPV-ECCO$_2$R). Mean values (±1 SE) of 105 determinations taken from six experiments. The values of total static compliance during CPPV and LFPPV-ECCO$_2$R are statistically different ($P < 0.05$)

No significant change was found in PAO_2 during the two different modes of ventilation (Table 1).

Blood Gases: In all experiments the ECCO$_2$R was sufficient to maintain a normal $PaCO_2$ despite ventilating the lungs at only 2 b.p.m. (Table 1). The PaO_2 was significantly lower during LFPPV-ECCO$_2$R (Table 2) while no change was found in $P\bar{v}O_2$ and arterial or mixed venous pH (Table 1). The mean $\dot{Q}_{va}/\dot{Q}$ was 0.328 in CPPV and 0.453 in LFPPV-ECCO$_2$R. Both in CPPV and in LFPPV-ECCO$_2$R the $\dot{Q}_{va}/\dot{Q}$ positively correlated with CO (r = 0.54, $P < 0.01$) (not shown).

Hemodynamics: No significant changes were found in heart rate, systolic and diastolic or mean arterial

Table 1. Alveolar $PO_2(PAO_2)$, PO_2, PCO_2 and pH values in arterial and mixed venous blood during Continuous Positive Pressure Ventilation (CPPV) and Low Frequency Positive Pressure Ventilation with Extracorporeal CO_2 Removal (LFPPV-ECCO$_2$R). Mean values (± 1 SE) of 105 determinations taken from six experiments

		PAO_2 (mmHg)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pHa	$P\bar{v}O_2$ (mmHg)	$P\bar{v}CO_2$ (mmHg)	pH$\bar{v}$
CPPV	$\bar{X}$	209	105.62	32.01	7.443	53.51	35.14	7.41
	S_E	±6.2	±4.23	±0.77	±0.01	±1.4	±0.9	±0.01
LFPPV-ECCO$_2$R	$\bar{X}$	200	80.02	34.39	7.446	51.52	32.34	7.44
	S_E	±6.0	±2.88	±0.84	±0.01	±1.2	±0.9	±0.02
	F	1.03	27.42	7.38	0.20	1.69	3.86	2.01
	P	N.S.	<0.01	<0.01	N.S.	N.S.	N.S.	N.S.

Table 2. Systolic (sAP), diastolic (dAP), mean systemic arterial pressure (mAP), mean pulmonary arterial pressure ($\overline{PAP}$) and heart rate (HR) during CPPV and LFPPV-ECCO$_2$R. Mean values (± 1 SE) of 110 determinations taken from six experiments

		sAP (mmHg)	dAP (mmHg)	mAP (mmHg)	PAP (mmHg)	HR (b.p.m.)
CPPV	$\bar{X}$	113	76.5	93.6	30	142
	S_E	±0.3	±0.3	±0.3	±2.1	±2
LFPPV-ECCO$_2$R	$\bar{X}$	113	76.5	93	28	147
	S_E	±0.3	±0.3	±0.2	±2	±2
	F	0.08	0.03	0.08	11.08	1.32
	P	N.S.	N.S.	N.S.	<0.01	N.S.

pressures at respiratory frequency of 16 b.p.m. and 2 b.p.m. However, the $\overline{PAP}$ was significantly lower during LFPPV (Table 1). During LFPPV-ECCO$_2$R compared with CPPV, the CO increased by 26% and oxygen transport by 25% (Fig. 2). The pulmonary vascular resistances decreased by 22%.

Renal and Liver Function: Urinary output and creatinine clearance (Fig. 3), as well as osmolar output and osmolar clearance (Fig. 4) significantly increased during LFPPV-ECCO$_2$R, compared to CPPV. SGOT, SGPT, bilirubin and alkaline phosphatase did not change in either group.

Coagulation: ACT was maintained between 200 and 350 sec, the fibrinogen did not change in either group while the fall in platelets was in accord with previous reports [33, 8, 5] and did not differ among the two groups.

Short Term Study: The overall data of the short term study (i.e. 20 min periods of CPPV and 20 min periods of LFPPV-ECCO$_2$R) were the same as one hour period studies. However, mixed venous saturation (as measured by "in line" Oxymeter) and urinary flow improvement was immediate: changes occurred in the first 5 minutes of shifting from CPPV to LFPPV-ECCO$_2$R.

Discussion

Pulmonary Function and Blood Gases

During LFPPV-ECCO$_2$R we were able to maintain the $PaCO_2$ in the normal range inspite of a RR of only 2 b.p.m. However, the PaO_2, at the same PAO_2, was lower in LFPPV-ECCO$_2$R than during CPPV due to increase in $\dot{Q}_{va}/\dot{Q}$. The rise in $\dot{Q}_{va}/\dot{Q}$ during LFPPV-ECCO$_2$R could result from one or a combination of several causes: impairement of oxygen diffusion, inequality of ventilation perfusion ratios ($\dot{V}A/\dot{Q}$) or pulmonary atelectasis.

However, it is difficult to believe that, in the same animal during random study periods, the reduction of respiratory frequency resulted in prompt (and reversible) changes in oxygen diffusion capacity through the natural lungs. The $\dot{V}A/\dot{Q}$ inequality could be an important factor in the increased $\dot{Q}_{va}/\dot{Q}$ in LFPPV-ECCO$_2$R, but we did not measure, in the present experiments, the continuous distribution of

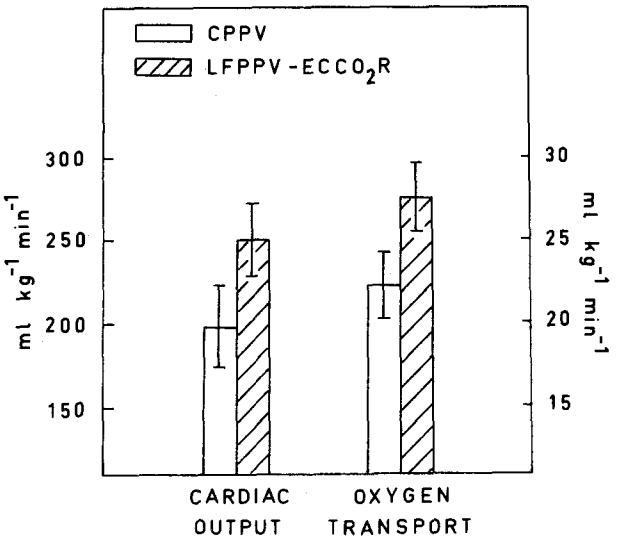

Fig. 2. Cardiac output and O_2 transport during CPPV and LFPPV-ECCO$_2$R. Mean values (±1 SE) of 85 measurements taken from six animals. Cardiac output values during CPPV and LFPPV-ECCO$_2$R are statistically different ($P < 0.05$)

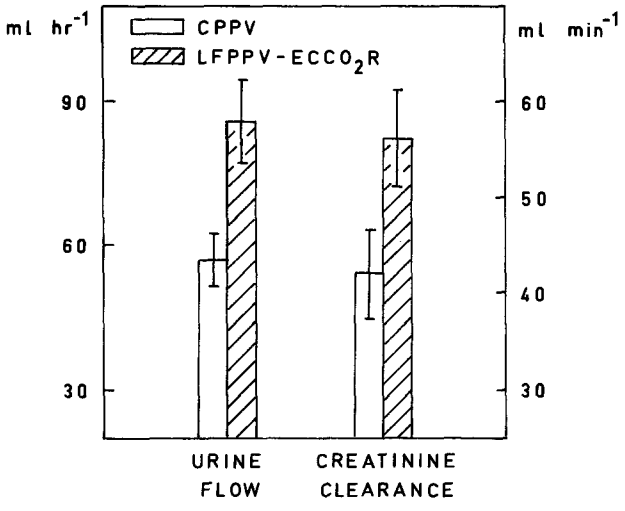

Fig. 3. Urinary flow and creatinine clearance during CPPV and LFPPV-ECCO$_2$R. Mean values (±1 SE) of 105 determinations. The values of urinary flow and creatinine clearance during CPPV and LFPPV-ECCO$_2$R are statistically different ($P < 0.001$ and $P < 0.01$ respectively)

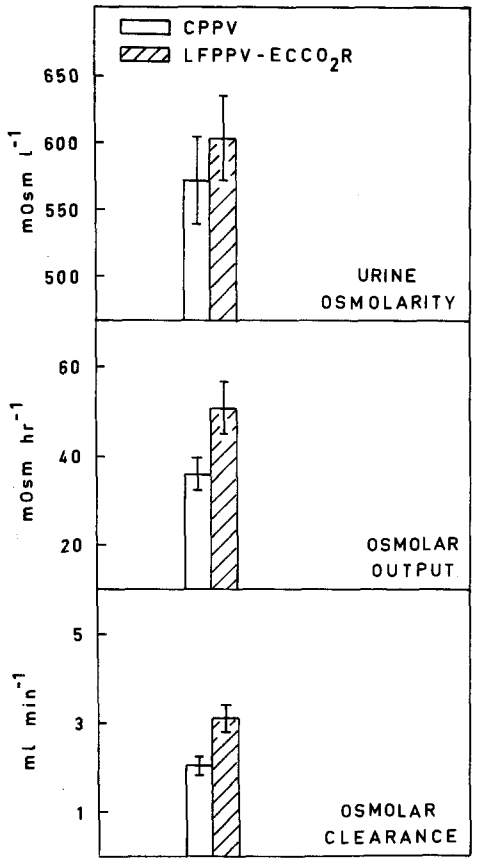

Fig. 4. Urine osmolarity, osmolar output and osmolar clearance during CPPV and LFPPV-ECCO$_2$R. Mean values (±1 SE) of 105 determinations. The values of osmolar output and osmolar clearance during CPPV and LFPPV-ECCO$_2$R are both statistically different ($P < 0.01$)

$\dot{V}A/\dot{Q}$. Increased atelectasis caused by LFPPV-ECCO$_2$R can be excluded as the FRC did not change during the two different modes of ventilation. Let us now consider the effect of CO on $\dot{Q}va/\dot{Q}$. It has been shown both experimentally [32] and clinically [15, 11, 27] that a linear positive correlation exists between CO and $\dot{Q}va/\dot{Q}$, i.e. when increasing the CO the pulmonary blood flow is more shifted towards "shunted areas" of the lung. In our experiments the CO increased by about 26% during LFPPV-ECCO$_2$R compared to CPPV and was positively correlated both in LFPPV-ECCO$_2$R, and in CPPV, with $\dot{Q}va/\dot{Q}$. It is possible that lower PaO_2 and increased $\dot{Q}va/\dot{Q}$ found in LFPPV-ECCO$_2$R are expressions of hemodynamic improvement and do not reflect pulmonary deterioration. Furthermore, oxygen transport is higher in LFPPV-ECCO$_2$R than in CPPV, even if this finding did not reach a level of statistical significance (Fig. 2).

Tissue oxygenation did not differ in LFPPV-ECCO$_2$R compared to CPPV, as shown by the normal $P\bar{v}O_2$, $pH\bar{v}$ and Base Excess.

Hemodynamics

Lowering respiratory rate from 16 to 2 b.p.m. caused a sudden increase in CO of 26% with no changes in heart rate and arterial pressure, thus indicating that

the changes in CO are due to an increase in stroke volume. The latter could be due to increase in preload, myocardial contractility and/or decrease in afterload.

As mechanical ventilation can impair venous return, it is reasonable to hypothesise that lower mechanical respiratory rate (with resulting lower mean airways pressure) decreases the obstacles to venous return and to pulmonary circulation, as suggested by a significant decrease in $\overline{PAP}$ and in pulmonary resistances.

Moreover, the changes in respiratory frequency caused a sudden decrease in systemic vascular resistances, one of the determinant of afterload [28]. This could be due to cardiovascular reflexes from preload increase. To discriminate grossly between "mechanical" effect (increase in preload) and "reflex" effect (decrease in afterload) two supplementary sheep were vagotomized in the neck. These experiments show that in vagotomized sheep lowering the frequency from 16 to 2 b.p.m. caused an increase of CO of 15% (instead of 26% observed in intact animals). However, the increase in CO was accompanied by an increase in mean arterial pressure and the computed vascular resistances did not change. These preliminary results grossly indicate that both mechanical effect (increase in preload) and reflex reactions (decrease in afterload abolished by vagotomy) can account for the hemodynamic changes observed in intact animals.

Renal Function

Undoubtedly, changes in CO and in vascular resistances can affect perfusion to various organ systems, as well as when the RR falls from 16 to 2 b.p.m.: the urinary output increased 50%: the glomerular filtration, as measured by creatinine clearance, 33%: the osmolar output by 41% and the osmolar clearance by 52%. These changes are of the same order of magnitude as the increase in CO during LFPPV-ECCO$_2$R. It would be suggestive to attribute the changes in renal function to a parallel change in renal blood flow. Decrease in urinary output during CPPV has been related to a decrease in renal blood flow, parallel to a decrease in CO [9]. However, Hall et al. [13] during mechanical ventilation found a similar decrease in CO and glomerular filtration when increasing the PEEP from 0 to 10 cmH$_2$O, yet they found no change in renal blood flow, measured by direct means. They attributed the changes in renal function to redistribution of blood in the kidney from cortical nephrons to juxtamedullary nephrons. The mechanism leading to kidney blood flow redistribution remains unclear. The possible role of ADH release has been suggested. Baratz and Ingraham [2] found an increase in ADH during CPPV. Baratz, Philbin and Patterson [3] also showed such an increase to be independent of atrial volume receptors. However, Kumar et al. [26] found inappropriate response to increased ADH during mechanical ventilation.

We cannot exclude a possible modification in ADH release during LFPPV-ECCO$_2$R compared with CPPV. However, the changes in urinary flow were almost immediate (less than 5 minutes) and were not accompanied by changes in urine osmolarity. Finally, it remains possible that cardiopulmonary receptors can influence the sympathetic activity of the kidney, with modification or redistribution of renal blood flow and consequent alteration in renal function [16, 17, 21, 34].

The central blood volume (CBV) could affect the cardiopulmonary receptor activity. It is interesting to note that in our experiments the lung compliance was lower in LFPPV-ECCO$_2$R than in CPPV, the FRC being the same. It is known that an increase in CBV can lower the lung compliance at the same FRC [7]. It is thus possible that during CPPV the decrease in CBV [22] can promote an antidiuresis via sympathetic nerve stimulation, while during LFPPV-ECCO$_2$R, where the CBV is presumably conserved, the reflex renal sympathetic function is not stimulated, with resulting increased diuresis. Furthermore, it is possible, although not proved, that the vagal input from pulmonary stretch receptors is greater when they are stimulated 16 times instead of 2 times per minute. Whatever the mechanism leading to improved renal function and hemodynamics during LFPPV-ECCO$_2$R, this form of ventilation could be potentially useful in the management of patients who require artificial ventilation, to lower the extrapulmonary (and pulmonary) complications of CPPV.

Although these experiments were specifically designed to study hemodynamics and renal function during LFPPV-ECCO$_2$R, there is some evidence that this approach may promote a considerable improvement in pulmonary oxygenation and mechanical properties of highly diseased lungs, with advantages not found in conventional extracorporeal membrane lung oxygenation (ECMO) technique [12].

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