Forty Years of The Fontan Operation: A Failed Strategy

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One of the most important contributions to the field of congenital heart disease has been the introduction and development of a management strategy for our most complex heart malformation, that of single ventricle type of congenital heart disease. Over the past 40 years pioneers such as Fontan,[1] Kreutzer,[2] de Leval,[3] and many others have contributed to creating a story of tremendous success. The unique and surprisingly effective framework of surgical reconstruction through systemic venous connection to the pulmonary circulation, absent the propulsive force of a pulmonary ventricle, has been life saving for these children. Since inception, numerous investigators have further contributed to improvements in our understanding of cavo-pulmonary physiology, as well as incremental improvements in operative survival. As a consequence of this body of work, we have a sound surgical approach to the management of this complex congenital anomaly. Uniformly lethal four decades ago, the newborn with single ventricle type congenital heart disease in 2010 is now not only likely - but expected - to survive.

However, as these children have grown into adolescence and adulthood, it is clear that there are significant limitations to this strategy. While life saving, the Fontan/Kreutzer operation (herewith referred to as FO) results in profound physiological disturbances with very serious consequences. Pervasive abnormalities of multiple organ systems are affected as time goes on. Realistically, it is unlikely that patients will survive into their third or forth decades of life untouched by some potentially life-threatening complication. Clearly stated, the FO is not a satisfactory long-term solution; it is a failed strategy.

Perhaps at one point in time, simply getting patients to survive to their third decade of life was a lofty goal. Settling for this goal alone in the current era is unacceptable. Why should the medical and surgical community caring for these patients set the bar so low? Our field needs to move forward with a shift in thinking about single ventricle. A major effort should be undertaken to better understand the long-term physiological consequences and identify treatments that may ameliorate the dysfunctional state of the FO. But most importantly, we need to encourage innovative thinking in order to focus on developing new and creative strategies that will provide a semblance of life closer to normal for these patients.

The Status of Our Patients After Fontan Operation: How are They Doing?

How are our patients doing? It is clearly a matter of perspective – is the glass partially empty or partially full?

Multiple studies looking at the results of the FO demonstrate a decrease in survival beyond 15 years after surgery. An ongoing significant risk of death with continuous attrition is present, regardless of surgical type of cavo-pulmonary connection. In a recent single-institutional study, actuarial freedom from death or transplantation was 87%, 83%, and 70% at 15, 20, and 25 years after surgery, respectively.[4] Death in this group was sudden, unexplained in 9%, thromboembolic in 8%, and heart failure related in 7%. In another study looking at morphologically single left ventricle after FO, actuarial survival was 73% at 15 years.[5] Atrial arrhythmias were present in 57%, protein-losing enteropathy in 9%, and thromboembolic events in 6%. In other words, odds are 1 out 4 that a child after FO will be dead by the time he or she reaches their late 20s.

In a large multi-center cohort, the Pediatric Heart Network reviewed 546 children who where an average 11.9 years of age at study and 8.5 years after FO, a relatively young group.[6] Stroke or thromboembolism was seen in 8% of patients. Exercise performance was abnormal. Peak oxygen consumption was only 65% predicted for age and gender. Adolescents (ie, "older" patients) faired worse than the younger children, suggesting a time-related decrement in functionality.[7] The health status of children and adolescents after FO is poor. In another Pediatric Heart Network study, parent-reported patient morbidities included deficits in vision in 33%, speech in 27%, and hearing in 7%, as well as problems with attention in 46%, learning in 43%, development in 24%, behavior in 23%,

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anxiety in 17%, and depression in 8%.[8] These are not findings that can be ignored, and certainly do not reflect a successful management strategy.

A Suboptimal Physiology

The basic purpose of the original Fontan operation, as stated by Fontan and Baudet,[1] is to separate the circulations and improve peripheral oxygen saturation. Directing systemic venous return to the pulmonary circulation results in reduction of cyanosis; however, it also creates the conditions of: 1) *elevated central venous pressure*, and 2) a *reduction in cardiac output*, relative to the normal two-ventricle state. These are the foundations of the hemodynamic aberration, which lead to the organ system failures seen after FO.

A number of elements contribute to impairment in cardiac output in the single ventricle after Fontan operation. First is the passive nature of flow through the lungs. Absence of a pulmonary ventricle not only alters the perfusion profile of the pulmonary circuit, but more importantly limits the filling potential of the systemic ventricle. After FO, the entire systemic venous return is obligated to passively traverse the pulmonary vasculature before filling the systemic ventricle, hence stroke volume is limited.[9] This explains why cardiac output is higher in the fenestrated versus non-fenestrated state, as the ventricle fills better through right-to-left shunting across the fenestration.[10-12] It also explains why cardiac output is higher still after bidirectional Glenn relative to after FO as the ventricle fills easily with inferior vena caval flow in the normal manner, without interposition of the pulmonary vasculature. Investigators have shown that cardiac output and stroke volume decrease when proceeding from Glenn to Fontan.[13] Furthermore, the compensatory ability to increase cardiac output through an increase in heart rate is limited because of sinus mode dysfunction commonly seen after FO.[14]

In addition to physiological limitations of ventricular filling inherent in the cavo-pulmonary connection, the abnormal nature of the ventricle itself hinders the ability to deliver a normal cardiac output. Multiple studies have demonstrated how the function and contractility of the single systemic ventricle differs from the left ventricle in a normal two-ventricle system. These differences are present very early in development, even before the effects of altered loading conditions as a consequence of palliation (eg, shunt placement) take place. Decreased right ventricular performance, ventricular functional inefficiency, and overall diminished cardiac output are found in the fetus with hypoplastic left heart syndrome relative to normal.[15] After FO, ventricular contractility and ventricular power are diminished.[16,17] Depressed ventricular contractility is present regardless of ventricular morphology, right or left.[18] Marked abnormalities of diastolic function are present, including poor ventricular compliance and a greater dependency on atrial contraction for filling,[19] as well as abnormal, "incoordinate" relaxation of the ventricle.[20] In one large cohort, more than 70% of subjects had evidence of abnormal diastolic function on echocardiography.[6] Systemic atrioventricular valve incompetence, a common finding, further contributes to the development of impaired ventricular mechanics. In total, these findings lead to a decrease in cardiac output. More importantly, and of utmost concern, these abnormalities appear to worsen over time.[21]

Systemic Impact of the Fontan Circulation

The chronic state of increased central venous pressure and low cardiac output have a pervasive effect on all of the organ systems. However, let us focus on two systems. Raising serious concern are recent findings of the impact of the FO with its associated physiological manifestations on the liver and mucosal epithelium of the intestinal tract and bronchial airways.

The Liver

Multiple investigators have found abnormalities of liver parenchyma and hepatic function in survivors of FO. Transient elastography, a non-invasive sonographic technique used to assess tissue characteristics, demonstrated abnormalities of liver texture in 36 of 39 children studied at an average of 12 years of age. The degree of liver "stiffness" correlated with number of years from FO.[22] In another study, liver biopsies were performed in 18 patients prior to conversion to an extracardiac type cavopulmonary operation, all demonstrating sinusoidal fibrosis. In 17 of the 18 there was histopathologic evidence of the beginnings of cirrhosis, with frank cirrhosis in two.[23] Ominously, in another series, findings of centrilobular necrosis, cardiac cirrhosis as well as hepatic adenoma in a 14-year-old and hepatocellular carcinoma in a 24-year-old were identified after FO.[24] A predilection toward neoplastic disorders exists in the face of cirrhosis; however, this occurring in such a relatively young population is quite disturbing. In another study, hepatic disease after FO was assessed by developing a composite liver score, including variables such as liver size, serological values, and hepatic Doppler flow indices.[25] Investigators found an inverse relationship between the degree of liver dysfunction as measured by the "score" and cardiac output, suggesting a relationship between the two. A study evaluating liver biopsies in an "older" group of patients after FO, at an average age of 25 years, found more disturbing data.[26] Hepatic cirrhosis was present in this series in seven out of 12 patients (58%), with the degree of cirrhosis correlating with hepatic vein pressure and with duration since FO.

Liver disease after FO is a direct consequence of chronic elevation in systemic venous pressure and low cardiac output. Chronic hepatic venous hypertension leads to the fibrotic changes described. Liver fibrosis predisposes to liver nodular regeneration and the specter of neoplastic disease. Hepatic centrilobular necrosis is a direct result of impaired perfusion. There is compelling evidence to suggest that as soon as the FO is performed, the liver is never the same, and that the longer the physiology of a FO exists, the greater is the damage incurred. Ironically, hepato-cellular dysfunction occurs only after extensive liver damage has taken place. Hence, simple evaluation of liver function tests or observation for clinical signs of liver failure, our most common means of

Figure 1 Expectorated bronchial casts from a 4-year-old child with plastic bronchitis after Fontan operation. These casts of the airway are composed of proteinaceous material and are typically acellular. The pathophysiology is presumed to be similar to that seen in PLE.

assessment, will not be helpful and do not reflect the extent of silent, steady, and extensive damage that is taking place.

### Protein Losing Enteropathy and Plastic Bronchitis

One of the most intriguing and poorly understood complications after FO is protein losing enteropathy (PLE). The loss of protein at the intestinal mucosa seems to occur inexplicably and at random, resulting in depletion of serum albumin levels and reduction in vascular oncotic pressure.[27] The disease manifests clinically as peripheral edema, ascites, effusions, and gastrointestinal symptoms. Diarrhea is common, but not a major presenting symptom in all. In fact, many cases are quite indolent, with slow progressive loss of protein in the stool, and no diarrhea whatsoever. It is only once gut edema is present in severe cases, resulting in malabsorption of intestinal nutrients with a change in gut flora and fauna, do we then see the findings of diarrhea. Therefore, PLE can be a silent disease, with a sub-clinical component in an as of yet unknown number of patients.

In severe PLE, many elements of serum protein are lost in the gut, including immunoglobulins leading to relative immune deficiency. Coagulation factors are lost, further exacerbating the risk of thromboembolism, which is present in all subjects after FO. A similar process with a break in mucosal integrity to protein loss can occur at the bronchial mucosal level, with leakage of proteinaceous material into the airways resulting in bronchial casts, or a "plastic bronchitis" (Fig. 1). As the airway passages are not as capacious as the gastrointestinal tract, hypoalbuminemia is not typically a consequence of plastic bronchitis. Instead, bronchial casts form occluding the airways. If these are not adequately mobilized and expectorated, they can result in obstruction, atelectasis, or at times life-threatening asphyxiation.

Although the mechanistic origins are not fully understood, PLE and plastic bronchitis are a model for what is fundamentally wrong with the physiological state of children following the FO. We have proposed a pathophysiological explanation,

which involves a cascade of events, starting with chronic low cardiac output (Fig. 2).[27] When in a low cardiac output state, compensatory mechanisms lead to redistribution of flow to essential organs, shifting blood supply away from non-essential vascular beds such as the gastrointestinal tract. In support of this notion, we have found increased mesenteric vascular resistance in children after FO relative to normal, with further increase in mesenteric vascular resistance in those with PLE.[28] Inflammation, both systemic and local, also plays a role. Low cardiac output states as seen in chronic heart failure lead to elevations in systemic inflammatory markers. Tumor necrosis factor alpha levels are elevated in children after FO.[29] Furthermore, upon endoscopic evaluation, we have found subtle evidence for inflammation/colitis in a number of patients with PLE. Therefore, we postulate that PLE after FO is caused by impaired mesenteric perfusion as a consequence of elevated central venous pressure and low arterial flow. This altered mesenteric blood flow profile, in conjunction with inflammation, causes a break in the mucosal epithelial barrier leading to extravascular protein loss. This hypothesis is supported by the response of patients to current treatment strategies. PLE after FO can be controlled by either improving blood flow (ie, increasing cardiac output) or by the use of anti-inflammatory agents.[27]

Elegant work has recently led to an improved understanding of the cellular and molecular nature of PLE. Epithelial cell
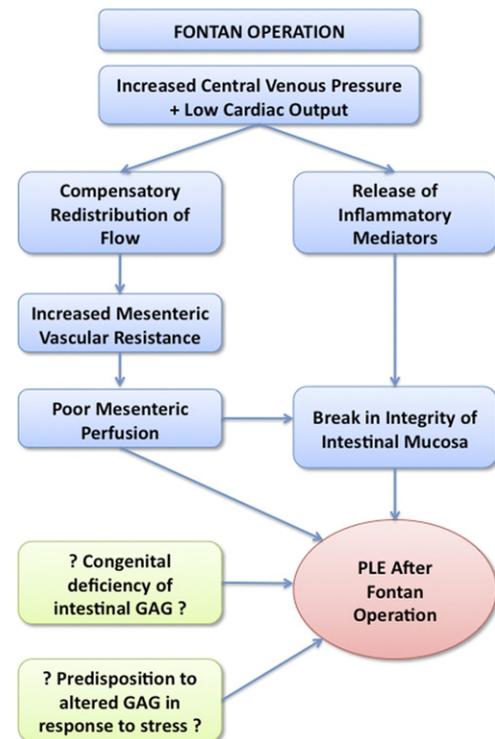
Figure 2 A proposed mechanism for protein losing enteropathy (PLE). Multiple factors likely contribute, including an alteration in the mesenteric perfusion profile, inflammation secondary to altered flow, and low cardiac output. The role of basal epithelial cell glycosaminoglycans (GAGs), while of importance as the molecular common pathway in other forms of PLE, has not yet been demonstrated in the Fontan population.

basal surface glycosaminoglycans (GAGs) such as syndecan-1 and heparan sulfate play an important role in maintaining integrity to protein leak into the gut lumen. A congenital form of PLE in which these molecules are absent results in death in infancy.[30] In an in vitro model, a monolayer of intestinal mucosal epithelial cells was created and albumin flux across was measured.[31] Cells were treated with heparinase to induce loss of heparan sulfate, which lead to an increased albumin flux across, of 1.6 times baseline. Treatment of the preparation with tumor necrosis factor alpha, an inflammatory marker, increased albumin flux 4-fold. The combination of GAG deficiency with tumor necrosis factor alpha treatment *and* an increased pressure gradient across the monolayer mimicking elevated central venous pressure, resulted in a significant break in the barrier and a massive flux of albumin across.[32] These data provide an intriguing and plausible explanation for PLE after FO. Documentation of the epithelial cell surface GAG content in patients after FO is an important link in our understanding of this disease. Our group is currently in the process of studying intestinal biopsy samples in patients with PLE to determine if GAG deficiency is present. Variability in the individual molecular make-up of intestinal epithelial cells in those with single ventricle type congenital heart disease may explain the variable expression of PLE and the vulnerability of the gut to the stressor conditions of elevated central venous pressure, low cardiac output, and inflammation that may be present.

What Next?

Much more investigational work needs to be done to better our understanding of the "unnatural" state of our patients after FO. Strategies targeted toward improving cardiac output and reducing central venous pressure will improve their overall well-being and mitigate against the impact of this deleterious physiology.

A promising agent in this regard is the drug sildenafil. A phosphodiesterase 5 inhibitor, it leads to increased cellular levels of cyclic GMP, vasodilation, and exerts a host of clinical pleiotropic effects. Extensive experience has proven sildenafil to be effective treatment in children and adults with pulmonary hypertension.[33] Although experience in the single ventricle population is limited, one can conceive of the theoretical benefits of such an agent that may lower pulmonary vascular resistance and improve forward flow through the pulmonary circuit, when no ventricle is present. Thus far, sildenafil has been shown to contribute to the resolution of PLE and plastic bronchitis in case reports,[34,35] and to improve exercise performance in patients after FO following a single dose.[36]

To better define the potential role of sildenafil after FO, we recently completed a clinical trial of this agent (Goldberg DA and Rychik J, personal communication). Twenty-eight subjects 14.9 ± 5.1 years of age who were considered well and "healthy" outpatients underwent a randomized, double blind, placebo controlled cross-over trial (SAFO [Sildenafil After Fontan Operation] trial). Subjects were started on either 20 mg of sildenafil taken 3 times daily, or a placebo for 6 weeks. Following a 6-week washout period of no agent, subjects returned for the alternate arm of the study for another 6 weeks, at which time those randomized to sildenafil at the initial phase were switched to placebo, and vice versa. Exercise testing and echocardiography were performed before and after each phase of the study. Sildenafil improved exercise ventilatory efficiency overall, and in a subgroup of subjects with elevated brain natriuretic peptide, it also resulted in a significant improvement in oxygen consumption at the anaerobic threshold. Interestingly, sildenafil also improved ventricular function as defined by a lower myocardial performance index. Inhibition of phosphodiesterase 5 in hypertrophied right ventricle human heart tissue has been shown to improve contractility, suggesting that sildenafil may have potential benefits above and beyond pulmonary vasodilation. Sildenafil may be an effective inotrope in our single ventricle patients with right ventricular morphology.[37]

One obvious and compelling solution to the single ventricle dilemma is to attempt to recreate the missing pulmonary ventricle. Research into developing a mechanical device to propel, or "impel," blood forward into the pulmonary vasculature is underway.[38-40] In theory, it should require relatively little energy from a mechanical device to increase blood flow to the lungs, in comparison to the demands necessary to mechanically support the systemic circulation. Yet, ventricular assist devices for systemic perfusion have evolved and currently exist for clinical use. Such a device for the Fontan population would be of extraordinary help. A number of prototype models have been designed, yet we are far off from a human clinical trial. The elements required for such a device, in addition to optimizing flow mechanics, include ease of implantation, self-sufficiency, an efficient power source, portability, low thrombotic potential, and an effective red cell preservation profile.

Conclusion

Admittedly, much of what has been described is a matter of perspective. Some is controversial and should be debated. My concern is that in the field of congenital heart surgery today, efforts are being exerted in "tinkering at the edges" of this problem, without directly confronting it. Alterations in surgical techniques and modifications to the Fontan operation may continue to improve on short-term outcomes and perhaps slightly reduce late morbidity, but they will not fundamentally change the inherent physiology. It is time to admit – the FO is a temporary measure and will not adequately provide for a decent quality of life for our adult survivors. Creative and innovative solutions must come from the surgical community. It seems most logical to me that a right-sided mechanical assist device is the future for our patients with single ventricle. Such a device should tackle the major hurdles and contribute to an improvement in cardiac output and a decrease in central venous pressure. Let us set the goal; when it is time to celebrate the 50 years of Fontan surgery in the next 10 years, such a device will be ready for clinical use. Our patients are waiting.

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