The Fontan Circulation: The Search for Targeted Therapy

Running title: Goldberg et al.; Fontan Circulation: Targeted Therapy

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Journal Subject Codes: Heart failure:[11] Other heart failure, Hypertension:[18] Pulmonary circulation and disease, Cardiovascular (CV) surgery:[41] Pediatric and congenital heart disease, including cardiovascular surgery

Key words: Editorial, Fontan procedure, exercise capacity, pulmonary hypertension
The Fontan operation has been the final palliation for children born with congenital heart defects with a functional single ventricle for more than four decades\(^1,2\). In the early days of the Fontan operation, focus was rightly on technical modifications and alterations in strategy in an attempt to decrease morbidity and mortality related to the operation itself\(^3\). In recent years that focus has shifted toward the long-term implications of a total cavopulmonary connection\(^4\). It is clear that while the Fontan operation can create a stable circulation through early adulthood, there are inherent limitations to this physiology that impact other organ systems leading to diminished functional capacity over time\(^5\). This has led to an intensified search for therapies that specifically and effectively target the deficiencies in the Fontan physiology.

In the current issue of *Circulation*, Hebert and colleagues present results of the TEMPO study. In this study, the authors evaluate the effect of bosentan, an endothelin-1 receptor antagonist (ERA), on exercise performance in adolescents and young adults with Fontan physiology\(^6\). The authors demonstrate a small but statistically significant improvement in oxygen consumption during peak exercise following 14 weeks of treatment compared to placebo. The TEMPO trial is well-designed and well-executed, and adds significantly to the growing literature evaluating the potential role of modulators of pulmonary vascular resistance (PVR) in those who have undergone the Fontan operation. Although this study is small relative to many adult heart failure studies, it is the largest placebo controlled study to date of a pulmonary vasodilator in the Fontan population. The findings from the TEMPO study are encouraging and highlight the need for continued clinical research in larger cohorts of patients with Fontan physiology over a longer period of time.

**The Role of Pulmonary Vascular Resistance**

The Fontan circulation, like other forms of heart failure, is characterized by low cardiac output
and elevated central venous pressure (CVP). However, unlike other forms of heart failure, the primary limitation of the Fontan circulation is not “pump failure,” but rather the absence of a sub-pulmonary ventricle. Usual heart failure therapies directed at improving pump function or decreasing afterload may not be as relevant in a circulation in which the primary problem is filling as opposed to emptying the ventricle. Instead, therapies targeted at the mediators of ventricular filling in the Fontan circulation are needed.

In the absence of a sub-pulmonary pump, passive flow of blood through the pulmonary vasculature depends on the gradient between CVP and ventricular end-diastolic pressure (EDP), as well as resistance to flow across the pulmonary vascular bed. Given the limited capacity to increase the pressure gradient across the pulmonary vasculature, the role of pulmonary vascular resistance (PVR) as a modulator of ventricular filling is heightened. Simplistically, PVR can be thought of as a dam restricting the flow of blood. By lowering the height of the dam (reducing PVR), blood flow across the pulmonary vascular bed will be improved for any given combination of CVP and EDP resulting in decreased venous congestion (lower CVP) and higher cardiac output.

In thinking about modulators of PVR, it is important to first explore what we know (or what we think we know) about PVR in the Fontan circulation. In a two-ventricle circulation, pulsatile blood flow in the pulmonary arteries triggers a release of vasoactive mediators through the nitric oxide pathway. This mechanism allows for a decline in PVR in response to increased blood flow as might occur in the setting of exercise. With passive, non-pulsatile blood flow, PVR may not be as responsive. Indeed, in patients who undergo heart transplant after the Fontan operation, PVR is often abnormally elevated, potentially as a result of prolonged exposure to non-pulsatile flow. In addition, the Fontan circulation is thought to be vulnerable to
microthrombi, related to the venous stasis associated with low flow in the systemic veins and pulmonary arteries, resulting in a decrease in total cross-sectional vascular area and a slow but steady elevation in PVR over time.

In the early days of the Fontan operation, pulmonary vascular resistance was often overlooked as the prevailing sentiment was: “If you’re alive with a Fontan, then your PVR must be low.” Over time that notion has been proven false, at least in a relative sense. It is true that a PVR in the range typically associated with pulmonary arterial hypertension is probably not compatible with survival in the Fontan circulation, but it’s also true that much smaller incremental increases in PVR can have profound implications for both CVP and cardiac output in the absence of a sub-pulmonary ventricle. Raising the dam, even a small amount, can have a significant impact on the ability of the single ventricle to achieve an adequate preload.

The consequences of this prolonged state of low cardiac output and elevated CVP are apparent when one examines the cardiovascular system itself as well as the other organ systems outside of the heart. While there is a broad range of cardiovascular fitness levels among patients with Fontan physiology, the general trend is towards a decrease in exercise capacity over time both when viewed in a cross sectional manner at different time points by age, and when evaluated longitudinally in individual patients. This has important consequences as exercise capacity is correlated with functional status. As exercise capacity falls below a threshold of about 45 to 50% of predicted for age and gender, the incidence of symptomatic heart failure resulting in hospitalization or mortality begins to rise.

The liver and kidney are examples of organ systems that are significantly impacted by the Fontan circulation. While not specifically proven, the prevailing understanding of liver fibrosis in the Fontan circulation is that it relates to the chronic congestion associated with
elevated CVP and the diminished oxygen delivery associated with low cardiac output. Similarly, diminished renal function is thought to be related to decreased renal perfusion in the setting of low cardiac output. Although experience with pulmonary vasodilators is limited in patients with single ventricle physiology, the clear advantage of “lowering the dam” for CVP and cardiac output suggest a successful therapy could lead to improvement or reversal of these non-cardiac sequelae of the total cavopulmonary connection.

Protein losing enteropathy and plastic bronchitis, two of the most troubling complications of the Fontan, can have profound consequences for survival after the Fontan. Although both complications can occur even with relatively "normal" Fontan hemodynamics, evidence suggests that modulation of PVR may be part of a reasonable treatment strategy in both cases\textsuperscript{16,17}; a reminder that “normal” Fontan hemodynamics are still markedly abnormal and further evidence of the potential utility of targeting PVR.

The Search for Targeted Therapies
The search for therapies specific to Fontan physiology has accelerated in the last decade as the experience with therapies for pulmonary hypertension has grown. After publication in 2008 of a study demonstrating an acute increase in exercise performance for Fontan patients following a single dose of sildenafil, there have been a number of studies, initially focusing on phosphodiesterase type 5 inhibitors (PDE5i), evaluating the potential impact of modulators of PVR on Fontan physiology\textsuperscript{18-20}. However, no study to date has addressed the essential question of therapy for the Fontan patient: will treatment with a PVR modulator alter the long-term outcome of this imperfect physiology.

Studying long-term outcomes in the Fontan population is a challenge. While the decline over time of the Fontan circulation is clear, the pace is slow and symptoms are often limited. In
studies of large populations of adults with heart failure, use of hard outcomes such as death and heart transplant are possible. We are fortunate that death and transplant are relatively rare in children with Fontan physiology, but this makes it a challenge to demonstrate a medication-related improvement in this population. For this reason, most of the studies in the Fontan cohort have been short-term, single center investigations and most have used exercise outcomes as surrogates of more traditional end-points.

As the exploration of PVR modulators as targeted therapy continues to grow, the need for a more substantial trial has come into clearer focus. A large trial that examines the impact of this class of medications on Fontan physiology over a longer time is needed. While a short- or medium-term improvement is important, and a pre-requisite for use in any subset of the Fontan population, only a truly long-term trial can demonstrate whether the short-term benefits of therapies modulating PVR are sustained over a longer period of time and whether they will alter the long-term natural history of this physiology. Similarly, while short-term safety is important, the longer-term effects of chronic use of PDE5i and ERAs in the Fontan population are not known. Both classes of drugs have significant side effects that could limit their utility as chronic therapies. Although liver toxicity was not noted in the TEMPO study, there was a statistically significant reduction in hemoglobin for those receiving bosentan. A small drop in hemoglobin might be well tolerated in the general population, but the impact may be more significant in the single ventricle group in whom cardiac output, and hence oxygen delivery, is chronically diminished.

While the results of the TEMPO trial are encouraging, the authors rightly point out that it would be premature to recommend universal therapy with ERAs for all patients with Fontan physiology. The same is also true for other modulators of PVR. The questions of long-term
efficacy and safety are unanswered and, as such, it would be unjustified to start otherwise asymptomatic patients on untested medications. For those patients with protein losing enteropathy, plastic bronchitis, or other serious complications of Fontan physiology, the calculus is different and the benefit of therapy, even without conclusive long-term data, may outweigh the risk. While medications capable of “lowering the dam” maintain an allure, it remains the task of the congenital heart disease community to design and execute a trial to definitively answer the question of whether these medications are capable improving the duration and quality of life of those with Fontan physiology.

Disclosures: None.

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Circulation. published online October 20, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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