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EDITORIAL COMMENT

Pulmonary Vascular Reserve in Fontan Patients

Looking Upstream for the True Heart of the Matter*

Marc Gewillig, MD, PhD,[a] Bjorn Cools, MD,[a] Alexander Van De Bruaene, MD, PhD[b]

In single ventricle patients, the Fontan palliation separates the pulmonary and systemic circulation, eliminating cyanosis and reducing volume load to the systemic ventricle. The Fontan operation is essentially an extracardiac, vascular surgery connecting the caval veins to the pulmonary arteries, leaving the ventricle(s) untouched. In doing so, the surgeon creates a new critical bottleneck upstream of the ventricle, profoundly changing the pathophysiology of the cardiovascular circuit. The pulmonary circulation, now functioning like a dam between systemic venous return and the systemic ventricle, sets new rules for the circulation since it becomes the limiting factor determining upstream congestion and downstream flow (1).

Flow across the critical bottleneck in a Fontan circuit is determined by 3 factors: resistance of the bottleneck (pulmonary vascular resistance), pressure above (central venous pressure), and pull below (atrial and diastolic ventricular function). Changes observed downstream of the dam (decreased contractility and increased end-diastolic pressures, exacerbated but blunted heart rate response, increased systemic vascular resistance) are secondary changes and are rarely the main driver of Fontan failure (1). Indeed, "heart" failure is often—barring a few exceptions (severe atrioventricular valve regurgitation [2] or severe ventricular dysfunction)—not the initial hemodynamic alteration causing Fontan decline, which explains why treatment strategies such as afterload reduction, pacing, and/or inotropes have disappointed (3). For the cardiologist, it may be difficult to accept that "heart" failure is a mere complication of Fontan circulatory failure, a reflection of chronic pre-load deprivation, just as cirrhosis is a reflection of chronic venous congestion and low flow. If our aim is to avoid and treat late Fontan complications, it is due time that we get to the true "heart" of the matter: the new critical bottleneck in Fontan patients is the pulmonary vasculature.

The adult Fontan circuit, including the pulmonary circulation, is the pre-determined end result of choices made during infancy and childhood. Current surgical connections impose only minimal energy losses relative to overall flow. At the same time, during early infancy, the pediatric cardiologist balances volume load to the ventricle against sufficient pulmonary blood flow, because that period prior to the Glenn shunt is the only phase where pulmonary artery (PA) catch-up growth can be achieved (4). Nevertheless, even with optimal results, evidence strongly suggests that chronic nonpulsatile decreased flow and absence of high-flow, high-pressure during exercise gradually increases pulmonary vascular resistance over time.

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In this issue of *Journal*, Egbe et al. (5) describe exercise hemodynamics and pulmonary vascular reserve in 29 symptomatic Fontan patients referred for cardiac catheterization. The authors have to be congratulated on completing a full hemodynamic assessment at rest and during exercise. They show

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From the [a]Pediatric Cardiology, University Hospitals Leuven, Leuven, Belgium; and the [b]Congenital Cardiology, University Hospitals Leuven, Leuven, Belgium.

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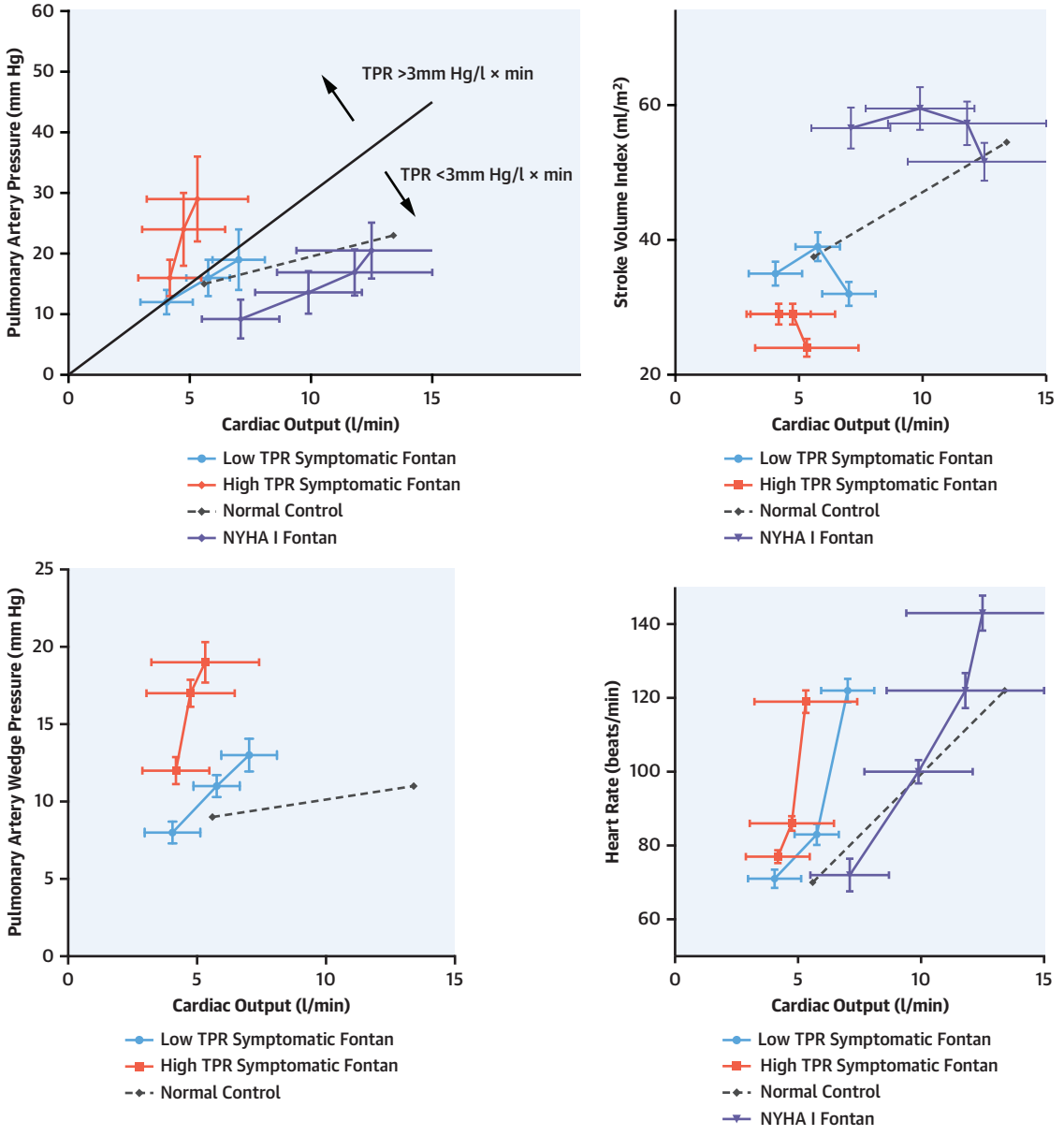
FIGURE 1 **Changes During Exercise in Fontan Patients**



Changes in mean pulmonary artery (PA) pressure, stroke volume index, heart rate, and PA wedge pressure relative to changes in CO during exercise in Fontan patients (high TPR >3 mm Hg/l•min and low TPR ≤3 mm Hg/l•min in symptomatic Fontan patients, and Fontan patients in New York Heart Association [NYHA] functional class I) and patients with noncardiac dyspnea. The better Fontan patients have a lower than normal TPR, whereas symptomatic Fontan patients have higher mean PA pressure, PA wedge pressure, and heart rate for any CO, with an early drop in stroke volume index, pointing toward the pulmonary circulation and pulmonary vascular reserve as the main driver of exercise intolerance. The exaggerated increase in PA wedge pressure with decreased filling warrants further study. Data taken from Egbe et al. (5), Borlaug et al. (18), and Van De Bruaene et al. (6). TPR = total pulmonary resistance.

that the slope of PA pressures and pulmonary blood flow (or total pulmonary resistance [TPR]) is more sensitive in detecting patients with pulmonary vascular problems when compared with a resting hemodynamic assessment alone, just as we observed when evaluating the acute effect of sildenafil (6). Patients with an elevated slope (TPR >3 mm Hg/l·min) had worse endothelial function, higher liver stiffness, worse renal function, lower exercise capacity, and lower quality of life when compared with those

with a normal slope. This definition of pulmonary vascular resistance outclasses all prior predictors of poor late outcome, suggesting that the authors got close to defining the critical bottleneck. Although it was a cross-sectional cohort study, the study provides a lot of much needed information on Fontan physiology.

Resting hemodynamic measurements are unlikely to completely capture pathology in Fontan patients. This is especially true for failing Fontan patients, where the low-flow state results in low pressure gradients causing proportionally larger measurement errors. It is therefore intuitive to evaluate the dam (the pulmonary vasculature) at different, higher flow rates. Exercise is the ideal physiological means to increase flow and has the potential to improve the signal-to-noise ratio to identify or unmask pathology, to distinguish different pathological phenotypes, and potentially, to assess the effect of any therapy (6).

Based on prior studies in health and disease, the authors used a cut-off of TPR >3 mm Hg/l·min. In normal individuals, mean PA pressures increase with 1 to 2 mm Hg per l/min increase in cardiac output (CO) (7) and a TPR >3 mm Hg/l·min has been shown to distinguish normal control subjects from patients with either pulmonary vascular disease or exaggerated increase in PA pressure due to left heart disease (8). It is intriguing that a similar cut-off works equally well in Fontan patients who lack a subpulmonary ventricle. Fontan patients with a higher TPR showed a marked increase in Fontan pressures (δ +13 mm Hg) for a limited increase in CO (δ +1.1 l/min), reflecting a higher pulmonary vascular resistance index (3.6 WU·m^2) at peak exercise. In concert, there is a decrease in stroke volume index (δ −17%) linking pulmonary vascular reserve to exacerbated pre-load limitation of the systemic ventricle during exercise. Although apparently similar to what is observed in a biventricular circulation, we wonder whether any Fontan is able to increase central venous pressure or PA pressure above 30 to 35 mm Hg (9). Indeed, data plots derived from the study clearly show that with increasing TPR, stroke volume index falls much earlier at relatively low CO and that heart rate is higher for any given CO when compared with control patients (6,10), all pointing toward the pulmonary circulation as the main driver of CO in the Fontan circulation (**Figure 1**).

Clinicians caring for failing Fontan patients frequently observe increased ventricular filling pressures at rest. This study first documented that some Fontan patients, especially those with higher TPR, have an abnormal and early increase in PA wedge pressure during exercise. Adequate ventricular filling is crucial as flow through the critical bottleneck is highly influenced by its run-off. The mechanism of increased ventricular stiffness at rest and exercise is still poorly understood. Similar to decreased cardiac compliance associated with aging in sedentary adults (11), and with severe mitral stenosis (12), failure to stretch the myocardium due to chronic pre-load deprivation will result in increased chamber stiffness, creating a vicious circle further reducing CO and increasing venous congestion.

WHERE SHOULD WE GO FROM HERE?

The current study emphasizes the pulmonary circulation as the critical bottleneck within the Fontan circulation. First, it stresses the importance of aiming for the best possible Fontan circuit (i.e., best possible pulmonary circulation with a good ventricle) during childhood, which involves optimization of the pulmonary vasculature, if needed at the expense of a certain degree of temporary ventricular volume overloading. Second, although the study may spark enthusiasm for using pulmonary vasodilator therapy in Fontan patients, we must not forget that recent randomized studies showed little improvement (13–15). The effect of pulmonary vasodilators is often limited and is highly variable between patients, as no effect can be expected in pulmonary vascular lesions such as pulmonary hypoplasia, stenosis, distortion, loss or exclusion, collateral flow, or obstruction by external compression (16). Pathology also pointed toward a different type of pulmonary vascular remodeling (17). Moreover, TPR alone may be unable to distinguish between increased PA pressure due to pulmonary vascular disease or increased chamber stiffness. Nevertheless, this study is a first logical step aiming at tailoring treatment options. Rather than prescribing drugs with little effect except on a small subgroup of patients, which is frustrating for patients, physicians, and medical insurers alike, exercise testing could identify those patients most likely to benefit from therapy.

What we now need to focus on:

- Mechanistic insight is needed into the precise molecular mechanisms responsible for pulmonary vascular remodeling.
- Are there different phenotypes of disease to be identified? What is the effect of pulmonary vasodilator therapy on pressure-flow slopes? Is there a noninvasive method to identify this subgroup?

- What is the mechanism of increased chamber stiffness in a chronically pre-load–deprived ventricle? Can it be avoided or treated?

There is still a long way to go to better understand Fontan physiology and fight Fontan failure, but this study is a beautiful step in the right direction addressing the true heart of the matter, the pulmonary circulation.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Marc Gewillig, Pediatric Cardiology, University Hospitals Leuven, B-3000 Leuven, Belgium. E-mail: Marc.gewillig@uzleuven.be. Twitter: @MarcGewillig, @alexvdbruaene.

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