Fontan System in Univentricular Hearts in Heart Transplantation

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The Fontan procedure (FP) is the standard surgical treatment for Univentricular heart diseases. Over time, the Fontan system fails, leading to pathologies such as protein-losing enteropathy (PLE), plastic bronchitis (PB), and heart failure (HF). FP should be considered as a transitional step to the final treatment: heart transplantation (HT).

Keywords: Fontan procedure ; univentricular heart ; heart transplantation

1. Introduction

Congenital heart disease (CHD) has an incidence of 8–10 cases per 1000 live births, and its overall survival is over 80% at 45 years [1][2], depending on the complexity of the malformations. In particular, univentricular heart diseases have the most complex spectrum of complications which occur at a high rate and are associated with lower survival.

The Fontan procedure (FP), or total cavopulmonary bypass, is the standard surgical treatment for univentricular heart diseases. It results in the creation of the Fontan System (FS), a circulatory rearrangement characterized by direct passive drainage of the systemic veins to the pulmonary circulation without the support of the subpulmonary ventricle. The cardiac mass is connected in series, dedicating its function as a pump exclusively to the systemic circulation. This is a palliative procedure, avoiding ventricular dysfunction by reducing the overload volume and controlling cyanosis [3][4].

The FP creates a new circuit by joining the systemic venous return and the pulmonary system, this is associate with a sudden lack of active right-heart pumping of blood into the pulmonary arterial tree, resulting in significant venous congestion, reduced ventricular filling, low cardiac output this conditions a pressure overload and a gradual remodeling in the venous vascular and lymphatic system [5], causing plastic bronchitis (PB) [6] and protein-losing enteropathy (PLE) [7][8]. The most frequent complication is ventricular dysfunction, which leads to death from heart failure (HF). Arrhythmias also develop, conditioned by the malformations of the conduction system and the flow redirection into the cavities [9]. The modified history of end-stage FP heart disease is accompanied by cardiac cirrhosis and cardio-renal syndrome [10]. Recently, there are authors who have investigated solutions to PF failures with venous Fontan ventricular assist such as Pekkan et al. [5]. Nevertheless, the FP is still considered as a transitional step to the final treatment, which is heart transplantation (HT) [11][12].

The proper functioning of the FP is the sum of morphological and hemodynamic variables; although they effectively increase survival, its primary objective is palliative. As time passes, the FP generates organic failures that deteriorate the quality of life, which can decrease the probability of success at the time of HT [13][14].

Analyzing the available scientific evidence is crucial in determining the mortality risk in transplant patients with univentricular physiology [15]. To this end, Tabarsi et al. published a meta-analysis [16] that reported a survival greater than 80% in the first year after HT in patients with FS. However, this study did not separately analyze survival according to the type of failure. Our study therefore aims to establish the risk of death after HT according to the presence of FS failures (PLE, PB, arrhythmias, HF, and chronic kidney disease [CKD]) in patients with univentricular heart disease.

2. Fontan System in Univentricular Hearts in Heart Transplantation

There is no association of death for failures of PLE, PB, HF, and arrhythmias, while the presence of Renal failure and the set of two failures if they represent risk and lower survival for patients who underwent HT after Fontan.

In the updated International Society for Heart and Lung Transplantation (ISHLT) database (as of 2020), there were a total of 30,130 patients with HT between 2004 and 2014. Of these, 1839 were related to CHD (one-year survival 78.3%), 16,444 to dilated cardiomyopathy (one-year survival 86.2%) and 12,247 to ischemic heart disease (survival of 84.3%) [17]. In this regard, patients with FP demonstrated 1.7-times higher risk of death from complications in the immediate postoperative period. The overall survival of HT performed from 5 to 10 years of age is greater than 60%, with a decrease after the first decade secondary to HF, which implies the need for retransplantation [18][19]. In the case of patients with FP, transplantation is useful to reverse the effects of failures, especially PLE and PB [13].

PLE is the consequence of increased pressure at different sites, such as the liver and splanchnic beds and the mesenteric network, which favors protein leakage into the intestinal lumen. Generally, patients who present with PLE also have other complications such as malnutrition, recurrent infections, and capillary leakage into the interstitial space. The present meta-analysis did not demonstrate a difference in mortality in the group of HT patients with PLE, which may be due to the fact that it is reversible when the etiological mechanism is removed.

PB occurs after FP with a frequency of 1–4%. Its etiological mechanism is similar to that of PLE, as well as lymphatic flow also being increased [20]. In this meta-analysis, the presence of PB was not associated with higher mortality. In the two articles analyzed, this complication was not reversible with HT as the lymphatic circulation does not fully improve; it is also associated with greater complications during immediate postoperative ventilatory support and pulmonary pressures are at high levels according to transplant criteria.

Rhythm disorders are a frequent complication of FP. The most frequent are supraventricular tachyarrhythmias (approximately 60%) which include atrial fibrillation (40%), atrial flutter (17.2%) and atrial ectopic tachycardia (17.2%) [21]. The second most frequent group are second and third degree blocks; these are mostly treated with epicardial pacemakers, and can be accompanied by ventricular failure secondary to desynchrony [22].

Hollander et al. reported that after HT in patients with univentricular hearts with CKD, the 8% progressed to the renal stage [23], and during follow-up, 10% were expected to die in the next 5 years [24]. In the sub-analysis of this work, the two included articles did not specify the diagnostic method and stage of CKD, which may represent a misclassification bias. In this study, the analyses are based on comparing the failures with each other, which is likely the reason for the lack of significance in mortality differences. However, when focusing the analysis on the coexistence of two simultaneous failures, a value of RR = 1.94 was found, mostly explained by the coexistence of PLE and HF. It is important to consider the potential biases caused by the temporality of this phenomenon and the reference bias. It should also be noted that articles reporting multiorgan transplantation were excluded from the analysis.

There are some systemic diseases in which it is not yet clear whether they will benefit from a heart transplant such as: Kearns–Sayre syndrome that belongs to a group of neuromuscular disorders known as mitochondrial encephalomyopathies that typically involves the central nervous system, eyes, skeletal muscles, and heart [25]. Acute onset of congestive HF possible expression of a rare form of dilated cardiomyopathy; Fabry disease that is an X-linked lysosomal storage disorder caused by mutations in the a-galactosidase A gene (GLA) that leads to reduced or undetectable a-galactosidase A (AGAL) enzyme levels and progressive accumulation of glycolipids—primarily globotriaosylceramide (Gb3) and its deacylated form, lysoGb3, in cells throughout the body including vascular endothelial and smooth muscle cells and cardiomyocytes. Heart disease is present in all forms of Fabry disease, with different grades of organ involvement, and the concentric left ventricular (LV) hypertrophy [26]. Systemic sclerosis that is a systemic autoimmune disease of heterogeneous pathogenesis in which vascular, cutaneous, and internal organ fibrosis are prominent [27], in the literature there are reports of successful HT [25][26][27]; however, each case should never fail to be evaluated individually, for patients with PF and specifically for patients with Failing Fontan, there is no doubt that the treatment is HT and the fact of knowing that the presence of a single fault that could be PLE, PB, HF, and arrhythmias are not associated with a greater risk of death. It is new information in the literature since failures have never been evaluated in this way and it is very useful for patient care.

In patients with congenital heart disease, survival of HT is lower compared to other cardiomyopathies, much due to the fact that the clinical state is compromised, this occurs more frequently in patients with PF and its failures. Most of the failures are not associated with mortality, except for CKD, which is not reversible. At the same time, we also found that the association of the presence of two or more failures has significant risk. These results are a first approach to having more information for the discrimination of patients who present greater risk and the selection of patients than if would benefit after the HT.

In conclusion, heart transplant in patients with a failing FP showed an immediate survival of 88%. To fully understand the contribution of failures of FS to mortality, further studies with greater follow-up and clarity around the detection of failures

is required.

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