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EDITORIAL

Transpulmonary thermodilution during extracorporeal organ support (ECOS): is it worth it?A brief commentary on the effects of the extracorporeal circuit on TPTD-derived parameters

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1 Why transpulmonary thermodilution (TPTD) can have a role during extracorporeal organ support (ECOS)?

In modern ICUs, critically ill patients with multiple organ dysfunction syndrome (MODS) may be adequately supported by different extracorporeal organ support (ECOS) devices [1]. Improvements in technology have made extracorporeal membrane oxygenation (ECMO) safer and easier to use, allowing potential more widespread application in patients with advanced respiratory failure [2, 3]. Similarly, kidney support can be provided by different intermittent and continuous blood purification techniques (Intermittent Hemodialysis, Slow Low-Efficiency Daily Dialysis, Continuous Veno-Venous Hemofiltration, Hemodialysis, or Hemodiafiltration).

Hemodynamic monitoring is essential in these conditions but, while transpulmonary thermodilution (TPTD) methods are well-accepted tools to guide goal direct therapy in critically ill patients, they remain poorly investigated during extracorporeal treatment. The main advantage of transpulmonary thermodilution is the ability to provide a full cardiovascular evaluation [4, 5]: continuous measurement of the cardiac output (CO) using pulse contour analysis is combined with intermittent volumetric measurement of cardiac preload like global end-diastolic volume (GEDV) and extravascular lung water (EVLW). The consequence of adding an extracorporeal circuit on the accuracy of the TPTD technique is poorly understood and the literature on the topic is scarce (see Table 1). Therefore, we have read with great interest the paper by Herner et al. on the potential loss of indicator into the extracorporeal circuit during veno-venous extracorporeal membrane oxygenation [6].

2 What were the study findings?

In the recent study by Herner et al. TPTD-derived parameters before and after initiation of ECMO were compared in 14 ICU-patients with veno-venous ECMO (VV-ECMO) and TPTD-monitoring (PiCCO®, Getinge, Solna, Sweden) [6]. Eight patients had a jugular and six patients had a femoral central venous catheter (CVC). The results of the study showed marked increases in GEDVI (791 ± 179 vs. 974 ± 384 mL/m^2; $p = 0.041$) and EVLWI (21.3 ± 9.1 vs. 27.7 ± 11.1mL/kg; $p=0.001$) after the onset of and during ECMO. The increases in GEDVI (378 ± 247 mL/m^2 vs 36 ± 210; $p = 0.02$) and EVLWI (10.5 ± 8.1 mL/kg vs. 3.4 ± 2.4; $p = 0.06$) were substantially more pronounced in patients with femoral compared to jugular indicator injection site [6]. However, cardiac index (CI) and haemodynamic parameters not derived from TPTD, but from pulse contour analysis (systolic and diastolic arterial pressure, stroke volume variation and pulse pressure variation) were not affected by the application of ECMO [6].

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Table 1 List of studies investigating the TPTD technique during extracorporeal treatment

Authors	Study	Year of publication	Number of patients	Extra Corporeal Treatment	ECC access	Blood flow	TPTD Injection Site	Thermistor Catheter Site	TPTD parameters without ECC	TPTD parameters during ECC	Change
Herner A [6]	Prospective	2019	14	VV-ECMO	Single lumen 19- 21 Fr femoral vein (n = 2)/ double lumen 24 Fr left jugulair vein (n = 12)	3.3 ± 1.5 L/min	Jugular (n = 8)/ femoral (n = 6)	Femoral artery	CI 4.5 ± 1.72 L/min/m^2 EVLWI 21 ± 9 ml/kg GEDVI 791 ± 179 mL/m^2	CI 4.4 ± 2.1L/min/m^2 EVLWI 28 ± 11 ml/kg GEDVI vs. 974 ± 384 mL/m^2	Decrease ΔCI 2% Increase ΔEVLWI 33.3% Increase ΔGEDVI 23.1%
Lahmer T [21]	Case report	2017	1	ECMO/RRT	Right femoral vein	2.5 L/min	Jugular CVC	Left femoral artery	CI 5.3 L/min/m^2	CI 3.44–4.72 L/min/m^2	Decrease ΔCI 11–35%
Redwan B [19]	Prospective	2016	5	Single-site low-flow Veno-venous ECLS	22 Fr twin-port Double-lumen Right jugular vein	1 L/min	Left subclavian vein	Right radial artery (n = 3) or left femoral artery (n = 2)	CI 2.98 ± 0.49 L/min/m^2 EVLWI 16.64 ± 0.84 ml/kg	CI 2.98 ± 0.55 L/min/m^2 EVLWI 16.04 ± 0.87 ml/kg	No change CI Decrease ΔEVLWI 4%
Sakka S.G [9]	Case report	2007	1	PECLA	13 Fr catheter right femoral artery/ 15 Fr left femoral vein	1 L/min	Superior vena cava	Left femoral artery	CO 5.6 ± 0.2 L/min EVLWI 11.3 ± 0.2 ml/kg GEDVI 768 ± 23 mL/m^2	CO 4.4 ± 0.1L/min EVLWI 11.3 ± 0.3 ml/kg GEDVI vs. 514 ± 3.2 mL/m^2	Decrease ΔCO 21.4% No change ΔEVLWI 0% Decrease ΔGEDVI 33.1%
Haller M [7]	Prospective	1995	7	ECLA	25 Fr femoral vein/ 21 Fr right internal jugular vein	50% of baseline CO	PAC in right pulmonary artery injection via right atrium	NA	CO 2.9 to 9.4 L/min	NA	ΔCO = 3.0 ± 2.41
Geith S [17]	Prospective	2018	24	SLED	13.5 Fr dialysis Superior vena cava (n = 19) Inferior vena cava (n = 5)	150–260 mL/min	Superior vena cava	NA	CI 3.27/3.79 ± 0.25/0.36 L/min/m^2 GEDVI 743/641 ± 44/43 mL/m^2 EVLWI 11/11 ± 1.45/1.42 ml/kg	CI 3.08/3.19 ± 0.21/0.22 L/min/m^2 GEDVI 758/606 ± 37/55 mL/m^2 EVLWI 11/10 ± 0.9/0.62 ml/kg	Decrease ΔCI 6%/15.8% No change ΔGEDVI 0% No change ΔEVLWI 0%
Huber W [18]	Prospective	2016	32	SLED	13 Fr 25 cm femoral vein 13 Fr 15–17.5 cm jugular vein	150 mL/min	Superior vena cava	Femoral artery	CI 4.41 ± 1.41 L/min/m^2	CI 4.18 ± 1.43 L/min/m^2	Decrease ΔCI 5% No change ΔGEDVI 0% No change ΔEVLWI 0%

Table 1 (continued)

Authors	Study	Year of publication	Number of patients	Extra Corporeal Treatment	ECC access	Blood flow	TPTD Injection Site	Thermistor Catheter Site	TPTD parameters without ECC	TPTD parameters during ECC	Change
Pathil A [22]	Prospective	2012	30	SLEDD	12 Fr Internal jugular Subclavian Femoral	400 ml/min	Internal jugular, Subclavian, Femoral		CO 4.71 ± 1.63 L/min EVLWI 10.3 ± 4.2 ml/kg GEDVI 865 ± 174 mL/m^2	CO 4.18 ± 1.38L/min EVLWI 10.0 ± 4.5 ml/kg GEDVI 775 ± 220 mL/m^2	Decrease ΔCO 11.3% No change ΔEVLWI 0% Decrease ΔGEDVI 10.4%
Heise D [10]	Prospective	2012	32	CRRT	Double-lumen, high-flow Femoral vein (n = 27), Subclavian vein (n = 3), internal jugular vein (n = 2)	183 ± 35 mL/min	Catheter in the superior vena cava		CO 5.32 L/min (IQR: 4.68–6.25)	CO 4.77 L/min (IQR: 4.17–5.91)	Decrease ΔCO 10.4%
Dufour N [23]	Prospective	2012	69	CVVH	14 Fr 25 cm Two lumen into the femoral vein (n = 62), 14 Fr 15–20 cm Two lumen into jugular vein (n = 7)	250 mL/min or 350 mL/min	Internal jugular vein	Femoral artery	CI 3.51 ± 0.99 L/min/m^2 GEDVI 765 ± 164 mL/ EVLWI 11.8 ± 4.4 ml/kg	CI 3.49 ± 0.96 or 3.44 ± 1.00 L/min/m^2 GEDVI 763 ± 182 or 744 ± 170 mL/ EVLWI 12.1 ± 4.5 or 12.1 ± 4.6 ml/kg	No change ΔCI No change ΔGEDVI 0% Increase ΔEVLWI 2.6%
Van Craenenbroeck A [24]	Retrospective	2010	29	CVVH	14 Fr Femoral (n = 9), 12 Fr jugular (n = 21)	180 ml/min	Superior vena cava Central venus line positioned in jugular or subclavian vein	NA	CI 4.4 ± 1.3 L/min/m^2 EVLWI 11.4 ± 4.6 ml/kg GEDVI 1001 ± 240 mL/m^2	CI 3.8 ± 1.1 L/min/m^2 EVLWI 12.4 ± 5.1 ml/kg GEDVI vs. 846 ± 164 mL/m^2	Decrease ΔCI 13.6% Increase ΔEVLWI 8.8% Decrease ΔGEDVI 15.5%
Sakka S.G [9]	Prospective	2007	24	RRT	12 Fr Dialysis catheter (Trilyse Expert, Vygon)	80–150 mL/min	Superior vena cava	Femoral artery	CI 3.9 ± 1.3 GEDVI 756 ± 204 EVLWI 8.3 ± 3.6	CI 3.8 ± 1.3 GEDVI 736 ± 197 EVLWI 8.4 ± 3.6	Decrease ΔCI 2.6% Decrease ΔGEDVI 2.6% No change ΔEVLWI 0%

Table 1 (continued)

Authors	Study	Year of publication	Number of patients	Extra Corporeal Treatment	ECC access	Blood flow	TPTD Injection Site	Thermistor Catheter Site	TPTD parameters without ECC	TPTD parameters during ECC	Change
Martinez-Simon [25]	Case report	2006	1	CVVH-D	Certofix Trio HF catheter right internal Jugular vein (distal 16 Fr, Middle 12 Fr, Proximal 12 Fr)	180 ml/min	Distal lumen of the same catheter	NA	CI > 3 ITBVI > 850 EVLWI < 10	CI < 3 ITBVI < 850 EVLWI > 10	Decrease CI Decrease ITBVI Increase EVLWI
Lopez-Herce J. [26]	Prospective (animals)	2009	34	CVVH	18 Fr Femoral vein and the right and the left Internal jugular veins	5–15-30 ml/h	PAC in right pulmonary artery, injection via right atrium		GEDVI 206.5 ± 49.1 mL/m^2 EVLWI 15.9 ± 3.9 ml/kg	GEDVI 184.1 ± 47.2 mL/m^2 EVLWI 16.3 ± 5.6 ml/kg	Decrease ΔGEDVI 10.9% No change ΔEVLWI 0%

CI cardiac index, *CO* cardiac output, *CRRT* continuous renal replacement therapies, *CVC* central venous catheter, *CVVH* continuous veno-venous hemofiltration, *CVVH-D* continuous veno-venous hemodialysis, *ECLS* extra-corporeal life support, *ECC* extra-corporeal circuit, *EVLWI* extravascular lung water index, *Fr* French, *GEDVI* global end-diastolic volume index, *PAC* pulmonary artery catheterization, *PECLA* pumpless extracorporeal lung assist, *RRT* renal replacement therapy, *SLED* sustained low-efficiency dialysis, *SLEDD* sustained low-efficiency daily dialysis, *TPTD* transpulmonary thermodilution, *VV-ECMO* veno-venous extracorporeal membrane oxygenation

3 What are the possible pitfalls of TPTD during ECOS?

First, if we think of the physiology of the extracorporeal circulation, it stands to reason that some part of the thermodilution bolus is going through the extracorporeal circuit, therefore, affecting the values of the parameters measured by TPTD. Haller et al. were the first to test the hypothesis that if the indicator used to determine CO is injected into the right atrium, adjacent to the drainage cannula, there can be an overestimation due to loss of the indicator (LOI) [7]. To address this issue, they compared the conventional thermodilution CO determinations with a dye dilution CO measurement. The results showed an overestimation of the CO up to a maximum of 300% (max 10 L/min higher) with a mean difference of 3.0 ± 2.41 L/min. The presence of dye concentration into the extracorporeal circuit confirmed the LOI. As a matter of fact, Sreenan et al. managed to quantify recirculation during VV-ECMO in a rabbit model using a thermodilution technique (Table 1) [8].

Second, the drainage and return cannula may be positioned too close to each other or in such a way that oxygenated blood will preferentially return to the VV-ECMO circuit rather than the right heart circulation, ending in a vicious circle in which ECMO is supporting itself rather than the patient. So, due to the closer proximity of the indicator injection to the femoral ECMO-drainage cannula, the LOI might be more pronounced in case of indicator injection via the femoral central venous catheter compared to jugular indicator injection. In fact, the multivariate analysis performed by Herner et al. showed that femoral indicator injection was independently associated with larger increases in GEDVI ($p = 0.004$) and EVLWI ($p = 0.035$) during ECMO [6]. These findings can be partially explained by the use of the large dual lumen single NovaPort® catheter in this study, which has a greater recirculation rate. Nevertheless, this drawback can be observed also during renal replacement therapy (RRT) and the effect will be more pronounced when the central venous and dialysis catheter are in the femoral and subclavian/internal jugular position respectively, a constellation that is best to be avoided.

Third, when turbulence in flow is present, created for instance by the ECMO device that is pumping blood back into the circulation, the area under the TPTD-curve can be substantially altered and this can affect the mean appearance and mean transit time of the indicator and thus also the different derived parameters. The area under the curve thus will increase because the cold saline needs more time to arrive at the tip of the thermistor through the long arterial line. We believe the same alterations can be produced by any catheter, if TPTD calibration is done during ECOS with a working pump. PiCCO® calibration during extracorporeal support through a central venous catheter may, therefore, produce erroneous measurements. Furthermore, during ECMO, the amount of turbulent flow can increase in proportion to the magnitude of aspiration pressure needed to match the flow rate of the extracorporeal circuit.

Fourth, high-flow ECMO might result in otherwise unexplained alterations of TPTD-derived parameters after the onset of and during ECMO. Observations from the literature review (Table 1) suggest that the influence of the extracorporeal circuit on the reliability of the TPTD-measurements is related to the ratio between the cardiac output and the extracorporeal flow rate. The effects of an extracorporeal circuit are probably more pronounced if CO is low and the blood flow over the circuit is high (blood flow during continuous veno-venous haemofiltration (CVVH) is generally around $150 - 180$ mL/min, compared to 450 mL/min during dialysis and 3 or more L/min during ECMO). However, some reports suggest that the EVLWI measurement is reliable if extracorporeal blood flow does not exceed 20% of cardiac output [7, 9].

Finally, other aspects that affect TPTD-derived parameters may also play a role such as the filtration rate and the blood temperature. Normally the use of CVVH causes a drop in temperature; stopping the CVVH momentarily may give a rise in central temperature after the inflow of colder fluids coming from the CVVH stops as suggested previously [10]. It also has been suggested to wait with TPTD-measurements when continuous renal replacement therapy (CRRT) is stopped or started until blood temperature has reached a steady state [11]. We shouldn't forget also the possible influence of mechanical ventilation on the functional haemodynamic indices of fluid responsiveness. Stroke volume variation (SVV) and pulse pressure variation (PPV) ideally require a tidal volume ≥ 8 mL kg^{-1} as a condition for correct interpretation. Although recent data show that the predictive value of functional hemodynamics retains its accurcy even at lower tidal volumes [12], it is appropriate to think that the ultra-protective ventilation strategy during ECMO can disturb proper fluid responsiveness evaluation.

4 Limitations

The study by Herner et al. has to be praised to have investigated a topic often underestimated but, to play the devil's advocate, we could argue that the findings raised even more questions. The attractiveness of the TPTD technique lays in the fact that it not only provides a static volumetric preload marker (GEDVI) but also an indicator of extra-vascular fluid overload (EVLWI). However, the cause of the rise of GEDVI in the study is not fully explained. It could be a consequence of reduced heart rate which allows better filling and ultimately better GEDVI or it could be due to fluid

administration. During the start-up phase of ECMO implementation, these patients usually receive some priming fluid that can be compensated to a certain degree with the blood circulating in the extra-corporeal circuit. Regarding EVLWI, the authors put a lot of emphasis on this parameter but as EVLWI is a marker of pulmonary edema, patients with acute respiratory distress syndrome (ARDS), by definition, should all have an increased EVLWI [13, 14]. Possibly, as suggested by Vasques et al., looking at the carbon dioxide production (VCO_2) of native lungs compared to the membrane lung may be more interesting from a physiological point of view, especially during VV-ECMO weaning [15].

Furthermore, the usual indication for VV-ECMO is severe respiratory failure due to hypoxemia and/or hypercapnia. In both situations, there is an adrenergic stimulation which increases the cardiac index, in order to compensate for hypoxemia or as an endogenous response to acidemia and hypercapnia. Therefore, after ECMO cannulation, there can usually be a rebound hemodynamic effect observed: heart rate goes down, pulmonary resistance decreases, as well as CI can be reduced. In the study by Heller et al., the authors did not observe a change in CI before and after ECMO (4.4 ± 1.6 *vs* 4.4 ± 1.2 L/min/m^2) but it remains unclear why (i.e. therapeutic interventions? fluid administration?). In addition, the fact that they didn't use a "gold standard" (e.g. echo-cardiography) to assess native CI independently from thermodilution is an issue that needs to be taken into account.

Finally, the use of different oxygenators may have biased some results due to the use of different ECC volume and flow patterns.

5 Conclusion

Optimized extra-corporeal blood flow adapted to CO is of paramount importance for effective extra-corporeal support. So, determining the baseline CO is of utmost importance in patients supported with ECOS, but many common monitoring tools lack validity during ECMO: by taking into account the unique physiology of the ECMO circulation, selected methods can aid in the care of these complex patients [16]. There is evidence to support that TPTD may lose accuracy during ECMO, but we don't have to generalize to all other types of ECOS. Indeed, CRRT (with blood flows below 200 ml/min) seems to have no major clinical impact with only a small observed decrease in CI and either no effect or slight changes in GEDVI and EVLWI (see Table 1). Furthermore, there is some evidence that TPTD is feasible during low-flow (up to 500 mL/min) extracorporeal organ support [17, 18]. Also, VV-ECMO with low flows seems to maintain the accuracy of TPTD-derived parameters. In a group of five patients on low-flow (0.5, 1, and 1.5 l/min), VV-ECMO for hypercapnic respiratory failure, TPTD (with injection of cold isotonic saline into the left subclavian vein and dual-lumen ECMO cannula in the right internal jugular vein) provided estimates of CO that were similar to those measured by pulse contour analysis [19].

Undoubtedly, alternatives to TPTD should be considered during extracorporeal treatment, especially when blood flows are high and CI is low. Point of care ultrasound could play a significant role in monitoring both global and regional perfusion [20]. A proper monitoring tool will allow us to optimize goal-directed therapy, with rigorous control of fluid balance, in order to lower the risk of further organ failure or poor outcome in these patients.

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Compliance with ethical standards

Ethical Approval Not required.

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