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Original Article

New concepts: development of a survivorship programme for patients with a functionally univentricular heart

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Abstract Children with functionally univentricular hearts are now surviving into their third and fourth decades of life. Although survival alone is a remarkable achievement, a lot must still be done to improve the quality and duration of life after the Fontan operation. Challenges that may be faced by these patients include the impact of the Fontan operation on the liver and the density of bone, protein-losing enteropathy, and plastic bronchitis. Paediatric cardiologists are familiar with the haemodynamic issues inherent in Fontan physiology; however, training in cardiology is often not sufficient to give us a complete understanding of the pathophysiology of the complications or of the options for treatment. Collaboration with other subspecialists including gastroenterologists, endocrinologists, and pulmonologists is essential in order to provide the rigorous and nuanced care that our patients need and deserve. A clinic in which a patient can see multiple subspecialists, and in which the subspecialists, as a group, can discuss each patient, can provide a unique and valuable service for patients with a functionally univentricular heart.

Keywords: Fontan; single ventricle; functionally univentricular heart; follow-up

Palliation of the patient with a functionally univentricular heart has evolved considerably since the original description of the Fontan operation.[1] Advances in surgical technique, perfusion strategies, and post-operative care have combined to improve outcomes such that morbidity is now an unexpected event. However, the Fontan operation is not the end of the story for children with functionally univentricular hearts. It is a milestone that marks the end of surgical palliation, but the beginning of a lifetime as a survivor with a functionally univentricular heart.

As a field, we are slowly gaining awareness of the non-cardiac impacts of the Fontan circulation. We know that:

- children with functionally univentricular physiology are shorter in stature than their peers with two ventricles;[2]
- their liver is at risk for fibrosis, cirrhosis, and hepatic neoplasm;[3,4]
- their bone density is likely abnormal;[5] and
- children with Fontan physiology are at risk for the development of protein-losing enteropathy[6] and plastic bronchitis.[7]

However, as paediatric cardiologists, we do not have the expertise necessary to manage these and other emerging and complex non-cardiac issues related to Fontan physiology. The involvement of our colleagues from other paediatric subspecialities in an organised and thoughtful manner is essential. Thus, we have developed a novel clinical service: "*The Children's Hospital of Philadelphia Single Ventricle Survivorship Program*". This programme is staffed by a team consisting of:

- paediatric cardiologists,
- a dedicated nurse practitioner, and
- dedicated non-cardiac paediatric subspecialists with a strong and passionate interest in focusing care on this unique population.

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A multi-disciplinary survivorship programme for patients with a functionally univentricular heart is required in different ways by different patients. The treatment and follow-up for a patient after Fontan operation with protein-losing enteropathy is very different from the treatment and follow-up for an 8-year-old with functionally univentricular physiology but normal ventricular function and normal growth, who is participating in the usual activities of childhood. However, both patients require serial care by a team of physicians that is able to understand the acute clinical challenges of protein-losing enteropathy, as well as the more subtle challenges and clinical consequences associated with it, and long-term elevations in central venous pressure and diminished cardiac output.

The impact of the Fontan operation on the liver

In children with Fontan physiology, the pressure in the hepatic venous system is substantially elevated. Although elevated hepatic venous pressure is well tolerated in the short-term, the long-term implications are of concern. A clear link exists between hepatic fibrosis and time from the Fontan operation, suggesting that hepatic architectural changes occur slowly and progressively.[8,9] Although the implications of the alterations in hepatic architecture are not yet fully understood, the presence of clinical hepatic cirrhosis can complicate quality of life, long-term outcome, and perhaps even negatively influence candidacy for future cardiac transplantation.

How to follow changes to the hepatic architecture remains an open question. A number of serum and/or imaging-based screening tools have been suggested, but none have proven efficacy in this population. The gold standard for assessment of the liver continues to be a biopsy of the liver. However, although the morbidity associated with a biopsy of the liver is low, it is an invasive test and bleeding and other complications are possible. In addition, a biopsy of the liver evaluates only a small portion of the liver, and the findings may not always be representative of the rest of the parenchyma. For these reasons, the timing and frequency of biopsies of the liver in patients with functionally univentricular hearts is the subject of some debate. It may be that routine early screening is best done non-invasively, despite the limitations of the studies, and that referral for biopsy should be reserved for the following patients:

- those with substantial abnormalities detected at early screening, and
- all patients at a specified age at which time the prevalence of advanced hepatic disease in the population is likely to be substantial.

Working with subspecialists with expertise in hepatology will help in developing the most appropriate strategy for best understanding and managing this growing problem.

Density of bone after the Fontan operation

Children with functionally univentricular hearts are at risk for abnormal mineralisation of the bone for a variety of reasons. Potential risk factors include:

- long-term exposure to loop diuretics,
- the long-term effect of chronically low cardiac output, and
- the use of corticosteroids as a treatment for protein-losing enteropathy.

To date, there have not been any systematic reviews of density of bone in children after the Fontan operation, but we are aware of many clinical anecdotes of

- increased rate of fracture,
- spinal compression fractures, and
- decreased density of bone observed on radiographic examinations (X-rays) or computerised axial tomograms (computerised tomography scans).

In the one limited study of density of bone in children with congenital cardiac disease, those with functionally univentricular physiology had substantially diminished health of their bone as compared with others in the cohort of this study.[5] Deficiency of vitamin D and calcium are a well-recognised problems in children with and without congenital cardiac disease; however, given the additional risk that functionally univentricular physiology poses, careful evaluation of biomarkers of the health of bone and routine assessments of the density of bone are warranted. Collaboration with paediatric subspecialists with expertise in the health of bone is important in understanding this condition.

Protein-losing enteropathy

Protein-losing enteropathy is a serious complication of Fontan physiology that is marked by the loss of albumin and other proteins through the gastrointestinal tract, resulting in a state of chronic hypoalbuminaemia and hypoproteinaemia. A low intravascular oncotic pressure leads to extravasation of fluid into interstitial spaces, resulting in peripheral oedema, ascites, and pleural effusions. The development of protein-losing enteropathy is likely related to the underlying haemodynamics of Fontan physiology coupled with a degree of inflammation and, possibly, a genetic predisposition.[6] In recent years, we have started to gain more understanding of the

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disease and of the treatment options, although, even with successful treatment, we can suppress but not cure the disease.

For children who develop protein-losing enteropathy in the early years after the Fontan operation without a clearly abnormal physiology, such as systemic venous obstruction or ventricular dysfunction, we have had good success with sustained release budesonide administered orally.[10] This corticosteroid has been part of the armamentarium for the treatment of inflammatory bowel disease for a number of years, but has only recently demonstrated efficacy in the treatment of protein-losing enteropathy. However, although budesonide given orally generally has first-pass hepatic metabolism, and therefore low systemic absorption, we have found that in patients who have undergone the Fontan operation, with the inherent abnormalities in hepatic function, systemic absorption is more than would typically be expected. Adrenal suppression is common and patients may require the administration of stress dose steroids at times of increased stress to supplement their endogenous production of steroids. Input from paediatric gastroenterologists and paediatric endocrinologists, who are familiar with Fontan physiology and have developed experience and comfort in co-management of these patients in tandem with cardiology, is of tremendous value in offering the most optimal treatment strategy possible to these complex patients.

Plastic bronchitis

Plastic bronchitis is another feared complication of Fontan physiology.[7] In this disease, protein is lost through the bronchial mucosa and epithelium, resulting in the formation of casts in the airway. These rubbery appearing casts can cause obstruction of the airways, leading to profound hypoxaemia and asphyxiation. As with protein-losing enteropathy, a cure for plastic bronchitis does not exist; however, a number of therapies have been used as suppressive agents with various efficacy. The first-line treatment for plastic bronchitis is the optimisation of haemodynamics with medical, catheter-based, or surgical intervention depending on the circumstance. If haemodynamics are optimised, but casts are frequent enough to cause alterations of lifestyle or are thought to be life threatening, then the only definitive therapy is cardiac transplantation.[11] However, we have had some success in limiting the formation of casts with inhaled tissue plasminogen activator.[12] This medication presumably works by interfering with the accretion of protein into large casts, which allows the smaller proteins to be expectorated with substantially less difficulty.

Summary

Children with functionally univentricular hearts are now surviving into their third and fourth decades of life. Although survival alone is a remarkable achievement, a lot must still be done to improve the quality and duration of life after the Fontan operation. As paediatric cardiologists, we are familiar with the haemodynamic issues inherent in Fontan physiology; however, although we are developing an understanding of the impact of this circulation on other organ systems, our training in cardiology is often not sufficient to give us a complete understanding of the pathophysiology of the complications or of the options for treatment. Collaboration with other subspecialists including gastroenterologists, endocrinologists, and pulmonologists is essential in order to provide the rigorous and nuanced care that our patients require and deserve. A clinic in which a patient can see multiple subspecialists, and in which the subspecialists, as a group, can discuss each patient, can provide a unique and valuable service for patients with functionally univentricular hearts.

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