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EDITORIAL COMMENTARY

A fairy tale future for Fontans: Fact or fable?

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Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Aug 20, 2015; accepted for publication Aug 21, 2015; available ahead of print Sept 19, 2015.

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J Thorac Cardiovasc Surg 2015;150:1370-1

0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2015.08.080>

Remarkable progress has been made in the surgical palliation and medical management of patients with functional single ventricles (FSV). In 1971, Francois Fontan described a novel surgical approach for patients with tricuspid atresia (Figure 1).¹ More than a decade later, William Norwood reported the first successful progression of an infant with hypoplastic left heart syndrome from stage I palliation to a successful Fontan circulation.² This staged surgical palliative approach has opened the doors for a generation of patients with FSV, which is no longer a death sentence. Although there remains significant mortality during the first 3 years of life,³ much attention is now focused on the medical management and optimization of patients after the Fontan operation. The morbidity and mortality of the Fontan circulation remains high,⁴ with a high incidence rates of late liver cirrhosis, venous thrombus, stroke, arrhythmia, exercise intolerance, and heart failure. Given this, optimization of the Fontan hemodynamics is of critical importance.

In this issue of the *Journal*, Kurishima and colleagues⁵ report a small series of 8 patients treated with isosorbide dinitrate (ISDN) and angiotensin-converting enzyme

From Fontan's original report. (Reproduced with permission by the BMJ Publishing Group Ltd.)

Central Message

Improving Fontan hemodynamics is important, but the impact of nitrates and ACE inhibitors will need to be replicated in larger studies.

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inhibitor (ACE-I) after the Fontan operation. Compared with a group of 23 control patients, at catheterization assessment 1 year after the Fontan procedure, the study patients had considerably lower Fontan baffle pressures (8.9 vs 14.1 mm Hg; $P < .001$), lower mean arterial pressures, and lower systemic vascular resistance.

ISDN, an organic nitrate and a stimulator of intracellular cyclic-GMP, is not commonly used in young patients with congenital heart disease. This agent is a well-known vasodilator of the vascular smooth muscles in the peripheral

FIGURE 1. From Fontan's original report. (Reproduced with permission from BMJ Publishing Group Ltd.)

(systemic) arteries and veins. This effect is most pronounced in the venous system, causing peripheral venous pooling of blood. In combination with its arterial vasodilatory effects, ISDN reduces caval return, systemic ventricular end-diastolic pressure, and systolic arterial and mean pressure, and also causes coronary artery dilation. Given these effects, ISDN is typically used in adults for the prevention of angina due to coronary artery disease.

The novel use of ISDN in this pediatric population raises substantial concerns. Most importantly, there is virtually no data on the long-term use of ISDN in children. Tolerance to nitrates is an incompletely understood but well-known problem.⁶ Headache is the most common side effect; systemic hypotension, the most significant. If administered with phosphodiesterase inhibitors (as done in 50% of the study patients), nitrates can be associated with severe systemic hypotension. This combination is generally contraindicated.

There is considerably more experience with the use of ACE-I in patients with FSV. The Pediatric Heart Network reports that the use of ACE-I in FSV is common, occurring in 57% of patients.⁷ ACE-I therapy has been shown to improve vascular endothelial function by decreasing pulmonary artery and end-diastolic pressures.⁸ Despite this, the data supporting improved outcomes associated with the use of ACE-I use in young patients with Fontan circulation is lacking. ACE-I use has not been shown to improve cardiac output or exercise capacity.⁹

Returning to the results of Kurishima and colleagues, the difference in Fontan baffle pressures between the

study and control cohorts is striking, in terms of both the relative difference and absolute magnitude of the results. Although simply decreasing the baffle pressure is not a goal of most medical therapies, lowering this pressure may have long-term benefits, especially for liver health. These data must be viewed in light of a number of significant limitations. First, this was a very small pilot study, with only 8 patients in the treatment arm. Second, although lower baffle pressures are generally considered better in the Fontan circulation, a hypothetical concern is the possibility that an excessively low baffle pressure might be associated with reduced cardiac output, particularly with exercise. Third, there are concerns regarding the side effect profiles of these drugs, particularly when taken in combination with other vasodilators. The question of whether these results can be sustained, due to ISDN drug tolerance, remains unanswered.

Optimizing Fontan hemodynamics is a critically important piece of the puzzle in the effort to optimize long-term health in this burgeoning population with palliated single-ventricle congenital heart disease. The intriguing data presented by Kurishima and colleagues will require further verification in larger trials, under carefully monitored conditions. Trial outcomes should be powered to improving not only baffle pressures, but also measures of functional capacity (eg, exercise tolerance). Some of the promise of these therapies may be in the patients at greatest risk (so-called "failing Fontans"), in whom even a slight improvement in hemodynamics may result in significant improvements in symptoms and outcomes. In the end, as is so often the case, more data and careful study will be needed to separate Fontan fact from fable.

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