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Extracorporeal Membrane Oxygenation Blood Flow and Blood Recirculation Compromise Thermodilution-Based Measurements of Cardiac Output

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The contribution of veno-venous (VV) extracorporeal membrane oxygenation (ECMO) to systemic oxygen delivery is determined by the ratio of total extracorporeal blood flow ($\dot{Q}_{EC}$) to cardiac output ($\dot{Q}$). Thermodilution-based measurements of $\dot{Q}$ may be compromised by blood recirculating through the ECMO (recirculation fraction; R*f*). We measured the effects of $\dot{Q}_{EC}$ and R*f* on classic thermodilution-based measurements of $\dot{Q}$ in six anesthetized pigs. An ultrasound flow probe measured total aortic blood flow ($\dot{Q}_{A0}$) at the aortic root. R*f* was quantified with the ultrasound dilution technique. $\dot{Q}_{EC}$ was set to 0–125% of $\dot{Q}_{A0}$ and $\dot{Q}$ was measured using a pulmonary artery catheter (PAC) in healthy and lung injured animals. PAC overestimated $\dot{Q}$ ($\dot{Q}_{Pa}$) at all $\dot{Q}_{EC}$ settings compared to $\dot{Q}_{A0}$. The mean bias between both methods was 2.1 L/min in healthy animals and 2.7 L/min after lung injury. The difference between $\dot{Q}_{Pa}$ and $\dot{Q}_{A0}$ increased with an $\dot{Q}_{EC}$ of 75–125%/$\dot{Q}_{A0}$ compared to Q_{EC} <50%/$\dot{Q}_{A0}$. Overestimation of $\dot{Q}_{Pa}$ was highest when $\dot{Q}_{EC}$ resulted in a high R*f*. Thus, thermodilution-based measurements can overestimate cardiac output during VV ECMO. The degree of overestimation of $\dot{Q}_{Pa}$ depends on the $\dot{Q}_{EC}/\dot{Q}_{A0}$ ratio and the recirculation fraction. *ASAIO Journal* 2022; 68;721–729

Key Words: veno-venous extracorporeal membrane oxygenation, recirculation fraction, cardiac output measurements, thermodilution, acute lung injury

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The main determinant of veno-venous (VV) extracorporeal membrane oxygenation (ECMO) efficacy with respect to improving systemic oxygenation is the ratio of total extracorporeal blood flow (total blood flow delivered through the return cannula [$\dot{Q}_{EC}$]) to cardiac output ($\dot{Q}$). Of importance, blood recirculation occurs when oxygenated blood is withdrawn through the drainage cannula into the extracorporeal circuit without passing into the systemic circulation.[1] This fraction of blood recirculating through the extracorporeal circuit (recirculation fraction [R*f*]) has to be subtracted from $\dot{Q}_{EC}$ to determine the effective extracorporeal flow ($\dot{Q}_{EFF}$; $\dot{Q}_{EFF} = \dot{Q}_{EC} \times (1 - Rf)$.[1]

Calculation of R*f* is clinically difficult as it requires cessation of ECMO sweep gas flow, maintenance of arterial oxygenation by more invasive mechanical ventilation and use of drainage cannula blood as a surrogate for mixed venous blood.[1] A less invasive saline dilution ultrasound technique allows bedside measurements of R*f* without alteration of ECMO sweep gas flow and ventilator settings.[2]

Recirculating blood does not contribute to systemic oxygen delivery (DO_2) but adds to the potentially deleterious side effects of VV ECMO therapy (large bore cannulas in conjunction with the need for systemic anticoagulation and blood exposure to a large nonendothelial surface area).[3–5] To quantify the "best DO_2" during VV ECMO and thus optimize therapy while reducing the inherent risks of ECMO therapy, exact measurements of cardiac output are pivotal. Haller *et al*.[6] demonstrated that thermodilution-based measurements of cardiac output can differ by several liters per minute when compared to cardiac output measurements with direct dye injection into the pulmonary circulation. Given the clinical setting of their work, the effects of different ECMO blood flows and blood recirculation fractions on measurements of cardiac output could not be quantified.

Here, we tested the accuracy of cardiac output measurements with the thermodilution technique using a pulmonary artery catheter (PAC) during VV ECMO in anesthetized pigs. The experimental setting was chosen to support a rigid comparison of the results obtained with the thermodilution technique with "true" aortic blood flow at a set of various standardized ECMO blood flows in pigs with and without lung injury.

Methods

General Procedures

After approval by the federal governmental authorities (LaGeSo G0177/15), experiments were performed in six anesthetized pigs (mean bodyweight 78 ± 9 kg) at the Department of

Experimental Medicine, Charité—University Medicine, Berlin, Germany (certified according to the EN DIN ISO 9001:2000). Premedication, general anesthesia, general cannulation techniques and induction of lung injury were performed as previously described.[7]

In brief, animals were orally intubated (endotracheal tube, ID 8.5 mm; Mallinckrodt Hi-Contour Oral/Nasal Tracheal Tube Cuffed; Covidien), mechanical ventilated (Evita Infinity V500; Dräger, Lübeck, Germany) with a fraction of inspired oxygen (F_IO_2) of 1.0, a tidal volume (V_T) of 6 ml/kg body weight, a positive end-expiratory pressure (PEEP) of 7 cm H_2O, inspiratory to expiratory time ratio (I:E) of 1:1.5 and with a respiratory frequency adjusted to achieve an end-expiratory partial pressure of carbon dioxide ($P_{et}CO_2$) of 35–40 mm Hg. Next, an introducer sheath, a central venous catheter (both left jugular vein) and an arterial catheter (femoral artery) were placed. A PAC (5 F, 75 cm length, model No. 132F5; Edwards Lifesciences Service GmbH, Unterschleissheim, Germany) was inserted *via* the introducer sheath.

Veno-Venous Extracorporeal Membrane Oxygenation

A heparin bolus (2,000 *I.E.*) was injected before cannulation for VV ECMO. Each femoral vein was cannulated with a 19 Fr drainage cannula of 38 cm length (HLS Cannulae Venous 19 Fr, No° BE PVS 1938, MAQUET Vertrieb und Service Deutschland GmbH, Rastatt, Germany), which were connected with a 3/8″ Y-piece to the drainage tubing to achieve high blood flows despite the relatively small diameter of porcine femoral veins compared to humans. A 15 cm 15 Fr return cannula (HLS Cannulae Arterial 15 Fr, model No° BE PAS 1515, MAQUET) was inserted into the right external jugular vein. Immediately after cannulation an ECMO circuit (Permanent Life Support Set, model No° BE-PLS 2050, consisting of a Quadrox PLS oxygenator with a polymethylpentene membrane, gas exchange area 1.8 m^2, filling volume 0.25 L, a ROTAFLOW centrifugal pump and heparin-coated tubing, operated with a ROTAFLOW console and drive unit; MAQUET) was connected and the initial extracorporeal flow ($\dot{Q}_{EC}$) was set at 2 L/min. The sweep gas flow was adapted to target an arterial pressure of carbon dioxide (P_aCO_2) of 35–50 mm Hg at a respiratory frequency of 12/min. All cannulas were always fully introduced at the described insertion sites. Thus, the positions of the cannulas were comparable in all animals. Furthermore, cannula position was controlled by postmortem examinations.

Aortic Blood Flow Measurements

After implementation of VV ECMO, pigs were placed in the right lateral decubitus position and a lateral left thoracotomy was performed between the third and fourth rib. The pericardium was opened and a 16 mm vascular flow probe (TTFM flow probe, PA100161, connected to a Butterfly Flowmeter, BF 2004; Medistim Deutschland GmbH, Deisenhofen, Germany) was placed around the ascending aorta as close to the heart as possible but distal to the coronary arteries. The right lateral decubitus position of the animals was not changed after thoracotomy for the entire experiment. After placement of the flow probe, the lungs were recruited by a recruitment maneuver while visually confirming good positioning of the aortic flow probe. The thoracic cavity was covered with a plastic film dressing to maintain optimal placement of the flow probe. All animals received an i.v. infusion 2 g of magnesium sulfate (Magnesiumsulfat 50%; Inresa Arzeneitmittel GmbH, Freiburg im Breisgau, Germany) and 300 mg of amiodarone (Cordarex; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany) before opening the pericardium to prevent tachyarrhythmias.

Study Protocol and Thermodilution-Based Measurements

Continuous aortic blood flow ($\dot{Q}_{A0}$) measurements obtained from the ascending aorta were used as reference blood flow of native cardiac output. Absolute ECMO blood flow was measured with the in-pump ultrasound flowmeter of the ECMO console and set to 25, 50, 75, 100, 125% of the aortic flow probe values ($[\dot{Q}_{EC}/\dot{Q}_{A0}] \times 100$) in randomized order, except for measurements at 25% and 0% $\dot{Q}_{EC}/\dot{Q}_{A0}$, which were performed last to prevent oxygenator clotting. Instead of stopping ECMO blood flow completely $\dot{Q}_{EC}$ was set to 0.25 L/min for 0% $\dot{Q}_{EC}/\dot{Q}_{A0}$. An additional heparin bolus of 1,000 *I.E.* was injected before measurements for 0% Q_{EC}/Q_{AO} minimize the risk of clotting.

An i.v. bolus of 250 ml of a colloid solution containing 4% gelatin (4% Gelafundin Ecoflac plus; B. Braun Melsungen AG, Melsungen, Germany) was infused up to three times if $\dot{Q}_{EC}$ could not be increased or the pressure in the drainage tubing decreased below −70 mm Hg.

All measurements were always obtained in the same standardized order. After allowing for 15 minutes of equilibration at each blood flow, thermodilution measurements with the PAC ($\dot{Q}_{Pa}$) were taken first in quintuples (highest and lowest values discarded) in randomized order over the respiratory cycle (0.9% saline, 4°C, 5 ml volume—Baxter, Vigilance Cardiac Output monitor; Edwards Critical Care Division, Irvine, California). All additional hemodynamic data were continuously recorded using a digital data acquisition system (LabChart; ADInstruments, Colorado Springs). Then, arterial, mixed venous, as well as pre- and postoxygenator blood gases were drawn. Last, the recirculation fraction was measured.

Recirculation Measurements

The recirculation fraction (R*f*) was measured with the ultrasound dilution technique (UDT, Transonic ELSA Monitor, Extracorporeal Life Support Assurance; Transonic Systems Inc., Ithaca, NY) as described previously.[8–11] The UDT is based on measuring a change in ultrasound velocity after injecting 20 ml 0.9% saline with two ultrasound sensors. One sensor was placed around the return tubing of the ECMO circuit while the other sensor was placed around the drainage tubing. Saline was injected directly before the oxygenator. The change in ultrasound velocity in the drainage tubing depends on how much blood (and saline) recirculates (Figure 1). The R*f* was also calculated using the oxygen content of mixed venous blood, preoxygenator and postoxygenator blood as published by the Extracorporeal Life Support Organization for comparison.[12]

Acute Lung Injury

After performing all measurements in healthy pigs, acute lung injury (ALI) was induced using the surfactant washout model

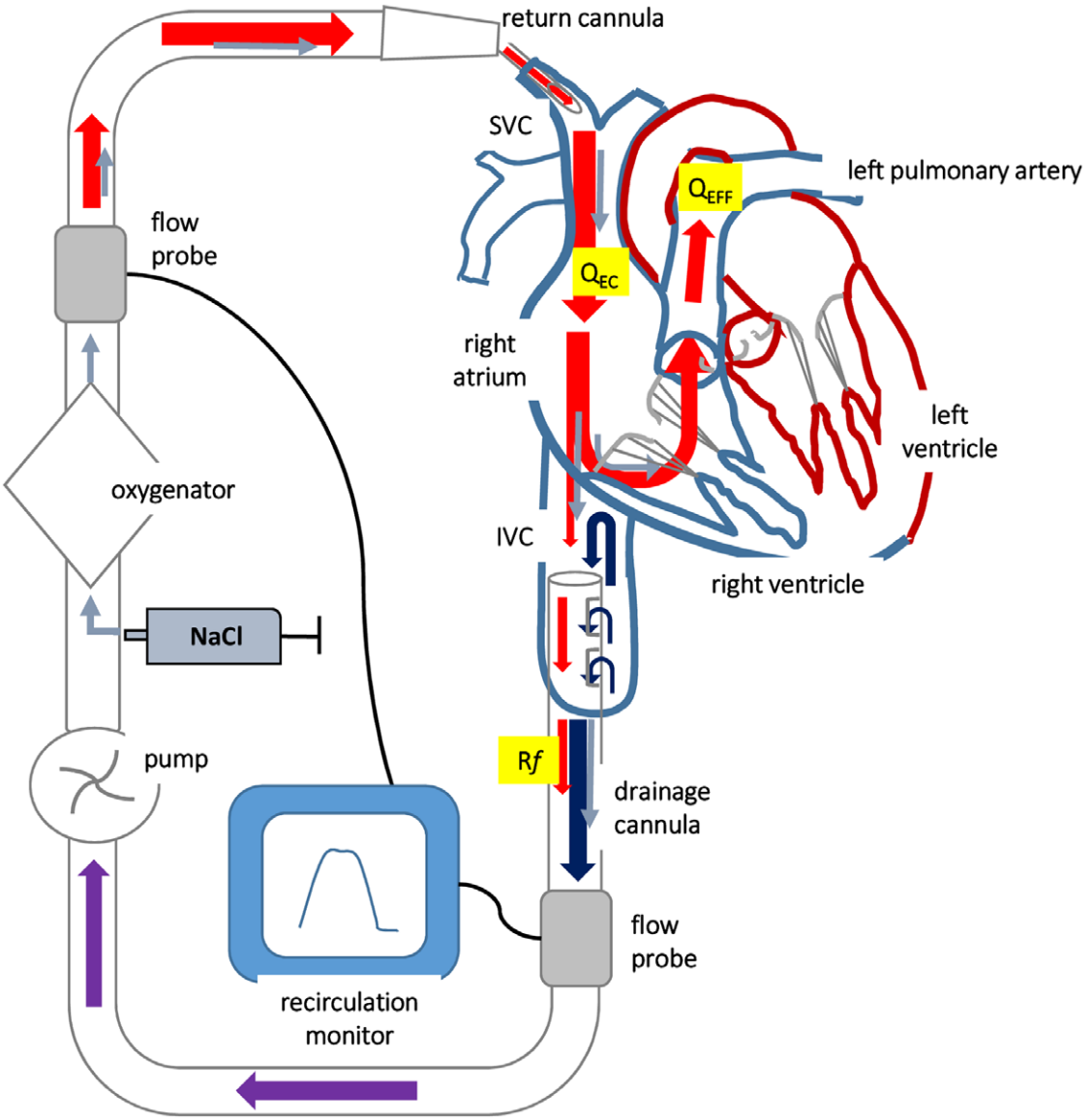

Figure 1. Cannula position, blood flow, measurement of the recirculation fraction during veno-venous extracorporeal membrane oxygenation. Total extracorporeal blood flow ($\dot{Q}_{EC}$) of the extracorporeal membrane oxygenation (ECMO) is (i) pumped by the right heart into the pulmonary artery and then further into systemic circulation—resulting in an effective ECMO blood flow ($\dot{Q}_{EFF}$) and (ii) partially drained into the drainage cannula and thus recirculates through the ECMO circuit. This is called recirculation fraction (R*f*). Red Arrows: oxygenated blood; deep blue arrows: deoxygenated blood; purple arrow: mixed blood; light blue arrows: saline injection. The R*f* is measured with the ultrasound dilution technique requiring the injection of 0.9% saline (NaCl) into the ECMO circuit before the oxygenator. The saline bolus alters the ultrasound transit-time of blood and the transit-time is measured with two ultrasound flow probes placed around the drainage and the return tubing of the ECMO circuit. The difference in the ultrasound transit-time measurements between return and drainage cannula is used to calculate R*f*. full color online

(2–5 lavages, 0.9% saline, 37°C, 50 ml/kg body weight).[7] For baseline measurements after lavages, $\dot{Q}_{EC}$ was set to 1 L/min and sweep gas flow was paused. Thus, the extent of lung injury was evaluated against only minimal oxygenation provided by the ECMO and no relevant extracorporeal carbon dioxide removal. Norepinephrine was used to maintain a steady mean arterial blood pressure (MAP; 70–80 mm Hg) with dosages up to 0.1 µg/kg/min after induction of ALI.

Statistics

Given the small sample size, nonparametric tests were used, although the Kolmogorov-Smirnov test did not demonstrate a significant difference from a normal distribution for the datasets ($p > 0.05$). Data were analyzed using Kruskal-Wallis test with post hoc testing according to Dunn for intergroup comparisons (*e.g.,* flow probe *vs.* PAC). The Friedman test with post hoc application of Kendall's W test was used for intragroup comparisons (*e.g.,* measured with the PAC at different points of time). All pairwise post hoc *p* values were adjusted for multiple comparisons with first-order Bonferroni correction. The data are presented as mean ± SD. A two-sided *p*-value of <0.05 defined statistical significance (SPSS Version 24; IBM Corp., Armonk, NY). The data were visualized as Bland-Altman plots and x/y scatterplots with Spearman correlation coefficient with GraphPad Prism 6 for Windows.

Results

Aortic Blood Flow and Acute Lung Injury

All six animals were included in the statistical analysis. In two animals, ECMO blood flow could not be reduced to 0% and 25% of aortic blood flow after induction of ALI because of severe hypoxemia. Induction of lung injury resulted in significant hypoxemia (P_aO_2/F_IO_2 97 ± 62.5 mm Hg) and hypercapnia (P_aCO_2 57 ± 14.9 mm Hg) and a twofold increase in mean pulmonary arterial pressure (MAP 30 ± 4.1 mm Hg) (Table 1).

Measurements of $\dot{Q}_{A0}$ were consistent throughout the experiments. The largest SD observed of $\dot{Q}_{A0}$ measurements was 0.91 L/min (Figure 2, A and B). On average, $\dot{Q}_{A0}$ was 4.3 ± 0.7 L/min in healthy animals and 4.3 ± 0.6 L/min after induction of ALI (Figure 2, A and B).

Thermodilution-Based Cardiac Output Measurements

$\dot{Q}_{Pa}$ overestimated cardiac output compared to $\dot{Q}_{A0}$ (difference of mean $\dot{Q}$ values of 1.38 L/min) even at low extracorporeal blood flows ($\dot{Q}_{EC}$) (Figure 2, A and B). This overestimation of $\dot{Q}_{Pa}$ values increased with higher $\dot{Q}_{EC}$ and with increased percentage of blood recirculating through the ECMO circuit (difference of mean $\dot{Q}$ values of 2.9 L/min) (Figure 2, A and C). The bias between $\dot{Q}_{Pa}$ and $\dot{Q}_{A0}$ was 2.1 L/min (Figure 2A) in healthy animals and 2.7 L/min after induction of ALI (Figure 2B), translating to a difference of 37% (healthy) or 44% (ALI). A stratification of the Bland-Altman plots to lower ECMO blood flow rates (0–50% $\dot{Q}_{EC}$ / $\dot{Q}_{A0}$) revealed a better agreement of both methods with a bias of 1.3 L/min (healthy animals) and 1.5 L/min (ALI) (online only, see Supplemental Figure 1, A and B, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A758), whereas the agreement decreased with higher ECMO blood flow rates (75 – 125% $\dot{Q}_{EC}$ / $\dot{Q}_{A0}$) to a bias of 2.7 L/min (healthy) and 3.7 L/min (ALI) respectively (see Supplemental Figure 1, C and D, Supplemental Digital Content 1, http://links.lww.com/ASAIO/A758).

Recirculation Fraction, Oxygen Delivery and Consumption

The recirculation fraction was 2.5 ± 4.2% in healthy pigs and 0.8 ± 2% after induction of ALI when ECMO blood flow was adjusted up to 75% of $\dot{Q}_{A0}$ (Figure 2, C and D), but increased to an R*f* above 25% (healthy and lung injured animals) when ECMO blood flow was set above $\dot{Q}_{A0}$ (Figure 2C and Table 1). Calculation of R*f* confirmed the increasing R*f* values with increasing $\dot{Q}_{EC}$, albeit calculated R*f* values were significantly lower at maximum $\dot{Q}_{EC}$ after ALI (see Supplemental Figure 2, Supplemental Digital Content 2, http://links.lww.com/ASAIO/A759).

Calculation of systemic oxygen delivery (DO_2) with $\dot{Q}_{Pa}$ values resulted in a comparably sloped graph when plotting the values against an increasing $\dot{Q}_{EC}$. By contrast with DO_2, calculation of systemic oxygen consumption ($\dot{V}O_2$) with $\dot{Q}_{Pa}$ values resulted in a downward-sloped graph when plotting the values against an increasing $\dot{Q}_{EC}$ (Figure 3, A–D).

Discussion

We measured cardiac output during VV ECMO in pigs using a PAC. Blood flow measurements at the aortic root served as the closest approximation of "true" cardiac output obtainable. We found that the classic thermodilution-based technique with the PAC measured cardiac output with a clinically significant difference from aortic blood flow. This overestimation of $\dot{Q}$ increased both with higher ECMO blood flow and with increasing fractions of blood recirculating through the extracorporeal circuit.

Extracorporeal Membrane Oxygenation Blood Flow and Thermodilution-Based Cardiac Output Measurements

We systematically tested the validity of thermodilution-based cardiac output measurements with a PAC during VV ECMO in pigs. Identical oxygenators, ECMO circuits, cannulas and insertion sites as well as depths of insertion were used in all experiments. In addition, animal age, size and bodyweight, anesthesia, F_IO_2 (ventilator and oxygenator), tidal volumes, PEEPs, respiratory frequencies as well as the ratio of $\dot{Q}_{EC}$ / $\dot{Q}_{A0}$ were standardized and comparable over the time course of the experiments. Thus, absolute extracorporeal blood flow and the recirculation fraction mainly influenced $\dot{Q}_{Pa}$.

Haller *et al.*[6] first demonstrated that $\dot{Q}_{Pa}$ measurements consistently overestimate cardiac output during VV ECMO for ARDS in the intensive care unit. "True" cardiac output was elegantly measured by injecting indicator dye directly into the pulmonary artery, hence avoiding partial recirculation of the indicator through the ECMO circuit. Yet, Haller *et al.* could neither quantify the influence of extracorporeal blood flow in relation to intrinsic cardiac output and recirculation volume nor could they equalize cannula sizes and sites or standardize mechanical ventilation due to the clinical nature of their study.

In our experiments, the difference between $\dot{Q}_{Pa}$ and $\dot{Q}_{A0}$ increased with increasing extracorporeal blood flow. Yet, at ECMO blood flows below 50% of $\dot{Q}_{A0}$ and measured recirculation volumes of smaller than 5%, the mean difference between both methods was 1.3–1.4 L/min despite the controlled experimental setting with constant injectate volume and temperature, speed and method of injection (PAC) as well as the prevention of changes in venous return by suppressed spontaneous breathing. In addition, the impact of positive pressure ventilation on cardiac output measurements was minimized by random injection in even intervals over the full respiratory cycle.

We observed a second peak in the temperature change *vs.* time curve during measurements at high ECMO blood flows (Figure 4). The strict order of measurements prevented an accidental admixture of a saline bolus from one method (*e.g.* UDT) to another method (cardiac output). Furthermore, erroneous measurements caused by an accidental mixture of a saline bolus from the different measuring methods could not result in an increasing difference between $\dot{Q}_{Pa}$ and $\dot{Q}_{A0}$ with increasing extracorporeal blood flow. Instead, we speculate that the observation could be explained by a rapid recirculation of cold injectate through the extracorporeal circuit without sufficient heating of the cold bolus in the oxygenator due to the short contact time at high $\dot{Q}_{EC}$ (extracardiac shunt). Erroneous measurements caused by "close" proximity of injection and detection point (*e.g.*, in the inferior caval vein and the aorta) is a known phenomenon in transpulmonary thermodilution and demonstrates the susceptibility to error of the sensitive thermal

Table 1. Hemodynamic Data, Gas Exchange, ECMO Settings, and Recirculation Fraction at the Targeted ECMO Blood Flows

	$\dot{Q}_{EC}/\dot{Q}_{Ao}$ —Healthy						$\dot{Q}_{EC}/\dot{Q}_{Ao}$ —Lung Injury					
	Baseline	25%	50%	75%	100%	125%	Baseline	25%	50%	75%	100%	125%
Heart rate (beats/min)	60 ± 7	64 ± 5	62 ± 4	63 ± 5	62 ± 5	63 ± 5	71 ± 13	72 ± 11	71 ± 11	72 ± 7*	68 ± 9	70 ± 6
Mean AP (mm Hg)	102 ± 15	84 ± 10	86 ± 16	89 ± 14	89 ± 13	90 ± 13	66 ± 14*	74 ± 9	79 ± 7	75 ± 9	82 ± 12	81 ± 7
Mean PAP (mm Hg)	15 ± 1	18 ± 4	18 ± 2	16 ± 4	16 ± 2	17 ± 2	30 ± 4*	30 ± 6*	27 ± 3*	24 ± 4*	25 ± 6*	25 ± 4*
PCWP (mm Hg)	9 ± 1	7 ± 3	8 ± 2	8 ± 2	8 ± 1	8 ± 4	12 ± 2*	11 ± 2	11 ± 3	11 ± 3	11 ± 3	13 ± 2*
CVP (mm Hg)	5 ± 3	5 ± 3	5 ± 1	4 ± 1	3 ± 1	2 ± 3	9 ± 3*	7 ± 2	8 ± 3	6 ± 3	6 ± 3	5 ± 2
SpO_2 (%)	100	100	100	100	100	100	87 ± 10*	98 ± 2	93 ± 6*	98 ± 5	99 ± 1	99 ± 2
P_aO_2 (mm Hg)	540 ± 26	461 ± 42	453 ± 62	424 ± 83	386 ± 73	420 ± 70	97 ± 63*	243 ± 137*	214 ± 143*	190 ± 112*	226 ± 85*	227 ± 99*
P_aCO_2 (mm Hg)	50 ± 9	43 ± 2	41 ± 2	38 ± 2	39 ± 1	39 ± 2	57 ± 15	43 ± 2	42 ± 2	43 ± 6	42 ± 4	42 ± 4
Arterial pH	7.43 ± 0.04	7.47 ± 0.01	7.51 ± 0.03	7.53 ± 0.02	7.52 ± 0.02	7.52 ± 0.02	7.34 ± 0.09	7.44 ± 0.02	7.44 ± 0.06*	7.44 ± 0.08*	7.46 ± 0.04*	7.44 ± 0.06*
Arterial HCO_3^- (mmol/L)	33 ± 2.4	30 ± 1.6	33 ± 1.3	32 ± 1.6	32 ± 1.2	32 ± 1.1	29 ± 1.5*	29 ± 2.2	28 ± 3*	28 ± 2.9*	29 ± 2.2*	26 ± 6
Hemoglobin (g/dL)	9.4 ± 1.2	7.3 ± 1	7.2 ± 0.8	7.1 ± 0.9	7 ± 0.9	6.6 ± 0.9	6.9 ± 0.8*	7.8 ± 0.8	6.9 ± 0.6	6.7 ± 1	6.9 ± 0.9	6.4 ± 1
ECMO blood flow (L/min)	2.6 (one pig)	1.12 ± 0.22	2.6 ± 0.35	3.19 ± 0.57	4.28 ± 0.62	5.36 ± 0.93	1.75 ± 0.82	1.05 ± 0.06	2.03 ± 0.38	3.33 ± 0.53	4.12 ± 0.49	5.5 ± 0.59
ECMO sweep gas flow (L/min)	2.5 (one pig)	8 ± 2	4 ± 1	4 ± 1	3 ± 1	3 ± 0.5	2 ± 2	9.5 ± 1	7 ± 2*	5 ± 1	5 ± 2*	4 ± 2
Rf (%)		0	0	2.5 ± 4.2	16.8 ± 8.4	28.3 ± 8.4		0	0	0.83 ± 2	11 ± 6.5	26.2 ± 6.5

Extracorporeal membrane oxygenation (ECMO) blood flow of $\dot{Q}_{EC}$ was set at a defined percentage of total aortic blood flow of ($\dot{Q}_{Ao}$) for each predefined measurement. The table presents the respective hemodynamic data, gas exchange and resulting ECMO settings measured in healthy animals and after induction of lung injury.

Data presented as mean ± SD. Mann-Whitney *U* test for comparison of parameters at corresponding ECMO blood flows.

*Marks $p < 0.05$ vs. healthy animal.

AP, arterial pressure; CVP, central venous pressure; HCO_3^-, bicarbonate concentration; P_aCO_2, arterial partial pressure of carbon dioxide; P_aO_2, arterial partial pressure of oxygen; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; S_pO_2, peripheral oxygen saturation.

filaments.[13–15] Interestingly, this notion is supported by the exact same observation of indicator loss into the ECMO circuit made by Haller *et al*.[6]

Recirculation of the indicator likely explains the increasing error of thermodilution-based cardiac output measurements with higher $\dot{Q}_{EC}$ and large recirculation fractions. The consistent difference between $\dot{Q}_{Pa}$ and $\dot{Q}_{A0}$ measurements at $\dot{Q}_{EC}/\dot{Q}_{A0}$ ratios below 50% are more likely to be caused by rapid changes of the injectate temperature by the constant flow of warmed blood through the return cannula during VV ECMO.[16] Togo and colleagues found an R*f* of 10% at a $\dot{Q}_{EC}$ of 2 L/min in goats.[17] The drainage cannula was inserted in the inferior caval vein and the return cannula in the superior caval vein with the help of angiography in their experiments. Thus, recirculation of blood and possibly the indicator can happen at low $\dot{Q}_{EC}$ despite an "optimal" cannula placement with respect to the distance between the cannula tips.

Alternatively, immeasurable amounts of injectate following the reinfusion jet from the superior vena cava toward the drainage cannula (inferior vena cava) may explain these differences. Mixing of the indicator with blood from the return cannula cannot be excluded independent of the position of return cannula and PAC (or central venous line in case of transpulmonary thermodilution) since turbulent flow is the predominant flow property close to side holes of drainage as well as return cannulas.[18–20]

Of note, increases in pulmonary vascular resistance and concomitant right ventricular dysfunction are common in ARDS and can cause tricuspid valve regurgitation in up to 50% of all patients that may additionally compromise thermodilution-based cardiac output measurements.[21–23] Pulmonary artery pressures increased almost twofold in our experiments after induction of lung injury, but we observed no change in the shape of the central venous pressure curve. While theoretically explaining the difference between $\dot{Q}_{Pa}$ and $\dot{Q}_{A0}$ after lung injury, regurgitation of cold injectate through an insufficient tricuspid valve would not explain the erroneous measurement of $\dot{Q}$ with the thermodilution technique in otherwise healthy animals with normal pulmonary vascular resistance and $\dot{Q}_{EC}/\dot{Q}_{A0}$ ratios of <50%.

Systemic Oxygen Delivery and Oxygen Consumption

Neither DO_2 nor VO_2 could be reliably calculated in these experiments. Both parameters are mathematically coupled to cardiac output and any methodological error in the determination of $\dot{Q}$ will falsify DO_2 or VO_2 by the degree of inaccuracy of $\dot{Q}$.[24] In addition, VO_2 is calculated as the product of $\dot{Q}$ and the difference between arterial and mixed venous oxygen content. The decrease in VO_2 values with higher ECMO blood flows was the result of the increasing admixture of oxygenated blood to mixed venous blood by the VV ECMO circuit.[25]

Recirculation Fraction During Veno-Venous Extracorporeal Membrane Oxygenation Therapy in the Intensive Care Unit

Blood recirculating through the extracorporeal circuit without contributing to systemic oxygen delivery is exclusive to VV ECMO. Recirculation is affected by cannula size-, configuration and cannula position and extracorporeal flow.[1, 17, 26, 27] In

addition, cardiac output, volume status, intra-thoracic, intra-cardiac and intra-abdominal pressures as well as venous vascular anomalies all affect the recirculation fraction and hence systemic oxygenation.[1, 28] Several methods exist to calculate the R*f* from blood gas analysis, but measuring R*f* in VV ECMO is technically not simple and prone to error.[1, 12, 29] All methods to calculate R*f* rely on the exact measurements of mixed venous blood oxygen saturation (S_vO_2) or central venous oxygen saturation as a surrogate of S_vO_2. But, S_vO_2 cannot be measured correctly in case of VV ECMO since reoxygenated blood from the ECMO return cannula inevitably mixes with central venous blood. We measured R*f* with the UDT which does not depend on S_vO_2.[2, 8–11]

Limitations

We did not evaluate the effect of changing PEEP levels on the amount of recirculation fraction in our pig study. This might

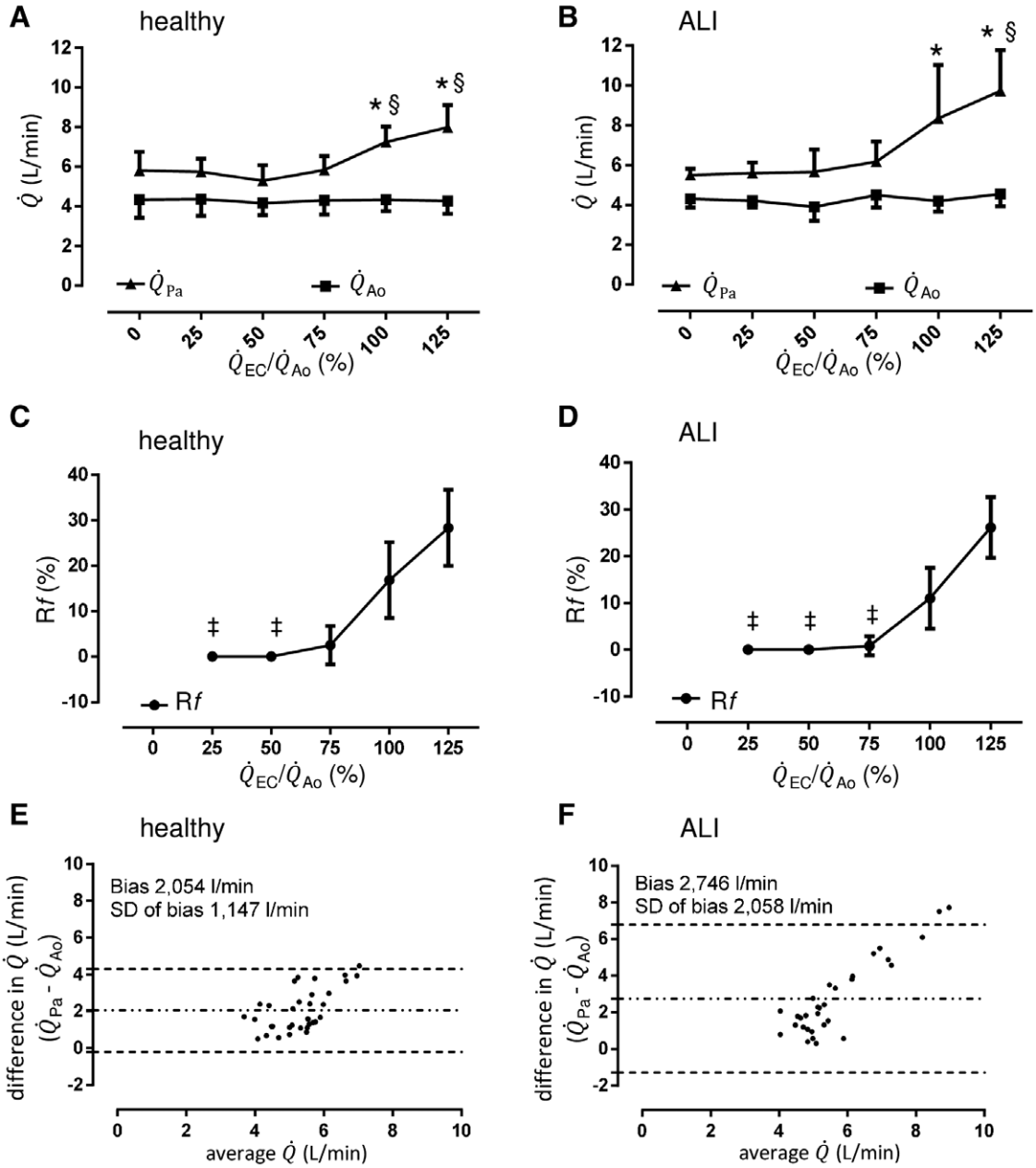

Figure 2. Measurements of cardiac output and blood recirculation during veno-venous extracorporeal membrane oxygenation. **A**: Cardiac output ($\dot{Q}$) measurements performed with an ultrasound-based flow probe placed around the ascending aorta (yielding total aortic blood flow ($\dot{Q}_{AO}$) compared to thermodilution-based measurements with a pulmonary artery catheter (yielding $\dot{Q}_{Pa}$) in healthy animals at different extracorporeal blood flows ($\dot{Q}_{EC}$) set at defined ratios of $\dot{Q}_{EC}$ / $\dot{Q}_{A0}$. **B**: Measurements as in A after induction of acute lung injury (ALI). **C**: Recirculation fraction (R*f*) of blood within the extracorporeal membrane oxygenation (ECMO) circuit measured with the ultrasound dilution technique at different $\dot{Q}_{EC}$ in healthy animals. **D**: R*f* as in C after induction of ALI. **E**: Bland-Altman plot of the difference in cardiac output ($\dot{Q}$) measurements as thermodilution-based measurements with a pulmonary artery catheter ($\dot{Q}_{Pa}$)—total aortic blood flow ($\dot{Q}_{A0}$) against average blood flow $\dot{Q}$ in healthy animals. **F**: Bland-Altman plot as in E after induction of ALI. Values are mean ± SD; **p* < 0.05 *vs.* ultrasound flow probe; §*p* < 0.05 *vs.* ECMO blood flow 50%; ‡*p* < 0.05 *vs.* ECMO blood flow 125%.

be important as changes in PEEP alter intra-thoracic pressures and venous return with unquantified contribution to the R*f* during VV ECMO therapy.

We measured $\dot{Q}_{A0}$ in pigs with a vascular flow probe placed around the ascending aorta. The major source of error using this technique is a misplacement of the vascular flow probe. The direction of the ultrasound must be perpendicular to blood flow to correctly quantify transit-time measurements of the passing red blood cells through the aorta. We placed the flow probes under direct view after left thoracotomy and did not move the animal afterwards. Furthermore, we did not close the thorax to allow repeated confirmation of its proper positioning. Yet, although the $\dot{Q}$ values obtained with flow probe were stable with a relatively small SD, we did not independently quantify the validity of our measurement by other independent techniques (e.g. the indocyanine dye method).

Of note, $\dot{Q}_{A0}$ can only approximate "true" cardiac output since it does not include total coronary blood flow (TBCF). TBCF of domestic pigs under anesthesia can reach 2.3 ml/kg body weight/min, but may quintuple during exercise.[30,31] The highest recorded heart rate in our experiments was 80 beats/min. Thus, we assume that TCBF in our experiments was comparable to values measured during deep anesthesia and rest by Ootaki and colleagues.[31] Based on calculations for a pig of 80 kg, CO measurements at the aortic root underestimated "true" CO by approximately 185 ml/min. Even if TCBF was fivefold $\dot{Q}_{A0}$ would have underestimated "true" CO by 925 ml/min. Thus, the error does not explain the total difference between $\dot{Q}_{A0}$ and $\dot{Q}_{Pa}$ measurements in our experiments. Furthermore, TCBF cannot explain the increasing difference between $\dot{Q}_{A0}$ and $\dot{Q}_{Pa}$ with increasing ECMO blood flow in healthy animals with a steady heart rate.

We did not control for PAC positioning with x-ray scans nor the presence of intracardiac shunts. While exact PAC positioning is important for the measurement of pulmonary artery pressure, it does not influence $\dot{Q}$ measurements in pigs.[32] In contrast, intracardiac shunts cause a positive deflection of the usual exponential downslope of the thermodilution curve, which was not observed in our experiments.[33]

A further limitation of our animal study is that we did not ensure equal cannula placement and distance either by ultrasound, x-ray or CT scans. Because of the standardization of animal size and age and insertion of the cannulae to maximal depth, we assumed that the distances between in- and outflow cannulae were comparable in our experiments. This assumption was verified by postmortem examinations.

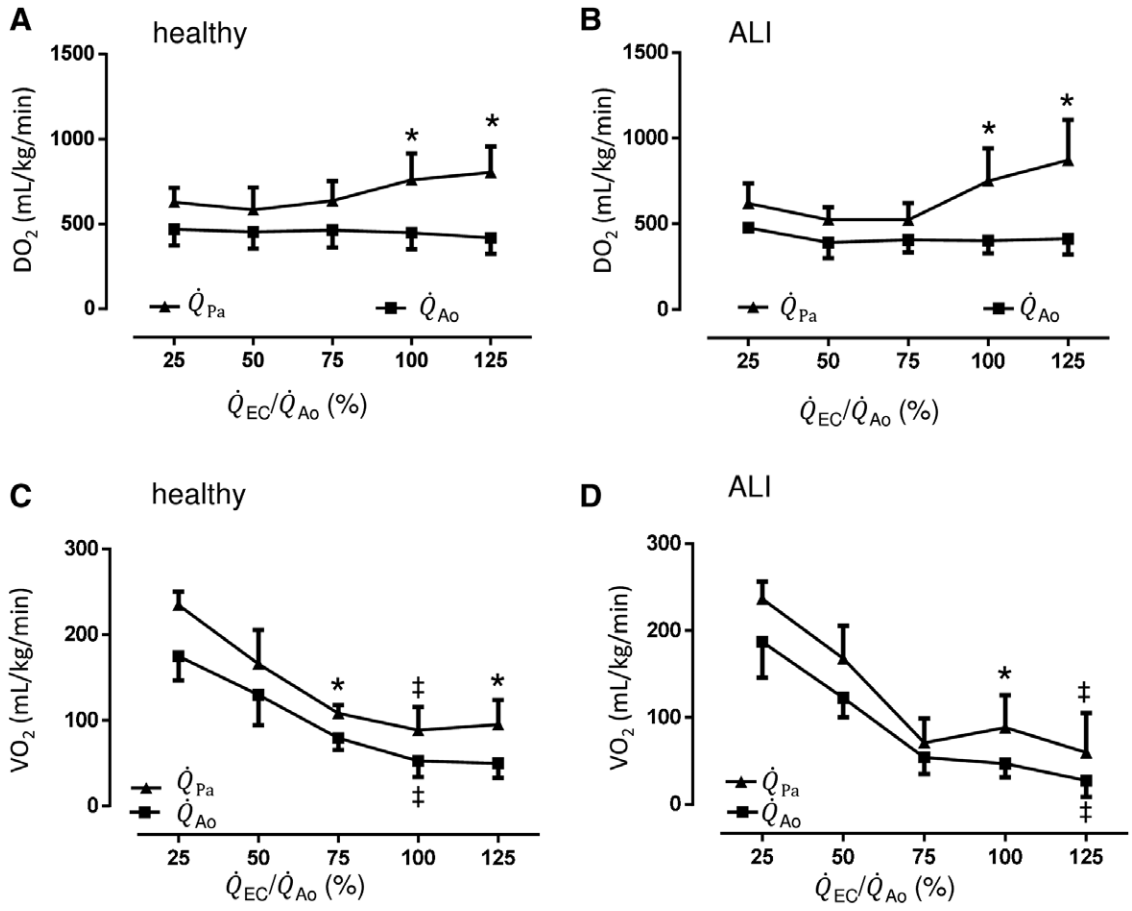

Figure 3. Relation of oxygen delivery and oxygen consumption values to measurements of cardiac output during veno-venous extracorporeal membrane oxygenation. **A**: Systemic oxygen delivery (DO_2) values calculated using cardiac output ($\dot{Q}$) measured with a pulmonary artery catheter ($\dot{Q}_{Pa}$) or measured with an ultrasound-based flow probe placed around the ascending aorta ($\dot{Q}_{A0}$) in healthy animals at different extracorporeal membrane oxygenation (ECMO) blood flows ($\dot{Q}_{EC}$) set at defined ratios of $\dot{Q}_{EC}$ / $\dot{Q}_{A0}$. **B**: Calculations as in A after induction of acute lung injury (ALI). **C**: Systemic oxygen consumption (VO_2) values calculated using $\dot{Q}_{Pa}$ or $\dot{Q}_{A0}$. **D**: Calculations as in C after induction of ALI. Values are mean ± SD; *$p < 0.05$ *vs.* ultrasound flow probe; ‡$p < 0.05$ *vs.* ECMO blood flow 25%.

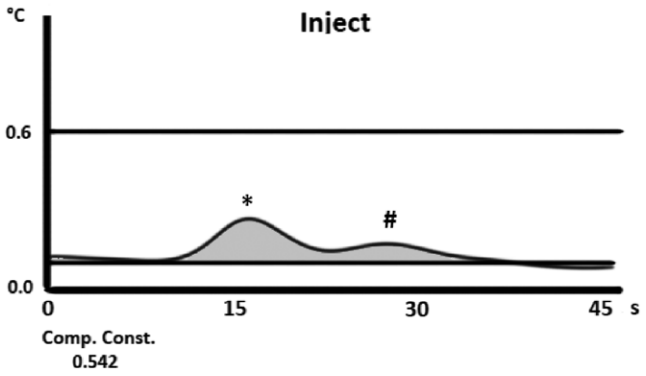

Figure 4. Temperature change *vs.* time graph of a thermodilution measurement using the pulmonary artery catheter during veno-venous extracorporeal membrane oxygenation. The graph was extrapolated from a photograph of the cardiac output monitor using SketchBook 5.1.0.0 and Paint for Windows. The photograph was taken while measuring cardiac output ($\dot{Q}$) with the pulmonary artery catheter at a extracorporeal membrane oxygenation (ECMO) blood flow of 75% of total aortic blood flow ($\dot{Q}_{A0}$) measured with a flow probe. *Highlights the expected first peak in the temperature change *vs.* time curve. The second peak (#) is likely caused by partial recirculation of the cold saline bolus through the ECMO circuit.

Conclusion

We measured cardiac output during VV ECMO in pigs and found that the classic thermodilution-based technique with a PAC measured $\dot{Q}$ with a clinically significant difference from cardiac output measured at the aortic root. The measured values for $\dot{Q}$ differed by several liters per minute from blood flow measured at the aortic root. Thus, the findings may suggest the futility of thermodilution-based measurements of cardiac output in the clinical application of VV ECMO.

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