

Fontan Circulation of the Next Generation: Why It's Necessary, What it Might Look Like

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Not many decades ago, it was the rare patient with a functionally univentricular heart who survived to adulthood.¹ While this grim prognosis has gradually improved over the years, the diagnosis of single ventricle in a fetus or an infant is still the initiating event in what will become a cascade of clinical transitions and events demanding difficult management decisions. Care in the current era is directed toward the objective of achieving successful separation of the systemic and pulmonary circulations, using the functionally single ventricle to support the systemic arterial circulation while relying on surgically created direct systemic venous-to-pulmonary arterial connections to deliver blood flow to the lungs. Proof of concept for this approach was demonstrated in patients with tricuspid atresia by Francis Fontan in the late 1960s,² and amplified almost contemporaneously by the work of Guillermo Kreutzer. Accepted indications for the evolving types and styles of “modified Fontan operation” have liberalized considerably since then, as surgical techniques have changed, facilitating the application of “total cavopulmonary connection (TCPC)” to an extremely broad spectrum of anomalies that are not amenable to biventricular repair.

Historical Overview

The technical evolution that resulted in “modified Fontan operation” reflects a parallel evolution in the understanding of functionally univentricular circulation. Fontan and Baudet, in 1971, as they described their innovative surgical repair of tricuspid atresia suggested the right atrium is “ventriclized,” thereby revealing their different expectation and perception of the physiology than is accepted today.² Nearly 2 decades later,

based initially on clinical observation, but convincingly demonstrated with elegant in vitro modeling of the “Fontan circuit,” Marc de Leval pronounced “the interposition of a valveless chamber, representing the right atrium, does not contribute positively to fluid energy. Moreover, pulsation occurs at the price of an increase in upstream pressure.”³ Full understanding of the consequences of right ventricular exclusion required acceptance of the truly non-contributory nature of a right atrial reservoir, which is anything but “ventriclized.”

When Fontan and Kirklin, in 1990, published *Outcome After a “Perfect” Fontan Operation*,⁴ they observed that hazard function (instantaneous risk of death at each moment in time after the operation) had an early rapidly declining phase at about 6 months, followed by a late hazard phase which increased by about 6 years after surgery. They could identify neither discrete risk factors nor an explanation for late decline in survival or the decline in functional status. They concluded, “The premature decline in survival and functional status and the late rise in hazard function are from the Fontan state *per se* and that the Fontan operation is, therefore, palliative but not curative.”⁴

Once the limitation of the classical atrio-pulmonary type of Fontan connection became clear, surgical innovators promoted the concept of TCPC, producing Fontan connections initially in the form of the lateral atrial tunnel, and later as variations of the extracardiac or intracardiac conduit. One important consequence of this was to allow the application of the principle of Fontan circulation to univentricular hearts of remarkably varied anatomy. Soon, patients with right or left atrioventricular valve atresia, unbalanced common atrioventricular valve, abnormalities of pulmonary venous connection, and even hypoplastic left heart syndrome were becoming “Fontan patients.” Their management remained an enormous challenge, with operative and short-term mortality exceeding that of most operations performed for congenital heart disease beyond the neonatal period and early infancy. Investigators emphasized the importance of judicious patient selection for creation of the Fontan circulation. The feasibility of palliation by means of superior cavopulmonary connection (the so-called bidirectional Glenn anastomosis) was widely recognized, and was used selectively by some as an alternative to the Fontan connection or as interim palliation for high-risk candidates.⁵ But it was Norwood who proposed and instituted a systematic 2-stage approach to

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Fontan operation to achieve series systemic and pulmonary circulations by supplying a superior cavopulmonary connection (hemi-Fontan operation) early in the first year of life, and completing TCPC by age 2 years. This “2-stage” approach was predicated on an effort to reduce the volume load of the ventricle as early as possible, to minimize intermediate mortality during the particularly vulnerable incompletely palliated stages, and to reduce the adverse consequences associated with rapid and profound changes in ventricular geometry and diastolic function when conversion to TCPC is achieved in 1 stage.⁶

Improving Survival

With the widespread acceptance of early superior cavopulmonary connection before TCPC, survival up to and beyond the achievement of Fontan circulation improved considerably.⁷ As importantly, the emphasis in patient management shifted from “selection for the Fontan procedure” to “preparation for the Fontan procedure.” When Dabal and associates revisited outcomes after the Fontan operation, they found that the 1-, 10-, and 20-year survival was 95%, 88%, and 76%, respectively, with no deaths in the last 6 years of the study.⁸ Of the 2017 patients, all underwent Fontan construction with an intracardiac or extracardiac tube, and 79% had previously undergone prior superior cavopulmonary connection. Patients receiving a Fontan procedure in the earlier era (1988–1997) had inferior 10-year survival compared with the recent era (1998–2011) (80% versus 92%). Hazard modeling showed a 1.3% risk of death per year 24 years after the Fontan procedure, with no increasing late hazard phase. The group in Melbourne, Australia, reported similar encouraging results in 2007 with 20-year survival of 84%.⁹ The moniker “palliative” with respect to the Fontan circulation likely still applies, but the prognosis is much more favorable than that described by Fontan and Kirklin decades earlier. The constant 1.3% risk of death per year, out to and beyond 20 years,⁸ is representative of the remarkably improved long-term survival replicated numerous times in the current era. Authors of the recently published American Heart Association scientific statement on evaluation and management of patients with the Fontan circulation set the context for their recommendations in the following way: “. . .it is estimated that patients operated on today may hope for a 30-year survival of >80%. Up to 70 000 patients may be alive worldwide today with Fontan circulation, and this population is expected to double in the next 20 years.”¹⁰

Challenge Today

Management of single ventricle hearts remains one of the great challenges in the broader context of congenital heart

disease. With the above-mentioned improvements in survival of patients who undergo Fontan palliation, the challenge today is to discover the means by which the outcome of the Fontan circulation can be further improved, encompassing not just avoidance of premature death, but improved functional status and health-related quality of life for individuals in this growing population. To achieve these ends will require an enhanced understanding of some of the most common complications and adverse events experienced by “Fontan patients,” and the development and critical assessment of strategies of prevention and mitigation.

Ventricular Failure

Long-term complications of the Fontan circulation are frequent, and while they can be considered on a system-by-system basis as in Table, it is recognized that there are many interrelationships among the complications. Late failure of the single ventricle is well recognized, and in a recent review of adults accounted for 34% of all deaths after Fontan.¹¹ Heart failure in the Fontan circulation is common,¹² progressive,¹³ can be systolic, diastolic, or both.^{12,14} It can contribute to progressive fatigue, dyspnea, and intolerance of exercise, which occurs commonly in this group of patients, in whom only about 50% are New York Heart Association Class I at 20 years after surgery.^{11,15} Ventricular failure in single ventricle may respond incompletely to standard medical management, and is associated with late mortality in Fontan circulation.^{16,17} Heart failure is known to occur after Fontan with either morphologic left or morphologic right ventricular dominance. Most reports^{13,18} find no heart failure rate differences based purely on right versus left ventricular anatomy, but some have found hypoplastic left heart syndrome and abdominal heterotaxy syndromes to be indicators of poor prognosis.^{7,17,19} Despite considerable concern that ventricular failure might limit long term survival, the general experience in the modern era is that a strong majority of patients to be alive with intact Fontan circulation 20 years after the operation. For example, Downing et al, report 74% freedom from death, transplant, or Fontan takedown in their series composed of patients receiving their operation since 1992 (Figure 1).²⁰ They identified improvements in this outcome among more recently operated patients (Figure 2A), but point out that era-related improvements are no longer noted when data conditional on survival to 1-year post-Fontan is analyzed (Figure 2B).

Valve Dysfunction

Often occurring in association with ventricular failure, atrioventricular valve regurgitation may be progressive, and can

Table. Organ Systems with Dysfunction after Fontan Operation

Cardiac
Ventricular failure
Systolic
Diastolic
Combined
Valve regurgitation
Atrioventricular
Semilunar
Channel disruption
Mechanical
Thrombotic
Collateral shunts
Aortico-pulmonary
Veno-venous
Arrhythmias
Atrial tachyarrhythmias
Ventricular tachyarrhythmias
Sinus node dysfunction
Pulmonary
Pleural effusion/chylothorax
Plastic bronchitis
Gastrointestinal
Protein losing enteropathy
Hepatic fibrosis
Hepatic malignancy
Central nervous system/psychiatric
Stroke
Developmental delay
Anxiety disorder
Attention deficit disorder
Hematologic
Thrombophilia
Endocrine
Thyroid disease
Pheochromocytoma
Paraganglioma
Renal
Decreased glomerular filtration rate
Albuminuria

result in an already dysfunctional single ventricle becoming even more inefficient in generating adequate cardiac output. Atrioventricular valve regurgitation is especially prevalent

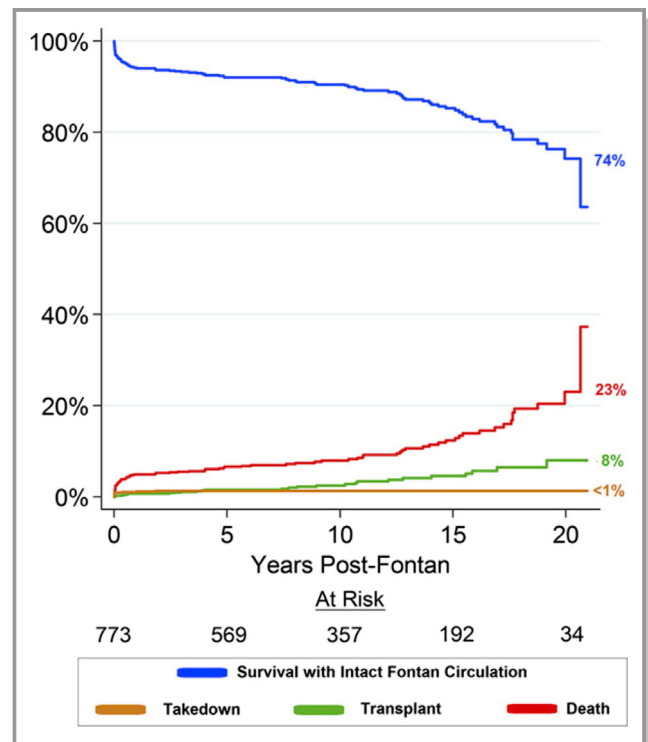


Figure 1. Survival and cumulative incidence of outcomes after Fontan. Kaplan-Meier survival estimate for composite outcome overlaid with cumulative hazard rates for death, transplant, and Fontan takedown. Reprinted from Downing et al²⁰ with permission. Copyright ©2017, Elsevier.

among those with common atrioventricular valve, 2 atrioventricular valves, and tricuspid valve as the systemic atrioventricular valve, and contributes substantially to failure of the overall palliation.^{17,21} Semilunar valve regurgitation, is seen less often, but regurgitation of moderate severity has been reported in up to 10% of Fontan circulations in the long term.¹² This may be particularly so in the presence of a proximal aorto-pulmonary amalgamation (Damus-Kaye-Stansel connection). Any impediment to systemic venous flow into the pulmonary arteries, whether it takes the form of channel obstruction, baffle leak, or collateral circulation, has the potential to impair single ventricle palliation. Fontan (cavopulmonary) pathway stenosis is rare early after surgery, with the exception of branch pulmonary artery hypoplasia. But pathway stenosis may occur late after surgery, and may have associated comorbidities including fatigue, cyanosis, and hepatic congestion or cirrhosis.²² The risk of stenosis varies with type of operation, size of conduit and time from surgery. The incidence of pathway stenosis has been reported in small series to be high with use of both the lateral tunnel and extracardiac Dacron conduits,^{23,24} however, current surgical techniques and conduit materials are expected to have a lower incidence of early and late stenosis.

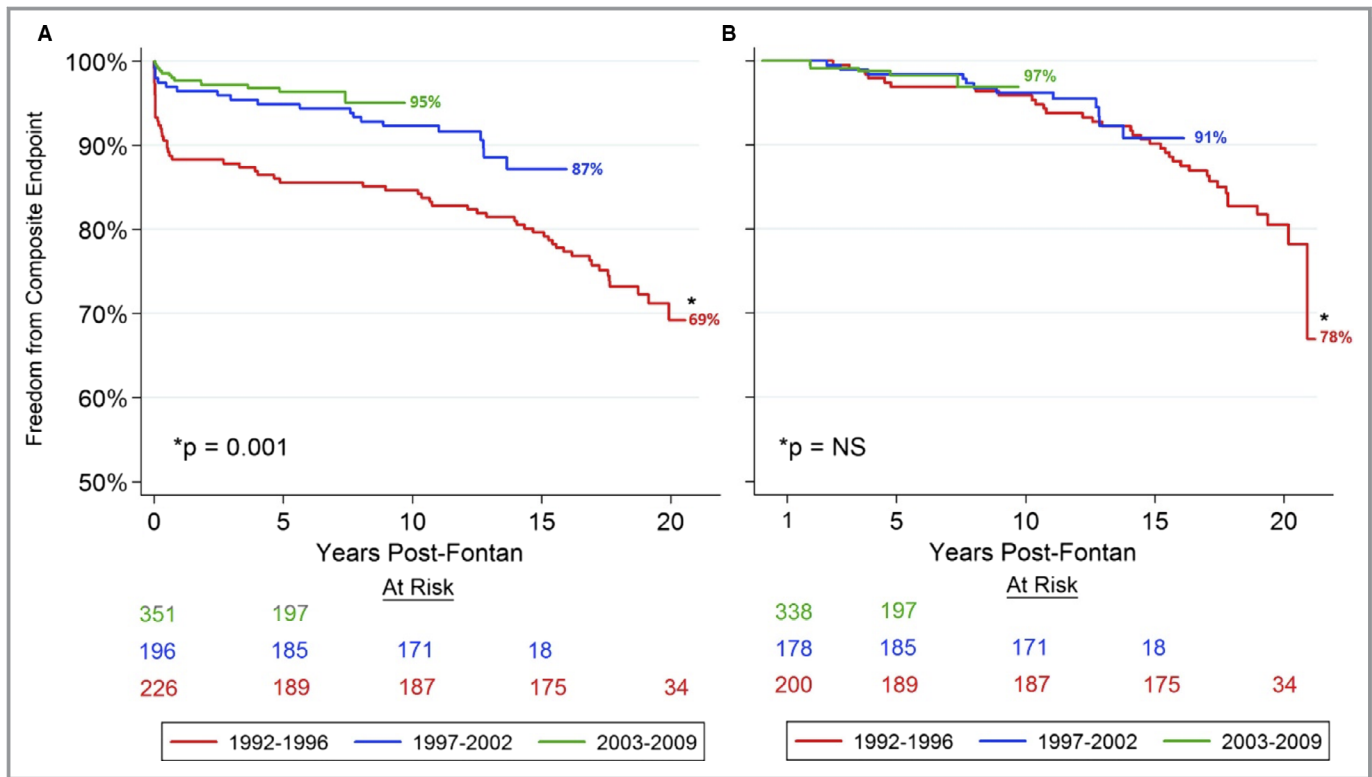


Figure 2. Impact of surgical era on transplant free survival. Kaplan–Meier survival estimate stratified by era of Fontan: (A) all patients, and (B) conditional on survival to 1 year with intact Fontan circulation. Reprinted from Downing et al²⁰ with permission. Copyright ©2017, Elsevier.

Development of systemic-to-pulmonary arterial collateral circulation after Fontan has been recognized for many years,²⁵ and based on a recent magnetic resonance based study,²⁶ it results in reduced effective systemic cardiac index and reduced prograde pulmonary arterial flow, as well as imposing a volume burden of the systemic ventricle. Venovenous collateral circulation is also relatively common and may be associated with high systemic venous pressures of the Fontan circulation, however interventions to close these can be associated with an adverse clinical course.²⁷

Arrhythmias

Cardiac arrhythmias occur commonly in the late follow-up after Fontan operation; some reports indicate that the majority of patients may experience arrhythmia at or beyond the 20th year following surgery.²⁸ The risk for arrhythmia may have an association with the surgical technique chosen to achieve the veno-pulmonary artery connection,²⁹ leading many centers to adopt the extracardiac conduit technique. Increased duration of experience with the various types of total cavopulmonary connections, however, suggests that time-related acquisition of atrial arrhythmias is a problem of all types of connections.³⁰ In a large series of patients with no arrhythmia prior to Fontan,

overall 10-, 20-, and 30-year freedom from arrhythmias was 71%, 42%, and 24%, respectively and 5% of the cohort had sudden cardiac death.²⁸ There is strong evidence to suggest that arrhythmias correlate with failure of the palliation.^{25,31} Moreover, sudden death is among the most common causes of mortality in this population,^{16,17,32,33} fueling speculation that arrhythmia may be responsible,³⁴ even when not observed directly.

Non-Cardiac Morbidity

As discouraging as the litany of adverse cardiac consequences associated with the Fontan circulation might be, there are serious non-cardiac morbidities as well. Early after the surgery, many patients struggle with prolonged pleural effusions. Despite efforts to minimize the early morbidity of prolonged pleural effusions by using extracardiac conduit surgical technique and/or fenestration of the Fontan pathway, chylothorax still occurred early in 24% of all patients in a recent series.³⁵ It appears these same patients are at particular risk somewhat later for plastic bronchitis and protein losing enteropathy.³⁶ Protein losing enteropathy is estimated to occur in as many as 3% to 8% of Fontan survivors.^{13,37} It can be a particularly difficult problem to reverse, and is associated with poor survival.^{7,17,32} Overall

mortality in 88 patients with protein losing enteropathy during follow-up of 7.0 ± 7.4 years was 72%.⁷ This is expected to improve with newer techniques aimed at addressing lymphatic abnormalities.

Abnormal lymphatic flow has recently been identified as an important cause of Fontan failure.³⁸ Lymph stasis leads to tissue edema and a cascade of events resulting in inflammation, fibrosis, and eventually end organ abnormalities. Greater degrees of neck and thoracic lymphatic abnormalities on T2-weighted MR mapping before Fontan were associated with poor outcomes after Fontan.³⁸ More structured diagnostic approaches (MR based lymphatic classification) and new interventional treatments are currently used for lymphatic disorders including chylothorax, plastic bronchitis, and protein-losing enteropathy.

Predisposition to thrombosis and thromboembolism is well known³⁹ and is the cause of as much as 9% of the deaths in 1 long-term follow-up study.³² In many instances thrombotic phenomena after Fontan is likely multifactorial, associated with a variety of factors including intestinal protein loss, diminished hepatic synthesis of anticoagulant proteins, and/or sluggish flow in the systemic venous to pulmonary arterial circulation.⁴⁰ Hepatic disease manifesting as congestion, fibrosis, and even cirrhosis is increasingly recognized as a consequence of the chronic Fontan circulation.^{41,42} Heart-liver transplantation is sometimes a last resort intervention to treat combined heart and liver failure in these ill patients.⁴³ Renal disease, with proteinuria and/or diminished glomerular filtration rate, is increasingly recognized among Fontan survivors late in the course, can occur with or without associated hepatic disease, and contributes to mortality.^{17,44} Immunologic abnormalities consisting of relative reduction in T-lymphocyte levels, spread across both CD4 and CD8 subtypes, with an increase in B-lymphocyte counts have been observed.⁴⁵ Even disorders that might not be expected, such as predisposition to thyroid disease,⁴⁶ pheochromocytoma and paraganglioma,⁴⁷ and malignancies,¹¹ are increasingly recognized late after Fontan. Given the concerns about prognosis, and the functional limitations of chronic disease, it is no surprise that psychologic consequences such as anxiety disorder and attention deficit disorder are observed.⁴⁸

Mortality

The prevalence of important cardiac and non-cardiac morbidity is discouragingly high late after Fontan palliation for single ventricle, and unfortunately this is reflected in mortality. Numerous single institution and multi-institution collaborative long-term follow-up studies have confirmed slow attrition in cohorts of patients after Fontan which continues for decades.^{11–13,16,18–20,31,32,49–53} In a meta-analysis composed

of 6707 patients reported in 28 studies, Alsaied and colleagues estimated the overall mortality rate after Fontan operation is about 2.1% per year.⁵⁴ They reported the 5 most frequent causes of death in this population are heart failure, arrhythmia, renal disease, respiratory failure, and a variety of clotting problems. Allen et al recently reviewed a single institution series of 773 cases, and determined that 20 years after the Fontan operation, only about half of the group remained free from a composite medical morbidity outcome defined as any of the following: protein-losing enteropathy, plastic bronchitis, serious thromboembolic event, or tachyarrhythmia.¹⁸ Moreover, the group with these morbidities was far more likely than their unaffected counterparts to die, to receive cardiac transplantation, or to undergo surgery to take down the Fontan. Many factors contribute not just to morbidity, but also to mortality in single ventricle. Alsaied et al derived a risk model in which they identified hypoplastic left heart, heterotaxy, atrio-pulmonary surgical method, protein losing enteropathy, renal and hepatic disease, moderate or severe heart failure, moderate or severe atrioventricular valve regurgitation, arrhythmia, and elevated pulmonary pressure as contributors to estimate high risk.¹⁷ Just 1 of these factors, the surgical method (atrio-pulmonary connection), is considered fully modifiable. Others, like arrhythmia, valve regurgitation, and heart failure potentially may be mitigated, but not eliminated by medical management. Still others, like the original cardiac anatomy are entirely out of the physician's hands. Minimizing variability of current practice and optimizing the delivery of currently available therapy through multidisciplinary clinical practice systems for care⁵⁵ will likely be helpful, but concurrently we must consider and evaluate innovative approaches to single ventricle management which could prove transformative.

Next Generation

Given the large fraction of all congenital heart disease accounted for by functionally univentricular anomalies, and the reality of the important morbidities, often diminished functional capacity, and less than normal life expectancy for patients with Fontan circulation, is there reason to hold out optimism that this unnatural history of the surgically treated state of single ventricle patients can be improved? We think so.

Personalized Fontan Circulation

Progress in advanced imaging, computational modeling based on digitized data from computed tomography, and especially from quantitative cardiac magnetic resonance have made possible the concept of the personalized Fontan connection. It is now possible for surgeons and cardiac imaging experts to

use actual individual patient-based data to model the Fontan circulation, and optimize the properties of planned surgical reconstructions.⁵⁶ This concept has found considerable application among patients with pulmonary artery distortion, for whom computational modeling can be helpful in planning and predicting the efficacy of pulmonary artery interventions (both surgical and catheter-directed), and in determining the optimal extent of these interventions. In general, and more specifically in the setting of asymmetric development of the right and left branch pulmonary arteries, computational modeling based on patient-specific data can help determine the optimal point of insertion, angulation, and offset options for placement of the Fontan conduit between the inferior caval vein and pulmonary arteries.⁵⁷ For certain diagnostic groups, presurgical modeling using patient data and computational techniques can be helpful in making the choice between lateral atrial tunnel, simple extracardiac conduit, or more complex arrangements such as the Y-shaped extracardiac conduit, based on simulations that predict relative distributions of superior and inferior caval flow to the right and left lungs, respectively. An example is the heterotaxy population with left isomerism who are especially prone to the development of pulmonary arteriovenous malformations if a satisfactory distribution of hepatic venous effluent to both lungs is not achieved at the time of completion of the cavopulmonary connections.⁵⁸ For patients with this anatomy who have already developed extensive pulmonary arteriovenous malformations, either after Kawashima procedure or after Fontan completion, computational modeling is helpful in choosing the most favorable strategy of vascular reconstruction, which may be a revision of the Fontan connections or may be hepatic vein-to-azygous vein connection. In addition, regardless of the specific underlying anatomy, computational modeling with patient-specific data can help predict exercise hemodynamics and ascertain the relative importance of hemodynamic alterations such as systemic-to-pulmonary collateral burden and atrioventricular valve regurgitation. Such quantitative information can aid in clinical decision-making.⁵⁹

Tissue-Engineered Fontan Pathway

One of the inevitable limitations of synthetic vascular grafts is their inability to “grow” with the patient. Another is the increased thrombogenicity of the material interface with circulating blood. The use of tissue-engineered grafts as Fontan conduit material has the potential to mitigate or even overcome both of these important obstacles. Computational flow studies of idealized cavopulmonary circuits have revealed that optimal conduit size for 3- to 6-year-old patients is 16 to 18 mm diameter.⁴⁹ In larger conduits, backward flow during the expiratory phase was prominent. Expiratory phase

backflow from the superior vena cava and pulmonary artery into the conduit was observed with size ≥ 18 mm. Stagnation volume at the expiratory phase increased with an increase of conduit size. Despite this reality, many surgeons feel obligated to place larger conduits when performing extracardiac Fontan completion on patients ranging in age from 2 to 6 years. The problems of circulatory inefficiency as well as the potential for thrombosis related to flow stagnation and thrombogenicity because of prosthetic material surfaces can be overcome by the use of conduits that are either manufactured from, or gradually populated with the patient’s own cells.⁶⁰ Despite decades of research on tissue engineering of valve substitutes and ventricle-to-pulmonary artery conduits, the extracardiac Fontan pathway is likely to be the first major successful application of tissue-engineered components in the solution of a cardiac surgical challenge.

Overcoming the “Fontan Paradox”

Many of the early challenges as well as the seemingly inevitable late morbidities associated with the Fontan circulation are consequences of what has become known as “the Fontan Paradox.” Many have described this unique circulatory phenomenon, recognized from the outset by Fontan, and characterized by relative caval hypertension and pulmonary artery hypotension. But no one has articulated the challenge, and the theoretical solution more clearly than Professor Marc de Leval: “In a normal biventricular circulation the mean caval pressures are <10 mm Hg and the mean arterial pressure is at least 15 mm Hg to keep the pulmonary vasculature patent. The paradox of the Fontan circulation is that it imposes caval hypertension—particularly in the splanchnic area—as well as relative pulmonary arterial hypotension. In pure hemodynamic terms, a mechanical device capable of producing a step down in pressure energy of 5 mm Hg in the inferior vena cava and producing a step up of 5 mm Hg in the pulmonary arteries could potentially reverse the Fontan paradox. Now that extracardiac conduits are commonly used to channel the inferior vena caval blood to the pulmonary artery, power generators capable of producing such changes in pressure energy might be feasible rather than those needed to support or serve the systemic vascular system.”⁶¹ One form of such a power generator is referred to as a “viscous impeller pump.” Rodefeld has demonstrated in vitro that deployment of viscous impeller pump in the total cavopulmonary connection could add enough energy to the circulation to raise pulmonary artery pressure by a few mm Hg while lowering central venous pressure by a few mm Hg.⁶² This concept, if successfully applied in vivo, would effectively overcome the “Fontan Paradox.” What is truly unique about this concept is that much of the efficiency and fundamental advantages of biventricular circulation would be replicated, by means of

small changes in the central venous and pulmonary artery pressures, without the requirement of a sub-pulmonary ventricle.

Regenerative Medicine

Stem cells are emerging treatments for preventing or even reversing dysfunction of the functionally single ventricle. The field of stem cell therapy has identified numerous cell populations, with preclinical and clinical experience demonstrating the potential utility of each cell type. The current understanding of stem cell therapy is undergoing a shift from a paradigm based on cellular engraftment and differentiation to one recognizing a primarily paracrine effect.⁶³ Recent studies have evaluated the individual components of the stem cells' secretomes responsible for therapeutic effects including neovascularization and favorable remodeling. Minimal clinical trials have shown stem cell-dependent improvements in ventricular function in congenital heart disease; several stem cell trials for the single ventricle are underway. Those trials using autologous preparations include: (1) the APOLLON (Cardiac Stem/Progenitor Cell Infusion in Univentricular Physiology, phase III) using cardiosphere-derived cells; and (2) a trial using bone marrow-derived mononuclear cells after the Fontan operation. The ELPIS (Allogeneic Human Mesenchymal Stem Cell Injection in Patients with Hypoplastic Left Heart Syndrome: An Open Label Pilot Study) (NCT02398604), is an ongoing phase I/II clinical trial that investigates the safety and feasibility of allogeneic mesenchymal stem cells (non-autologous) used at the time of the Glenn palliation in 10 patients. A randomized phase II ELPIS trial is planned based on the results of safety and efficacy.⁶³ These trials may provide key insights about this emerging field, and the mechanisms by which stem cell therapy might affect right ventricular regeneration and function in the Fontan circulation.

Conclusions

The Fontan operation, in its many variations, remains the most prevalent surgical method for cardiac anomalies which lack 2 well-developed ventricles, and those for which septation resulting in systemic and pulmonary circulations in series cannot be safely achieved. Operative survival associated with a staged approach to establish the Fontan circulation has greatly improved in recent decades. However, the Fontan circulation itself is associated with several key morbidities, some of which manifest years after the operation; these result in decreased functional capacity and health-related quality of life, and increased risk of premature death, which highlight the need for new and better methods of care.

Advancements are already on the horizon to capitalize on the results of multidisciplinary research from teams of clinicians, basic scientists, and bioengineers. These advancements form the basis for innovative therapies with the potential to improve the outlook for patients with congenital heart disease for whom the Fontan circulation is the most effective therapeutic strategy.

Disclosures

None.

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