

# FUELing the Search for Medical Therapies in Late Fontan Failure

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The Fontan operation has become the final step in the palliation of many patients with single-ventricle disease.<sup>1</sup> Although outcome has undoubtedly improved over the years, late failure is common and notoriously difficult to treat.<sup>2,3</sup> In the face of increasing numbers of young patients with failing Fontan circulation with heart transplantation as the only, but high-risk, exit strategy, the quest for medical therapies to prevent decline or to treat Fontan failure has reached a new level of urgency.

In this issue of *Circulation*, Goldberg et al<sup>4</sup> report their experience with udenafil, a long-acting phosphodiesterase type 5 inhibitor, in 400 adolescents with a Fontan circulation. The authors have to be congratulated for completing a long-awaited large, prospective, multicenter, placebo-controlled trial that showed a small, non-significant improvement in peak oxygen consumption (primary aim) and multiple significant but limited improvements at the ventilatory anaerobic threshold (secondary aims). Although essentially a nearly negative study, and with the clinical relevance of the changes observed still uncertain, this work nevertheless provides invaluable information for clinical practice and further research.

This study can now be added to an expanding list of studies aimed at evaluating medical therapies avoiding or treating Fontan failure. Should it surprise us that these studies so far were unable to demonstrate a significant and clinically relevant effect of any drug on systemic venous congestion or cardiac output? To answer this question, we need to understand what controls blood flow in a Fontan circulation.

Currently, the Fontan operation is reduced to its essence by connecting the superior and inferior caval veins to the pulmonary arteries (the total cavopulmonary connection). The pulmonary circulation is thus put like a dam between the systemic venous return and the systemic ventricle, creating, like any dam, upstream congestion and downstream decreased flow. These 2 features are the root cause of all early and late Fontan complications.

Fundamentally, the Fontan operation is an extracardiac, vascular surgery<sup>5</sup> that leaves the ventricle untouched by the surgeon but creates a new critical bottleneck upstream of that ventricle.<sup>2,6</sup> Therefore, changes observed downstream of the new bottleneck at the ventricular level (decreased contractility and increasing end-diastolic pressures, blunted heart rate response, increased systemic vascular resistance) are secondary changes.<sup>6</sup> By definition, it is highly unlikely that altering secondary changes will overcome the primary effects of the Fontan dam.

This explains the frustration experienced by clinicians when trying to improve Fontan hemodynamics using classic cardiac strategies such as afterload reduction, pacing, or inotropes. Cardiologists, almost by default and on the basis of little pathophysiological evidence, have tried to extrapolate results of heart failure

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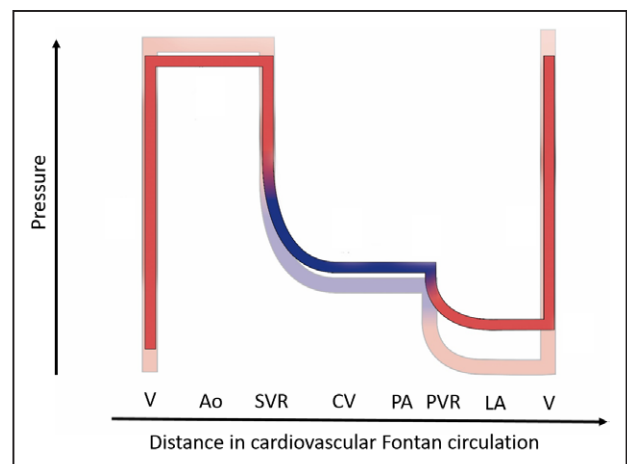
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studies such as renin-angiotensin-aldosterone blockade, effective in heart failure with (primary) reduced ejection fraction, to the Fontan population.<sup>7</sup> These efforts have had little success; preload deprivation, not systolic ventricular failure, represents the Achilles' heel of Fontan physiology. Despite these considerations and despite the 1 randomized study showing lower cardiac index during exercise in the active treatment group,<sup>8</sup> angiotensin-converting enzyme inhibitors remain among the most commonly used medications in patients with Fontan circulation. Acknowledging that the Fontan dam is the new critical bottleneck of the circulation has logically shifted treatment strategies away from the heart.

A circuit may have several bottlenecks, but only one can be critical. Only changing or bypassing that bottleneck will affect flow downstream and, in our closed circuit, the overall cardiovascular system.<sup>6</sup> In a Fontan circulation, a fenestration (bypassing the Fontan dam) effectively lowers venous congestion and increases overall flow, proving that the critical bottleneck lies between the systemic veins and the pulmonary atrium. Flow through any critical bottleneck is determined by upstream push (venous congestion), resistance across the Fontan dam, and downstream pull (ventricular diastolic filling pressure or suction); a change in any of these elements will immediately influence overall flow.<sup>9</sup> The Fontan dam consists of the surgical venous connection, the pulmonary arteries, the pulmonary capillary vasculature, the pulmonary veins, and their atrial connection. Current surgical connections impose only minimal energy losses relative to overall flow, with little future improvement to be expected.<sup>5</sup> But even with an optimal surgical result, Fontan hemodynamics predispose the circuit to deteriorate over time. One observes a steady increase of pulmonary vascular resistance and ventricular filling pressures, steadily decreasing flow downstream and increasing congestion upstream (Figure). Ideally, medical therapies aimed at preventing Fontan decline should keep pulmonary vascular resistance and ventricular filling pressure low.

Because the pulmonary vasculature now represents the largest resistance in the critical bottleneck and with pulmonary vasodilators available in our medical armamentarium, these drugs have emerged as a promising medical therapy. However, the pulmonary vasculature in patients with a single ventricle may have many impairments such as pulmonary hypoplasia, stenosis, distortion, loss or exclusion, collateral flow, or obstruction by external compression. Furthermore, the Fontan state itself imposes chronically decreased flow, minimal to mild desaturation, increasing collateral flow, turbulence and flow collision, suboptimal mixing of inferior and superior caval flow streams, absence of pulsatility, endothelial



**Figure. Flow/pressure/saturation diagram of the Fontan circulation: changes over time.**

Fontan hemodynamics late (full color) superimposed on Fontan early (transparent). With time, the pulmonary vascular resistance increases, but ventricular end-diastolic pressure increases more, resulting in overall decreased flow and increased caval vein pressure/congestion. A downward progressive spiral ensues. Line thickness reflects output; color reflects oxygen saturation. Ao indicates aorta; CV, caval veins; LA, left atrium; PA, pulmonary artery; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; and V, single ventricle. Adapted from Gewillig and Brown.<sup>2</sup>

dysfunction, and absence or attenuated intermittent shear stress or recruitment as is observed in regular exercise.<sup>9</sup> All of these factors may increase pulmonary vascular resistance, but only a few will respond to pulmonary vasodilators, explaining why the effect of such vasodilators is often limited and highly variable between patients.

The effect of pulmonary vasodilators on Fontan hemodynamics has now been studied in both the short term<sup>10,11</sup> and long term.<sup>12–14</sup> The larger randomized studies, including the current FUEL trial (Fontan Udenafil Exercise Longitudinal Assessment Trial),<sup>4</sup> report treatment effects for peak  $\text{Vo}_2$  of 3% to 5%.<sup>4,12,14</sup> Whether this is clinically meaningful for adolescent patients with Fontan circulation is open for debate. For patients with failing Fontan circulation (not studied in FUEL), these improvements are minimal but may be relevant. However, these patients are looking for lasting increases of output of 50% or even more. Whether the observed vasodilation is enough to prevent Fontan decline cannot be inferred from either study.

Where should we go from here?

Before being tempted to repeat this well-designed and well-executed study all too soon, we should learn from the data gathered during the FUEL study, the related FUEL-OLE (Open Label Extension) and FALD (Fontan Associated Liver Disease) studies and the upcoming RUBATO trial (Clinical Study Assessing the Efficacy and Safety of Macitentan in Fontan-Palliated Subjects; NCT03153137). We should be critical rather than blindly following our wishes and beliefs often elicited by such “borderline-positive” studies. Negative studies are not to be ignored (as we previously did with those

evaluating angiotensin-converting enzyme inhibitors); doing so drains money and time (the latter of which our patients have little) and may prevent or postpone progress on other fronts.

We now need to focus on include the following:

- Creating algorithms to determine which patients with Fontan circulation may benefit from current pulmonary vasodilators;
- Finding new, more potent pulmonary vasodilators or combining drugs to achieve lower pulmonary vascular resistance; and
- Finding lusitropic drugs to keep ventricular filling pressure low and to enhance ventricular pull. However, because the reason for the progressive decrease in ventricular compliance is still unclear, we can only speculate on whether drugs can influence this process.

Without being too pessimistic, it seems unlikely that cardiologists will soon match the solution for the Fontan conundrum provided by millions years of evolution: a subpulmonary pump. Indeed, a cavopulmonary assist<sup>15</sup> or heart transplantation can instantly solve the Fontan problems, albeit at the expense of a high-risk intervention and all its related concerns.

The present study again underscores that manipulating the Fontan circuit is extremely challenging; once created, the circuit runs almost by itself with minimal effect of exterior forces, including medical therapies. This observation stresses the importance of carefully preparing the most limiting building block of such a circuit: the pulmonary vasculature. Priorities in pre-Fontan management may need to be redefined. Should we aim for a Fontan circuit with the best possible ventricle as is currently the dogma, or should we aim for the best possible Fontan circuit? The latter involves optimization of the pulmonary vasculature, if needed, at the expense of a certain degree of temporary ventricular volume overloading. This discussion is ongoing and should be intensified to avoid or postpone late Fontan failure as much as possible.<sup>6</sup>

## ARTICLE INFORMATION

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## Disclosures

None.

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