

Numerical Investigation of an Idealized Total Cavopulmonary Connection Physiology Assisted by the Axial Blood Pump With and Without Diffuser

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Abstract: In order to improve the surgical treatment of the congenital heart disease patient with single ventricle defect, two axial flow blood pumps, one with diffuser and the other without diffuser, were designed and virtually implanted into an idealized total cavopulmonary connection (TCPC) model to form two types of Pump-TCPC physiological structure. Computational fluid dynamics (CFD) simulations were performed to analyze the variations of the hemodynamic characteristics, such as flow field, wall shear stress (WSS), oscillatory shear index (OSI), relative residence time (RRT), between the two Pump-TCPC models. Numerical results indicate that the Pump-TCPC with diffuser has better flow field stability, less damage on endothelial cell of vessel wall, and lower risk of vascular injury and thrombosis formation than that without diffuser.

Keywords: Computational fluid dynamics; total cavopulmonary connection; axial flow blood pump; vascular damage; thrombosis probability

1 Introduction

More than 1 million children with congenital heart anomalies are born every year around the world [1]. Single ventricle physiology is a sub-group of congenital heart anomalies, which refers to a variety of cardiac defects where only one of the heart's two ventricles functions properly, such as hypoplastic left heart syndrome, tricuspid atresia, double outlet left ventricle, etc. Common symptoms include cyanosis, difficulty breathing, lethargy, etc. About two out of every thousand infants suffering from single ventricle physiology [2]. In most cases, children with single ventricle physiology require surgical intervention soon after birth. Generally, a three-stage palliative surgery is taken for the treatment of single ventricle patients, which includes Norwood, Glenn and Fontan [3]. As the final step, the Fontan procedure has been optimized in the past 30 years [4].



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In one surgical approach of the extra-cardiac Fontan, the inferior vena cava (IVC) and superior vena cava (SVC) are directly connected to the pulmonary artery to form the total cavopulmonary connection (TCPC) physiological structure. The application of a single or bilateral SVC has been discussed in previous research, and the results showed that bilateral SVC has advantages in the flow distribution between the left and right pulmonary arteries [5]. Besides, after this surgery, the single ventricle provides power for both systemic and lung circulation, which leads to an increased workload on that ventricle. About 40% Fontan patients developed premature heart failure, with a 5-year mortality rate of 50% [6]. Research recommended that the surgical operation combined with mechanical support, especially the implantation of an axial flow blood pump into the IVC can improve Fontan hemodynamics and decrease patients' mortality [7]. However, excessive pressure rise may worsen the patients' condition. Farahmand et al. [8] used a numerical model of the failing Fontan physiology to evaluate the Fontan hemodynamic response to a left ventricular assist device (VAD), and found that IVC support did not benefit the hemodynamics in the patient cases simulated, resulting in the SVC pressure increasing to an unsafe level of >20 mmHg. Migliavacca et al. [9] used a lumped parameter model to perform a 3D-0D coupled hemodynamic analysis of the Fontan operation area of the case, proposed a design reference for the cavopulmonary circulation assist device (CPAD), and considered that a pressure rise of 10 mmHg of CPAD was appropriate. Bhavsar et al. studied the output characteristics of the axial flow blood pump and the changes in pulmonary artery pressure during virtual implantation and vitro experiments, and concluded that a pressure rise of 6–10 mm Hg is more suitable for the design of CPAD. This pressure rise can effectively avoid a series of problems such as excessive pulmonary artery pressure, decreasing blood flow to the heart, and reducing pulmonary perfusion [10]. Farahmand et al. elucidated the hydraulic operating regions that should be targeted for designing cavopulmonary blood pumps in another research. Furthermore, they used these desired flow-pressure operating regions to evaluate off-label use of commercially available left-side blood pumps for failing Fontan cavopulmonary support [11]. Our group designed a magnetically levitated axial flow blood pump based on the prototypes of systemic Ventricle Assisted Devices (VADs) from Throckmorton et al. [12] and the Jarvik 2000 (Jarvik Heart Inc., New York, NY, USA) to support the TCPC physiology. The blood pump was expected to serve as a long-term bridge to transplant, recovery, or surgical reconstruction [13]. Now, we considered a novel design by removing blades of diffuser. This study virtually implanted two types of blood pumps into the IVC. Based on CFD simulations of the Pump-TCPC models, the differences in the improvement of Fontan hemodynamics between the axial flow blood pump with and without diffuser were compared.

2 Method

In previous research, the blood pump was designed with reference to existing VADs. The core part was optimized according to the design of Jarvik 2000. We adjusted the size and output characteristics of the pump so that it can better meet the requirements of cavopulmonary circulation power assistance. The intravascular axial flow blood pump consists of protective housing, inducer, impeller, diffuser and straightener. The optimized design aimed at providing a suitable pressure augmentation of blood flow from the IVC to the pulmonary arteries. And the enhanced cardiovascular hemodynamics would be achieved for improving systemic pressure, increasing ventricular filling and increasing cardiac output [13]. The diffuser is a key component that converts kinetic energy into potential energy (pressure rise) of blood flow, and its design optimization plays a key

role in the output of the blood pump meeting the needs of the cavopulmonary circulation. We considered a novel design compared with the original one, in which the number of blades of the diffuser is reduced from 4 to 0 to achieve a further reduction in the pressure rise provided by the blood pump. Two types of axial flow blood pumps are shown in Fig. 1.

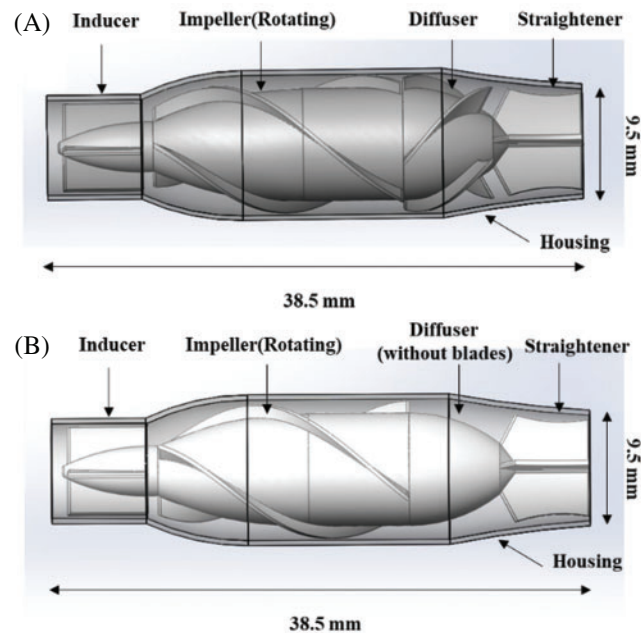


Figure 1: The structures of two types of axial flow blood pumps. (A) shows the pump with diffuser and (B) shows the pump without diffuser

By using CAD software SolidWorks 2015 (SolidWorks Corporation, Concord, MA, USA), based on the model of the original pump, the blades in diffuser were removed to create the pump without diffuser. An idealized TCPC geometric model was also constructed by SolidWorks 2015 and assembled to the outlet of the axial flow blood pumps to complete virtual implantation. The Pump-TCPC models obtained after implanting the blood pumps in the ideal TCPC model are shown in Fig. 2. The grid was constructed using the software ICEM (ANSYS Incorporated, Canonsburg, PA, USA), which generates high-quality structured hexahedral elements for two types of pump models and the tetrahedral triangular prism element for the TCPC analysis. Besides, grid density and convergence of pump and TCPC models were evaluated for grid quality assurance in our previous research [13]. The maximum sizes of the axial blood pump grid and TCPC grid were set to 0.7 mm and 0.6 mm, respectively. The element counts of two types of axial flow blood pumps and TCPC are listed in Tab. 1. Fig. 3 shows details of TCPC grids and grids of all components of axial flow blood pumps. We used computational fluid dynamics software CFX 16.0 (ANSYS Incorporated, Canonsburg, PA, USA) to simulate hemodynamics of Pump-TCPC models. The Reynolds-Averaged Navier–Stokes (RANS) solver and the standard $k-\varepsilon$ turbulence model were used in these simulations.

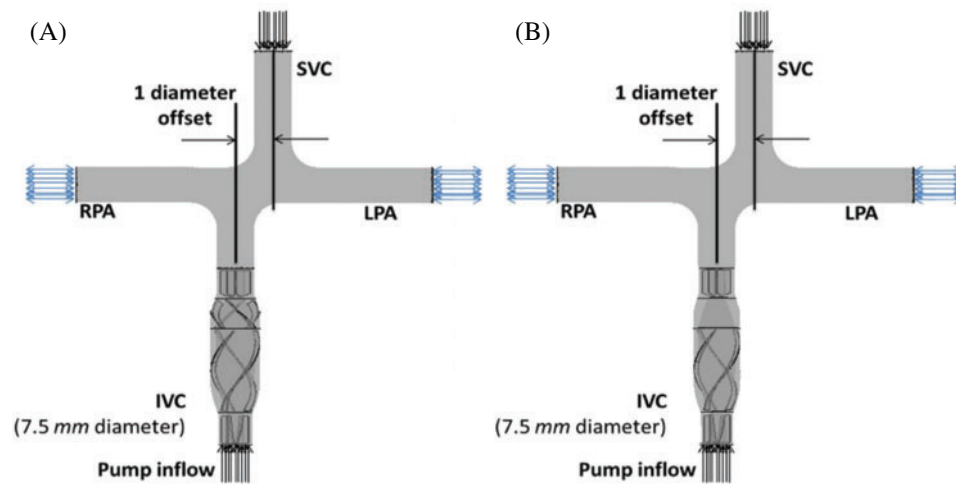


Figure 2: The Pump-TCPC model. (A) shows the Pump-TCPC with diffuser, (B) shows the Pump-TCPC without diffuser

Table 1: Elements counts of the numerical models

Model	Element counts
The axial flow blood pump with diffuser	1332324
The axial flow blood pump without diffuser	1236602
TCPC	795486

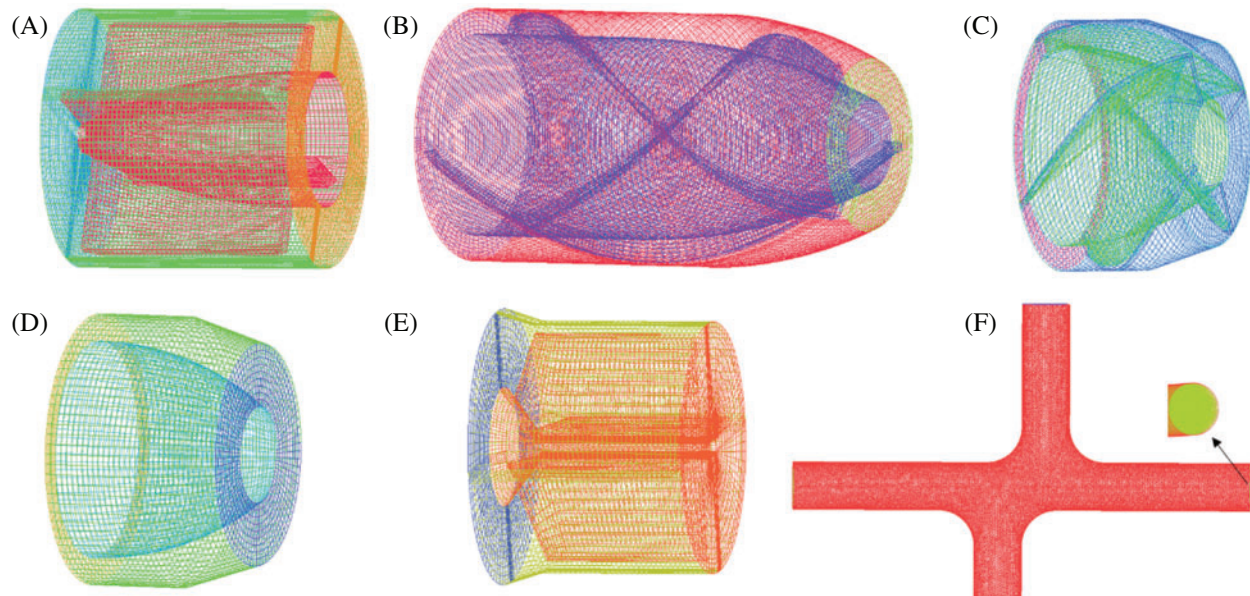


Figure 3: The grids of TCPC and all components of axial flow blood pumps. (A–F) shows the grid of inducer, impeller, diffuser with blade, diffuser without blade, straightener and TCPC, respectively

The boundary conditions are imposed as follows: the inlet flow boundary condition was specified at the inducer of pump and SVC, and the inflow rates were 1.8 L/min and 1.2 L/min, respectively, corresponding to the cardiac output of 3 L/min in Fantan patients. According to the output characteristics of the pump, left pulmonary artery (LPA) and right pulmonary artery (RPA) were given open boundary condition with a static pressure of 20 mmHg. Vessel walls of TCPC and all the housing and blades of the pumps were modeled as rigid. Besides, the smooth and no-slip boundary condition was applied to the vessel walls of TCPC and all the housing and blades of the pumps. The impeller domains of the pumps were designed as counter-clockwise rotating region, while other domains were stationary. After a series of pre-simulations, the impeller speeds were set to 4000 rotations per minute (RPM) in pump with diffuser and 10000 RPM in pump without diffuser for simulation and comparison. The simulation was set to the transient solution with the steady boundary conditions. The timestep was 0.00033 s, and the total calculation time was 0.05 s including 150 steps. In addition, we saved calculation results every ten timesteps. The whole blood density, dynamic viscosity and specific heat capacity were set as 1060 kg/m³, 0.0035 Pa·s and 3.594 kJ/kg/K, respectively [14].

In this study, blood was set as incompressible fluid. The continuity equation of blood flow is shown in Eq. (1):

$$\frac{\partial u_i}{\partial x_i} = 0 \quad (1)$$

Due to the high rotation speed of the impeller, flow regime ranges from laminar through transitional to turbulent [15]. For analysis of turbulent flow, Reynolds equations were used:

$$\frac{\partial}{\partial t}(\rho \bar{u}_i) + \frac{\partial}{\partial x_j}(\rho \bar{u}_i \bar{u}_j) + \frac{\partial}{\partial x_j}(\rho \bar{u}'_i \bar{u}'_j) = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} \left[\mu \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) \right] \quad (2)$$

In the above equations, $i, j = 1, 2, 3$, x_1, x_2, x_3 represent coordinate axes, u_i, u_j and p are the velocity vector and the pressure, ρ and μ are blood density and viscosity, and t is time. $\bar{u}_1, \bar{u}_2, \bar{u}_3$, are time averaged velocity components, $\bar{u}'_1, \bar{u}'_2, \bar{u}'_3$, are fluctuating velocity components. The standard $k-\varepsilon$ model was used in this study, as which has been successfully applied in the optimization of ventricular assist devices (VADs) [16,17], the terms $(\rho \bar{u}'_i \bar{u}'_j)$ in Eq. (2) are defined as:

$$\rho \bar{u}'_i \bar{u}'_j = -\mu_t \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) + \frac{2}{3} \rho k \delta_{ij} \quad (3)$$

And the motion of turbulent fluid can be expressed by Eq. (4), the differential equation of turbulent kinetic energy k (5) and the differential equation of turbulent dissipation rate ε (6).

$$\frac{\partial}{\partial t}(\rho \bar{u}_i) + \frac{\partial}{\partial x_j}(\rho \bar{u}_i \bar{u}_j) = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} \left[(\mu + \mu_t) \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) - \frac{2}{3} \rho k \delta_{ij} \right] \quad (4)$$

$$\frac{\partial}{\partial t}(\rho k) + \frac{\partial}{\partial x_j}(\rho \bar{u}_j k) = \frac{\partial}{\partial x_j} \left(\Gamma_k \frac{\partial k}{\partial x_j} \right) + P_k - \rho \varepsilon \quad (5)$$

$$\frac{\partial}{\partial t}(\rho \varepsilon) + \frac{\partial}{\partial x_j}(\rho \bar{u}_j \varepsilon) = \frac{\partial}{\partial x_j} \left(\Gamma_\varepsilon \frac{\partial \varepsilon}{\partial x_j} \right) + \frac{\varepsilon}{k} (C_{\varepsilon 1} P_k - \rho C_{\varepsilon 2} \varepsilon) \quad (6)$$

where $P_k = -\rho \overline{u'_i u'_j \frac{\partial \overline{u_i}}{\partial x_j}}$, $\delta_{ij} = \begin{cases} 1, & \text{if } i=j \\ 0, & \text{if } i \neq j \end{cases}$, $\Gamma_k = \mu + \frac{\mu_t}{\sigma_k}$, $\Gamma_\varepsilon = \mu + \frac{\mu_t}{\sigma_\varepsilon}$. Parameters ε and μ_t are defined as follows:

$$\varepsilon = \frac{\mu}{\rho} \overline{\left(\frac{\partial u'_i}{\partial x_j} \right)^2} \quad \mu_t = \rho C_\mu \frac{k^2}{\varepsilon} \quad (7)$$

The constants of k - ε model are as follows: $C_\mu = 0.09$, $C_{\varepsilon 1} = 1.44$, $C_{\varepsilon 2} = 1.92$, $\sigma_k = 1.0$, $\sigma_\varepsilon = 1.3$ [18].

In hemodynamic simulations, parameters such as time-averaged wall shear stress magnitude (TAWSS), oscillatory shear index (OSI) and relative residence time (RRT) [19] are often used to evaluate the effect of blood flow to the vessel wall. Wall shear stress (WSS) refers to the tangential, frictional stress caused by the action of blood flow on the vessel wall. TAWSS is calculated by integrating the WSS magnitude over the cardiac cycle, as shown in Eq. (8). OSI measures the directional change of WSS during the cardiac cycle [20], which is calculated by Eq. (9). OSI varies from 0 to 0.5, and the value of OSI reaches the minimum and maximum when the instantaneous shear vector is collinear with the time-average vector throughout the cardiac cycle and $\left| \int_0^T wss_i dt \right| = 0$. Himburg et al. [21] showed that residence time of blood near the wall can be reflected by the combination of TAWSS and OSI. RRT was defined to quantify the state of disturbed flow, which is inversely proportional to the value of time-averaged WSS vector, as shown in Eq. (10) [22]. The calculations of above parameters are as follows:

$$TAWSS = \frac{1}{T} \int_0^T |wss_i| dt \quad (8)$$

$$OSI = \frac{1}{2} \left\{ 1 - \frac{\left| \int_0^T wss_i dt \right|}{\int_0^T |wss_i| dt} \right\} \quad (9)$$

$$RRT = \frac{1}{(1 - 2 \times OSI) \times TAWSS} = \frac{1}{\frac{1}{T} \left| \int_0^T wss_i dt \right|} \quad (10)$$

In three formulas, wss_i is the instantaneous tangential stress vector of the vessel wall caused by the blood flow and T is the calculation period.

In the study of cardiovascular biomechanics, it has been found that abnormal WSS can lead to the damage of endothelial cells. In addition, the long-term relative retention of blood represented by abnormally high OSI and RRT will aggravate the damage of endothelial cells, which may eventually develop into blood cell damage or atherosclerosis, triggering stroke. Therefore, we can evaluate the influence of blood pumps on hemodynamics based on the above parameters.

3 Results

3.1 Flow Field

The flow field obtained from transient simulation that reaches the stable state is basically consistent with that obtained from the steady simulation. Given that the simulation was set to transient solution with steady boundary conditions, and the total calculation time is 0.05 s, we

selected the calculation result at 0.04 s as the steady state for flow field analysis, as shown in Fig. 4. The blue line indicates the inflow from the inferior cava, and the red line indicates the inflow from the superior cava. Fig. 4 shows that the inflow from the inferior cava mainly enters the RPA, while the inflow from superior cava mainly enters the LPA. The streamlines show that there is a certain vortex in the connecting area of the axial flow pump and TCPC. In the flow field of Pump-TCPC with diffuser, the secondary flow in IVC gradually weakens and the streamlines are gradually orthogonal to the cross section of vessel. However, in the flow field of Pump-TCPC without diffuser, blood flow always exhibits vortex characteristics when passing through IVC. It is not until the anastomosis of the IVC and the pulmonary artery that regular blood flow appears and the secondary flow weakens.

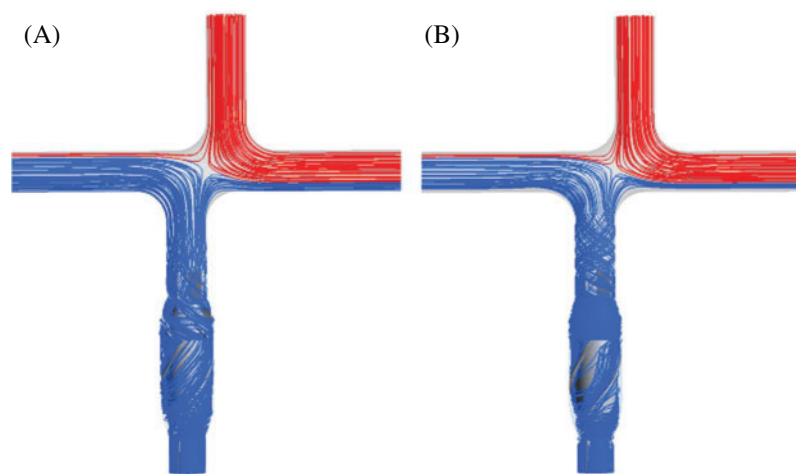


Figure 4: The flow field in two Pump-TCPC. (A) shows the flow field in Pump-TCPC with diffuser when the rotation speed of the blood pump is 4000 RPM, (B) shows the flow field in Pump-TCPC without diffuser when the rotation speed of the blood pump is 10000 RPM

In addition, it can be observed that the streamlines in the LPA and RPA in Fig. 4B are slightly sparser than that in the LPA and RPA in Fig. 4A. It shows that the fluid in the Pump-TCPC without diffuser has a certain hysteresis compared with the fluid in the Pump-TCPC with diffuser, which is mainly distributed in the diffuser and the connecting area of the axial flow pump and TCPC. There is a certain area of low flow velocity in the crossing part of the TCPC. According to Ryu et al. [23], the offset of the SVC and IVC, which is about equal to the diameter of blood vessel, can effectively prevent the blood flow of the SVC and IVC from colliding, and reduce energy loss. Whether the existence of this low-velocity region will have a significant impact on local hemodynamic parameters will be discussed in the following analysis. Overall, the flow field in Pump-TCPC with diffuser is more stable than that in Pump-TCPC without diffuser.

3.2 Wall Shear Stress

We selected the results of ten consecutive saving steps after the flow field reached stable state to calculate TAWSS, OSI and RRT. WSS on blood vessels is normal about 1.5 Pa [23], long-term abnormally high or extremely low shear stress will cause lesions on the vessel wall. The distribution of TAWSS is plotted in a range of 0 to 3 Pa, as shown in Fig. 5. There are abnormal TAWSS areas in both the outlet area of the axial flow blood pump and the crossing

anastomosis in TCPC. The TAWSS is abnormally high in the outlet area of the axial flow blood pump in Pump-TCPC without diffuser, this abnormality is more obvious, more widely distributed and extends to the vicinity of the anastomosis of IVC and pulmonary artery, which is consistent with the secondary flow distribution in the flow field. However, the TAWSS is extremely low in the anastomotic region of TCPC, and the low TAWSS region in the Pump-TCPC without diffuser is smaller than that in the Pump-TCPC with diffuser. Combined with the streamlines in Fig. 4, we estimated that the vortex flow can decrease the area of the low TAWSS.

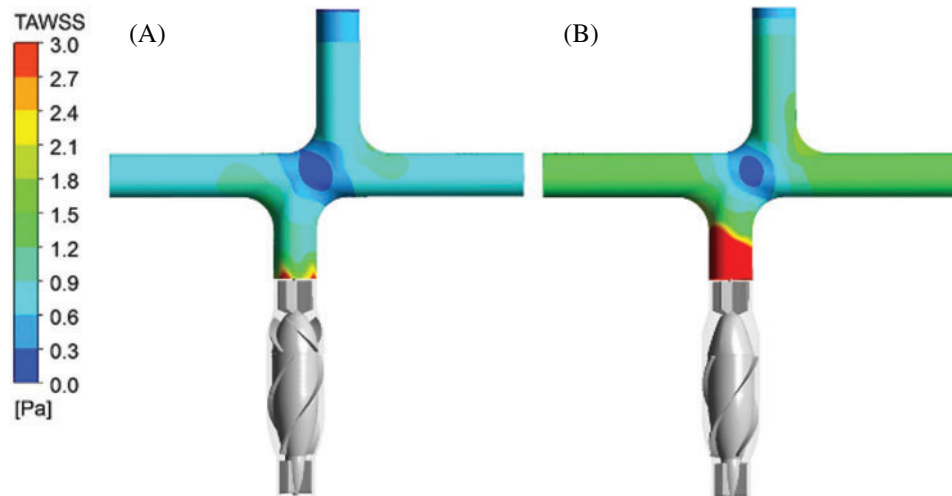


Figure 5: The TAWSS distribution on the wall of TCPC. (A) shows the TAWSS distribution on the wall of TCPC when the rotation speed of the blood pump with diffuser is 4000 RPM, (B) shows the TAWSS distribution on the wall of TCPC when the rotation speed of the blood pump without diffuser is 10000 RPM

3.3 Oscillatory Shear Index

It is generally believed that there will be hemodynamic abnormality in areas with OSI higher than 0.2 [24]. As it can be seen from Fig. 6, the high OSI region is mainly concentrated in the connecting area of the axial flow pump and TCPC, and it is larger in Pump-TCPC without diffuser. The swirling and reversal flow in this region cause the direction of the shear stress on the wall constantly changing, resulting in the high OSI. By contrast, there is no obvious abnormality in the anastomotic region of TCPC. Combined with Fig. 5, it can be seen that high TAWSS appears in areas with high OSI. This situation verifies that the pump without diffuser will result in a larger oscillation area, which will adversely affect the vessel wall. Since the OSI values in both models are small, the hysteresis of the fluid in the TCPC cannot be clearly expressed by OSI, a further explanation will be given by the analysis of RRT.

3.4 Relative Residence Time

RRT is a dimensionless parameter, which combines TAWSS and OSI to represent the hysteresis of the flow field near the vessel wall and the accumulation of the shear effect on vascular endothelial cells. The distribution of RRT in two Pump-TCPC model is shown in Fig. 7. In the crossing anastomosis in TCPC, an obvious region with abnormally high RRT can be observed. Combined with the lower TAWSS in this region, it can be obtained that there is a higher risk of

fluid stagnation in this region. Meanwhile, comparison of Figs. 7A and 7B shows the advantage of non-diffuser model in reducing the fluid stagnation in the low velocity region. Based on the analysis of the flow field and TAWSS, we can see that the high-speed vortex flow in the Pump-TCPC without diffuser decreases the area of the low TAWSS region, and the fluid stagnation is improved. There is no abnormality in the RRT in the connection area between the axial flow blood pump and IVC, the hysteresis effect is not significant because the blood flow velocity is relatively fast.

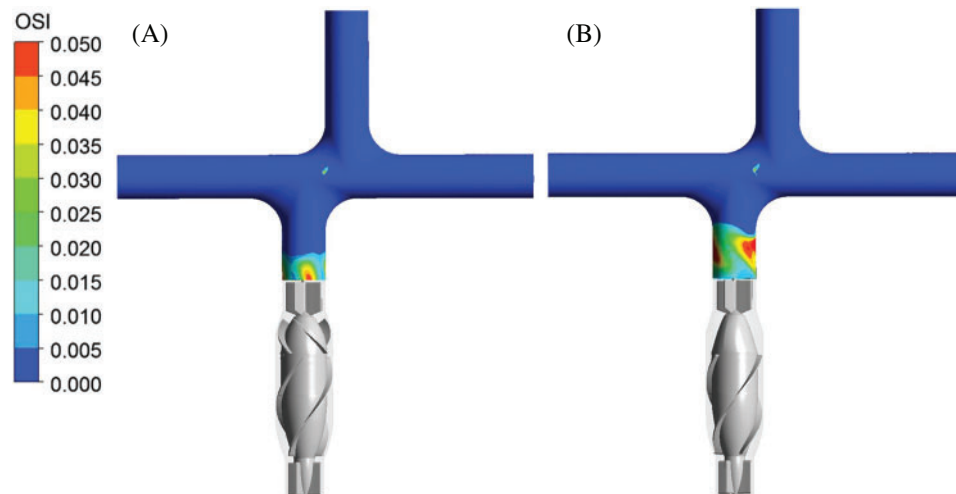


Figure 6: The OSI distribution on the wall of TCPC. (A) shows the OSI distribution on the wall of TCPC when the rotation speed of the blood pump with diffuser is 4000 RPM, (B) shows the OSI distribution on the wall of TCPC when the rotation speed of the blood pump without diffuser is 10000 RPM

4 Discussion

Based on the above analysis, it can be obtained that the abnormal hemodynamic parameters on the Pump-TCPC models mainly appear in the outlet area of the axial flow blood pump and the crossing anastomosis in TCPC. TAWSS, OSI and RRT can effectively characterize the shear effect of the local blood flow on the vessel wall, the complexity of the direction changes of the shear stress and the long-term cumulative effect of the shear stress. In the Pump-TCPC without diffuser, the high-speed swirling flow causes abnormal TAWSS and high OSI on the vessel wall in the outlet area of the axial flow blood pump, but it can decrease the area with abnormally TAWSS and RRT in anastomosis of TCPC. Further analysis of Figs. 5–7 shows that the average TAWSS and average OSI of the vessel wall are higher in Pump-TCPC without diffuser, while the difference in average RRT is not significant. Therefore, it can be concluded that the Pump-TCPC with diffuser has less damage on endothelial cells of vessel wall and lower risk of thrombosis formation than Pump-TCPC without diffuser.

High-speed swirling flow can weaken the fluid hysteresis in the region with extremely low shear stress. According to Zhang et al. [25], swirling flow is a normal physiological phenomenon in the human circulatory system. For example, the blood flow from the left ventricle to the aortic arch is swirling flow. Liu et al. [26] found that swirling flow may be beneficial to the protection

of the inner wall of the artery and the repair of vascular endothelial cells injury. In this study, the reduction in area with extremely low TAWSS and abnormally high RRT due to the swirling flow is consistent with this finding. Therefore, during the construction of Pump-TCPC structure, appropriate swirling flow is beneficial to improve the abnormal hemodynamic environment and protect the inner wall of the blood vessel. The research on the swirling flow for the power-assisted Fontan circulation will be carried out in the future.

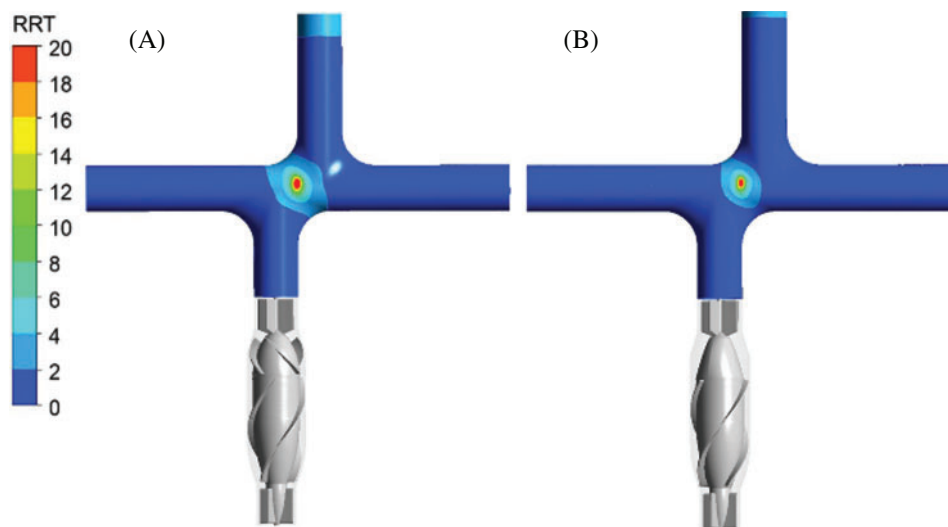


Figure 7: RRT distribution on the wall of TCPC. (A) shows the RRT distribution on the wall of TCPC when the rotation speed of the blood pump with diffuser is 4000 RPM, (B) shows the RRT distribution on the wall of TCPC when the rotation speed of the blood pump without diffuser is 10000 RPM

5 Conclusion

In this study, the difference of the flow field and hemodynamic parameters TAWSS, OSI, RRT in Pump-TCPC with and without diffuser was analyzed by numerical modeling and simulation, and the following conclusions were obtained:

- (1) In the Pump-TCPC with diffuser, the vorticity of the flow field and the secondary flow area are weaker and smaller than those in the Pump-TCPC without diffuser.
- (2) In the Pump-TCPC without diffuser, high-speed swirling flow causes abnormal TAWSS and high OSI in the connecting area of the axial flow blood pump and TCPC. But it can improve TAWSS and RRT in the anastomotic region in TCPC.
- (3) The Pump-TCPC with diffuser has better flow field stability, less damage on endothelial cell of vessel wall, and lower risk of vascular injury and thrombosis formation than that without diffuser.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

References

1. Christianson, A., Howson, C. P., Modell, B. (2006). March of dimes global report on birth defects: The hidden toll of dying and disabled children. <https://www.marchofdimes.org/global-report-on-birth-defects-the-hidden-toll-of-dying-and-disabled-children-full-report.pdf>.
2. Pekkan, K., De Zélicourt, D., Ge, L., Sotiropoulos, F., Frakes, D. et al. (2005). Physics-driven CFD modeling of complex anatomical cardiovascular flows? A TCPC case study. *Annals of Biomedical Engineering*, 33(3), 284–300. DOI 10.1007/s10439-005-1731-0.
3. Pekkan, K., Dasi, L. P., De Zélicourt, D., Sundareswaran, K. S., Fogel, M. A. et al. (2009). Hemodynamic performance of stage-2 univentricular reconstruction: Glenn vs. hemi-Fontan templates. *Annals of Biomedical Engineering*, 37(1), 50–63. DOI 10.1007/s10439-008-9591-z.
4. De Zélicourt, D. A., Marsden, A., Fogel, M. A., Yoganathan, A. P. (2010). Imaging and patient-specific simulations for the Fontan surgery: Current methodologies and clinical applications. *Progress in Pediatric Cardiology*, 30(1–2), 31–44. DOI 10.1016/j.ppedcard.2010.09.005.
5. Calvaruso, D. F., Rubino, A., Ocello, S., Salviato, N., Guardì, D. et al. (2008). Bidirectional Glenn and antegrade pulmonary blood flow: Temporary or definitive palliation? *Annals of Thoracic Surgery*, 85(4), 1389–1396. DOI 10.1016/j.athoracsur.2008.01.013.
6. Throckmorton, A. L., Lopez-Isaza, S., Downs, E. A., Chopski, S. G., Gangemi, J. J. et al. (2013). A viable therapeutic option: Mechanical circulatory support of the failing Fontan physiology. *Pediatric Cardiology*, 34(6), 1357–1365. DOI 10.1007/s00246-013-0649-9.
7. Sundareswaran, K. S., Pekkan, K., Dasi, L. P., Whitehead, K., Sharma, S. et al. (2008). The total cavopulmonary connection resistance: A significant impact on single ventricle hemodynamics at rest and exercise. *American Journal of Physiology-Heart and Circulatory Physiology*, 295(6), H2427–H2435. DOI 10.1152/ajpheart.00628.2008.
8. Farahmand, M., Kavarana, M. N., Kung, E. O. (2020). Risks and benefits of using a commercially available ventricular assist device for failing Fontan cavopulmonary support: A modeling investigation. *IEEE Transactions on Biomedical Engineering*, 67(1), 213–219. DOI 10.1109/TBME.2019.2911470.
9. Migliavacca, F., Balossino, R., Pennati, G., Dubini, G., Hsia, T. et al. (2006). Multiscale modelling in biofluidynamics: Application to reconstructive paediatric cardiac surgery. *Journal of Biomechanics*, 39(6), 1010–1020. DOI 10.1016/j.jbiomech.2005.02.021.
10. Bhavsar, S. S., Moskowitz, W. B., Throckmorton, A. L. (2010). Interaction of an idealized cavopulmonary circulation with mechanical circulatory assist using an intravascular rotary blood pump. *Artificial Organs*, 34(10), 816–827. DOI 10.1111/j.1525-1594.2010.01080.x.
11. Farahmand, M., Kavarana, M. N., Trusty, P. M., Kung, E. O. (2020). Target flow-pressure operating range for designing a failing Fontan cavopulmonary support device. *IEEE Transactions on Biomedical Engineering*, 67(10), 2925–2933. DOI 10.1109/TBME.2020.2974098.
12. Throckmorton, A. L., Lim, D. S., McCulloch, M. A., Jiang, W., Song, X. et al. (2005). Computational design and experimental performance testing of an axial-flow pediatric ventricular assist device. *ASAIO Journal*, 51(5), 629–635. DOI 10.1097/01.mat.0000177541.53513.a8.
13. Liu, X., Cai, Y., Jia, B., Wang, S., Ding, G. (2018). Numerical analyses of idealized total cavopulmonary connection physiologies with single and bilateral superior vena cava assisted by an axial blood pump. *Computer Modeling in Engineering & Sciences*, 116(2), 215–228. DOI 10.31614/cmcs.2018.04158.
14. Ou, C., Huang, W., Yuen, M. M., Qian, Y. (2016). Hemodynamic modeling of leukocyte and erythrocyte transport and interactions in intracranial aneurysms by a multiphase approach. *Journal of Biomechanics*, 49(14), 3476–3484. DOI 10.1016/j.jbiomech.2016.09.017.

15. Fraser, K. H., Zhang, T., Taskin, M. E., Griffith, B. P., Wu, Z. J. (2012). A quantitative comparison of mechanical blood damage parameters in rotary ventricular assist devices: Shear stress, exposure time and hemolysis index. *Journal of Biomechanical Engineering*, 134(8), 1–11. DOI 10.1115/1.4007092.
16. Pekkan, K., Frakes, D., De Zélicourt, D., Lucas, C. W., Parks, W. J. et al. (2005). Coupling pediatric ventricle assist devices to the Fontan circulation: Simulations with a lumped-parameter model. *ASAIO Journal*, 51(5), 618–628. DOI 10.1097/01.mat.0000176169.73987.0d.
17. Throckmorton, A. L., Patel-Raman, S. M., Fox, C. S., Bass, E. J. (2016). Beyond the VAD: Human factors engineering for mechanically assisted circulation in the 21st century. *Artificial Organs*, 40(6), 539–548. DOI 10.1111/aor.12600.
18. Launder, B. E., Spalding, D. B. (1974). The numerical computation of turbulent flows. *Computer Methods in Applied Mechanics and Engineering*, 3(2), 269–289. DOI 10.1016/0045-7825(74)90029-2.
19. Xiang, J., Natarajan, S. K., Tremmel, M., Ma, D., Mocco, J. et al. (2011). Hemodynamic-morphologic discriminants for intracranial aneurysm rupture. *Stroke*, 42(1), 144–152. DOI 10.1161/STROKEAHA.110.592923.
20. He, X., Ku, D. N. (1996). Pulsatile flow in the human left coronary artery bifurcation: Average conditions. *Journal of Biomechanical Engineering*, 118(1), 74–82. DOI 10.1115/1.2795948.
21. Himburg, H. A., Grzybowski, D. M., Hazel, A. L., LaMack, J. A., Li, X. et al. (2004). Spatial comparison between wall shear stress measures and porcine arterial endothelial permeability. *American Journal of Physiology-Heart and Circulatory Physiology*, 286(5), H1916–H1922. DOI 10.1152/ajpheart.00897.2003.
22. Lee, S., Antiga, L., Steinman, D. A. (2009). Correlations among indicators of disturbed flow at the normal carotid bifurcation. *Journal of Biomechanical Engineering*, 131(6), 1–7. DOI 10.1115/1.3127252.
23. Ryu, K., Healy, T. M., Ensley, A. E., Sharma, S., Lucas, C. et al. (2001). Importance of accurate geometry in the study of the total cavopulmonary connection: Computational simulations and in vitro experiments. *Annals of Biomedical Engineering*, 29(10), 844–853. DOI 10.1114/1.1408930.
24. Liu, J. L., Qian, Y., Umezumi, M., Itatani, K., Miyaji, K. et al. (2009). Hemodynamic simulation for congenital heart disease. http://www.cfd.com.au/cfd_conf09/PDFs/211YAN.pdf.
25. Zhang, Z., Fan, Y., Deng, X., Wang, G., Zhang, H. et al. (2008). Simulation of blood flow in a small-diameter vascular graft model with a swirl (spiral) flow guider. *Science in China Series C: Life Sciences*, 51(10), 913–921. DOI 10.1007/s11427-008-0118-5.
26. Liu, X., Sun, A., Fan, Y., Deng, X. (2015). Physiological significance of helical flow in the arterial system and its potential clinical applications. *Annals of Biomedical Engineering*, 43(1), 3–15. DOI 10.1007/s10439-014-1097-2.