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Long-term results and consequences of single ventricle palliation

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ABSTRACT

Severe hypoplasia of the right ventricle leads to the need to offer an alternative strategy beyond two-ventricle repair for the infant with pulmonary atresia and intact ventricular septum. Although the relative short-term results for the Fontan operation have improved considerably over the past two decades, long-term results are worrisome. The Fontan circulation with resultant elevation in systemic venous pressure and low cardiac output leads to end-organ dysfunction and a series of new diseases. In this review, we discuss the physiological consequences of the Fontan circulation, its effect on the liver and gastrointestinal tract, and propose a new clinical care model for the management of these unique patients.

A variety of strategies exist for the surgical management of pulmonary atresia with intact ventricular septum [1]. When the right ventricle is severely hypoplastic and inadequate in make-up to sustain the pulmonary circulation, then a single ventricle approach utilizing the strategy of cavopulmonary surgery and Fontan operation can be applied. Oftentimes, right ventricular hypoplasia is only of a moderate degree. In such cases a tension exists between the allure of right ventricular recruitment with the possibility of achieving a more natural two-ventricle system, versus right ventricular abandonment and the application of a single ventricle approach culminating in the Fontan operation. The latter is often presumed to be the more assured and reliable pathway to take in a border-line case, as short-term results for superior cavopulmonary connection followed by the Fontan operation in the current era are excellent [2,3].

Surgical decisions in infancy are frequently dictated by the more gratifying immediate short-term results of the single ventricle strategy. After 40 years of experience with the Fontan operation in thousands of patients, however, serious doubts are being raised about the long-term efficacy of our strategy for patients with a single ventricle heart. There is a growing sense in our medical community that we are creating a new breed of patients, young adults who will demand substantial care for new and poorly understood disorders, acquired as a consequence of the unique status created by the Fontan circulation [4,5].

In this article we will review some of the physiological consequences of the Fontan operation and the clinical complications seen, as well as address some of the hopes and promises for improvements in care of patients with only one effective ventricle.

1. Physiological consequences of the Fontan circulation

The Fontan operation (FO) is based upon the fundamental principle that adequate pulmonary blood flow is possible without the use of a ventricular pumping chamber. Fontan's and Kreutzer's original objective in designing this procedure, was essentially to overcome cyanosis. While sufficient pulmonary blood flow for survival is in fact possible, overall cardiac output after the FO is diminished and central venous pressure is elevated in comparison to normal. It is these two features — low cardiac output and increased systemic venous pressure, which over time form the basis for many of the clinical complications seen.

Low cardiac output after a FO is due to a number of factors. One way to conceptualize the physiology and its limitations is to consider the downstream forces which potentially influence the rate of movement of red blood cells from the systemic veins through the pulmonary circuit, into the systemic ventricle and out the aorta. The characteristics of the ventricle play a key role. Without the propelling force of a pulmonary ventricle, the compliance of the systemic ventricle must be low in order to receive an adequate volume of blood to provide a reasonable stroke volume. Ventricular compliance, a factor of active relaxation and the passive mechanical properties of the myocardium, is abnormal in the patient with a single ventricle [6,7]. Relaxation may be altered due to hypertrophy acquired secondary to chronic volume loading early in life [8]. On a histological scale, tissue characteristics of the single left ventricle differ from normal with a greater amount of non-contractile elements present [9].

The shape of the systemic ventricle, whether of right or left ventricular morphology, may also differ from the normal left ventricle creating the potential for dyssynchronous and inefficient contraction [10]. In the case of pulmonary atresia with intact ventricular septum, a hypoplastic and hypertensive right ventricle can negatively influence both diastolic relaxation and systolic contraction of the left ventricle.

Coronary abnormalities, including both right ventricle to coronary artery connections and associated myointimal lesions are commonly

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present in this anomaly. Myocardial perfusion patterns may be altered as a result and also adversely affect contractility.

In the normal heart, the apical displacement of the atrioventricular valve plane creates a driving force for blood to fill the pulmonary venous atrium, by drawing blood forward in the pulmonary veins. This systolic phenomenon has also been shown to exert an important influence on pulmonary blood flow in the cavopulmonary connection [11]. Consequently, abnormalities in movement of the atrioventricular valve annulus towards the apex of the heart due to the altered architecture of the single ventricle or inefficient contractility may diminish this impetus for forward flow.

An important variable influencing passive forward flow in the Fontan circulation is the condition of the pulmonary vasculature itself. The systemic venous return must traverse the entire pulmonary vascular cross-sectional area without the driving force of a pulmonary ventricle before filling the systemic ventricle. Any factor that increases pulmonary vascular resistance will significantly hinder the impetus for forward flow. In patients with congenital heart disease, the pulmonary vasculature itself may be inherently abnormal adding resistance to passive forward flow. A naturally decreased number of vessels or increased muscularity of vessels can contribute to increased vascular resistance. Distortion of pulmonary architecture can occur as a result of aortopulmonary shunt placement, often necessary to augment pulmonary blood flow in the neonatal period. Such shunts are commonly required for infants with pulmonary atresia.

Chronic pulmonary thromboembolism can be an unrecognized ongoing process in many patients after the FO [12]. The passive, low velocity flow in addition to an inherent hypercoagulable state, may lead to the formation of thrombi which diminish the vascular cross-sectional area and raise pulmonary vascular resistance.

Some investigators argue that limited preload is the most critical component contributing to the relatively low cardiac output witnessed after the FO [13]. This makes sense because the systemic ventricle is unable to fill adequately when the entire venous return must passively traverse the pulmonary vasculature in the absence of a pulmonary pumping chamber. Ventricular volume and cardiac output decreases in subjects when transitioning from a superior cavopulmonary connection to the Fontan circulation. Inferior vena caval flow which previously filled the ventricle directly, must first traverse the pulmonary circuit after Fontan completion [14]. Creation of a fenestration after FO improves cardiac output as some fraction of systemic venous return can bypass the lungs and fill the ventricle directly [15,16]. Although arterial saturation is decreased after fenestration, oxygen delivery in general is improved as stroke volume and cardiac output increases. The delivery of more blood to the tissues, albeit at a lower oxygen saturation, is better than lesser quantities of blood at higher oxygen saturation, as the former provides greater oxygen delivery than the latter.

Investigators have also demonstrated some interesting physiological findings which bode poorly for the long-term status of the Fontan circulation. Afterload and aortic impedance is increased after FO, because the systemic vascular resistance itself is increased and the pulmonary circuit is added on to it as part of the load imposed upon the single ventricle. Although at first, the inherent contractility may not be significantly diminished, the chronic mismatch of the increased afterload with marginal contractility will continue to be detrimental to ventricular performance [17]. Furthermore, the FO is associated with an higher power expenditure per unit cardiac output, providing an inherent disadvantage in ejection efficiency relative to the normal circulation [18]. Studies looking at cardiac function during pacing further demonstrate the sensitivity of the system to impaired preload capacity [19]. The inability to adequately fill the ventricle at rest and at higher heart rates is the fundamental reason contributing to the inability to increase cardiac output during exercise after the FO [13].

The fragile construct of the FO works best under the most ideal conditions with a compliant, well functioning ventricle and a pristine, low resistant pulmonary vasculature. Unfortunately, this is commonly not the case. Deterioration of these physiological conditions over a relatively short course of time, within two to three decades of life, is expected. Systolic performance of the morphological right or single left ventricle when in the systemic position and the diastolic performance of the single ventricle appears to worsen over time [20]. Pulmonary vascular resistance naturally increases with age, and is likely to be accelerated in the face of the chronic risk of pulmonary thromboembolism. Changes in endothelial function and increased oxidative stress with age will also likely be detrimental to vascular function and increase pulmonary vascular resistance [21]. What then?

2. Clinical implications: the liver and the gastrointestinal tract

The chronic state of low cardiac output and elevated systemic venous pressure created by the FO exerts a variety of deleterious affects on the human body with a number of clinical consequences. While some patients may exhibit sufficient ventricular filling and cardiac output to maintain baseline metabolism and function at rest, during exercise this can be a challenge [22]. The inability to increase stroke volume and the impairment of the ability to increase heart rate common after FO, makes it difficult to match cardiac output demands to the needs of the body during stress and exercise. Furthermore, chronic low cardiac output and elevated venous pressure take their toll on organ perfusion. Two such target organs include the liver and gastrointestinal tract.

Abnormalities of liver parenchyma and hepatic function are being discovered with increasing frequency in survivors of FO. Abnormal liver texture as detected by transient elastography, a non-invasive sonographic technique used to assess tissue characteristics, was demonstrated in 36 of 39 children studied with the degree of abnormality correlating with the number of years from the FO [23]. Liver biopsies performed in 18 patients prior to conversion to an extracardiac type cavopulmonary operation, all demonstrated sinusoidal fibrosis with a majority showing histopathological evidence of the beginnings of cirrhosis [24]. In another series, findings of centrilobular necrosis, cardiac cirrhosis as well as hepatic adenoma were identified in adolescents and young adults after FO [25]. Liver dysfunction as measured by a composite score is inversely related to cardiac output and directly related to hepatic vein pressure and duration since FO [26].

It appears 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. Liver disease after FO is clearly a direct consequence of chronic elevation in systemic venous pressure and low cardiac output. Chronic hepatic venous hypertension leads to the fibrotic changes described. Hepatic centrilobular necrosis is a direct result of impaired perfusion. Liver fibrosis predisposes to liver nodular regeneration and raises the specter of neoplastic disease. Hepatocellular dysfunction occurs only after extensive liver damage has taken place, which is why simple evaluation by obtaining liver function tests is not typically useful as a screen. This is a silent disease and of serious concern for our Fontan patients.

A much more clinically obvious but yet still poorly understood complication after the 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]. In severe PLE, many serum proteins are lost in the gut, including immunoglobulins leading to relative immune deficiency. Coagulation factors are also lost which further exacerbates the risk of thromboembolism, present in all after the FO. The disease is manifested clinically as peripheral edema, ascites, pleural effusions and gastrointestinal symptoms. Diarrhea is common, but not a major presenting symptom in all. In many cases there is a slow, progressive loss of protein in the stool and no apparent diarrhea. It is only after gut edema is present which results in malabsorption of