Analysis of Transpulmonary Thermodilution Data Confirms the Influence of Renal Replacement Therapy on Thermodilution Hemodynamic Measurements

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BACKGROUND: Transpulmonary thermodilution (TPTD) is used frequently in the intensive care unit to determine cardiac index (CI), intrathoracic blood volume index (ITBVI), and extravascular lung volume index (EVLWI). Renal replacement therapy (RRT) influences TPTD results, but the underlying mechanisms are not completely understood. We hypothesized that RRT blood flow induces errors in TPTD measurements.

METHODS: We analyzed TPTD data available from the PiCCO® plus hemodynamic measurement device on a personal computer using a proprietary Pulsion Medical Systems software. By using the dialysis catheter to inject the thermal indicator, 20 measurement series were performed in 12 intensive care unit patients determining CI, ITBVI, and EVLWI during RRT with the blood pump stopped, and at flows of 100 and 200 mL/min, respectively.

RESULTS: Data export was successful in 17 measurement series and showed a significant decrease in measured CI (6.5 ± 2.5 vs 5.4 ± 1.9 L/min/m^2, $P < 0.001$) and ITBVI (1358.8 ± 274.5 vs 1132.8 ± 218.3 mL/m^2, $P < 0.001$) with RRT and a significant increase in EVLWI (8.6 ± 4.4, 10.2 ± 4.5 mL/kg, $P < 0.001$). Blood temperature before and the temperature decrease after injection of the thermal indicator were unchanged by RRT. Mean transit time and downslope time of the thermodilution curve, however, were both increased with the RRT blood pump running ($P \leq 0.001$).

CONCLUSIONS: Analysis of TPTD data shows that thermodilution curve forms are modified with RRT, resulting in an erroneous calculation of thermodilution-derived hemodynamic parameters. (Anesth Analg 2016;XXX:00–00)

Cardiac output (CO) monitoring has evolved as a standard of care for critically ill patients, and transpulmonary thermodilution (TPTD) allows not only the determination of CO but also the estimation of additional hemodynamic parameters used to assess fluid status: intrathoracic blood volume (ITBV) as a measure of preload and extravascular lung volume (EVLW) as an indicator of excess pulmonary fluid.[1] With TPTD, a thermodilution curve is plotted from the changes in blood temperature detected in the systemic circulation after injection of a defined bolus of cooled saline solution into the central venous circulation.[2] CO is then calculated from the area under this thermodilution curve, and ITBV and EVLW are estimated using mean transit time (MTt) and downslope time (DSt) determined by advanced analysis of the curve[1] (Fig. 1). MTt is calculated as the mean value of the time the indicator particles need to travel between point of injection and point of detection. Therefore, it divides the thermodilution curve into half. DSt is defined as the exponential elution time and calculated by plotting the thermodilution curve on a logarithmic (temperature)-linear (time) graph and determining the time between 85% and 45% of the maximum temperature response.

The precision of thermodilution measurement depends on the undisturbed injection of the correct amount of thermal indicator into the central venous circulation.[3,4] Loss of indicator during injection results in an overestimation of CO, which is a relevant problem with extracorporeal lung assist where blood is continuously drained from the central venous circulation into an extracorporeal device and returned to the patient.[4–6]

Renal replacement therapy (RRT) is an extracorporeal therapy frequently necessary in critically ill hemodynamically unstable patients, and, as with extracorporeal device lung assist, blood is pumped through an extracorporeal unit and back into the patient, albeit at a far smaller rate (100–300 mL/min with RRT vs 2–5 L/min with extracorporeal lung assist). In studies examining the influence of RRT on TPTD measurements to date, however, overestimation of CO has not been reported.[7–10] In contrast, several studies showed a decline in CO and ITBV with RRT.[7,8,10] In addition to an actual change in CO caused by RRT, several other mechanisms have been proposed to explain these findings, including changes in blood temperature caused by RRT, turbulences in blood flow, and recirculation, and location of the injection port in relation to the arterial thermistor and the dialysis catheter.[11]

To further investigate these potential effects, we took a closer look at the data used to calculate CO, ITBV, and

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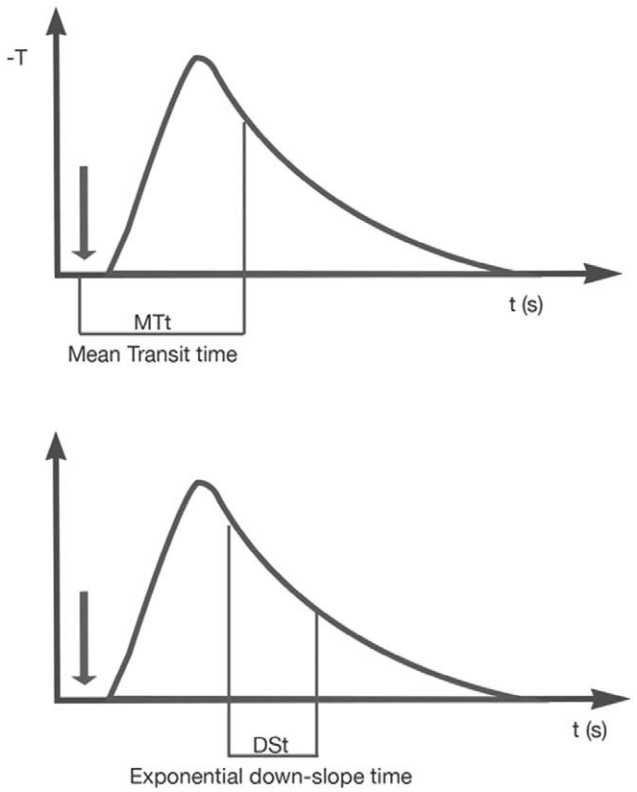

Figure 1. Calculation of mean transit time (MTt) and downslope time (DSt) from the transpulmonary thermodilution curve (T = temperature, t = time, ↓ = injection time). As indicated in the figure, MTt divides the thermodilution curve into half, whereas DSt is calculated determining the time between 85% and 45% of the maximum temperature response. Reprinted with kind permission of Pulsion Medical Systems.

EVLW. Exclusively using the third lumen of a triple lumen dialysis catheter for the injection of the thermal indicator, we analyzed extended TPTD measurement data, including blood and injectate temperatures (Tinjs) as well as MTt and DSt used to calculate the volumetric hemodynamic indices.

METHODS

This study was approved by the IRB of the Charité Berlin (EA4/092/08) who waived the need for informed consent.

Patients

The prospective study was conducted in the medical intensive care unit (ICU) of the Charité Campus Benjamin Franklin university hospital in Berlin, Germany. All patients were monitored with a PiCCO® hemodynamic monitoring system (Pulsion Medical Systems, Feldkirchen, Germany) as part of their clinical treatment and were receiving RRT. Twenty measurement series were performed in 12 patients. A measurement series consisted of 9 measurements taken at 3 different RRT blood pump flow rates (pump stopped, pump at 100 mL/min, and pump at 200 mL/min) with 3 measurements each per pump setting. In 6 patients, >1 RRT session was included in the study; in 4 patients, data from 2 RRT sessions were analyzed; and in 2 patients, 3 RRT sessions were included. Thus, a total of 180 measurements were performed as part of the study. Both intermittent hemodialysis (IHD) and continuous venovenous hemofiltration (CVVH) sessions were included. With CVVH, circuits were heated to 38.0°C, and when IHD was performed, dialysate was heated to 36.5°C.

TPTD Measurements

For TPTD measurement with the PiCCO hemodynamic monitoring system, all patients had a thermistor-tipped femoral artery catheter (Ø 5 F, length 20 cm, Pulsiocath PV2015L20, Pulsion Medical Systems) and a triple lumen dialysis catheter (Mahurkar™ 12F Triple Lumen High Pressure Catheter, Covidien Deutschland GmbH, Neustadt, Germany), inserted either through the left jugular vein (length, 20 cm) or the femoral vein (length, 24 cm). The Mahurkar triple lumen dialysis catheter has a modified double-D lumen design that allows for incorporation of a separate 19-gauge (0.4–0.5 mL deadspace) injection lumen in addition to the 2 large-bore dialysis lumens. The opening of the outflow ("arterial") lumen is located on the side of the catheter approximately 3 cm proximal to the catheter tip. Blood is returned via 1 ("venous") inflow lumens with 2 openings, one located at the catheter tip and the other approximately 2.3 cm away from the tip on the opposite side of the catheter. The additional lumen recommended for injection or infusion of medication and for blood sampling is also located on the side of the catheter, approximately 2 cm from the catheter tip and at a 90° angle to the inflow and outflow side lumens. To determine CO and thermodilution-derived volumetric hemodynamic parameters (ITBV and EVLW), a bolus of 20 mL of cold normal saline solution (0°C–6°C) was manually injected (injection time, ≤10 seconds) into this additional lumen of the dialysis catheter and detected by the thermistor-tipped arterial catheter in the iliac artery or descending aorta, depending on patient anatomy. A separate jugular venous catheter was used for vasopressor therapy in all instances.

Study Protocol

TPTD measurement series were performed during RRT sessions at 3 different RRT blood pump settings. Baseline values were obtained with the blood pump stopped and comparison measurements were taken at a blood pump flow of 100 and 200 mL/min, respectively. The 3 blood flow rates were set in a random order 30 seconds before TPTD measurements and returned to high flow (200 mL/min with CVVH and >250 mL/min with IHD) immediately after 3 TPTD measurements CO, ITBV, and EVLW were calculated as a mean of these 3 individual measurements. Results were indexed to body surface area and body weight, respectively, and are referred to as cardiac index (CI), ITBV index (ITBVI), and EVLW index (EVLWI). All TPTD data, consisting of CI, ITBVI, EVLWI, MTt, DSt, Tinj, blood temperature before injection (Tblood), and maximum temperature decrease after injection (ΔT), were recorded with a PiCCO plus device (PC 8100, software version 6.0, Pulsion Medical Systems) and exported to a personal computer using a proprietary software (PICCO-VoLEF-WIN software, version 4.0, Pulsion Medical Systems) along with basic hemodynamic data (heart rate and mean arterial pressure).

Statistical Analysis

On the basis of clinical experience and previous reports, we expected RRT to result in changes in measured CI of at

least 0.8 L/min/m² with a SD of 1 L/min/m² when using the injection lumen of the dialysis catheter for thermodilution measurements.[7,9,10,12] A sample size of 15 has an 80% power to detect this difference with an α significance of 0.05 (sample size calculation for paired differences). To account for technical problems with data export, a sample size of 20 measurement series was, therefore, deemed adequate. Results are expressed as mean ± SD and median. This pretest–posttest design induced correlated data. Furthermore, multiple measurements were made for some patients. Thus, a linear mixed model with random intercepts was used for the statistical analysis. This model accounts for variability between individuals and correlation within individuals.[13] For the residual covariance, an equal covariance was assumed. By using this model, the effect of different RRT blood flow rates was assessed comparing the baseline values obtained when the blood pump was stopped with those obtained at a blood pump flow rate of 100 and 200 mL/min, respectively. These 3 conditions were included as a classification variable into the model. Accordingly, least square means estimates were obtained, and differences between the different conditions were calculated. Adjustment for multiple comparisons is based on the method by Tukey–Kramer method. Confounding factors (ultrafiltration, arterial and venous catheters adjacent) were assessed by including these parameters in the analysis as covariates. $P < 0.01$ was considered to be statistically significant. Statistical analyses were performed with the SAS procedure GLIMMIX (SAS Institute Inc., Cary, NC).

Table 1. Patient Characteristics (n = 11)

Age (y), mean ± SD (median)	70.3 ± 13.4 (72)
Sex (male), *n* (%)	7 (64)
Length of ICU stay (d), mean ± SD (median)	60.8 ± 38.5 (54)
ICU mortality, *n* (%)	3 (27)
SAPS, mean ± SD (median)	61.4 ± 25.0 (73)
Diagnostic categories, *n* (%)	
Sepsis	6 (55)
Gastrointestinal bleeding	3 (27)
Pneumonia	2 (18)
Weight (kg), mean ± SD (median)	85.2 ± 20.6 (90)
Height (cm), mean ± SD (median)	173.7 ± 10.4 (180)
Body mass index (kg/m²), mean ± SD (median)	27.9 ± 4.7 (27.8)
Thermodilution measurement series analyzed (total)	17
Patients with 1 measurement series	6
Patients with 2 measurement series	4
Patients with 3 measurement series	1

ICU = intensive care unit; SAPS = simplified acute physiology score.

RESULTS

Of the 20 measurement series performed in 12 patients, 3 series had to be excluded because of failed data export. Thus, a total of 17 measurement series from 11 patients were available for analysis. In 5 measurement series, data export was incomplete, so that measurements taken at the RRT blood pump flow of 100 mL/min could not be analyzed. Patient characteristics are given in Table 1. At the time of measurement, all patients were sedated and on invasive mechanical ventilation. All but 1 received continuous vasopressor therapy with a mean norepinephrine dose of 0.42 ± 0.951 μg/kg/min (median, 0.11 μg/kg/min), which remained unchanged during measurements. In 10 patients, measurements were performed during IHD, whereas 7 patients were on CVVH at the time of measurement. RRT was performed without net ultrafiltration in 6 cases, and mean ultrafiltration rate in the other 11 measurement series was at 318 ± 222 mL/h (median, 200 mL/h).

Hemodynamic measurement results are shown in Table 2. Heart rate and mean arterial pressure remained unchanged between measurements taken with the RRT blood pump stopped or running at either 100 or 200 mL/min. However, we found that CI and ITBVI measurements were significantly lower with the blood pump running both at a 100 and 200 mL/min, and EVLWI was higher (Fig. 2). Both MTt and DSt increased significantly with the blood pump running (Fig. 3), whereas no changes were observed in Tinj, Tblood, or Δt.

In 12 of the 17 measurement series, the dialysis catheter was in the femoral position and inserted on the same side as the femoral arterial catheter used for TPTD measurement; in 5 measurement series, the RRT catheter was either jugular venous or femoral, but contralateral to the arterial catheter. When entered in the statistical analysis as a covariate, although, no significant influence of the catheter position on CI (P = 0.092), ITBVI (P = 0.894), or EVLWI (P = 0.327) was found. The presence (n = 6) or absence (n = 11) of net ultrafiltration on RRT also had no significant impact on CI (P = 0.589), ITBVI (P = 0.749), and EVLWI (P = 0.350).

Table 2. Hemodynamic Measurement Series (n = 17) on Renal Replacement Therapy

Parameter	Blood pump stopped (n = 17), patients = 11, mean ± SD (median)	Blood flow 100 mL/min (n = 12), patients = 9		Blood flow 200 mL/min (n = 17), patients = 11	
		Mean ± SD (median)	*P* value[a]	Mean ± SD (median)	*P* value[a]
Heart rate (per min)	93.4 ± 21.0 (93.7)	86.9 ± 16.0 (87.7)	0.994	94.0 ± 20.7 (93.0)	0.975
MAP (mm Hg)	74.0 ± 10.0 (72.0)	72.2 ± 7.6 (71.8)	0.555	74.1 ± 8.3 (74.7)	0.996
CI (L/min/m²)	6.5 ± 2.5 (6.0)	4.9 ± 2.2 (4.0)	<0.001	5.4 ± 1.9 (5.1)	<0.001
ITBVI (mL/m²)	1358.8 ± 274.5 (1379.4)	1072.6 ± 182.8 (1014.8)	0.001	1132.8 ± 218.3 (1027.1)	<0.001
EVLWI (mL/kg)	8.6 ± 4.4 (8.0)	9.6 ± 5.4 (8.3)	0.004	10.2 ± 4.5 (9.3)	<0.001
MTt (s)	24.4 ± 7.9 (25.8)	27.4 ± 9.5 (29.3)	0.004	26.1 ± 8.5 (27.9)	0.001
DSt (s)	8.5 ± 3.2 (8.1)	10.8 ± 4.7 (11.4)	<0.001	10.3 ± 3.9 (10.7)	<0.001
Tinj (°C)	3.0 ± 1.2 (2.7)	3.5 ± 1.1 (3.6)	0.528	2.9 ± 1.0 (2.8)	0.900
Tblood (°C)	37.0 ± 0.8 (36.8)	36.8 ± 0.6 (36.8)	0.946	36.9 ± 0.9 (36.8)	1.0
ΔT (°C)	0.29 ± 0.07 (0.29)	0.32 ± 0.06 (0.33)	1.0	0.31 ± 0.06 (0.31)	0.776

[a]Adjusted *P* values according to Tukey–Kramer method based on a linear mixed model: reference condition = blood pump stopped.

CI = cardiac index; DSt = downslope time; EVLWI = extravascular lung water index; ITBVI = intrathoracic blood volume index; MAP = mean arterial pressure; MTt = mean transit time; Tblood = blood temperature before injection; Tinj = injectate temperature; ΔT = maximum temperature decrease after injection.

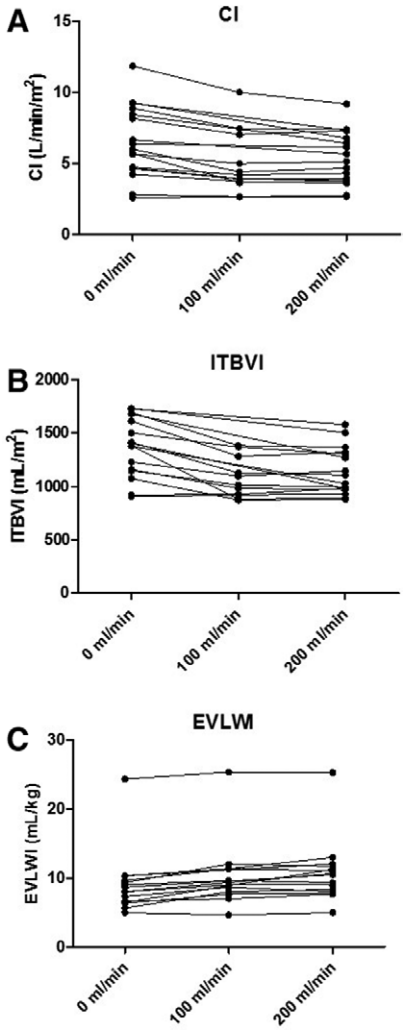

Figure 2. Cardiac index (CI; A), intrathoracic blood volume index (ITBVI; B), and extravascular lung water index (EVLWI; C) with renal replacement therapy blood pump stopped and at a blood flow of 100 and 200 mL/min, respectively.

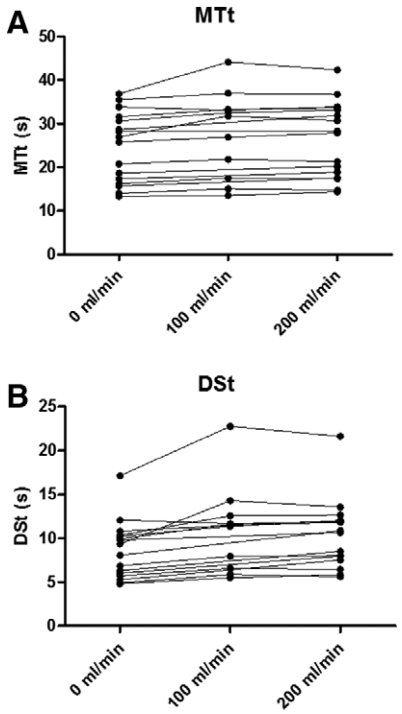

Figure 3. Mean transit time (MTt; A) and downslope time (DSt; B) with renal replacement therapy blood pump stopped and at a blood flow of 100 and 200 mL/min, respectively.

DISCUSSION

Our results show that RRT influences TPTD measurement results and point toward errors in TPTD measurements rather than real hemodynamic changes caused by RRT. Thermodilution CO measurement has certain inherent sources of error, including the precision of injectate amount and temperatures, the injection process, the distribution and recirculation of the indicator, and variations in patient physiology, such as baseline temperature fluctuations.[3–5] Extracorporeal therapies, especially RRT, are frequently necessary in the ICU and can interfere with indicator distribution and circulation, thus aggravating errors in thermodilution hemodynamic measurements.[6,11] However, alternative methods of CO determination are less suitable for ICU use. Some require specialized equipment (impedance cardiography, partial CO_2 rebreathing); others are invasive, operator dependent, and cannot be performed over a prolonged period of time (e.g., transesophageal Doppler ultrasound or echocardiography); still others also require the use of an indicator (e.g., indocyanine green indicator dilution, lithium dye dilution) and are, therefore, prone to the same errors as thermodilution techniques.[4,14] Under these circumstances, an understanding of how and to what extent RRT affects thermodilution hemodynamic measurements is of particular importance, but only few studies have been published concerning this question.[7–10]

Heise et al.[8] examined the influence of continuous RRT on pulmonary artery and TPTD measurements and found CO to be decreased during RRT with both techniques. Pulmonary artery thermodilution is used less frequently in the ICU in Europe because less invasive TPTD has yielded comparable CO results and to allow for calculation of additional volumetric hemodynamic parameters (ITBVI and EVLWI).[2]

CI reductions with RRT were also reported in 2 of the 3 other available studies examining TPTD measurements, whereas Dufour et al. and others found no changes in TPTD or pulse contour–derived CI with RRT, respectively.[7,9,10]

We found both measured CI and ITBVI to be decreased during RRT blood flow. ITBVI reductions had been reported in 2 of the aforementioned studies, but none of the investigations also including ITBVI and EVLWI found an increase in EVLWI, as with our study.[7,9,10]

In contrast to our study, in all previous investigations, a separate central venous catheter, and not the dialysis catheter itself, was used for injection of the thermal indicator, an approach that could possibly reduce RRT influence on TPTD measurements, especially if both catheters are not close to each other. Exact relations between catheter positions, although, are reported only in 1 study where no CI reduction was found with RRT.[9] We chose to use the triple lumen dialysis catheter for indicator injection because large, clinically relevant decreases in CI had been previously reported with this approach.[12]

With injection of the thermal indicator via the dialysis catheter injection lumen, we found a 26% reduction of median CI with RRT, a difference far greater than reported in the studies using a separate injection catheter, where only small changes in CI < 7%were observed.[7,8,10] The large median CI decrease with RRT of 1.8 L/min/m^2 in our study suggests an association with the use of the dialysis catheter for injection of the thermal indicator and, thus, supports the findings of the case report mentioned earlier.[12] Turbulent blood flow during RRT had been hypothesized by the authors of that report to be the cause of the erroneous CI measurement.[12]

In our study, no apparent thermodilution curve form distortions were noticed. Retrospective analysis of all thermodilution curves could not be conducted after data export to the personal computer using the PICCO-VoLEF-WIN software, but analysis of the thermodilution curve form related parameters MTt and DSt provided some clues. We found that both MTt and DSt were prolonged when measured with the RRT blood pump running, a finding that also explains the decrease in ITBVI and increase in EVLWI we observed. The equations used to calculate the volumetric hemodynamic indices infer that—with all other variables unchanged—an increase in DSt leads to an increase in EVLW, and an increase in MTt produces a decrease in ITBV[15]:

$$\text{Intrathoracic thermal volume (ITTV)} = \text{CO} \times \text{MTt}$$

$$\text{Pulmonary thermal volume (PTV)} = \text{CO} \times \text{DSt}$$

$$\text{Global end – diastolic volume (GEDV)} = \text{ITTV} - \text{PTV}$$

$$\text{Intrathoracic blood volume (ITBV)} = 1.25 \times \text{GEDV}$$

$$\text{Extravascular lung water (EVLW)} = \text{ITTV} - \text{ITBV}.$$

McGrath and Columb[11] hypothesized that the effect of RRT on ITBV and DSt was because of turbulent blood flow and recirculation, which would be caused by RRT and would flatten the downslope of the thermodilution curve, thus overestimating MTt. However, the prolongation of DSt we found cannot be explained by this mechanism. Further research will be necessary to better understand this phenomenon.

Besides recirculation-associated thermodilution curve form distortion, other potential RRT-related influences on thermodilution hemodynamic measurements have to be discussed.

Extracorporeal circulation has the potential to influence blood temperature, an effect that has been reported before.[9] Dufour and coworkers observed a significant increase in blood temperature after stopping the RRT blood pump.[9] This increase did not lead to significant changes in CI or ITBVI, however, probably because the maximum temperature decline after thermal indicator injection remained unchanged. In our study, we did not observe changes in blood temperature (Tblood), nor in maximum temperature decline after injection (Δt), or in the Tinj itself. This does not exclude an influence of the extracorporeal circulation on the injectate temperature as the injectate passes through the dialysis catheter adjacent to the warmed RRT fluids returned to the patient. The Tinj can only be measured as it enters the injection port of the dialysis catheter (Tinj) not when it exits the dialysis catheter into the blood stream. However, warming of the injectate as it passes through the dialysis catheter would equal a loss of the thermal indicator, thus leading to an overestimation not an underestimation of CI.[4–6]

Another parameter unlikely to have influenced hemodynamic results is the use of norepinephrine in all but one of our study patients. Because vasopressors can be removed by RRT, hemodynamic changes with RRT could potentially be caused by changes in vasopressor levels.[16] In our study, however, blood pressure and heart rate remained unchanged during the different RRT blood flow measurements. Norepinephrine was infused exclusively through a separate central venous catheter located in the superior vena cava, whereas all but 1 dialysis catheter were inserted through femoral access.

Another potential influence on hemodynamic results could be fluid shifts caused by RRT circuit connection/disconnection. To minimize such effects, we compared hemodynamic results after and during RRT without disconnection of the extracorporeal circuit—in contrast to the study by Pathil et al.[10] who compared pre-RRT hemodynamic measurements with those obtained with RRT running. To avoid blood clotting and minimize RRT blood pump stop, measurements were taken 30 seconds after the blood pump was set to target value in our study. A similar protocol had also been used in another study.[9] We cannot rule out the possibility that the changes in RRT blood pump speed caused short-term hemodynamic destabilizations and thus influenced our results, but the lack of change in blood pressure and norepinephrine dose suggests that the hemodynamic effect of RRT was minimal.

Therefore, we conclude that a true decrease in CI caused by RRT was not a likely explanation for the changes in hemodynamic measurements observed in our study. Without simultaneously applying a second, independent, method of CI determination, however, this hypothesis cannot be excluded completely, but unchanged blood pressure, heart rate, and norepinephrine doses during the measurement series make it unlikely. As discussed earlier, the MTt and DSt increases rather point toward the measurement artifacts related to RRT, as do other findings of our study.

In 12 of 17 measurements, femoral dialysis and thermistor-tipped arterial catheters were located on the same side, and thus close to each other, so that hemodynamic measurements could have been influenced by the so-called cross-talk phenomenon: Arteriovenous "cross-talk" has been postulated to explain early arterial detection of the thermal indicator after adjacent venous injection.[17,18] When adjacent catheter position was examined as a covariate in our analysis, however, no significant influence on hemodynamic measurements was detected.

There are several shortcomings of our study. First, data export was incomplete, and despite adequate statistical power, our sample size was small.[8–10] Measurements were undertaken both during IHD and CVVH, and with and without net ultrafiltration, so that the study group was also rather inhomogeneous. In 2 of the studies published to date, only patients on CVVH had been included.[7,9] Pathil et al. and others had investigated only patients on slow-extended IHD, whereas in one other study, the mode of continuous RRT had not been stated.[8,10] Also, TPTD was the only

method used to measure CI in our study. Finally, we did not obtain thermodilution measurements using a separate central venous catheter for indicator injection for comparison.

CONCLUSIONS

When TPTD is run concurrently with RRT, a reduction in measured CI and ITBVI results. Although the mechanism of this effect is unclear, use of the dialysis catheter to inject the thermal indicator may intensify the effects of RRT on hemodynamic measurements, and analysis of TPTD data indicates that erroneous measurements could be caused by distortions in thermodilution curve form or be influenced by the "cross-talk" phenomenon if adjacent venous and arterial catheters are used. Therefore, hemodynamic measurements during RRT must be interpreted with caution, especially when using the dialysis catheter for injection of the thermal indicator or when venous injection and arterial detection site are in close proximity.

DISCLOSURES

Name: Sven Schmidt, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Sven Schmidt has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Conflicts of Interest: Sven Schmidt declares no conflicts of interest.
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Contribution: This author helped design the study, analyze the data, and write the manuscript.
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Conflicts of Interest: Timm Westhoff declares no conflicts of interest.
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Conflicts of Interest: Walter Zidek declares no conflicts of interest.
Name: Friederike Compton, MD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Friederike Compton has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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This manuscript was handled by: Avery Tung, MD.

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