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Hemodynamic Response to Device Titration in the Shunted Single Ventricle Circulation - A Patient Cohort Modeling Study

Chet Villa

Farha Zafar

Angela Lorts

Ethan Kung

TITLE

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ABSTRACT

Clinical outcomes of ventricular assist device (VAD) support for shunted single ventricle patients trail the larger population due in part to the challenges in optimizing VAD support and balancing systemic and pulmonary circulations. We sought to understand the response to VAD titration in the shunted circulation using a lumped-parameter network modeling six patient-specific clinical cases. Hemodynamic data from six patients (mean BSA=0.30m^2) with a systemic-to-pulmonary shunt was used to construct simulated cases of heart failure and hemodynamic response to increasing VAD flow from 5 to 10 L/min/m^2. With increasing VAD flow, the pulmonary arterial pressure stayed relatively constant in 5 patient cases and increased in one patient case. The mean VAD flow needed to attain an AVO_2 of 30% was 6.5 +/- 1.2 L/min/m^2, which is higher than that in the equivalent non-shunted scenario due to the partial diversion of flow to the pulmonary circulation. The hemodynamic responses to VAD support can vary significantly between specific patient cases; therefore hemodynamic modeling may help guide an individualized approach to perioperative VAD management in the shunted single ventricle circulation and to understand the patients who may benefit the most from VAD support.

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GLOSSARY

AVO_2	Arterial-venous O_2 saturation difference
BSA	Body surface area
$CapO_2$	Blood O_2 carrying capacity
$ConsO_2$	O_2 consumption
CO	Cardiac output
Q_p/Q_s	Pulmonary-to-systemic flow ratio
Q_p	Pulmonary blood flow
Q_s	Systemic blood flow
R_{SUC}	Ventricular suction resistance
SaO_2	Arterial O_2 saturation
$SpvO_2$	Pulmonary vein O_2 saturation
SvO_2	Venous O_2 saturation
VAD	Ventricular assist device

Introduction

The number of children supported with ventricular assist devices (VADs), has grown significantly over the last two decades. The percentage of children bridged to transplant with a VAD has increased from 13% to 33%.[1] Increased VAD utilization has led to improved waitlist mortality and improved post-transplant outcomes when compared to ECMO.[2, 3]

However, improvements in outcome due to increased VAD utilization are not uniform across the population of children with heart failure. Patients $\leq$ 1 year of age and those with congenital heart disease are less likely to be bridged to transplant on a VAD and only 5-6% of infants with congenital heart disease <1 year of age are bridged to transplant with a VAD.[1] Decreased device utilization in this cohort is likely driven by early experiences with VAD therapy showing increased mortality in small children (<10kg), especially those with congenital heart disease, where the mortality rate was ~70%.[4] The mortality rate reached 100% for Stage 1 single ventricle patients supported with the Berlin EXCOR.[5]

Subsequent maturation of the field, the use of alternate cannulation strategies, and the use of paracorporeal continuous flow devices in select patients have resulted in marked improvements in survival for small patients and those with congenital heart disease.[6, 7] While there have been significant improvements in survival, clinical outcomes for patients with univentricular physiology continue to trail the larger overall cohort. A recent analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) found that 64% of Stage 1 patients achieved a positive outcome. Adverse clinical outcomes are likely driven in part by the challenges in balancing the systemic and pulmonary circulations in patients with shunted physiology, and in understanding fundamental concepts including pump selection (size and type) and patient management.[5] Historically, individual centers have been reticent to increase VAD flows due to concerns that increased cardiac output may result in pulmonary over-circulation and by reports suggesting that the use of a large for body surface area (BSA) EXCOR pump may contribute to stroke risk[8] and inadequate VAD filling.[9] Unfortunately there is no significant literature regarding ramp studies in the shunted circulation to help understand the hemodynamic effects of VAD titration and help guide patient management. Recently, individual centers have reported successful support in Pre-Glenn patients using a management strategy incorporating higher VAD flows.[10, 11] However, it is unclear whether this approach is broadly generalizable and there is no concrete conviction across the clinical community for prescribing higher VAD flows to shunted patients and if so the values generally needed to provide adequate systemic blood flow without compromising respiratory status through overcirculation and elevation of pulmonary artery pressures. Previous data using mathematical modeling underscored the potential pitfalls of VAD support in the setting of shunted physiology, however, those assumed a pre-specified device revolutions-per-minute setting and did not examine the individual, potentially divergent, hemodynamics for a given patient.[12] Thus, in this study, we employed patient-specific lumped-parameter physiology models of VAD therapy to quantify the hemodynamic response to VAD titration in the systemic-pulmonary shunted circulation.

Methods

The overall flow of the methods (Fig 1) involves creating patient-specific computational models that describe VAD-supported heart failure scenarios. Using the blood flow information from these simulation results, we computed O_2 related parameters for the simulated shunted scenarios, as well as for the trivial case if the simulated patient had non-shunted circulations given the resulting *CO* in each simulated scenario. Finally, we quantified the cardiac indices required to achieve specific levels of oxygenation comparing between the shunted and non-shunted scenarios. The details for each component of the methods are described in the sections below.

VAD Support Hemodynamic Simulations

The hemodynamics of patient-specific VAD support scenarios were simulated according to our previous work.[9] Briefly, we started with clinical measurements of six systemic-pulmonary shunted single ventricle patients (age: 3-6 month, BSA: 0.26-0.34 m^2) (Table S1) from the Great Ormond Street Hospital, Medical University of South Carolina, and University of Michigan.[13] Institutional review board study approval was obtained for each clinical site with informed consent for data use obtained from the participants' legal guardians. For each patient, we tuned a lumped-parameter physiology model based on the individual patient's clinical measurements to create the pre-support model.[14, 15] Once tuning was complete, we set the ventricular contractility to zero to simulate heart failure and connected a continuous flow VAD model between the ventricle and the aorta to arrive at the VAD supported scenario (Fig 2). While in clinical practice the outflow cannula could be attached to one of several locations near the aorta, since the lumped-parameter model is a simplified representation of vasculature, these locations each correspond to the aortic node as shown in Fig 2.

The lumped-parameter model formulation includes implementations that capture ventricular suction, suction release, and negative ventricular pressure behaviors. The ventricular suction is relevant to the ventricular collapse induced by a VAD if it attempts to draw blood from the ventricle below its reference volume, resulting in a negative pressure and collapse. When these suction events occur, tissue may be drawn into the cannula or the septum may be drawn closer to the cannula, both of which can inhibit blood flow.[16] If complete flow obstruction occurs, the inflow cannula attaches to the collapsed ventricular wall; in such a case a "pop off" pressure is needed to overcome the negative cannula pressure and release the cannula from the wall. Finally, the pressure-volume relationship of the ventricle has two different regimes depending on whether ventricular pressure is positive or negative. All of these behaviors are captured in our physiology model formulation.[9]

Due to the similar centrifugal designs of commercially available continuous flow VADs, they would produce similar hemodynamics when generating the same pressure outputs according to the device-specific HQ curves. We simulated a range of VAD pressure outputs in each patient case resulting in a range of cardiac indexes depending on the specific patient physiologies. For the purposes of the analyses in this study, the blood flow serves as the independent variable affecting oxygen related parameters. Results are reported across the spectrum of flow up-titration until suction-induced ventricular collapse occur in the model (as in patients A and B) where the ventricular suction resistance (R_{SUC}) ≥0.04 mmHg.s/ml.

O_2 Related Parameter Calculations

Based on the hemodynamic simulation results, we calculated arterial and venous oxygen saturations for the systemic-to-pulmonary shunted circulation via the following equations:

$$SaO_2 = \frac{Q_p\, SpvO_2}{CO} + \frac{Q_s\, SvO_2}{CO} \quad (1)$$

$$ConsO_2 = Q_s(SaO_2 - SvO_2)\, CapO_2 \quad (2)$$

where Q_p, Q_s, CO, $ConsO_2$, $CapO_2$, $SpvO_2$, SaO_2, and SvO_2 are mean values of pulmonary blood flow, systemic blood flow, cardiac output, O_2 consumption, blood O_2 carrying capacity, pulmonary vein O_2 saturation, arterial O_2 saturation, and venous O_2 saturation, respectively. SaO_2 and SvO_2 are the quantities to be solved. The blood flow related parameters Q_p, Q_s, and CO are quantities available from the hemodynamic simulation results. $SpvO_2$ is assumed to be 97%. We estimated the value of $CapO_2$ to be 0.151 ml-O_2/ml-blood based on previously published hemoglobin O_2 carrying capacity (1.31 ml-O_2/gHb consistently across fetal to adult population) and hemoglobin concentration in 3-month old infants (0.115 gHb/ml-blood).[17, 18] Finally, we estimated the value of $ConsO_2$ using the regression model reported by Seckeler et al.[8] for critically ill children and adults with congenital heart defects; since this regression model requires patient age and weight as inputs, we used the relationship between BSA and weight in children to obtain the patient's weight estimate from the BSA measurement which is available in our clinical data.[19]

Finally, using the O_2 Saturation results we calculated the oxygen delivery by multiplying Qs by $CapO_2$ and SaO_2.

O_2 Parameters for the Non-shunted Circulation

We calculated what the SvO_2 and oxygen delivery would be if the simulated patient cases had non-shunted circulations given the resulting CO in each simulated scenario. In a non-shunted circulation, SaO_2 is equaled to $SpvO_2$, the oxygen delivery is CO multiplied by $CapO_2$ and SaO_2, and SvO_2 is solved from the equation

$$ConsO_2 = CO(SaO_2 - SvO_2)\, CapO_2 \quad (3)$$

Surplus Cardiac Index

Comparing the shunted to the non-shunted scenario for each simulated patient, we quantified the additional cardiac index required to achieve any specific level of desired arterial-venous O_2 saturation difference (AVO_2). To perform this direct comparison, we first mathematically quantified the cardiac index as a function of AVO_2 by fitting a power equation to relate these two quantities using the simulation results from each patient model; this resulted in a total of six functions (one for each simulated patient) for the shunted scenario and six functions for the non-shunted scenario. We then used these fitted functions to directly compute the difference between the cardiac indexes for the shunted and non-shunted scenarios at different AVO_2 levels and defined the resulting quantity as the "Surplus Cardiac Index."

Results

At any particular CI, the shunted circulation produced lower O_2 delivery and AVO_2 than the non-shunted circulation (Fig 3). The increase in O_2 delivery with increasing CI, while linear in both cases, had a shallower slope for the shunted compared to the non-shunted circulation (Fig 3A). The mean VAD flow needed to achieve an AVO_2 of at least 30% for the shunted-circulation was 6.5 L/min/m^2, with a standard deviation of 1.2 L/min/m^2.

In terms of hemodynamics, the ratio of pulmonary to systemic flow (Q_p/Q_s) slightly decreased with increasing CI in all patient cases (Fig 4A), while the pulmonary arterial pressure stayed relatively constant with changing CI in 5 of the patients (Fig 4B). One patient experienced sequential increases in pulmonary arterial pressure as VAD flow was titrated.

To achieve any particular AVO_2, the shunted circulation required a "surplus cardiac index" (as defined in the Methods section) in all patient cases compared to the non-shunted circulation (Fig 5). This surplus cardiac index is a function of the desired AVO_2. At 30% AVO_2 the mean and standard deviation of the surplus cardiac index in the six simulated patients was 3.07 and 1.16 L/min/m^2, respectively.

Discussion

The early experiences supporting children with shunted single ventricle physiology were poor;[5] none of the patients with shunt physiology survived. These poor outcomes were theorized to be driven by the difficulty in selecting an appropriate pump size for patients with parallel circulation, prominent aortopulmonary blood flow, and the challenge of anticoagulating neonates and infants due to developmental hemostasis.[20] Since the initial reports, some strides have been made from adjustments in hemodynamic support and anticoagulation management. The field has rapidly shifted toward the use of paracorporeal continuous flow devices in order to offset some of the concerns of selecting an appropriate pump size.[7] There has also been a rapid shift toward the use of direct thrombin inhibitors in infants and children supported with paracorporeal VADs.[21] While outcomes continue to trail those in patients with non-shunted physiology, survival has clearly improved over time as recent analysis of the PediMACS data showed that 64% of shunted patients achieved a positive outcome.[7] Despite these gains, questions remain about the ability to balance pulmonary blood flow and oxygen delivery and there are no significant ramp studies to help inform management.[11] Thus, while the hemodynamic challenges inherent to the shunted circulation have been known for decades, the quantifiable impact of VAD therapy on the circulation has not been investigated.

In the current study, a lumped-parameter model assessed the interactions between O_2 delivery, VAD flow, pulmonary blood flow, systemic blood flow and pulmonary arterial pressures to begin to quantify the impact of VAD therapy in shunted physiology. The patient-specific simulations demonstrated that the hemodynamic response to increasing VAD flows to ensure adequate oxygen delivery is variable and patient-specific. This is notable for patient management in that it helps to define plausible and expected device titration needs in the shunted circulation, but also because it expands upon the previous work using lumped parameters models in the shunted circulation. Previous modeling suggested a 40% increase in pulmonary artery pressure with device implantation, however, it was unclear whether these results are

universal.[22] The current study suggests this pulmonary artery pressure elevation is not inevitable and that serial titration of the VAD with concomitant decreases in atrial pressure may mitigate this effect in select patients.

In order to further inform patient management, we also compared the shunted and non-shunted circulation. The O_2 delivery increases with uptitrating VAD flow in the shunted circulation, but at a shallower slope when compared to the non-shunted circulation due to partial diversion of flow to the pulmonary vascular bed. The fact that not all of the CI contributes to systemic flow (i.e. O_2 delivery) in the shunted circulation also results in higher AVO_2 at any particular CI suggesting larger increments of device uptitration will be needed in order to effectively increase systemic oxygen delivery. Compared to the non-shunted circulation, a surplus VAD flow of 3.07 L/min/m^2 on average was needed to offset pulmonary blood flow and achieve similar tissue oxygen delivery at an AVO_2 of 30%; however, there was a 40% standard-deviation of this surplus flow among patient cases. The scale of the variation is notable and suggests that patient-specific estimates of flow based on physiologic parameters or diagnostics (including MRI or existing catheterization) would be valuable especially when selecting cannulae and pump sizes. The shallower slope of pulmonary artery pressure associated with VAD titration in the shunted circulation is also notable. Providers are often hesitant to increase flow in larger increments due to concerns that this will disproportionately increase pulmonary artery pressure;[12, 22] the current study suggests conservative uptitration will provide inadequate systemic oxygen delivery and potentially also result in higher pulmonary artery pressures given the majority of patients saw a decrement in atrial pressures (and subsequently pulmonary artery pressures) as the devices are uptitrated. This point is likely fundamental to understanding which shunted patients may benefit from VAD support. In patients where elevated common atrial pressure due to ventricular dysfunction drives elevation of pulmonary artery pressure, and who have an appropriately restrictive shunt, VAD support provides a means to improve oxygen delivery and decrease pulmonary artery pressure. The ability to drop common atrial pressures while improving systemic output is likely different from the non-VAD supported shunted patient where initiation of inotropic support may increase systemic oxygen delivery, but does so at the expense of increases in common atrial pressure due to residual systolic dysfunction, diastolic dysfunction, and systemic valve regurgitation.

Thus, the current modeling approach may help providers accommodate for both the increased flow needs at time of implant and understand the hemodynamic effects of titration. This approach may also help to understand the long term hemodynamic implications of patient growth on support. While the variation reported may make device titration appear a daunting task, it underscores the utility in using mathematical models to help guide initial management. It also suggests centers should have a low threshold to consider hemodynamic ramp studies for any patient not progressing clinically.

The initial modeling work by Di Molfetta et al. demonstrated that while VAD support improves systemic blood flow, this may come at the expense of increasing pulmonary arterial pressure by 40% or more.[12] This clinical scenario is well described and has led centers to optimize shunt size and medical management (i.e. low systemic vascular resistance state) in order to balance Q_p/Q_s in an individual patient.[23, 24] The current study finds that increases in pulmonary arterial pressure are not universal with

up-titration of VAD flow, but also confirms the well-described challenges of VAD support in patients with a minimally restrictive shunt where Q_p/Q_s is high. We suspect the latter situation is what is occurring in the case of patient F (Fig 4). Patient F has the highest Qp/Qs, implying that their shunt is large for the body size, this then allows more of the aortic pressure to translate to the pulmonary artery. The increases in VAD flow needed to ensure adequate systemic blood flow resulted in adverse changes in pulmonary artery pressure (>15 mmHg). In situations that mimic the hemodynamics of patient F, alternate methods such as maintaining a low systemic vascular resistance may be needed to optimize hemodynamics. Further studies are needed to help identify patients likely to respond in a similar manner (e.g. those with larger shunt to body size ratios) and to understand the impact that clinical management approaches such as lowering the systemic vascular resistance may have on hemodynamic support. Patient-specific modeling may help define the circumstances where adequate hemodynamics will be difficult to achieve even with optimal device titration and medical therapy. This is consistent with the literature in the two ventricle circulation where the device optimization has become an important part of clinical care due to the discrepant physiologic responses to device titration.[25, 26]

Limitations

Our study presents six patient-specific scenarios as example cases to illustrate the hemodynamic response at different levels of VAD support. These cases do not represent the comprehensive combinations of physiologic parameters that can potentially occur in a patient. Even though the full range of patient scenarios (e.g. high vascular resistance state, significant collateral burden, etc) were not specifically included as part of the current simulation and analyses, these circumstances can be captured and modeled using the method described and this work is ongoing. This further emphasizes the importance of patient-specific assessment and the unique needs of each patient. While there was some variation in the characteristics of the patients in the current study, the hemodynamic profile of shunted patients listed for transplant may be different. The clinical data used to construct the model did not originate from patients with heart failure, and heart failure was simulated via adjustments of the contractility parameter in the computational model. The fact that the model assumes no inherent ventricular contribution is worth noting when interpreting the results as any residual ventricular ejection would alter the cardiac output. Aortopulmonary collateral flow, shunt anatomy, hematocrit variations, and pulmonary artery anatomy also have marked effects on hemodynamics and oxygen delivery; we have not accounted for these in the current study and are working to understand the potential impact of these factors on patient hemodynamics. Lastly, future modeling studies can benefit from incorporating cardiovascular feedback mechanisms to capture the patient's auto-regulation response to surgery, VAD titration, and hemodynamic manipulation.[27]

Conclusions

Clinical management of VAD patients involves the unique challenge of needing to determine appropriate device titration. Due to the partial diversion of flow to the pulmonary circulation, the mean “surplus VAD flow” in order to achieve systemic oxygen delivery similar to that in the non-shunted circulation was >3 L/min/m^2. This needed additional flow replenishes the flow diverted by the shunt and therefore can be determined via an estimation of pulmonary blood flow. An increase in VAD flow does

not necessarily result in dramatic increases in pulmonary arterial pressure and may allow decreases in common atrial pressure and improved systemic oxygen delivery. These results suggest that for shunted patients on VAD support, prescribing higher (compared to non-shunted patients of similar body sizes) VAD flows can be considered as a potentially beneficial therapeutic option. Understanding the quantities and range of VAD outputs needed to effectively support patients with a shunted circulation is integral to surgical planning and to improving support outcomes in this patient population. Larger studies describing the hemodynamics effects across the range of patient hemodynamic and anatomic profiles will be valuable to further understand the potential hemodynamic effects of VAD support in the shunted circulation.

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FIGURES

Fig 1. Overall flow diagram of the study methods.

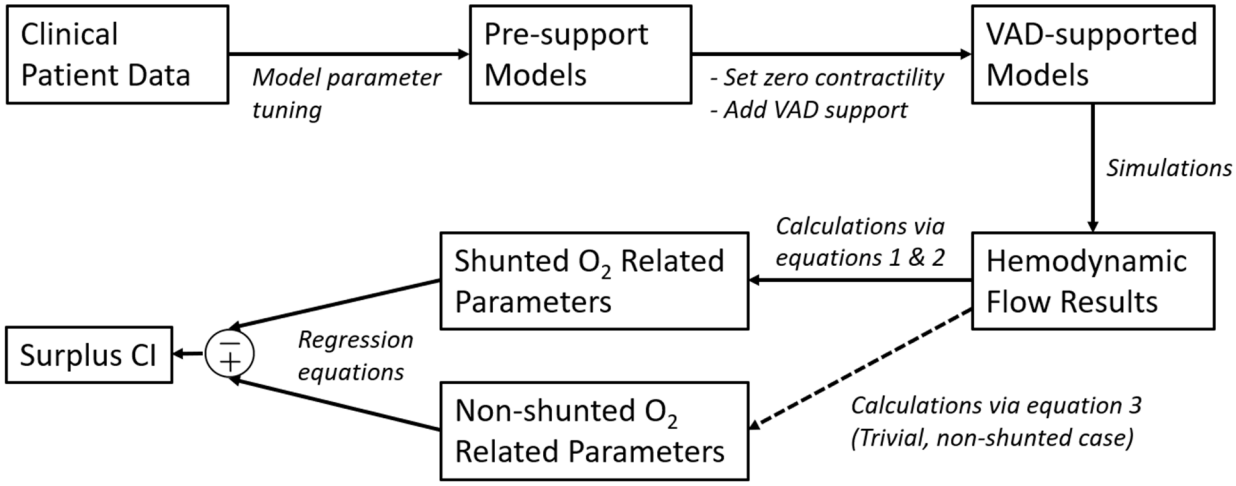

Fig 2. Circuit model of the VAD-supported systemic-to-pulmonary shunted circulation. Labels "AO" and "R_{SUC}" denote the aortic node and the ventricular suction resistance, respectively. Detailed model formulation is described in reference.[9]

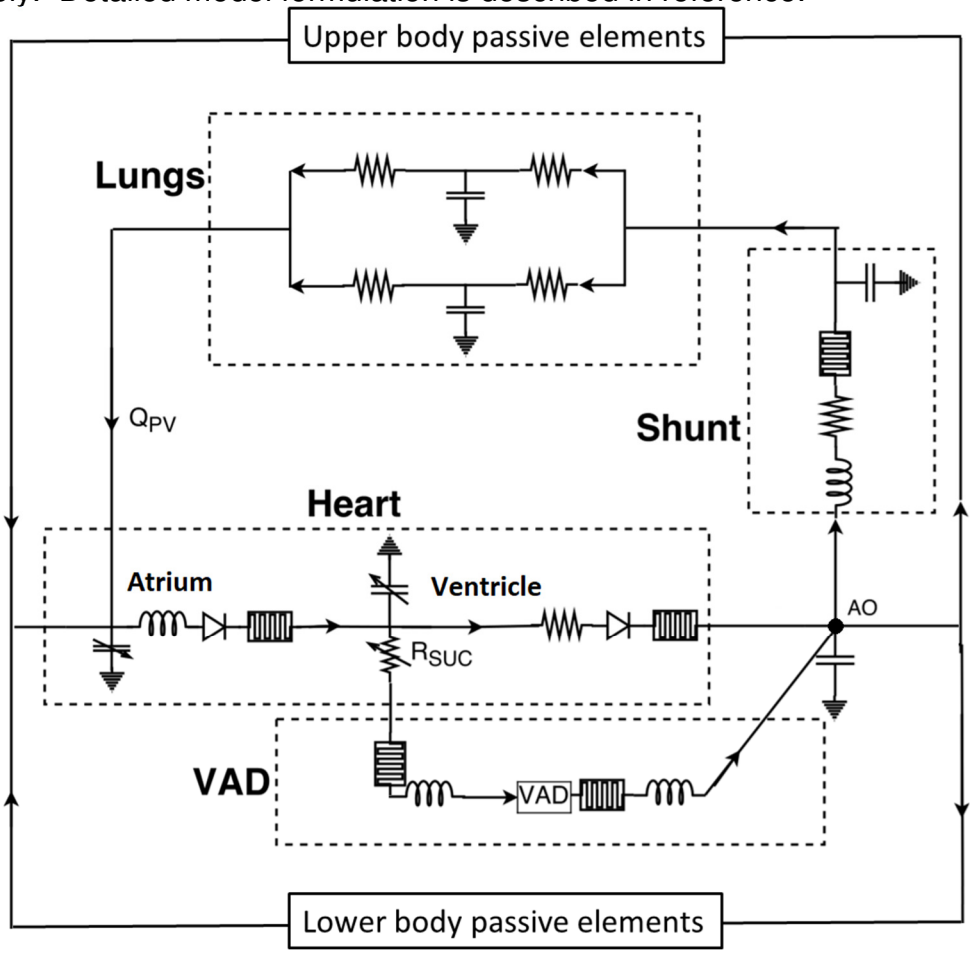

Fig 3. O_2 related parameters versus cardiac index for six patient-specific simulated cases. Solid (also black) and dotted (also red) lines represent the systemic-to-pulmonary shunted, and non-shunted (normal), scenario, respectively.

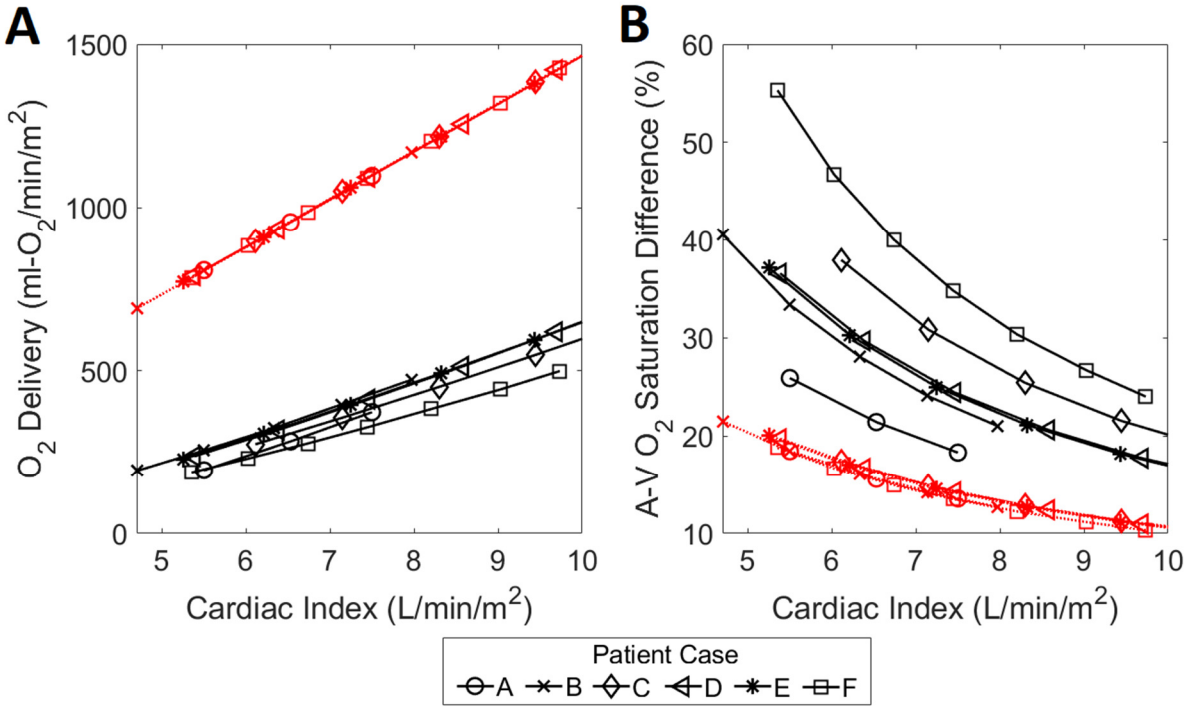

Fig 4. Hemodynamic parameters versus cardiac index for six patient-specific simulated cases of systemic-to-pulmonary shunting circulation.

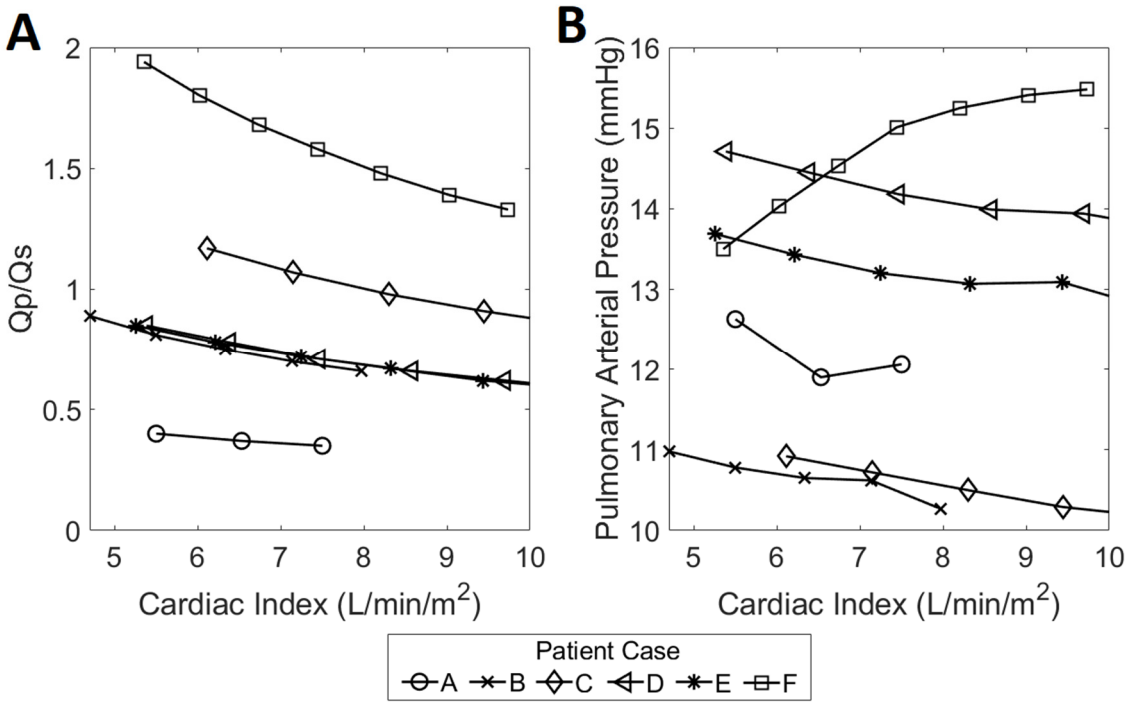

Fig 5. The surplus cardiac index reveals in each patient-specific simulated case the additional flow required to achieve the same AVO_2 for the systemic-to-pulmonary shunted scenario relative to the non-shunted (normal) scenario.