Late Consequences of the Fontan Operation

Jack Rychik, MD; David J. Goldberg, MD

Case Presentation
A 15-year-old boy with hypoplastic left heart syndrome presents with new-onset abdominal swelling and pretibial edema. The patient has been previously without symptoms from the cardiovascular perspective but is not very active and does not participate in sports. He is growing poorly, with height and weight <5th percentile for age, and has no signs of puberty (Tanner stage 1). Blood laboratories reveal low serum protein (albumin, 2.2 g/dL; total protein, 4.5 g/dL); liver enzymes are slightly elevated (aspartate aminotransferase, 60; alanine transaminase, 72); platelet count is diminished at 105,000/dL. Stool sample is tested for α1-antitrypsin, which is markedly elevated (382 mg/dL), indicating protein-losing enteropathy (PLE). Abdominal ultrasound demonstrates ascites and an enlarged, heterogeneously echogenic liver. Echocardiography demonstrates unobstructed systemic and pulmonary venous pathways, good right ventricular function, and mild tricuspid regurgitation, and unobstructed aortic arch. Cardiac catheterization shows pulmonary artery pressure of 12 mm Hg and right ventricle end diastolic pressure of 6 mm Hg. Gastrointestinal endoscopy with biopsy is recommended, which reveals small-bowel lymphangiectasia and inflammation localized to the terminal ileum.

Patients born with a univentricular heart manifest one of the most challenging-to-manage forms of congenital heart disease. Over the past 30 years, a successful staged surgical strategy has emerged. The task of systemic perfusion is assigned to the one effective ventricle that nature has provided, whereas pulmonary blood flow is achieved through passive channeling of systemic venous return directly to the pulmonary arteries, absent an interposed ventricle. Today, this is typically achieved in a 2-stage process. Superior vena caval flow is directed into the branch pulmonary arteries (bidirectional Glenn operation) at 4 to 6 months of age, and inferior vena caval flow is diverted directly to the pulmonary arteries (Fontan operation), either via a tunnel through the atrium or an extracardiac conduit, at 2 to 3 years of age.

That sufficient cardiac output and oxygen delivery for human existence can be achieved without the presence of a pulmonary ventricle is hard to imagine but true. Application of a surgical strategy culminating in the Fontan operation has led to the current anticipated survival of most infants born with a single-ventricle type of heart malformation, a remarkable achievement considering the lethal nature of the condition if untreated. However, as survivors make their way into adolescence and adulthood, they become susceptible to a variety of late consequences (Table).

Pathophysiology of the Fontan Circulation
Although perhaps sufficient for basic survival, the circulation created after Fontan operation exhibits a number of physiological limitations. Absence of a pulmonary ventricle leads to obligatory systemic venous hypertension. With direct connection of the superior and inferior vena cavae to the pulmonary arteries, vena caval and pulmonary artery pressures are equal and generally in the range of 10 to 20 mm Hg, 2 to 4 times that of normal. Because systemic venous return is obligated to passively traverse the pulmonary vascular bed without the force generating benefits of a pump, there is diminished capacity to deliver a normal quantity of blood volume to fill the systemic ventricle, thereby creating a state of ventricular preload deficiency. Ventricular afterload...
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The Fontan circulation can affect a number of organ systems and body functions, with negative influences on quality of life.

Exercise capacity is limited. Physical activity levels in general are reduced after Fontan operation, often independent of measured exercise capacity. At preadolescence, peak oxygen consumption during exercise testing is only 65% of that predicted for age, with a steady progressive decline of 2% to 3% per year thereafter. Reduced peak oxygen consumption is associated with increased mortality.

Thromboembolism is common. A low flow venous state with potential for stasis, multiple suture sites, and synthetic materials, as well as a relatively low cardiac output, all increase the risk. Chronic venous insufficiency in older survivors is another risk factor. Abnormalities of the coagulation profile are commonly noted and are related to altered production because of hepatic thrombocytopenia. Chronic depletion through enteric protein loss, or an inherited associated congenital or acquired coagulopathy. Thromboembolism was the cause for death in 8% in a large series. Silent pulmonary thromboemboli have been reported in ≤17% of adult Fontan survivors. The prevalence of silent small, pulmonary thromboemboli is probably underestimated, and likely contributes to a worsening impedance to forward flow across the pulmonary vasculature over time.

Luminal protein loss is an enigmatic and intriguing consequence of the Fontan circulation. It can manifest as either a break in the integrity of the intestinal mucosa with the development of PLE or as a break in the bronchial mucosa with accumulation of proteinaceous material in the airways forming bronchial casts, or plastic bronchitis. Plastic bronchitis, PLE is identified by the onset of ascites or peripheral edema, with low serum albumin levels <3.0 g/dL, and is confirmed by an abnormally high stool α1-antitrypsin level >54 g/dL. Patients with PLE after Fontan operation experience the consequences of chronic protein depletion with low-oncotic pressure-induced tissue edema, acquired coagulopathy, loss of immunoglobulins, and delayed growth and development, in particular if onset is during the pubescence years. The inability to adequately compensate for protein loss leads to a state of negative nitrogen balance and peripheral wasting. Unlike PLE, plastic bronchitis does not lead to hypoalbuminemia, because the capacity for protein loss through the airway is limited in comparison with the intestine. However, comparatively small amounts of protein accumulation in the bronchial tree can result in significant cast formation that, if not expectorated, can cause asphyxiation (Figure 1).

PLE and plastic bronchitis after Fontan operation are significant risk factors for mortality. The precise cause of these luminal protein-loss syndromes is unclear but is likely related in part to alterations in organ blood flow. All patients after Fontan operation have elevation in systemic venous pressure relative to normal. However, cardiac catheterization assessment in those with PLE often reveals hemodynamic data that are no different compared with a patient with Fontan circulation without PLE, as noted in our case example. Abnormal elevation in mesenteric vascular resistance has been reported, suggesting a role for regional circulatory abnormalities as a contributor to PLE. Inflammation likely also plays a role. The chronic low cardiac output state after Fontan operation can lead to the release of inflammatory markers. Gut-directed anti-inflammatory steroid therapy is effective in treating PLE in some. Recent imaging data indicate an important role for derangements of the lymphatic system as a possible source for protein leakage. Chronically elevated central venous pressure no doubt influences lymph production and flow, which may overcome lymphatic channel capacities, resulting in overflow spillage into the gut or airway lumen in select patients.

Of growing concern is the state of the liver after Fontan operation. Multiple reports describe the development of hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma in the young. Clinically, patients may manifest findings such as hepatomegaly, mild elevation in liver enzymes, delayed growth and development, in particular if onset is during the pubescent years. The inability to adequately compensate for protein loss leads to a state of negative nitrogen balance and peripheral wasting. Unlike PLE, plastic bronchitis does not lead to hypoalbuminemia, because the capacity for protein loss through the airway is limited in comparison with the intestine. However, comparatively small amounts of protein accumulation in the bronchial tree can result in significant cast formation that, if not expectorated, can cause asphyxiation (Figure 1).

Table. Known Clinical Complications Seen in Survivors Late After Fontan Operation

<table>
<thead>
<tr>
<th>Complication</th>
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<tr>
<td>Exercise intolerance</td>
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<tr>
<td>Arrhythmia</td>
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<td>Thromboembolism</td>
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<tr>
<td>Delayed somatic growth and development</td>
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<tr>
<td>Delayed pubertal development</td>
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<tr>
<td>Protein-losing enteropathy</td>
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<tr>
<td>Plastic bronchitis</td>
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<tr>
<td>Liver fibrosis</td>
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<tr>
<td>Renal dysfunction</td>
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<td>Venous insufficiency, varicose veins</td>
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<tr>
<td>Neurocognitive deficits</td>
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is increased after Fontan operation because of the impedance imposed by the sum of the systemic vasculature, systemic venous (Fontan connection) pathway, and pulmonary vasculature. Absence of pulsatile flow may influence pulmonary vascular resistance, leading to an abnormal basal tone. Endothelial and systemic vascular dysfunction are present with late findings of vascular remodeling. Variables related to the single ventricle malformation itself further contribute to deterioration of the overall circulation. Relaxation properties of the ventricle are often abnormal, leading to diastolic dysfunction and further impairment to ventricular filling. Abnormal contractile mechanics inherent in the malformed single ventricle can potentially lead to alterations in systolic performance or development of atrioventricular valve regurgitation.

Patients after Fontan operation exist in a unique chronic state of central venous hypertension, with relatively diminished cardiac output. Furthermore, the capacity to increase blood flow through the system during periods of increased demand is hampered. As this population matures, this state of chronic circulatory insufficiency exerts indolent, negative effects on organ system development and functionality.

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and mild diminution in platelet count because of splenic consumption. Fulminant liver failure is uncommon except in cases of overt circulatory failure. However, the degree of fibrosis appears to be associated with time from Fontan operation, suggesting that progressive hepatic scarring is underway as long as the physiological stressors of chronic, sustained central venous hypertension and relatively low cardiac output are in effect (Figure 2).

Management Strategies for Late Consequences of the Fontan Operation

How can the clinician manage the late consequences of the Fontan operation? Large-scale randomized, clinical trials identifying best practices are lacking because of the relatively small numbers of patients. However, basic principles for clinical practice are emerging.

To reduce the risk of thromboembolism, antithrombotic therapy through the use of chronic daily low-dose aspirin may be of benefit. Patients at relatively high risk, such as those with PLE, previous history of a thromboembolic event, or with additional risk factors such as inherited thrombophilia, may benefit from more aggressive therapy, such as warfarin or low molecular weight heparin. Benefits of new-generation oral anticoagulants have not yet been investigated in this population.

Absent the ability to exchange the Fontan circulation with a competent 2-ventricle system, options for improvement are limited. We believe that any degree of reduction to impedance of forward flow in the Fontan circuit can be of clinical importance. It might result in lowering of central venous pressure but, more importantly, improve filling of the ventricle with a greater quantity of oxygenated blood, thereby contributing to potential improvement in oxygen delivery. Drugs such as phosphodiesterase-5 inhibitors have demonstrated an improvement in exercise capacity, likely through lowering of pulmonary vascular resistance and improving flow. Endothelin-1 antagonists have also been used successfully in the clinical management schema for PLE or plastic bronchitis. Whether chronic daily use of pulmonary vasodilator therapy will reduce or eliminate the risk of late consequences after Fontan operation is still a question to be answered.

Reports of liver fibrosis after Fontan operation are concerning. Studies suggest that all patients after Fontan operation exhibit some degree of fibrosis. Fibrotic changes are primarily located in a sinusoidal or centrilobular pattern, consistent with the etiology of central venous congestion.

Knowledge of the extent and degree of liver disease after Fontan operation are concerning. Studies suggest that all patients after Fontan operation exhibit some degree of fibrosis. Fibrotic changes are primarily located in a sinusoidal or centrilobular pattern, consistent with the etiology of central venous congestion.

At our center, we recommend that all
patients who are >10 years out from their Fontan operation return for a comprehensive assessment of their circulatory state through cardiac catheterization and cardiac magnetic resonance imaging, as well as a liver biopsy. This allows for identification of patients who may appear ostensibly well but who may, on detailed evaluation, exhibit latent findings that provide an opportunity for optimization of the circulation. Identification of bridging fibrosis or cirrhosis on biopsy provides opportunity for referral to liver specialists, who can then offer care and guidelines for living with hepatic fibrosis and surveillance for neoplastic transformation. Ultimately, strategies for minimizing or even reversing hepatic fibrosis may be possible. Whether circulatory improvement through pharmacologic manipulation or even heart transplantation with normalization of central venous pressure and improved cardiac output can reverse hepatic fibrosis remains unclear.

Liver fibrosis, however, does not appear to negatively affect outcome after heart transplant, and there is promise for the development of antifibrotic drugs.

The current management strategy culminating in the Fontan operation leads to survival of most patients with a single ventricle type of congenital heart disease. Survival, however, appears to come at a cost, with progressive decline and circulatory failure in a growing number of subjects as they enter their second and third decades of life. Our challenge is to better understand the determinants of decline and thus discover and implement effective clinical strategies that will slow the rate of progression of late complications and ultimately create a normal duration and quality of life for these unique patients.

Case Resolution

Treatment is commenced using a combination of sildenafil (Revatio) for pulmonary vasodilation and oral controlled-release budesonide (Entocort) as an anti-inflammatory steroid. Remission of PLE occurs after 4 months of medical treatment. Budesonide is weaned to a maintenance low dose, and the patient remains symptom free for 2 years. At age 17, PLE returns after a viral respiratory illness, with failure to respond to reintroduction of high-dose budesonide. Liver biopsy is performed, which reveals sinusoidal fibrosis with areas of bridging fibrosis but no cirrhosis. He is listed for heart transplant and receives an organ 6 months later, with resolution of PLE within 3 months after transplant.

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Disclosures

None.

References

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