Fontan and the pulmonary circulation: a potential role for new pulmonary hypertension therapies

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ABSTRACT

In recent decades, the Fontan procedure and its variations have resulted in markedly improved outcomes of patients with single-ventricle physiology. These improvements are expected to increase greatly the number of surviving patients, particularly those surviving long into adulthood. However, there is still a progressive risk of attrition and failure of the Fontan circulation over time, the underlying pathophysiology of which is not fully understood. Current evidence suggests that alterations in the structure and function of the pulmonary vasculature may play a pivotal role. Recent evidence suggests that therapies approved for pulmonary arterial hypertension may provide benefits in this increasingly important patient population.

Since its first description over three decades ago,[1] the Fontan operation and its variations [2 3] have become the procedures of choice in the management of patients with congenital heart disease with a single anatomical or functional ventricle. Since its inception, significant improvements in patient selection, surgical technique and medical management have led to improved perioperative morbidity, mortality and long-term outcomes.[4] With this improved outcome and the increasing number of procedures being performed, the number of surviving patients is expected to rise substantially. Although life saving, the Fontan procedure results in a pulmonary circulation very different from physiological conditions, with a progressive risk of attrition over time.[5] The number likely to be affected is unknown, but Fontan circulation may fail in many patients, leading to serious and potentially life-threatening sequalae.[3] Overall, Fontan patients have decreased long-term survival, progressively deteriorating functional status and an increased risk of late sudden death, which means that the procedure is considered to be palliative rather than curative.[6] Aside from the impact of Fontan physiology, the process of ageing itself has potentially important effects such as increasing pulmonary artery pressure (PAP)[7] and ventricular diastolic dysfunction. Preservation of Fontan physiology and prevention of failure is therefore of potential importance, but no treatment has been demonstrated to be efficacious. Should Fontan circulation fail, there are currently limited surgical or medical options and a lack of evidence-based guidelines to assist in management. The current review aims to give an overview of the Fontan procedure and physiology and its impact on morbidity over the longer term. Current treatment options and the high need and demand for new strategies to manage the failing Fontan are also discussed, focussing on therapies targeting elevated pulmonary vascular resistance (PVR) and the rationale for their use.

EPIDEMIOLOGY

There are few epidemiological estimates of patients who have undergone Fontan procedures. The prevalence of conditions requiring Fontan surgery in Egypt was estimated to be 0.9 per 100 000 school-aged children,[8] and the frequency of Fontan procedures in Australia was estimated to be 10.0 per 100 000 live births.[9] The number of patients with Fontan physiology is expected to increase as more procedures are performed and patients' survival continues to improve. In the UK, for example, 150 Fontan procedures were performed in 2006–7.[10] These numbers transposed worldwide emphasise the increasing number of Fontan patients we may encounter in the future. Refinement of the surgical technique and pre and postoperative care has resulted in a decrease in short and intermediate-term mortality. Taken together, these developments mean there is a growing number of surviving patients and problems associated with long-term survival post-Fontan are becoming increasingly prevalent and important.

THE FONTAN PROCEDURE

The Fontan procedure is used mainly in patients who have complex cardiac malformations with a single functional ventricle (eg, tricuspid atresia, pulmonary atresia with intact ventricular septum, double inlet ventricle, hypoplastic left heart syndrome). The procedure effectively places the systemic and pulmonary circulation in series, aiming to allow both systems to be driven by the single ventricular chamber. However, while the systemic circulation is driven effectively by the single ventricle, the majority of the pulmonary blood flow, which comes directly from the venae cavae, is driven by negative intrathoracic pressure.

The procedure has been modified since its introduction (figure 1).[2] The earliest method of atriopulmonary connection resulted in a high incidence of re-operation and arrhythmias and is generally considered to be obsolete. Total cavopulmonary connection (TCPC) is considered the method of choice and is usually performed using a two-stage operation. Connection of the superior vena cava to the right pulmonary artery (Glenn procedure or hemi-Fontan) is generally performed at 3–9 months of age, with TCPC being performed at approximately 1–5 years of age. TCPC can be achieved using two different techniques (intracardiac or extracardiac) to join the inferior vena cava to the pulmonary artery and is preferentially used

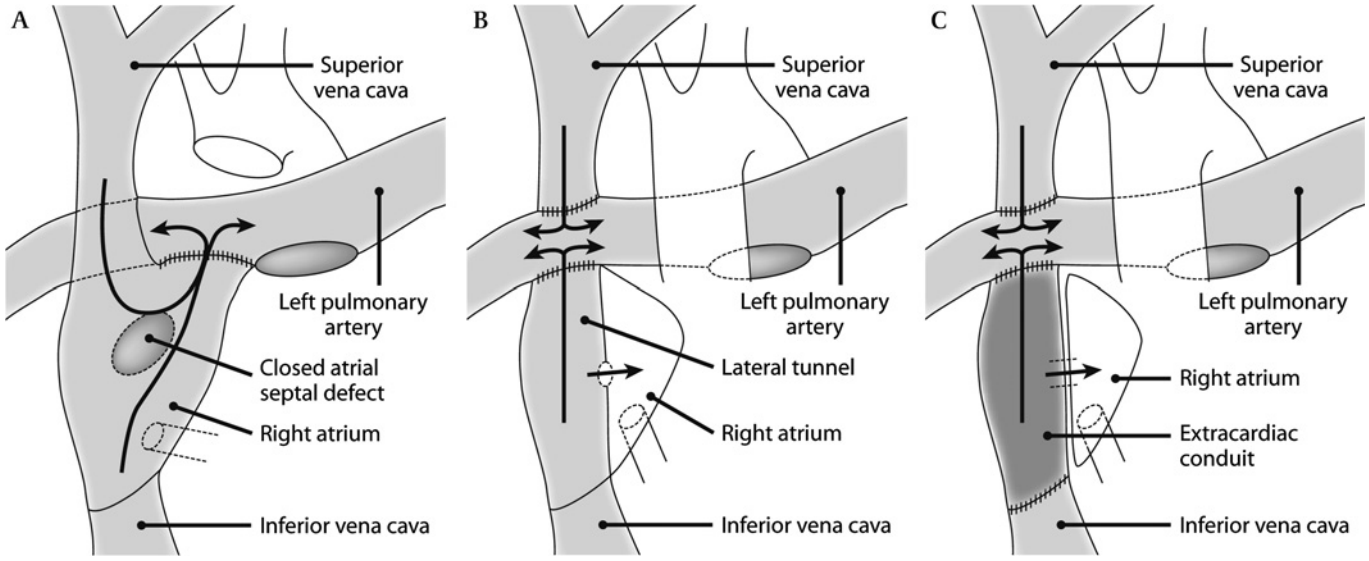

Figure 1 Different types of Fontan circulation. (A) Atriopulmonary connection; (B) intracardiac total cavopulmonary connection (lateral tunnel); (C) extracardiac total cavopulmonary connection. Reprinted with permission from Macmillan Publishers Ltd: Nature Reviews Cardiology (2), copyright (2005).

in patients aged over 3 years.[2] In high-risk patients, the use of a small fenestration allowing a residual right-to-left shunt limits caval congestion and increases cardiac output, reducing perioperative mortality and morbidity.[11]

Recommendations for successful outcome include unobstructed ventricular inflow, (ideally) normal systolic and diastolic ventricular function, unobstructed outflow, pulmonary arteries of sufficient size, absence of atrioventricular valve regurgitation or stenosis, well-developed distal vascular bed, unobstructed pulmonary venous return and (near) normal PVR. In general, patients with increased PVR (>2–3 Wood units) and mean PAP greater than 15 mm Hg are not considered suitable candidates.

FONTAN PHYSIOLOGY

A successful procedure is associated with a range of benefits including improved arterial saturation and the abolishment of chronic volume overload. Most patients with successful Fontan are able to live a fairly normal everyday life. The vast majority of parents of children with Fontan physiology describe their child's general health as being excellent or good, and rate their school performance as better than or equal to average.[12] Several studies, however, have shown that Fontan patients have decreased maximal exercise capacity largely related to reduced cardiac output and pulmonary blood flow.[13–15]

Despite the benefits of the Fontan procedure, it has an impact on the single systemic ventricle and the systemic and pulmonary circulation. The 'normal' haemodynamic situation in a patient with Fontan physiology is typically characterised by elevated pressure in the cava system with decreased, non-pulsatile blood flow causing recurrent blood stasis and even reverse flow. This can lead to malfunction of the lymphatic system and hepatic congestion, which may cause coagulation factor abnormalities and chronic (micro) thrombosis. Fontan physiology is also characterised by decreased preload and increased afterload, which has a profound effect on the single ventricle, leading to hypertrophy that may regress over time, persistent abnormal ventricular relaxation and reduced compliance.[2] Fontan physiology exerts a considerable impact on the pulmonary circulation, characterised by increased pulmonary vascular impedance. The lack of a pulsatile blood flow has major effects on endothelial function, vascular recruitment and lung vessel growth, which in turn influence PVR, a key contributor to cardiac output. The long-term consequences of these abnormalities are becoming of increasing concern as the population of survivors increases.

LONG-TERM OUTCOMES OF FONTAN PHYSIOLOGY: THE FAILING FONTAN

Several complications have been identified that may occur after the postoperative period following the Fontan operation (see box 1). Such complications may arise at any time, in any patient, and frequently progress over the years. With improved survival, more cases of failing Fontan are emerging, with progressive deterioration associated with declining functional status, reduced health-related quality of life and, in severe cases, premature death. The consequences of failing Fontan include below-average cognitive development, retarded growth, decreased exercise tolerance, ventricular dysfunction, systemic venous thrombi, ascites, peripheral oedema and hepatomegaly. Lymphatic dysfunction is also observed in Fontan patients, including protein-losing enteropathy (PLE), which is associated with very high mortality and is characterised by lymphatic fluid

Box 1 Complications arising in patients with Fontan circulation

- Ventricular dysfunction
- Atrial dysrythmia (intra-atrial re-entry tachycardia; atrial flutter)
- Hypoxaemia
- Exercise intolerance
- Elevated pulmonary vascular resistance
- Protein-losing enteropathy
- Plastic bronchitis
- Hepatic complications (fibrosis, cirrhosis; oesophageal varices)
- Thrombosis (pulmonary embolism, stroke)
- Renal complications

leaking into the gut and intestinal lymphangiectasia.[16 17] Another rare condition associated with the lymph system is plastic bronchitis, which occurs when casts of fibrinomucoid material form in the tracheobronchial tree, causing obstruction of the airways. Both of these complications could possibly lead to increased PVR and pulmonary hypertension,[3] as typified by patients with pulmonary hypertension associated with lymphangiomatosis (group 5 pulmonary hypertension). However, data related to these conditions are limited, so it is difficult to draw conclusions on possible treatment and disease progression. Although the effect of Fontan circulation on the kidneys has not been fully defined, data suggest that there is a high incidence of pathological microalbuminuria, an indicator of renal injury, in Fontan patients.[18] Long-term complications related to the liver have also been observed in Fontan patients. Chronically increased hepatic venous pressure resulting from the Fontan procedure might lead to chronic passive congestion, cardiac cirrhosis, hepatic adenoma and hepatocellular carcinoma.[19]

The recognition of risk factors may facilitate management decisions and several have been identified. Preoperative ventricular function and elevated PAP are major risk factors, and older age at operation, higher postoperative PAP at 24 h, arrhythmia postoperatively or during follow-up and requirement for anticoagulation during follow-up are related to morbidity.[5 20] Patient age—independent of age at operation—may also be a factor given the natural deterioration in cardiopulmonary function. For example, there is a progressive increase in mean PAP with age in normal individuals, which may be due to vascular or ventricular dysfunction, and mean PAP during exercise is significantly higher in older individuals (>50 years) and frequently exceeds 30 mm Hg.[7]

As the Fontan procedure was developed approximately three decades ago, the first patients are only now reaching their third and fourth decades of life and data in older patients with Fontan physiology will increasingly become available. Although the underlying pathophysiology of the failing Fontan is probably multifactorial, it is likely that a major underlying cause is alterations in, and damage to, the pulmonary vasculature. Therefore, other factors relating to pulmonary vascular bed function, such as pre-Fontan pulmonary blood flow due to systemic-to-pulmonary artery shunting and the presence or timing of palliation may also prove important. It is noteworthy that the pulmonary vascular bed may be affected before the Fontan procedure itself due to increased pulmonary blood flow. For example, in infants with a functional single ventricle and unobstructed pulmonary blood flow, palliation (eg, pulmonary artery banding, pulmonary artery division and shunt) is recognised as being important in protecting the pulmonary vascular bed and ensuring suitability for a subsequent Fontan procedure. The timing of this palliation may also have implications for later pulmonary vascular function.

Many post-Fontan complications arise as a result of increased venous pressure and congestion, and chronic low cardiac output. Given the lack of ventricular force to drive blood flow through the pulmonary arteries, a low PVR is mandatory for a well-functioning Fontan circuit. In the postoperative period, even small increases in PVR can lead to systemic venous hypertension associated with low cardiac output syndrome despite a technically successful operation.[21] In fact, a slight increase in PVR at any time to levels that would be readily tolerated in normal physiology may result in progressive failure of Fontan circulation. Unfortunately, the measurement of PVR using right heart catheterisation remains difficult, especially if there is a low cardiac output, collateral arteries, or fenestration. This is further complicated by the fact that the transpulmonary gradient can double when biventricular circulation is restored following the Fontan procedure.[22] There is therefore a potential role of MRI in the future for non-invasively estimating PVR.

The underlying mechanism behind increased PVR in Fontan patients is unclear and is likely to be multifactorial. In Fontan physiology, blood flow through the pulmonary arteries is non-pulsatile and largely driven by negative intrathoracic pressure (plus systemic blood pressure) rather than by the right ventricle. Pulsatile pulmonary blood flow plays an important role in the reduction of PVR by passive capillary recruitment.[23] When cardiac output increases in a normal individual, as in response to exercise, previously unperfused and underperfused pulmonary vessels are recruited, thereby responding to the increase in flow by decreasing PVR, resulting in a small increase in mean PAP relative to the increase in cardiac output. In the absence of pulsatile flow recruitment is reduced, potentially resulting in increased PVR.[23 24] Pulsatile flow is also important in regulating the shear-stress-mediated release of a number of endothelium-derived vasoactive molecules, and dysregulation of this mechanism may also lead to endothelial dysfunction.[25]

A number of endothelium-derived vasoactive factors have been implicated in the pathophysiology of the endothelial dysfunction characteristic of diseases such as pulmonary arterial hypertension (PAH).[26] The combination of chronic impairment in the production of vasoactive mediators, such as endothelium-derived nitric oxide (NO) and prostacyclin, together with prolonged overexpression of vasoconstrictors such as endothelin 1, leads not only to abnormalities in vascular tone, but also characteristic vascular remodelling and proliferation, endothelial dysfunction and associated increases in PVR.[26] Studies of the expression of a number of these factors suggest that Fontan patients also have endothelial dysfunction, although there is a lack of histological data directly demonstrating changes to the vascular bed.

Exogenous NO, a vasorelaxant that also acts to prevent the proliferation of smooth muscle cells, reduces basal PVR in Fontan patients.[24] Patients with failing Fontan have been shown to overexpress endothelial NO synthase relative to normal controls and patients with good surgical outcomes, possibly indicating a role in endothelial dysfunction.[27] Endothelin is a potent vasoconstrictor with proliferative and hypertrophic effects on vascular smooth muscle cells. Although data are conflicting, it appears that endothelin levels are increased in Fontan patients in the acute postoperative phase and long after surgery. In the acute postoperative phase, plasma endothelin is elevated and positively correlates with PVR[28] and central venous pressure.[29] Such acute postoperative increases in endothelin, and thus PVR, were prevented by removing endothelin and other factors from the blood using ultrafiltration.[30] Endothelin was found to be elevated in late-phase Fontan patients compared with healthy controls.[31] However, although levels were significantly increased in proximal intra-acinar pulmonary arteries in patients with failing Fontan relative to controls, elevated endothelin was not observed in the distal vasculature and did not predict failure.[30]

MANAGEMENT OF PATIENTS WITH A FAILING FONTAN CIRCULATION

Currently, few treatment options exist for failing Fontan and management remains a major challenge. Surgical or interventional procedures aimed at correcting specific defects, such as obstruction of the systemic venous connection or pulmonary venous return, may be considered. Atrial arrhythmia resulting

from older Fontan circuits can be successfully treated by converting to a lateral tunnel, combined with a right atrial maze procedure; lack of atrioventricular synchrony and sinus node dysfunction may be treated with pacemaker therapy if appropriate.[32] Surgery may also be required to treat complications arising from Fontan physiology. The recognised treatment for plastic bronchitis, for example, is bronchoscopic extraction supported by acute therapy to aid the removal and expectoration of casts.[33]

Heart transplantation may be the only option for some patients; outcomes can be good in children, [34] although there are presently fewer data in adults.[35 36] However, risks are greater than in most other heart transplant recipients due to the severity of illness in these patients, with observed mortality rates as high as 23%.[37] Technical complications (complex anatomy, adhesions from previous surgery, increased risk of bleeding, etc), and an increased risk of immune responses due to previous perioperative transfusions contribute to this risk.[38] Importantly, high PVR is a strong predictor of mortality[39]; as very few Fontan patients have a PVR higher than 5 Woods units—the usual upper limit for considering transplantation and a value indicating a very unsuccessful Fontan procedure—further data are required. It might be advantageous to treat patients in a period before surgery with a therapy that lowers PVR, as a 'bridging' treatment. This approach has been suggested in other conditions in which high PVR is associated with high postoperative mortality.[40] Again, there are no clinical data to inform us about this interesting possibility in Fontan patients and clinical trials are required if this is to be considered. It is worth remembering that a Fontan patient with a severe increase in PVR would be in a very serious condition; it is uncommon to have PVR in a range that does not allow for cardiac transplant. The shortage of donor organs is a further limitation.

Medical management has involved treating specific manifestations such as ventricular dysfunction, PLE and increased PVR. A variety of agents has been used to treat ventricular dysfunction in Fontan patients, but there are few supportive data, and evidence suggests such agents generally have little or no benefits due to lack of impact on reduced preload. Inotropes have been shown to exert positive short-term effects in acute ventricular dysfunction,[41 42] although their effects in chronic ventricular dysfunction are unknown. ACE inhibitors have no effect on exercise capacity, systemic vascular resistance, resting cardiac index, or diastolic function in Fontan patients,[43] and even long-term use does not affect cardiac autonomic nervous activity indexes.[44] Despite this lack of evidence, however, many long-term Fontan patients are treated with ACE inhibitors. Similarly, although β-adrenoceptor antagonists are used in Fontan patients with heart failure, evidence to support their efficacy is very limited.[45]

Treatment of PLE generally involves multiple strategies based on improving ventricular dysfunction, membrane stabilisation and improving protein homeostasis through nutritional support and protein replacement.[41] However, as the underlying aetiology of PLE is unknown, treatment tends to be arbitrary and success variable. Subcutaneous heparin has been reported to induce remission in children and adults,[46–48] although findings are inconsistent, and a recent study reported that, despite subjective improvement of PLE symptoms, treatment did not appear to improve outcome compared with conventional therapy alone.[49] Recent data suggest that the steroid budesonide, which is metabolised first in the liver, was effective at treating PLE.[50] Other therapies with reported benefits in PLE following Fontan include spironolactone,[51] somatostatin[52] and sildenafil.[53]

Low cardiac output, excessive hypoxaemia, or PLE may all be clinical manifestations of increased PVR, the prevention or management of which is therefore potentially of critical importance. Therapies approved for PAH may therefore provide benefits in this patient population. These treatments have led to considerable improvements in survival for paediatric PAH patients, with recent overall survival rates of 90.5%, 82.8% and 64.2% at 1, 3 and 5 years, respectively, compared with a survival time of less than a year in historical untreated controls.[54] The predicted survival for paediatric patients with postoperative congenital heart disease at 1 and 3 years is 88.2% and 73%, respectively.

Inhaled NO is predominantly effective in patients with central venous pressure of 15 mm Hg or greater, a transpulmonary pressure gradient of 8 mm Hg or greater, or both.[55] Inhaled NO in combination with milrinone in the early postoperative phase reduces the transpulmonary pressure gradient more than either drug alone.[56 57] Prostacyclins have been rarely used in perioperative Fontan patients; beraprost reduces mean PAP and PVR in preoperative Fontan candidates with mild pulmonary hypertension, [58] and epoprostenol has been shown to prevent the rebound effect after inhaled NO cessation in the early postoperative phase.[59] When oral administration becomes possible, sildenafil is often used in the postoperative period as it is perceived as safe, with fast onset and good effectiveness. However, sildenafil is not approved for this use and there are no published data to support its efficacy or safety in this indication.

There are few observations describing the effects of PVR-lowering drugs in the treatment of patients with failing Fontan. Treatment of late Fontan patients with inhaled NO reduces PVR, although it has no significant effect on cardiac index.[19] A single dose of sildenafil has been shown to improve exercise capacity and haemodynamic response to exercise (figure 2).[60] There are also single-case studies showing improvement in a patient with plastic bronchitis and a patient with PLE following sildenafil.[53 61] The effect of sildenafil on exercise tolerance, ventricular function and health-related quality of life is currently under investigation in children who have undergone the Fontan procedure.[62]

Bosentan has been shown to improve exercise capacity, functional class, health-related quality of life and haemodynamic parameters (including PVR and PAP) in patients with PAH.[63 64] Long-term treatment with bosentan improved symptoms and aortic oxygen saturation, functional class, maximal and submaximal exercise capacity, the Borg dyspnoea index, mean PAP, pulmonary blood flow and PVR in a patient with plastic bronchitis following Fontan.[65] In a small study, oxygen saturation

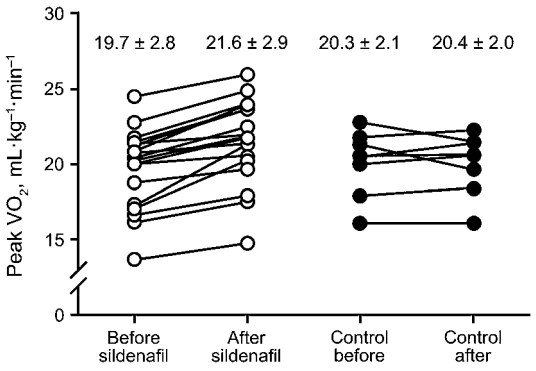

Figure 2 Individual changes in post-exercise peak oxygen uptake (VO_2) following a single dose of sildenafil or no treatment (controls) in Fontan patients. Numerical data are presented as mean±SD.

improved in five of nine patients during a 16-week treatment period with bosentan.[66] No data are available describing the use of ambrisentan or sitaxentan in Fontan patients. The effect of long-term bosentan treatment on the liver is a potential concern for treating Fontan patients, especially in patients with hepatic complications. Elevated aminotransferases are a recognised class effect of endothelin receptor antagonists such as bosentan, and monthly liver function tests are required. However, data from adults with portopulmonary hypertension treated with bosentan show there was no evidence of drug-related liver injury.[67] Moreover, data from the post-marketing surveillance of patients with PAH suggest that patients with PAH associated with congenital heart disease are less likely to develop liver enzyme problems than those with other types of PAH.[68]

Given the important role of the pulmonary vascular circulation in Fontan physiology, the demonstrated increase in PAP with age, and the current lack of data, there is a major requirement for clinical studies on the efficacy and safety of potential therapies for failing Fontan on which to base much needed management recommendations.

CONCLUSIONS

Since its inception in the early 1970s, the Fontan procedure has become the method of choice for patients with a single anatomical and/or functional ventricle. Over the years, the procedure has undergone a range of modifications and improvements that has led to an exponential increase in the number of post-Fontan survivors. The procedure is considered to be palliative rather than curative and there is continual attrition of Fontan physiology over time associated with a range of clinical features, which, in some patients, result in Fontan failure. Although the exact pathophysiology of failing Fontan remains to be fully established, one important consideration is the maintenance of low PVR, which is essential for a functioning Fontan physiology. Ideally, long-term management should prevent increasing PVR, but to date there are no data on how to support this goal. Currently available PAH therapies have been tested for the treatment of pulmonary vascular dysfunction and/or the preservation of endothelial function. Experience in PAH associated with and limited data with these agents in Fontan patients provide a rationale for the conduct of clinical trials in patients with Fontan circulation. The results of such trials would help in the development of much needed treatment strategies and guidelines for this increasingly important patient population.

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