The Fontan operation has been the final palliation for children born with congenital heart defects with a functional single ventricle for ~4 decades. 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. In recent years, that focus has shifted toward the long-term implications of a total cavopulmonary connection. It is clear that although the Fontan operation can create a stable circulation through early adulthood, there are inherent limitations to this physiology that affect other organ systems, leading to diminished functional capacity over time. This has led to an intensified search for therapies that specifically and effectively target the deficiencies in the Fontan physiology.

Role of PVR

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 subpulmonary 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 subpulmonary pump, passive flow of blood through the pulmonary vasculature depends on the gradient between CVP and ventricular end-diastolic pressure, 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 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 end-diastolic pressure, 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 2-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, nonpulsatile blood flow, PVR may not be as responsive. Indeed, in patients who undergo heart transplantation after the Fontan operation, PVR is often abnormally elevated, potentially as a result of prolonged exposure to nonpulsatile 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, PVR was often overlooked because 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 is also true that much smaller incremental increases in PVR can have profound implications for both CVP and cardiac output in the Fontan circulation.
absence of a subpulmonary 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. Although there is a broad range of cardiovascular fitness levels among patients with Fontan physiology, the general trend is toward 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 because exercise capacity is correlated with functional status. As exercise capacity falls below a threshold of ≈45% to 50% of predicted for age and sex, 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 affected by the Fontan circulation. Although 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 suggests that a successful therapy could lead to improvement or reversal of these noncardiac sequelae of the total cavopulmonary connection.

Protein-losing enteropathy and plastic bronchitis, 2 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; this is a reminder that “normal” Fontan hemodynamics are still markedly abnormal and further evidence of the potential utility of targeting PVR.

**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 after a single dose of sildenafil, a number of studies, initially focusing on phosphodiesterase type 5 inhibitors, have evaluated the potential impact of modulators of PVR on Fontan physiology. However, no study to date has addressed the essential question of therapy, even without conclusive long-term data, may recommend universal therapy with endothelin-1 receptor antagonists 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. Although 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 of improving the duration and quality of life of those with Fontan physiology.

**Disclosures**

None.

**References**


