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Influence of Blood Purification and Differential Injection Sites of Cold Saline on Transpulmonary Thermodilution Values

Takahiro Kawaji,[1] Toshikazu Sakai,[1] Kazuhiro Moriyama,[2] Yoshitaka Hara,[1] Tomoyuki Nakamura,[1] Naohide Kuriyama,[1] Yasuyo Shimomura,[1] Yu Kato,[1] Hidefumi Komura,[1] Chizuru Yamashita,[1] Yasuyoshi Kurimoto,[1] Daisuke Hasegawa[1], and Osamu Nishida[1]

[1]*Department of Anesthesiology and Critical Care Medicine and* [2]*Laboratory for Immune Response and Regulatory Medicine, Fujita Health University School of Medicine, Toyoake, Japan*

Abstract: We aimed to investigate the effects of blood purification and cold saline injection sites on the transpulmonary thermodilution values. We measured the cardiac output of eight pigs in every combination of cold saline injection (left jugular and femoral veins) and blood purification sites (right jugular and femoral veins), with or without blood purification. We examined the influence of the difference between the presence and absence of blood purification, vascular sites for blood purification, and sites for cold saline injection on the transpulmonary thermodilution values. Cardiac output measured during blood purification using transpulmonary thermodilution was underestimated; however, there was no difference between vascular sites. Cardiac output measured via injection of cold saline into the femoral vein was higher than that obtained through injection of cold saline into the jugular vein, with or without blood purification. **Key Words:** Blood purification, Cold saline injection sites, Hemodynamic monitoring, Transpulmonary thermodilution, Vascular access sites.

Hemodynamic monitoring devices using transpulmonary thermodilution (TPTD) are increasingly used for hemodynamic evaluations in critically ill patients and have been associated with improved prognosis (1,2). Nevertheless, correct monitoring is extremely important; there have been discrepancies reported in the TPTD values when intravenous cold saline injection was administered via the jugular vein versus the femoral vein (3–5). Furthermore, wide margins of errors were reported in the TPTD values when blood purification was both performed and discontinued (6–9). On the other hand, previous studies suggested that differences in vascular sites for blood purification do not affect TPTD values (10).

We performed three investigations to study the effects of vascular sites for blood purification and sites for cold saline injection (as well as these factors in combination) on the TPTD values:

1. Investigating the difference between measured TPTD when blood purification is performed and discontinued
2. Investigating the difference in the TPTD values via different sites for cold saline injection (jugular versus femoral veins)
3. Investigating the difference in the TPTD values via different vascular access sites for blood purification (jugular versus femoral veins)

This examined the influence of the difference between the presence and absence of blood purification, the vascular site of blood purification, and sites for cold saline injection on the TPTD values.

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Address correspondence and reprint requests to Osamu Nishida, Professor and Chairman, Department of Anesthesiology and Critical Care Medicine, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan.Email: nishida@fujita-hu.ac.jp
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MATERIALS AND METHODS

This study protocol was approved by the Fujita Health University Experimental Animal Care and Use Committee. Eight pigs (body weight: 35–40 kg) were used in this study. The TPTD hemodynamic monitoring device used was the EV1000 system (Edwards Lifesciences, Irvine, CA, USA). An indwelling catheter equipped with a temperature sensor was placed in the left femoral artery. To enable intravenous cold saline injection, central venous catheters (Certofix, B. Braun-Aesculap AG, Tuttlingen, Germany) were placed in the left jugular and left femoral veins, with the ends of each catheter placed in the superior and inferior venae cavae. Blood purification catheters (GamCath, Gambro Dialysatoren GmbH, Hechingen, Germany) were placed in the right jugular and right femoral veins. Blood purification was performed with extracorporeal circulation forming only a circuit, with no filter (Fig. 1). Approximately 4000 IU of heparin was injected intravenously, at a continuous drip rate of 4000 IU/h. The blood flow rate was set at 80 mL/min. Room temperature was set at 25°C, and blood returning to the body was set to be approximately 1°C cooler than the blood leaving the body. Cold saline solution was injected at a rate of 10 mL in 5 s. We evaluated the cardiac output (CO) for every pig in every combination of cold saline injection and blood purification sites and whether blood purification was performed or not. To offset the effects of duration, we changed the order of instituting the various combinations of factors. CO measurement was conducted 32 times per pig, and investigations 1 through 3 were performed and analyzed using the 256 CO measurements obtained from the eight pigs (Fig. 2). Furthermore, we calculated the mean transit time (MTt) and downslope time (DSt) that constitute the thermodilution curve parameters using the formulae given below (11,12). MTt is the time from cold water injection until the area under the curve (AUC) of the thermodilution curve is halved. DSt is obtained from the exponential decay time of the thermodilution curve. The data thus generated is expressed as a median value (interquartile range), and statistical analysis was conducted using the Wilcoxon signed-rank test, with the significance level set at $P < 0.05$.

$$\mathrm{MTt} = (\mathrm{EVLW} + \mathrm{ITBV})/\mathrm{CO} \quad (1)$$

$$\mathrm{DSt} = (\mathrm{EVLW} + \mathrm{ITBV} - \mathrm{GEDV})/\mathrm{CO} \quad (2)$$

Note: GEDV (global end-diastolic volume), EVLW (extra-vascular lung water), and ITBV (intrathoracic blood volume) are all parameters measured by the EV1000 device.

RESULTS

The results of investigations 1–3 are shown in Table 1.

Investigation 1 showed that the CO with blood purification was 2.60 (2.30–3.40) L/min, while the CO without blood purification was 2.85 (2.40–3.50)

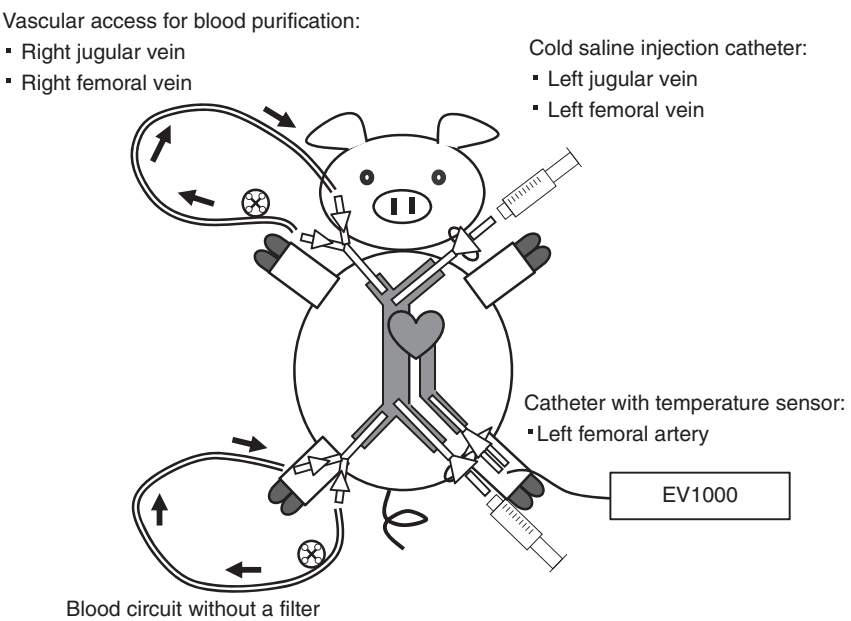

FIG. 1. Experimental setup. The transpulmonary thermodilution (TPTD) hemodynamic monitoring device used was the EV1000. The catheter with temperature sensor was placed in the left femoral artery. The catheters for cold saline injection were placed in the superior vena cava through the left jugular vein and in the inferior vena cava through the left femoral vein. The vascular sites for blood purification were in the right jugular vein and right femoral vein.

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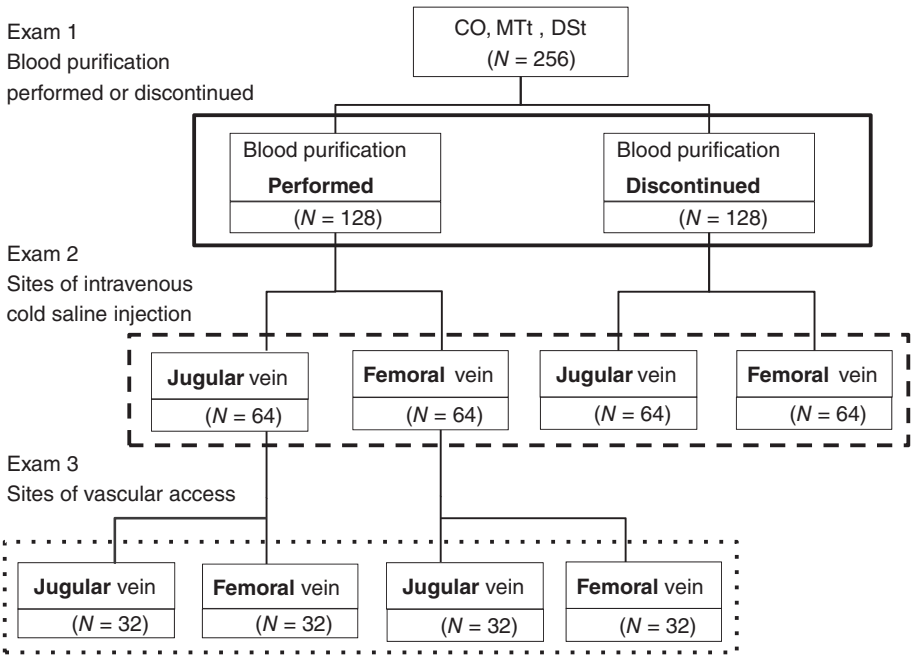

FIG. 2. Three investigations were conducted using the cardiac output (CO), mean transit time (MTt), and downslope time (DSt). Investigation 1. Investigating the difference between measured transpulmonary thermodilution (TPTD) when blood purification is performed and discontinued or when blood purification is running and stopping. Investigation 2. Investigating the difference in measured TPTD via different intravenous cold saline injection (jugular versus femoral veins). Investigation 3. Investigating the difference in measured TPTD via different vascular access sites for blood purification (jugular versus femoral veins).

L/min, indicating a significant decrease. Furthermore, the increase in the MTt and DSt was observed when blood purification was performed.

Investigation 2 compared the results when the intravenous cold saline injection site was moved from the jugular vein to the femoral vein. When blood purification was performed, the CO, measured by injecting cold saline into the femoral vein, was 2.65 (2.40–3.40) L/min, which is significantly higher than that obtained when the injection site used was the jugular vein: 2.6 (2.30–3.40) L/min. The results were the same when blood purification was not performed. MTt and DSt increased in all cases when cold saline was injected into the femoral vein.

TABLE 1. *Results of the three investigations*

Investigation 1. Blood purification performed or discontinued			
Blood purification	Performed	Discontinued	*P*-value
CO (L/min)	2.60 (2.30–3.40)	2.85 (2.40–3.50)	<0.001
MTt (s)	19.0 (15.7–21.6)	18.6 (15.6–20.9)	<0.001
DSt (c)	9.6 (8.0–11.0)	9.2 (7.7–10.5)	<0.001

Investigation 2. Sites of intravenous cold saline injection						
Blood purification	Performed			Discontinued		
Sites of intravenous cold saline injection	Jugular vein	Femoral vein	*P*-value	Jugular vein	Femoral vein	*P*-value
CO (L/min)	2.60 (2.30–3.40)	2.65 (2.40–3.40)	0.004	2.85 (2.30–3.55)	2.85 (2.40–3.40)	<0.001
MTt (s)	17.6 (14.4–19.8)	20.0 (16.6–23.2)	<0.001	17.1 (14.3–19.8)	19.5 (16.8–22.0)	<0.001
DSt (s)	8.9 (7.5–10.6)	9.8 (8.2–11.5)	<0.001	8.6 (7.4–10.2)	9.4 (8.0–11.3)	<0.001

Investigation 3. Sites of vascular access						
Sites of intravenous cold saline injection	Jugular vein			Femoral vein		
Sites of vascular access	Jugular vein	Femoral vein	*P*-value	Jugular vein	Femoral vein	*P*-value
CO (L/min)	2.65 (2.30–3.60)	2.60 (2.50–2.80)	0.53	2.70 (2.30–3.60)	2.65 (2.50–3.00)	0.56
MTt (s)	18.2 (13.6–20.8)	17.2 (15.1–19.6)	0.32	20.5 (15.7–23.7)	19.6 (18.1–22.8)	0.30
DSt (s)	9.4 (7.1–10.8)	8.8 (6.2–10.1)	0.44	10.3 (7.8–11.8)	9.9 (8.7–11.5)	0.37

Results are expressed as median (25%–75% interquartile range). CO, cardiac output, MTt, mean transit time, DSt, downslope time.

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Investigation 3 showed that when comparing the results of blood purification done via the jugular vein and the femoral vein, no significant differences in the CO, MTt, and DSt values were observed. The results were consistent when cold saline injection was administered via the jugular vein and femoral vein.

DISCUSSION

Investigation 1 revealed that the CO was significantly reduced when blood purification was performed. Previous studies have shown that the CO and cardiac index significantly reduced when blood purification was performed (6). CO is calculated using the Stewart Hamilton formula (12,13), as shown below:

$$CO = (TB - TI) \times V \times K / \int TB(t)dt \quad (3)$$

TB: blood temperature, TI: cold saline injection temperature, V: injection volume, K: arithmetic constant, ∫TB(t)dt: thermodilution curve AUC.

In short, when blood temperature, cold saline injection temperature, and injection volume remain constant, the CO is inversely correlated to the AUC of the thermodilution curve. The details of how the EV1000 calculates the AUC are not available. Furthermore, the measurement value for the AUC is not shown. Thus, we calculated the values of MTt and DSt—which are the parameters of the thermodilution curve—based on other parameters and then investigated the factors affecting the CO measurement values. The results showed that MTt and DSt increase significantly when blood purification is performed, which is in agreement with the findings of the study conducted by Schmidt et al. (6). In reality, the temperature of the blood returning to the body is frequently lower than the temperature of the blood leaving the body (14). We set the blood purification circuit model used in our experiments so that the blood returning to the body would be approximately 1°C cooler than the blood leaving the body. The cold saline was then mixed with the returning blood that was already below body temperature, leading to the increase in MTt and DSt, possibly affecting the thermodilution curve (Fig. 3).

Investigation 2 revealed that whether blood purification was performed or not, CO was significantly higher when cold saline injection was administered via the femoral vein rather than the jugular vein. Furthermore, a significant increase was observed in both the MTt and DSt. The distance to the temperature-sensor-equipped catheter is greater when cold saline is injected via the femoral vein, thus increasing the MTt, than that when cold saline is injected via the jugular vein. Additionally, it is also possible that the DSt increases due to the cold

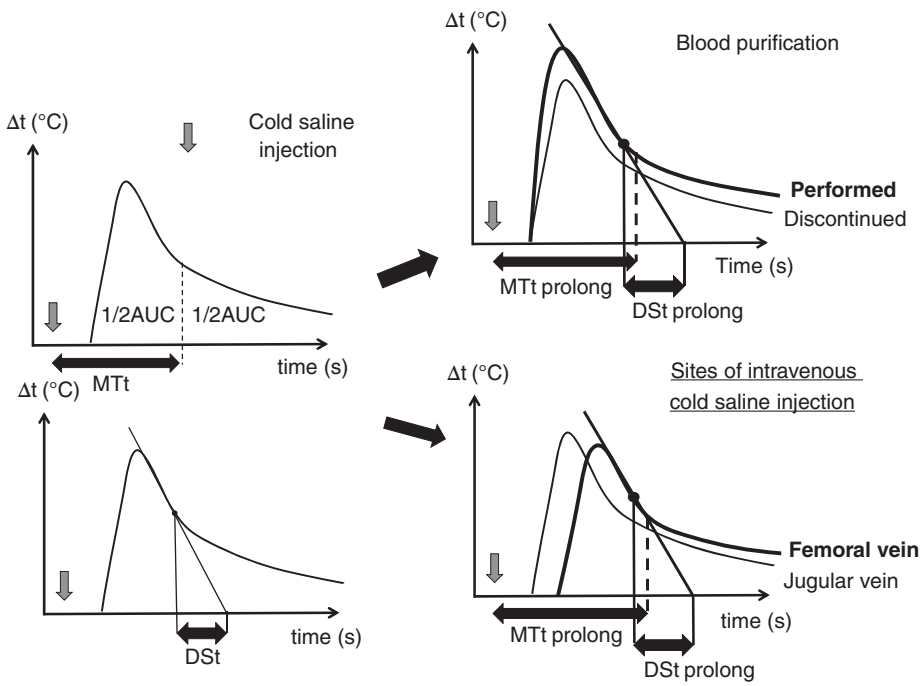

FIG. 3. Changes in the thermodilution curve. Mean transit time (MTt) is the time from cold water injection until the area under the curve (AUC) of the thermodilution curve is halved. downslope time (DSt) is obtained from the exponential decay time of the thermodilution curve. Changes in the thermodilution curve due to blood purification from the obtained cardiac output (CO), MTt, and DSt and changes in thermodilution curve due to differences in cold saline injection sites are illustrated.

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saline solution diffusing as the blood reaches the sensor; the sensor will record slight changes in temperature. Therefore, the AUC of the thermodilution curve as calculated by the EV1000 will possibly decrease, and the CO will increase (Fig. 3).

In Investigation 3, the results of the changes in vascular access sites for blood purification were compared. No change in the CO was observed when blood purification was performed via the jugular vein versus the femoral vein. In addition, these results remained unchanged even if the site for cold saline injection was changed. Sakka et al. reported that there was no difference in the patients' TPTD values when the vascular access site for blood purification was changed (10). In Investigation 3, the patients varied in terms of body weight and the type of existing disorders; however, conditions and body weights were standardized in this study, and the results were the same: no significant difference was observed. In this study, we investigated the influence of blood purification on the CO measurement value using MTt and DSt, the parameters of the thermodilution curve. However, other factors should be investigated in future studies. Furthermore, the exact mechanism by which blood purification affects the TPTD measurement values generated by the EV1000 remains unclear. Some authors hypothesize that the effects of blood purification on TPTD measurement value may stem from the turbulence induced by the purification process (15). In addition, in this study, the temperature of the blood returned was lower than that of the blood ejected by 1°C. However, we have not verified how much this temperature difference affects the measurement value. From now on, we will clarify the factors and mechanisms affecting the measured values by changing the difference between the temperature of the blood returned and that of the ejected blood.

CONCLUSION

The cardiac output measured via transpulmonary thermodilution decreases significantly due to blood purification; however, no significant effect was observed when the vascular access site of blood purification was changed. Investigation on the site of intravenous cold saline injection revealed that cardiac output increased significantly when cold saline injection was administered via the femoral vein with or without blood purification.

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Conflict of Interest: The authors have no conflicts of interest to declare.

REFERENCES

1. Monnet X, Teboul JL. Transpulmonary thermodilution: advantages and limits. *Crit Care* 2017;21:147.
2. Chung FT, Lin SM, Lin SY, Lin HC. Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit. *Respir Med* 2008;102:956–61.
3. Schmidt S, Westhoff TH, Hofmann C et al. Effect of the venous catheter site on transpulmonary thermodilution measurement variables. *Crit Care Med* 2007;35:783–6.
4. Huber W, Phillip V, Höllthaler J, Schultheiss C, Saugel B, Schmid RM. Femoral indicator injection for transpulmonary thermodilution using the EV1000/VolumeView: do the same criteria apply as for the PiCCO? *J Zhejiang Univ-Sci B (Biomed & Biotechnol)* 2016;17:561–7.
5. Saugel B, Umgelter A, Schuster T, Phillip V, Schmid RM, Huber W. Transpulmonary thermodilution using femoral indicator injection: a prospective trial in patients with a femoral and a jugular central venous catheter. *Crit Care* 2010;14:R95.
6. Schmidt S, Westhoff T, Schlattmann P, Zidek W, Compton F. Analysis of transpulmonary thermodilution data confirms the influence of renal replacement therapy on thermodilution hemodynamic measurements. *Anesth Analg* 2016;122:1474–9.
7. Compton F, Vogel M, Zidek W, van der Giet M, Westhoff T. Changes in volumetric hemodynamic parameters induced by fluid removal on hemodialysis in critically ill patients. *Ther Apher Dial* 2015;19:23–9.
8. Nakamura K, Inokuchi R, Hiruma T, Doi K. Efficacy of continuous veno-venous haemofiltration on transpulmonary thermodilution measurements using the EV1000 system. *Anaesth Intensive Care* 2015;43:541–3.
9. Heise D, Faulstich M, Mörer O, Bräuer A, Quintel M. Influence of continuous renal replacement therapy on cardiac output measurement using thermodilution techniques. *Minerva Anestesiol* 2012;78:315–21.
10. Sakka SG, Hanusch T, Thuemer O, Wegscheider K. The influence of venovenous renal replacement therapy on measurements by the transpulmonary thermodilution technique. *Anesth Analg* 2007;105:1079–82.
11. Hofkens PJ, Verrijcken A, Merveille K et al. Common pitfalls and tips and tricks to get the most out of your transpulmonary thermodilution device: results of a survey and state-of-the art review. *Anaesthesiol Intensive Ther* 2015;47:89–116.
12. Reyter DA, Huang C, Edrich T, Shernan SK, Eltzschig HK. Cardiac output monitoring using indicator-dilution techniques: basics, limits, and perspectives. *Anesth Analg* 2010;110:799–811.
13. Kiefer N, Hofer CK, Marx G et al. Clinical validation of a new thermodilution system for the assessment of cardiac output and volumetric parameters. *Crit Care* 2012;16:R98.
14. Yagi N, Leblanc M, Sakai K, Wright EJ, Paganini EP. Cooling effect of continuous renal replacement therapy in critically ill patients. *Am J Kidney Dis* 1998;32:1023–30.
15. Ariès P, Leclerc T. Influence of renal replacement therapy on transpulmonary thermodilution: turbulence in blood flow is key. *Anesth Analg* 2016;123:1331.

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