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In silico parametric analysis of femoro-jugular venovenous ECMO and return cannula dynamics

Louis P. Parker [a], Anders Svensson Marcial [b,c], Torkel B. Brismar [b,c], Lars Mikael Broman [d,e], Lisa Prahl Wittberg [a,*]

[a] *FLOW, Department of Engineering Mechanics, Royal Institute of Technology, KTH, Stockholm, Sweden*
[b] *Department of Clinical Science, Intervention and Technology, Karolinska Institute, Division of Medical Imaging and Technology, Stockholm, Sweden*
[c] *Department of Radiology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden*
[d] *ECMO Centre Karolinska, Pediatric Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden*
[e] *Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden*

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ABSTRACT

Background: : Increasingly, computational fluid dynamics (CFD) is helping explore the impact of variables like: cannula design/size/position/flow rate and patient physiology on venovenous (VV) extracorporeal membrane oxygenation (ECMO). Here we use a CFD model to determine what role cardiac output (CO) plays and to analyse return cannula dynamics.

Methods: : Using a patient-averaged model of the right atrium and venae cava, we virtually inserted a 19Fr return cannula and a 25Fr drainage cannula. Running large eddy simulations, we assessed cardiac output at: 3.5–6.5 L/min and ECMO flow rate at: 2–6 L/min. We analysed recirculation fraction (R_f), time-averaged wall shear stress (TAWSS), pressure, velocity, and turbulent kinetic energy (TKE) and extracorporeal flow fraction (EFF = ECMO flow rate/CO).

Results: : Increased ECMO flow rate and decreased CO (high EFF) led to increased R_f ($R = 0.98$, log fit). Negative pressures developed in the venae cavae at low CO and high ECMO flow (high CR). Mean return cannula TAWSS was >10 Pa for all ECMO flow rates, with majority of the flow exiting the tip (94.0–95.8 %).

Conclusions: : Our results underpin the strong impact of CO on VV ECMO. A simple metric like EFF, once supported by clinical data, might help predict R_f for a patient at a given ECMO flow rate. The return cannula imparts high shear stresses on the blood, largely a result of the internal diameter.

1. Background

Venovenous (VV) extracorporeal membrane oxygenation (ECMO) is a treatment for severe acute respiratory distress syndrome, whereby blood is drained from the patient's venous side and oxygenated in a membrane lung before finally being returned. The drainage and return functions may be carried out by one dual lumen cannula or two dedicated single-lumen cannulas (SLCs). When using single lumen cannulas, it is most common to position the drainage cannula in the inferior vena cava (IVC) and the return in the superior vena cava (SVC) (Fig. 1), this being referred to as a femoro-jugular configuration in accordance with the recent Maastricht treaty [1], previously also called femoro-atrial cannulation [2]. There is currently a clinical preference for femoro-jugular, largely based on the work of Rich et al. suggesting superior performance over jugulo-femoral [3], whereby the position of the drainage and return cannulas is swapped. More recent studies however contradict these findings [4], or report very similar outcomes under each cannulation strategy [5].

The ECMO physician is faced with a multitude of variables when starting a patient on ECMO support. A complex interplay between cannula position, design, size with ECMO flow rate and the patient-specific physiology determines how efficiently oxygenated blood can be delivered to the arterial side. The efficiency, or lack thereof, of oxygen delivery can be monitored via recirculation fraction (R_f), the fraction of newly oxygenated return blood directly drained before passing to the patient's pulmonary and subsequently, arterial system.

In recent times computational fluid dynamics (CFD) has been used to model the venous system under ECMO for a range of operating

* Corresponding author at: Osquars backe 18, SE-100 44 Stockholm, Sweden.
E-mail address: prahl@kth.se (L. Prahl Wittberg).

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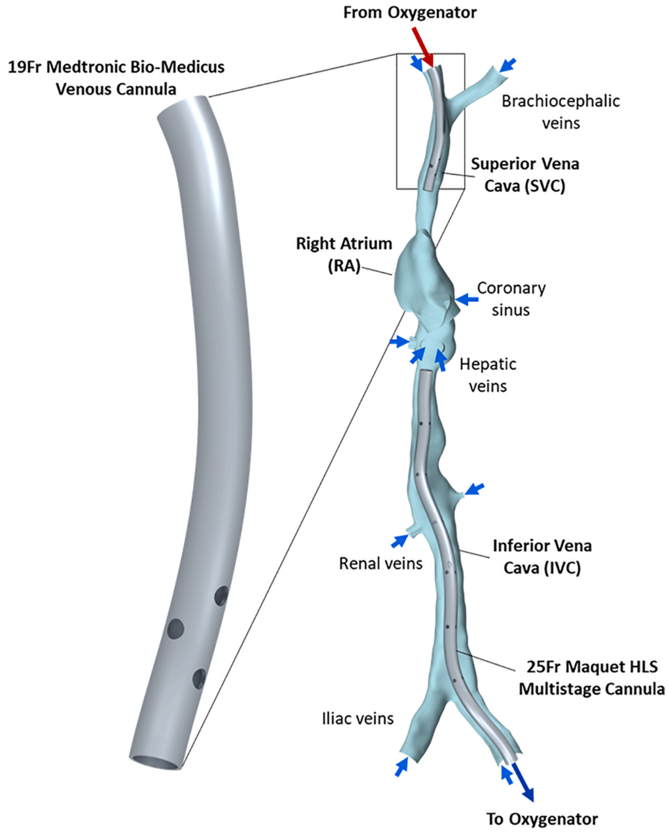

Fig. 1. The venous model with return and drainage VV ECMO cannulas inserted. The illustration shows a femoro-jugular configuration with drainage from the IVC and return via jugular approach, with the tip in the SVC.

conditions [6–8]. Free from the ethical concerns about patient welfare, CFD is a powerful tool to quantify R_f whilst varying the plethora of clinical variables. CFD simulations also provide data on the precise dynamics of the cannula in a resolution that is not clinically possible. To date, cannula position and design have been the focus of these research efforts in ours and other groups [6,8–10]. At any given ECMO flow rate, the effect of cardiac output (CO) on R_f is yet to be explored. Our hypothesis is that interplay between CO to ECMO flow affects treatment efficiency and subsequently patient outcomes in the clinic. Similarly, the bulk of the research so far has focussed on drainage cannula dynamics [11,12], as the results are applicable to both VV and venoarterial (VA) ECMO. Whilst return cannula flow has been modelled in VA ECMO [13–15], and VV ECMO in idealised computational or experimental work [16,17], and some patient-specific geometries[10,18] there is yet to be an investigation of their dynamics in a patient model including the entire IVC and SVC with varied cardiac output.

In the present study we apply CFD to investigate and map the effect of ECMO flow rate and CO on R_f. Secondarily, we investigate the dynamics of the return cannula positioned in a patient-derived geometry of the SVC.

2. Methods

Using the same previously published model of the SVC, IVC and right atrium (RA) [7,8,19,20], we positioned CAD models of the return and drainage cannulas. Cannulas were selected by an ECMO specialist (LMB) at Karolinska University Hospital and were sized specifically for the patient-averaged model. The geometry of a 19Fr/18 cm Medtronic Bio-Medicus Life Support (Medtronic, Tolochenaz, Switzerland) return cannula was positioned in the SVC with the tip 2.5 cm from the entrance to the RA. The drainage cannula was a 25Fr/55 cm Maquet HLS Multistage cannula (Getinge, Rastatt, Germany) placed in the IVC with the tip 3 cm from the RA. Venous inflows were constant over time and distributed as shown in Fig. 2, corresponding to 38 %, 2 %, 25 %, 20 % and 15 % to the brachiocephalic veins, coronary sinus, liver, kidneys, and distal peripheries, respectively [21]. In our analysis we assessed the

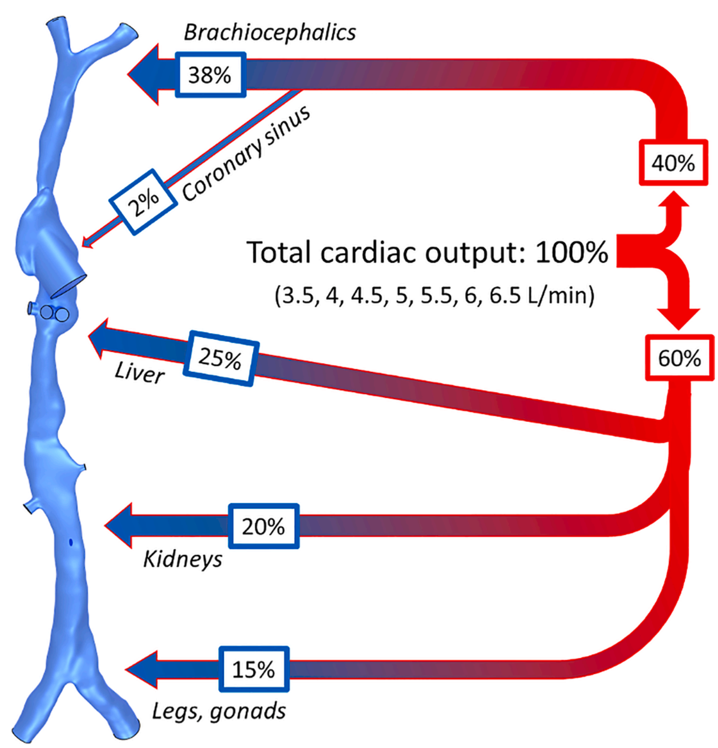

Fig. 2. Schematic of the distribution of venous inflows to the model.

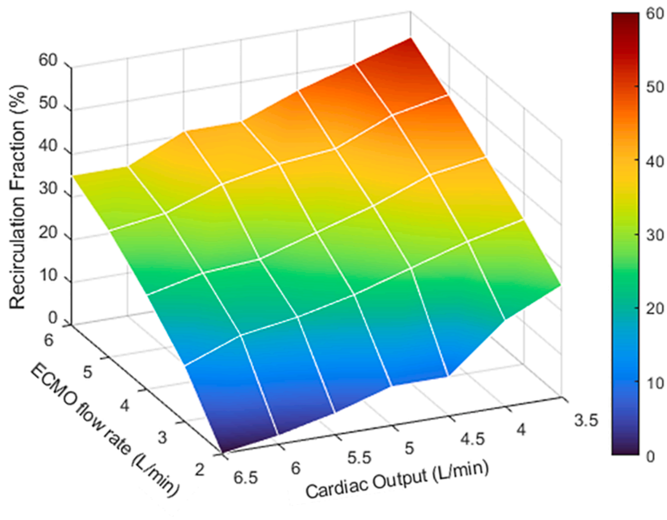

Fig. 3. Graph of recirculation fraction as a function of varied ECMO flow rate and cardiac output in a patient-averaged VV ECMO model. The colour bar to the right references the recirculation fraction (%).

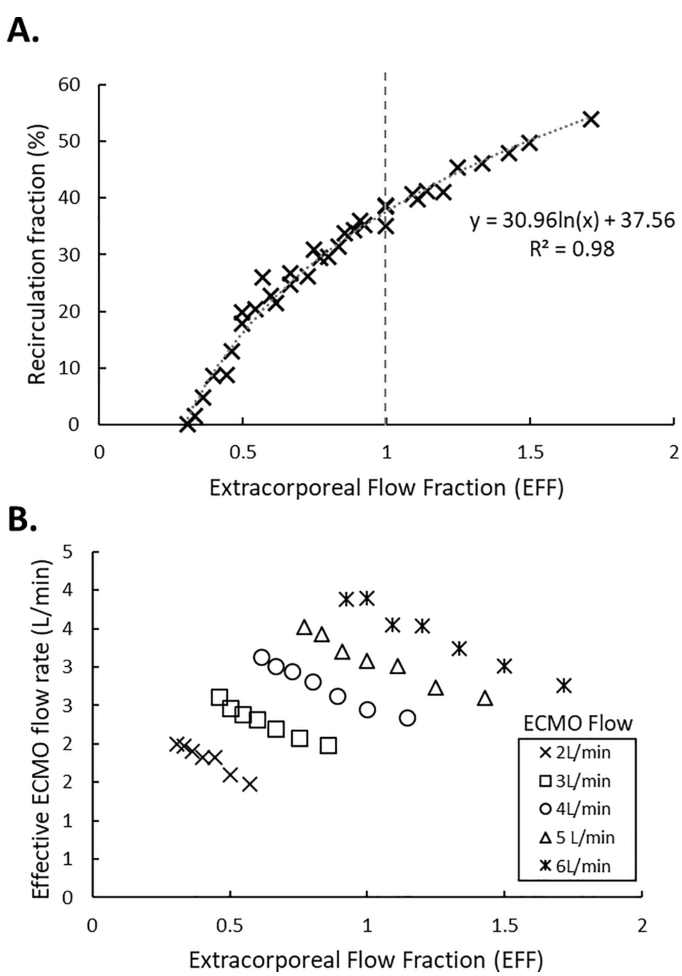

Fig. 4. **A.** Recirculation fraction for all simulations plotted against the extracorporeal flow fraction (EFF): ECMO flow rate/cardiac output. A logarithmic trendline is also presented. **B.** Effective ECMO flow rate: ECMO flow rate × (1-recirculation fraction) plotted against EFF.

ratio: ECMO flow rate/CO which we refer to as the extracorporeal flow fraction (EFF).

Following previously reported methods [7,8,19,20], simulations were initialised with a steady-state k-ω Reynold-averaged Navier Stokes (RANS) simulation. Once initialised, a large eddy simulation (LES) with wall-adapting local eddy viscosity (WALE) sub-grid scale model was run for 1.5 s of physical time on 500 cores of a supercomputer, requiring ~21 hrs each (Tetralith, NSC, Linköping). A constant timestep of 10^{-4} s was used with a 2nd order temporal discretization scheme and the 'all $y+$' wall treatment within Star-CCM+ (Siemens, Munich). A LES model was chosen to capture the transitional flow previously observed for this geometry [19]. Blood was given a density of 1050 kg/m^3 and was treated as non-Newtonian using a Quemada model with a hematocrit of 35 % [22,23]. Grid convergence for the same model was confirmed in a previous publication, showing adequate convergence of fluid velocity and WSS [8]. All time-averaged parameters were computed using a sliding widow of 100 samples taken over the final 1 s. ECMO flow rate was simulated at 2, 3, 4, 5, 6 L/min and CO was simulated at 3.5, 4, 4.5, 5, 5.5, 6, 6.5 L/min, resulting in 35 simulations.

3. Results

Our results support the consensus that an increased ECMO flow rate, increases R_f during femoro-jugular VV ECMO (Fig. 3). Conversely, R_f decreased with increasing total CO (Fig. 3), due to the greater supply of venous flow for drainage. There was a strong (R = 0.98) logarithmic relationship between the EFF and R_f, across all simulations (Fig. 4A). When considering effective ECMO flow rate (Q_{eff}): ECMO flow rate × (1-R_f) against the same ratio, we observed a decrease in Q_{eff} at any given ECMO flow rate as CO decreases (Fig. 4B).

Surface vena cava pressures averaged over the surfaces shown in Fig. 5 were plotted for all simulations. Negative caval pressures were observed at high ECMO flow rates and low CO the minima for the SVC and IVC were -4.8 and -4.3 mmHg, respectively. SVC and IVC pressure maxima were 8.6 and 5.7 mmHg, respectively.

The vast majority of return flow (94.0–95.8 %) was delivered through the cannula tip across all ECMO flow rates (Fig. 6). Increased ECMO flow rate marginally increased the proportion exiting the tip. Side hole return was relatively consistent, delivering on average 1.7 ± 0.8 % per pair (Fig. 6). Side-hole flow produced low velocity jets almost perpendicular to the cannula wall across all ECMO flow rates (Fig. 7).

The return cannula produced a reinfusion jet >3 m/s at high ECMO flow rates entering the RA (Fig. 7) towards the drainage cannula tip (Figure S1). This high-velocity jet increased volume-averaged turbulent kinetic energy (TKE) in the SVC (Fig. 8A/B). Return cannula TAWSS increased with ECMO flow rate (Fig. 9), largely due to the TAWSS on the internal surface. Given the larger diameter of the drainage cannula compared to the return cannula, drainage cannula TAWSS was 73.1 ± 2.1 % lower than the return cannula across all ECMO flow rates (Supplemental Material, Figure S2).

4. Discussion

4.1. ECMO performance: recirculation fraction

Computational models of VV ECMO when combined with modern high-performance computing (HPC) clusters have great potential to investigate a wide range of clinical operating conditions. In the present study, we demonstrated how a range of patient CO (3.5–6.5 L/min) and ECMO flow rates (2–6 L/min) can be applied to a patient-averaged VV ECMO model, mapping out clinical indicators of performance like R_f, pressure, TKE and wall shear stress (WSS). The *in silico* nature of this study allowed us to make a comprehensive sweep of the parameter space without ethical concerns for the well-being of a vulnerable patient population. The HPC resources leveraged for this study was another critical aspect. Our chosen parameter space required 402,500 core hours

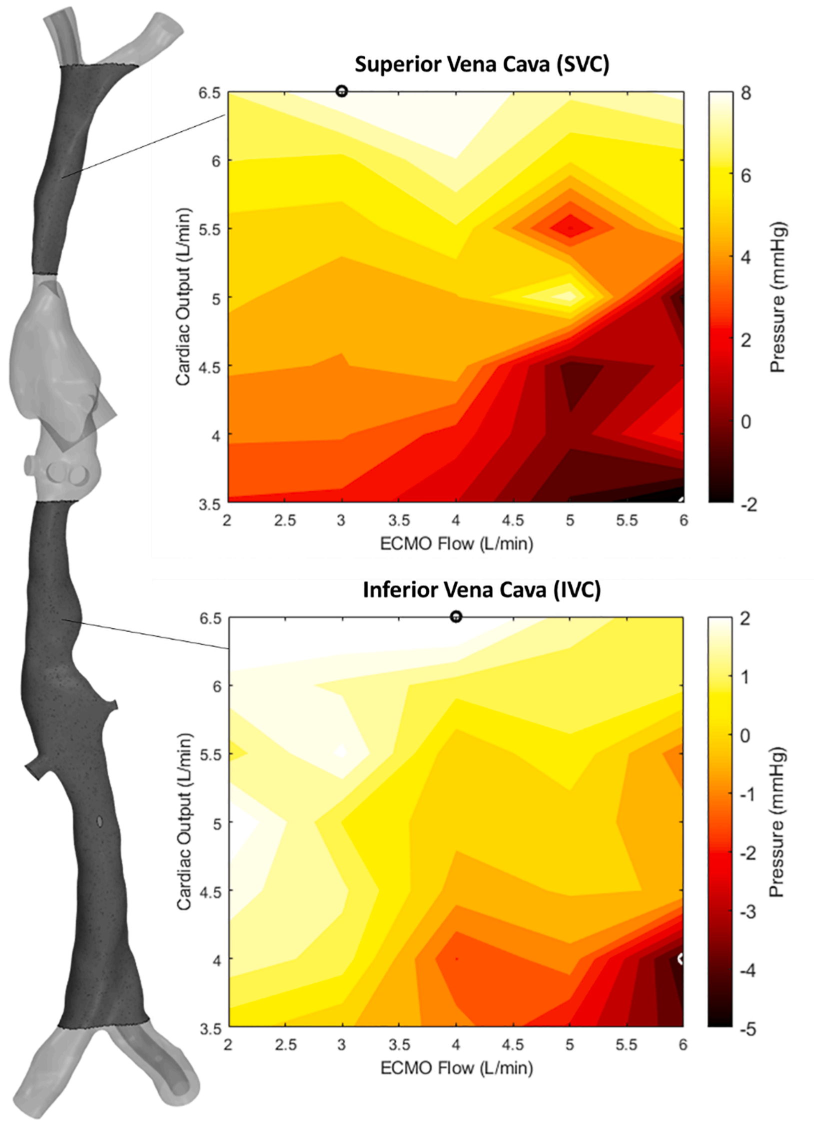

Fig. 5. SVC and IVC pressures for a range of cardiac output (CO) and ECMO flow rates. The surfaces used for SVC and IVC averages are indicated to the left. The maxima and minima are indicated by the black and white circles, respectively.

in total, equivalent to 11.5 years on a standard quad core computer. Such studies in the past would not have been practically possible.

Recirculation is a common issue, unique to VV ECMO [24]. Whilst oxygen saturations give a real-time indication of treatment effectiveness, it reflects the contributions of both the ECMO circuit and patient's residual lung function. R_f provides a useful measure of performance, independent to lung function. Recently, Fisser et al. characterised recirculation for a cohort of 55 VV ECMO patients, of which 37 were cannulated in the femoro-jugular configuration [4]. The Q_{eff} curves are in agreement at low ECMO flow rates but our Q_{eff} tails off at higher ECMO flow rates (Supplemental Material, Figure S3), the result of higher R_f. Fisser et al. discussed the need to run the femoro-jugular group at a lower ECMO flow rate (mean = 3.0 L/min), compared to jugulo-femoral (3.6 L/min), consistent with other studies [4]. A lack of data at higher ECMO flow rates may explain why the regression curve deviates at higher flow rates. Additionally, the mean cannula tip-tip distance reported was 19 cm compared to 11 cm in the present study.

The data presented in Fig. 3 shows how the interplay between ECMO flow rate and CO determines R_f. The "Red Book" is a reference text published by the Extracorporeal Life Support Organisation (ELSO). When discussing recirculation, Bartlett and Conrad write: "As cardiac output decreases, the [recirculation] fraction increases, and becomes markedly elevated when cardiac output drops below extracorporeal flow" [25]. Our data supports this with a mean R_f of 45.1 $\pm$ 4.6 % when CO drops below ECMO flow rate (EFF $>$ 1), versus 21.9 $\pm$ 10.8 % when the CO exceeds ECMO flow rate (EFF $<$ 1).

The author's clinical experiences, and the results of the current work, all suggest that the use of β-blocking agents (negative inotropy) to reduce R_f is counter-productive, unless to optimize cardiac output in cases with atrial fibrillation, etc. The positive effect in VV ECMO using short-acting β-blocker (esmolol) only looked at the arterial oxygen saturation where the fraction of oxygen rich ECMO blood increases in the mix with native blood as CO decreases, not the key item, oxygen delivery [26]. In a more detailed analysis of COVID-19 patients supported with VV ECMO, Kim and colleagues also observed an increase in arterial oxygen saturation, but a 6 to 33 % decrease in oxygen delivery due to a 20 to 39 % decrease in cardiac output during esmolol administration [27]. Any benefits from use of β-blockers are likely due to other metabolic and/or physiologic pathways than via reduced R_f. Thus, use of β-blockers to reduce R_f may be tried when physiologically reasonable and monitored using echocardiography, total oxygen delivery, and when feasible, ultrasound dilution technology [5,24,28].

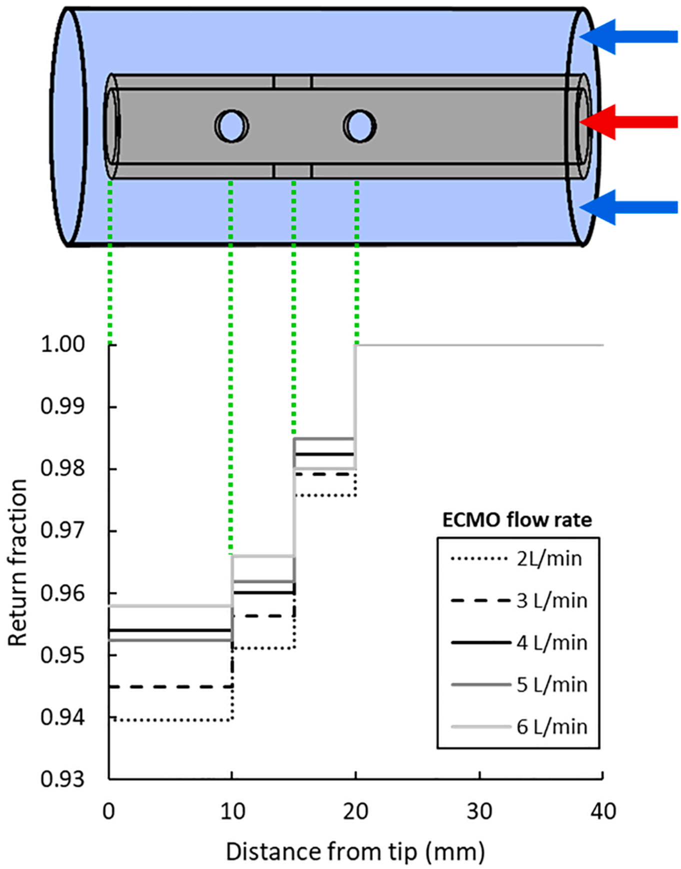

Fig. 6. Return flow from the tip and side holes at 5 L/min total cardiac output.

4.2. Impact on caval pressures

The venae cavae are highly compliant and will change in diameter according to local venous pressure. This can be problematic during VV ECMO (also VA) when a negative pressure develops at the drainage cannula, causing the vein to collapse onto the drainage cannula resulting in what is termed "chugging" of "chattering" [29]. The IVC is particularly susceptible to pressure-induced changes in dimension, and is the reason some centres still opt to drain from the SVC [28]. Our results suggest that patients with a low CO are susceptible to a negative IVC pressure, and associated drainage issues, at high ECMO flow rates. The same situation with low pressures in the IVC with secondary drainage problems may occur in the hypovolemic patient or develop in the hypervolemic patient subject to rapid fluid removal.

High caval pressures carry their own risks. In a previous study we have noted the impact dual lumen cannulas have on SVC pressure during VV ECMO [7], sometimes leading to unphysiologically high pressures, which may play a role in the increased risk of intracranial hemorrhage when using such large cannulas [30]. The highest pressures observed in the present study were not unphysiologically high and were in fact slightly below normal central venous pressure of 8–12 mmHg according to most simulations [31].

4.3. Return cannula dynamics

Hemolysis is a potential complication of any extracorporeal life support [32]. The components of the ECMO circuit expose blood to unphysiologically high shear rates, sometimes rupturing a significant portion of the red blood cells. Hemolysis is counter-productive during ECMO, where the objective is to raise the patients oxygen saturation. In recent years, extensive experimental and computational studies have sought to analyse and improve ECMO oxygenators [33,34], pumps [35,36], connectors [37] and cannulas [11,12,38,39] to minimise shear. The results from this present study show the expected increase in TAWSS with increased with ECMO flow rate. The mean TAWSS on the return cannula's surface was unphysiologically high (>10 Pa) [40,41] across all ECMO flow rates (Fig. 9B). Internal cannula TAWSS, largely a result of the cannula size/ECMO flow rate ratio, was orders of magnitude higher than external TAWSS. This underpins the importance of appropriate cannula selection in relation to the expected ECMO flow rate. The relative lack of flow exiting the cannula side holes means that any redesign of this aspect is unlikely to significantly reduce WSS, at least with ideal positioning in the centre of the vessel [16].

4.4. Limitations

There are several limitations to the present study that should be considered. Firstly, the same patient-averaged model of the venous system and cannulas were used for all simulations. It would be expected

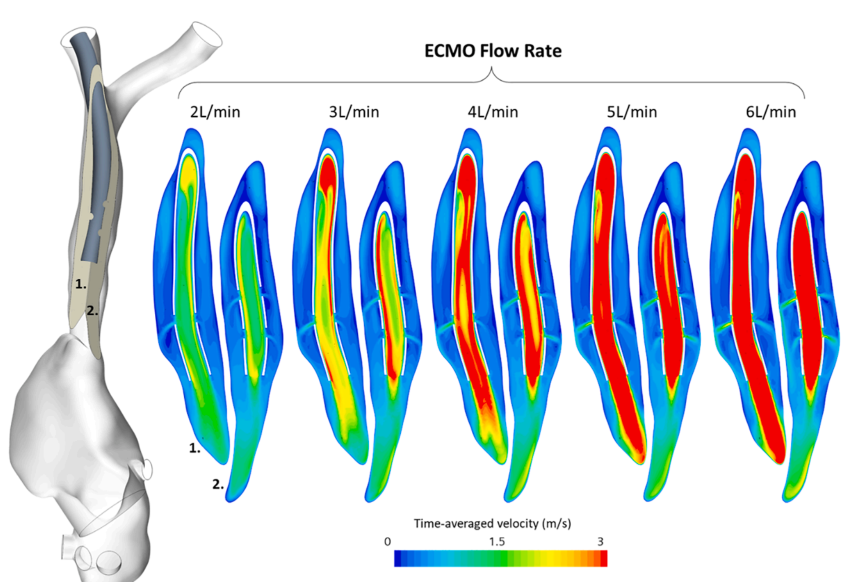

Fig. 7. Time-averaged velocity shown on two cross-sectional planes through the return cannula, at 5 L/min total cardiac output and for ECMO flow rates from 2 to 6 L/min.

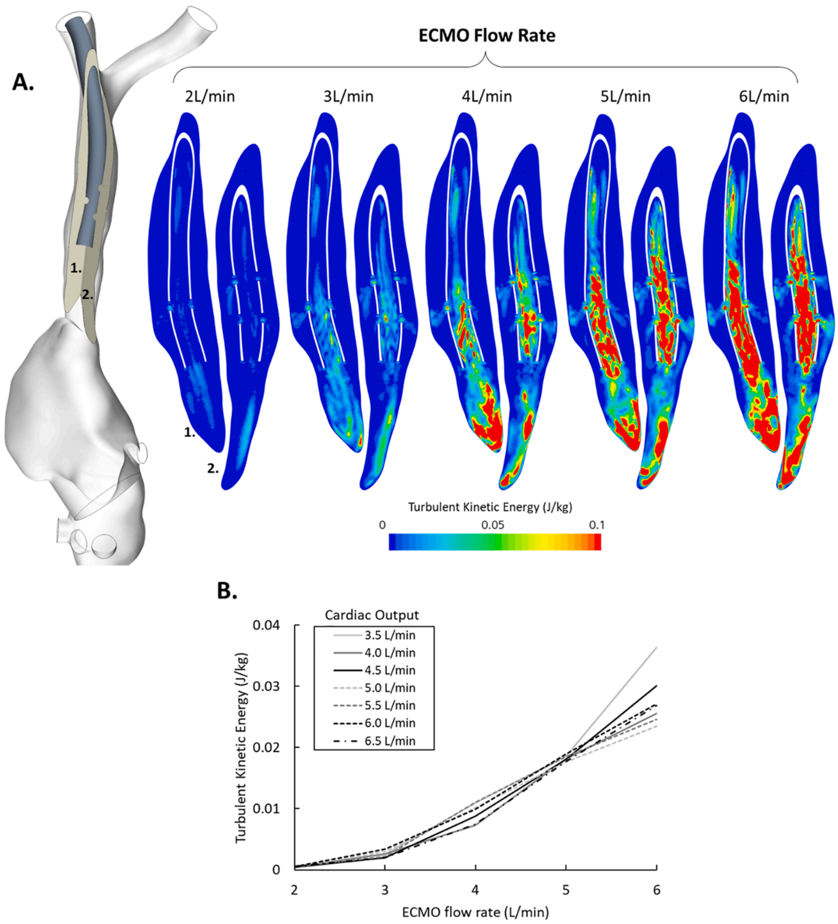

Fig. 8. **A.** Turbulent kinetic energy (TKE) shown on two cross-sectional planes through the return cannula, at 5 L/min total cardiac output for ECMO flow rates from 2 to 6 L/min. **B.** Volume averaged superior vena cava TKE for a range of cardiac output (CO) and extracorporeal membrane oxygenation (ECMO) flow rates.

that CO is correlated with the size of the venous system and in turn the cannulas that would be selected. It is unclear how accurately a scaling of the model size would impact results, but this should be investigated and compared with clinical R_f measurements from patients. There is also a significant degree of heterogeneity in vena cavae morphology and though we present a patient-averaged model, cannula dynamics are likely to differ in a large cohort. Secondly, we apply to the model constant inlet flow rates, whilst the venous side still exhibits some degree of pulsatility in its flows. As reported previously, we have examined the sensitivity of the model to this assumption showing little impact on time-averaged data [19]. Lastly, we present here a rigid model of both the venous system and cannulas. The venae cavae, in reality are highly compliant and would likely adapt according to local changes in pressure. An impact of this may be that recirculation increases under a negative caval pressure in the IVC as cannula side holes are occluded, as previously indicated [8]. Similarly, the right atrium itself would have a degree of contractility. Given the large parameter space considered, a much more computationally expensive fluid structure interaction (FSI) model would be impractical to implement and the lack of vessel compliance data further increases the uncertainties. Moreover, our time-averaged R_f results using this model show good agreement when compared with clinical data [8].

5. Conclusion

Our *in silico* investigation of femoro-jugular VV ECMO shows a clear interplay between patient CO and the level of recirculation. The higher the CO, the higher the permissive ECMO blood flow rate for acceptably low R_f. The combined impact of CO and ECMO flow rate appears to be adequately captured by EFF. These results need further evaluation on other basic configurations and in the clinic.

Ethics approval and consent to participate

All subjects gave informed consent and ethics approval was obtained from the Swedish Ethical Review Authority (Ethical permit 2018/438-31).

Consent for publication

All participants provided consent for publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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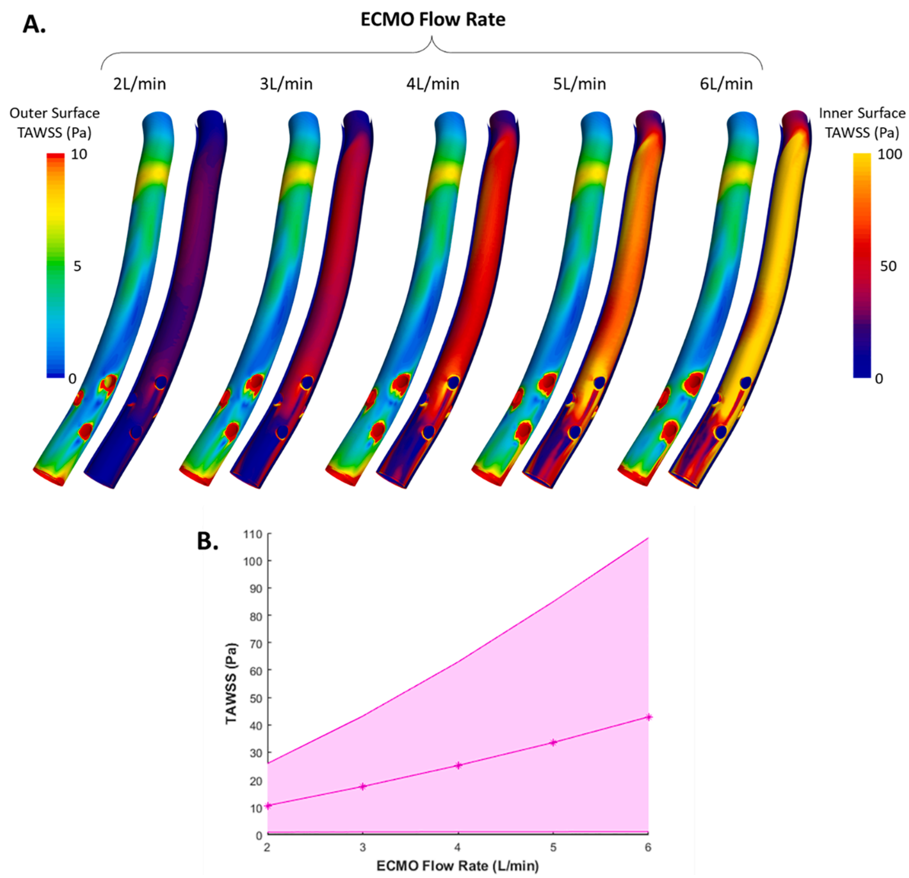

Fig. 9. **A.** Time-averaged wall shear stress (TAWSS) on the outer and inner surfaces of the return cannula for a range of ECMO flow rates. All contour plots depict a cardiac output (CO) of 5 L/min. **B.** Surface-average return cannula TAWSS plotted against ECMO flow rate (for CO = 5 L/min). The shaded region represents the 10th–0th percentile of TAWSS values.

CRediT authorship contribution statement

Louis P. Parker: Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Anders Svensson Marcial:** Conceptualization, Data curation. **Torkel B. Brismar:** Conceptualization, Data curation. **Lars Mikael Broman:** Conceptualization, Formal analysis, Writing – review & editing. **Lisa Prahl Wittberg:** Conceptualization, Formal analysis, Writing – review & editing.

Declaration of competing interest

L.M.B. is a member of the Medical Advisory Boards of Eurosets Srl., Medolla, Italy; and Xenios AG, Heilbronn, Germany; and HemoCue AB, Ängelholm, Sweden.

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