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Original article

Effects of systemic ventricular assist combined with fenestration in failing Fontan: A theoretical analysis

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ABSTRACT

Biventricular assist for failing Fontan circulation remains challenging. Because fenestration effectively reduces stressed blood volume and central venous pressure in Fontan patients with increased pulmonary vascular resistance (PVR), systemic ventricular assist device (VAD) combined with fenestration may improve hemodynamics in failing Fontan patients with increased PVR who would require biventricular assist. To validate this hypothesis, we performed a computational hemodynamic simulation of the failing Fontan circulation using a lumped parameter model. We compared hemodynamic variables between the models with and without fenestration while the PVR index was increased sequentially from 3.01 to 6.81 Wood Units m^2. Following VAD initiation and stressed blood volume reduction, central venous pressure was maintained at a lower level in the fenestration models. This positive effect was greater in the model with larger fenestration diameter. However, excessive fenestration caused significant desaturation. In failing Fontan circulation with elevated PVR, systemic VAD combined with fenestration significantly improved hemodynamics.

1. Introduction

In the Fontan circulation, both systemic and pulmonary circulations can be maintained by a single ventricle. This surgically created circulation is a surgical goal for patients with single ventricle physiology [1]. Although survival after Fontan operation has improved over the past five decades due to technical advances and improvements in patient selection and management [2], Fontan failure has become a major clinical problem in the long term. Some patients with Fontan failure may require ventricular assist devices (VADs) while waiting for a heart transplant. However, ventricular assist for failing Fontan patients has been challenging due to the absence of a sub-pulmonary ventricle to maintain pulmonary circulation. We have previously reported that a systemic (left-sided) VAD improves the hemodynamics of Fontan failure caused by systolic or diastolic ventricular dysfunction or atrioventricular valve regurgitation, but not that due to severely elevated pulmonary vascular resistance (PVR) index above 5.0 Wood units m^2 [3]. Patients with elevated PVR may require right-sided or bi-ventricular assist. However, cases in which patients have undergone implantation of a right-sided VAD or bi-VAD are extremely rare in clinical settings.

In patients at high risk of Fontan failure, a fenestration is often created [4–6]. A fenestration is a small communication between the conduit of the total cavopulmonary connection and the single atrium, and has been reported to increase single ventricular preload and improve cardiac index. Our previous simulation study showed that fenestration effectively increased ventricular preload and improved cardiac index only in a Fontan circulation model with elevated PVR index [7]. Therefore, a combination of systemic VAD and fenestration (Fig. 1) may effectively improve the hemodynamics of Fontan failure with elevated PVR. To validate this hypothesis, we performed a computational simulation of Fontan circulation using a lumped parameter model.

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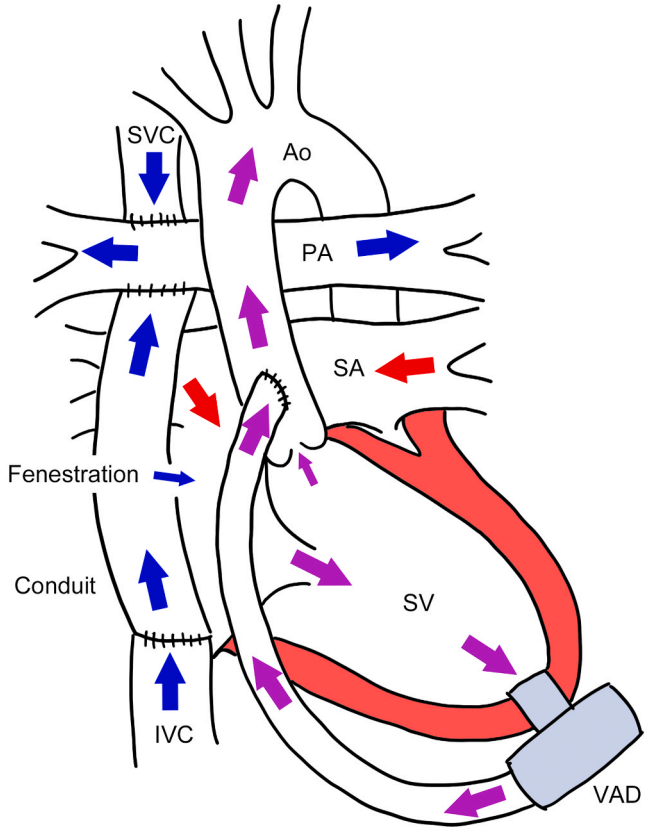

Fig. 1. Illustration of systemic ventricular assist with fenestration in the Fontan circulation. Ao, aorta; PA, pulmonary artery; SVC, superior vena cava; IVC, inferior vena cava; SA, single atrium; SV, single ventricle; VAD, ventricular assist device.

2. Materials and methods

The electrical analog of the simulated cardiovascular system is shown in Fig. 2. Details of our simulation model have been described in our previous reports [3, 7–9].

2.1. Heart

The single atrial or single ventricular chamber is each represented by the time-varying elastance model [10]. The instantaneous change in volume [dV(t)/dt] of the atrial or ventricular chamber is calculated by the difference between its total inflow (Q_{in}) and outflow (Q_{out}).

$$\frac{dV(t)}{dt} = \Sigma Q_{in}(t) - \Sigma Q_{out}(t)$$

The instantaneous pressure [P(t)] of each chamber is described by the sum of end-diastolic pressure (P_{ed}) and the developed pressure (difference between end-systolic pressure (P_{es}) and P_{ed}) scaled by normalized elastance curve [e(t)].

$$P(t) = [P_{es}(V(t)) - P_{ed}(V(t))] \bullet e(t) + P_{ed}(V(t))$$

where t is the time from the start of systole.

The functions P_{es} and P_{ed} are described as:

$$P_{es}(V(t)) = E_{es} \bullet [V(t) - V_0]$$

$$P_{ed}(V(t)) = A \bullet [\exp(B \bullet (V(t) - V_0)) - 1]$$

where E_{es} is end-systolic elastance, V_0 is the volume when end-systolic pressure is 0 mmHg, and A and B are constants.

The function e(t) is described as:

$$e(t) = \begin{cases} 0.5\left[1 - \cos\left(\frac{\pi t}{T_{es}}\right)\right] & (0 \le t < 2T_{es}) \\ 0 & (2T_{es} \le t < T_c) \end{cases}$$

where T_{es} and T_c are the durations of systole and cardiac cycle, respectively.

The atrioventricular or aortic valve is represented as an ideal diode with a serial resistor (Fig. 2). The parameters E_{es}, V_0, A, B, and T_{es} are different between the atrial and ventricular chambers (Table 1) [3, 7–9, 11].

2.2. Vascular systems

Systemic and pulmonary vasculatures are represented by the modified Windkessel model with three linear resistances and two capacitances as shown in Fig. 2. Each vasculature has a characteristic impedance (R_c), an arterial resistance (R_a), a resistance of venous return (R_v), an arterial capacitance (C_a), and a venous capacitance (C_v) (Table 1) [3, 8, 9]. These obey the laws of electrical circuit theory, such as Ohm's law.

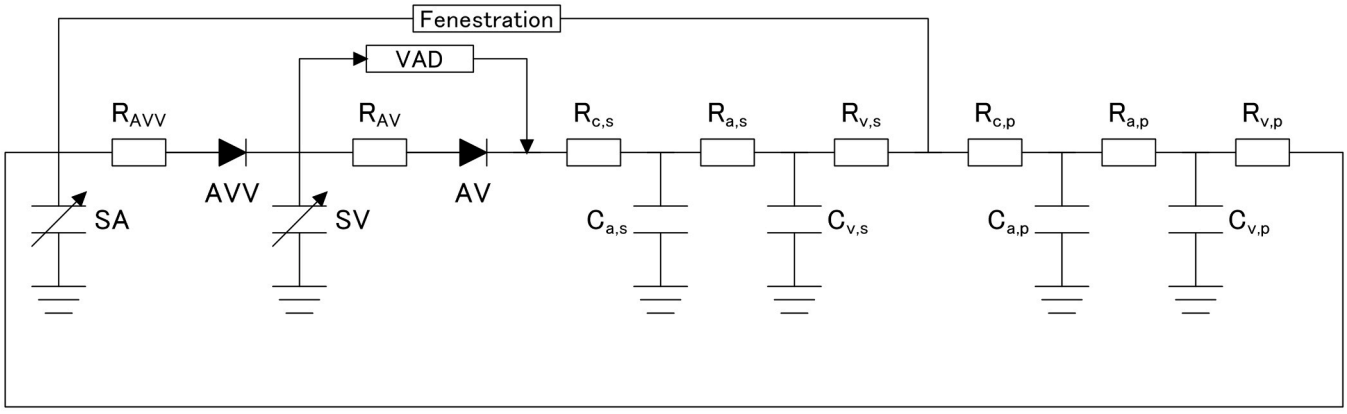

Fig. 2. Electrical analog of the cardiovascular system of a simulated model of Fontan circulation with ventricular assist device and fenestration. SA, single atrium; SV, single ventricle; AVV, atrioventricular valve; AV, aortic valve; VAD, ventricular assist device; R_{AVV} and R_{AV}, atrioventricular and aortic valvular resistances, respectively; $R_{c,s}$ and $R_{c,p}$, characteristic impedances of systemic and pulmonary arteries, respectively; $R_{a,s}$ and $R_{a,p}$, systemic and pulmonary arterial resistances, respectively; $R_{v,s}$ and $R_{v,p}$, systemic and pulmonary venous resistances, respectively; $C_{a,s}$ and $C_{a,p}$, systemic and pulmonary arterial capacitances, respectively; $C_{v,s}$ and $C_{v,p}$, systemic and pulmonary venous capacitances, respectively.

Table 1
Parameters used in hemodynamic simulation.

Heart model		
Heart rate, beats/min	75	
Duration of cardiac cycle (T_c), ms	800	
Time advance of atrial systole, ms	16	
	Ventricle	Atrium
Time to end systole (T_{es}), ms	200	120
End-systolic elastance (E_{es}), mmHg/mL	1.0	0.5
Scaling factor of EDPVR (A), mmHg	0.35	0.44
Exponent for EDPVR (B), mL^{-1}	0.033	0.049
Unstressed volume (V_0), mL	0	5
Aortic valvular resistance (R_{AV}), mmHg s mL^{-1}	0.001	
Atrioventricular valvular resistance (R_{AVV}), mmHg s mL^{-1}	0.001	
Vasculature model	Systemic circulation	Pulmonary circulation
Arterial resistance (R_a), mmHg s mL^{-1}	0.7	0.06
Characteristic impedance (R_c), mmHg s mL^{-1}	0.03	0.02
Venous resistance (R_v), mmHg s mL^{-1}	0.015	0.015
Arterial capacitance (C_a), mL/mmHg	1.32	13
Venous capacitance (C_v), mL/mmHg	70	8
Ventricular assist device model		
K_A, mmHg/rpm^2	3.45×10^{-6}	
K_B, mmHg L/min/rpm	-5.9×10^{-5}	
K_C, mmHg L^2/rpm^2	-1.45	
Fenestration model		
Diameter (D), mm	4.0	

2.3. Fenestration and ventricular assist device

Using a simplified Bernoulli equation [7], volumetric flow across fenestration (Q_f) was calculated as a function of the pressure difference between central venous pressure (equal to pulmonary arterial pressure in this model) and single atrial pressure (ΔP_f):

$$\Delta P_f = \frac{64 Q_f^{\,2}}{\pi^2 D^4}$$

where D is the diameter of fenestration.

The relation between pump flow (Q_{pump}) and pressure head (ΔP) of VAD is described as a non-linear function [3, 12]:

$$\Delta P = K_A \bullet r^2 + K_B \bullet r \bullet Q_{pump} + K_C \bullet \left(Q_{pump}\right)^2$$

where r is the rotational frequency and K_A, K_B, and K_C are constant (Table 1).

2.4. Stressed blood volume

Stressed blood volume is calculated from the sum of atrial and ventricular chamber volumes and volumes of all the capacitances.[3,8]

2.5. Arterial and venous oxygen saturation

The relation between arterial and venous oxygen saturation (SaO_2 and SvO_2) is calculated from the following equations:

$$SaO_2 \bullet \left(Q_s + Q_{pump}\right) = S_{PV}O_2 \bullet Q_p + SvO_2 \bullet Q_f$$

$$CVO_2 \bullet BSA = 13.4 \bullet Hb \bullet \left(Q_s + Q_{pump}\right) \bullet \left(SaO_2 - SvO_2\right)$$

where Q_s and Q_p are systemic flow through the aortic valve and pulmonary flow, respectively, $S_{PV}O_2$ is pulmonary venous oxygen saturation (0.97), CVO_2 is whole body oxygen consumption (185 mL O_2 min^{-1} m^{-2}), BSA is body surface area (1.9 m^2), and Hb is hemoglobin concentration (16.0 g/dL).

2.6. Protocol

First, we examined the effects of VAD on the failing Fontan circulation without fenestration. To simulate Fontan failure with systolic ventricular dysfunction, E_{es} of the single ventricle was decreased from 3.0 (normal value) to 1.0 mmHg/mL. Next, ventricular assist was introduced at a rotational frequency of 4000 rpm. Stressed blood volume was then reduced to achieve single ventricular pressure and volume near zero but above zero.

Before the initiation of VAD, the pulmonary arterial resistance ($R_{a,p}$) was increased sequentially from 0.06 to 0.18 mmHg s mL^{-1} (PVR index: 3.01–6.81 Wood Units m^2). At each $R_{a,p}$, mean arterial pressure was controlled to approximately 58.4 mmHg by adjusting the stressed blood volume, and hemodynamic variables comprising mean arterial pressure, central venous pressure, cardiac index, and arterial oxygen saturation were calculated. Next, at each $R_{a,p}$, VAD was initiated at a rotational frequency of 4000 rpm, and the hemodynamic variables were again calculated. After initiation of VAD, the stressed blood volume was reduced to achieve near-zero ventricular pressure and volume, with calculation of the hemodynamic variables.

Using the same protocol, the effects of VAD with 4.0 mm fenestration on the failing Fontan circulation model were also studied. For comparison, simulations were performed with 3.0 mm and 5.0 mm fenestration models.

All simulations were performed on MATLAB/Simulink R2022b (MathWorks Inc., Natick, MA, USA).

3. Results

Baseline hemodynamic variables in the failing Fontan circulation model with systolic ventricular dysfunction are shown in Table 2. Simulated hemodynamic variables when PVR index was increased sequentially in the non-fenestration model and in the 4.0 mm fenestration model are shown in Tables 3 and 4, respectively. In addition, the results obtained in the 3.0 mm and 5.0 mm fenestration models are shown in Tables 5 and 6, respectively.

When the PVR index was 3.01 Wood Units m^2 in the failing Fontan circulation model without fenestration, initiation of VAD at 4000 rpm immediately increased mean arterial pressure and cardiac index (94.5 mmHg and 3.20 L/min/m^2, respectively) compared to those before ventricular assist (58.4 mmHg and 1.66 L/min/m^2, respectively). However, central venous pressure remained almost unchanged even after VAD was started. Only when stressed blood volume was reduced from 2000 to 1050 mL did the central venous pressure decrease from 19.2 mmHg before ventricular assist to 10.0 mmHg (Table 3).

Even when PVR index was increased gradually from 3.01 to 6.81 Wood Units m^2, VAD improved mean arterial pressure and cardiac index immediately after its initiation (Table 3). However, as PVR index increased, it became more difficult to maintain near zero ventricular pressure/volume by reducing the stressed blood volume. When the PVR index was 6.81 Wood Units m^2, a stressed blood volume of 2070 mL was

Table 2
Simulated baseline hemodynamic variables of the failing Fontan circulation model with systolic ventricular dysfunction.

Variables	
Heart rate, bpm	75
Systolic arterial pressure, mmHg	75.8
Diastolic arterial pressure, mmHg	44.8
Mean arterial pressure, mmHg	58.4
Central venous pressure, mmHg	19.2
Cardiac index, L/min/m^2	1.66
Arterial oxygen saturation, %	97.0
Systemic vascular resistance index, Wood Units m^2	23.6
Pulmonary vascular resistance index, Wood Units m^2	3.01
Stressed blood volume, mL	2000

Table 3
Effects of systemic ventricular assist on hemodynamic variables when PVRI was sequentially varied in the failing Fontan circulation model without fenestration.

PVRI, WU m^2	3.01			3.96			4.91			5.86			6.81		
RF, rpm	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000
MAP, mmHg	58.4	94.5	85.6	58.4	95.6	88.6	58.4	96.8	91.7	58.4	98.0	94.7	58.4	99.3	97.8
CVP, mmHg	19.2	18.9	10.0	20.1	20.0	13.0	21.0	21.2	16.1	21.9	22.4	19.1	22.6	23.7	22.1
CI, L/min/m^2	1.66	3.20	3.20	1.62	3.20	3.20	1.58	3.20	3.20	1.55	3.20	3.20	1.51	3.20	3.20
SaO_2, %	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0	97.0
SBV, mL	2000	2000	1050	2070	2070	1300	2140	2140	1560	2200	2200	1810	2260	2260	2070

PVRI, pulmonary vascular resistance index; WU, Wood Units; RF, rotational frequency; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; SaO_2, arterial oxygen saturation; SBV, stressed blood volume.

Table 4
Effects of systemic ventricular assist on hemodynamic variables when PVRI was sequentially varied in the failing Fontan circulation model with 4.0 mm fenestration.

PVRI, WU m^2	3.01			3.96			4.91			5.86			6.81		
RF, rpm	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000
MAP, mmHg	58.3	93.7	83.9	58.3	94.5	86.1	58.4	95.3	88.2	58.3	96.0	90.3	58.4	96.7	92.3
CVP, mmHg	18.5	18.1	8.3	19.2	18.9	10.5	19.8	19.7	12.6	20.2	20.4	14.7	20.8	21.1	16.7
CI, L/min/m^2	1.69	3.20	3.20	1.66	3.20	3.20	1.64	3.20	3.20	1.61	3.20	3.20	1.59	3.20	3.20
SaO_2, %	84.0	91.6	91.3	80.9	90.5	90.4	77.9	89.6	89.5	74.8	88.8	88.7	71.7	88.0	88.0
SBV, mL	1950	1950	900	2000	2000	1090	2050	2050	1270	2080	2080	1450	2120	2120	1610

PVRI, pulmonary vascular resistance index; WU, Wood Units; RF, rotational frequency; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; SaO_2, arterial oxygen saturation; SBV, stressed blood volume.

Table 5
Effects of systemic ventricular assist on hemodynamic variables when PVRI was sequentially varied in the failing Fontan circulation model with 3.0 mm fenestration.

PVRI, WU m^2	3.01			3.96			4.91			5.86			6.81		
RF, rpm	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000
MAP, mmHg	58.3	94.0	84.6	58.4	95.0	87.2	58.3	95.9	89.7	58.4	96.8	92.0	58.3	97.7	94.5
CVP, mmHg	18.8	18.4	9.0	19.6	19.4	11.6	20.3	20.3	14.0	20.9	21.2	16.4	21.4	22.0	18.9
CI, L/min/m^2	1.68	3.20	3.20	1.64	3.20	3.20	1.61	3.20	3.20	1.59	3.20	3.20	1.56	3.20	3.20
SaO_2, %	89.9	94.0	93.9	88.2	93.5	93.4	86.6	93.0	93.0	84.9	92.6	92.6	83.1	92.3	92.2
SBV, mL	1970	1970	960	2030	2030	1180	2080	2080	1390	2130	2130	1590	2170	2170	1800

PVRI, pulmonary vascular resistance index; WU, Wood Units; RF, rotational frequency; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; SaO_2, arterial oxygen saturation; SBV, stressed blood volume.

Table 6
Effects of systemic ventricular assist on hemodynamic variables when PVRI was sequentially varied in the failing Fontan circulation model with 5.0 mm fenestration.

PVRI, WU m^2	3.01			3.96			4.91			5.86			6.81		
RF, rpm	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000	0	4000	4000
MAP, mmHg	58.3	93.4	83.1	58.3	94.0	84.9	58.4	94.7	86.7	58.4	95.2	88.3	58.3	95.7	89.9
CVP, mmHg	18.3	17.8	7.5	18.8	18.4	9.3	19.3	19.1	11.1	19.7	19.6	12.7	20.0	20.1	14.3
CI, L/min/m^2	1.70	3.20	3.20	1.68	3.20	3.20	1.66	3.20	3.20	1.64	3.20	3.20	1.62	3.20	3.20
SaO_2, %	75.9	88.2	87.6	70.8	86.3	86.0	65.8	84.7	84.5	60.9	83.2	83.1	55.9	81.9	81.8
SBV, mL	1930	1930	840	1970	1970	990	2010	2010	1140	2040	2040	1280	2060	2060	1410

PVRI, pulmonary vascular resistance index; WU, Wood Units; RF, rotational frequency; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; SaO_2, arterial oxygen saturation; SBV, stressed blood volume.

required to maintain the minimum ventricular pressure and volume above zero, and an extremely high central venous pressure of 22.1 mmHg persisted even after the initiation of VAD (Table 3).

In the failing Fontan circulation model with 4.0 mm fenestration, initiation of VAD also immediately improved mean arterial pressure and cardiac index (Table 4). When the PVR index was 3.01 Wood Units m^2, the initiation of VAD at 4000 rpm increased mean blood pressure from 58.3 to 93.7 mmHg, cardiac index from 1.69 to 3.20 L/min/m^2, and arterial oxygen saturation from 84.0 % to 91.6 %. The reduction in stressed blood volume from 1950 to 900 mL significantly decreased central venous pressure from 18.5 mmHg before ventricular assist to 8.3 mmHg, while cardiac index was maintained (Table 4).

A gradual increase in PVR index from 3.01 W to 6.81 Wood Units m^2 significantly decreased arterial oxygen saturation before initiation of VAD (84.0 % at PVR index of 3.01 Wood Units m^2 to 71.7 % at PVR index of 6.81 Wood Units m^2; Table 4). However, once ventricular assist was initiated, the beneficial effects of ventricular assist on mean arterial pressure, cardiac index, and arterial oxygen saturation remained almost unchanged with increase in PVR index. The presence of fenestration allowed efficient reduction of the stressed blood volume even under high PVR index condition. When the PVR index was 6.81 Wood Units m^2, the stressed blood volume was reduced from 2120 mL before VAD initiation to 1610 mL, and the central venous pressure also decreased from 20.8 mmHg before initiation to 16.7 mmHg (Table 4).

When hemodynamic variables were compared between the models with and without fenestration under ventricular assist with sufficient reduction in stressed blood volume, the central venous pressure (Fig. 3A) and stressed blood volume (Fig. 3B) were significantly lower in the models with fenestration than in the non-fenestration model. The presence of 4.0 mm fenestration reduced arterial oxygen saturation to approximately 90 % even under ventricular assist (Fig. 3C). When comparing the 4.0 mm fenestration with the 3.0 mm and 5.0 mm

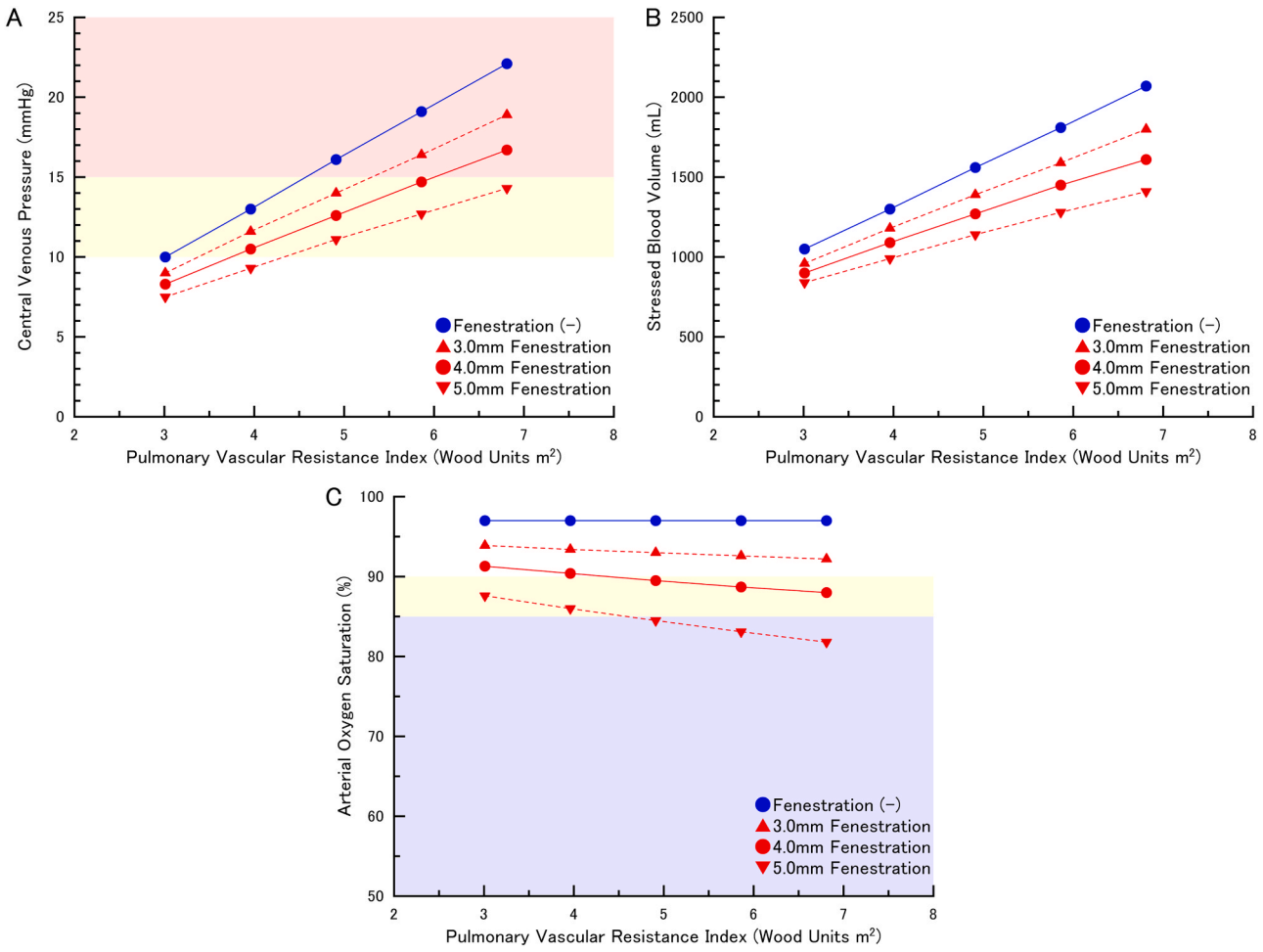

Fig. 3. The relationship between pulmonary vascular resistance index and central venous pressure (**A**), stressed blood volume (**B**), and arterial oxygen saturation (**C**) in the failing Fontan models under ventricular assist. Blue circle, model without fenestration; red upright triangle, 3.0 mm fenestration model; red circle, 4.0 mm fenestration model; red inverted triangle, 5.0 mm fenestration model.

fenestration models, fenestration with larger diameter resulted in greater reductions in stressed blood volume and central venous pressure compared to the non-fenestration model (Figs. 3A and 3B), but the larger fenestration also caused significant desaturation (Fig. 3C).

4. Discussion

This simulation study demonstrated that systemic ventricular assist combined with fenestration significantly reduced stressed blood volume and central venous pressure even under the condition of elevated PVR. However, this study also showed that large fenestration of 5 mm has the disadvantage of inducing severe desaturation, which is not ideal in the clinical setting.

4.1. Fontan failure and ventricular assist

Biventricular assist in failing Fontan patients remains a challenging issue due to the difficulties of surgical implantation and separate control of the two pumps [13, 14]. Therefore, it is important to select failing Fontan patients who can be managed appropriately by systemic VAD alone. Our previous study has demonstrated that systemic ventricular assist effectively improves the hemodynamics of Fontan failure due to systemic ventricular dysfunctions, such as systolic and diastolic ventricular dysfunction and atrioventricular valve dysfunction [3]. However, the effectiveness of systemic VADs is reduced under conditions of extremely high PVR. In the case of PVR index $>$ 5.0 Wood Units m^2, a large stressed blood volume is required to maintain pump flow, resulting in an increase in central venous pressure to above 15 mmHg [3]. Because high central venous pressure has been reported to be a significant risk factor for multiple organ dysfunction, including acute kidney injury and liver injury [15–17], right heart support may be an option to consider in such a situation, despite the difficulty of implantation and flow control against systemic VAD.

4.2. Fontan failure and fenestration

The fenestration is surgically created as a modification of the Fontan operation, in which an extracardiac conduit and a single atrium are connected through a small window [18]. Although fenestration is additional procedure in patients at high risk for Fontan failure [4, 19], its efficacy remains controversial [20, 21]. Our previous simulation study has shown that fenestration effectively reduces stressed blood volume and central venous pressure only in Fontan failure with elevated PVR [7]. On the other hand, in Fontan failure with systolic or diastolic ventricular dysfunction or elevated systemic vascular resistance, the effectiveness of fenestration is suboptimal because fenestration only reduces arterial oxygen saturation in these situations.

4.3. Ventricular assist combined with fenestration

Systemic VAD in fenestrated Fontan patients has been described in a few case reports [22, 23]. Tokunaga et al. reported successful conversion

from biventricular VAD to systemic VAD by establishing a fenestrated Fontan-like circulation in a patient with fulminant myocarditis [24]. Considering the results of our previous simulation studies [3, 7], we hypothesized that systemic VAD combined with fenestration may improve hemodynamics even in the failing Fontan circulation with increased PVR. The present study demonstrates that systemic VAD combined with an appropriately sized fenestration reduces stressed blood volume and central venous pressure, and maintains arterial oxygen saturation at approximately 90 % in failing Fontan circulation due to systolic ventricular dysfunction with elevated PVR.

As shown in Tables 3 and 4, the initiation of VAD immediately restored mean arterial pressure and cardiac index in both models with and without fenestration. However, minimum stressed blood volume to maintain minimum ventricular pressure and volume above zero were significantly lower in the fenestration model. When the PVR index was 5.86 Wood Units m^2, the stressed blood volume in the 4.0 mm fenestration model (1450 mL) was 360 mL less than that in the non-fenestration model (1810 mL). This resulted in a significantly lower central venous pressure in the fenestration model (14.7 mmHg) compared to the non-fenestration model (19.1 mmHg). The effectiveness of fenestration depends on its diameter. Larger fenestration, i.e., 5.0 mm or larger, results in greater reductions in stressed blood volume and central venous pressure (Fig. 3A and B). Therefore, patients with higher PVR will require a larger fenestration to maintain an appropriate central venous pressure below 15 mmHg.

One of the biggest disadvantages of fenestration is an increase in right to left shunt, resulting in desaturation [20]. In the fenestration model, arterial oxygen saturation before ventricular assist was significantly lower than that after the initiation of VAD (Table 4). Therefore, the presence of fenestration before VAD implantation will result in remarkable desaturation at the onset of Fontan failure. Arterial oxygen saturation was restored to approximately 90 % immediately after VAD initiation in the 4.0 mm fenestration model (Table 4). Therefore, VAD implantation may be an effective treatment to improve oxygenation in failing Fontan patients with fenestration.

Since larger fenestration results in greater desaturation, as shown in Fig. 3C, the optimal diameter of the fenestration should be determined carefully before creation, based on PVR. The appropriate range of arterial oxygen saturation in fenestrated Fontan patients remains controversial. However, Ko et al. reported that survival and freedom from Fontan failure in fenestrated Fontan patients with median oxygen saturation of 89 % were equivalent to those in Fontan patients without fenestration [20]. When the PVR index was 5.86 Wood Units m^2, the levels of arterial oxygen saturation after stressed blood volume reduction under ventricular assist were 92.6, 88.7, and 83.1 % in the 3.0, 4.0 mm, and 5.0 mm fenestration models, respectively. Then, the central venous pressures were 16.4, 14.7, and 12.7 mmHg, respectively (Tables 4, 5 and 6). Therefore, a 4.0 mm fenestration may be optimal for the present simulation condition (Fig. 4). Although more research is needed, patient-specific hemodynamic simulation before the creation of fenestration may be helpful for determining the optimal diameter.

In this study, we used the parameters of the normal left ventricle for end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively) of the single ventricle model. However, the pathophysiology of single ventricles varies widely from patient to patient. For patients with the right heart-type single ventricle such as those with hypoplastic left heart syndrome, the use of parameters of right ventricular ESPVR and EDPVR may be required. Furthermore, a mixed model of the left and right ventricles may be necessary for patients with large ventricular septal defect. Therefore, a patient-specific simulation is necessary in order to determine the optimal size of the fenestration.

Even in patients with optimal size of fenestration, spontaneous closure of the fenestration may become a problem. Gorla et al. demonstrated that 22 % of patients with fenestrated Fontan procedure experienced spontaneous closure of the fenestration [25]. They also reported that elevated preoperative PVR is predictive of fenestration persistence.

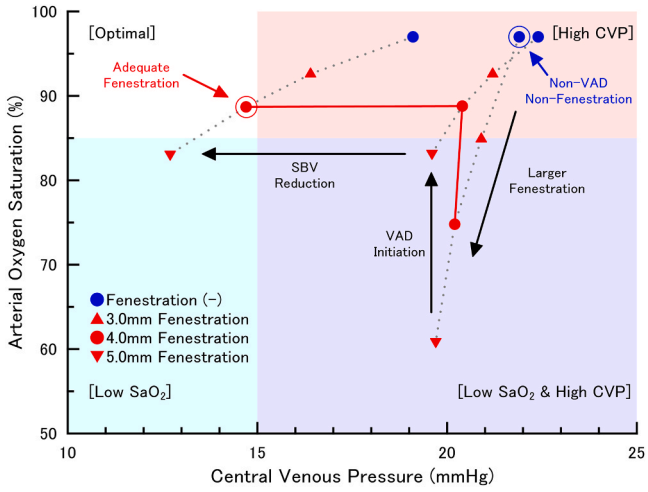

Fig. 4. Comparison of changes in central venous pressure and arterial oxygen saturation between the models with and without fenestration at a pulmonary vascular resistance index of 5.86 Wood Units m^2. The three sets of data connected by the dotted line were obtained before ventricular assist, after initiation of ventricular assist, and after stressed blood volume reduction. Blue circle, model without fenestration; red upright triangle, 3.0 mm fenestration model; red circle, 4.0 mm fenestration model; red inverted triangle, 5.0 mm fenestration model. CVP, central venous pressure; SaO_2, arterial oxygen saturation; SBV, stressed blood volume; VAD, ventricular assist device.

Since our previous study demonstrated that fenestration improved hemodynamics most effectively in patients with elevated PVR [7], elevated PVR may be one of the most important factors for fenestration patency. In addition, the fenestration orifice may become smaller over time. Surgeons should take this into account when creating the fenestration, as additional interventions may be needed in the long term.

4.4. *Clinical implications*

Although the number of reports of right VAD (RVAD) implantation in Fontan patients is limited, there are several successful case reports of RVAD as a bridge to heart transplantation in Fontan patients with preserved systolic ventricular function [26, 27]. For RVAD implantation in Fontan patients, takedown of the cavopulmonary anastomoses, followed by connection of the superior and inferior venae cavae, may be necessary for RVAD inflow [27]. The technical difficulty may cause surgeons to hesitate when applying RVAD.

On the other hand, biventricular assist may sometimes be unavoidable in Fontan patients complicated by systolic ventricular dysfunction. In two successful cases of biventricular assist, heart transplant was performed within 1 month of VAD implantation [13, 28]. Although Davies et al. reported a case of longer duration of biventricular assist of approximately 300 days to heart transplantation [14], long-term biventricular assist beyond 1 month may be quite difficult in Fontan patients compared to patients with biventricular physiology, as 58 % of mortality occurs in the first month even after initiation of systemic VAD in Fontan patients [29]. This simulation study demonstrates that systemic VAD combined with fenestration improves the hemodynamics of a failing Fontan circulation model with systolic ventricular dysfunction (reduced E_{es}), even in the setting of severe elevated PVR that would require RVAD. Although verification by animal and/or clinical studies are needed, fenestration should provide high tolerance of systemic VAD under the condition of increased PVR. Thus, systemic VAD combined with fenestration may be more appropriate than biventricular assist devices for long-term support during bridge to transplantation in failing Fontan patients.

4.5. Limitations

First, parameters used in this simulation were not patient-specific. Therefore, simulation with patient-specific parameters is needed to decide the optimal diameter of fenestration. Second, interactions between parameters were not considered in the present study. A change in one parameter may affect other parameters. Third, a model of systolic ventricular dysfunction was used as a cause of Fontan failure in this study. However, there are several other potential causes of Fontan failure, such as diastolic ventricular dysfunction and atrioventricular valve regurgitation. Therefore, specific simulations may be necessary depending on the cause of Fontan failure. Forth, intrapulmonary and veno-venous shunts, which are often observed in Fontan patients, were not included in the simulation. The presence of these shunts may affect simulation results. Further investigations are necessary to overcome these limitations.

5. Conclusions

In a simulated model of failing Fontan circulation, systemic ventricular assist combined with fenestration significantly improves hemodynamics even under the condition of elevated PVR. However, the optimal fenestration diameter should be determined, as too large a fenestration will cause severe desaturation.

CRediT authorship contribution statement

Toshiaki Shishido: Writing – review & editing, Supervision, Investigation. **Koji Uemura:** Investigation, Formal analysis. **Yoshinori Miyahara:** Supervision, Investigation. **Eiri Kisamori:** Formal analysis, Data curation. **Naohiro Horio:** Formal analysis, Data curation. **Yasuhiro Kotani:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Shuji Shimizu:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Shingo Kasahara:** Writing – review & editing, Supervision, Investigation.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

SS and YK conceived and designed the study. SS, NH and EK performed the simulation. SS, YK, NH, EK and KU analyzed data. SS, YK, YM, KU, TS and SK interpreted the results of the simulation. SS and YK prepared the figures and drafted the manuscript. SS, YK, TS and SK edited and revised the manuscript. All authors read and approved the final manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

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

References

[1] Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240–8.
[2] Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, et al. Evaluation and management of the child and adult with Fontan circulation: a scientific statement from the American heart association. Circulation 2019;140:e234–84.
[3] Kisamori E, Kotani Y, Shishido T, Kasahara S, Shimizu S. Effects of systemic ventricular assist in failing Fontan patients: a theoretical analysis using a computational model. J Physiol Sci 2024;74:53.
[4] Bridges ND, Mayer Jr JE, Lock JE, Jonas RA, Hanley FL, Keane JF, et al. Effect of baffle fenestration on outcome of the modified Fontan operation. Circulation 1992;86:1762–9.
[5] Snir E, Raanani E, Birk E, Zeevi B, Berant M, Vidne BA. Total cavopulmonary connection (TCPC) for complicated congenital heart malformations. J Cardiovasc Surg 1994;35:141–4.
[6] Nakano T, Kado H, Tatewaki H, Hinokiyama K, Oda S, Ushinohama H, et al. Results of extracardiac conduit total cavopulmonary connection in 500 patients. Eur J Cardiothorac Surg 2015;48:825–32.
[7] Horio N, Shimizu S, Kotani Y, Miyahara Y, Kasahara S. Evaluation of the effects of fenestration in Fontan circulation using a lumped parameter model. J Physiol Sci 2024;74:58.
[8] Shimizu S, Kawada T, Une D, Fukumitsu M, Turner MJ, Kamiya A, et al. Partial cavopulmonary assist from the inferior vena cava to the pulmonary artery improves hemodynamics in failing Fontan circulation: a theoretical analysis. J Physiol Sci 2016;66:249–55.
[9] Shimizu S, Une D, Kawada T, Hayama Y, Kamiya A, Shishido T, et al. Lumped parameter model for hemodynamic simulation of congenital heart diseases. J Physiol Sci 2018;68:103–11.
[10] Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. Circ Res 1973;32:314–22.
[11] Morley D, Litwak K, Ferber P, Spence P, Dowling R, Meyns B, et al. Hemodynamic effects of partial ventricular support in chronic heart failure: results of simulation validated with in vivo data. J Thorac Cardiovasc Surg 2007;133:21–8.
[12] Girfoglio M, Ballarin F, Infantino G, Nicoló F, Montalto A, Rozza G, et al. Non-intrusive PODI-ROM for patient-specific aortic blood flow in presence of a LVAD device. Med Eng Phys. 2022;107:103849.
[13] Nathan M, Baird C, Fynn-Thompson F, Almond C, Thiagarajan R, Laussen P, et al. Successful implantation of a Berlin heart biventricular assist device in a failing single ventricle. J Thorac Cardiovasc Surg 2006;131:1407–8.
[14] Davies RR, Lantz JL, Mullowney SK, Butts RJ, Pirolli T, Jaquiss RDB, et al. Heart failure after cavopulmonary connection: conversion to biventricular circulatory support. Ann Thorac Surg 2021;112:e185–8.
[15] Patterson T, Hehir DA, Buelow M, Simpson PM, Mitchell ME, Zhang L, et al. Hemodynamic profile of acute kidney injury following the Fontan procedure: impact of renal perfusion pressure. World J Pedia Congenit Heart Surg 2017;8:367–75.
[16] Broda CR, Sriraman H, Wadhwa D, Wang Y, Tunuguntla H, Akcan-Arikan A, et al. Renal dysfunction is associated with higher central venous pressures in patients with Fontan circulation. Congenit Heart Dis 2018;13:602–7.
[17] Matsuda H, Covino E, Hirose H, Nakano S, Kishimoto H, Miyamoto Y, et al. Acute liver dysfunction after modified Fontan operation for complex cardiac lesions. Analysis of the contributing factors and its relation to the early prognosis. J Thorac Cardiovasc Surg 1988;96:219–26.
[18] Ruiz E, Guerrero R, d'Udekem Y, Brizard C. A technique of fenestration for extracardiac Fontan with long-term patency. Eur J Cardiothorac Surg 2009;36:200–2.
[19] Miwa K, Iwai S, Kanaya T, Kawai S. Impact of optimal fenestration size on outcomes of high-risk Fontan patients. World J Pedia Congenit Heart Surg 2024;15:65–73.
[20] Ko H, Song J, Chi SA, Lee SY, Kim SJ, Lee CH, et al. The long-term effects of the fenestration in patients with extracardiac Fontan circulation-a multicenter Korean cohort study based on national Fontan registry. Front Cardiovasc Med 2024;11:1341882.

[21] Daley M, Buratto E, King G, Grigg L, Iyengar A, Alphonso N, et al. Impact of Fontan fenestration on long-term outcomes: a propensity score-matched analysis. J Am Heart Assoc 2022;11:e026087.
[22] Cardarelli MG, Salim M, Love J, Simone S, Tumulty J, Conway D, Griffith B. Berlin heart as a bridge to recovery for a failing Fontan. Ann Thorac Surg 2009;87:943–6.
[23] Nakamura Y, Windsor J, Ueda K, Ricci M. A systemic ventricular assist device with a fenestration in a failing Fontan patient. World J Pedia Congenit Heart Surg 2020; 11:232–4.
[24] Tokunaga C, Iguchi A, Nakajima H, Hayashi J, Takazawa A, Akiyama M, et al. Fenestrated Fontan-like circulation under durable left-ventricular assist device support in fulminant myocarditis. J Artif Organs 2023;26:233–6.
[25] Gorla SR, Jhingoeri NK, Chakraborty A, Raja KR, Garg A, Sandhu S, et al. Incidence and factors influencing the spontaneous closure of Fontan fenestration. Congenit Heart Dis 2018;13:776–81.
[26] Seitz S, Buchholz H, Rebeyka I, Ross D, West L, Urschel S. Mechanical ventricular assist device as a bridge to recovery post-ABO-incompatible heart transplantation for failed Fontan circulation. Transpl Int 2014;27:e54–7.
[27] Moosmann J, Dittrich S, Purbojo A, Cesnjevar R. RVAD implantation in a Fontan patient with protein-losing enteropathy as a bridge to transplant: prêtre modification. J Card Surg 2020;35:1721–4.
[28] Valeske K, Yerebakan C, Mueller M, Akintuerk H. Urgent implantation of the Berlin Heart Excor biventricular assist device as a total artificial heart in a patient with single ventricle circulation. J Thorac Cardiovasc Surg 2014;147:1712–4.
[29] Bedzra EKS, Adachi I, Peng DM, Amdani S, Jacobs JP, Koehl D, et al. Systemic ventricular assist device support of the Fontan circulation yields promising outcomes: an analysis of the society of thoracic surgeons pedimacs and intermacs databases. J Thorac Cardiovasc Surg 2022;164:353–64.