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Review

After planned surgeries, there is still work to be done: Medical therapies

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ABSTRACT

The Fontan operation was first described in 1971 and has become a successful surgical strategy to palliate patients with single ventricle heart disease. While mortality has improved remarkably over the decades since its introduction, long-term sequelae of this unique physiology have become apparent. There is presently significant variability in medical therapy for Fontan patients without evidence to drive prescribing patterns. Medications that modulate pulmonary vascular resistance may be uniquely suited to help overcome the physiologic challenges imposed by Fontan physiology. In this review, we will discuss the evidence supporting the use of these medications in Fontan patients.

1. Introduction

The Fontan operation was first described in 1971 for patients with tricuspid atresia as a means to direct systemic venous return to the lungs without the assistance of a sub-pulmonary pumping chamber [1,2]. Since that time this concept has been expanded to other forms of single ventricle heart disease and the procedure has been modified to improve the efficiency and durability of the cavopulmonary connection [3–5]. At present, the Fontan operation serves as the final step in a series of palliative surgeries for those with single ventricle heart disease and allows for survival through childhood and adolescence for those born with this heterogeneous group of cardiac malformations.

The modern Fontan operation connects the superior and inferior vena cava directly to the pulmonary arteries creating a total cavopulmonary connection, generally using either an extracardiac conduit graft or an intracardiac lateral tunnel baffle. In this physiology, blood is propelled through the pulmonary vasculature by the gradient between the systemic venous pressure and the ventricular end-diastolic pressure. The importance of maintaining a low ventricular end-diastolic pressure and a low pulmonary vascular resistance is magnified in this circulation as any elevations in these values can have significant consequences for the degree of systemic venous hypertension required to drive ventricular preload [6].

Even in the most efficient Fontan circulation, the absence of a subpulmonary ventricle creates a physiology characterized by low cardiac output and elevated central venous pressure. While this may be well tolerated for many years, these two inherent characteristics of the Fontan circulation do have consequences for the cardiovascular system, and for organ systems beyond the heart. In recent years we have learned about Fontan associated liver disease, lymphatic insufficiency, progressive cardiac dysfunction, sub-clinical renal insufficiency, and abnormal bone, muscle and pubertal development [7–15]. However, while our understanding of the consequences of the Fontan circulation has improved, our understanding of how best to medically support this circulation remains limited. This review will examine the current practice regarding the use of medical therapies for those with Fontan physiology and will consider future directions for targeted medical therapy as a means of potentially improving long-term outcomes.

2. Current approach to medical therapy

Despite increasing experience with single ventricle heart disease, there remains a paucity of data on optimal medical management. In the absence of data supporting any specific strategy, widespread practice variability has emerged in the approach to therapy. The most comprehensive look at medication use in the United States came from the Pediatric Heart Network's (PHN) cross-sectional study nearly a decade ago [16,17]. In this study of 546 Fontan patients, substantial practice variability was noted between centers and also within individual centers. Antithrombotics were the most commonly used medication, followed by angiotensin converting enzyme (ACE) inhibitors, glycosides, and diuretics. Data from the Australia – New Zealand Fontan registry (ANZ) demonstrated a similar variability in the use of ACE inhibitors [18]. In this cohort of 1268 Fontan patients, 36% were treated with an ACE inhibitor with indications including systolic or diastolic dysfunction (29%), no indication provided (25%), and atrioventricular valve

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insufficiency (19%).

Despite the absence of supportive data, ACE inhibitors were the most commonly used medications outside of anti-thrombotics in both the PHN and the ANZ studies. In adult congestive heart failure patients ACE inhibitors are commonly used and have been shown to reduce ventricular remodeling and to improve left ventricular systolic dysfunction [19]. While this class of medications makes sense for adult heart failure patients, their role for those with single ventricle heart disease is substantially less clear. In the one randomized study evaluating ACE inhibitor use for those with Fontan physiology, there was no discernible improvement in diastolic function, systemic vascular resistance, cardiac index, or exercise capacity in the enalapril group [20]. At maximal exercise, there was no difference in cardiac index or oxygen consumption between the enalapril and placebo groups. Another prospective study compared 10 Fontan receiving ACE inhibitors for at least six months to 8 control patients. In this study, there was again no significant improvement in those who received ACE inhibitors [21].

3. Pulmonary vascular resistance

In recent years there has been a growing interest in the use of pulmonary vasodilators for those with single ventricle heart disease. Pulmonary vascular resistance is the gatekeeper of flow through the pulmonary vasculature, and it makes intuitive sense that maintaining as low a resistance as possible would lead to lower systemic venous pressure, improved ventricular filling and, therefore, improved cardiac output. The rationale for this intuitive strategy is augmented by what appears to be a tendency toward elevated pulmonary vascular resistance in those with Fontan physiology. Human and animal studies suggest that the change from pulsatile to passive pulmonary blood flow likely affects endothelial nitric oxide release and overall vasoreactivity at a cellular level [22,23]. To characterize these changes further, several studies have shown that Fontan patients have abnormal expression of endothelial-derived factors in the pulmonary vasculature. Notably, there are increased levels of nitric oxide synthase, endothelin-1, and endothelin receptors as well as decreased bone morphogenetic protein receptor type 2 [24–26]. Post-mortem studies have shown adverse vascular remodeling, perhaps related to non-pulsatile flow, characterized by a small smooth muscle medial layer, smooth muscle cell apoptosis, and eccentric intimal fibrosis [27].

The initial reports on the use of pulmonary vasodilators for those with single ventricle heart disease were in patients with various forms of Fontan circulatory failure, including for the treatment of protein losing enteropathy and plastic bronchitis [28,29]. Since those initial reports interest in pulmonary vasodilators has grown and there are now a number of studies evaluating the short- and medium-term impact of pulmonary vasodilators on those with Fontan physiology, even without overt complications [30–39]. There are three primary targets for pulmonary vasodilators, the nitric oxide pathway, the endothelin pathway, and the prostacyclin pathway [40]. Medications targeting these pathways have been used for many years in patients with pulmonary hypertension and, in recent years, studies have emerged evaluating their utility for patients with Fontan physiology.

4. Pulmonary vasodilator therapy

The most commonly studied pulmonary vasodilator in single ventricle heart disease is sildenafil, a drug that modulates the nitric oxide pathway. Sildenafil acts by promoting cyclic guanosine monophosphate (cGMP) via inhibition of phosphodiesterase-5, an enzyme that otherwise breaks down cGMP. Typically, cGMP is produced in response to nitric oxide. By inhibiting the breakdown of cGMP, sildenafil begins a cascade that results in vasodilatory and anti-proliferative effects on vascular smooth muscle and downward modulation of pulmonary vascular resistance [40,41].

Many of the studies evaluating the use of sildenafil in those with single ventricle heart disease focus on the acute impact of a single dose. The first of these evaluated the change in exercise capacity in 18 Fontan patients who had received a single dose of sildenafil and compared them to 9 Fontan patients who had received placebo [31]. The group receiving sildenafil had improved cardiac index, pulmonary blood flow, and peak exercise oxygen uptake. A more recent study employed supine MRI ergometry in 10 Fontan patients who had vascular and arterial access for blood samples. These patients were tested at multiple levels of exercise before and after receiving a single dose of sildenafil [42]. After sildenafil, there was increased cardiac index, stroke volume index, and ejection fraction at all levels of exercise. Indexed pulmonary vascular resistance decreased and end diastolic volume was unchanged. While the single dose studies demonstrate an acute improvement in hemodynamics after treatment with sildenafil, it is hard to extrapolate long-term benefit from these single dose studies.

To further evaluate the effect of pulmonary vasodilator therapy in Fontan patients, a randomized, double-blind, cross-over trial was conducted in 28 patients [32]. A baseline exercise stress test was completed followed by 6 weeks of treatment with either sildenafil or placebo, then a 6-week washout period, then 6 weeks of treatment with placebo or sildenafil. This study design allowed subjects to serve as their own control. While there was no observed difference between the sildenafil and placebo groups in oxygen consumption at peak exercise, there was a trend toward a difference in oxygen uptake at the anaerobic threshold. This effect was statistically significant among Fontan patients with brain natriuretic peptide levels greater than 100 pg/mL. Evaluating the same patients by echocardiography revealed improved myocardial performance index, a measurement of global ventricular function [33].

A more recent prospective study was completed evaluating the effect of prolonged sildenafil use on pulmonary vascular resistance and exercise capacity in Fontan patients specifically with elevated baseline pulmonary vascular resistance [36]. In this study, the 24 included Fontan patients underwent a baseline cardiac catheterization and 6-min walk test followed by 3 months of treatment with sildenafil and then a repeat catheterization and 6-min walk test. Notably, three patients were also on bosentan, five patients were on inhaled prostacyclin analog, and one patient was on home oxygen. Over the 3-month study period pulmonary vascular resistance decreased, pulmonary blood flow increased, and mean pulmonary artery pressure and transpulmonary pressure gradient decreased, although the estimated cardiac index did not change significantly. The 6-minute walk test was likewise improved.

Endothelin-1 receptor antagonists are another class of pulmonary vasodilators, typically used as second line therapy for patients with pulmonary hypertension, that may have utility as a potential therapy for those with the Fontan circulation [40,41]. Endothelin-1 is produced by endothelial cells and is involved in vascular vasoconstriction and cell proliferation and therefore may be responsible for elevations in pulmonary vascular resistance. There is evidence of increased endothelin-1 and its receptors in the pulmonary arteries of patients with failed Fontan circulations and there are also reports suggesting that Fontan patients with increased central venous pressure have higher plasma endothelin-1 levels [43].

While the rationale for the use of endothelin-1 receptor antagonists in Fontan patients is clear, the evidence supporting their use is mixed. The TEMPO trial was a randomized, placebo-controlled, double-blind study evaluating the effect of 14 weeks of bosentan treatment on exercise capacity in adolescent and adult Fontan patients [35]. Patients in the treatment group had increased peak oxygen consumption and exercise test time, and decreased pro-BNP levels, all suggesting a treatment benefit, but there was a concerning trend toward toward a relative anemia in the treatment group. Another study examined the effects of endothelin-1 receptor antagonists on both hemodynamic and exercise outcomes over a six month period [30]. After six months, catheterization data showed demonstrated decreased pulmonary vascular resistance and increased pulmonary blood flow as well as increased

cardiac output in adolescent and adult patients. In cardiopulmonary exercise testing, there was increased maximal oxygen consumption in adolescent and adult patients, though not in children. However, in contrast to these studies, an open-label trial of bosentan in adult Fontan patients showed no improvement in exercise capacity after six months of treatment [38].

The prostacyclin pathway is a third pathway that has also been targeted to decrease pulmonary vascular resistance in pulmonary hypertension patients. Prostacyclin is created by endothelial cells, promotes vasorelaxation, and inhibits vascular smooth muscle cell proliferation [40,41]. Prostacyclin analogues include epoprostenol, treprostinil, beraprost, and iloprost. Each of the aforementioned medications has a different mode of administration due to inherent limitations relating to short half-life and drug instability. A randomized, double-blinded, placebo-controlled trial evaluating the effect of a single dose of inhaled iloprost on Fontan patients' exercise capacity demonstrated improved peak oxygen consumption, improved oxygen pulse, and improved predicted work [37]. There was a trend toward improved oxygen consumption at the ventilatory anaerobic threshold, but the small number of subjects in the study limited the power to find statistical significance.

5. Ongoing clinical trials

While studies evaluating the effect of pulmonary vasodilators in Fontan patients have been encouraging, they range from single dose effect studies to mid-term studies and have not truly answered the question regarding the potential benefit of chronic therapy. In an effort to evaluate the long-term utility of this class of drugs, there are currently two ongoing clinical trials. The RUBATO study is a phase III clinical trial evaluating the effect of macitentan on exercise capacity and is currently enrolling adult Fontan patients (NCT03153137). The Fontan Udenafil Exercise Longitudinal Trial (FUEL, NCT0274115 and NCT03013751) was designed to evaluate the effect of udenafil on exercise capacity, myocardial function, vascular function, and serum brain natriuretic peptide [44]. The FUEL trial has recently completed enrollment ($n = 400$) and data are expected in the coming months. In the phase I/II trail prior to FUEL, udenafil was shown to be well tolerated and improved the myocardial performance index at a dose of 87.5 mg twice daily [34].

6. Conclusion

The Fontan operation has been revolutionary for the palliation of patients with single ventricle heart disease. In the decades since its introduction, there have been remarkable improvements in morbidity and mortality but long-term challenges remain an issue. With a growing and aging Fontan population, new medical therapies are needed to sustain these patients into adulthood and beyond. Although studies have demonstrated little benefit from the use of ACE inhibitors in this population, this class of medication remains the most commonly prescribed class of drug. Pulmonary vasodilator medications make intuitive sense and have shown promise in short and mid-term studies by modulating pulmonary vascular resistance to decrease systemic venous pressure and improve cardiac output and exercise capacity. Randomized controlled clinical trials are ongoing and will provide insight into the long-term safety and efficacy of pulmonary vasodilator medications in patients single ventricle heart disease who have undergone the Fontan procedure.

Declaration of competing interest

Dr. Goldberg receives grants support from the Pediatric Heart Network and from Mezzion Pharmaceuticals – the two sponsors of the Fontan Udenafil Exercise Longitudinal Trial. Dr. Finkelstein has no conflicts of interest.

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