Haemodynamics in children with a Fontan circulation: effects of afterload reduction

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Chapter 1

General introduction and outline thesis

Background

The Fontan operation is a palliative procedure performed in patients with a univentricular heart to improve survival and quality of life. A univentricular heart defect is defined by the presence of only one functional ventricle (Single Ventricle; SV). The incidence lies between 0.08-0.4 per 1000 live births (1). A variety of underlying heart defects can lead to a functional SV. Most SV patients can be divided by either having a functional left or right ventricle (Figure 1).

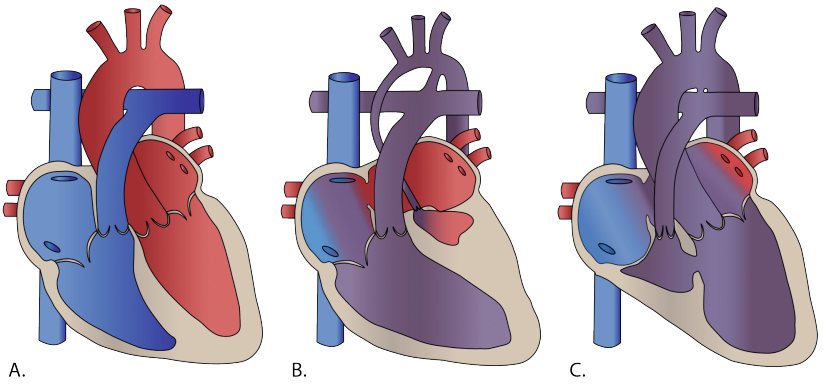

Figure 1. Anatomy of a normal heart **(A)**, an example of a univentricular heart with a functional right ventricle **(B)**, an example of a univentricular heart with a functional left ventricle **(C).**

In a univentricular heart circulation, the pulmonary and systemic circulations are in parallel rather than in series, resulting in chronic cyanosis due to mixing of saturated and desaturated blood, and volume overload of the SV as it receives and ejects blood from both circulations. Without intervention patients will suffer from early morbidity and mortality (2).

In 1971, Fontan and Baudet described a concept of a palliative procedure by which the systemic and pulmonary circulations are separated by directing the systemic venous return directly into the pulmonary arteries, bypassing the heart. As a result, the pulmonary circulation is connected in series with the systemic circulation, leading to reduced volume overload and higher oxygen saturations (3). Originally, the right atrium was directly connected to the pulmonary arteries with an atriopulmonary connection (APC). Over the past decades, however, Fontan palliation has evolved towards the development of staging of the operation, with first the creation of a partial cavopulmonary connection by connecting the superior caval vein to the pulmonary arteries (a bidirectional Glenn procedure) at about 3-6 months of age,

followed by the construction of a total cavopulmonary connection (TCPC, Fontan tunnel) by connecting the inferior caval vein to the pulmonary arteries through an intra-atrial lateral tunnel (ILT) or an extracardiac conduit (ECC), a conduit bypassing the atrium completely, usually performed between 18 months and 4 years of age (1). A fenestration, a small hole between the ILT or ECC and right atrium, can be included in the Fontan tunnel to allow a right-to-left shunt, allowing the circulation to adjust to the TCPC during the direct post-operative period after which it can be closed percutaneously by a device. In addition to these stages, some patients require an additional 'first' stage to palliation. In patients with unobstructed pulmonary blood flow a pulmonary artery banding may be used to prevent pulmonary overcirculation. In patients with severe pulmonary stenosis a systemic to pulmonary artery shunt may be necessary to improve cyanosis. An example of a staged Fontan palliation is shown in Figure 2.

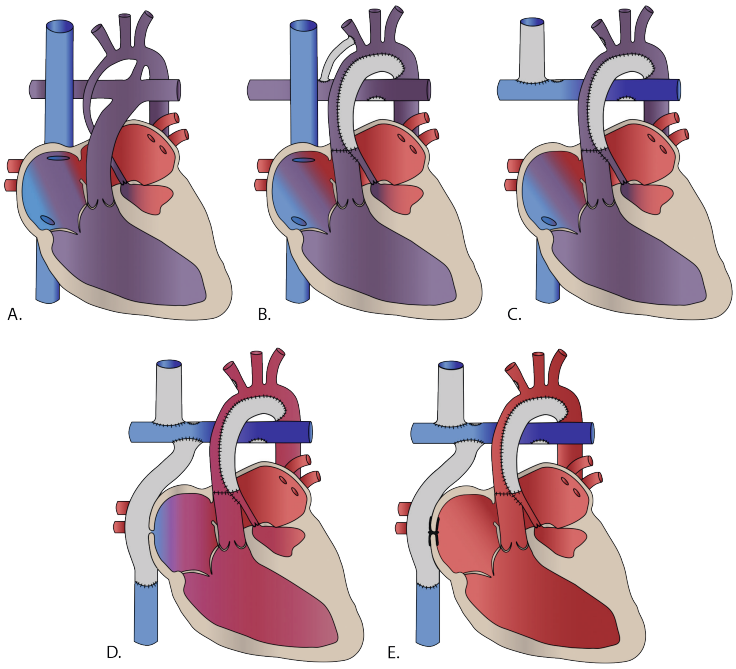

Figure 2. Example of a staged Fontan palliation in a heart with hypoplastic left heart syndrome (HLHS). **(A)** Heart with HLHS. **(B)** Norwood procedure: aortic reconstruction with insertion of a patch, a Damus-Kaye-Stansel (DKS) procedure to join the pulmonary artery and the aorta, an atrial septectomy, and placement of a systemic to pulmonary artery shunt for pulmonary blood flow. **(C)** Partial cavopulmonary connection with a bidirectional Glenn anastomosis; and removal of the systemic to pulmonary artery shunt. **(D)** Total cavopulmonary connection with an extracardiac conduit with the inclusion of a small fenestration from the conduit to the right atrium. **(E)** Fenestration closure by a device.

When the Fontan palliation is completed, the circulation lacks a ventricle that pumps the blood into the pulmonary arteries. Therefore, venous pressure is necessary to overcome pulmonary vascular resistance and drive blood through the pulmonary vascular bed (Figure 3*).* Any increase in pulmonary vascular resistance will lead to increased central venous pressure and results in venous congestion and decreased cardiac output (4). Furthermore, transpulmonary flow is also dependent on atrial pressure, as an increase of atrial pressure will lead to a decrease of the transpulmonary gradient and reduced pulmonary flow. The result is a preload dependent circulation where there is a delicate balance between systemic and pulmonary resistance and a critical fluid balance (5).

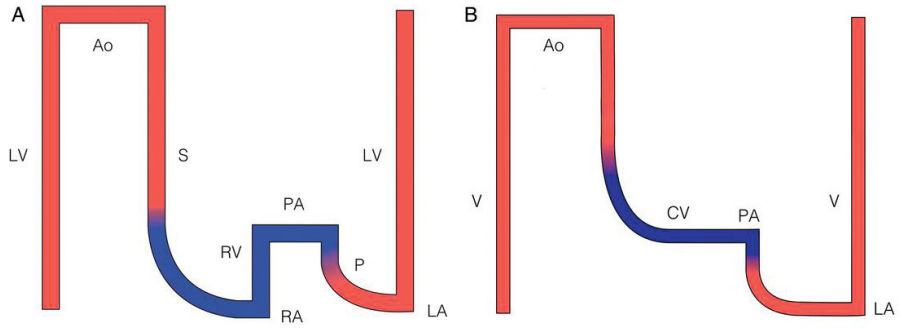

Figure 3. Scheme of pressures (vertical axis) in the normal circulation **(A)** and the Fontan circulation **(B)**. **(A)** Normal biventricular circulation: the pulmonary circulation (P) is connected in series to the systemic circulation (S). The compliance of the right ventricle (RV) ensures that the right atrial (RA) pressure remains lower than the left atrial (LA) pressure and delivers the driving force to the blood to overcome pulmonary impedance. **(B)** Fontan circuit: the caval veins are directly connected to the pulmonary arteries (PA); systemic venous pressures (CV) are markedly elevated. Ao, aorta; CV, caval veins; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; V, single ventricle. Line thickness reflects output, and colour reflects oxygen saturation. This figure has been reproduced and reprinted from Gewillig and Brown (4).

Although the Fontan operation has improved survival for patients born with a functional SV in recent decades, it is only palliative, and patients still suffer from reduced life expectancy and significant morbidities (6, 7). More than half of the patients experience at least one complication within the first 20 years, including arrhythmias, thromboembolic events, and heart failure (6-8). Furthermore, the

chronically elevated central venous pressure and low cardiac output will eventually cause the Fontan circulation to fail, which in a late stage can manifest itself as ascites, protein losing enteropathy or plastic bronchitis. Unfortunately, a clear therapeutic strategy to improve the Fontan circulation, lower the burden of morbidities and prevent Fontan failure is still lacking.

Since heart failure, with or without preserved systolic ventricular function, is one of the causes of late mortality in Fontan patients, treatment strategies have focussed on prevention or treatment of ventricular dysfunction (9-11). Angiotensin converting enzyme (ACE) inhibitors are effective in reducing mortality and improving exercise performance in patients with a biventricular heart and mild to severe systolic heart failure (12-19). Despite the lack of evidence of its efficacy in Fontan patients (10, 11) many Fontan patients are currently treated on a routine basis with ACE inhibitors, including those without overt systolic ventricular dysfunction. Furthermore, ACE inhibition has several side effects, e.g., it may lead to orthostatic hypotension (20, 21). In Fontan patients these effects may even be more deleterious. Despite its widespread use there is question about the effectiveness of afterload reduction in Fontan patients as the systemic circulation is highly preload dependent and the critical bottleneck of the circulation is not the ventricle, but the pulmonary vasculature. Since many Fontan patients are treated with ACE inhibitors it is important to understand the efficacy and hemodynamic effects of afterload reduction in these patients. Furthermore, the effect of ACE inhibition on the orthostatic response in Fontan patients has not yet been investigated.

To understand the possible beneficial and detrimental effects of ACE inhibition in Fontan patients detailed evaluation of the hemodynamic mechanisms of the Fontan circulation is needed which may also lead to better understanding of the evolution of the failing Fontan circulation. Challenging the Fontan circulation by exercise stress testing or by acute fluid loading or depletion may lead to new insights.

During exercise, the cardiovascular system is maximally challenged; any restrictions in the cardiovascular system will therefore lead to reduced exercise performance. For good exercise performance, an adequate increase of cardiac output is required, which in turn necessitates an adequate increase in stroke volume and heart rate. In Fontan patients, one of the main limiting factors of exercise performance is the inability to adequately increase stroke volume; the absence of a sub-pulmonary ventricle results in an inability to augment venous return (22). However, there

are also other factors that influence stroke volume and heart rate and may contribute to limited exercise performance in Fontan patients, such as chronotropic incompetence, diastolic and systolic ventricular function, and arterial stiffness (23-28).

Besides exercise stress testing, acute fluid challenges can be used to further investigate the Fontan circulation, which is particularly interesting because the fluid balance is more critical because of the lack of a ventricle for the pulmonary circulation it. In Fontan patients a fluid bolus may result in an increased preload and subsequent increase in cardiac output, but it may also lead to an increase of end-diastolic pressure, which may lead to a decrease of the transpulmonary gradient and pulmonary blood flow, resulting in a decrease of cardiac output (29). Moreover, in Fontan patients the response to acute fluid depletion may also differ from the response in patients or healthy individuals with a biventricular circulation. Acute fluid depletion occurs during orthostatic stress and when it occurs, activation of the sympathetic nervous system and concurrent vagal withdrawal is required to increase heart rate, systemic vasoconstriction, and venous return to maintain adequate blood pressure and cerebral blood flow (30, 31). However, in Fontan patients, several of these mechanisms, such as the cardiac autonomic nervous system (ANS) activity, has been described to be impaired (26, 32-35).

Aim

The aim of this thesis is to obtain better insight into cardiovascular and hemodynamic properties of the Fontan circulation in a homogeneous group of paediatric patients with univentricular hearts, and to evaluate the effects of ACE inhibition in this group. This is performed by detailed echocardiographic assessment of cardiovascular function parameters, evaluation of hemodynamic effects of acute fluid loading and depletion, ANS activity, and exercise tests.

Lastly, as little is known about plastic bronchitis, a severe complication of the Fontan circulation, the literature of plastic bronchitis in Fontan patients was systematically reviewed to evaluate the characteristics, survival, and management.

Outline of thesis

In **chapter 2**, the research design and data collection of the studies in chapter 4,5,6, and 7 is described in detail. In **chapter 3**, we conducted a study in healthy children and adolescents to evaluate the normal maturation and provide normative values of cardiac sympathetic and parasympathetic ANS activity. To be able to have a large sample covering the age range of 0.5 to 20 years, data from 5 different

cohorts were combined in this study. In the following three chapters, 4,5, and 6, we evaluated the haemodynamics and limitations of the Fontan circulation in a homogeneous group of paediatric Fontan patients with an extracardiac conduit and moderate to good systolic ventricular function. In **chapter 4**, we evaluated the Fontan circulation by comparing various non-invasively measured cardiovascular parameters between Fontan patients and healthy controls and determined the influence of these parameters on exercise limitation in Fontan patients. In **chapter 5** we further investigated the Fontan circulation by studying the difference in hemodynamic response of paediatric Fontan patients to a fluid challenge by passive leg raising compared to healthy controls. Passive leg raising is a non-invasive and reversible manoeuvre that is reliable in predicting the responsiveness of a fluid bolus. Furthermore, in **chapter 6**, we further evaluated hemodynamic mechanisms of the Fontan circulation by non-invasively examining the cardiovascular response to orthostatic stress, induced by head-up tilt testing, between paediatric Fontan patients and healthy paediatric controls. Besides evaluating the orthostatic stress response of Fontan patients, we also investigated the effect of a three-month enalapril treatment on the orthostatic stress response in paediatric Fontan patients in **chapter 6**. In **chapter 7**, following on from the previous chapter, we investigated the effects of ACE inhibition by examining the short-term effects of a three-month enalapril treatment on exercise capacity, vascular and ventricular function in paediatric Fontan patients with moderate to good systolic ventricular function. In **chapter 8**, we systematically reviewed the literature for all case reports and series of SV patients with plastic bronchitis to give insight into the characteristics, survival, and treatment management of these patients. **Chapter 9** summarizes the main findings of our studies, discusses these in view of present literature and provides future perspectives. Finally, in **chapter 10** a Dutch summary of our work is provided.

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