Veno-venous extracorporeal CO_2 removal improves pulmonary hemodynamics in a porcine ARDS model

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Conflicts of interest
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Background: Protective lung ventilation is recommended in patients with acute respiratory distress syndrome (ARDS) to minimize additional injuries to the lung. However, hypercapnic acidosis resulting from ventilation at lower tidal volume enhances pulmonary hypertension and might induce right ventricular (RV) failure. We investigated if extracorporeal veno-venous CO_2 removal therapy could have beneficial effects on pulmonary circulation and RV function.

Methods: This study was performed on an experimental model of ARDS obtained in eight anaesthetized pigs connected to a volume-cycled ventilator. A micromanometer-tipped catheter was inserted into the main pulmonary artery and an admittance micromanometer-tipped catheter was inserted into the right ventricle. RV–arterial coupling was derived from RV pressure-volume loops. ARDS was obtained by repeated bronchoalveolar lavage. Protective ventilation was then achieved, and the pigs were connected to a pump-driven extracorporeal membrane oxygenator (PALP, Maquet, Germany) in order to achieve CO_2 removal.

Results: ARDS induced severe hypercapnic acidosis. Systolic pulmonary artery pressure significantly increased from 29.6 ± 1.8 to 43.9 ± 2.0 mmHg ($P < 0.001$). After the PALP was started, acidosis was corrected and normocarbia was maintained despite protective ventilation. Pulmonary artery pressure significantly decreased to 31.6 ± 3.2 mmHg ($P < 0.001$) and RV–arterial coupling significantly improved (RV–arterial coupling index = 1.03 ± 0.33 vs. 0.55 ± 0.41, $P < 0.05$).

Conclusion: Veno-venous CO_2 removal therapy enabled protective ventilation while maintaining normocarbia during ARDS. CO_2 removal decreased pulmonary hypertension and improved RV function. This technique may be an effective lung- and RV-protective adjunct to mechanical ventilation.

Editorial comment: what this article tells us
In adult respiratory distress syndrome, hypercarbia and increased pulmonary vascular resistance can place strain on the right heart. The findings in this large animal experimental model show that extracorporeal carbon dioxide elimination in this setting can lead to improvement in pulmonary vascular resistance and right ventricular–arterial coupling.

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Acute respiratory distress syndrome (ARDS) is responsible for injuries to the alveolar epithelium and microvascular endothelium, which result in severe hypoxemia, decreased pulmonary compliance, and increased pulmonary vascular resistance (PVR).[1,2] Acute pulmonary hypertension increases right ventricular (RV) afterload. Positive-pressure ventilation, required to correct ARDS-induced hypoxemia, further increases pulmonary hypertension and RV afterload, leading to acute cor pulmonale and RV failure.[3,4] Moreover, mechanical ventilation induces additional lung injuries due to overdistention, repeated stretch to the alveoli, and increased inflammatory mediator levels.[5–7] Despite new strategies in mechanical ventilation, ARDS continues to be a devastating disease.[8] Mortality rates for ARDS decreased over time but still remain around 40%, which, in large part, is caused by hemodynamic complications to this syndrome.[9,10] In order to reduce deleterious effects of positive-pressure ventilation, protective ventilation strategies have been developed, showing improvement in the outcome of mechanically ventilated patients. The ARDSnet investigators reported a 25% reduction in mortality with a ventilation strategy involving limitation of mean tidal volume to 6 ml/kg, as compared with a more traditional tidal volume of 12 ml/kg.[11] However, low tidal volumes required by such ventilation strategies increase hypercapnia associated to ARDS. Most clinicians seldom use very low tidal volumes in practice because of the clinical acceptability of this 'permissive' hypercapnia. Indeed, despite some potential beneficial anti-inflammatory effects, it is well established that hypercapnic acidosis (HCA) has deleterious effects, in particular by contributing to increase constriction within the pulmonary vasculature.[4,12–14]

Thus, modern care for ARDS requires decision to maximally reduce ventilator settings to ensure lung protection and reduce exacerbation of lung injury while facing the deleterious consequences of this intervention. In order to supplement or replace the lung function and to avoid ventilator-induced lung injury, gas exchange via an extracorporeal device has been developed.[15] Such a device may make it possible to avoid mechanical ventilation altogether in selected patients.[16] Extracorporeal membrane oxygenation (ECMO) allows blood oxygenation and carbon dioxide (CO_2) removal but requires high blood flow and, as a result, placement of large cannulas. Moreover, this technique is too costly for routine use as a lung rest strategy in adult ARDS patients.[15] When compared with oxygenation, removal of CO_2 from blood can be accomplished at lower blood flows. Indeed, due to its high solubility and diffusing capacity in blood, high amount of CO_2 can be removed from a venous blood sample as compared with the small amount of oxygen that can be added.[17,18] As a result, less invasive veno-venous devices have been specifically designed for CO_2 removal with high gas exchange efficiency at relatively low blood flow rates (400–1500 ml/min). The invasiveness of these devices, called 'low flow extracorporeal veno-venous CO_2 removal therapy ($ECCO_2RT$)', is reduced by use of percutaneous dual lumen catheters, comparable with catheterization for dialysis. The aim of our study was to determine if $ECCO_2RT$ used at early stage of ARDS could have beneficial effects on pulmonary circulation and improve RV function in a pig model.

Material and methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the ethical committee of the Medical Faculty of the University of Liege and conformed to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH publication no. 85-23, revised 1996). Primary end points were changes in pulmonary artery pressure (PAP) and RV–arterial coupling. Experiments were performed from November 2013 to April 2014 on eight healthy pure Pietran pigs of either sex, weighing from 21 to 33 kg. The animals were premedicated with intramuscular administration of tiletamine (250 mg) and zolazepam (250 mg). Anesthesia was then induced and maintained by a continuous infusion of sufentanil (0.5 μg/kg/h) and pentobarbital (5 mg/kg/h). Spontaneous movements were prevented by cisatracurium bésilate (0.5 mg/kg/h). After endotracheal intubation via a cervical tracheostomy, the pigs were connected to a volume-cycled ventilator (Servo 300, Maquet, Rastatt, Germany) set to deliver a tidal volume of 10 ml/kg at a respiratory rate of 20 breaths/min with an inspired O_2 fraction (FiO_2) of 0.5 and an end-expiratory pressure of

5 cm H_2O. End-tidal CO_2 measurements (Capnomac, Datex, Helsinki, Finland) were used to monitor the adequacy of ventilation. The pulmonary trunk was exposed via a median sternotomy. A micromanometer-tipped catheter (Scisense, London, Canada) was inserted into the main pulmonary artery through a stab wound in the RV outflow tract in order to measure PAP. Pressure in the left auricle (Pla) was measured with a micromanometer-tipped catheter (Scisense) inserted into the cavity through the left atrial appendage. Systemic arterial blood pressure (SAP) was monitored via a micromanometer-tipped catheter (Scisense) inserted into the aorta through the left carotid artery. RV volume was measured from admittance catheterization.[19] A 5-F, 5-electrode admittance micromanometer-tipped catheter (Scisense) was inserted through the RV infundibulum into the RV and positioned so that all electrodes were in the RV cavity. A central venous line was inserted into the right jugular vein and placed inside the superior vena cava. A 4F fluid-filled catheter (Pulsiocath, Pulsion Medical System, Munich, Germany) was inserted into the right femoral artery for pulse pressure analysis. A 6F Fogarty balloon catheter (Baxter Healthcare Corp., Oakland, CA, USA) was advanced into the inferior vena cava through a right femoral venotomy. Inflation of this balloon produced a gradual preload reduction.

Experimental protocol

After surgical preparation, the animals were allowed to stabilize for 60 min ('baseline state'). Baseline hemodynamic recording was performed, including PAP, Pla, mean arterial blood pressure, and heart rate (HR). ARDS was achieved by repeated bronchoalveolar lavage (37°C, 60 ml/kg of 0.9% saline solution). Ventilator settings were reduced to achieve 'protective ventilation' (tidal volume = 6 ml/kg) after the induction of ARDS. When PaO_2/FiO_2 was < 200 and $PaCO_2 >$ 60 mmHg, hemodynamic recording was performed ('ARDS state') and $ECCO_2RT$ was started. Hemodynamic recording was repeated after 30 min of $ECCO_2RT$ ('$ECCO_2RT$ state'). $ECCO_2RT$ was stopped after 60 min. A last hemodynamic recording was performed 30 min after $ECCO_2RT$ was stopped ('OFF state'). Arterial blood gas analysis was performed at each stage of the experiment. End-tidal CO_2 was continuously monitored. Fluid administration with Hartmann's solution was continuously controlled by preload responsiveness. When pulse pressure variation was $\leq 11\%$, animals were considered as adequately filled. A warming blanket and a heated operating table were used to prevent hypothermia.

Description and insertion of the $ECCO_2RT$

$ECCO_2RT$ was achieved with the PALP module (Cardiohelp, Maquet), which consists of a unit in which gas exchange and pump take place with an integrated control console. The system was interfaced with the pig through an inflow catheter (13F) inserted into the inferior vena cava and an outflow catheter (10F) inserted into the superior vena cava. The pump withdrew venous blood from the inferior vena cava, which, after CO_2 removal, was re-infused into the right atrium through the superior vena cava. The PALP unit was primed with 345 ml of normal saline. Plastic tubing provided by the manufacturer was immediately connected to each venous catheter, and the PALP unit was started. Pump speed was adjusted to reach an aspiration pressure of 60 mmHg and sweep gas flow was set to the maximum value (10 l/min).

Heparin bolus was given before the PALP connection and assessed by the activated clotting time (ACT; in seconds) using a Hemochron Signature Microcoagulation System (International Technidyne, Edison, NJ, USA). The target ACT was 180 s.

Data collection

All analog signals were continuously digitized and recorded (Notocord, Paris, France): HR (beats per minute), SAP (mmHg), PAP (mmHg), Pla (mmHg), RV end-systolic volume (ml), and RV end-diastolic volume (ml). PALP blood flow (l/min) was directly recorded from the PALP console.

Arterial tension of oxygen (PaO_2, mmHg), CO_2 ($PaCO_2$, mmHg), and arterial pH were measured at each stage of the experiment (Baseline, ARDS, $ECCO_2RT$, OFF).

Extravascular lung water (EVLW) and pulmonary vascular permeability index (PVPI) were

Table 1 Arterial blood gas data.

	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	pH	Hemoglobin (g/dl)	Temperature
Baseline	178,8 ± 42†	41,7 ± 3,6†	7,44 ± 0.05†	9,2 ± 1.2	36,6 ± 0.4
ARDS	54,7 ± 12,3*	78,6 ± 8,1*	7,13 ± 0.05*	9,7 ± 1.3	36,6 ± 0.6
$ECCO_2RT$	72,2 ± 21,0*	39,8 ± 5,6†	7,36 ± 0.05†	8,6 ± 0,8	36,3 ± 0.4
OFF	61,1 ± 15,12*	70,5 ± 11,2*	7,15 ± 0.05*	8,8 ± 0,7	36,0 ± 0.5

*Significant difference vs. baseline at $P < 0.05$; †Significant difference vs. ARDS at $P < 0.05$. All data are means ± standard deviation. Basal, baseline conditions; ARDS, acute respiratory distress syndrome; $ECCO_2RT$, extracorporeal CO_2 removal therapy; OFF, stop of extracorporeal CO_2 removal.

measured using a transpulmonary thermodilution method at baseline, after ARDS and at the end of the experiment.[20] Transpulmonary thermodilution was not performed during PALP therapy because of the right atrium reinfusion.

Data analysis

Maximal and minimal PAP defined systolic and diastolic pressures, respectively. Systolic ejection interval (*t*s) was measured from the foot of the pulmonary arterial pressure wave to its incisura, and the diastolic interval was *t*d = *T* − *t*s, where *T* is the cardiac cycle length. Pulmonary blood flow (PBF) was derived from RV stroke volume given by RV admittance catheter and HR. RV contractility was assessed by end-systolic elastance (Ees). The slope of the end-systolic pressure (ESP)–volume relation was obtained from transient occlusions of the inferior vena cava using the Fogarty balloon, during apnea. Pulmonary arterial elastance (Ea) was assessed from the ratio of RV ESP minus Pla to RV stroke volume (SV). Mean PVR was calculated as the ratio of mean PAP minus Pla divided by PBF.

Statistical analysis

Changes in hemodynamic parameters and blood gas data at each stage of the experiment were evaluated by a repeated-measures analysis of variance followed by Scheffé post-hoc tests. Correlation analysis was performed using Pearson's correlation coefficient. Data were expressed as mean ± standard deviation.

Results

EVLW and PVPI increased during ARDS (229 ± 95 ml to 441 ± 95 ml, $P < 0.01$ and from 2.21 ± 0.49 to 4.40 ± 0.49, $P < 0.001$, respectively).

Arterial blood gases and acid-base equilibrium during the experiment are depicted in Table 1. Appropriate hypercapnia was obtained in all pigs. When compared with baseline, mean $PaCO_2$ more than doubled during the ARDS, returned to baseline when the PALP was started, and increased again when $ECCO_2RT$ was stopped. PaO_2 decreased during ARDS. The arterial pH decreased during ARDS, returned to normal values during $ECCO_2RT$, and decreased again when the PALP was stopped.

Hemodynamic data are depicted in Table 2. The amount of fluid (Hartmann's solution) used to achieve adequate filling was 1.08 ± 0.18 l. Mean blood flow in the PALP was 645 ± 84 ml/min. Systolic PAPs increased by more than half during ARDS, decreased during $ECCO_2RT$, and increased again after the PALP was stopped (Figs 1 and 2). Changes in PAPs were highly correlated with changes in $PaCO_2$ (r = 0.87) and with changes in pH (r = −0.84) resulting from PALP therapy. Changes in PAPs were poorly correlated with changes in PaO_2 due to PALP therapy (r = −0.55). Similarly, PVR increased during ARDS, decreased during $ECCO_2RT$, and increased again after the PALP was stopped (Table 2). Cardiac index (CI) and Pla did not change during the whole experiment. SV decreased during ARDS and increased during PALP therapy. Ea near doubled during ARDS, returned to normal values during $ECCO_2RT$ and increased again when the PALP was stopped (Fig. 3). RV contractility, assessed with Ees, increased when the PALP was stopped (Fig. 3). Ventriculo–arterial coupling, assessed by the ratio of Ees on Ea decreased under the unit during ARDS, come back at or around the unit during $ECCO_2RT$ and decreased again when the PALP was stopped (Fig. 3).

Table 2 Hemodynamic data.

	HR	sAP	CI	SV	Pla	PAPm	PVR	Ea	Ees	Ees/Ea
Baseline	73 ± 11†	104 ± 25	2,11 ± 0,59	30,1 ± 10,6†	7,5 ± 1.9	19,8 ± 3,9†	6,57 ± 3,50†	1,12 ± 0,42†	0,93 ± 0,25	0.92 ± 0,27†
ARDS	103 ± 25*	105 ± 11	2,29 ± 0.48	21,7 ± 5,3*	6,5 ± 3,9	32,8 ± 6,2*	11,92 ± 3,40*	1,99 ± 0,45*	0,99 ± 0,42	0,52 ± 0,20*
$ECCO_2RT$	82 ± 17	91 ± 11	2,58 ± 0.67	32,0 ± 9,2†	8,1 ± 1,9	23,8 ± 4,5†	6,76 ± 3,36†	1,08 ± 0,42†	0,95 ± 0.22	0,98 ± 0,27†
OFF	76 ± 11	95 ± 11	2,24 ± 0.45	28,1 ± 6,4	9,1 ± 2,1	32,7 ± 7,0*	11,56 ± 5,68*	1,88 ± 0,76*	1,05 ± 0,31	0,60 ± 0,14*

*Significant difference vs. baseline at $P < 0.05$; †significant difference vs. ARDS at $P < 0.05$. All data are means ± standard deviation. HR, heart rate; sAP (mmHg), systolic arterial pressure (mmHg); CI (l/min/m^2), cardiac index; SV (ml), stroke volume; Pla (mmHg), left atrial pressure; PAPm (mmHg), mean pulmonary arterial pressure; PVR(mmHg/min/l/m^2), indexed mean pulmonary vascular resistance; Ea (mmHg/ml), pulmonary arterial elastance; Ees (mmHg/ml), RV end-systolic elastance; Ees/Ea, RV ventriculo–arterial coupling index. Basal, baseline conditions; ARDS, acute respiratory distress syndrome; $ECCO_2RT$, extracorporeal CO_2 removal therapy; OFF, stop of extracorporeal CO_2 removal.

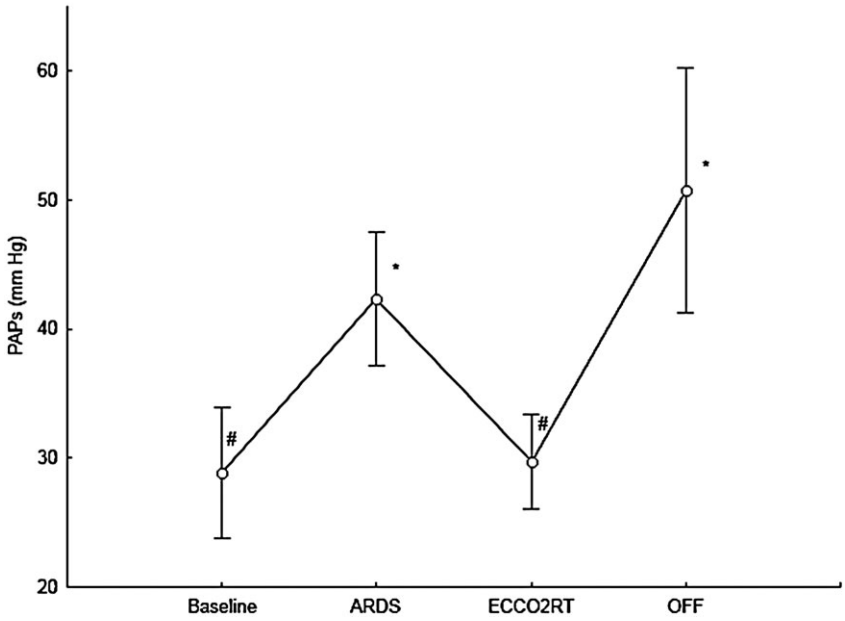

Fig. 1. Evolution of systolic pulmonary artery pressure (PAPs). *Significant difference vs. baseline at $P < 0.05$, #significant difference vs. ARDS at $P < 0.05$. Baseline, baseline conditions; ARDS, acute respiratory distress syndrome; $ECCO_2RT$, extracorporeal CO_2 removal therapy; OFF, stop of extracorporeal CO_2 removal.

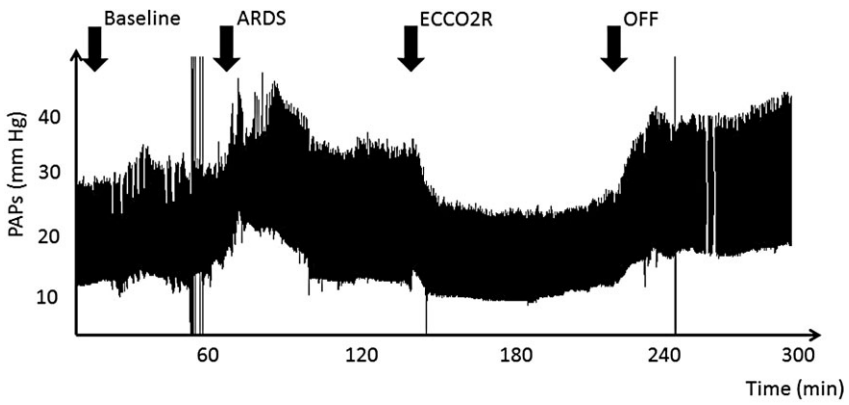

Fig. 2. Example of the time course of systolic pulmonary artery pressure (PAPs). Baseline, baseline conditions; ARDS, acute respiratory distress syndrome; $ECCO_2RT$, extracorporeal CO_2 removal therapy; OFF, stop of extracorporeal CO_2 removal.

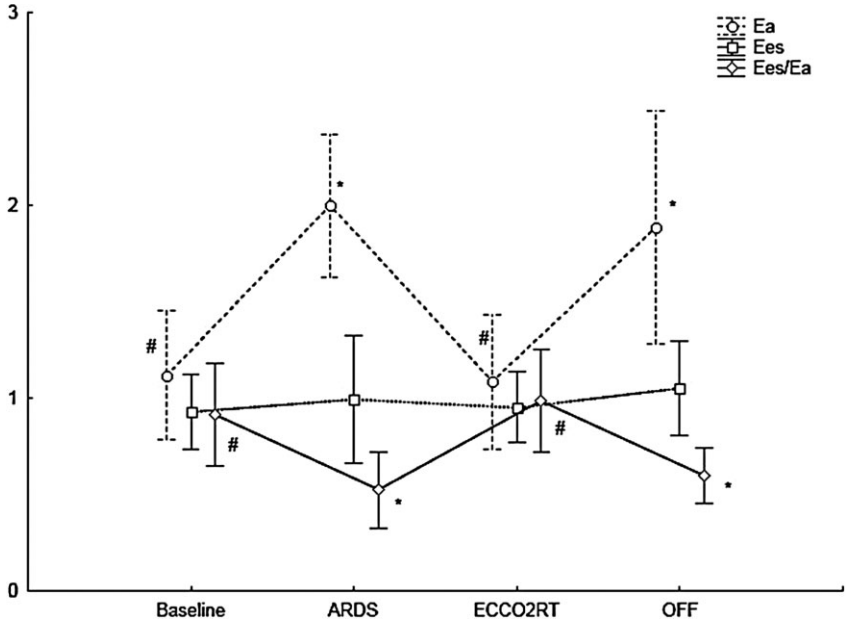

Fig. 3. Evolution of pulmonary arterial elastance (Ea, mmHg/ml), RV end-systolic elastance (Ees, mmHg/ml) and RV ventriculo–arterial coupling index (Ees/Ea). Significant differences: *Significant difference vs. baseline at $P < 0.05$, #significant difference vs. ARDS at $P < 0.05$. Baseline, baseline conditions; ARDS, acute respiratory distress syndrome; $ECCO_2RT$, extracorporeal CO_2 removal therapy; OFF, stop of extracorporeal CO_2 removal; RV, right ventricular.

Discussion

This is the first study precisely analyzing the respiratory and hemodynamic effects of CO_2 removal with an extravascular device in an experimental model of ARDS. The findings were:

1. CO_2 removal during ARDS with the PALP device was very effective to achieve normocarbia and to normalize acidosis, while maintaining protective ventilation.
2. Pulmonary vascular tone was significantly reduced and RV–arterial coupling was improved during $ECCO_2RT$.

Artificial lung support systems are medical devices designed to supplement or replace the respiratory function of the natural lung. ECMO was introduced for treatment of neonatal respiratory failure. ECMO is an effective but costly and very invasive technique for selected patients with severe pulmonary failure. ECMO requires highly trained staff and is currently used in adults only in a few centers. Several simpler devices have been developed allowing a reduction in minute ventilation, reduced airway pressure, improved PaO_2-to-FIO_2 ratio, and improved survival in animal models of ARDS. Recently, Batchinsky et al. demonstrated that such simpler devices can provide a 50% reduction in minute ventilation while maintaining normocarbia and may be an effective lung-protective adjunct to mechanical ventilation.[21] Our results showed that the PALP device was efficient for CO_2 removal during ARDS, enabling lung protective ventilation at low tidal volume. Alteration of the permeability of the alveolar-capillary membrane during ARDS was demonstrated by impaired gas exchanges and increased PVPI.[22] The device achieved correction of HCA in less than 15 min in all pigs. The PALP technology uses the same technique as ECMO and is composed of a centrifugal pump, a microporous hollow-fiber oxygenator, two venous cannulas, and tubing. The gas exchange membrane is very efficient and specifically designed for CO_2 removal with low resistance to blood flow. However, as compared with ECMO, cannulas are substantially smaller with almost the same size as dialysis cannulas.

The main finding of our study was a significant reduction in PAP and PVR during $ECCO_2RT$. This reduction was clearly related to the correction of HCA. HCA enhances pulmonary vasoconstriction.[12,23] Several clinical studies demonstrated that HCA causes an increase in mean PAP in ARDS.[4,24,25] Our study is concordant with those findings with a significant increase in PAP during ARDS. However, the relative roles of hypercapnia and acidosis in the mechanism of pulmonary vasoconstriction remain unclear. Acute PHT increases RV afterload,[26,27] which individually

and collectively with microvascular obstruction effects of positive-pressure ventilation, and HCA exacerbate RV failure in ARDS.[4] Acute cor pulmonale in ARDS patients is associated with high mortality rates.[28] Impaired RV function at early stage of ARDS may be underdiagnosed, and yet it might be the harbinger of a downward spiral in the patient's condition.[4] We previously established that PVR and RV ejection fraction are poor indicators of RV–arterial performance.[26] RV–arterial coupling is beneficial for cardiovascular performance and is assessed by the ratio of Ees to Ea, where Ees and Ea characterize the RV system and the pulmonary vascular system, respectively.[29] Ees precisely determines the contractility of the right ventricle independently of the loading conditions, and Ea is a precise measure of RV afterload. Indeed, afterload is not only characterized by PVR, but also results from a dynamic interplay among resistance, compliance, and wave reflection.[26] The ratio of Ees to Ea reflects the mechano-energetic aspects of RV–vascular coupling. It can be demonstrated that efficiency of energy transfer from the RV to the pulmonary circulatory system is optimal when Ees/Ea = 2, whereas RV stroke work is maximal when Ees/Ea = 1. However, when Ees/Ea < <1, there is a mismatch between RV contractility and pulmonary vascular load.[29] In ARDS patients, increased RV afterload is responsible for increased Ea, whereas Ees may decrease because of HCA, hypoxia, and often associated sepsis, leading to uncoupling between the right ventricle and the pulmonary circulation, and finally precipitating RV failure.[30] Therapies should be ideally oriented to restore the coupling between the heart and pulmonary vasculature by avoiding any increase in pulmonary vascular tone as well as depression in RV contractility.[24,30] Our study showed that Ea was significantly increased during ARDS and was significantly reduced during $ECCO_2RT$. The effects of HCA on myocardial function are contradictory. Acidosis decreases myocardial contractility because hydrogen ions inhibit Ca^{2+} influx into the myocardial fiber.[31] However, hypercapnia causes coronary vasodilatation leading to better myocardial perfusion and performance.[32] We did not observe significant changes in Ees during ARDS and during $ECCO_2RT$. During ARDS, the animals were unable to maintain an optimal ventriculo–arterial coupling despite a trend to increase RV contractility, and Ees/Ea ratio dropped below the unit. The $ECCO_2RT$, however, helped to restore a ratio around the unit mainly by lowering Ea. When the PALP was stopped, we again observed an RV–arterial coupling index (Ees/Ea ratio) lower than the unit. Uncoupling between RV and pulmonary arterial system resulted in decreased SV, whereas CO did not change because of increased HR.

In ARDS, pulmonary vasoconstriction may not result only from HCA, but also from other factors like hypoxia or inflammatory mechanisms. Hypoxic pulmonary vasoconstriction is a widely conserved, homeostatic, and adaptive vasomotor response to alveolar hypoxia, which redistributes blood to optimally ventilated lung segments by an active process of vasoconstriction.[33,34] This response to hypoxia is strongly enhanced when HCA is superimposed.[34] Conversely, improved blood oxygenation without changes in alveolar oxygenation should not affect PVR. However, changes in $PaCO_2$ indirectly influenced changes in alveolar oxygenation by the alveolar gas equation, and this mechanism could have played a role in pulmonary vasomotor tone.[34] In our study, changes in PaO_2 due to $ECCO_2RT$ were non-significant and poorly correlated with changes in PAP, whereas changes in $PaCO_2$ and pH were highly significant and highly correlated with changes in PAP. Similarly, when the PALP was stopped, pulmonary vasoconstriction occurred again, whereas PaO_2 did not significantly change.

Blood temperature slightly, but non-significantly, decreased along the experiment. Hemoglobin tended to decrease during PALP therapy, which may be explained by hemodilution resulting from the priming of the device (Table 1). As a result, neither temperature nor hemoglobin changes should have significantly influenced CO_2 exchanges during the experiment. Others methodological issues should be taken into account: The experimental model of ARDS used in this study is different from ARDS observed in human beings. Although injury to the pulmonary circulation has been clearly demonstrated in human ARDS,[35,36] our model induced lung injury without direct aggression to the pulmonary vasculature, allowing this study to focus on the effects of hypercapnia on pulmonary circulation and RV function.

In conclusion, use of the PALP device for $ECCO_2RT$ in a pig model of ARDS allowed protective ventilation while maintaining normocarbia. The PALP device made it possible to rapidly initiate extracorporeal lung support with a relatively low invasive extracorporeal lung support technology, thus avoiding ventilator-induced barotrauma, which should have been necessary to limit hypercapnia. Moreover, this device showed beneficial hemodynamic effects by reducing pulmonary vascular constriction related to HCA in ARDS. The beneficial effect on Ea improved RV–arterial coupling and consequently RV function in this experimental model of ARDS.

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