Table 3 Long term Fontan surveillance

	Parameters	Monitoring
Constitutional	Adequate growth in childhood Weight or muscle loss in adulthood Avoid overweight Blood pressure: normotensive Functional classification, Aerobic activity Daily napping	Aerobic activity Exercise testing
Cardiac haemodynamics	Heart size Atrial dilatation Atriopulmonary anastomosis Pulmonary narrowing, distortion Pulmonary venous or atrioventricular (AV) inflow obstruction AV valve regurgitation or stenosis Aortic insufficiency Ventricular outflow obstruction Arch obstruction Ventricular function	Echocardiogram Periodic chest radiograph Cardiac MRI or CT
Rhythm	Presence of atrial versus junctional rhythm Resting heart rate Chronotropic response to exertion Arrhythmia development	Periodic 24 h ambulatory monitoring; event monitoring
Pulmonary	Hypoxaemia Vascular resistance	Oxygen saturation, resting and exertional
Endocrine	Thyroid function	Thyroid stimulating hormone (TSH), thyroxine (T4)
Renal		Blood urea nitrogen, creatinine
Hepatic	Hepatomegaly Cardiac cirrhosis Synthetic function	Liver function: enzymes, coagulation Abdominal ultrasound, CT or MR Liver biopsy Serum α-fetoprotein
Gastrointestinal	Bloating, distension, diarrhoea, ascites, gallstones	Stool α-1 anti-trypsin
Haematologic	Anaemia, polycythaemia, thrombocytopenia	Blood count, platelets
Metabolic		B-type natriuretic peptide, albumin, alkaline phosphatase
Neurologic	Cerebrovascular accident Depression	

the collective memory of the earlier high mortality or prolonged hospital courses associated with primary Fontan surgery in past decades has made many clinicians reluctant to recommend additional interventions, particularly without overt symptoms.

In addition to standard haemodynamic evaluations, more global assessment of the impact of the Fontan physiology on other organ systems needs to become part of routine surveillance (table 2). It cannot be assumed that the patient has other healthcare providers with adequate knowledge of the impact of the Fontan circulation to monitor these systems. Growth failure in childhood and weight loss in adulthood are advanced manifestations of inadequate haemodynamic status. In adulthood, exercise intolerance may result in extremes of a sedentary lifestyle and result in obesity. By contributing to alterations in pulmonary function[w22] and increased systemic vascular resistance, overweight contributes rapidly to Fontan failure. Patients should be counselled on the importance of regular aerobic activity for conditioning, and avoidance of overweight as essential to limiting Fontan failure.

In the USA, the cardiologist caring for Fontan patients is now asked to routinely monitor and assess other organ systems, including haematologic, endocrine, pulmonary, hepatic and gastrointestinal, within the confines of decreased reimbursement for testing and shorter office visits. The barriers to sophisticated medical care for the older Fontan patient encompass difficulties in education of the patient relative to the need for regular cardiac care, availability of comprehensive integrated care centres with sufficient expertise, and in many countries the lack of healthcare coverage. Nonetheless, it is apparent that a change in practice for the routine long term follow-up of Fontan patients is necessary in order to detect progressive subtle decline in status and to have a favourable impact on the functional status of these unique survivors (table 3). Failure to change our standard methods of routine cardiac care in this setting constitutes a failure of optimal medical management. Chronic pulmonary vasodilator therapy, in addition to chronic diuresis, may become part of routine long term medical therapy as this population ages.[w25]

Management of the failing Fontan circulation: key points

- Symptoms develop at an advanced stage of declining Fontan circulation.
- Identification of the 'failing' Fontan before the development of ascites or protein-losing enteropathy is essential to improve outcomes.
- Monitoring functional status, rhythm, serum biomarkers, and liver changes is essential to long term assessment of 'cardiac' status.
- Ablation procedures for atriopulmonary Fontan patients have a low likelihood of success.
- Aggressive therapy for rhythm and haemodynamic abnormalities may improve long term functional status.

The Fontan operation: the long-term outlook

Daphne T. Hsu

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PINION

Purpose of review

As perioperative survival following the Fontan procedure has improved and more patients are reaping the benefits of physiologic palliation, the costs of longstanding systemic venous hypertension and the functional limitations of a single ventricle are becoming clearer. Arrhythmias, heart failure, protein-losing enteropathy, hepatic cirrhosis, pulmonary hypertension, and ventricular dysfunction are common in late survivors and result in significant morbidity and mortality. Current research is focused on characterizing late morbidities and developing risk-prediction models for worse outcomes in long-term survivors.

Recent findings

Ten-year survival following the Fontan procedure is now 94–98%; however, estimated conditional survival in survivors aged above 18 years is 60% at 40 years of age. Atrial arrhythmias and heart failure are the leading causes of morbidity and mortality. Hypoplastic left heart syndrome, hepatic dysfunction, decreased exercise tolerance, lower quality of life, and markers of neurohormonal activation have been associated with worse outcome. Improvements in exercise tolerance are seen with selective pulmonary vasodilator therapy and exercise training. Heart transplant continues to be an effective therapy for end-stage Fontan failure, and reports of the use of traditional mechanical assist devices and the development of right heart assist devices in the setting of passive venous flow are ongoing.

Summary

Over a generation has passed since the Fontan procedure revolutionized the care of patients with a single ventricle. Data generated from retrospective and prospective observational studies in long-term survivors are identifying patients at risk.

Keywords

adult congenital heart disease, common ventricle, Fontan procedure, heart failure

INTRODUCTION

during open heart surgery, and the presence of residual lesions and chronic cyanosis all contribute to the occurrence of systolic and diastolic ventricu- lar dysfunction in long-term survivors.

The clinical manifestations of venous conges- tion and ventricular dysfunction after the Fontan procedure have been recognized for many years, and include arrhythmias, protein-losing enteropathy, chronic effusions, malnutrition, growth failure, exercise intolerance, and heart failure. Only recently has the population of long-term survivors reached sufficient numbers to allow identification of risk

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The introduction of the Fontan procedure in 1971 as a treatment for patients with tricuspid atresia was a milestone in the field of congenital heart surgery. The benefits of separating the pulmonary and systemic circulations and establishing near-normal systemic oxygen saturation have been realized as evidenced by a growing population of patients with a single ventricle who are surviving into adulthood. These long-term survivors are manifesting a variety of new diseases related to the chronic elevation of systemic venous pressure inherent in the establish- ment of a direct connection between the systemic veins and the pulmonary arterial bed (Table 1). As the diagnoses treated with the Fontan procedure have expanded far beyond tricuspid atresia to include patients with right ventricular and univen- tricular systemic ventricles, traditional signs and symptoms of heart failure are also impacting on quality of life and survival. Abnormal ventricular morphology, volume overloaded circulation in early life, repeated exposure to controlled ischemia factors for these morbidities and their resultant mortality. The current literature includes a growing body of reports from single-center and multicenter retrospective analyses and secondary analyses of databases. Interpretation of these data can be lim- ited by variations in surgical approach between eras and between centers, variation in medical care between centers, and inaccuracies in data collection for nonclinical purposes. The feasibility of perform- ing prospective, observational studies is improving with the increased availability of electronic data capture, the emphasis on quality metrics, and the commitment on the part of the

clinicians to main- tain data integrity. Therapeutic trials in this popu- lation are beginning to be performed, although feasibility is limited for a number of reasons includ- ing insufficient power to detect clinical endpoints, lack of validated surrogate outcomes for relatively rare clinical events, paucity of research infrastruc- ture to support multicenter collaboration, and wide variations between centers in the approach to care. This summary will highlight several areas of ongoing research in long-term survivors of the Fon- tan procedure ranging from current survival stat- istics to the development of a mechanical right ventricular assist device.

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Table 1. Long-term morbidities of the Fontan procedure

Arrhythmia

Protein-losing enteropathy

Plastic bronchitis

Hepatic cirrhosis

Thrombosis and thromboembolism

Pulmonary hypertension

Heart failure

CURRENT OUTCOMES

In 2008, investigators from the congenital cardiac centers in Australia and New Zealand established a population-based registry of patients who had undergone the Fontan procedure after 1975 and survived hospital discharge [1&&]. Retrospective data collection was performed for those enrolled prior to 2010 with ongoing data collection after enrollment, and patients who underwent the Fontan procedure after 2010 were enrolled prospectively on an opt-out basis. An analysis of the first 1006 hospital survivors indicates that overall Kaplan–Meier estimates of survival at 15, 20, and 25 years are 93, 90, and 83%, respectively, although the 25-year survival of the oldest patients who received an atriopulmonary connection was 75% (Fig. 1) [2&&]. Risk factor analyses identified the type of Fontan (atriopulmo- nary), age at Fontan, hypoplastic left heart syn- drome, and length of stay after the Fontan as the most common risk factors for late mortality and heart failure.

There are indications that modifications of the Fontan procedure, in particular, the use of an extrac- ardiac conduit, have improved survival, although it is difficult to distinguish the beneficial effects of a particular surgical approach from improved perio- perative management. In the Australia and New Zealand Fontan registry cohort, survival in patients who underwent an extracardiac conduit Fontan procedure was 96% at 14 years; however, hypoplas- tic left heart syndrome remained a risk factor for late adverse events and late failure [3&&]. Reports from the Japan and the United States estimate a similar 10-year survival of 94–96% in patients who received an extracardiac conduit [4,5]. Dabal et al. reported no late phase of increasing death with this approach, raising the possibility that late morbidity and mortality will also be significantly improved [4].

LATE MORTALITY

Adult congenital specialists at the Toronto General Hospital modeled Kaplan – Meier survival curves using a cohort of single ventricle patients who had survived to age 18 years and were able to estimate future survival to be 60% at 40 years of age (Fig. 2) [6&&]. During 2003–2004, the United States National Institutes of Health/National Heart Lung and Blood Institute-funded Pediatric Heart Network performed a cross-sectional study including exercise testing, quality-of-life assessments, echocardiograms, and serum B-type natriuretic peptide (BNP) levels in a group of relatively asymptomatic Fontan survivors between the age of 6 and 18 years. In 2015, the investigators published a follow-up study reporting the mortality and incidence of adverse events in this cohort and analyzing the predictive value of serum BNP, exercise testing, and quality-of-life measures [7&&]. The incidence of death or transplant was 5% during the 7-year follow-up period, and patients with an elevated BNP greater than 21 pg/ml and a lower Child Health Questionnaire score (<44) at enrollment were significantly more likely to have met the primary endpoint during the time interval between the assessments.

LATE MORBIDITY

An analysis of the current single ventricle popu- lation in the North of England estimates that the

population of adult single ventricle patients will increase 60% over the next 10 years [8]. Although newer surgical approaches offer the possibility of a smoother course in the future, the vanguard patients are at a high risk for the development of cardiac and noncardiac complications related to elevated atrial and systemic venous pressure and ventricular failure. In the Australia and New Zealand Fontan Registry, freedom from Fontan failure (defined as death, trans- plantation, takedown, conversion to extracardiac conduit, New York Heart Association class III/IV, or protein losing enteropathy/plastic bronchitis) was 70% by 20 years after the Fontan [2&&]. Freedom from adverse events (failure, supraventricular tachycardia, stroke, pulmonary embolism, pacemaker insertion) was 29% by 25 years.

In an analysis of the Nationwide Inpatient Sample from 2000 to 2011, 40% of adult patients with single ventricle were admitted with the diag- nosis of an arrhythmia and 24% of the patients were admitted with heart failure. In-hospital mortality was 7% in the heart failure patients and 2.5% in those with arrhythmias [9&]. The incidence of comorbidities such as obesity, hypertension, diabe- tes, hepatic disease, pulmonary disease, renal dis- ease, and coagulopathy was striking in the heart failure patients who were a mean of 34 years old. In

a different cohort of adult patients studied more than 15 years after the Fontan procedure, portal hypertension, systemic oxygen desaturation, and the presence of a pacemaker were identified as risk factors for major adverse events [10].

ARRHYTHMIAS

In the Australia and New Zealand Fontan Registry, the incidence of atrial tachyarrhythmias was high. Patients who had an atriopulmonary connection had an incidence of atrial tachyarrhythmias of 50% by 15 years post-Fontan [2&&]. Atrial isomerism was associated with supraventricular tachycardia, with a hazard ratio of 15.2. The rationale for intro- ducing the extracardiac conduit approach was based on the hope that it would be associated with a lower incidence of atrial arrhythmias compared to the atriopulmonary and lateral tunnel Fontan. This has been proven to be true when compared to the atriopulmonary connection [2&&,11]. However, a large multicenter study comparing the incidence of atrial arrhythmias in patients following the extracardiac conduit versus the lateral tunnel found no difference in the 20 – 25% incidence of late arrhythmias seen in both groups [12&].

PROTEIN-LOSING ENTEROPATHY AND PLASTIC BRONCHITIS

Protein-losing enteropathy and plastic bronchitis are two of the most intractable morbidities associ- ated with the Fontan procedure. Schumacher et al. [14&] used social media to power a survey of Fontan patients and described patient-specific factors associated with a diagnosis of protein-losing enter- opathy or plastic bronchitis. Seventy-six patients with protein-losing enteropathy and 46 patients with plastic bronchitis were compared with controls matched by year of Fontan surgery. A history of hypoplastic left ventricle and cardiothoracic surgery post-Fontan were associated with protein-losing enteropathy. A history of chylothorax was associ- ated with both protein-losing enteropathy and plastic bronchitis. The Mayo Clinic reviewed 42 patients who developed protein-losing enteropathy from 1992 to 2010 and reported an 88% 5-year survival. These investigators proposed a systematic approach to evaluation and individualized treat- ment based on the underlying physiologic and ana- tomic abnormalities [15&]. Similarly, Avitabile et al. [16&] reported on a small series of patients with plastic bronchitis and proposed a step-wise evalu- ation and treatment algorithm.

atrial tachyarrhythmias. A recent study described the mechanisms of tachycardia in patients with the total cavopulmonary connection and found that the arrhythmia mechanisms were highly variable. The mechanisms of arrhythmia were not all related to

sites of surgical anastomoses, but could also be attributed to underlying conduction abnormalities [13&]. Macro-re-entrant (30% of cases) and atrioven- tricular nodal re-entry (8% of cases) were the most common mechanisms identified. In this series, the arrhythmia recurred in 50% of patients within 18 months of ablation. In patients who had a recur- rence, ablation was demonstrated to favorably modify arrhythmia severity. An interesting retrospective analysis compared the ratio of arterial elastance to ventricular end- systolic elastance in nine patients with protein-los- ing enteropathy to eight patients without protein- losing enteropathy undergoing cardiac catheteriza- tion [17]. Patients who had protein-losing enterop- athy had a contractility-afterload mismatch caused by an increased afterload, suggesting that therapies aimed at decreasing afterload may be beneficial. A description of successful selective lymphatic embo- lization demonstrates a possible mechanism for plastic bronchitis by documenting retrograde flow from the thoracic duct into a lymphatic collateral supplying a dilated peribronchial lymphatic net- work surrounding the right hilum [18].

THROMBOSIS AND THROMBOEMBOLISM

A recent literature review focused on thrombosis and thromboembolic complications in Fontan patients and found a variable incidence of 3–20% with mortality rates up to 38% [19]. A treatment algorithm was proposed by the authors that recom- mended the use of warfarin for the first year after the Fontan procedure, followed by aspirin in low-risk patients and continued use of warfarin in patients with a persistent fenestration, poor ventricular func- tion, arrhythmia, protein-losing enteropathy, or prior thrombosis. One small series of adult Fontan recipients reported a lower platelet count and an increased level of platelet activation markers, indi- cating relative platelet resistance – a finding that requires further study [20].

Ohuchi et al. [21&] reported a large retrospective analysis of thrombotic and hemorrhagic events in 412 patients treated at a single center with 21 differ- ent anticoagulation protocols. Comparisons of treatment efficacy were not feasible; however, the overall incidence of hemorrhagic events was higher than thrombotic events and was related to the use of warfarin. This highlights the need to tailor antico- agulation therapy on an individual basis, weighing carefully the risk of thrombosis against the risk of a hemorrhagic event.

HEPATIC FIBROSIS AND CIRRHOSIS

Hepatic fibrosis and cirrhosis are becoming widely recognized as important morbidities in long-term survivors of the Fontan procedure. Progressive hep- atic cirrhosis is a risk factor

for the development of hepatocellular carcinoma, gastrointestinal bleeding, hepatic failure, and hepatic encephalopathy, and may be a contraindication to heart transplantation [22 – 25]. In a small series of asymptomatic patients a mean of 16 years post-Fontan, a liver biopsy was performed during cardiac catheterization and hep- atic fibrosis was present in 18/21 (85%) patients. Hepatic and renal function and platelet count did not correlate with the degree of fibrosis [26&]. There is a great deal of effort being made to identify a sensitive, noninvasive method to serially monitor patients for progressive hepatic fibrosis and avoid the need for liver biopsy. In the symptomatic patient, abnormalities in the transaminases and platelet count may be present, but are not sensitive predictors of the degree of fibrosis [27]. The quanti- fication of liver stiffness by transient elastography, supersonic shear imaging, or magnetic resonance (MR) elastography as a measure of the degree of fibrosis holds some promise, but these techniques have not been widely adopted as screening tools [23,28 – 31].

PULMONARY HYPERTENSION

The pulmonary vascular bed is an important factor in the success or failure of the Fontan circulation. A small study of pulmonary vascular histomorphom- etry and immunohistochemistry was performed using tissue obtained at autopsy in 12 Fontan patients who died more than 5 years after Fontan completion [32&]. This study demonstrated a decrease in medial thickness and an increase in intimal thickness that correlated with the age at death and time since Fontan, and also revealed a reduction of vascular smooth muscle cells in the media and an increase in acellular fibrosis in the intima. The use of selective pulmonary vasodilators such as sildenafil and bosentan to treat Fontan fail- ure is undergoing investigation [33,34&&,35]. The results of the TEMPO study – a randomized, placebo-controlled, double-blinded study compar- ing the effects of Bosentan to placebo in a group of 75 adolescents and adults – were published in 2014 [34&&]. Peak VO2 was statistically significantly higher in the Bosentan group after 14 weeks of therapy, but the absolute increase was only 2ml/kg/m2. There was also a significant improvement in heart failure class and exercise time in the Bosentan group. There were no significant adverse effects.

HEART FAILURE

Heart failure in the Fontan patient has a slow, insidious course characterized by a progressive deterioration of exercise capacity. It is exacerbated by arrhythmias, protein-losing enteropathy, and malnutrition. In adolescents, a decline in physical

functioning was found to be associated with the development of asthma and protein-losing enter- opathy [36&]. Elevated BNP levels have been shown in several studies to be associated with worsening heart failure [7&&,37,38].

Heart transplantation remains an important therapy for the treatment of end-stage heart failure in the Fontan patient. A recent report from the European Congenital Heart Centers describes an overall 82% hospital survival in a group of 61 Fontan patients who were transplanted after 2001 [39&]. Similar to prior reports, survival was better in patients who were transplanted late after the devel- opment of Fontan failure compared to those trans- planted early – 82 versus 33%, respectively. Early mortality after transplant was due to infection and graft failure. Overall mortality in this series was better than reported in prior series, likely due to improvements in surgical and postoperative man- agement. Patients with protein-losing enteropathy had a higher mortality compared to those without protein-losing enteropathy. In contrast, a report from the Pediatric Heart Transplant Study group did not find a statistically significant difference in pre or post-transplant mortality between Fontan patients with and without protein-losing enterop- athy; however, overall survival in the protein-losing enteropathy cohort was 60% compared to 80% in the patients without protein-losing enteropathy [40].

The search for a mechanical assist device that can be utilized to augment the Fontan circulation is ongoing. Several case reports of the use of commer- cially available implantable left ventricular assist devices have recently been published [41–43]. Bio- mechanical engineers are developing an axial flow impeller device for cavopulmonary assist, a mech- anical circulation pulsation device using shape memory alloy fiber to augment inferior vena cava (IVC) to pulmonary artery flow, and there are animal studies of the use of the Jarvik device as a right-sided pump to augment flow from the IVC to the pulmonary artery [44–46].

QUALITY OF LIFE AFTER THE FONTAN PROCEDURE

An increasing emphasis on patient-centered out- comes has raised the level of interest in quality-of- life studies in children with congenital heart disease. A study from the NIH/NHLBI-funded Pediatric Heart Network compared generic and disease-specific assessments of physical functioning with medical history variables and laboratory assessments of car- diac function and demonstrated a poor correlation with both assessment tools [36&]. This study pro- vides interesting data from the generic Child Health Questionnaire. Fontan patients scored significantly lower for physical functioning, but

significantly higher for freedom from physical, emotional, and behavioral limitations on roles, freedom from bod- ily pain, and mental health issues, with no differ- ence from the normal population in the domains of behavior problems, self-esteem, and general health perceptions [36&]. Using the Pediatric Quality of Life Inventory (PedsQL) study, another study demon- strated that single ventricle patients scored signifi- cantly lower on both physical and psychosocial assessments, highlighting the variability in results seen with different quality-of-life tools [47]. Adoles- cents with a single ventricle exhibit limitations in executive functioning that include deficits in flexibility/problem-solving and verbally mediated executive function along with impairment of visuo-spatially mediated abilities [48].

In a small series of 35 adult patients after the Fontan procedure, 57% reported a good to excellent quality of life. They tended to be more anxious and used adaptive coping strategies (in particular active coping, planning, acceptance, positive reframing, and self-distraction) rather than maladaptive cop- ing. Quality of life was not related to initial diag- nosis, presence of long-term complications, number of medications per day, or oxygen saturation.

CONCLUSION

Survival following the Fontan procedure is improv- ing and a growing number of patients are becoming adults. Late complications include arrhythmias, protein-losing enteropathy, plastic bronchitis, hep- atic fibrosis, thrombosis, pulmonary hypertension, and heart failure. New therapeutic interventions under investigation include selective pulmonary vasodilation and mechanical assist devices for the pulmonary circulation. Quality of life is in general good, and not related to the presence of ongoing medical needs.

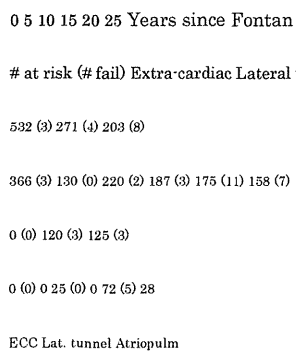

FIGURE 1. Kaplan–Meier survival by Fontan type. Reprinted with permission from Circulation [2&&].

1.0 0.8 0.6 0.4 0.2 0.0

Number at risk

127 100 63 36 20 10 3

20 25 30 35 40 45 50 Age (years)

FIGURE 2. Survival of cohorts of adults with complex congenital heart disease compared to age and sex-matched Canadian population. Graphs show Kaplan–Meier survival estimates of patients that entered the cohort at age below
30 years (mean survival is depicted by solid line with 95% confidence intervals shown as dashed lines). Survival in the general Canadian population is depicted by the solid bold line [6&&]. Reprinted with permission Congenital Heart Disease.

Hemodynamic Phenotype of the Failing Fontan in an Adult Population

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Fontan failure can occur even with normal systolic ventricular function and often in the context of significant liver disease. We hypothesized that Fontan failure is hemodynamically distinct from traditional heart failure and characterized by low systemic vascular resistance (SVR) index and preserved cardiac index. Twenty-seven symptomatic adult Fontan (SAF) patients who underwent catheterization from 2001 to 2011 constituted our study group. Fifty-four predominantly asymptomatic pediatric Fontan (PF) patients who underwent catheterization during the same period were randomly selected to perform a control:case cohort analysis. Clinical comparisons were made between the 2 groups. The adults were more symptomatic than the PF cohort (New York Heart Association classes I and II or III and IV: 48% or 52% [SAF] vs 94% or 6% [PF], respectively, p <0.01). SAF versus PF mean catheterization findings were central venous pressure 18 ± 6 versus 14 ± 3 mm Hg (p <0.01), SVR index 1,680 ± 368 versus 1,960 ± 550 dyn s/cm^5/m^2 (p = 0.02), and cardiac index 2.7 ± 0.8 versus 2.8 ± 0.7 L/min/m^2 (p = 0.25). By imaging, the SAF cohort demonstrated a greater incidence of abnormal liver texture changes (96% vs 75%, p = 0.04) and nodularity (77% vs 42%, p = 0.02). In conclusion, adult patients with failing Fontan circulation had a lower SVR index and similar cardiac index compared with the pediatric cohort. Liver disease in the adults was more advanced. Our data suggest that Fontan failure is a distinct circulatory derangement with hemodynamic features similar to portal hypertension, albeit with limited ability to augment cardiac output. **(Am J Cardiol 2013;112:1943–1947)**

Single ventricle palliation, culminating in the Fontan operation, has been described as a failed strategy in terms of long-term survival and quality of life.[1] Among survivors, only 70% actuarial freedom from death or cardiac transplantation 25 years after Fontan palliation has been reported.[2] "Fontan failure" is a term used to characterize much of the associated morbidity; however, it is itself variably defined. Descriptions include low cardiac output in the absence of ventricular failure,[3] "myocardial failure",[4] and "death, (Fontan) takedown, transplantation, or New York Heart Association (NYHA) classes III and IV".[5] Depiction of the hemodynamic profile of Fontan failure has been similar to traditional heart failure: elevated central venous pressure, pulmonary capillary wedge pressure, and systemic vascular resistance (SVR), with a low cardiac index.[1,6–8] However, clinical deterioration can occur in the absence of ventricular dysfunction,[3,9] suggesting that distinct mechanisms are contributive. Based on the growing evidence of liver pathology in Fontan patients over time,[10,11] we hypothesized that portal hypertension might play a significant role in failing Fontan pathophysiology. We sought to define the hemodynamic phenotype of patients with Fontan failure using catheterization data from symptomatic adult Fontan (SAF) patients and then compared our data with a pediatric Fontan (PF) cohort.

Methods

We performed a retrospective review of the Emory Adult Congenital Heart Center database for patients with the single ventricle physiology status after Fontan palliation who underwent a heart catheterization from January 2001 to December 2011. Surveillance catheterizations are not performed on all patients with Fontan palliation at our adult center and instead are done because of clinical deterioration. We defined clinical deterioration (Fontan failure) as development of significant symptoms such as refractory edema, ascites, protein-losing enteropathy, or considerable exercise intolerance, regardless of ventricular function. A total of 27 patients (NYHA functional classes III and IV: 52%) met the inclusion criteria. We also identified predominantly asymptomatic Fontan patients (NYHA functional classes I and II = 94%), aged 10 to 19 years, who had a catheterization performed during the study period. At our institution, catheterizations are routinely performed in PF patients at 10 and 15 years after the Fontan palliation. A total of 54 patients were randomly selected to perform a 2:1 control: case cohort analysis.

Clinical data, echocardiograms, catheterization findings, and liver imaging were compared between the SAF and PF

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See page 1946 for disclosure information.

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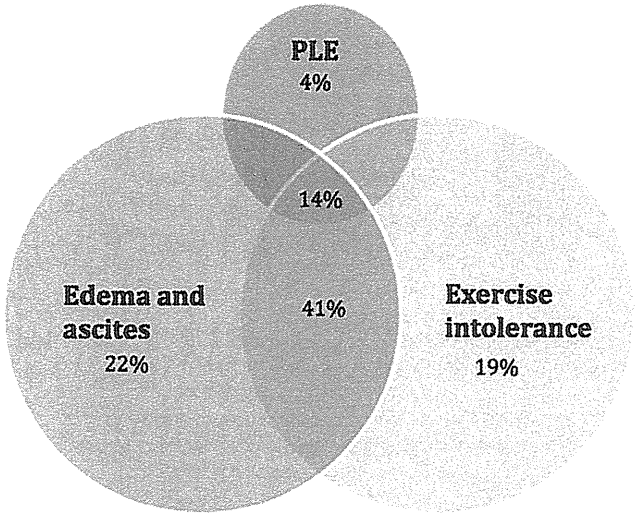

Figure 1. Symptoms in the adult Fontan cohort (n = 27). PLE = protein-losing enteropathy.

cohorts. Echocardiogram interpretations are those of the attending cardiologist, with the evaluation of ventricular function accomplished by subjective assessment, modified Simpson's method, and triplane 3-dimensional reconstruction. Cardiac catheterizations were performed using local anesthesia and conscious sedation. Measurements were made using an end-hole catheter and a transducer using the standard technique. Systemic blood flow was calculated using the Fick method, and SVR and cardiac output were indexed to account for discrepant body surface area between the 2 patient populations. Pulmonary vascular resistance was not calculated because of known difficulties in measuring pulmonary blood flow in the failing Fontan circulation[12,13]; however, transpulmonary gradients were normal in each cohort. Hepatic vein wedge pressures were not routinely obtained and are likely not useful in Fontan patients with postsinusoidal portal hypertension.[14] Finally, although pertinent medications are listed for each cohort, all such medications were held on the day of catheterization in each group.

At our institution, PF patients routinely undergo hepatic magnetic resonance imaging (MRI) or ultrasound at the age of 13 years, whereas adult Fontan patients receive liver imaging as part of their intake assessment. Computed tomography and ultrasound are used only when MRI is contraindicated. Imaging findings consistent with liver disease include changes in echogenicity by ultrasound or heterogenous enhancement of the parenchyma on delayed phase postcontrast imaging by MRI. Liver nodularity is a well-described imaging finding in patients with cirrhosis, indicative of the underlying distortion of hepatic architecture by formation of regenerative nodules.[15] Varices were documented by imaging and not endoscopy. Liver imaging interpretations are those of the attending radiologist.

Analysis of the comparisons was completed using paired *t* test for continuous variables and Fisher's exact test for categorical variables. We used SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina). Data are expressed as mean values ± SDs. Statistical significance was defined as p value ≤ 0.05.

Table 1
Clinical features in symptomatic adult versus pediatric Fontans

Variable (Mean ± SD)	Adults, n = 27 (%)	Pediatric, n = 54 (%)	p
Age at catheterization (yrs)	31.3 ± 9.3	13.7 ± 2.9	<0.01
Age at Fontan (yrs)	10.6 ± 8	2.9 ± 2	<0.01
Time from Fontan to catheterization (yrs)	20.7 ± 5.9	10.7 ± 3.8	<0.01
Male (%)	52	46	0.71
Height (cm)	165.9 ± 33.5	150.8 ± 14.6	0.03
Weight (kg)	81.2 ± 18.8	45.7 ± 18.6	<0.01
Body surface area (m^2)	2 ± 0.3	1.4 ± 0.3	<0.01
NYHA functional class*			
I and II	48	94	<0.01
III and IV	52	6	
Atriopulmonary Fontan	67	2	<0.01
Lateral tunnel Fontan	33	69	<0.01
Extracardiac Fontan	0	29	<0.01
Fontan fenestration	11	87	<0.01
Systemic left ventricle	81	44	<0.01
Systemic right ventricle	19	56	<0.01
ACE inhibitor†	41	74	<0.01
β Blocker†	67	26	<0.01
Furosemide	63	41	0.10
Aldactone	48	37	0.12
Digoxin	30	39	0.2
Hemoglobin (g/dl)	14.9 ± 2	14.6 ± 1.7	0.42

ACE = angiotensin-converting enzyme.

* Among the adult Fontan cohort, 13 (48%) of the 27 patients were NYHA class I and II; however, only 2 of these were NYHA class I. Both patients had significant fluid overload despite diuretics.

† ACE inhibitor and β-blocker use was not mutually exclusive. In the adult cohort, 8 patients (30%) were prescribed both medication classes, whereas 8 pediatric patients (15%) were prescribed both medicine types.

Results

A total of 27 SAF patients (aged 21 to 55 years) underwent a catheterization during the study period. All the patients had Fontan circulatory failure, reflected by clinical deterioration, as the indication for catheterization. Symptoms at the time of catheterization are depicted in Figure 1. Pertinent mean catheterization findings of the cohort include central venous pressure of 18 ± 6 mm Hg, pulmonary capillary wedge pressure of 13 ± 5 mm Hg, systemic arteriovenous oxygen saturation difference of 24 ± 6%, SVR index of 1,680 ± 368 dyn s/cm^5/m^2, and cardiac index of 2.7 ± 0.8 L/min/m^2.

Clinical features of the SAF and PF cohorts are listed in Table 1. Compared with the PF cohort, the adult patients were statistically older at the time of Fontan palliation and farther removed from the Fontan at the time of catheterization. The SAF cohort was more symptomatic than the PF cohort by NYHA classification. Furthermore, of the 13 SAF patients (48%) who were in NYHA classes I and II, only 2 were in NYHA class I. Both these patients had severe fluid overload despite diuretics. NYHA class itself did not predict hemodynamic profile among the SAF cohort; there was no significant difference between patients in NYHA classes I and II and those in classes III and IV within this group. The SAF cohort contained a greater percentage of atriopulmonary Fontan palliations, whereas the PF group contained

Table 2
Catheterization data in symptomatic adult versus pediatric Fontans

Parameters (Mean ± SD)	Adults (n = 27)	Pediatric (n = 54)	p
Central venous pressure (mm Hg)	18 ± 6	14 ± 3	<0.01
Pulmonary capillary wedge pressure (mm Hg)	13 ± 5	10 ± 3	<0.01
Aortic pressure (mm Hg)	76 ± 12	79 ± 12	0.34
Systemic arteriovenous pressure difference (mm Hg)	57 ± 12	65 ± 12	<0.01
Mixed venous saturation (%)	66 ± 8	68 ± 6	0.45
Aortic saturation (%)	91 ± 5	92 ± 4	0.46
Systemic arteriovenous saturation difference (%)	24 ± 6	24 ± 5	0.75
Cardiac index (L/min/m^2)	2.7 ± 0.8	2.8 ± 0.7	0.57
SVR index (dyn s/cm^5/m^2)	1,680 ± 368	1,960 ± 550	0.02

Table 3
Echocardiographic data in symptomatic adult versus pediatric Fontans

Parameters	Adults (%)	Pediatric (%)*	p
At least moderate RV systolic dysfunction†	80	12	<0.01
At least moderate TR†	20	8	0.42
Moderate or greater RV dysfunction or TR†	80	15	<0.01
At least moderate LV systolic dysfunction‡	18	5	0.21
At least moderate MR‡	23	19	0.78
Moderate or greater LV dysfunction or MR‡	27	24	0.93

LV = left ventricle; MR = mitral regurgitation; RV = right ventricle; TR = tricuspid regurgitation.

* Echocardiographic data were unavailable for 7 pediatric patients.

† In those patients with a systemic right ventricle (n = 5 adult and n = 26 pediatric patients).

‡ In those patients with a systemic left ventricle (n = 22 adult and n = 21 pediatric patients).

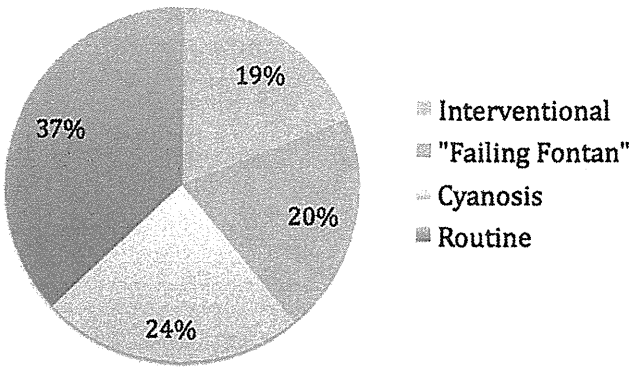

Figure 2. Pediatric Fontan catheterization indications (n = 54).

almost exclusively lateral tunnel and extracardiac Fontan patients. Finally, although angiotensin-converting enzyme inhibitors were more likely to be used in the PF cohort, β blockers were used with greater frequency in the SAF patients.

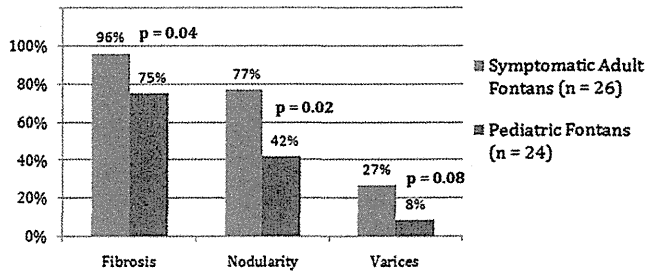

Figure 3. Extent of liver disease in adult versus pediatric Fontan patients. Although fibrosis is technically a histologic diagnosis, it is used here to indicate imaging changes likely consistent with the finding. Varices were documented by imaging and not endoscopy.

Tables 2 and 3 highlight differences in catheterization and echocardiographic findings between the SAF and PF cohorts. The hemodynamic profiles of the adult atriopulmonary versus lateral tunnel Fontans did not significantly differ and therefore were combined for analysis. The pediatric cohort had statistically lower values for central venous pressure and pulmonary capillary wedge pressure but greater SVR index. There was no significant difference in the cardiac index between the 2 groups. Indications for catheterization among the PF cohort are shown in Figure 2.

The results of liver imaging in each cohort are given in Figure 3. Liver imaging was available in 26 (96%) of 27 adults and 24 (44%) of 54 pediatric patients. In the adults, MRI (42%), computed tomography (50%), and ultrasound (8%) were used, whereas only MRI (58%) and ultrasound (42%) were used in the pediatric patients.

Discussion

As we enter the 5th decade of caring for patients palliated with the Fontan procedure, it is apparent that adult survivors face significant morbidity and mortality. Although selected medicines may ameliorate symptoms,[16] mortality benefit has not been demonstrated. Furthermore, there is evidence that circulatory failure rather than ventricular failure is most important—Fontan patients with preserved ventricular function have been shown to do worse after heart transplantation compared with patients with decreased ventricular function.[3]

We theorized that the hemodynamics of a SAF cohort would be divergent from those described in traditional, adult onset, systolic heart failure (elevated central venous pressure, pulmonary capillary wedge pressure, and SVR, with low cardiac index).[8,17,18] In the SAF patients, although mean central venous and pulmonary capillary wedge pressures were elevated, SVR index was low and cardiac index was preserved. Although others have noted these hemodynamics,[3,9] further interpretation was not included. SVR was indexed to control for cohort body size differences and is low compared with published norms.[19,20]

The SAF cohort had higher central venous and pulmonary capillary wedge pressures than the PF cohort, as might be expected. SVR index, however, was lower in the adults and cardiac index was preserved, even in the context of more severe symptoms. This suggests additional mechanisms influencing the hemodynamics and contributing to the

symptoms of Fontan failure. Discrepant SVR index was present despite increased use of angiotensin-converting enzyme inhibitors in the PF cohort. Although β blockers were used more frequently in the adults, their effect on SVR has been shown to be neutral in large studies.[21,22] Echocardiographic data were also informative. Among patients with a systemic left ventricle, there was no significant difference between the cohorts in the incidence of significant mitral regurgitation or left ventricular dysfunction. Adults with a systemic right ventricle, however, were more likely to have significant systolic ventricular dysfunction. Our interpretation of this data is threefold. First, a traditional heart failure model does not explain the difference in symptoms between the 2 cohorts. Second, the hemodynamic profile instead resembles that described in portal hypertension, with the exception being limited ability to augment cardiac output above a certain threshold in a Fontan circulation.[23] The catalyst for this pathophysiology is most likely time-related exposure to elevated postsinusoidal Fontan pressure, leading to liver damage and eventually portal hypertensive–type circulatory derangement. Third, patients with a systemic right ventricle likely face both limitations of a systemic right ventricle and failing Fontan pathophysiology.

What evidence is there that elevated Fontan pressures can lead to liver damage and furthermore that the resulting circulatory dysfunction resembles that seen in our adult cohort? Evidence of liver pathology in Fontan patients over time is robust.[10,11] Animal models, specifically data showing that rat livers exposed to elevated postsinusoidal pressure go on to develop fibrosis and portal hypertension,[24] provide further support. Postsinusoidal obstructive disease such as Budd-Chiari syndrome is a useful model for this pathophysiology and is a well-described cause of cirrhosis and portal hypertension.[25,26] Finally, the mechanism of circulatory dysfunction seen with portal hypertension and cirrhosis has been described and resembles catheterization findings of our study.[27,28] With significant portal hypertension, there is a reduction in hepatic perfusion by the portal venous system and a compensatory shift to increased hepatic arterial perfusion. This compensatory response occurs through splanchnic arterial vasodilation, likely mediated by local vasodilators such as nitric oxide, which leads to decreased SVR. As splanchnic vasodilation becomes more intense, arterial hypotension, renal hypoperfusion, and then reflexive activation of the sympathetic nervous system and renin-angiotensin-aldosterone system develop. Although an increase in cardiac output can be expected in patients with a normal heart, vasoconstriction of the renal vasculature also occurs, which leads to sodium and water retention and the eventual development of edema and ascites once entering a decompensated state. With time-related exposure to the Fontan as the catalyst, we believe failing Fontan pathophysiology has similar characteristics: elevated central venous pressure, low SVR, preserved cardiac output, and fluid retention. A final point is that, as mentioned earlier, Fontan patients cannot proportionately augment their cardiac output above a certain threshold, thus potentiating renal hypoperfusion and leading to refractory symptoms.

Understanding Fontan circulatory failure has important implications. Medicines such as systemic vasodilators used in heart failure may not be tolerated over time as SVR decreases. Befitting therapies can instead be applied by appreciating the unique hemodynamics present. As an example, systemic vasoconstrictors are often used to improve renal blood flow in patients with hepatorenal syndrome, a hemodynamically similar population.[29] Finally, our study highlights the necessity of a catheterization in symptomatic Fontan patients to guide therapy.

The limitations to this study include those inherent to a retrospective review. The study design allows for us to describe the association of catheterization findings in SAF patients with liver imaging changes but does not allow for proving causation. A further limitation is the heterogenous nature of Fontan failure—it is likely that not all patients "fail" in the same way, and each patient should be evaluated individually when looking for underlying causes. Discrepant medication use should be mentioned. However, angiotensin-converting enzyme inhibitors, which may decrease SVR, were more commonly used in the adolescents and β blockers should have a neutral effect on SVR. Finally, our study cohorts were relatively small, and we lacked asymptomatic adult Fontan patients as a control group. Further studies with larger data sets are necessary to confirm and expand on our findings.

Disclosures

The authors have no conflicts of interest to disclose.

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