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Modified Thermodilution for Simultaneous Cardiac Output and Recirculation Assessment in Veno-venous Extracorporeal Membrane Oxygenation: A Prospective Diagnostic Accuracy Study

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ABSTRACT

Background: Thermodilution is unreliable in veno-venous extracorporeal membrane oxygenation (VV-ECMO). Systemic oxygenation depends on recirculation fractions and ratios of extracorporeal membrane oxygenation (ECMO) flow to cardiac output. In a prospective *in vitro* simulation, this study assessed the diagnostic accuracy of a modified thermodilution technique for recirculation and cardiac output. The hypothesis was that this method provided clinically acceptable precision and accuracy for cardiac output and recirculation.

Methods: Two ECMO circuits ran in parallel: one representing a VV-ECMO and the second representing native heart, lung, and circulation. Both circuits shared the right atrium. Extra limbs for recirculation and pulmonary shunt were added. This study simulated ECMO flows from 1 to 2.5 l/min and cardiac outputs from 2.5 to 3.5 l/min with recirculation fractions (0 to 80%) and pulmonary shunts. Thermistors in both ECMO limbs and the pulmonary artery measured the temperature changes induced by cold bolus injections into the arterial ECMO limb. Recirculation fractions were calculated from the ratio of the areas under the temperature curve (AUCs) in the ECMO limbs and from partitioning of the bolus volume (flow based). With known partitioning of bolus volumes between ECMO and pulmonary artery, cardiac output was calculated. High-precision ultrasonic flow probes served as reference for Bland–Altman plots and linear mixed-effect models.

Results: Accuracy and precision for both the recirculation fraction based on AUC (bias, –5.4%; limits of agreement, –18.6 to 7.9%) and flow based (bias, –5.9%; limits of agreement, –18.8 to 7.0%) are clinically acceptable. Calculated cardiac output for all recirculation fractions was accurate but imprecise ($Recirculation_{AUC}$: bias 0.56 l/min; limits of agreement, –2.27 to 3.4 l/min; and $Recirculation_{FLOW}$: bias 0.48 l/min; limits of agreement, –2.22 to 3.19 l/min). Recirculation fraction increased bias and decreased precision.

Conclusions: Adapted thermodilution for VV-ECMO allows simultaneous measurement of recirculation fraction and cardiac output and may help optimize patient management with severe respiratory failure.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Veno-venous extracorporeal membrane oxygenation is a commonly performed rescue technique for patients experiencing severe respiratory failure
- While veno-venous extracorporeal membrane oxygenation improves the patient's oxygenation, some patients remain with poor cardiac or respiratory function because of poor residual lung function, low cardiac index, and increased fraction of blood flow that recirculates within the extracorporeal membrane oxygenation circuit without passing through the lungs
- While thermodilution methods are the gold standard for measuring cardiac output in patients not on extracorporeal membrane oxygenation, these methods are not suitable for extracorporeal membrane oxygenation without adaption

What This Article Tells Us That Is New

- The authors built an *in vitro* simulator representing whole-body circulation and a veno-venous extracorporeal membrane oxygenator
- With this bench setup, the authors demonstrated that adapting the classical thermodilution technique with an additional temperature measurement at the extracorporeal membrane oxygenation inlet allows simultaneous cardiac output and recirculation assessment
- Translation to the bedside of this novel approach may help optimize extracorporeal membrane oxygenation and cardiac function during veno-venous extracorporeal membrane oxygenation

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Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is an established rescue technique for severe hypoxemic respiratory failure.[1] Blood is drained from the central venous compartment, oxygenated and decarboxylized by an extracorporeal membrane lung, and then reinfused into a central vein.[1] In severe cases of hypoxemic respiratory failure, arterial oxygen saturation may remain low despite extracorporeal support. Safe margins for tolerable hypoxemia are unknown.[2] In addition to the residual lung function, the main determinants of arterial oxygen saturation are the extracorporeal pump blood flow, its ratio to venous return (*i.e.*, to cardiac output) for a given mixed venous oxygen saturation, and hemoglobin concentration.[2–5] Recirculation is the fraction of decarboxylized and oxygenated blood, which drains directly from a return cannula back into the extracorporeal circuit.[6] It does not take part in the gas exchange of the body and limits the delivery of oxygen from the extracorporeal device. The recirculation fraction can in theory be measured by comparing the extracorporeal membrane oxygenation (ECMO) inlet oxygen content to the patient's mixed-venous oxygen content, which is not readily available. Therefore, various indicator dilution techniques may be used.[6,7]

Empirical studies show that adequate oxygenation requires an extracorporeal blood flow of roughly two thirds of the native cardiac output.[4] Thermodilution methods are the clinical gold standard for the determination of cardiac output,[8] but thermodilution is inaccurate in the setting of veno-venous or veno-arterial ECMO, since part of the cold indicator is drawn into the extracorporeal circuit. This has been shown for transcardiac and transpulmonary thermodilution in veno-venous and veno-arterial ECMO configurations.[9–13] As both recirculation fraction and the ratio of extracorporeal blood flow to cardiac output are major determinants of the patient's oxygen saturation,[3,14] assessment of these variables is essential for an optimized treatment, which is currently an unmet clinical need.[15]

The aim of this study is to test whether recirculation fraction and simulated pulmonary blood flow can be assessed simultaneously with an adapted thermodilution technique. Based on our previous studies,[10] we hypothesize that injections into the ECMO outlet and simultaneous measurement of the temperature signal in both the ECMO inlet and pulmonary artery allow assessment of recirculation and native cardiac output with clinically acceptable accuracy and precision.

Materials and Methods

This prospective study was performed from July to September 2022 at the experimental surgical facility of the Department for Biomedical Research, University of Bern, Bern, Switzerland. No ethical approval was necessary due to the *in vitro* nature of this study. It follows the applicable Standards for Reporting Diagnostic Accuracy (STARD) guidelines.

Experimental Setup

Based on a simulator for veno-arterial ECMO,[16] we built an *in vitro* setup representing a whole-body circulation including a VV-ECMO (fig. 1A): A fluid reservoir represented the right atrium from which the native cardiopulmonary and VV-ECMO unit drained fluid simultaneously. The cardiac unit consisted of a rotation pump (Affinity CP AP40, Medtronic, Ireland) pumping into the pulmonary unit, which consisted of an oxygenator (Quadrox-I pediatric oxygenator, Maquet, Germany) and a simulated, adjustable shunt, which bypassed the oxygenator (fig. 1). Pulmonary and shunt flows were merged at the simulated left atrium, from which the fluid passed through two oxygenators (Quadrox-I pediatric oxygenator) in a series for heating. The circuit was closed at the right atrium.

The VV-ECMO unit drained fluid from the right atrium to another rotational pump (Affinity CP AP40) and an oxygenator (Quadrox-I pediatric oxygenator). The VV-ECMO outlet led back to the simulated pulmonary unit. A bridge between the VV-ECMO outlet and inlet allowed for controlled recirculation of fluid. Our system allowed the simulation of individual cardiopulmonary and VV-ECMO flows. Recirculation flow and shunt flow were adjusted using flow restrictors on the tubing. The system (total length, 1,100 cm) was primed with a total of 1,900 ml of lactated Ringer's solution. A heating system (HCV, type 20-602, Jostra Fumedica, Switzerland) connected to all oxygenators kept the circuit temperature at 37°C to prevent unstable and abruptly changing circuit (or body) temperature, which may mimic temperature boluses. To minimize heat loss, the tubes were wrapped with aluminum foil.

Measurements and Experimental Protocol

Circuit flows were measured using five ultrasonic flow sensors (LFS-04, Levitronix, Switzerland, precision ±1% of reading) located in the ECMO outlet (total ECMO flow including recirculation), in the recirculation bridge, in the simulated pulmonary artery and simulated shunt, and after the heating chamber (total body flow; fig. 1A). The indicator injection port was located 3 cm after the oxygenator in the ECMO outlet. Three pulmonary artery catheters (131F7 pulmonary artery catheter, Edwards Lifesciences, USA) were introduced through a Y-sheath (HMT Medizintechnik GmBH, Germany) at the ECMO outlet (65 cm after the injection port), ECMO inlet (193 cm after injection port), and simulated pulmonary artery (322 cm after injection port). An additional pulmonary catheter in the ECMO outlet (97 cm after the injection port) monitored circuit temperature.

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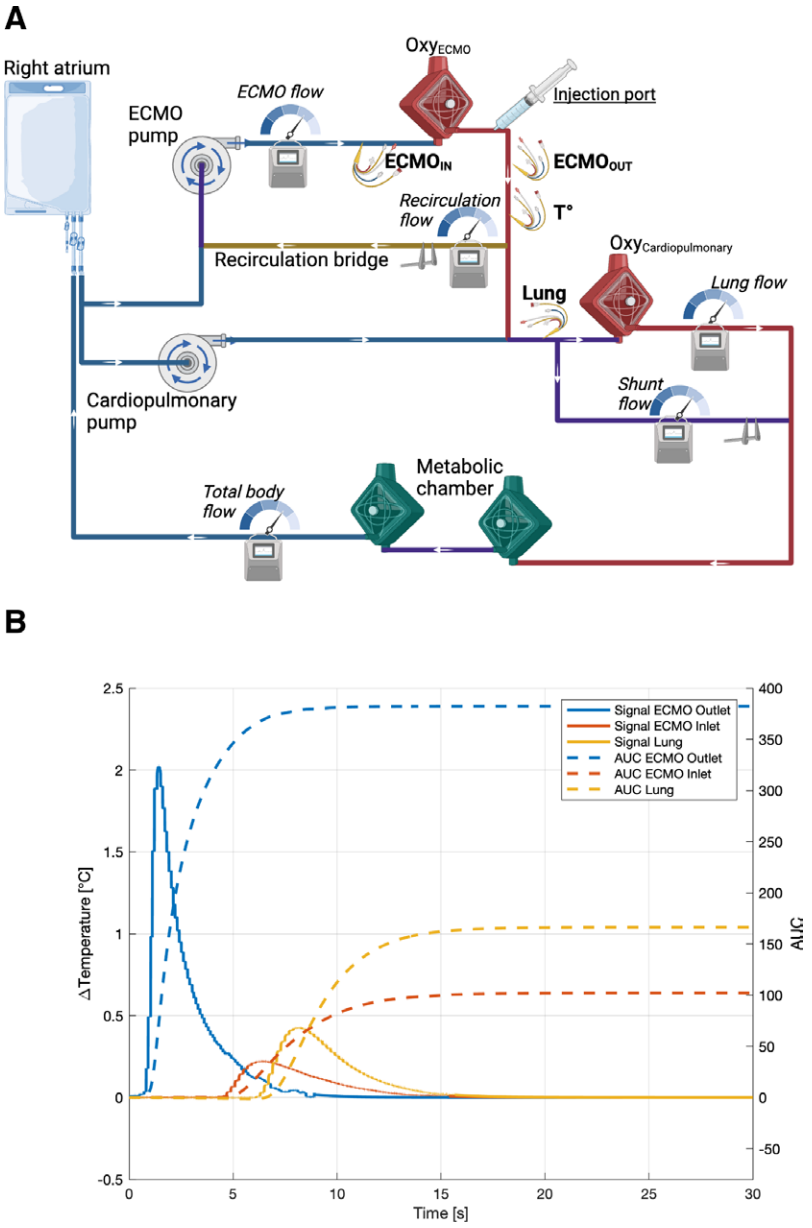

Fig. 1. (*A*) Experimental setup of the simulated cardiopulmonary and extracorporeal membrane oxygenation (ECMO) unit. Flow measurements (Levitronix, Switzerland) are represented by flow probes and tachometers, and thermodilution catheters are represented by pulmonary artery catheters. Oxygenators were connected to a heating system to maintain a temperature of 37°C, as controlled by a pulmonary artery catheter (T°). $ECMO_{OUT}$: ECMO outlet, $ECMO_{IN}$: ECMO inlet. (*B*) Exemplary thermodilution signals and resulting areas under the temperature curve (AUCs) from all three catheters in the following conditions: ECMO flow, 2,024.2 ml/min; total body flow, 2,529.4 ml/min; shunt, 36.1%; and recirculation fraction, 40.3%. Recirculation can be estimated either by dividing AUC ECMO inlet by AUC ECMO outlet or by solving equation 1 for injection volume using the measured blood flow at the ECMO and AUC ECMO inlet and dividing it by total injected volume (see eq. 3a and eq. 3b). Image created with BioRender.com.

There were two phases in the protocol. Phase 1 assessed the system's catheter constant.[10,17] Phase 2 assessed recirculation and simulated native cardiac output using our novel thermodilution technique. Phase 1 consisted of five cold indicator injections (0.9% saline at room temperature, 22°C) at ECMO circuit flows of 1,000, 1,500, 2,000, and 2,500 ml/min and 4 different injection volumes (3, 5, 7, and 10 ml) summing up to 80 individual injections for all combinations of flow and injection volume. These injections were used to define the catheter constants of the system, as previously described.[10,17] Phase 2 included 200 injections to assess recirculation and simulated pulmonary blood

Table 1. Important Estimates and *P* Values for Multivariable Statistical Models

Predicted Variable	Significant Predictors	Estimates [95% CIs]	*P* Value	Supplemental Digital Content Model
AUC_{ECMOIn} [C · s · 10^{-2}]				2
	Change per 1% of recirculation fraction	4.4 [3.8 to 4.8]	< 0.001	
	Change per 1 l/min of ECMO flow	−76.6 [−99.6 to −53.5]	< 0.001	
AUC_{Lung} [C · s · 10^{-2}]				3
	Change per 1% of recirculation fraction	−2.6 [−2.7 to −2.4]	< 0.001	
	Change per 1 l/min of simulated cardiac output	−49.8 [−60.4 to −39.0]	< 0.001	
$Recirculation_{AUC}$ minus measured recirculation [bias, %]				6
	Change per 1 l/min of simulated cardiac output	4.5 [2.6 to 6.5]	< 0.001	
	Change per 1% of recirculation fraction	−0.097 [−0.129 to −0.065]	< 0.001	
$Recirculation_{Flow}$ minus measured recirculation [bias, %]				7
	Change per 1 l/min of simulated cardiac output	4.6 [2.6 to 6.6]	< 0.001	
	Change per 1% of recirculation fraction	−0.077 [−0.110 to −0.044]	< 0.001	
Estimated CO ($Recirculation_{AUC}$) minus measured CO [bias, l/min]				10
	Change per 1% of recirculation fraction	0.016 [0.007 to 0.025]	< 0.001	
Estimated CO ($Recirculation_{Flow}$) minus measured CO [bias, l/min]				11
	Change per 1% of recirculation fraction	0.013 [0.004 to 0.021]	0.004	

The full models with all estimates and variables can be found in Supplemental Digital Content 1 (https://links.lww.com/ALN/D436).
AUC, area under the temperature curve; ECMO, extracorporeal membrane oxygenation.

flow. We performed 5 injections of 10 ml each at varying simulated cardiopulmonary flow, ECMO flow, shunt fraction, and recirculation fractions (table 1). After each set of 10 injections (100 ml), we removed 100 ml from the right atrium with a 50-ml syringe to keep the fluid balance of the system at ±100 ml. No sweep gas flow was used. We did not expect an effect on the temperature curves.

Data Acquisition

Thermodilution curves were acquired using Vigilance I ($ECMO_{Out}$ and circuit temperature, Edwards Lifesciences) or Vigilance II ($ECMO_{In}$ and Lung, Edwards Lifesciences) systems connected to an analog–digital converter board (BNC-2111, National Instruments, USA) and recorded in MatLab (version 2022a, Mathworks, USA). Circuit flows were recorded using Levitronix service software (version 2.0.8.0, Levitronix). Thermistor data were sampled at a rate of 200 Hz, and circuit flow data (Levitronix) were sampled at a rate of 1 Hz.

Signal Processing

Multiple passes of the indicator bolus through the circuit were identified in the thermodilution curves using the differential of the signal. If multiple passage was detected, an exponential decay function (f(x) = a × e^(−b × x) was fitted from the maximum of the signal until the detection point using a nonlinear least squares method. The portion of the signal after the additional passage (*e.g.*, positive differential) until the end of the signal was replaced by the fitted data.

If temperature changes were larger than 2°C, the signals were clipped by the Vigilance monitors. They had to be reconstructed by fitting a higher degree polynomial through the adjacent points of the saturated signal.[17] All raw and refitted signals were visually inspected for plausibility and artifacts. The area under the temperature curve (AUC) was calculated using the trapezoidal method with unit spacing and corrected to unit spacing of 100 Hz to allow comparability to our previous works.

Calculations

Each injection generated three thermodilution signals: the ECMO outlet signal ($ECMO_{OUT}$), the ECMO inlet signal ($ECMO_{IN}$), and the pulmonary artery signal (lung). We hypothesized that the injection volumes split according to the ratio of respective circuit flows.[10] Without recirculation, the entire bolus should pass through the cardiopulmonary unit. Based on our previous studies,[10] we expect that with increasing recirculation, linearly increasing amounts of injectate can be measured in the ECMO inlet.

Calculations were based on modifications or rearrangements of the classical Stewart–Hamilton equation, where CC indicates the catheter constant:

$$\text{Circuit flow} = \frac{\text{CC} \times \text{injection volume} \times (\text{circuit temperature} - \text{injection temperature})}{\text{AUC}} \quad (1)$$

Catheter constants were calculated based on injections in phase 1 using the flow, as well as the AUC recorded at the ECMO outlet by solving equation 1 for CC.[10,17] We used the mean catheter constant (80 injections) throughout phase 2. The catheter constant CC is a composite of the heat capacity factor K1 ($[\sigma_0 \times \rho_0]/[\sigma_1 \times \rho_1]$, where σ and ρ describe the specific heat and density of the injectate and blood and a correction factor C_T. C_T scales CC to the properties of the catheter (priming volume, distance from injection port to thermistor, injection volume). C_T and CC are dimensionless.[10,17,18] Circuit flow (cardiac output) is inversely proportional to the AUC. Although higher flows create a higher peak, the decay is faster, resulting in smaller AUC compared to low flows.[17]

Calculation of the Recirculation Fraction

We assessed two methods for the calculation of the recirculation fraction:

I. We assumed that the recirculation fraction is proportional to the ratio of AUC ECMO_{OUT} to AUC ECMO_{IN}.[6] This value is referred to as $\text{Recirculation}_{\text{AUC}}$.

$$\text{Recirculation}_{\text{AUC}} = \frac{\text{AUC}_{\text{ECMO IN}}}{\text{AUC}_{\text{ECMO OUT}}} \quad (2)$$

II. We used the AUC ECMO_{IN} and measured ECMO flow to calculate the injection volume passing the ECMO inlet by solving formula 1 for the injection volume. The ratio of this volume to the total injected volume represents the recirculation fraction. This value is referred to as $\text{Recirculation}_{\text{FLOW}}$. It is independent of any measurement in the ECMO outlet and constitutes a determination method similar to our previously published approach.[10,19]

$$\text{Injection volume}_{\text{ECMO in}} = \frac{\text{ECMO inlet flow} \times \text{AUC}_{\text{ECMO In}}}{\text{CC} \times (\text{circuit temperature} - \text{injection temperature})} \quad (3a)$$

$$\text{Recirculation}_{\text{Flow}} = \frac{\text{Injection volume}_{\text{ECMO In}}}{\text{Injection volume}_{\text{Total}}} \quad (3b)$$

The total injection volume is known (10 ml).

Calculation of Cardiac Output

From the recirculation fraction (calculated from AUC ratio or injection volumes), we calculated the injection volume passing into the ECMO inlet as

$$\text{Injection volume}_{\text{ECMO In}} = \text{recirculation fraction} \times 10 \text{ ml} \quad (4)$$

As such, the injection volume that passes into the simulated cardiopulmonary unit was derived[10]:

$$\text{Injection volume}_{\text{Lung}} = \text{injection volume}_{\text{ECMO Out}} - \text{injection volume}_{\text{ECMO In}} \quad (5)$$

We calculated the injection volume passing into the cardiopulmonary unit using both methods of recirculation assessment ($\text{Recirculation}_{\text{AUC}}$ and $\text{Recirculation}_{\text{FLOW}}$) and could derive pulmonary flow (*e.g.*, cardiac output) using equation 1.

$$\text{Circuit flow} = \frac{\text{CC} \times \text{injection volume}_{\text{Lung}} \times (\text{circuit temperature} - \text{injection temperature})}{\text{AUC}_{\text{Lung}}} \quad (1b)$$

Statistical Analysis

The data are expressed as means with standard deviations, visually presented as scatter plots or box plots. QQ plots assessed normality. Comparison between ultrasonic recirculation fraction and thermodilution recirculation fraction and comparison between ultrasonic circuit flow and thermodilution circuit flow was performed using linear mixed-effect models and Bland–Altman analysis, where bias (difference between reference and test methods) represents accuracy, and limits of agreement (95% CI of the bias) represent precision.[20] Clinical acceptance of a new test for cardiac output relies on limits of agreement of ±30%.[21]

Because our reference method has a very small error of measurement and may render Bland–Altman analysis partially invalid, we additionally performed bivariable regression analysis proposed by Taffé,[22,23] in which systematic bias is represented by the intercept of the model, and proportional bias is represented by 1 − the regression coefficient. The percentage error was calculated as (upper limit of agreement − bias)/mean total body flow.[21,24]

The impact of shunt, ECMO flow, native cardiac output, and recirculation fraction on our results was assessed using multivariable linear mixed-effects models. Because there were multiple injections per condition, we added the 40 different conditions (table 1) as random effects to account for the repeated measurements. Goodness of fit was assessed using R^2. A two-tailed P value < 0.05 defined statistical significance.

Results

Catheter Constant

ECMO circuit flows for phase 1 were well within protocol (1,012.8 ± 25.9 ml/min, 1,492.6 ± 1.0 ml/min, 2,015.5 ± 2.4 ml/min, and 2,502.4 ± 1.7 ml/min, respectively). The mean catheter constant produced from the 80 injections was 5.071 ± 0.879. The multivariable regression model showed no association between flow (P = 0.202) or injection volume (P = 0.623) and catheter constants (see supplementary statistical model 1, Supplemental Digital

Content 1, https://links.lww.com/ALN/D436). This averaged catheter constant of 5.071 was used for all cardiac output calculations performed in phase 2. Targeted circuit, recirculation, and shunt flows were set and maintained according to protocol (supplementary table 1, https://links.lww.com/ALN/D436).

Variables Associated with AUC

Multivariable models showed that AUC_{ECMOin} increased with increasing recirculation fraction and decreased with increasing ECMO flows (table 1). AUC_{Lung} decreased with increasing recirculation fraction and decreased with increasing native cardiac (table 1; fig 2, A and B). Shunt had no impact on measured AUC ($P = 0.76$ and $P = 0.576$, respectively). The resulting injection volumes passing each circuit (calculated from $Recirculation_{AUC}$ or $Recirculation_{FLOW}$) are inversely proportional to each other (fig. 2, C and D).

Assessment of Recirculation

The recirculation fraction was assessed based on AUC ($Recirculation_{AUC}$) and bolus volume ($Recirculation_{FLOW}$). Both methods showed similar bias and limits of agreement for all data points (fig. 3). Bias became more negative and limits of agreement became wider with increasing recirculation fraction (fig. 3; table 2). Bivariable linear mixed-effects regression models suggest high agreement between measured and estimated recirculation fraction ($Recirculation_{AUC}$ = −0.9 [−3.2 to 1.3] + 0.90 [0.86 to 0.95] × measured recirculation, $P < 0.001$, $R^2 = 0.950$ and $Recirculation_{FLOW}$ = −0.9 [−3.2 to 1.3] + 0.92 [0.88 to 0.97] × measured recirculation, $P < 0.001$, $R^2 = 0.968$; supplementary statistical models 4 and 5, Supplemental Digital Content 1, https://links.lww.com/ALN/D436). This translates to a systematic bias of −0.9% for both methods and a proportional bias of 0.1 and 0.08 per 1% change in measured recirculation fraction, respectively. Multivariable regression shows that the difference in $Recirculation_{AUC}$ − measured

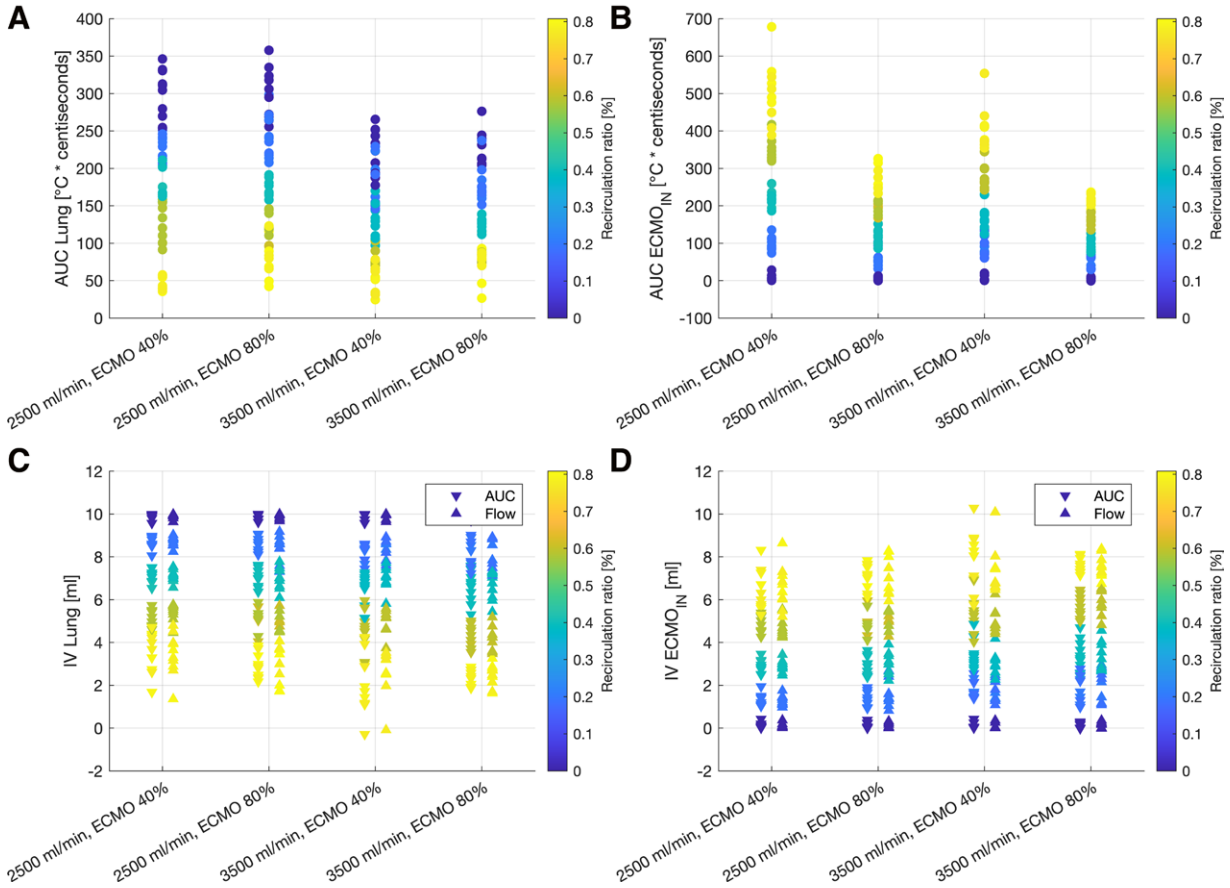

Fig. 2. (*A*) Area under the temperature curve (AUC) values measured at simulated cardiopulmonary unit. (*B*) AUC values measured at extracorporeal membrane oxygenation inlet ($ECMO_{In}$). (*C*) Calculated injection volumes passing simulated cardiopulmonary unit, either calculated from $Recirculation_{AUC}$ or $Recirculation_{Flow}$. (*D*) Calculated injections volumes passing $ECMO_{In}$, either calculated from $Recirculation_{AUC}$ or $Recirculation_{Flow}$. Colors represent set recirculation fractions. ECMO flows are given as percentages of the cardiac output.

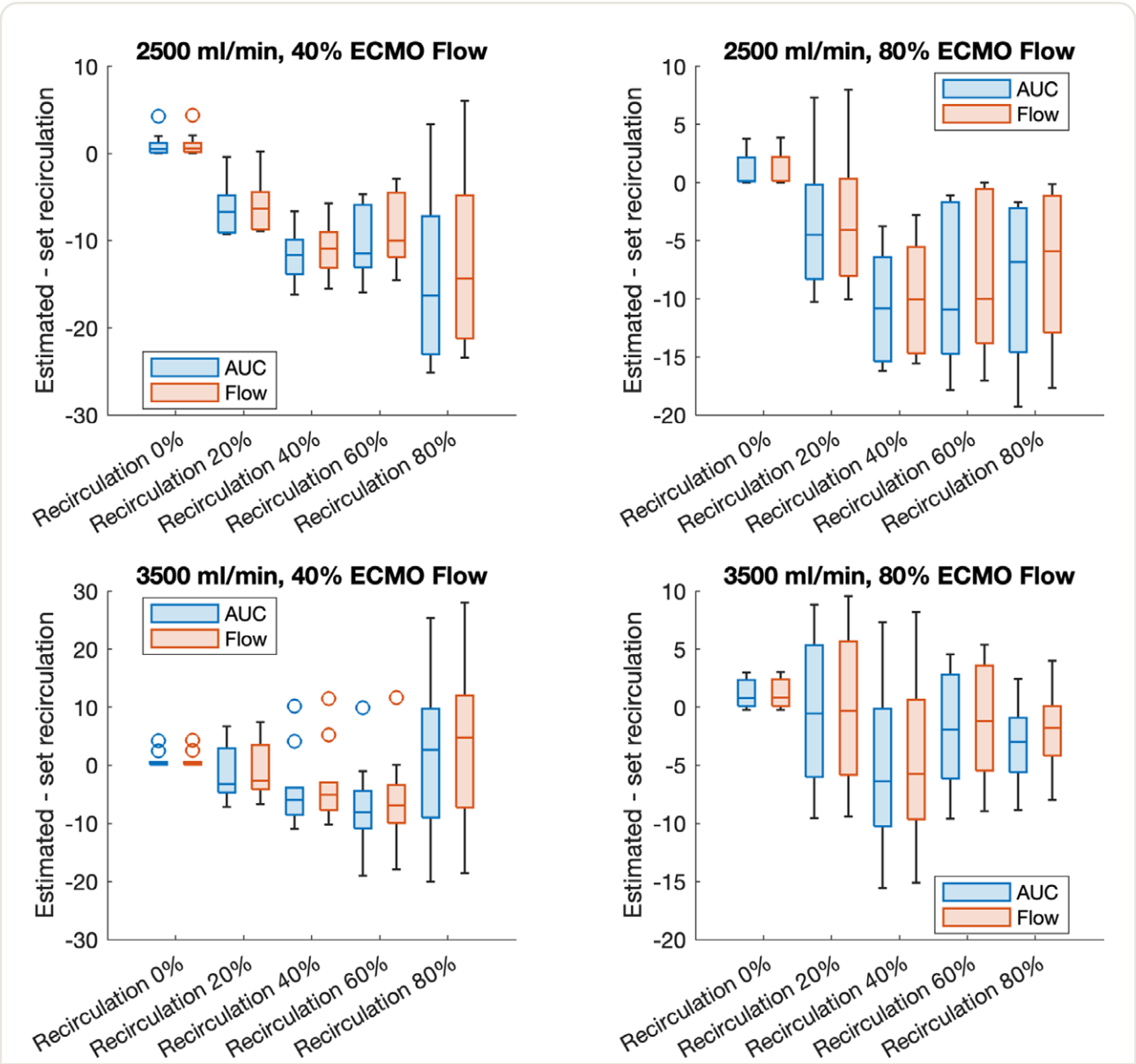

Fig. 3. Differences between estimated and set recirculation fraction, presented as box plots and according to experimental conditions. Area under the temperature curve (AUC) refers to the $Recirculation_{AUC}$ method, while "flow" refers to the $Recirculation_{Flow}$ method. Bland–Altman analysis showed the following results: $Recirculation_{AUC}$, bias −5.4 [−5.9 to −4.8] % and limit of agreement −18.6% [−20.2 to −17.1%] to 7.9% [6.3 to 9.4%]; and $Recirculation_{FLOW}$, bias −5.9% [−6.4 to −5.3%] and limit of agreement −18.8% [−20.3 to −17.3%] to 7.0% [5.5 to 8.6%]. ECMO, extracorporeal membrane oxygenation.

recirculation (*e.g.*, bias) is significantly associated with native cardiac output and set recirculation fraction (table 1; R^2 = 0.243). Shunt fraction (P = 0.583) and ECMO flow (P = 0.257) had no significant association with the differences in estimated ($Recirculation_{AUC}$) and set recirculation fraction (see supplementary statistical model 6, Supplemental Digital Content 1, https://links.lww.com/ALN/D436). Native cardiac output and set recirculation fraction were significantly associated with the bias of $Recirculation_{Flow}$ in multivariable regression (table 1; R^2 = 0.193). Shunt (P = 0.588) and ECMO flow (P = 0.425) had no significant association with the differences in estimated ($Recirculation_{Flow}$) and set recirculation (see supplementary statistical model 7, Supplemental Digital Content 1, https://links.lww.com/ALN/D436).

Assessment of Cardiac Output

Using the estimates for $Recirculation_{AUC}$ and $Recirculation_{Flow}$ and the resulting transcardiac injection volumes (fig. 2, C and D), we calculated simulated cardiac output (fig. 4). Bland–Altman analysis shows that bias

Table 2. Bland–Altman Analysis for Calculated Recirculation Fractions According to $Recirculation_{Flow}$ and $Recirculation_{AUC}$

Total Body Flow [ml/min]	ECMO Flow [% of Total Body Flow]	Recirculation (%)	$Bias_{AUC}$	Lower LoA_{AUC}	Upper LoA_{AUC}	$Bias_{Flow}$	Lower LoA_{Flow}	Upper LoA_{Flow}
2,500	40	0	1.0 [0.6 to 1.4]	−1.5 [−2.8 to −0.2]	3.5 [2.2 to 4.8]	1.0 [0.6 to 1.5]	−1.6 [−2.9 to −0.2]	3.6 [2.3 to 5.0]
2,500	40	20	−6.5 [−7.4 to −5.6]	−12.0 [−14.9 to −9.2]	−0.9 [−3.7 to 2.0]	−6.1 [−7.0 to −5.1]	−11.8 [−14.8 to −8.9]	−0.3 [−3.3 to 2.6]
2,500	40	40	−11.7 [−12.6 to −10.8]	−17.3 [−20.2 to −14.4]	−6.1 [−9.0 to −3.3]	−11.0 [−11.9 to −10.0]	−16.7 [−19.6 to −13.8]	−5.2 [−8.2 to −2.3]
2,500	40	60	−10.2 [−11.5 to −9.0]	−17.9 [−21.8 to −14.0]	−2.6 [−6.5 to 1.3]	−8.8 [−10.1 to −7.6]	−16.7 [−20.8 to −12.7]	−1.0 [−5.0 to 3.1]
2,500	40	80	−14.6 [−17.6 to −11.6]	−33.1 [−42.6 to −23.6]	3.9 [−5.6 to 13.4]	−12.5 [−15.6 to −9.4]	−31.6 [−41.4 to −21.8]	6.6 [−3.2 to 16.4]
2,500	80	0	1.0 [0.6 to 1.4]	−1.6 [−3.0 to −0.3]	3.6 [2.3 to 4.9]	1.0 [0.6 to 1.4]	−1.7 [−3.1 to −0.3]	3.7 [2.3 to 5.1]
2,500	80	20	−3.3 [−5.3 to −1.4]	−15.2 [−21.3 to −9.1]	8.5 [2.4 to 14.6]	−2.9 [−4.9 to −1.0]	−15.1 [−21.3 to −8.9]	9.2 [3.0 to 15.5]
2,500	80	40	−10.9 [−12.3 to −9.5]	−19.6 [−24.1 to −15.2]	−2.2 [−6.6 to 2.3]	−10.1 [−11.6 to −8.7]	−19.1 [−23.7 to −14.5]	−1.2 [−5.8 to 3.4]
2,500	80	60	−9.7 [−11.7 to −7.7]	−22.0 [−28.3 to −15.7]	2.7 [−3.7 to 9.0]	−8.7 [−10.7 to −6.7]	−21.3 [−27.7 to −14.8]	3.9 [−2.6 to 10.3]
2,500	80	80	−8.5 [−10.5 to −6.6]	−20.7 [−27.0 to −14.5]	3.7 [−2.6 to 10.0]	−7.2 [−9.1 to −5.2]	−19.3 [−25.6 to −13.1]	5.0 [−1.2 to 11.3]
3,500	40	0	0.8 [0.4 to 1.3]	−2.0 [−3.4 to −0.5]	3.6 [2.2 to 5.0]	0.8 [0.4 to 1.3]	−2.0 [−3.4 to −0.5]	3.6 [2.2 to 5.1]
3,500	40	20	−1.4 [−2.9 to 0.1]	−10.7 [−15.5 to −5.9]	7.9 [3.1 to 12.7]	−0.9 [−2.4 to 0.7]	−10.3 [−15.2 to −5.5]	8.6 [3.8 to 13.4]
3,500	40	40	−4.4 [−6.5 to −2.3]	−17.4 [−24.1 to −10.7]	8.7 [2.0 to 15.4]	−3.5 [−5.6 to −1.3]	−16.9 [−23.8 to −10.0]	9.9 [3.1 to 16.8]
3,500	40	60	−7.3 [−9.9 to −4.8]	−23.1 [−31.1 to −15.0]	8.4 [0.3 to 16.4]	−6.2 [−8.8 to −3.6]	−22.3 [−30.5 to −14.0]	9.9 [1.7 to 18.2]
3,500	40	80	0.5 [−3.8 to 4.9]	−26.5 [−40.3 to −12.6]	27.6 [13.7 to 41.4]	2.6 [−1.9 to 7.1]	−25.2 [−39.4 to −10.9]	30.3 [16.1 to 44.6]
3,500	80	0	1.1 [0.7 to 1.5]	−1.3 [−2.6 to −0.1]	3.5 [2.3 to 4.8]	1.1 [0.7 to 1.5]	−1.4 [−2.6 to −0.1]	3.6 [2.3 to 4.9]
3,500	80	20	−0.8 [−2.9 to 1.3]	−13.9 [−20.6 to −7.2]	12.3 [5.6 to 19.0]	−0.4 [−2.6 to 1.7]	−13.9 [−20.8 to −7.0]	13.0 [6.1 to 19.9]
3,500	80	40	−5.4 [−7.7 to −3.1]	−19.6 [−26.9 to −12.3]	8.8 [1.6 to 16.1]	−4.7 [−7.0 to −2.4]	−19.2 [−26.6 to −11.8]	9.8 [2.4 to 17.2]
3,500	80	60	−2.2 [−3.9 to −0.6]	−12.3 [−17.5 to −7.1]	7.9 [2.7 to 13.1]	−1.5 [−3.1 to 0.2]	−11.7 [−17.0 to −6.5]	8.7 [3.5 to 14.0]
3,500	80	80	−3.1 [−4.2 to −2.0]	−10.1 [−13.7 to −6.5]	3.9 [0.3 to 7.5]	−1.9 [−3.1 to −0.7]	−9.1 [−12.9 to −5.4]	5.4 [1.7 to 9.1]

The table shows the Bland–Altman analysis for calculated recirculation fractions (in %) according to the described methods $Recirculation_{Flow}$ and $Recirculation_{AUC}$. The results are shown according to the set recirculation fractions and experimental conditions (fig. 3). Bias and limits of agreement are presented with their 95% CI.

AUC, area under the temperature curve; ECMO, extracorporeal membrane oxygenation; LoA, limit of agreement.

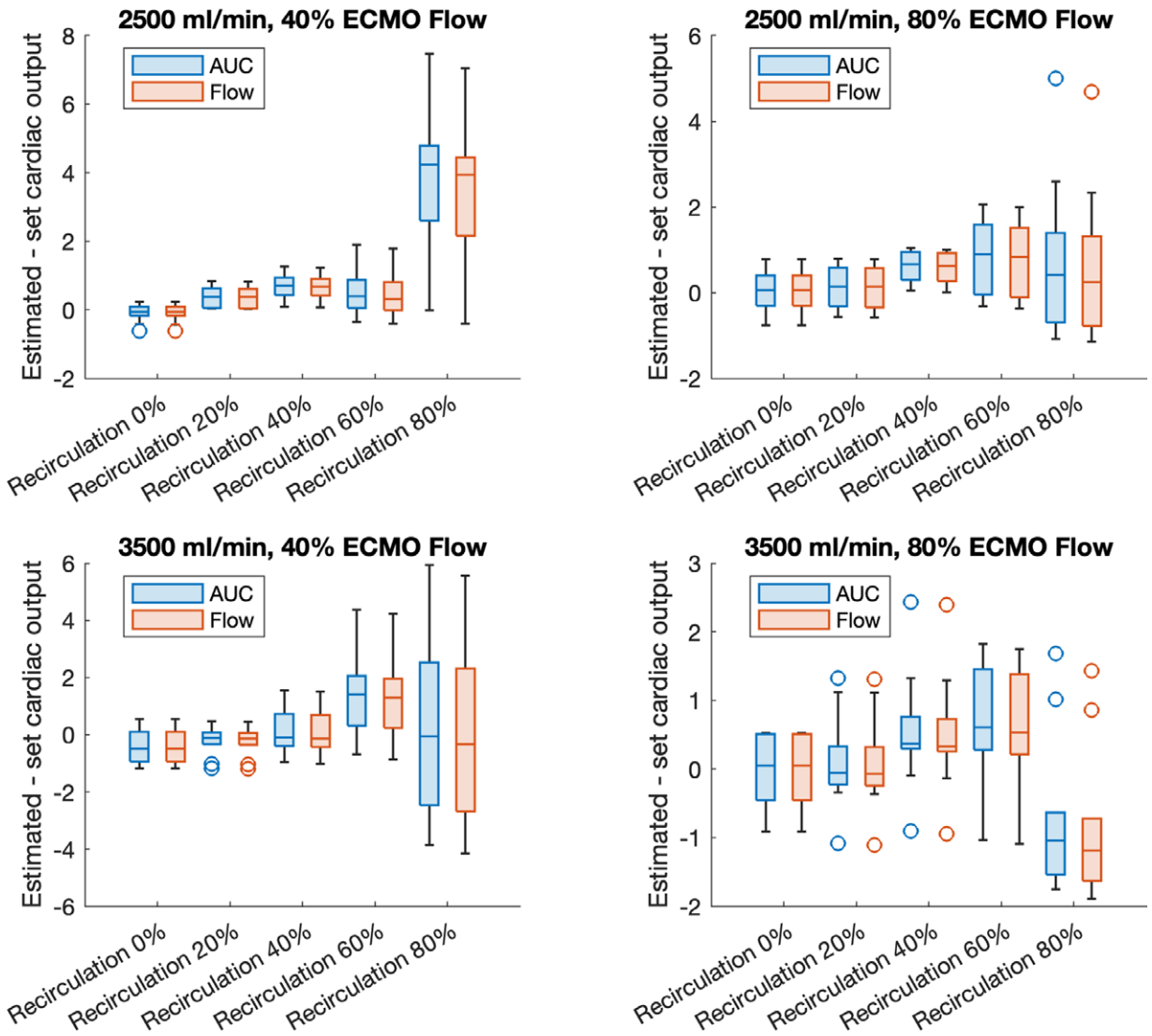

Fig. 4. Differences between estimated and set cardiac output, presented as box plots and according to experimental conditions. Area under the temperature curve (AUC) refers to the $Recirculation_{AUC}$ method, while "flow" refers to the $Recirculation_{Flow}$ method. Bland–Altman analysis showed the following results: $Recirculation_{AUC}$, bias 0.56 [0.44 to 0.68] l/min and limit of agreement –2.27 [–2.60 to –1.93] to 3.4 [3.05 to 3.72] l/min; and $Recirculation_{FLOW}$, bias 0.48 [0.37 to 0.60] l/min and limit of agreement –2.22 [–2.54 to –1.90] to 3.19 [2.87 to 3.50] l/min. ECMO, extracorporeal membrane oxygenation.

was low with wide limits of agreement (fig. 4; table 3). This result is influenced by a significant decrease in precision, expressed as limits of agreement and percentage error, at high recirculation fractions (table 3; fig. 4). Estimated cardiac output was not significantly linked to simulated cardiac output in bivariable linear mixed-effect regression models (see supplementary statistical models 8 and 9, Supplemental Digital Content 1, https://links.lww.com/ALN/D436), which represent a high systematic and proportional bias. In multivariable regression, the differences in estimated ($Recirculation_{AUC}$) and set native cardiac output were only significantly affected by the set recirculation fraction (table 1; R^2 = 0.257). Set cardiac output (P = 0.123), shunt fraction (P = 0.710), and ECMO flow (P = 0.202) had no significant association with these differences (see supplementary statistical model 10, Supplemental Digital Content 1, https://links.lww.com/ALN/D436). Similarly, differences in estimated ($Recirculation_{Flow}$) and set native cardiac output were only affected by the set recirculation fraction (table 1; R^2 = 0.218). The remaining parameters (native cardiac output [P = 0.092], shunt fraction [P = 0.677], and ECMO flow [P = 0.258]) had no significant association with these differences (see supplementary statistical model 11, Supplemental Digital Content 1, https://links.lww.com/ALN/D436).

Table 3. Bland–Altman Analysis for Calculated Cardiac Output Estimated with Calculated Injection Volumes Based on $Recirculation_{Flow}$ and $Recirculation_{AUC}$

Total Body Flow (ml/min)	ECMO Flow (% of Total Body Flow)	Set Recirculation (%)	$Bias_{AUC}$	Lower LoA_{AUC}	Upper LoA_{AUC}	PE_{AUC}	$Bias_{Flow}$	Lower LoA_{Flow}	Upper LoA_{Flow}	PE_{Flow}
2,500	40	0	–0.1 [–0.2 to –0.0]	–0.6 [–0.9 to –0.3]	0.4 [0.1 to 0.6]	19.7	–0.1 [–0.2 to –0.0]	–0.6 [–0.9 to –0.3]	0.4 [0.1 to 0.6]	19.7
2,500	40	20	0.4 [0.3 to 0.5]	–0.2 [–0.5 to 0.1]	1.0 [0.7 to 1.3]	23.2	0.4 [0.3 to 0.5]	–0.2 [–0.5 to 0.1]	1.0 [0.7 to 1.3]	23.4
2,500	40	40	0.7 [0.6 to 0.8]	–0.0 [–0.4 to 0.3]	1.4 [1.1 to 1.8]	29.5	0.7 [0.6 to 0.8]	–0.1 [–0.4 to 0.3]	1.4 [1.0 to 1.8]	29.5
2,500	40	60	0.6 [0.3 to 0.8]	–0.9 [–1.7 to –0.1]	2.1 [1.3 to 2.8]	59.9	0.5 [0.3 to 0.7]	–1.0 [–1.7 to –0.2]	2.0 [1.2 to 2.7]	58.4
2,500	40	80	3.9 [3.2 to 4.6]	–0.5 [–2.8 to 1.7]	8.4 [6.1 to 10.6]	178.0	3.5 [2.8 to 4.3]	–0.9 [–3.2 to 1.4]	8.0 [5.7 to 10.3]	177.8
2,500	80	0	0.0 [–0.1 to 0.2]	–1.0 [–1.5 to –0.5]	1.0 [0.5 to 1.5]	39.5	0.0 [–0.1 to 0.2]	–1.0 [–1.5 to –0.5]	1.0 [0.5 to 1.5]	39.5
2,500	80	20	0.1 [–0.0 to 0.3]	–0.8 [–1.3 to –0.3]	1.1 [0.6 to 1.5]	37.0	0.1 [–0.0 to 0.3]	–0.8 [–1.3 to –0.3]	1.0 [0.6 to 1.5]	37.2
2,500	80	40	0.6 [0.5 to 0.7]	–0.1 [–0.5 to 0.2]	1.3 [0.9 to 1.7]	28.7	0.6 [0.4 to 0.7]	–0.2 [–0.5 to 0.2]	1.3 [0.9 to 1.7]	29.0
2,500	80	60	0.9 [0.6 to 1.2]	–0.9 [–1.8 to 0.0]	2.6 [1.7 to 3.5]	70.2	0.8 [0.5 to 1.1]	–0.9 [–1.8 to –0.0]	2.6 [1.7 to 3.5]	70.0
2,500	80	80	0.8 [0.2 to 1.3]	–2.9 [–4.8 to –1.0]	4.4 [2.5 to 6.3]	146.2	0.6 [0.0 to 1.2]	–2.9 [–4.7 to –1.1]	4.1 [2.3 to 5.9]	140.7
3,500	40	0	–0.4 [–0.6 to –0.2]	–1.7 [–2.3 to –1.0]	0.9 [0.2 to 1.5]	35.8	–0.4 [–0.6 to –0.2]	–1.7 [–2.3 to –1.0]	0.9 [0.2 to 1.5]	35.8
3,500	40	20	–0.2 [–0.4 to –0.1]	–1.2 [–1.8 to –0.7]	0.8 [0.3 to 1.3]	29.1	–0.2 [–0.4 to –0.1]	–1.3 [–1.8 to –0.7]	0.8 [0.3 to 1.3]	29.1
3,500	40	40	0.1 [–0.1 to 0.4]	–1.4 [–2.2 to –0.6]	1.7 [0.9 to 2.5]	44.7	0.1 [–0.2 to 0.4]	–1.5 [–2.3 to –0.7]	1.7 [0.9 to 2.5]	44.7
3,500	40	60	1.4 [0.9 to 1.9]	–1.6 [–3.1 to –0.0]	4.4 [2.9 to 5.9]	85.5	1.3 [0.8 to 1.8]	–1.7 [–3.2 to –0.2]	4.3 [2.8 to 5.8]	85.3
3,500	40	80	0.2 [–0.7 to 1.2]	–5.9 [–9.0 to –2.7]	6.4 [3.2 to 9.5]	174.3	–0.1 [–1.0 to 0.9]	–6.1 [–9.1 to –3.0]	5.9 [2.9 to 9.0]	171.2
3,500	80	0	0.1 [–0.2 to 0.4]	–1.7 [–2.6 to –0.8]	1.9 [1.0 to 2.8]	49.9	0.1 [–0.2 to 0.4]	–1.7 [–2.6 to –0.8]	1.9 [1.0 to 2.8]	49.9
3,500	80	20	0.1 [–0.1 to 0.3]	–1.3 [–2.0 to –0.6]	1.5 [0.8 to 2.2]	39.0	0.1 [–0.1 to 0.3]	–1.3 [–2.0 to –0.6]	1.5 [0.8 to 2.2]	39.2
3,500	80	40	0.5 [0.3 to 0.8]	–1.2 [–2.1 to –0.3]	2.2 [1.4 to 3.1]	48.8	0.5 [0.2 to 0.8]	–1.2 [–2.1 to –0.3]	2.2 [1.3 to 3.1]	49.0
3,500	80	60	0.6 [0.3 to 0.9]	–1.1 [–1.9 to –0.2]	2.3 [1.4 to 3.2]	48.0	0.5 [0.3 to 0.8]	–1.1 [–2.0 to –0.3]	2.2 [1.4 to 3.1]	47.9
3,500	80	80	–0.7 [–1.1 to –0.3]	–3.0 [–4.2 to –1.8]	1.6 [0.4 to 2.7]	64.8	–0.9 [–1.2 to –0.5]	–3.1 [–4.2 to –1.9]	1.4 [0.2 to 2.5]	62.8

The table shows Bland–Altman analysis for calculated cardiac output (in l/min), estimated with calculated injection volumes passing the cardiopulmonary unit (fig. 2) based on the described methods $Recirculation_{Flow}$ and $Recirculation_{AUC}$. The results are shown according to the set recirculation fractions and experimental conditions (fig. 4). Bias and limits of agreement are presented with their 95% CI.

ECMO, extracorporeal membrane oxygenation; LoA, limit of agreement; PE, percentage error.

The relationships between estimated and measured set cardiac output and the resulting systematic and proportional bias could be dramatically improved, if only data with a recirculation fraction of 40% or lower were analyzed ($Recirculation_{AUC}$ = 0.89 [0.19 to 1.59] + 0.76 [0.53 to 0.99] × measured recirculation, $P < 0.001$, $R^2 = 0.257$ and $Recirculation_{FLOW}$ = 0.89 [0.19 to 1.58] + 0.75 [0.53 to 0.98] × measured recirculation, $P < 0.001$, $R^2 = 0.257$; see supplementary statistical models 12 and 13, Supplemental Digital Content 1, https://links.lww.com/ALN/D436).

Discussion

This study demonstrates that an adapted thermodilution technique in VV-ECMO is feasible and allows estimation of recirculation and, if recirculation fraction is less than or equal to 40%, cardiac output with clinically acceptable accuracy and precision in this high-fidelity bench simulation. Our adaptation of classical thermodilution demonstrates that only a single indicator injection is necessary to determine recirculation and native cardiac output simultaneously. Given the importance of these parameters for a patient's oxygenation, such a simple technique may be of high clinical value.

Both transcardiac thermodilution with a pulmonary artery catheter or transpulmonary thermodilution overestimate native cardiac output in the setting of VV-ECMO due to indicator loss into the extracorporeal circuit.[9,11,13] Echocardiography may be a good alternative but is operator dependent, is noncontinuous, and does not assess recirculation. The partitioning of the injection volume between the artificial (extracorporeal net "loss") and native circuit can be calculated from thermodilution. Cipulli *et al.*[6] recently proposed recirculation determination using the ratio of AUC_{In} and AUC_{Out}.[6] We had developed a method for cardiac output calculation on veno-arterial ECMO by calculating the passing injectate in the ECMO inlet and determining the injectate passing the pulmonary circulation.[10] We translate this method to VV-ECMO, in which recirculation can be calculated through the partition of injection volume, which is a direct function of recirculation. Using this calculated volume passing in the native circulation allows calculation of the native cardiac output using the adapted thermodilution technique with formula 1b.[10]

Our technique provides adequate estimates of recirculation and native cardiac output if the recirculation fractions do not exceed 40% (table 3). Higher recirculation fractions are recognized by both techniques, $Recirculation_{AUC}$ and $Recirculation_{Flow}$ (fig. 3), but the resulting cardiac output estimation based on a very small injection volume passing the cardiopulmonary unit and thus small resulting AUC (fig. 2A) is erroneous. High recirculation fractions usually are recognized by the absence of a color change between the cannulae. This simple method allows for the correction of cannula position under visual or oxymetric control of cannula saturations. The strength of our method is the *simultaneous* assessment of recirculation and cardiac output. Recirculation contributes to worsening oxygenation, but the most important factor is a high ratio of ECMO blood flow to cardiac output,[4] which our method provides on a continuous basis.

Our models show that the set recirculation fraction heavily affects the accuracy of our method. This is in line with findings from other studies in which high recirculation fractions or shunts impaired accuracy and precision.[13,25] Small indicator bolus sizes are known to increase variability[26] in thermodilution measurements.[27,28] For future applications, higher injection volumes may increase accuracy in the setting of high recirculation fractions. As a limitation, we have operated our simulation with pediatric oxygenators and relatively low blood flows for the set cardiac output. In adult clinical scenarios, higher cardiac outputs are expected, which may contribute to increased precision. Overestimation of cardiac output at low blood flows with thermodilution has been reported in several studies.[10,29,30] From a clinical perspective, however, recirculation fractions of more than 50% would clearly necessitate optimization of ECMO canulae as a first step to optimize patient care before native cardiac output is assessed further.

The $Recirculation_{AUC}$ technique has already been optimized.[6,19] Cipulli *et al.*[6] found a small bias of −0.21% with very narrow limits of agreement (−3.36 to 2.94%), which is considerably better than data from our model and below what generally can be expected of thermodilution techniques where limits of agreement of approximately 20% is common and accepted.[21,29] In our study, the variability in the catheter constant may account for approximately ±17% of the error. Cipulli *et al.*[6] used an elaborate setup with blood instead of lactated Ringer's solution and continuous hemofiltration to keep circuit volume constant. The carrier solution (blood *vs.* Ringer's lactate) will influence the catheter constant *via* the specific heat and specific gravity of the fluid.[8,10] This will have no influence on the ratio of AUC and cannot therefore explain the differing results. The main differences to our setup are the simulated native cardiac output, the circuit length and priming volume (1,100 cm *vs.* 660 cm overall tubing and 1.9 l *vs* 5.2 l of priming volume). Despite our measures to minimize heat loss, the larger surface and smaller priming volume and the use of injectate at room temperature in our setup may have contributed to our larger bias and limits of agreement. If a low bias and limits of agreement could be reproduced in an *in vivo* setting, it would increase the accuracy and precision of our proposed method significantly because the volume passing into the pulmonary circuit could be estimated more precisely.

We and other groups have shown that the distance between injection port and the thermistor does not necessarily influence the AUC, but it does influence the downslope of thermal decay.[17,31] This has important implications for future use of adapted thermodilution techniques in ECMO therapy. While the varying decay may alter results for ejection fraction estimates for thermodilution curves,

the constant AUC independent of catheter position allows for calibration of catheter constants in the *in vivo* system.[10,17] The injection into either the $ECMO_{IN}$ or $ECMO_{OUT}$ with simultaneous measurement of the full thermodilution signal can be used to derive a catheter constant for each individual patient condition. The derived catheter constants are independent of injection volume, as demonstrated in this and previous studies.[17] For this project, we used an averaged catheter constant, but accuracy and precision may improve with more frequent calibration.

$Recirculation_{AUC}$ requires simultaneous measurements of the ECMO outlet and inlet temperature signal.[6] In contrast, our suggested method of $Recirculation_{Flow}$, in which the injection volume passing the ECMO inlet is calculated directly from the ECMO inlet flow and is therefore independent of a measurement in the ECMO outlet, makes measurements in the ECMO outlet obsolete. Our results prove that our new method shows similar precision and accuracy (fig. 3) and may therefore simplify procedures.

We have used a high precision reference method with almost no percentage error (±1% of true value). While it is well known that the precision of the reference technique influences the precision of the test method in Bland–Altman analysis,[24] it only recently came to attention that in situations of a highly precise reference method—as in our case (figs. 3 and 4)—the underlying statistical assumptions for a Bland–Altman analysis may not be met. In Bland–Altman analysis, similar precision of the compared methods and constant precision and bias over the measured range of values are assumed, as demonstrated by Taffé et al.[22,23] An approach to overcome this problem is a linear regression analysis between the reference and test method, with reporting the systemic bias (y axis intercept of the regression) and the proportional bias (1 − the slope of the regression). Therefore, the limits of agreement and percentage errors presented in table 3 and figures 3 and 4 may only be interpreted with caution. While the estimated percentage errors at low recirculation fraction are below the clinically accepted 30%,[24] an overlooked proportional bias may considerably influence the interpretation.[22] The highly precise reference method allows for a percentage error of up to 30% to be accepted,[24] as the percentage error stems almost entirely from the test method.[24] Excluding data with high recirculation fractions where precision deteriorates, our regression analysis for cardiac output data with recirculation fractions of 40% or below estimates a systematic bias of approximately 0.9 l/min with a proportional bias of approximately 0.25 per 1 l/min, which we would deem clinically acceptable and in line with other thermodilution studies.[29]

Our study group has focused on the measurement of native cardiac output through gas exchange and thermodilution in veno-arterial ECMO.[10,16,25,32] The current work translates our previous knowledge in the setting of VV-ECMO in a first prospective bench study. Should future studies, either *in vitro* or *in vivo*, confirm the validity of our approach, adapted thermodilution may help guide VV-ECMO therapy in a bench-to-bedside approach. Because right ventricular failure is a hallmark of acute respiratory distress syndrome and may be a driver of morbidity and mortality, monitoring of right ventricular function is warranted,[33] including pulmonary artery catheters as per guideline.[34] Additionally to a pulmonary artery catheter, temperature measurements at the ECMO inlet allows for direct application of our method at the bedside. Temperature measurements may be possible through introduction of a pulmonary artery catheter into the ECMO circuit or by simple thermistors.[6,35,36] Other study groups use thermodilution to assess recirculation during ECMO.[6] Whether our technique for simultaneous assessment of cardiac output may also help to assess right ventricular function during acute respiratory failure with VV-ECMO should be further evaluated.

Conclusions

Our adapted thermodilution technique for VV-ECMO allows for simultaneous measurement of the recirculation fraction and cardiac output with an accuracy and precision that is expected for thermodilution. In scenarios of recirculation fractions less than or equal to 40%, the accuracy and precision of our method appear to be clinically acceptable. Further research including computational studies, as well as animal models, should validate this novel methodology. A translation to the bedside could be achieved by rapid temperature measurements at the ECMO inlet in addition to a pulmonary artery catheter.

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Competing Interests

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Supplemental Digital Content

Supplemental Digital File 1. Supplementary table and statistical models, https://links.lww.com/ALN/D436

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