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WILEY Congenital Heart Disease

"Frontiers in Fontan failure: A summary of conference proceedings"

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Abstract

"Frontiers in Fontan Failure" was the title of a 2015 conference sponsored by Children's Healthcare of Atlanta and Emory University School of Medicine. In what is hoped to be the first of many such gatherings, speakers and attendees gathered to discuss the problem of long-term clinical deterioration in these patients. Specific focuses included properly defining the problem and then discussing different treatment strategies, both medical and surgical. The health of the liver after Fontan palliation was a particular point of emphasis, as were quality of life and future directions.

KEYWORDS

Fontan, congenital heart disease, cirrhosis, circulatory failure, hepatology, cardiac surgery

1 | INTRODUCTION (FRED RODRIGUEZ III, MD)

The Fontan operation is currently considered the optimal final stage of palliation for single ventricle heart disease. However, Dr. Fontan himself realized that even in the best of circumstances, the resultant anatomy and physiology "imposed a gradually declining functional capacity and premature late death after an initial period of often excellent palliation."[1] The aims of this conference were to accrue expert opinion on the problem of Fontan failure, identify improved treatment options, and explore potential ways to circumvent it altogether.

Strategies and outcomes of the Fontan operation have changed over time. Based on the Society of Thoracic Surgeons congenital heart surgery database, the current mean age at the time of Fontan worldwide is 3.0 ± 0.6 years, with the lateral tunnel being done at a slightly

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younger age than the extracardiac conduit.[2] There is some evidence to show that younger age at Fontan has been associated with decreased survival and increased postoperative complications.[3,4] Exercise performance data has been mixed, with different author groups reporting superiority of the earlier Fontan,[5] later Fontan,[6] or no difference at all.[7] Neurodevelopmental outcome studies are limited at this time. Most recently, reports have surfaced suggesting alternative options to palliate single ventricle heart disease that may allow for longer-term survival, such as balanced univentricular circulations (with or without palliative surgery),[8,9] and a Fontan circulation with hepatic vein exclusion. These may provide hope for the future.

2 | SURGICAL OVERVIEW (BRIAN KOGON, MD)

Fontan design has changed over the years, transitioning primarily from an atriopulmonary connection to a total cavopulmonary connection. From a hemodynamic standpoint, it is logical that the Fontan design with the most streamlined flow from the vena cava into the pulmonary arteries should be better. While in vitro computational fluid dynamic studies have evaluated and rated various Fontan configurations, in-vivo studies have shown no major differences between the designs.[10–12] Also, catheter-based studies show similar postoperative Fontan pressures and functional studies show comparable parameters, irrespective of Fontan design. From a technical standpoint, the extracardiac Fontan may be easiest to perform, but the tradeoff comes with difficulties creating and maintaining a patent fenestration. Also, although it would seem that the extracardiac Fontan may be associated with shorter cardiopulmonary bypass and limited ischemic times, these times are quite similar to the lateral tunnel Fontan.[13] From an arrhythmia standpoint, studies have shown an incidence of 39% at 15 years in atriopulmonary Fontans, compared with 15% at 15 years with the total cavopulmonary techniques.[14] However, between the total cavopulmonary designs, there is no demonstrable difference. The differences in arrhythmia incidences within studies and between studies can often be accounted for by differing arrhythmia definitions, differences in follow-up duration, heterogeneous populations, and variable surgical technique. A large Pediatric Heart Network study showed no difference in actuarial arrhythmia free survival between the total cavopulmonary Fontan types.[15] When arrhythmias arise, transvenous ablations can most easily be performed in the presence of a lateral tunnel Fontan via direct baffle puncture or via the fenestration. While access in an extracardiac Fontan is more difficult, numerous methods of accessing the pulmonary venous atrium have been proven successful: percutaneous transthoracic computed tomography (CT)-guided access, left ventricular apical access, and access via a transconduit puncture.[16–18] Finally, total cavopulmonary Fontans do not seem to confer a survival advantage over the atriopulmonary Fontan at the current time. In a study following Fontans over 20 years, no difference in survival was demonstrated.[19]

In summary, there is not much difference in clinical outcomes between the various Fontan designs. The primary problem is that, regardless of design, the longevity of Fontan anatomy and physiology is limited, and mortality is not uncommon in the 20–40 year range. At that time, surgical options are limited. While ventricular assist devices have the potential to extend survival, the Fontan circulation presents numerous challenges. A device placed in the systemic ventricle continues to subject the patient to Fontan physiology. This does not help the patient with preserved ventricular function and limits the device's appeal for destination therapy. Heart transplantation also has the potential to extend survival; however, patients after Fontan palliation face unique challenges. Those with preserved ventricular function have low survival independent of transplant, patients with cirrhosis may need combined heart-liver transplant, anatomy often makes the operation technically challenging, and previous Fontan operation has a high relative risk factor for early phase mortality.

3 | LONG-TERM OUTCOMES (ROBERT ELDER, MD)

Twenty-year freedom from death or transplantation is >80%; however, event-free survival is only 35% at 20 years due to complications such as liver disease, protein losing enteropathy (PLE), plastic bronchitis, arrhythmias, stroke, or need for a pacemaker.[19,20] With regard to liver disease, studies have shown that injury begins even prior to operation and that serial insults occur over time,[21,22] with the end product being liver fibrosis and eventual cirrhosis. Screening is challenging; laboratory abnormalities are often not discriminative, biopsy is limited by the heterogeneous pattern of tissue involvement, and hemodynamic assessments do not always correlate with extent of fibrosis and severity of disease. Liver imaging may be helpful, but primarily for the early detection of hepatocellular carcinoma. Given the difficulty in assessing the Fontan liver, different centers have developed liver-specific clinical risk scores. Assenza et al. showed that MELD-XI (Model for End Stage Liver Disease) score predicted worse outcomes including death,[23] while Elder et al. showed that features of portal hypertension (varices, ascites, splenomegaly, and thrombocytopenia) predicted worse outcomes.[24] With regard to PLE, ~5–15% of adult patients are affected. While survival has previously been reported at 50% at 5-years, newer studies have shown that survival closer to 80% at 8 years is possible.[25] Newer treatment options such as thoracic duct ligation and transcatheter selective lymphatic embolization have been developed and may be beneficial in refractory cases.[26,27] Finally, thromboembolism, bleeding, renal dysfunction, and obesity are other complications of Fontan physiology that can adversely affect long-term outcomes.[28]

4 | FONTAN PHYSIOLOGY (MAAN JOKHADAR, MD)

Fontan physiology is characterized by organ system interaction, with the heart, lungs, vasculature, kidneys, and liver all being affected by and causing effects on other parts of the circulation. These interactions are unique and the consequence unusual: central venous pressure is relatively high and pulmonary artery pressure is relatively low.

TABLE 1 Fontan failure–clinical phenotypes based on pathophysiology

Phenotype	Clinical	Hemodynamics
1. Systolic heart failure -reduced EF	Pulmonary and hepatic congestion	Low cardiac output, elevated SVR
2. Diastolic heart failure -preserved EF	Pulmonary and hepatic congestion	+/− Low cardiac output, elevated SVR
3. Fontan circulatory failure -preserved EF -normal EDP	Portal venous outflow obstruction, ascites, cirrhosis	+/− Elevated PVR, preserved cardiac output, low SVR
4. Lymphatic failure -PLE, plastic bronchitis	Lung and lymphatic disease	Normal Fontan hemodynamics

EDP, end diastolic pressure; EF, ejection fraction; PLE, protein losing enteropathy; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Over time, veno-venous collaterals often develop, despite relatively low pulmonary artery pressure and estimated pulmonary vascular resistance. Embolization of these collaterals is often undertaken in order to improve cyanosis. Unfortunately, studies have also shown decrease in survival in those that undergo the procedure.[29] Pulmonary arterial histology is abnormal, with biopsy studies showing increased wall thickness, smooth muscle proliferation, and intimal thickening with fibrosis.[30,31] Given these findings, pulmonary vasodilator therapy has been used with increasing frequency but studies have shown mixed results.[32–35] The lack of efficacy is explained in part due to intrinsic problems with the lungs rather than the vasculature alone. Restrictive lung disease is prevalent and closely associated with decreased exercise capacity.[36] Diastolic dysfunction is also common and is associated with worse exercise performance and postoperative outcome.[37,38] Diastolic dysfunction can arise for many reasons, including the cardiomyopathy associated with liver fibrosis and cirrhosis.

5 | FONTAN FAILURE CLASSIFICATION (WENDY BOOK, MD)

Fontan failure in adults differs pathologically from failure in adolescents. Adults are more symptomatic, have higher central venous pressures, have lower systemic vascular resistance, and have ubiquitous liver disease. Cardiac output, however, can be quite similar.[39]

Adult Fontan failure can be classified into four phenotypes, see Table 1. Phenotype 1 (systolic dysfunction): high filling pressures, reduced ejection fraction, congestion in the pulmonary and systemic venous beds, and often coinciding atrioventricular (AV) valve regurgitation. Phenotype 2 (diastolic dysfunction): high filling pressures, normal ejection fraction, congestion in the pulmonary and systemic venous beds, and often coinciding AV valve regurgitation. Phenotype 3 (circulatory failure): normal filling pressures, preserved ejection fraction, and cirrhosis. In cirrhotic patients without a Fontan, cardiac output is elevated in response to splanchnic arterial vasodilation (which occurs in response to cirrhosis). Fontan patients, in contrast, have a limited ability to increase cardiac output, thus circulatory failure is potentiated. When decompensated, the pathophysiology devolves into renal failure and refractory ascites and edema. The triggers are unclear but may be related to elevated central venous pressure and portopulmonary hypertension.[40] Finally, phenotype 4 is unique in that the hemodynamics are often "normal," but lymphatic pathophysiology is present. Specifically, this phenotype would include plastic bronchitis and PLE. Moving forward, treatments tailored to the clinical phenotype may improve outcomes.

6 | MEDICAL MANAGEMENT OF THE FAILING FONTAN (ANNE MARIE VALENTE, MD)

Appropriate medical management of the failing Fontan is controversial and regimens vary widely between centers. Comparing regimens is challenging due to limited sample size, heterogeneity of diagnoses, limited duration of therapy and follow-up, and choice of appropriate endpoints. Additionally, the majority of studies that have been done exclude patients with failing physiology.

Diuretics have not been extensively studied. In one study, a short course of spironolactone did not improve endothelial function or alter serum cytokine levels in adults with Fontan physiology.[41] The angiotensin converting enzyme (ACE) inhibitor enalapril did not improve exercise capacity in a small group of patients.[42] There is some evidence that beta-blockers, carvedilol in particular, may have beneficial effects on the ejection fraction in children with Fontan physiology, but the benefits have not yet been demonstrated in adults.[43] Several pulmonary vasodilators have been studied; there is conflicting evidence as to whether sildenafil or bosentan improve exercise capacity.[32,33,44–46] Improved peak oxygen consumption (VO2) and O2 pulse (forward stroke volume) have been demonstrated in Fontan patients taking iloprost.[47] The best anticoagulant to use in these patients is also debatable. While the superiority of either aspirin or warfarin in comparison to the lack of any anticoagulant has been demonstrated (reduced risk of thromboembolism),[48,49] neither anticoagulant has been shown to be superior to the other.[48] In the treatment of PLE, oral budesonide has been shown to be effective in children.[50] Its use in adults, however, is limited by systemic absorption and concern for hepatic dysfunction.[51]

Nonpharmacologic therapies, with attention to the role of the peripheral vasculature, can also be beneficial. Studies in patients

after Fontan palliation have demonstrated impaired endothelial function,[52] reduced blood flow to the lower extremities,[53] and decreased venous capacitance.[54] Over 60% of adult Fontan patients have significant lower extremity venous insufficiency, with a third of these patients being classified as severe.[55] Interventions such as leg elevation (especially during sleep—ankles above the heart, raising the foot of the bed), graduated compression stockings (greatest pressure at the foot, knee high, starting with 20–30 mm Hg pressure), and resistance training to improve muscle strength (to improve "muscle pump" venous return back to the heart) are also beneficial.[55,56] Additionally, there is preliminary data that inspiratory muscle training may be associated with improvement in exercise performance and peak work rate in adults with Fontan physiology.

7 | THE ROLE OF PACING (MICHAEL LLOYD, MD)

In an EKG survey analysis of over 500 pediatric patients after Fontan palliation, 69% were in sinus rhythm.[57] Most commonly, sinus rhythm was replaced by a paced or slow escape rhythm. However, a lower resting heart rate and increased heart rate reserve have been associated with improved exercise tolerance and overall health in these patients.[57] Given this finding, it is unclear whether pacing is truly helpful. With atrial pacing, the unique hemodynamics of a Fontan circulation must be considered, and the concept of preload reserve is important. Normal exercise physiology is associated with an increase in pulmonary artery pressure, which can be overcome with a well-functioning subpulmonary ventricle. Because the subpulmonary ventricle is absent in Fontan patients, transpulmonary flow, systemic ventricular filling, cardiac output, and thus exercise tolerance are limited, regardless of an increase in heart rate. Therefore, heart rate plays much less of a role in augmenting cardiac output in these patients.[58] As a result, artificially increasing heart rate with pacing would not be particularly effective in increasing cardiac output. Studies seem to support this assertion: in a cohort of over 500 pediatric Fontan patients, those with pacemakers had lower ejection fraction, poorer functional status, and an increased incidence of thrombosis, arrhythmias, and additional cardiac surgical procedures (not including pacemaker insertion).[59]

The clear indications for a pacemaker in a patient with a Fontan are: (1) substantial (>3 s) sinus pauses when awake, or frequent symptomatic pauses, or AV block, (2) atrial tachycardia proven to be pace terminable, and (3) clear cases of sinus node dysfunction, such as iatrogenic causes, or resting severe symptomatic sinus bradycardia with a heart rate < 40 bpm.

Unfortunately, even when necessary, pacemaker implantation can be challenging after Fontan palliation. The standard transvenous approach is unhelpful in a total cavopulmonary Fontan, epicardial atrial leads are often prone to failure and should be avoided if possible, and ventricular pacing can be complicated by pacemaker-induced cardiomyopathy.

8 | FONTAN-RELATED LIVER DISEASE (RENE ROMERO, MD, RYAN FORD, MD, AND GRUSCHEN VELDTMAN, MD)

After Fontan palliation, the liver is exposed to elevated, nonpulsatile systemic venous pressure and diminished cardiac output. The lymphatics are also affected, with lymphostasis combining with elevated venous pressure to form a "double hit" to the patient.[60] Normally, the liver receives 70% of its inflow from the portal vein and the remainder from the hepatic artery. Therefore, the majority of hepatic blood flow is dependent on the pressure difference between the portal vein and hepatic veins, known as the portal venous pressure gradient (PVPG).[61] While it is relatively easy to obtain hepatic vein pressures via catheterization, direct pressure measurements of the portal vein are not routinely performed. Portal venous pressure and PVPG can instead be estimated by determining the hepatic wedge pressure gradient (HWPG)—the difference between a wedged hepatic vein pressure (wedged balloon-tipped catheter in the right hepatic vein) and the free hepatic vein pressure. In normal patients with normal livers, HWPG is <5 mm Hg. With progressive hepatic scarring, resulting in alteration of blood flow patterns through the liver and dynamic vascular responses to reduced portal venous blood flow, the increased intrahepatic vascular resistance gives rise to portal hypertension.[62] Portal hypertension is typically defined as HWPG > 5 mm Hg, and is clinically evident, with the formation of esophageal varices, when the HWPG is > 10 mm Hg. Portal hypertension is traditionally classified by the location of the restriction of portal venous blood flow—prehepatic, sinusoidal, and postsinusoidal. The restrictive physiology in Fontan physiology is postsinusoidal—elevated central venous pressure (CVP). In this situation, free hepatic venous pressures are elevated, as are wedged hepatic vein pressures, but the HWPG is usually normal.[63] Therefore, HWPG is an underestimation of the true portal pressure in these patients. The HWPG may not be as predictive of specific portal hypertensive complications in Fontan patients as it is in other patients with sinusoid-based cirrhosis and two normal ventricles.[63]

What are the anticipated consequences of portal hypertension? Splanchnic vasodilation occurs due to local and systemic vasodilators in an attempt to augment liver flow via the hepatic artery. As vasodilation progresses, systemic hypotension, plasma volume expansion, and neoangiogenesis occur.[39,64] In cirrhotic patients with normal hearts, marked increase in cardiac output occurs. This response is limited in Fontan patients due to their unique circulatory anatomy and limitations in augmenting pulmonary blood flow.[39]

Screening for presence and extent of liver disease remains a challenge. Physical exam can show abnormalities, but often late in the disease process. Routine liver function tests are frequently normal. Liver biopsies typically show bland central vein to central vein pattern of fibrosis, nearly universal sinusoidal fibrosis, and some specimens with typical portal fibrosis.[21,65] The patchy nature of the liver histology has been emphasized.[65] Noninvasive imaging modalities, therefore, may have an advantage for screening. Bulut et al. reported their results using magnetic resonance imaging (MRI) to detect liver disease in Fontan recipients at least 5 years postoperative.[66] All screened patients

TABLE 2 Initial assessment of Fontan-related liver disease

Imaging
A. Screening begins at age 5–7 years post-Fontan completion
B. Abdominal imaging will be ordered with initial assessment
C. If there is no pacemaker or MRI incompatible appliance, then MRI of the abdomen with and without contrast should be performed
D. If an MRI incompatible appliance is present, initial assessment should be with CT arteriography
E. MR elastography will be used when available
F. Abdominal US with shear wave elastography should be performed around the same time as the baseline MRI
Laboratory assessment
A. Initial laboratory work should include: CBC with differential, CMP, GGT, Direct bilirubin, PT/PTT, Protein S, Protein C, ATTIII, Ammonia, AFP, Alpha 1 antitrypsin phenotype, ceruloplasmin, HAV total Ab, Anti HBs, HBV DNA PCR, HCV PCR (qualitative), Iron/TIBC, and Ferritin
B. Serial laboratory work will depend on initial findings

Ab, antibody; AFP, alpha fetoprotein; ATIII (NOT ATTIII), antithrombin III; CBC, complete blood count; CMP, complete metabolic profile; CT, computed tomography; GGT, gamma-glutamyl transferase; HAV, hepatitis A; HBV, hepatitis B; HBs, hepatitis B surface antigen; HCV, hepatitis C; MR, magnetic resonance; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PT, prothrombin time; PTT, partial thromboplastin time; TIBC, total iron binding capacity; US, ultrasound.

demonstrated varying degrees of reticular contrast enhancement compatible with fibrosis and congestion. Reticular contrast enhancement was often nonuniform; nine patients (35%) had multifocal arterially enhancing lesions. The importance of screening for Fontan-related liver disease is vital for overall care: multiple publications have concluded that the presence of liver disease correlates with risk of adverse events over time.[22,67,68] Best practices for screening are unclear, and many centers have derived their own algorithms to standardize care and organize research regarding utility. At Children's Healthcare of Atlanta, pediatric hepatology has developed an outpatient protocol, see Table 2.[69] Screening begins at age 5–7 years and favors use of blood testing and MR imaging instead of catheterization and biopsy as initial tools.

Difficult questions, such as determining if a liver can tolerate heart transplant or if a combined liver and heart transplant should be performed, are best answered by recognizing decompensated liver disease. Possible factors to consider include Model for End Stage Liver Disease (MELD) score, liver biopsy results, HWPG, platelet count, and the presence of varices. Unfortunately, many of these factors are not helpful in patients after Fontan palliation. MELD scoring can be influenced by unrelated factors that elevate creatinine and bilirubin. Biopsy results, as previously discussed, can be misleading, and the HWPG is often normal. While varices can be seen in up to 25% of patients being assessed for liver transplantation, there seems to be less risk of bleeding than in other disease processes. Newer techniques such as FibroSURE and FibroSPECT serum marker panels are not ready to be used in this population. Therefore, using Varices Ascites Splenomegaly Thrombocytopenia score (which incorporates platelet count) and determining if clinical decompensation is present are useful.[67] While hepatic encephalopathy is exceedingly rare, risk for hepatocellular carcinoma is significant and findings such as ascites requiring large volume paracentesis and relative hypotension with renal insufficiency are differentiating factors. Current management recommendations then, include diagnosing and determining the extent of portal hypertension, vaccinating against hepatitis A and B, utilizing an esophagogastroduodenoscopy in at risk patients going to surgery, screening for liver cancer, and avoiding medications that could further exacerbate the clinical picture, such as nonsteroidal anti-inflammatory and ACE inhibitors (when relative hypotension is present). Strategies that delay the onset of liver disease should also be considered. Delaying the Fontan when possible is reasonable—in the absence of significant cyanosis or exercise intolerance the Fontan can wait until later childhood. Addressing any anatomic issues is important—stenosis in the branch pulmonary arteries should be treated to prevent additional elevation in posthepatic pressure.

9 | LIVER TRANSPLANTATION (PREETI RESHAMWALA, MD)

While over 6 000 liver transplantations are performed annually in the United States, over 17 000 patients are currently on a wait list for liver transplantation. The MELD scoring system is used to help determine liver transplant listing status and specifically predicts 90-day mortality for those awaiting transplant. Congenital heart patients often have a lower MELD score at time of transplantation listing. For all patients, survival at 10-years posttransplant is $\sim$ 65%. Cellular rejection in the first month posttransplant is present in 15–25% of recipients; however, only 4–8% have chronic rejection and antibody-mediated rejection is rare. Liver transplantation alone for Fontan patients is not typically performed, and data are limited. The concern with this approach is that the underlying cardiac disease is still present and the new graft will not tolerate the baseline abnormal hemodynamics well. Cardiac transplantation alone is sometimes considered, particularly in younger patients. If advanced fibrosis is present but severe portal hypertension is not, some would advocate for early cardiac transplantation knowing that regeneration of the liver may occur. Combined cardiac and liver transplantation is the least frequent approach taken, with most large centers only having between 0 and 5 patients in their experience. If cardiac disease plus hepatocellular carcinoma or portal hypertension is present, then combined transplantation is considered. It must be stated, however, that elevated central venous pressure often present after cardiac transplantation is particularly poorly tolerated by the graft liver, making

the recovery period very difficult. Low systemic vascular resistance postoperatively in these patients is also very difficult to treat. Many centers use elevated pulmonary vascular resistance or the presence of significant kidney disease as reasons to forgo a combined transplantation approach.

10 | SURGICAL STRATEGIES FOR FONTAN PALLIATION (KIRK KANTER, MD)

Current Fontan surgical results are quite good. Of the last 236 consecutive cases at Emory/Children's Healthcare of Atlanta, the discharge mortality rate is 0.4%. However, improving long-term survival needs attention, and it is unclear whether minimizing energy loss through the Fontan circuit over time may be a means to do so. The pediatric cardiothoracic surgery division partnered with the Georgia Institute of Technology to investigate this concept.

Computational fluid dynamic modeling was used to model flow within various Fontan pathways, predict turbulent flow patterns, identify areas of energy inefficiency, and create the most streamlined Fontan design. It was noted that offsetting the superior and inferior vena cava from each other decreased the power loss by half, and that flaring the vena cava at the cavopulmonary anastomosis further decreased power loss by 68%.[10,70] Finally, the idealized Fontan design was created, the "Optiflow" design, with bifurcated superior and inferior vena cava flow flared into each branch pulmonary artery. Although difficult from a surgical technique standpoint, a "Y-graft" Fontan, which closely mimics this design, has been utilized at Emory since 2010 based on its theoretically superior flow dynamics.[10] The surgery has been performed on 45 patients so far. While surgical technique and short-term results have been favorable, long-term results and exercise MRI findings are still needed.

Improving current surgical outcomes by designing the best-fit Fontan procedure is also an area of active research. MRI modeling is used to create three-dimensional anatomic reconstructions of a patient's actual Glenn and possible Fontan connections, which then is virtually tested for flow dynamics. Different Fontan types (extra-cardiac, lateral tunnel, interrupted inferior vena cava (IVC) with azygous continuation, etc.) can be studied to determine favorable vs. unfavorable energetics. Flows at rest and during exercise are modeled in order to determine best performance. Perhaps most exciting, a virtual surgery environment has been created that allows for the design and testing of patient specific models. The optimal anatomic Fontan construction for each patient can then be determined prior to surgery. This is particularly helpful in complex heterotaxy patients, where achieving bilateral pulmonary artery distribution of hepatic blood flow is challenging.

11 | ALTERNATIVE SURGICAL APPROACHES TO THE FAILING FONTAN (BRIAN KOGON, MD)

There are numerous long-term single ventricle survivors in our program who have never undergone Fontan completion. They have unoperated balanced physiology, Glenn physiology, or Kawashima physiology, and are alive in their eighth, seventh, and sixth decades, respectively. These patients may serve as models for alternative strategies.

The first alternative approach is a return to balanced physiology. There are reports of single ventricle patients surviving into adulthood unoperated. These patients typically have double inlet left ventricle with transposed great vessels and pulmonary stenosis. They have physiology with restricted pulmonary blood flow that allows survival well into adulthood with good quality of life.[9] Unfortunately, Fontan takedown to balanced physiology raises numerous procedural questions: will the single ventricle tolerate the volume load, what will be the new source of pulmonary blood flow, and what size shunt will maintain adequate saturations? Such an operation has not been previously attempted.

The second alternative approach is a return to bidirectional Glenn physiology. There are numerous reports suggesting that Glenn physiology, with or without augmented pulmonary blood flow, may be a reasonable final palliative strategy.[71–73] At Emory University, we have performed this operation in two patients, both with atriopulmonary Fontan connections, intractable arrhythmias, preserved ventricular function, progressive liver disease, and social issues that would preclude transplantation. In both patients pulmonary blood flow was augmented with a Blalock-Taussig shunt. One patient suffered from excessive pulmonary blood flow, heart failure, and was taken back to the operating room for a successful standard total cavopulmonary Fontan. The other suffered from shunt thrombosis, but is doing well with oxygen saturations > 70% in room air. Unfortunately, this strategy also raises numerous questions: will the single ventricle tolerate the volume load, is an additional source of pulmonary blood flow needed, and if so, will it be a shunt or an upper extremity or neck arteriovenous fistula? This alternative is feasible but challenging.

A third alternative approach is to replicate Kawashima physiology. There are numerous reports suggesting that such anatomy can serve as a final palliative strategy for single ventricle heart disease. This strategy has been previously proposed and performed in an animal model study.[74] At Emory University, we have performed this operation in two patients, again, both with atriopulmonary Fontan connections, intractable arrhythmias, preserved ventricular function, progressive liver disease, and social issues that would preclude transplant.[75] The extracardiac Fontan was created utilizing the infrahepatic inferior vena cava rather than the suprahepatic vena cava. Both patients have improved symptoms, oxygen saturations 80–85%, and normal hepatic venous Doppler signals. Takedown of a failing Fontan to Kawashima physiology may be a promising alternative. It does not change the volume load of the single ventricle, the resultant hemodynamics and saturations are adequate, and the liver and intestines, which are often major drivers of Fontan circulatory failure, are excluded from the Fontan pathway.

12 | QUALITY OF LIFE, (ADRIENNE H. KOVACS, PhD)

Health status can be assessed using measures such as the (Short Form) SF-36 survey and health-related quality of life using the Minnesota Living with Heart Failure Questionnaire. Not surprisingly, the physical

health status and functioning of adults with Fontan physiology is known to be diminished. However, a broader conceptualization of quality of life, namely one of life satisfaction that is "positively or negatively influence by individuals' perception of certain aspects of life important to them, including matters both related and unrelated to health"[76] yields less consistent findings. In fact, when defined more broadly, quality of life among adults with congenital heart disease has been found to be similar or even better than controls.[77,78] Adults who have undergone the Fontan procedure face challenges that affect quality of life—physical limitations, restrictions in diet, compliance with diet, need for medical appointments and hospitalizations, and concern for shortened lifespan.[79] It is not surprising then, that up to 33% of these patients have clinically significant anxiety or depression. What is concerning is that many of these patients are not treated, which might impact clinical care as depression is associated with increased medical utilization and decreased compliance.[80,81] Pike et al. specifically evaluated quality of life in adolescents and adults after Fontan palliation.[82] While physical composite scores were lower, mental composite scores were statistically similar. Bordin et al. showed that many patients report being satisfied or extremely satisfied with their quality of life, which at least in their study was unrelated to ventricular systolic function or exercise capacity.[83] In their study, however, they found that anxiety and depression were often present despite satisfaction with life overall.

Work by the Pediatric Heart Network demonstrated that the physical and emotional functioning of Fontan survivors may decline with age.[84] It is unclear whether treatment aimed at reducing symptoms or improving exercise capacity is always as impactful as would be thought. An example comes from the Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled, Double-Blind Study Measuring Peak Oxygen Consumption trial, which evaluated the effectiveness of bosentan in patients after Fontan palliation.[45] While peak oxygen consumption and New York Heart Association functional class improved, SF-36 scores were unchanged. This highlights the importance of specifically targeting the psychosocial health of the patient. One strategy is to actively engage patients in their healthcare decision-making. Techniques such as having patients keep a list of concerns, bringing a "note-taker" to clinic, or summarizing their understanding of what was decided at the end of a visit can alleviate anxiety and foster a better patient-physician relationship. By encouraging patients to be active listeners, misunderstandings can be minimized, which will foster optimal patient-provider communication when patients are faced with difficult medical choices in the future.

The importance of patient-provider communication is perhaps no more important than when faced with end-of-life decision-making. End-of-life care is specifically addressed in the 2008 American Heart Association guidelines, which emphasize the use of advanced directives. Furthermore, guidelines highlight the importance of understanding patient preferences and initiating the discussion about advance directives in a nonurgent manner. In reality, however, most providers do not address this topic adequately. In one study, it was reported that only 5/48 (10%) of adults with congenital heart disease who died in-hospital had end-of-life discussions documented in their medical charts, and only 3/48 (6%) had these discussions documented prior to their final admission.[85] This contrasts to what patients desire—80% of outpatients reported that they want their health care experts, preferably cardiologists, to raise end-of-life discussions.[86] When holding end-of-life discussions, some particular concepts are key. For example, it is helpful to normalize these discussions ("many of my patients"), schedule specific visits, ask the patients to include trusted loved ones in the discussion and to document the discussion for future review.

13 | TRANSITION OF CARE (ANNE MARIE VALENTE, MD)

Transitioning care from a pediatric care provider and facility to an adult care provider and facility is a difficult process for the patients in general, including those with Fontan palliation. Successful transfer is predicted by older age at last pediatric visit, greater number of surgeries, and a documented recommendation to follow-up with an adult congenital heart program. Aside from transition, other challenges can result in lapse of care. Patients may feel well, not know they need to continue care, or have financial or family issues.[87] Importantly, Yeung et al. have shown that congenital heart patients with a lapse in care of more than two years are three times more likely to require an urgent intervention, often soon after returning to care.[88] Return to care occurs due to a desire to prevent future problems, new symptoms, or recommendations from others.[87,89]

Means to prevent lapses in care include the use of databases to link patient information at the local, regional, and national level, patient education with an emphasis on self-management, documentation of the transition plan, ensuring adequate resources, and collaboration between the pediatric and adult providers. An area of interest that may be helpful is the use of social media, if done correctly and in compliance with HIPAA regulations.

14 | FUTURE DIRECTIONS (KEVIN MAHER, MD)

Ongoing collaboration between Georgia Institute of Technology and Children's Healthcare of Atlanta/Emory University has built upon the computational fluid dynamic modeling previously mentioned. An additional area of interest is the retrograde flow in the inferior vena cava seen in Fontan patients. The idea of using a valve, perhaps a transcutaneous Melody valve within the IVC near the level of the diaphragm, has been proposed. Interestingly, such a valve was part of the original operation conceived by Dr. Fontan, but due to risk of stenosis and thrombosis, it was eventually abandoned. It is unclear whether newer generation valves may be less problematic that the past era homografts. Drs. Maher and Yoganathan published early in vitro results in 2013, where they showed that the implantation of a valve into a total cavopulmonary connection resulted in acute reduction in hepatic venous pressure and energy loss.[90] In vivo data is available from Europe.[91] While the immediate hemodynamics were not significantly different, IVC flow did improve with more forward flow during inspiration.

Another area of interest lies in the field of mechanical support. While a ventricular assist device in the systemic ventricle is not very attractive, a mechanical assist device within the Fontan circuit has numerous theoretical benefits. Dr. Rodefeld's group in Indianapolis has the most experience with this subject and continues to pursue perfecting the technology.[92] Finally, identification of "hepatic factor," remains a focus of research at Emory. Using proteomics and metabolomics, Dr. Maher and coworkers have identified candidate proteins for further investigation.

15 | STEM CELL THERAPY (REBECCA D. LEVIT, MD)

Stem cell therapy may have some benefits when applied to Fontan hemodynamics. Stem cell research for cardiac applications has focused mainly on animal models of ischemic and nonischemic cardiomyopathy. Unfortunately, results from randomized clinical trials in adult patients have showed lower than expected benefit. A meta-analysis of 16 stem cell clinical trials reported only a small improvement in ventricular ejection fraction. However, the adult myocardium is an inhospitable environment for stem cells. The heart is highly inflamed after myocardial ischemia, and chronic diseases (diabetes, hypertension) and unhealthy habits (smoking, lack of physical activity) have been linked to poor stem cell function and viability.[93] Furthermore, regenerative capacity declines precipitously with age. Younger patients therefore are likely much better hosts for transplanted stem cells due to preserved innate regenerative capacity and lack of comorbidities. Small, nonrandomized trials of stem cell treatment in pediatric congenital heart patients have shown promise.[94]

Poor cell retention has limited stem cell efficacy in vivo and is a current area of active research. Biocompatible materials that can support the cells in vivo, and may increase their therapeutic benefit, are currently being investigated.

There are many applications of stem cells and biomaterials to single ventricle patients. Early diagnosis, in utero in some cases, allows for intervention during the time of greatest cardiac plasticity. Materials seeded with cells could be used to correct the anatomy of the developing heart by growing septa, muscular cardiac chambers, or valves. In older patients, biological valves or functional myocardium could be used at the time of surgical intervention. Valves, conduits, or patches made from patient derived cells would be more durable, have greater growth potential, and be less thrombogenic. Stem cells supported by biomaterials may open new therapeutic avenues for congenital patients.

16 | PATIENT AND PHYSICIAN PERSPECTIVE

A cardiologist that underwent Fontan palliation and Fontan revision shared his perspectives as both patient and physician. He emphasized several key points in the care of these patients. (1) Families should identify a "resource person(s)" to serve as a source of continual support for the patient. Ideally, these persons would also serve as role models and/or mentors, providing the patient a sense of normalcy that main caretakers cannot, due to stress, and exhaustion. (2) The patient-doctor relationship is essential for how patients face their challenges. Avoid being the doorkeeper to limitations and instead emphasize all the ways a patient can thrive. Allow patients to discover their own limitations, with few exceptions (e.g., contact sports). Our job is to enable the heart, not to enfeeble the person. (3) Planned hospitalizations and procedures should be tied to positive experiences such as a family vacation to make the memory less traumatic and to create a positive association for future care. Lastly, as with any human being, faith, having a sense of purpose, and having good role models are essential to morale and eventual outcome.

CONFLICT OF INTEREST

The authors have no conflicts of interest or industry relationships to disclose.

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All listed authors were speakers at the conference except authors Hebson and McConnell. Author Hebson wrote the article in its entirety and authors Hebson, Rodriguez, and McConnell were primary authors in terms of Concept/Design. All authors provided critical revision of the article.

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