The Relentless Effects of the Fontan Paradox
Jack Rychik

The Fontan operation is the anticipated palliative strategy for children born with single-ventricle type of congenital heart disease. As a result of important circulatory limitations, a series of end-organ complications are now increasingly recognized. Elevated central venous pressure and impaired cardiac output are the hallmarks of cavo-pulmonary flow, which result in a cascade of pathophysiological consequences. The Fontan circulation likely impacts all organ systems in an indolent and relentless manner, with progressive decline in functionality likely to occur in many. Liver fibrosis, altered bone density, decreased muscle mass, renal dysfunction, lymphatic insufficiency, and a host of other conditions are present. Standardized screening and evaluation of survivors as they grow through childhood and beyond is indicated and can be facilitated through dedicated multidisciplinary clinical programs. Invasive assessment at specific milestones can provide important actionable information to optimize individual status. More detailed characterization and understanding of these end-organ complications is necessary to contribute to the goal of achieving a normal duration and quality of life for these unique individuals.

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One of the greatest achievements in the field of congenital heart care is our capacity to create survival for children born with only half a heart. Surgical strategies have developed and continue to evolve that allow for patients with a variety of forms of single-ventricle type congenital heart disease (CHD) to live. The management strategy hinges upon the concept of passive cavo-pulmonary flow, a profound notion that adequate circulation can be achieved by directing systemic venous return directly to the lungs without the use of ventricular derived propulsive thrust.

Today, the construct of care provided for these patients is truly amazing. One can make a detailed diagnosis of single-ventricle CHD early in fetal life and provide prenatal counseling in which risk stratification can be offered, yet also inform families that, by and large, there is a strong likelihood their child will survive into adulthood. Newborns are cared for in highly specialized units with experienced practitioners, have a variety of potential initial surgical options individually tailored, and are observed and scrutinized between stages of surgery in a systematic fashion, all in an effort to optimize outcome. Although far from ideal, early survival rates are the highest they have ever been. The course of early care is well scripted and outlined for most; however, what happens next, once patients have completed the rigors of surgical reconstruction, is much less well defined.

A generation of human beings is now alive who have previously never walked the face of the earth. This is an achievement our community should be extremely proud of, with gratitude to pioneers such as Glenn, Kreutzer, Fontan,
An Imperfect Circulatory Physiology

One of the objectives of Fontan’s original operation was to eliminate the problem of cyanosis. Channeling systemic venous return directly to the pulmonary circulation achieves this goal. However, in a prescient manner, Fontan and Baudet and DeLeval, as well as to the many surgeons and cardiologists who have followed and continue to contribute to modifications and improvements in care.¹

Yet, in conjunction with this success, has come the growing and sobering realization that all is not well. Circulatory deficiency leads to a myriad of organ system consequences, some subtle and others of ostensible clinical significance. End-organ dysfunction as a consequence of sustained cavo-pulmonary flow plagues survivors, with some comparing the condition after Fontan operation to that of an indolent and progressive state of chronic heart failure. Whether related to the intrinsic substrate of the cardiac anomaly or secondary to the imposition of the Fontan circulatory physiology, or a combination of both, onset of overt complications can be sudden and unexpected, crossing from an underlying subclinical physiology to the threshold of clinical symptomatology and detection at any time.

The Fontan state is a paradox, both a physiological as well as an existential one. From the physiological perspective, negative effects of elevated central venous pressure and its detrimental consequences are a natural result of the life-saving Fontan surgical strategy. Existence is achievable for the lethal condition of single-ventricle type CHD, but there are growing concerns about whether these patients will ever attain a fully normal quality and duration of life.

How should we proceed at this point in time? First, it is imperative for us to characterize and understand the unique effects of the Fontan circulation to the best of our abilities. Clinical and physiological characterization must be integrated into a more basic biological understanding of organ system function in these unique beings. In tandem with improving our comprehension of how organ systems function differently, we should look at preventative and therapeutic strategies that might improve the Fontan circulatory state. There is no need to await a total and complete understanding of the pathophysiology before initiating common sense and innovative care plans that may have an important impact. The effects of the Fontan circulation are sustained and relentless, but some aspects may very well be modifiable. This concept is finally catching on as cardiac surgeons and cardiologists begin to agree: it is no indictment of the beauty and benefits of the Fontan operation to admit to and realize the physiological limitations it creates, and to work toward improving the condition of survivors. This is not a fatalist’s, but a realist’s viewpoint, with the intent to motivate those of us within the community who care for these children to consider what should come next.

Let us review some of the consequences of the Fontan circulation.

Their original description² cautioned “this procedure is not an anatomical correction, which would require the creation of a right ventricle, but a procedure of physiological pulmonary blood flow restoration, with suppression of right and left blood flow mixing.”

Absence of ventricular thrust and creation of passive venous flow through the cavo-pulmonary circuit leads to obligatory elevated central venous pressure, typically in the range of 10 to 15 mm Hg, up to three times normal. The determinants driving blood forward in this situation are a combination of passive and weakly active forces. Systemic venous pressure exceeds downstream pulmonary venous and left atrial pressure. This, in addition to peripheral muscle contraction, encourages forward venous drainage. Respiratory inspiration creates negative pressure, further drawing blood into the chest cavity. Importantly, and perhaps underappreciated, is the downstream ventricular effect of apically directed descent of the atrioventricular valve and overall ventricular mechanics during systole, which expands atrial volume, drawing blood forward through the pulmonary veins.³ Diastolic compliance and end-diastolic pressure of the single ventricle has been argued to be of importance from a passive filling perspective,⁴ but the predominance of pulmonary venous flow after cavo-pulmonary connection takes place during ventricular systole, highlighting the importance of systolic ventricular mechanics exerting a forward force on upstream cavo-pulmonary flow.

Absence of ventricular thrust and passive cavo-pulmonary flow after Fontan operation leads to a relatively low cardiac output state in comparison to normal. There is an impaired ability to deliver a normal quantity of blood volume across the pulmonary vascular bed, thus diminished ventricular filling and low stroke volume. Some consider the Fontan state to be one of chronic ventricular volume depletion.⁵ There is also an inability to adequately increase stroke volume during periods of increased demand, such as during exercise.⁶ The operation itself can result in impaired chronotropy because of manipulation of atrial tissue, possible interruption of sinus node arterial supply, or scarring in the region of the sinus node. Impaired chronotropy further limits cardiac output and proper response to demand. Overall vascular resistance and ventricular afterload is increased after Fontan operation because blood must traverse the systemic arterial system, systemic venous system, Fontan pathway, and pulmonary venous system before returning to the ventricle. Increased peripheral vascular resistance, in particular endothelial dysfunction, is present.⁷ Furthermore, increased mesenteric vascular resistance may occur in response to low cardiac output and a compensatory attempt to shift blood flow away from non-vital organs.⁸

The natural inherent substrate of single-ventricle type CHD can sometimes work against the desired goals that provide for an optimal passive cavo-pulmonary flow state. Not necessarily prohibitive at the time of initial surgery, a number of intrinsic factors may play a role in the progressive decline of the circulation over time. The pulmonary vascular bed, so essential for proper functionality of passive cavo-pulmonary flow, can be abnormal because of altered flow patterns in utero related to the cardiac anomaly.⁹ Further deterioration in pulmonary vascular state can take place because of the iatrogenic effects of
aorto-pulmonary shunt placement with proximal structural distortion or altered flow characteristics, negatively influencing peripheral pulmonary vascular development. An apparent natural, biological attempt at compensation for chronic passive pulmonary blood flow – development of aorto-pulmonary collateralization – itself can impede passive forward flow and create additional challenges of ventricular volume overload. Chronic venous hypertension and low cardiac output promote a pro-inflammatory state, increase the risk for thromboembolism, and lead to marked abnormalities of the lymphatic system. In addition, independent of the Fontan circulation are the risks of ventricular and atrioventricular valve dysfunction inherent in the single-ventricle type of CHD, with the possibility of a natural decline in function over time.

All of these factors have the potential to alter end-organ perfusion and impair functionality. While recent studies show operative mortality to be satisfactorily low after Fontan surgery, with intermediate-term survival of approximately 80% at 15 to 20 years, it is reasonable to conclude that freedom from morbidity is likely to be close to zero for survivors.

**Fontan and Liver**

The liver is the first organ upstream of the Fontan pathway. Elevated central venous pressure and the impedance to hepatic venous egress created by imposition of a Fontan circulation produces a state of chronic congestion in this highly vascularized organ. The hepatic parenchyma is particularly vulnerable to hypoperfusion because it is situated between the pulmonary vascular bed and the splanchnic bed. Mesenteric circulation may be compromised as a consequence of diminished cardiac output. A compensatory increase in mesenteric vascular resistance exists in the chronic heart failure state after Fontan, to shift flow away from the gut and redistribute blood flow to more vital organs. Hepatic venous congestion is believed to induce hepatic stellate ganglion cells to transform into fibroblasts that lay down collagen leading to progressive hepatic fibrosis. Thus, risk for ischemia and progressive fibrosis are the hallmarks of hepatic injury after Fontan.

Manifestations are often sub-clinical. Mild hepatomegaly is common. Thrombocytopenia and mild to moderate elevations in serum liver enzymes are typical. Synthetic function is usually preserved; however, in circumstances of failing Fontan circulation at end-stage, there can be difficulties with drug clearance and hepatic encephalopathy. Neoplastic transformation has been reported. Ascites directly related to fluid produced by liver fibrosis can occur. Varices are relatively uncommon because decompression from a high-pressure portal circulation to a lower-pressure systemic venous system is not possible because elevated systemic venous pressure is the inciting culprit.

Assessment and evaluation can be challenging. Although serological tests exist to characterize liver fibrosis, they are specific for the most common form of fibrotic change caused by hepatitis C disease. Liver ultrasound can provide a gross sense of size and overall structure, which can be of some value, but is not helpful in gauging for histological changes. Computed tomography and magnetic resonance imaging (MRI) can similarly provide information on gross abnormalities but not degree of fibrosis. A reliable method for serial non-invasive evaluation of fibrotic change is needed. Utilizing either ultrasound or MRI, elastography is a technique that can provide a quantitative measure of biological tissue stiffness through shear wave analysis, and may offer promise as a tool for serial assessment of liver fibrosis. Reliable validation in the Fontan population is still needed. Limitations of the techniques, such as measurement of tissue stiffness not related to fibrosis but rather to vascular engorgement, will need to be differentiated one from the other before this technique can be widely applied for clinical use and quantification of liver fibrosis.

Short of the potential promise of elastography, one is left with invasive evaluation through liver biopsy as the best means for evaluation. Following a careful consideration of the issues and a risk-benefit analysis, our group at The Children’s Hospital of Philadelphia came to the consensus that detailed cardiovascular characterization through cardiac catheterization, cardiac MRI, and a needle liver biopsy at 10 years following Fontan operation was the best proactive way to gauge the state of our patients. Information gathered could be used to design management plans to optimize the Fontan state in each individual patient, and used to understand the status of the liver within the context of the hemodynamics present. Starting in late 2012 up until mid 2015, thus far over 100 asymptomatic well-appearing patients have come through evaluation. A substantial number have had discovery of coincidental, unexpected findings (such as pathway or pulmonary artery narrowing, prominent aorto-pulmonary collateral flow, or relatively elevated pulmonary artery pressures [> 15 mm Hg] without any specific explanation). These are hemodynamic findings that would otherwise not have been detected without these invasive assessments.

We have learned that no patient following Fontan is free of hepatic fibrosis. In essence, all have some degree of hepatic fibrosis ranging from mild centrilobular changes, to bridging fibrosis across regions and tracts, to frank cirrhosis. The patterns of hepatic fibrosis are unique in that it can be found surrounding portal tracts as well as centrilobular regions, thereby not lending itself in an ideal fashion to standard pathological grading systems.

To best quantify the overall total burden of fibrotic change incorporating the combination of centrilobular and portal fibrosis, we have applied the technique of sirius red staining to highlight collagen deposition and then utilized automated quantitative methods to provide a percentage of collagen deposition within a field of view (Fig. 1). In a series of 74 patients assessed in our program by liver biopsy and cardiac catheterization at an average of 14.9 ± 4 years after Fontan, percent collagen deposition (%CD) was noted to be 24 ± 10%. A control group of patients of the same age who had liver biopsy for other reasons besides anticipated fibrosis had %CD of 3 ± 0.3%. Of note, %CD was not associated with central venous pressure but was significantly associated with time from Fontan operation (CHOP, unpublished data). Simply
having a sustained abnormally elevated central venous pressure for an extended period of time, even a pressure that one would consider within a reasonably acceptable range for a patient with a Fontan circulation, may be detrimental to the liver. In other words, having a Fontan circulation, regardless of status, is associated with liver fibrosis. The implications of this discovery are still unfolding as the community just now begins to appreciate this phenomenon and begins to face the challenges of serial follow-up with consideration of potential therapeutic strategies.

Luminal Protein Loss Syndromes and the Lymphatic System

Protein-losing enteropathy (PLE) and plastic bronchitis are troubling and potentially life-threatening complications seen after Fontan operation. These conditions share the end result of a break in the integrity of the mucosal lining with spillage of highly proteinaceous material into a luminal cavity. In PLE, protein loss is abundant because transit passage through the gut is high, with continuing protein leak leading to hypoproteinemia and a cascade of consequences. In plastic bronchitis, protein leak is limited by the bronchial spaces and the capacity to expectorate the formed casts. Small amounts of protein leak in plastic bronchitis can be of significance because airway blockage, atelectasis, and at times life-threatening asphyxiation can occur if the material is not properly cleared.

The pathophysiology of these Fontan-related “endoluminal protein loss syndromes” is complex and likely includes mechanistic processes such as elevated venous pressure, impaired tissue perfusion, and inflammation. Improving overall Fontan circulation by lowering central venous pressure and increasing cardiac output, the ultimate of which is a heart transplant, have been demonstrated to be effective treatment strategies in some. Initial onset of PLE can be effectively managed utilizing intestinal specific anti-inflammatory agents such as oral controlled release budesonide. The symptoms of plastic bronchitis can be mitigated by using aerosolized tissue plasminogen activator, which acts as an airway clearing agent by effectively breaking down cast material that can then be more easily passed. Aggressive treatment with pulmonary vasodilator agents such as sildenafil or bosentan may theoretically lower impedance to forward passive cavo-pulmonary flow, thereby placing the circulation at a point just beneath the threshold for protein spillage and has been an important component of the treatment strategy for both plastic bronchitis and PLE.

An important but to date poorly understood aspect to PLE, plastic bronchitis, and overall Fontan circulatory physiology is the role of the lymphatic system. Elevated central venous pressure acts to increase tissue fluid and lymphatic fluid generation. At the same time there is impediment to drainage because, ultimately, lymphatic channels join the thoracic duct, which normally connects with the innominate vein, itself a vessel under high pressure. This situation of increased production plus impaired drainage can lead to generalized lymphatic insufficiency. When the lymphatic system is

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Figure 1 (A) Trichrome stain of liver biopsy specimen from a 14-year-old patient with Fontan circulation. Blue indicates areas of fibrosis. (B) Sirius red stain of the same liver biopsy specimen. Red areas indicate collagen deposition. Automated percent collagen deposition reading for this sample was 25%.
overwhelmed, the result is a breach of the lymphatic system into lower pressure cavities such as the intestinal lumen or bronchial airway tree, with spillage of proteinaceous material.

To date, imaging and characterizing the lymphatic system in disease states has been a challenge. The capacity to image the lymphatic system is now possible using T2-weighted MRI techniques focusing on high water content structures, as well as through novel techniques of direct cannulation of lymphatic channels and lymphangiography. Such imaging in the Fontan population reveals marked abnormalities with significant distortion and tortuosity of lymphatic channels. Catheter access to such lymphatic channels also allows the possibility for intervention and potential treatment of abnormalities. We have successfully treated a number of children with plastic bronchitis after Fontan through lymphangiography imaging of channels abnormally draining into the bronchial airway and occlusive embolization of these channels using biological glue.

Lymphatic imaging in those with PLE reveals abnormal drainage of a multitude of lymphatic vessels from the liver into the intestinal lumen. Therapeutic strategies that could be developed to occlude these channels or re-direct lymphatic flow away from the intestinal lumen may prove to be an effective treatment for PLE.

### Comprehensive Monitoring and Evaluation After Fontan Operation: The Single Ventricle Survivorship Program

A great number of end-organ system deficiencies are being recognized as more patients survive Fontan operation. Growth and development can be delayed. Bone health and muscle mass are different than normal in patients with Fontan circulation, with decreased whole body and leg lean muscle mass correlating with exercise capacity. Vitamin D, an important component of health for both bone and the vascular system, is remarkably low in our Fontan population. Parathyroid hormone levels are elevated, which may reflect a compensatory attempt to maintain serum calcium at the expense of bone calcium stores, thereby leading to bone density abnormalities on dual energy x-ray absorptiometry (DXA) scanning. Significant renal insufficiency is uncommon early. However, glomerular filtration rate diminishes with advancing age, with 10% of patients demonstrating evidence of chronic renal failure in early adulthood (CHOP, unpublished data). As body mass is diminished, creatinine levels may be spuriously low and, hence, a low serum creatinine level may be falsely reassuring. Cystatin C levels are likely better at gauging renal function. Infection risk is not seriously increased after Fontan operation, except for those with asplenia syndrome. However, lymphopenia and hypogammaglobulinemia are recognized with increasing frequency. These findings are present not just in those with PLE, in whom enteric lymphopenia and immunoglobulin loss might be expected, but in non-PLE Fontan survivors as well. An interesting clinical manifestation we have noted is the significantly increased prevalence of viral warts and molluscum.

To manage these and other emerging organ system comorbidities after Fontan operation, we have developed a multidisciplinary clinic approach we call the Single Ventricle Survivorship Program. Talented specialists from the disciplines of endocrinology, hepatology, immunology, pulmonology, and nephrology have been recruited to join in a collaborative effort offering comprehensive services to Fontan patients within a single clinic setting. As knowledge and understanding of these systemic organ processes are just now emerging, it is of practical benefit to identify a specific, dedicated group of specialists who can gain experience and familiarity with the unique issues at hand. This allows for a collegial atmosphere of health care providers, all of whom are familiar and comfortable with Fontan physiology, and are able to more effectively collaborate on management schema. It also optimizes the potential for academic and investigational activity through engagement of a dedicated team of physicians and nurses with varying specialty strengths, sharing and learning from each other.

In Philadelphia, the Single Ventricle Survivorship Program does not replace standard care offered by the primary cardiologist caring for the patient. Rather, it is designed as an additional layer of care offered as a consultative service, with close collaboration with the primary cardiologist caring for the patient. Our group has developed a screening and testing scheme, which continues to evolve, but currently provides a reasonable method and guideline to serially assess the patient after Fontan operation. In addition to routine cardiac evaluation with EKG and echocardiogram, which conventionally occurs every 6 to 12 months, additional assessments are recommended every 3 to 4 years (Table 1). A comprehensive invasive evaluation to include a cardiac catheterization, cardiac MRI, and a percutaneous liver biopsy is suggested for approximately 10 years after completion of the Fontan operation, at age 12 to 14 years. Information gathered forms the basis for baseline assessment and allows for serial data as the patient progresses over time. In many instances, the evaluation informs on specific actions to improve the immediate state. For example, abnormal low DXA scan findings in light of vitamin D deficiency results in a recommendation for supplementation. Cardiac catheterization assessment has yielded actionable information in approximately 20% of patients at the 10-year post-Fontan mark, including relief of pulmonary artery narrowing or embolization of important aorto-pulmonary collateralization. The finding of significant fibrosis, such as bridging fibrosis within the context of elevated pulmonary artery pressure of >15 mmHg has prompted consideration of individual treatment with pulmonary vasodilator therapy such as sildenafil. These actions theoretically provide for optimization of the circulation as the child enters the adolescent years.

Initiation of effective preventative strategies to deflect or mitigate some of the deleterious end-organ consequence of the Fontan circulation is strongly warranted. However, administration of specific agents at this time lacks a strong body of evidence base. Hence, there is reluctance in offering medications to relatively well-appearing children without further data. There are a number of potentially beneficial candidate agents.
Sildenafil is demonstrated to improve exercise capacity, as is endothelin blockade with bosentan. Utilizing these agents in children with Fontan-related complications such as PLE or plastic bronchitis is warranted. However, routine use in all patients should be discouraged at this time. Further information will be available following completion of larger clinical trials utilizing pulmonary vasodilator therapy. A case can be made for possible utilization of low-risk agents such as spironolactone or perhaps angiotensin converting enzyme inhibition, not just for direct cardiovascular purposes, but rather for hepatic protection because each of these agents also exhibit anti-fibrotic properties. Anticoagulation using either aspirin, warfarin, or a combination of the two is common after Fontan operation, to prevent thromboembolic events. Despite the widespread use of aspirin or warfarin, the data supporting the efficacy of this strategy is weak at best.

What Comes Next?

A number of objectives must be met to best manage our patients with Fontan circulation as they grow in numbers and in age. As our community turns more attention to these end-organ consequences, focus must be placed on identifying modifiable variables that contribute to decline. Development of strategies to mitigate decline, perhaps through pharmacological mediation, is crucial. For example, the rate of progression of liver fibrosis must be ascertained, in as gentle a manner as possible, with reliable serial means for non-invasive assessment. Once variables contributing to decline are identified, a discriminative score that can help guide health care providers in deciding when to move from one management strategy of care to another will be extremely useful. Development of a discriminative characterization score that predicts demise would be critically useful in the setting of chronic debilitating PLE or overall Fontan circulatory failure, in which decisions must be made for timing of heart transplantation listing. Realizing that the source of much of the trouble relates to the physiological limitations of cavo-pulmonary flow, development of a safe and practical means for supporting and augmenting pulmonary blood flow through auxiliary means (mechanical or biological) would be very helpful. There is much to learn and we are only at the beginning of the endeavor, as we move to the next era of care for patients afflicted with the misfortune of being born with only half a heart.

### References


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*Cardiac testing may be performed more frequently based on clinical indications.
†If Vitamin D supplementation offered, then blood levels should be followed closely to avoid toxicity.
‡If normal initial DXA scan, with subsequent normal growth/puberty, normal albumin, normal Vitamin D and calcium levels, and no history of fractures the DXA is not repeated.