Gas exchange calculation may estimate changes in pulmonary blood flow during veno-arterial extracorporeal membrane oxygenation in a porcine model

Kaspar F. Bachmann,1,2 Matthias Haenggi,2 Stephan M. Jakob,2 Jukka Takala,2 Luciano Gattinoni,3 and David Berger2

1Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; 2Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; and 3Department of Anesthesiology, Emergency and Intensive Care Medicine, University of Göttingen, Göttingen, Germany

Submitted 8 April 2019; accepted in final form 10 April 2020

Bachmann KF, Haenggi M, Jakob SM, Takala J, Gattinoni L, Berger D. Gas exchange calculation may estimate changes in pulmonary blood flow during veno-arterial extracorporeal membrane oxygenation in a porcine model. Am J Physiol Lung Cell Mol Physiol 318: L1211–L1221, 2020. First published April 15, 2020; doi:10.1152/ajplung.00167.2019.—Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is used as rescue therapy for severe cardiopulmonary failure. We tested whether the ratio of CO₂ elimination at the lung and the V-A ECMO (VCO₂ECMO/VCO₂Lung) would reflect the ratio of respective blood flows and could be used to estimate changes in pulmonary blood flow (Q̇lung), i.e., native cardiac output. Four healthy pigs were centrally cannulated for V-A ECMO. We measured blood flows with an ultrasonic flow probe. VCO₂ECMO and VCO₂Lung were calculated from side-stream capnographs under constant pulmonary ventilation during V-A ECMO weaning with changing sweep gas and/or V-A ECMO blood flow. If ventilation-to-perfusion ratio (V/Q) of V-A ECMO was not 1, the VCO₂ECMO was normalized to V/Q = 1 (VCO₂ECMONorm). Changes in pulmonary blood flow were calculated using the relationship between changes in CO₂ elimination and V-A ECMO blood flow (Q̇ECMO). Q̇ECMO correlated strongly with VCO₂ECMONorm (r² 0.95–0.99). Q̇lung correlated well with VCO₂Lung (r² 0.65–0.89, P < 0.002). Absolute Q̇lung could not be calculated in a nonsteady state. Calculated pulmonary blood flow changes had a bias of 76 (−266 to 418) mL/min and correlated with measured Q̇lung (r² 0.974–1.000, P = 0.1 to 0.006) for cumulative ECMO flow reductions. In conclusion, VCO₂ of the lung correlated strongly with pulmonary blood flow. Our model could predict pulmonary blood flow changes within clinically acceptable margins of error. The prediction is made possible with normalization to a V/Q of 1 for ECMO. This approach depends on measurements readily available and may allow immediate assessment of the cardiac output response.

ECMO treatment challenging. Monitoring of the cardiac function and the evolution of native cardiac output during V-A ECMO treatment is not well standardized. Echocardiography is often used, but it requires specific knowledge (1) and routine echocardiographic parameters may not be useful in this context because of altered circulatory physiology and changing cardiac loading conditions (12). Monitoring of the evolution of native cardiac output based on simple, noninvasive, and readily available measurements would therefore be helpful in clinical practice, particularly during weaning, since early weaning success is associated with a favorable prognosis (9).

Gas exchange during V-A ECMO should reflect the combined effect of ventilation and perfusion of the native lung and those of the V-A ECMO circuit (21). We hypothesize that during V-A ECMO weaning the ratio between changes in CO₂ elimination at the lung and the V-A ECMO (VCO₂ECMO and VCO₂Lung) is the same as the ratio between changes in the respective flows (Q̇ECMO and Q̇Lung). We tested this hypothesis in this preliminary, hypothesis-generating study by measuring the elimination of CO₂ over the native lung and the V-A ECMO and the respective blood flows and compared the calculated flow changes with those directly measured from the pulmonary artery and V-A ECMO circuit.

METHODS

Animal care, surgery, and anesthesia. This study was performed as a preliminary, independent substudy of a yet-unpublished project evaluating regional abdominal circulation during V-A ECMO and systemic inflammation, where measurements were done before the main study protocol was started. The study complied with the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences, 1996) and Swiss National Guidelines and was approved, including an amendment for this substudy, by the Commission of Animal Experimentation of Canton Bern, Switzerland (BE119/17).

We studied a convenience sample of four animals (2 male and 2 female, 51.5 ± 1.3 kg) before the main study protocol was started. The pigs fasted for 12 h with free access to water. After anesthesia induction with intravenous midazolam and atropine and oral intubation, anesthesia was maintained with propofol and fentanyl, and the depth was controlled by repeatedly testing the response to nose pinch in additional to bispectral index target < 60 (BIS Quatro; Covidien, Mansfield, MA). Additional injections of fentanyl (50 μg) or midazolam (5 mg) were given as needed. Muscle relaxation was induced with rocuronium (0.5 mg/kg). Mechanical ventilation [volume control mode, positive end-expiratory pressure (PEEP) 5 cmH₂O, fraction of
inspired O₂ (Ḟ\textsubscript{\text{O₂}}) 0.3] was initiated with a tidal volume (V\text{̇\textsubscript{T}}) of 7 mL/kg and a respiratory rate aiming at an end-tidal PCO\textsubscript{2} (PET\text{\textsubscript{CO₂}}) of 45 mmHg. A 5-Fr introducer sheath was placed in the right carotid artery for arterial blood pressure measurement and arterial blood gas sampling. Two three-lumen central venous lines were placed in the right and left jugular veins for right atrial pressure measurement and continuous administration of sedatives and vasopressors. V-A ECMO with right atrial-aortic cannulation and a left atrial vent (Maquet Cardioline, Quadrox MECC oxygenator, Rastatt, Germany; Medtronic cannula and vent, Minneapolis, MN) were installed via a sternotomy, and a bolus of 2,500 IE of unfractioned heparin was given. An appropriately sized ultrasonic flow probe was placed on the pulmonary artery (16- or 18-mm internal diameter, Transonic PAU series, Ithaca, NY). During surgery, fluid was supplemented with Ringer lactate at an initial rate of 5 mL·kg\textsuperscript{-1}·min\textsuperscript{-1} and increased to 10 mL·kg\textsuperscript{-1}·min\textsuperscript{-1}. Any visible blood loss was replaced by hydroxyethyl starch (HES; 6% Voluen; Fresenius Kabi, Bad Homburg, Germany), and V-A ECMO pump speed was adjusted to achieve a mixed or central venous saturation > 50%.

**Measurements and data recording.** Pulmonary blood flow, i.e., cardiac output (Q\text{\textsubscript{Lung}}) and V-A ECMO blood flow (Q\text{\textsubscript{ECMO}}), was measured on the pulmonary artery main trunk and arterial ECMO tubing (Transonic PAU series, Ithaca, NY). Pulmonary end-tidal PCO\textsubscript{2} (PET\text{\textsubscript{CO₂}}\text{\textsubscript{ECMO}}) and PCO\textsubscript{2} at the membrane lung (peCO\textsubscript{2}\text{\textsubscript{ECMO}}) were measured with a sidestream capnograph (GE Medical, Module E-COVX with automated correction to BTPS conditions). The carbon dioxide production (V\text{\textsubscript{CO₂}}) was calculated individually for native and CO\text{\textsubscript{VOX}} with automated correction to BTPS conditions. The carbon dioxide production (V\text{\textsubscript{CO₂}}) was calculated from the expiratory partial pressure of CO\textsubscript{2} at the V-A ECMO exhaust and used to calculate V\text{\textsubscript{CO₂}}(16, 23), using actual barometric pressures (on average 722 mmHg). The experiments were performed at 540 m above sea level.

\[ \dot{V}_{\text{CO₂}} = F_{\text{ECO₂}} \times \dot{V}_{\text{ECMO}} \times \frac{\text{peCO}_2_{\text{ECMO}}}{\text{barometric pressure}} \]  

(1)

**Calculation of \( V_{\text{CO₂}} \) for the lung.** Mean pulmonary expired carbon dioxide (PECO\textsubscript{2}) was calculated by averaging the end-tidal carbon dioxide (PET\text{\textsubscript{CO₂}}) curve over the respiratory cycle with correction for the inspiratory-to-expiratory (I:E) ratio:

\[ P_{\text{E CO₂}} = \frac{P_{\text{ET CO₂}} \times (1 + E)}{E} \]  

(2)

This was verified by integration of the expiratory P\text{\textsubscript{CO₂}} curve, which delivers the same result.

We then calculate V\text{\textsubscript{CO₂}}\text{\textsubscript{Lung}}:

\[ \dot{V}_{\text{CO₂Lung}} = F_{\text{ECO₂}} \times \dot{V}_{\text{Lung}} \times \frac{P_{\text{ECO₂}}}{\text{barometric pressure}} \]  

(3)

**Blood flow calculations.** Figure 2 depicts the situation during V-A ECMO schematically. We define the following relationships, whereby Q is flow and Δ\text{\textsubscript{v-aCO₂}} is the inflow-outflow difference in blood CO\textsubscript{2} content in a given segment (Δ\text{\textsubscript{v-aCO₂}}\text{\textsubscript{ECMO}} is the difference between venous and aortal CO\textsubscript{2} content, Δ\text{\textsubscript{v-aCO₂}}\text{\textsubscript{Lung}} is the difference between venous and left atrial CO\textsubscript{2} content, and Δ\text{\textsubscript{v-pmCO₂}} is the difference between venous and postmembrane CO\textsubscript{2} content):

\[ \dot{Q}_{\text{total}} = \dot{Q}_{\text{Lung}} + \dot{Q}_{\text{ECMO}} \]  

(4)

\[ \dot{V}_{\text{CO₂total}} = \dot{V}_{\text{CO₂Lung}} + \dot{V}_{\text{CO₂ECMO}} \]  

(5)

**Experimental protocol.** The experiment consisted of three phases with varying sweep gas-to-blood flow ratios (i.e., the V/Q of the membrane lung) to determine how the sweep gas-blood flow relationship at the V-A ECMO influences extracorporeal CO\textsubscript{2} elimination (V\text{\textsubscript{CO₂ECMO}}). First, we reduced Q\text{\textsubscript{ECMO}} and V\text{\textsubscript{ECMO}} in parallel (stable V/Q = 1; “reduction of V&Q” phase, rV&Q\text{\textsubscript{ECMO}}). Then we lowered V\text{\textsubscript{ECMO}} with a constant Q\text{\textsubscript{ECMO}} (V/Q toward shunt; “reduction of V” phase, rV\text{\textsubscript{ECMO}}). Finally, we tested a V-A ECMO weaning trial, where Q\text{\textsubscript{ECMO}} was reduced but V\text{\textsubscript{ECMO}} was kept constant (V/Q toward dead space; “reduction of Q” phase, rQ\text{\textsubscript{ECMO}}).

Q\text{\textsubscript{ECMO}} and V\text{\textsubscript{ECMO}} were set at 4 L/min each at baseline and afterward reduced, depending on the respective phase, to 75%, 50%, and 25% of baseline with an interval of 1 min for each condition (Fig. 1). The left atrial vent was clamped during these procedures, and the stepwise reduction of blood flow was not supported by vasopressors or inotropes.

**Calculation of \( V_{\text{CO₂}} \) for V-A ECMO.** Expiratory concentration of CO\textsubscript{2} at the V-A ECMO exhaust was calculated from the inspiratory partial pressure of CO\textsubscript{2} at the V-A ECMO exhaust and used to calculate V\text{\textsubscript{CO₂}}(16, 23), using actual barometric pressures (on average 722 mmHg).
We then implement Eqs. 4 and 6 into Eq. 5:

\[ Q_{\text{total}} \times \Delta_{v-\text{CO}_2} = Q_{\text{ECMO}} \times \Delta_{v-\text{CO}_2}. \] (6)

We now solve Eq. 7 for \( Q_{\text{ECMO}} \):

\[ \dot{Q}_{\text{ECMO}} = \frac{(Q_{\text{ECMO}} \times \delta_{v-\text{CO}_2} - Q_{\text{total}} \times \delta_{v-\text{CO}_2})}{\delta_{v-\text{CO}_2} - \Delta_{v-\text{CO}_2}} \] (7)

As we aim to calculate \( Q_{\text{ECMO}} \) with expired gas phase measurements only rather than calculating blood gas content from multiple blood gas samples, we modify Eq. 8 with the following assumptions. As carbon dioxide production and carbon dioxide elimination are mathematical opposites, we use the absolute value function, thus eliminating negative values:

\[ \Delta_{v-\text{CO}_2} = |\dot{V}_{\text{CO}_2\text{total}}| \] (8)

\[ \Delta_{v-\text{CO}_2} = |\dot{V}_{\text{CO}_2\text{Lung}}| \] (9)

\[ \Delta_{v-\text{CO}_2} = |\dot{V}_{\text{CO}_2\text{ECMO}}| \] (10)

\[ \Delta_{v-\text{CO}_2} = |\dot{V}_{\text{CO}_2\text{Lung}}| \] (11)

We now implement Eqs. 9–11 into Eq. 8:

\[ Q_{\text{ECMO}} = \dot{Q}_{\text{ECMO}} \times \frac{|\dot{V}_{\text{CO}_2\text{ECMO}}| - |\dot{V}_{\text{CO}_2\text{total}}|}{|\dot{V}_{\text{CO}_2\text{total}}| - |\dot{V}_{\text{CO}_2\text{Lung}}|} \] (12)

Equation 5 simplifies Eq. 12 to:

\[ Q_{\text{Lung}} = Q_{\text{ECMO}} \times \frac{|\dot{V}_{\text{CO}_2\text{Lung}}|}{|\dot{V}_{\text{CO}_2\text{ECMO}}|} \] (13)

There is a fixed relationship of \( Q_{\text{Lung}} \) and \( Q_{\text{ECMO}} \) with the respective eliminated \( \text{CO}_2 \). This expresses our hypothesis that the ratio between the differences in \( \dot{V}_{\text{CO}_2\text{ECMO}} \) and \( \dot{V}_{\text{CO}_2\text{Lung}} \) is the same as the ratio between the differences in the respective flows (\( Q_{\text{ECMO}} \) and \( Q_{\text{Lung}} \)). In our experimental setup, we cannot expect to reach a steady state, as step changes were set at 1 min. Therefore, we calculate pulmonary blood flow using the differences in \( \dot{V}_{\text{CO}_2} \) and \( Q_{\text{ECMO}} \) during V-A ECMO weaning rather than applying it to steady-state conditions.

\[ \Delta Q_{\text{Lung}} = \Delta Q_{\text{ECMO}} \times \frac{\Delta \dot{V}_{\text{CO}_2\text{Lung}}}{\Delta \dot{V}_{\text{CO}_2\text{ECMO}}} \] (14)

Normalization of uneven \( V/Q \) at the V-A ECMO. During phase \( rV/Q_{\text{ECMO}} \) with a constant \( V/Q_{\text{ECMO}} \) of 1, we expect the relationship in Eq. 14 to work. However, \( \Delta V_{\text{CO}_2\text{ECMO}} \) is influenced by \( V_{\text{ECMO}} \) and \( Q_{\text{ECMO}} \). \( Q_{\text{ECMO}} \) determines the amount of \( \text{CO}_2 \) transported toward the membrane lung, and \( V_{\text{ECMO}} \) determines the amount of \( \text{CO}_2 \) eliminated over the membrane lung with a major impact on \( \Delta V_{\text{CO}_2\text{ECMO}} \). \( \Delta V_{\text{CO}_2\text{ECMO}} \) therefore does not necessarily represent \( \Delta Q_{\text{ECMO}} \) when \( V/Q_{\text{ECMO}} \) differs from 1. During phase \( rV_{\text{ECMO}} \), \( V_{\text{ECMO}} \) may decouple from \( Q_{\text{ECMO}} \). Accordingly, the ratio \( \Delta V_{\text{CO}_2\text{ECMO}}/\Delta V_{\text{CO}_2\text{Lung}} \) is affected by \( V_{\text{ECMO}} \) despite unchanged blood flows.

To correct for uneven \( V/Q \), we normalized \( \Delta V_{\text{CO}_2\text{ECMO}} \) into a new variable, \( \Delta V_{\text{CO}_2\text{ECMO}}\text{Norm} \), only dependent on \( Q_{\text{ECMO}} \) and independent of \( V_{\text{ECMO}} \), with Eq. 15. The correction factor \( f \) is expressed in Eq. 16.

\[ \Delta Q_{\text{ECMO}} = \Delta Q_{\text{ECMO}} \times \frac{\Delta V_{\text{CO}_2\text{Lung}}}{\Delta V_{\text{CO}_2\text{ECMO}}} \] (15)

\[ f(V, Q) = \frac{Q \times \left( \frac{V - c}{Q} \right)}{V \times (1 + c)} \] (16)

A formal deduction of this normalization is found in the appendix.

Statistical analysis. For statistical, mathematical, and graphical analysis, we used MATLAB 2019a (MathWorks, Natick, MA), including an extension pack under a creative commons license for the creation of Bland–Altman plots (15). Data are presented either individually or as a range. Correlation coefficients were calculated with Pearson’s square (\( r^2 \)). Agreement between methods (calculated and measured \( Q_{\text{Lung}} \)) was assessed with Bland–Altman analysis.

RESULTS

Baseline. At baseline \( V_{\text{ECMO}} \) and \( Q_{\text{ECMO}} \) of 4 L/min, \( V_{\text{CO}_2\text{ECMO}} \) was between 202 and 243 mL/min, whereas \( V_{\text{CO}_2\text{Lung}} \) was between 13 and 193 mL/min, corresponding to a measured \( Q_{\text{Lung}} \) of 10–964 mL/min and representing a normal \( V_{\text{CO}_2} \) production for swine (6) (step 1 for \( V \), \( Q \), and \( V/Q \) in Table 1).

Measurements at the V-A ECMO. Per protocol, \( Q_{\text{ECMO}} \) remained unchanged from baseline during phase \( rV_{\text{ECMO}} \) (98–100% of baseline or 3,989–4,186 mL/min) and was reduced to a quarter of baseline in phase \( rV_{\text{ECMO}} \) (641–1,178 mL/min, 16–29% of baseline). In phase \( “rV\text{ECMO}” \), \( Q_{\text{ECMO}} \) was reduced to approximately a quarter in all animals except animal 3 because of hemodynamic instability (25.4–49.5% of baseline or 1,048–1,994 mL/min) (Table 1).

The normalization function was calculated by fitting our data points into Eq. 16 and retrieving the constant \( c = 1.157 \).
Calculating Cardiac Output during V-A ECMO via Gas Exchange

Table 1. Individual data sets

| Step | V | Q | CO2 | CO2Norm | V | Q | CO2 | Qcalc |
|------|---|---|-----|---------|---|---|-----|-------|
| V    | Q | QCO2 | QCO2Norm | Qcalc |
| 1    | 4,000 | 1,043 | 222 | 223 | 1,800 | 1,039 | 52 | 935 |
| 2    | 3,000 | 1,018 | 194 | 229 | 1,800 | 1,033 | 61 | 1,077 |
| 3    | 2,000 | 1,293 | 150 | 229 | 1,800 | 1,030 | 66 | 1,141 |
| 4    | 1,000 | 1,394 | 186 | 233 | 1,800 | 1,025 | 60 | 1,065 |

Values (in mL/min) are individual data for all animals at baseline [step 1 at reduction of ventilation (V), reduction of blood flow (Q), and reduction of both (VQ)] and every step of blood flow reduction. Extracorporeal membrane oxygenation (ECMO) Q and Lung Q denote readings from the respective flow probes. CO2 elimination (VCO2) values were calculated according to Eqs. I–3 in METHODS with the reported barometric pressure for each day (728, 726, 711, and 721 mmHg). Note that f) in animal 1 ventilation is high because baseline settings at respirator were 5.6 L/min [tidal volume (VT) 465 mL, frequency 12 times/min] and that 2) during reduction of Q the phase the cardiovascular system of animal 3 did not support the ECMO reduction to 25% of baseline, and therefore no measurement is available (N/A). VCO2Norm refers to a calculated CO2 for a sweep gas-to-blood flow ratio normalized toward 1 (for details see APPENDIX). Qcalc, calculated lung Q.

(r² = 0.995, P < 0.001). VCO2ECMONorm correlated highly with QECMO, and the normalization improved correlation significantly (Fig. 3, A and B, respectively). In phase rV&QECMO, reducing VECMO without any change in QECMO, VCO2ECMONorm was 194–249 mL/min or 93.3–100.1% of baseline. Without normalization, VCO2ECMO decoupled from QECMO, with a decrease from 205–246 mL/min to 73–96 mL/min in this phase (Table 1, Fig. 3A). VCO2ECMO values for phase rV&QECMO dropped to roughly a quarter of baseline (64–74 mL/min, 25–33% of baseline) in parallel with reduced QECMO. During phase rQECMO, VCO2ECMONorm was 84–156 mL/min or 38–58% of baseline.

Measurements at the lung. During unchanged QECMO (phase rVECMO), Qlung remained close to baseline (2–980 mL/min) and did not change much within one animal, and VCO2 stayed constant, accordingly.

During reduction of QECMO in phase rV&QECMO and phase rQECMO, Qlung increased from its low baseline values to 928–1,550 mL/min, and 328–1,914 mL/min, respectively (Table 1). VCO2lung followed the changes in Qlung to 74–232 mL/min (rise of 28–57 mL/min from baseline, with stepwise increases in every animal) for phase rV&QECMO and 39–233 mL/min for phase rQECMO (rise of 18–45 mL/min from baseline) and remained steady at full QECMO (phase rVECMO, 21–188 mL/min; change of 7–8 mL/min from baseline) (Table 2). Qlung and VCO2lung showed a high correlation (Fig. 4).

Calculation of Qlung. The calculation of pulmonary blood flow from absolute VCO2 values is imprecise and leads to a consistent overestimation (Table 1). This overestimation increases with increasing V/Q at the lung, which is shown in animal 1, where we had increased ventilation compared with the other animals. In phase rVECMO, we observe no change in measured Qlung as well as calculated changes in Qlung. When differences between the short stepwise flow reductions are considered (Table 2), correlations are reestablished (Fig. 5B) and the respective Bland–Altman plot (Fig. 5A) shows a small bias with acceptable limits of agreement. True blood flow changes are underestimated since bias is positive. Bias stays constant over the measured range (R² = −0.16, P = 0.5).

When phase rVECMO is excluded due to no expected change in blood flow, out of 23 blood flow change calculations, an opposite direction of the flow change is calculated in 4 in-

AJP-Lung Cell Mol Physiol • doi:10.1152/ajplung.00167.2019 • www.ajplung.org
strokes. In all of these instances, the value of the change is below the least significant change, which is 113 mL/min. When the entire reduction steps are summarized (Table 2 and Fig. 5C), the relationship becomes overt.

**DISCUSSION**

We show in a preliminary analysis that measurements of $V_{CO2}$ at both lung and V-A ECMO are possible with simple sidestream technology. Our model for the estimation of changes in $Q_{Lung}$ predicts the directional change of pulmonary blood flow, i.e., cardiac output with acceptable accuracy in this small sample size (3). The measurements needed for our calculations ($Q_{ECMO}$, $V_{ECMO}$, $V_{Lung}$, $p_{CO2ECMO}$, $p_{ETCO2Lung}$) are easily performed with the use of standard sidestream capnographs, all of which are readily available in an ICU setting or an operating theater and require no specific training.

As expected from the ventilation-perfusion concept and the gas content equations in Fig. 2 (14), we found that decrease in $Q_{ECMO}$ and the consecutive increase in $Q_{Lung}$ leads to a respective change in $V_{CO2Lung}$ and $V_{CO2ECMONorm}$. A closer look at Eq. 8 as the background of our hypothesis shows an adaptation of the classic Berggren shunt equation (11). This seems intuitive, as the V-A ECMO is in concept an anatomical right-to-left shunt, where the ability to ventilate and oxygenate the shunted blood will clearly affect its functional influence right-to-left shunt, where the ability to ventilate and oxygenate seems intuitive, as the V-A ECMO is in concept an anatomical adaptation of the classic Berggren shunt equation (11). This ECMO are kept at a ratio of 1 (in phase $rQ_{ECMO}$). For shunt correctly as long as sweep gas/blood flow on the V-A shunt correctly as long as sweep gas/blood flow on the V-A ECMO will vary the function of this anatomical shunt from (Fig. 2). Changing the sweep gas-to-blood flow ratio on the sweep gas-to-blood flow ratio on the shunted blood will clearly affect its functional influence.

whether this might be applicable to a veno-venous configuration would need to be investigated. In a veno-arterial configuration, normalization might allow accurate estimations of V-A ECMO flow.

**Fig. 3. Effect of the normalization of the sweep gas flow-to-blood flow ratio on the veno-arterial extracorporeal membrane oxygenation (V-A ECMO).** A: scatterplot for V-A ECMO blood flow ($Q_{ECMO}$) vs. elimination of $CO2$ at V-A ECMO ($V_{CO2ECMO}$). Smallest points represent phase $rV_{ECMO}$; medium-sized points represent phase $rQ_{ECMO}$; large points represent phase $rV_{ECMO}$. No correlations reached significant levels ($P < 0.05$). B: scatterplot for $Q_{ECMO}$ vs. $V_{CO2ECMONorm}$ normalized to ventilation-to-perfusion ratio ($V/Q_{ECMO}$) = 1 ($V_{CO2ECMONorm}$), all data points considered. Smallest points represent phase $rQ_{ECMO}$; medium-sized points represent phase $rV_{ECMO}$; large points represent phase $rV_{ECMO}$. In phase $rE_{ECMO}$, animal 3 did not tolerate the last reduction in V-A ECMO flow.

A high $V/Q_{Lung}$ will significantly increase the overall amount of $CO2$ eliminated and thus lead to an overestimation of pulmonary blood flow, whereas a reduction in $V_{ECMO}$ will lead to a decrease in eliminated $CO2$ and thus to a rise in venous $CO2$ content. This in turn increases $V_{CO2Lung}$, to achieve a new steady state. However, as the V-A ECMO and the lung both drain venous blood from the right atrium, $V_{CO2ECMO}$ should increase simultaneously with the new steady state to fulfill Eq. 5. Our short measurement periods did preclude a steady state for $CO2$ elimination. Calculations of total blood flow for any given moment may therefore be

---

**DISCUSSION**

We show in a preliminary analysis that measurements of $V_{CO2}$ at both lung and V-A ECMO are possible with simple sidestream technology. Our model for the estimation of changes in $Q_{Lung}$ predicts the directional change of pulmonary blood flow, i.e., cardiac output with acceptable accuracy in this small sample size (3). The measurements needed for our calculations ($Q_{ECMO}$, $V_{ECMO}$, $V_{Lung}$, $p_{CO2ECMO}$, $p_{ETCO2Lung}$) are easily performed with the use of standard sidestream capnographs, all of which are readily available in an ICU setting or an operating theater and require no specific training.

As expected from the ventilation-perfusion concept and the gas content equations in Fig. 2 (14), we found that decrease in $Q_{ECMO}$ and the consecutive increase in $Q_{Lung}$ leads to a respective change in $V_{CO2Lung}$ and $V_{CO2ECMONorm}$. A closer look at Eq. 8 as the background of our hypothesis shows an adaptation of the classic Berggren shunt equation (11). This seems intuitive, as the V-A ECMO is in concept an anatomical right-to-left shunt, where the ability to ventilate and oxygenate the shunted blood will clearly affect its functional influence right-to-left shunt, where the ability to ventilate and oxygenate seems intuitive, as the V-A ECMO is in concept an anatomical adaptation of the classic Berggren shunt equation (11). This ECMO are kept at a ratio of 1 (in phase $rQ_{ECMO}$). For shunt correctly as long as sweep gas/blood flow on the V-A shunt correctly as long as sweep gas/blood flow on the V-A ECMO will vary the function of this anatomical shunt from (Fig. 2). Changing the sweep gas-to-blood flow ratio on the sweep gas-to-blood flow ratio on the shunted blood will clearly affect its functional influence.

whether this might be applicable to a veno-venous configuration would need to be investigated. In a veno-arterial configuration, normalization might allow accurate estimations of V-A ECMO flow.

**Fig. 3. Effect of the normalization of the sweep gas flow-to-blood flow ratio on the veno-arterial extracorporeal membrane oxygenation (V-A ECMO).** A: scatterplot for V-A ECMO blood flow ($Q_{ECMO}$) vs. elimination of $CO2$ at V-A ECMO ($V_{CO2ECMO}$). Smallest points represent phase $rV_{ECMO}$; medium-sized points represent phase $rQ_{ECMO}$; large points represent phase $rV_{ECMO}$. No correlations reached significant levels ($P < 0.05$). B: scatterplot for $Q_{ECMO}$ vs. $V_{CO2ECMONorm}$ normalized to ventilation-to-perfusion ratio ($V/Q_{ECMO}$) = 1 ($V_{CO2ECMONorm}$), all data points considered. Smallest points represent phase $rQ_{ECMO}$; medium-sized points represent phase $rV_{ECMO}$; large points represent phase $rV_{ECMO}$. In phase $rE_{ECMO}$, animal 3 did not tolerate the last reduction in V-A ECMO flow.

A high $V/Q_{Lung}$ will significantly increase the overall amount of $CO2$ eliminated and thus lead to an overestimation of pulmonary blood flow, whereas a reduction in $V_{ECMO}$ will lead to a decrease in eliminated $CO2$ and thus to a rise in venous $CO2$ content. This in turn increases $V_{CO2Lung}$, to achieve a new steady state. However, as the V-A ECMO and the lung both drain venous blood from the right atrium, $V_{CO2ECMO}$ should increase simultaneously with the new steady state to fulfill Eq. 5. Our short measurement periods did preclude a steady state for $CO2$ elimination. Calculations of total blood flow for any given moment may therefore be
Table 2. Calculation of stepwise reductions

| Step | ECMO  | Lung  |
|------|-------|-------|
| V    | ΔV    | ΔQ    | ΔVCO2 | ΔVCO2 LQ | ΔV    | ΔQ    | ΔVCO2 | ΔQCO2 LQ |
| 1-2  | −1.000 | −13.37 | −37   | −6      | 0     | −47   | 0     | −1      |
| 2-3  | −1.000 | −43.42 | −42   | −2      | 0     | 208   | 7     | 122     |
| 3-4  | −1.000 | 22.59  | 59    | −7      | 0     | −145  | 1     | −2      |
| Summed up | −3.000 | −34.138 | −138  | −15     | 0     | 16    | 7     | 119     |
| Q    | ΔQ    | ΔV    | ΔVCO2 | ΔVCO2 LQ |
| 1-2  | 0     | −966.24 | −24   | −50     | 0     | 115   | 3     | 66      |
| 2-3  | 0     | −1089.29 | −29   | −51     | 0     | 423   | 15    | 313     |
| 3-4  | 0     | −851.32  | −32   | −40     | 0     | 457   | 28    | 605     |
| Summed up | 0     | −2906.86 | −86   | −142    | 0     | 995   | 47    | 984     |
| VQ   | ΔV    | ΔQ    | ΔVCO2 | ΔVCO2 LQ |
| 1-2  | −1.000 | −837.43 | −43   | −38     | 0     | 314   | −3    | −59     |
| 2-3  | −1.000 | −1040.47 | −47   | −48     | 0     | 219   | 28    | 612     |
| 3-4  | −1.000 | −1013.54 | −54   | −54     | 0     | 174   | 15    | 286     |
| Summed up | −3.000 | −2890.144 | −144 | −140    | 0     | 707   | 41    | 838     |

Continued

Calculations of stepwise reductions [reduction of ventilation (V), reduction of blood flow (Q), and reduction of both (VQ)] for all lung and extracorporeal membrane oxygenation (ECMO) data. Values (in mL/min) are individual data for all animals for measurements performed at the lung. The summed up category refers to the cumulative change from step 1 to step 4. Note that during reduction of Q phase the cardiovascular system of animal 3 did not support the ECMO reduction to 25% of baseline, and therefore no measurement is available (N/A). Q(calc), calculated lung Q.

impossible, because the lack of a steady state does not allow for sufficient accuracy. As we calculated Q(calc) through V-A ECMO via a deliberate step change in VCO2, a steady state is not necessary, as there is no need for an absolute reference point. This also allows calculations for different settings of V(Lung) (as shown with animal 1), as long as V(Lung) remains constant.

The ratio of ventilation to perfusion in the lung will vary with hypoxic vasoconstriction, shunt, alveolar collapse, and dead space. Our VCO2(Lung), estimated from end-tidal PCO2 in healthy lungs, showed an acceptable relationship with Q(Lung), but stable minute ventilation on the lung was mandatory. As Q(Lung) is the quantity to be calculated, a normalization procedure is not possible. As VCO2(Lung) can only represent blood flow that participates in gas exchange, shunt due to supine positioning of the animals could explain the bias of underestimation of changes in pulmonary blood flow with our method.

There are several possible limitations to our method: First, a V/Q mismatch (e.g., high shunt and/or high dead space) might result in a decrease of Q(Lung) and VCO2(Lung) correlation and might thus increase the bias significantly. Second, we did not document every V-A ECMO flow change with blood gas samples, because our aim was to calculate Q(Lung) with gaseous measurements. Nevertheless, a meticulous documentation of blood gas status would strengthen our hypothesis and allow for alternative calculations of gas content and direct calculations of the normalization function. Third, VCO2 was calculated with sidestream capnography, which is of limited accuracy. Signal shifts in the PCO2-time tracing may introduce an error here. We did not rely on a breath-by-breath measurement, but averaged values over 1 min may help to minimize this possible influence. Mainstream calorimetric models are available and used in assessing cardiac output, alveolar and dead space ventilation (7, 18–20). Mainstream capnography at the V-A ECMO gas outlet is feasible and may deliver accurate results for oxygen intake (V(O2)) and VCO2 (4, 22). This might improve our results and overall accuracy compared with our calculations from sidestream end-tidal carbon dioxide. Fourth, this study was conducted in a small, clearly preliminary set of healthy animals and without any cardiovascular support.

The large scatter in pulmonary flow reflects the individual variability of native cardiac output during V-A ECMO treatment. In conclusion, we show that measurements of VCO2 at the V-A ECMO are easily performed. A normalization procedure allows estimation of VCO2 only dependent on blood flow without the influence of a V/Q mismatch. This in turn lays the basis of blood flow calculations using VCO2 values. Calcula-
tions of pulmonary blood flow using absolute values of carbon dioxide elimination are not possible in a nonsteady state with our method. The concept can be derived from basic physiological equations. Whether our method may result in a clinically useful approach and support V-A ECMO weaning, where assessment of cardiac output may help to evaluate weanability, has to be further evaluated. These preliminary findings need further confirmation in a larger study, also investigating low and high V˙/Q˙ states at the lung before exploring clinical applications.

APPENDIX: NORMALIZATION FUNCTION

Formal derivation of a normalized V˙CO2 for a ventilation-to-perfusion ratio of 1. As V˙CO2ECMO is dependent on the sweep gas flow (17), normalization of the V˙CO2 at any given ventilation-to-perfusion ratio (V˙/Q˙t) to a V˙/Q˙ of 1 (V˙CO2ECMOnorm) will render a variable dependent on blood flow (Q˙ECMO) only and independent from ventilation (V˙ECMO). This may facilitate the prediction of blood flow in the lung.

The theoretical deduction of this normalization is based on the description of V˙/Q˙ as

$$\frac{V}{Q} = \frac{\sigma_{CO2} \cdot R \cdot T \cdot (1 + K_c)}{PV_{CO2} - P_{PM_{CO2}}} \quad (A1)$$

$\sigma_{CO2}$ is the solubility of CO2 in blood, R is the gas constant, and T is temperature. PVCO2 is venous CO2 partial pressure, and PPMCO2 is the postmembrane CO2 partial pressure. We assume that PPMCO2 is equal to PeCO2ECMO, which is measured at the V-A ECMO gas outlet. Kc indicates the equilibration constant of the CO2 + H2O ⇌ HCO3⁻ + H⁺ reaction at a given pH. It describes the additional liberation of gaseous carbon dioxide from bicarbonate during the passage through the membrane lung. pK is the acid dissociation constant.

$$K_c = \frac{k_1}{k_{-1} \cdot [H^+]}$$

where log10 $\left( \frac{k_1}{k_{-1}} \right) = 6.1 = pK$

We assume the following values for BTPS conditions:

$$R = 62.363 \left[ \frac{\text{L} \cdot \text{mmHg}}{\text{K} \cdot \text{mol}} \right]$$

$$T = 310.5 \text{ kelvin (K)}$$

$$K_c = 12$$

$$\text{pH} = 7.35$$

$$\sigma_{CO2} = 3.3 \times 10^{-5} \text{ molar mmHg}$$

Under the assumption of a constant pH, we can combine these individual constants into one overall constant c:

$$c = \sigma_{CO2} \cdot R \cdot T \cdot (1 + K_c)$$

For the derivation, we assume a constant venous carbon dioxide partial pressure and calculate gas fraction of expired CO2 (FeCO2):

$$PV_{CO2} = 45 \text{ mmHg}$$

$$FeCO2 = \frac{P_{E_{CO2}}}{bp}; \text{bp = barometric pressure} = 760 \text{ mmHg}$$

We solve Eq. A1 for PPMCO2:

$$PPM_{CO2} = \frac{PV_{CO2}}{Q} \times \left( \frac{\sigma_{CO2}}{R \cdot T \cdot (1 + K_c)} \right) \quad (A2)$$

A plot of this function shows the known hyperbolic dependence of alveolar, i.e. postmembrane, PCO2 from ventilation (V and Q values are assumed from 0 to 4 with an interval of 0.25 L/min) (Figs. A1 and A2).
The next step is to calculate \( V\dot{O}_2_{ECMO} \) and plot the function (Fig. A3). Note that the factor 1,000 is needed to convert the results in milliliters per minute.

\[
V\dot{O}_2_{ECMO} = F_{rCO_2} \times \dot{V} \cdot c \cdot \frac{P_{VCO_2}}{\left(\frac{\dot{V}}{Q} + c\right)} \cdot \frac{1,000}{760} \quad (A3)
\]

The diverging effects of the ventilation on the ECMO on PCO2 and \( V\dot{O}_2 \) become apparent. In order to represent blood flow, we now normalize the given \( V\dot{O}_2 \) to a \( V/Q \) of 1.

We define the correction factor \( f \) as the ratio of \( V\dot{O}_2 \) at \( V/Q = 1 \) to the \( V\dot{O}_2 \) at any \( V/Q \). We plot this correction factor \( f \) against \( V/Q \):

\[
f(V, Q) = \frac{V\dot{O}_2\left(\frac{\dot{V}}{Q} = 1\right)}{V\dot{O}_2} = \frac{\dot{V}}{Q} = 1
\]

As \( V/Q = 1 \) is equal to \( Q \), we can write

\[
f(V, Q) = \frac{\dot{Q} \times \left(\frac{\dot{V}}{Q} + c\right)}{\dot{V} \times (1 + c)} = \frac{\dot{V}}{Q} \times \left(\frac{\dot{V}}{Q} + c\right) \quad (A4)
\]

This describes a hyperbolic dependence of \( f \) from \( V/Q \) scaled with \( V/Q \) and \( c \) (Fig. A4). Note that for a \( V/Q \) of 1 the scaling and correction factor is 1.

Now, \( V\dot{O}_2_{Norm} \) can be calculated with Eqs. A3 and A5. We plot this new function \( V\dot{O}_2_{Norm} \), which is independent of \( V \) or \( V/Q \) (Fig. A5):
\[ \dot{V}_{\text{CO}_2}^{\text{Norm}} = V_{\text{CO}_2} \times f(\dot{V}, Q) \]
\[ = \dot{V} \cdot c \cdot \frac{P_V}{Q + c} \cdot \frac{1,000}{760} \cdot \frac{Q \times \left( \frac{\dot{V}}{Q} + c \right)}{V \times (1 + c)} \]
\[ = \dot{Q} \cdot c \cdot \frac{P_V}{1 + c} \cdot \frac{1,000}{760} \]

It is clear from this resolved Eq. A6 that \( \dot{V}_{\text{CO}_2}^{\text{Norm}} \) is dependent on \( Q \) and \( P_V \), as well as the constant \( c \), which itself is dependent on temperature and pH.

It seems intuitive that Eq. A6 can simply be achieved by implementing \( V/Q = 1 \) and substituting \( Q \) for \( V \) in Eq. A3. This calculation eliminates the dependence of ventilation, and \( \dot{V}_{\text{CO}_2}^{\text{Norm}} \) will represent blood flow at any \( V/Q \) (see Fig. A5).

This derivation assumes perfect conditions and depends on venous \( P_V \) and pH, which are as a limitation of our study unknown. Therefore, the function has to be approximated from measured data, as described in the following section.

Retrieving the normalization function from measured data. We calculated the necessary correction factors using the measured data and Eq. A4.

Then, the correction factors were plotted against \( V/Q \) and the coefficient \( c \) was received (Fig. A6).

This Fig. A2. Three-dimensional mesh plot showing postmembrane \( PCO_2 \) (\( P_{PM CO_2} \), mmHg) as a function of ventilation (L/min) and blood flow (L/min).

This Fig. A2. Three-dimensional mesh plot showing elimination of \( CO_2 \) at veno-arterial extracorporeal membrane oxygenation (\( V_{\dot{CO}_2}^{\text{ECMO}} \), mL/min) as a function of ventilation (L/min) and blood flow (L/min).

\[ f\left(\dot{V}_{\text{ECMO}}, \dot{Q}_{\text{ECMO}}\right) = \frac{\dot{Q}_{\text{ECMO}} \times \left( \frac{\dot{V}_{\text{ECMO}}}{\dot{Q}_{\text{ECMO}}} + c \right)}{\dot{V}_{\text{ECMO}} \times (1 + c)} \]
\[ c = 1.157; \text{ CI interval: } [1.097, 1.216]; r^2 = 0.9954 \]
It is a limitation of our study that our measurements of sweep gas flow (set and read by hand) are much more inaccurate than the blood flow readings. Additionally, instantaneous $P_{\text{vCO}_2}$ and pH measurements to calculate $c$ are not available. Inexact ventilation measurements will introduce an error in the position of the normalization curve, where a small shift around a V/Q of 1 will have a large impact on the slope of the function. Small errors in measurement of $V_{\text{CO}_2}$, $V$, or $Q$ will therefore largely influence $c$ (Fig. A4). However, the calculated function with empirically derived $c$ shows almost perfect goodness of fit and the normalization of $V_{\text{CO}_2\text{ECMO}}$ with this correction function shows very strong correlations between $V_{\text{CO}_2\text{ECMONorm}}$ and $Q_{\text{ECMO}}$ within the range of our measurements (Fig. 3, main text).

**GRANTS**

The Department of Intensive Care Medicine has received unrestricted educational grants from the following organizations for organizing biannual postgraduate courses in the fields of critical care ultrasound, management of ECMO and mechanical ventilation: Pierre Fabre Pharma AG (formerly known as RobaPharm), Pfizer AG, Bard Medica S.A., Abbott AG, Anancid Medical Systems, PanGas AG Healthcare, Orion Pharma, Bracco, Edwards Lifesciences AG, Hamilton Medical AG, Fresenius Kabi (Schweiz) AG, Getinge Group Maquet AG, Dräger Schweiz AG, and Teleflex Medical GmbH.

**DISCLOSURES**

The Department of Intensive Care Medicine has received unrestricted educational grants from the following organizations for organizing biannual postgraduate courses in the fields of critical care ultrasound, management of ECMO and mechanical ventilation: Pierre Fabre Pharma AG (formerly known as RobaPharm), Pfizer AG, Bard Medica S.A., Abbott AG, Anancid Medical Systems, PanGas AG Healthcare, Orion Pharma, Bracco, Edwards Lifesciences AG, Hamilton Medical AG, Fresenius Kabi (Schweiz) AG, Getinge Group Maquet AG, Dräger Schweiz AG, and Teleflex Medical GmbH.

**AUTHOR CONTRIBUTIONS**

K.F.B. and D.B. conceived and designed research; K.F.B., M.H., and D.B. performed experiments; K.F.B. analyzed data; K.F.B., M.H., L.G., and D.B. interpreted results of experiments; K.F.B. prepared figures; K.F.B. and D.B. drafted manuscript; K.F.B., S.M.J., J.T., L.G., and D.B. edited

---

**Fig. A4.** Correction factor $f$ calculated as a function of ventilation-to-perfusion ratio (V/Q). Colors refer to different V/Q data points resulting from the chosen interval of 0.25.

**Fig. A5.** Three-dimensional mesh plot showing elimination of $\text{CO}_2$ at veno-arterial extracorporeal membrane oxygenation ($V_{\text{CO}_2\text{ECMO}}$, mL/min) normalized to ventilation-to-perfusion ratio $= 1$ as a function of ventilation (L/min) and blood flow (L/min). With normalization, the influence of ventilation on $V_{\text{CO}_2}$ is eliminated.

**Fig. A6.** Curve fitting for correction factor $f$ as a function of ventilation-to-perfusion ratio (V/Q).
and revised manuscript; K.F.B., M.H., S.M.J., J.T., L.G., and D.B. approved final version of manuscript.

REFERENCES

1. Cavarschi NC, Pitcher HT, Yang Q, Karbowskii P, Miessau J, Hastings HM, Hirose H. Weaning of extracorporeal membrane oxygenation using continuous hemodynamic transesophageal echocardiography. J Thorac Cardiovasc Surg 146: 1474–1479, 2013. doi:10.1016/j.jtcs.2013.06.055.

2. Combes A, Brodie D, Chen YS, Fan E, Henriques JPS, Hodgson C, Lepper PM, Leprince P, Maekawa K, Muller T, Nuding S, Ouweeel DM, Roch A, Schmidt M, Takayama H, Vuyykesteke A, Werdan K, Papazian L. The ICM research agenda on extracorporeal life support. Intensive Care Med 43: 1306–1318, 2017. doi:10.1007/s00134-017-4803-3.

3. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. J Clin Monit Comput 15: 85–91, 1999. doi:10.1023/A:1009982611386.

4. De Waele E, van Zwam K, Mattens S, Staessens K, Diltoer M, Honoré J. Factors predicting early- and long-term survival in patients undergoing extracorporeal membrane oxygenation: a preliminary clinical experience with a proposed theoretical model. Acta Anaesthesiol Scand 59: 1296–1302, 2015. doi:10.1111/aas.12564.

5. Duscio E, Cipulli F, Vasques F, Collino F, Rapetti F, Romitti F, Behnemann T, Niewenhuys J, Tonetti T, Pasticci I, Vassalli F, Reupke J. CO2 clearance by membrane lungs. Perfusion 33: 249–253. 2018. doi:10.1177/0267659117736379.

6. Hannon JP, Bossone CA, Wade CE. Normal physiological values for conscious pigs used in biomedical research. Lab Anim Sci 40: 293–298, 1990.

7. Jonson B. Volumetric capnography for noninvasive monitoring of acute respiratory distress syndrome. Am J Respir Crit Care Med 198: 396–398, 2018. doi:10.1164/rccm.201801-0093LE.

8. Keener JS, Snoey J. Ventilation and perfusion. In: Mathematical Physiology: Systems Physiology (2nd ed.). New York: Springer, 2009, p. 694–701.

9. Lee SH, Chung CH, Lee JW, Jung SH, Choo SJ. Factors predicting early- and long-term survival in patients undergoing extracorporeal membrane oxygenation (ECMO). J Card Surg 27: 255–263, 2012. doi:10.1111/j.1540-8191.2011.01400.x.

10. Lehle K, Philipp A, Hiller KA, Zeman F, Buchwald D, Schmid C, Dornia C, Lunz D, Müller T, Luhnaw M. Efficiency of gas transfer in venovenous extracorporeal membrane oxygenation: analysis of 317 cases with four different ECMO systems. Intensive Care Med 40: 1870–1877, 2014. doi:10.1007/s00134-014-3489-z.

11. Leigh JM, Tyrrell MF, Strickland DA. Simplified versions of the shunt and oxygen consumption equations. Anesthesiology 30: 468–470, 1969. doi:10.1097/00000542-196904000-00020.

12. Morimont P, Lambermont B, Guiot J, Tchana Sato V, Clotuche C, Gofoy J, Defraigne JO. Ejection fraction may not reflect contractility: example in veno-arterial extracorporeal membrane oxygenation for heart failure. ASAIO J 64: e68–e71, 2018. doi:10.1097/MAT.0000000000000661.

13. Park M, Costa EL, Maciel AT, Silva DP, Friedrich N, Barbosa EV, Hirota AS, Schettino G, Azevedo LC. Determinants of oxygen and carbon dioxide transfer during extracorporeal membrane oxygenation in an experimental model of multiple organ dysfunction syndrome. PLoS One 8: e54954, 2013. doi:10.1371/journal.pone.0054954.

14. Radermacher P, Maggiore SM, Merca A. Fifty years of research in ARDS. gas exchange in acute respiratory distress syndrome. Am J Respir Crit Care Med 196: 964–984, 2017. doi:10.1164/rccm.201610-2156SO.

15. Rik, BlandAltmanPlot. MATLAB Central File Exchange. https://www.mathworks.com/matlabcentral/fileexchange/71052-blandaltmanplot [20 April 2020].

16. Scaravilli V, Kreyer S, Belenkiy S, Linden K, Zanella A, Li Y, Dubick MA, Cancio LC, Pesenti A, Batchinsky AI. Extracorporeal carbon dioxide removal enhanced by lactic acid infusion in spontaneously breathing conscious sheep. Anesthesiology 124: 674–682, 2016. doi:10.1097/ALN.0000000000000955.

17. Sun L, Kaesler A, Fernando P, Thompson AJ, Toomasian JM, Bartlett RH. CO2 clearance by membrane lungs. Perfusion 33: 249–253, 2018. doi:10.1177/0267659117736379.

18. Tusman G, Groisman I, Maidana GA, Scandurra A, Arca JM, Bohm SH, Suarez-Sipmann F. The sensitivity and specificity of pulmonary carbon dioxide elimination for noninvasive assessment of fluid responsiveness. Anesth Analg 122: 1404–1411, 2016. doi:1213/ANE.000000000001047.

19. Tusman G, Suarez-Sipmann F, Bohm SH, Borges JB, Hedenstierna G. Capnography reflects ventilation/perfusion distribution in a model of acute lung injury. Acta Anaesthesiol Scand 55: 597–606, 2011. doi:10.1111/j.1399-6571.2011.02404.x.

20. Verschueren S, Massion PB, Verschuren F, Dams P, Magder S. Capnography: lessons from the past and current clinical applications. Crit Care 20: 184, 2016. doi:10.1186/s13054-016-1377-3.

21. West JB. Understanding pulmonary gas exchange: ventilation-perfusion relationships. J Appl Physiol (1985) 97: 1603–1604, 2004. doi:10.1152/japplphysiol.00128.2004.

22. Wollersheim T, Frank S, Müller MC, Skrypnikov V, Carbon NM, Pickerodt PA, Spies C, Mai K, Spranger J, Weber-Carstens S. Measuring energy expenditure in extracorporeal lung support patients (MEEP)—protocol, feasibility and pilot trial. Clin Nutr 37: 301–307, 2018. doi:10.1016/j.clnu.2017.01.001.

23. Zanella A, Mangili P, Gianì M, Redaelli S, Scaravilli V, Castagna L, Sosio S, Pirrone F, Albertini M, Patroniti N, Pesenti A. Extracorporeal carbon dioxide removal through ventilation of acidified dialysate: an experimental study. J Heart Lung Transplant 33: 536–541, 2014. doi:10.1016/j.healun.2013.12.006.