Effect of mechanical assistance of the systemic ventricle in single ventricle circulation with cavopulmonary connection

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Background: Previous attempts to support single ventricle circulation mechanically have suggested that a custom-built assist device is needed to push, rather than pull, through the pulmonary circulation. We hypothesized that using a conventional ventricular assist device, with or without conversion of a total cavopulmonary connection to a bidirectional Glenn cavopulmonary connection, would allow assistance by pulling blood through the circuit and improve the cardiac index (CI).

Methods: Cavopulmonary connections were established in each of 5 Yorkshire pigs (25 kg) using ePTFE conduits in a Y configuration with appropriate clamping of the limbs of the Y to achieve a total cavopulmonary Fontan connection (TCPC), superior vena cava cavopulmonary connection (SVC Glenn), and inferior vena cava cavopulmonary connection (IVC Glenn). A common atrium had been established previously by balloon septostomy. Mechanical circulatory assistance of the single systemic ventricle was achieved using a centrifugal pump with common atrial inflow and proximal ascending aortic outflow. The CI was calculated using an ultrasonic flow meter placed on the distal ascending aorta and compared between the assisted and nonassisted circulation for 3 conditions: TCPC, SVC Glenn, and IVC Glenn. The mean pulmonary artery pressure, common atrial pressure, arterial oxygen saturation, partial pressure of arterial oxygen, and oxygen delivery were calculated.

Results: The unassisted SVC Glenn CI tended to be greater than the TCPC or IVC Glenn CI. Significant augmentation of total CI was achieved with mechanical assistance for SVC Glenn (109% ± 24%, P = .04) and TCPC (130% ± 109%, P = .01). The assisted CI achieved at least a mean baseline biventricular CI for all 3 support modes. Oxygen delivery was greatest for assisted SVC Glenn (1786 ± 1307 mL/L/min) and lowest for TCPC (1146 ± 386 mL/L/min), with a trend toward lower common atrial and pulmonary artery pressures for SVC Glenn.

Conclusions: SVC bidirectional Glenn circulation might allow optimal augmentation of the CI and oxygen delivery in a failing single ventricle using a conventional pediatric ventricular assist device. The results from our model also suggest that the Fontan circulation itself can be supported with systemic ventricular assistance of the single ventricle. (J Thorac Cardiovasc Surg 2014;147:1271-5)

Despite tremendous improvement in the outcomes of adult patients with ventricular assist devices (VADs), the options for pediatric patients have continued to be limited. A failing single ventricle circulation imposes particular challenges to providing mechanical circulatory support.

Previous attempts to support the single ventricle circulation mechanically have suggested that a custom-built assist device is needed to push, rather than pull, through the pulmonary circulation. We hypothesized that using a conventional VAD, with or without conversion of a total cavopulmonary connection to a bidirectional Glenn cavopulmonary connection, would allow assistance by pulling blood through the circuit and improve the cardiac index (CI).

METHODS

The Animal Care and Use Committee of the Children’s National Medical Center approved the study, and all animals received humane care in compliance with the “Guide for Care and Use of Laboratory Animals,” published by the National Institutes of Health (Bethesda, Md). Five 25-kg, naive Yorkshire swine (Archer Farms, Darlington, Md) were used for the present study. The pigs underwent percutaneous atrial septostomy at the National Institutes of Health, followed by surgical construction of univentricular cavopulmonary connection at the Children’s National Medical Center.

Percutaneous Balloon Atrial Septostomy

The pigs were anesthetized with atropine, butorphanol, ketamine, and xylazine and maintained with isoflurane and mechanical ventilation.
Percutaneous arterial and venous access was obtained. If a patent foramen ovale was not present, a standard Mullins technique transseptal puncture was performed. The atrial septal communications were enlarged by inflation of large (18-20 mm in diameter) balloon angioplasty catheters. The experiments were guided by radiographic fluoroscopy (Siemens Medical, Erlangen, Germany) and intracardiac angioplasty catheters. The experiments were guided by radiographic fluoroscopy (Siemens Medical, Erlangen, Germany) and intracardiac angioplasty catheters. The experiments were guided by radiographic fluoroscopy (Siemens Medical, Erlangen, Germany) and intracardiac angioplasty catheters. The experiments were guided by radiographic fluoroscopy (Siemens Medical, Erlangen, Germany) and intracardiac angioplasty catheters.

**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CI</td>
<td>cardiac index</td>
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<tr>
<td>IVC</td>
<td>inferior vena cava</td>
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<tr>
<td>IVC Glenn</td>
<td>IVC cavopulmonary connection</td>
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<tr>
<td>MPA</td>
<td>main pulmonary artery</td>
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<tr>
<td>PAP</td>
<td>pulmonary artery pressure</td>
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<tr>
<td>SVC</td>
<td>superior vena cava</td>
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<tr>
<td>SVC Glenn</td>
<td>SVC cavopulmonary connection</td>
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<tr>
<td>TCPC</td>
<td>total cavopulmonary Fontan connection</td>
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<td>VAD</td>
<td>ventricular assist device</td>
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**Surgical Creation of Univentricular Circulation**

After premedication with intramuscular ketamine and xylazine, the anesthesia was maintained by a continuous intravenous infusion of fentanyl, midazolam, and pancuronium and mechanical ventilation. Using a median sternotomy, after systemic heparinization and proximal ascending aortic and bivacal venous cannulation, normothermic cardiopulmonary bypass was established using a continuous flow pump (Rotaflow, Maquet Inc, Wayne, NJ) and membrane oxygenator (Terumo Minn) placed around the distal ascending aorta measured the cardiac output, which indexed to body surface area provided the CI. In the superior caval venous cannula was removed and the inferior caval cannula moved to the right atrial appendage to drain the common atrium. By excluding the oxygenator and cardiectomy reservoir using a bypass line, the cardiopulmonary bypass circuit was converted to function as a continuous flow VAD. Pressure was monitored in the common atrium (using a catheter placed through the left atrial appendage) and in the cavopulmonary connection using a pulmonary arterial catheter.

All the pigs were weaned off cardiopulmonary bypass to achieve baseline biventricular data. Each of the 3 study conditions (TCPC, SVC Glenn, and IVC Glenn) was created in random sequence in each pig. The endpoints were measured after achievement of steady state in each of the 3 conditions in their native state (unassisted) and when assisted by the continuous flow VAD (assisted). Although the flow measurements were available for all the pigs, the data required for calculation of tissue oxygen delivery were available for 3 pigs only.

At the end of the study, all the pigs were humanely killed.

**Statistical Analysis**

Continuous data are reported as the mean ± standard deviation. Paired t tests were used to compare the assisted and unassisted state for each of the 3 conditions. The statistical analyses were performed using IBM SPSS Statistics, version 19 (SPSS Inc, Chicago, Ill).

**RESULTS**

The baseline CI in the pigs after the surgical procedure with both limbs of the Y graft clamped was low (1221 ± 451 mL/m²/min), suggesting the marginal status of their circulation after the extensive procedure. The CI was even lower in the unassisted state after appropriate clamp removal and placement for all 3 cavopulmonary connection conditions. However, it was higher for the SVC Glenn (1191 ± 747 mL/m²/min) than for the TCPC (754 ± 357 mL/m²/min) or IVC Glenn (781 ± 389 mL/m²/min; Table 1 and Figure 2).

Significant augmentation of the total CI was achieved with mechanical assistance for each of the 3 conditions. A greater than twofold increase in the total CI was seen in all the 3 cavopulmonary conditions and was statistically significant for SVC Glenn (109% ± 24%, P = .04) and TCPC (130% ± 109%, P = .01; Table 1 and Figure 2). Assisted CI achieved at least a mean baseline biventricular CI for all 3 support modes. The amount of flow contribution to the total cardiac output from the VAD was 60% in SVC Glenn, 64% in IVC Glenn, and 76% in TCPC.

The common atrial pressure tended to be lower in the “assisted” state in all 3 conditions compared with that in the “unassisted” state (Table 1).

The mean pulmonary artery pressure was greater in all the 3 cavopulmonary connection conditions in the unassisted state than with the baseline biventricular circulation (baseline, 21.0 ± 13.6 mm Hg; SVC Glenn, 25.3 ± 4.6 mm Hg; IVC Glenn, 28.0 ± 4.9 mm Hg; TCPC, 27.8 ± 5.6 mm Hg). The mean pulmonary artery pressure (PAP) was lower in the assisted state than in the unassisted state in all 3 cavopulmonary connection conditions for 4 of the 5 study animals (Figure 3), resulting in a lower group mean PAP in the assisted state for all 3 conditions (Table 1). A paradoxical increase in the PAP was seen in 1 study animal.

The oxygen saturation and arterial oxygen tension (partial pressure of oxygen in arterial blood) decreased in both partial cavopulmonary connection conditions (SVC Glenn and IVC Glenn) in the assisted state compared with that in the unassisted state. However, the overall augmentation of the cardiac output offset the desaturation and resulted in greater oxygen delivery in the assisted state for both conditions. No decrease in oxygen saturation or arterial oxygen tension was seen from the unassisted to assisted state for TCPC. Oxygen delivery was greater in the assisted state for all 3 conditions and was greatest for assisted SVC Glenn (1786 ± 1307 mL/L/min) and lowest for TCPC (1146 ± 386 mL/L/min; Table 1).
FIGURE 1. Total or partial connections were established by application of clamps (clamps 1 and 2) or snares (snares 1 and 2) to achieve superior vena cava (SVC) cavopulmonary connection (SVC Glenn), inferior vena cava (IVC) cavopulmonary connection (IVC Glenn), or total cavopulmonary connection (TCPC). Application of snare 1 and clamp 2 achieved SVC Glenn; snare 2 and clamp 1, IVC Glenn; and snares 1 and 2 without any clamps, TCPC. The snare on the main pulmonary artery (MPA) was on for all 3 cavopulmonary connection conditions. Application of clamps to exclude the membrane oxygenator at sites denoted by X, and unclamping of the recirculating line-arrow, allowed conversion of the cardiopulmonary bypass circuit to a continuous flow ventricular assist device.

DISCUSSION

With improved outcomes of single ventricle palliation, an increasing number of patients will be Fontan survivors. The inherent inefficiencies of the Fontan circulation, however, have led to delayed Fontan failure in some patients and can lead to late mortality and morbidity.6-9

Previous reports have focused on mechanical assistance for this failing circulation using subpulmonary blood pumps to drive the blood forward through the pulmonary circuit3,4,5,10-14 or a viscous impeller pump, based on the Von Karman principle.3,15 Although clinical success10 has been seen with this approach of pushing blood through the pulmonary circuit, significant surgical modifications to the existing cavopulmonary circuit, or custom-made pumps are required to implement this strategy.

Decompression of the systemic circulation in a patient with cavopulmonary circulation should ideally draw the blood (pull) through the pulmonary circuit. This can be easily accomplished by the already tried and tested1,2 and readily available, commercial continuous flow VADs in a standard left VAD configuration. The strategy would also be effective, irrespective of the type of the cavopulmonary circuit without the need for any modifications. Although anecdotal case reports16-22 and computer simulation studies12 have been published, the lack of an optimal, single ventricle, large animal model have prevented systematic preclinical studies to date. In particular, it has been unclear whether the bidirectional Glenn circulation might be preferable to the TCPC circulation for this method of single ventricle mechanical assistance.

We developed our acute single ventricle porcine model to test the hypothesis that a standard method of ventricular assistance would be feasible with single ventricle circulation and that the bidirectional Glenn would be optimal for mechanical assistance. The achievement of univentricular circulation was achieved by a combination of percutaneous (balloon atrial septostomy) creation of a common atrium, followed by surgical creation of the cavopulmonary connection. The novel Y graft configuration allowed establishment of total (Fontan) or partial (SVC [superior] or IVC [inferior]) cavopulmonary connection. The surgical procedure was performed using cardiopulmonary bypass to improve the safety. Although this model will be good for acute studies, the pigs tolerated the procedure poorly, which was suggested by the low baseline CI at the end of the procedure. Thus, additional refinements are necessary for longer term studies. Also, all endpoints were measured soon after achievement of steady-state hemodynamics in each of the conditions (approximately 5-10 minutes after the establishment of each condition).

We noted a significant improvement in the total CI in all 3 cavopulmonary conditions with the assistance of a

TABLE 1. Assisted versus unassisted circulation for 3 study conditions: SVC Glenn, IVC Glenn, and TCPC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Unassisted</th>
<th>Assisted</th>
<th>Unassisted</th>
<th>Assisted</th>
<th>Unassisted</th>
<th>Assisted</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (mL/m²/min)</td>
<td>1221 ± 451</td>
<td>1191 ± 747</td>
<td>2517 ± 1741</td>
<td>781 ± 389</td>
<td>2120 ± 1832</td>
<td>754 ± 357</td>
<td>1494 ± 658</td>
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<tr>
<td>PAP (mm Hg)</td>
<td>21.0 ± 13.6</td>
<td>25.3 ± 4.6</td>
<td>22.6 ± 7.3</td>
<td>28.0 ± 4.9</td>
<td>25.6 ± 7.8</td>
<td>27.8 ± 5.6</td>
<td>26.4 ± 8.7</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>14.8 ± 2.6</td>
<td>16.6 ± 4.4</td>
<td>14.5 ± 2.7</td>
<td>16.8 ± 7.0</td>
<td>14.0 ± 6.7</td>
<td>18.2 ± 6.3</td>
<td>16.2 ± 6.3</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>89.8 ± 19.1</td>
<td>63.7 ± 11.9</td>
<td>50.5 ± 16.6</td>
<td>84.7 ± 6.4</td>
<td>73.8 ± 13.9</td>
<td>78.7 ± 15.5</td>
<td>73.8 ± 15.1</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>151.2 ± 131.1</td>
<td>33.7 ± 5.9</td>
<td>30.8 ± 9.4</td>
<td>52.7 ± 11.6</td>
<td>42.1 ± 11.2</td>
<td>47 ± 13.8</td>
<td>45.2 ± 15.7</td>
</tr>
<tr>
<td>DO₂ (mL/L/min)</td>
<td>1212 ± 566</td>
<td>909 ± 571</td>
<td>1786 ± 1307</td>
<td>862 ± 207</td>
<td>1715 ± 1622</td>
<td>733 ± 147</td>
<td>1146 ± 386</td>
</tr>
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</table>

Data presented as mean ± standard deviation. SVC Glenn, Superior vena cava cavopulmonary connection; IVC Glenn, inferior vena cava cavopulmonary connection; TCPC, total cavopulmonary connection; CI, cardiac index; SpO₂, arterial oxygen saturations; PAP, pulmonary artery pressure; LAP, left atrial pressure; PaO₂, partial pressure of oxygen in arterial blood; DO₂, oxygen delivery. *Significant differences between assisted and unassisted conditions. 11Number of pigs was 3 for these variables.
continuous flow pump. This was accompanied by a decrease in the mean PAP and left atrial pressure, suggesting that decompression of the systemic circulation is transmitted to the cavopulmonary circuit and will be effective in pulling or drawing blood through the pulmonary circulation. The decrease in PAP was noted in 4 of the 5 study animals and was found to be paradoxically higher in 1. Surgical dissection and ligation of the ductus arteriosus to exclude any effect of patency did not change the outcome. No other aortopulmonary collaterals could be found on intrapericardial dissection.

The common atrial pressure was lower in the assisted state than in the unassisted state; however, complete decompression of the systemic atrium was not achieved. This could have resulted from our choice of atrial inflow versus the preferred ventricular inflow used for most left VADs, which would provide better systemic decompression. We, however, avoided direct ventricular apical cannulation to avoid any additional ventricular dysfunction in an already marginal circulatory state. We have speculated that the better decompression with ventricular inflow cannulation would provide a larger decrease in the mean PAP in the failing Fontan circulation and could offer more effective relief from the detrimental effects of the high venous pressure in these patients. The return from the thebesian veins directly to the right ventricle could be a problem over time in the setting of a competent tricuspid valve. In our model, this was easily managed by pushing the tip of the atrial inflow cannula into the tricuspid valve to make it incompetent. Future studies with apical inflow cannulation might require direct procedures to induce tricuspid incompetence.

The augmentation in the cardiac output was maximum in the SVC Glenn and lowest in the TCPC. This possibly resulted from the added direct effect of the systemic circuit decompression on the IVC return, in addition to additional flow through the cavopulmonary circuit.

![FIGURE 2. Mechanical assistance of the systemic single ventricle in partial or total cavopulmonary connection. Paired t tests revealed significantly greater cardiac index (CI) for assisted versus unassisted for *superior vena cava cavopulmonary connection (SVC Glenn; P = .04) and *total cavopulmonary connection (TCPC; P = .01) but not for the †inferior vena cava cavopulmonary connection (IVC Glenn; P = .13).](image)

![FIGURE 3. A reduction in the mean pulmonary artery pressure (PAP) was seen in 4 of the 5 study animals with mechanical assistance in each of the 3 cavopulmonary connection conditions. A, Superior vena cava cavopulmonary connection (SVC Glenn); B, inferior vena cava cavopulmonary connection (IVC Glenn); and C, total cavopulmonary connection (TCPC).](image)
This was supported by the decrease in arterial oxygen saturation and arterial oxygen tension with mechanical assistance.

Similar effects were seen with the IVC Glenn, probably attributable to the direct effect on SVC flow. However, the difference did not achieve significance, probably owing to the proportional flow differences between the SVC and IVC territories, compounded by the small number of study animals. Remarkably, the augmentation in the flow offset this decrease in the oxygen content in the blood to achieve oxygen delivery similar to, or greater than, the baseline biventricular levels in all the 3 assisted conditions. Although significant augmentation of the CI and oxygen delivery can be achieved in Fontan circulation with this approach, more resistant cases might need a combination of takedown of the TCPC to a partial cavopulmonary circulation and a systemic VAD to effectively palliate a failing circulation. Because this approach relies on augmenting the blood flow through the low-resistance cavopulmonary circuit by systemic decompression, the efficacy of this therapy could vary with the etiology of Fontan failure (eg, systemic side failure vs high pulmonary vascular resistance or anatomic issues with the Fontan circuit).

Although our study was underpowered to detect anything other than differences in the CI, it is the first large animal model of a univentricular heart with a systemic mechanical assist device that allows a comparison of the hemodynamics of the bidirectional Glenn versus TCPC circulation.

CONCLUSIONS

The SVC bidirectional Glenn circulation might allow optimal augmentation of CI and oxygen delivery in a failing single ventricle using a conventional pediatric VAD. The results from our model have also suggested that the Fontan circulation itself can be supported with systemic ventricular assistance of the single ventricle.

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References