Pulmonary Vascular Disease in the Single-Ventricle Patient: Is it Really Pulmonary Hypertension and if So, How and When Should We Treat it?

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Despite significant improvements in the surgical and postoperative care for patients with single-ventricle physiology culminating in the Fontan circulation, significant late morbidity and mortality remains. In the setting of passive (ie, non-"pump" driven) pulmonary blood flow, pulmonary vascular resistance (PVR) plays a key role in determining cardiac output, and even slight elevations in PVR may result in significant morbidity. There is now great interest to treat Fontan patients with pulmonary vasodilators in an attempt to "optimize" PVR (and by extension, quality of life) and/or improve an elevated PVR. This review discusses the hemodynamic implications of the Fontan circulation, the evidence for use of pulmonary vasodilator therapy, and possible target physiologic mechanisms.

The "single-ventricle" population represents a spectrum of congenital heart defects (eg, hypoplastic left heart syndrome or tricuspid atresia) where only one ventricular chamber is developed adequately enough to support systemic cardiac output. Principles in surgical management include early palliation to provide adequate pulmonary blood flow while "protecting" the pulmonary vascular bed from prolonged elevated pressures and the associated development of pulmonary vascular disease while maintaining systemic outflow. This is followed subsequently by separation of the pulmonary and systemic circulations to function in parallel, with the single pump delivering systemic output and the passive flow system delivering pulmonary blood flow. The first step is accomplished using a controlled shunt/conduit or a pulmonary artery band. Additional portions of the first operation may address structural or hemodynamic issues related to systemic cardiac output. The latter stages are accomplished with the Glenn and Fontan operations, which sequentially separate the upper body venous return from the superior vena cava (SVC) and then lower body venous return from the inferior vena cava (IVC) by anastomosing the systemic veins directly to the pulmonary arteries.[1,2] Both the Glenn and Fontan operations lead to a passive flow system where systemic venous return and pulmonary blood flow are dependent on low pulmonary vascular resistance (PVR) for adequate ventricular preload (Figure 1).

Over time, the surgical results and overall survival for single-ventricle palliation to a Fontan circulation have improved dramatically.[3-5] Despite improved early mortality, however, significant late attrition remains. This can be attributed to a number of causes including primary cardiac dysfunction, arrhythmias, and comorbidities unique to the single-ventricle population such as protein losing enteropathy (PLE), plastic bronchitis (PB), and thromboembolic complications. With only 47% freedom from composite morbidity at 20 years, much work remains to improve quality and longevity of life in these patients.[6] Given the reliance on low PVR for the "system" to run smoothly, there is much interest in whether FDA-approved pulmonary vasodilator therapy could improve single-ventricle circulation.[7]

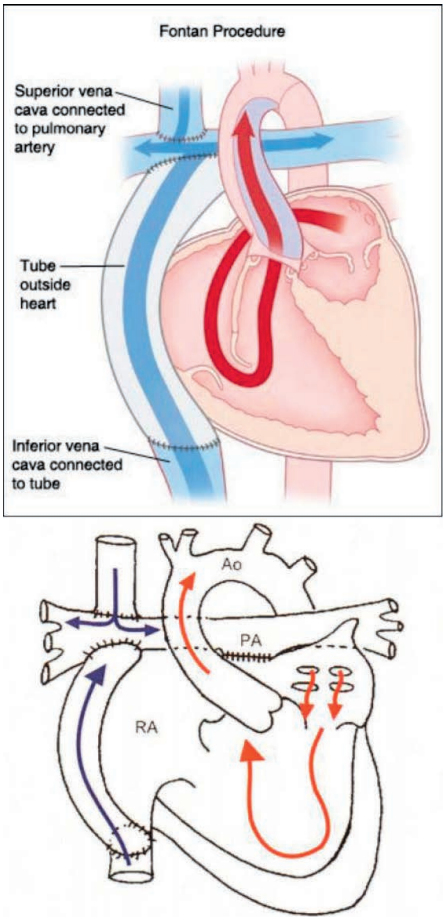

Figure 1: Fontan Circulation. Passive flow of systemic venous return directly to the pulmonary arteries. RA: right atrium, PA: pulmonary artery, Ao: aorta. May LE. *Pediatric Heart Surgery: A Ready Reference for Professionals*. Fifth Edition. maxiSHARE; 2012.

Key Words—endothelial function, Fontan circulation, pulmonary blood flow, pulmonary vasodilator therapy, single-ventricle physiology
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Disclosure: Stephanie Handler has no relevant financial relationships to disclose. Jeffrey Feinstein has received an Institutional Grant/Research Support from United Therapeutics Corporation.

 DOI:10.21693/1933-088X-18.1.14

Table 1. 10 Commandments

Age >4 years
Sinus rhythm
Normal systemic venous return
Normal right atrial volume
Mean pulmonary artery pressure <15 mm Hg
Pulmonary arteriolar resistance <4 Wood units/m^2
Pulmonary artery-aorta ratio >0.75
Left-ventricular ejection fraction >0.60
Competent mitral valve
Absence of pulmonary artery distortion

SINGLE-VENTRICLE HEMODYNAMICS

In 1977, Choussat et al. delineated 10 selection criteria for a successful Fontan operation, which are casually deemed the Ten Commandments (Table 1).[8] Although surgical and medical techniques have improved our ability to manage deviations from several desired anatomic and functional criteria, the concept of low PVR (anecdotal evidence now suggests <2 Wood units (WU)*m^2 may provide the best outcomes) and low mean pulmonary artery pressure (<15 mm Hg) still hold.

Specifically, as passive flow (ie, without a subpulmonic ventricle) is dependent on a low transpulmonary gradient, even modest elevations in PVR can greatly limit pulmonary blood flow. These elevations both increase the Fontan pressure (the central venous pressure to the body) and decrease cardiac output (through decreased preload to the ventricle). This combination may result in low cardiac output from ineffective Fontan circulation even in the absence of systolic or diastolic ventricular dysfunction, rendering typical treatment strategies for low cardiac output ineffective.

Determining the optimal PVR and transpulmonary gradient in a Fontan circulation remains elusive and accurate calculation of PVR may be difficult. Furthermore, additional sources of pulmonary blood flow from a native outflow tract and/or aortopulmonary collaterals that develop over time contribute to the inaccuracies in measuring/calculating pulmonary blood flow. Regardless, the original commandment using a PVRI cutoff of 4 WU*m^2 is likely too high, with most providers accepting that a normal PVR <3 WU*m^2 or even lower at <2 WU*m^2 is likely to portend more favorable long-term outcomes and prevention of late complications.

Transpulmonary gradient may be an even better estimate of pulmonary vascular health, though again differences in pulmonary artery pressure as well as interpretation of postcapillary pressure (pulmonary capillary wedge pressure vs direct atrial pressure vs ventricular end diastolic pressure) may provide different values.[9] Anecdotally, it appears that a transpulmonary gradient >5 mm Hg is likely abnormal in this circulation.

Cardiac catheterization remains the gold standard for evaluation of Fontan hemodynamics, and cardiac magnetic resonance imaging (CMR) now adds additional flow data that may help with calculation of pulmonary blood flow and therefore PVR. Currently, there is no standard way to assess the response to pulmonary vasodilator therapy in Fontan patients similar to vasoreactivity testing performed in patients with pulmonary arterial hypertension (PAH). Anecdotally, some centers may perform testing with nitric oxide in Fontan patients to assess for a change in transpulmonary gradient or PVR, without accepted criteria for a "responder" and no data to support treatment with pulmonary vasodilators based on a response.

This is certainly an area of interest where research could identify patients who have a positive response of some sort in the catheterization lab who may benefit from more aggressive medical treatment with pulmonary vasodilators, starting with a standard way to measure hemodynamics and administer vasodilator testing. Using the standard definition of pulmonary hypertension (PH) (mean pulmonary artery pressure ≥25 mm Hg) cannot be applied to single-ventricle patients as it is uncommon to have a pulmonary artery pressure over 15 or 20 mm Hg in a patient who is tolerating the Glenn or Fontan circulation. There is a lower pulmonary artery pressure (and PVR) threshold for consideration of treatment when compared to patients with PH. Finally, the definition of vasoreactivity for PH patients based on the adult or pediatric criteria will likely never apply to single-ventricle patients.[10,11]

EVIDENCE FOR PULMONARY VASODILATOR THERAPY

Given the considerable interest in improving long-term outcomes for Fontan patients and the recognition that exercise tolerance even in "asymptomatic" patients is not the same as their age-matched peers, there have been several randomized studies comparing the effects of pulmonary vasodilator therapy on exercise performance in Fontan patients. In one study, the impact of sildenafil on exercise capacity in Fontan patients was assessed by exercise stress test in a randomized, crossover trial after 6 weeks of placebo or sildenafil. The group receiving sildenafil had a significant decrease in respiratory rate and minute ventilation at peak exercise. Although not significant, there was a suggestion of improvement in peak oxygen consumption at the anaerobic threshold and brain natriuretic peptide ≥ 100 pg/mL in patients with single left or mixed ventricular morphology.[12]

Similarly, a placebo-controlled trial investigating the effect of bosentan on exercise capacity in Fontan patients demonstrated a significant increase in peak oxygen consumption (by 2 mL/kg/min) after 14 weeks of treatment. Importantly, the side effects were not different between groups and there were no patients with hepatotoxicity, an important consideration when choosing pulmonary vasodilator therapy in Fontan patients given the population's known risk for hepatic dysfunction.[13]

An additional randomized crossover trial was performed comparing cardiopulmonary exercise test performance following a single dose of iloprost or placebo showed a significant increase in oxygen consumption following iloprost. Interestingly, the patients with low peak oxygen consumption at baseline (<30 mL/kg/min) all had higher oxygen consumption following iloprost compared to only 50% of those who at baseline had higher peak oxygen consumption. Despite only studying a single dose, this suggests that there

may be a potentially beneficial effect in those with impaired exercise capacity at baseline.[14]

Finally, the Pediatric Heart Network is conducting a phase 3 study of the efficacy and safety of udenafil in Fontan patients 12 to 18 years of age. This randomized, placebo-controlled trial aims to assess the change in exercise capacity after 6 months of treatment with udenafil. The study does exclude those with heart failure or Fontan-related complications such as PLE and PB but may help answer the question of the utility of phosphodiesterase-5 inhibitors in asymptomatic Fontan patients.[15]

FAILING FONTAN POPULATION

Even more concerning than the patients who are otherwise well but at risk for long-term complications solely related to Fontan physiology are those with poor New York Heart Association (NYHA) functional class and overt symptoms of Fontan "failure." Fontan failure may refer to systolic or diastolic ventricular failure where low cardiac output is a result of pump failure, or elevated Fontan pressures as a result of elevated ventricular end diastolic pressure with a low transpulmonary gradient. It could also take the form of PLE or PB, which represent abnormal lymphatic drainage. Patients with PLE lose albumin, immunoglobulins, and clotting factors, resulting in significant fluid overload secondary to low oncotic pressure, and an increased risk for infection and thrombosis. Patients with PB develop deposits within the airways referred to as casts, which can lead to airway obstruction and respiratory compromise.

In some patients with PLE and PB, high venous pressures directly contribute to failure of normal lymphatic drainage. The thoracic duct is unable to drain normally to the venous system, and the lymphatic flow is redirected to the abdomen and thorax. Those patients may be a target for pulmonary vasodilator therapy to reduce Fontan pressure and allow improved lymphatic flow through normal channels. It remains unclear exactly what level of Fontan pressure elevation results in PLE or PB, especially as patients with expected "normal" Fontan pressures can develop these complications.

Even in the absence of typical post-Fontan complications, patients may experience Fontan failure related to elevated transpulmonary gradient alone that limits cardiac output and the ability to exercise. Typical hemodynamics in these patients would show low atrial filling pressures/ventricular end diastolic pressures and elevated Fontan pressure. As there is no way to convert the Fontan circuit to a pump to overcome this resistance in the lungs, pulmonary vasodilator therapy is particularly intriguing in this group.

Several small cohort studies have reported the effects of treatment on these Fontan patients with oral pulmonary vasodilators. Sildenafil was shown to improve PLE and PB in one study of 13 patients and to improve oxygen saturation, pulmonary artery pressure, and PVR in another of 6 patients.[16,17] Another study showed no effect on oxygen saturation, 6-minute walk test distance, or quality of life in 10 patients treated with bosentan for 16 weeks.[18] On the contrary, 8 children and 8 adolescents with PVRI ≥ 2 WU*m^2 treated with bosentan had reduction of PVRI after 6 months of treatment.[19] Finally, a study of 6 Glenn and 12 Fontan patients showed improvement in pulmonary compliance and Nakata index of pulmonary artery size after treatment with sildenafil (n=1), bosentan (n=16), or ambrisentan (n=1).[20]

As illustrated, much of the literature has focused on the Fontan population because earlier failure of single-ventricle palliation either after neonatal palliation (depending on the anatomy and amount of pulmonary blood flow after birth) or Glenn operation is more commonly related to ventricular dysfunction or other inherent patient risk factors. In addition, early attrition from the single-ventricle pathway related to pulmonary vascular disease may be better treated with heart transplantation as PVR in this group is rarely high enough to preclude transplantation and long-term outcomes in high-risk single-ventricle patients remain poor.

We retrospectively examined a group of single-ventricle patients treated with subcutaneous treprostinil who were otherwise being considered for heart transplantation based on failing single-ventricle hemodynamics. Eighteen patients in the initial cohort received treprostinil (6 stage 1, 6 Glenn, 6 Fontan) with significant improvement in oxygen saturation and PVR in each group. In addition, 50% of patients initially ineligible for next-stage palliation were able to undergo stage 2 or 3 palliation after treatment with treprostinil and another 4 patients underwent transplantation.[21]

Along those lines, there is likely a group of high-risk patients ineligible for continued staged palliation with elevated PVR that may benefit from pulmonary vasodilator therapy. Even if heart transplantation remains the best long-term option, pulmonary vasodilator therapy may be able to reduce cyanosis and improve exercise tolerance and functional class prior to transplantation.

PATHOPHYSIOLOGY OF FONTAN CIRCULATION

Pulmonary vasodilator therapy promotes vascular smooth muscle relaxation by increasing the effect of endothelium-derived vasodilators (phosphodiesterase-5 inhibitors, prostacyclin analogues) or decreasing the effect of vasoconstrictor factor (endothelin receptor antagonists). In PAH this results in a reduction in PVR, which has been shown to improve exercise capacity in adults with an improvement in mortality over time in pediatric patients since the approval of pulmonary vasodilator therapy.[11]

Providing nonpulsatile pulmonary blood flow, the Fontan circulation may result in alteration of pulmonary endothelial function and loss of the normal vasorelaxation response.[22] One study examined lung biopsies at the time of the Fontan, grouped based on whether the Fontan was successful. In patients whose Fontan failed, there was significantly increased wall thickness of the distal pulmonary arteries and an overexpression of nitric oxide synthase.[23] Another study of autopsy specimens from 10 Fontan patients showed increased expression of endothelin-1 and endothelin receptors in the pulmonary arteries of failed Fontan patients compared to nonfailed and controls.[24] In addition, there

was significant medial hypertrophy with intimal thickening in the failed Fontan group with significant lower expression of endothelial bone morphogenetic protein receptor type 2 (BMPR2).[25] Determining the alteration in endothelial function and balance of vasodilatory factors specific to the Fontan operation would be essential to tailoring PAH therapy to this population.

There are also data that suggest long-term pulmonary vascular remodeling in the Fontan circulation may be quite different than in PAH. In a series of 12 Fontan patients who died either early after the Fontan operation (n=5) or >5 years following the Fontan (n=7), analysis of intra-acinar pulmonary vessels from lung tissue obtained at autopsy showed decreased medial thickness with a reduction in vascular smooth muscle, which was proportional to the length of time since the Fontan operation.[26] This suggests approved PAH therapy may not have the same effect in the long-standing Fontan circulation. However, even late after the Fontan operation, the pulmonary vasculature has been shown to be reactive to nitric oxide with a reduction in PVR, suggesting there may be a response to pulmonary vasodilator therapy and stressing the importance of developing a protocol for a form of vasoreactivity testing to determine which patients may benefit from therapy.[27]

CONCLUSION

Experts recently published a letter to the editor following a meta-analysis that concluded that pulmonary vasodilator therapy improves exercise capacity, hemodynamics, and functional class in Fontan patients.[28] The letter, entitled "Pulmonary vasodilator therapy as treatment for patients with a Fontan circulation: the Emperor's new clothes?" raises concerns about the heterogeneity of the populations previously studied, limited knowledge about pulmonary vascular remodeling in the Fontan circulation, and current lack of randomized controlled trials, especially late after the Fontan operation involving more than a single dose of therapy.[29]

Overall, there are several promising studies, particularly in subgroups of symptomatic patients, that suggest some patients with Fontan circulation may benefit from pulmonary vasodilator therapy. At this time, however, there is no evidence to routinely recommend pulmonary vasodilator therapy for all Fontan patients. We have yet to determine who would benefit from long-term therapy and research should continue to focus on understanding the hemodynamic and clinical effects of pulmonary vasodilator therapy in Fontan patients as well as identifying which patients would benefit most from therapy.

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