1

General introduction
The univentricular circulation

A normal circulation has the same design in all mammals: the heart is divided by the septum into two halves, each consisting of an atrium and a ventricle. The right half supports the pulmonary circulation and the left half the systemic circulation. This means that a double pump and two circulations are present, and this is called a biventricular circulation. Some congenital cardiac defects challenge this design. In the Netherlands, around 1200 children with congenital cardiac defects are born every year. Over a hundred different congenital cardiac defects are described, ranging from ‘simple’ cardiac defects (for instance an atrial septal defect) to multiple complex congenital cardiac defects. Certain complex congenital cardiac defects have a common denominator: only one ventricle is fully developed and serves both the pulmonary and systemic circulation. The other ventricle is usually underdeveloped or absent. Hence, in these patients, the circulatory anatomy consists of a single pump serving a double circulation. These so-called functional univentricular hearts form 4-5% of the total group of congenital cardiac diseases. This group includes, among others, patients with tricuspid atresia, hypoplastic left heart syndrome, double inlet ventricles, unbalanced (atrio) ventricular septal defects, and pulmonary atresia with an intact ventricular septum.

As a consequence of the functional univentricular morphology, the single ventricle is volume-overloaded and continuous mixing of saturated and desaturated blood occurs. Depending on the degree of pulmonary stenosis, these patients have either a pulmonary “overcirculation” and are prone to develop heart failure in early life, or suffer from severe cyanosis and die of profound hypoxemia.

The Fontan operation

In 1971/72, both Fontan and Kreutzer in respectively France and Argentina published an exceptional operation to treat the ventricular volume overload or cyanosis of a univentricular heart. Their reports described the creation of a direct connection between the right atrium and the pulmonary arteries in patients with tricuspid atresia. This operation created a unique, unphysiologic circulation, in which the functionally single ventricle is used to support the systemic circulation, and the systemic venous return flows “passively”, without the help of a ventricular pump, through the pulmonary vascular bed. As a result, the patients are relieved from the chronic cyanosis or ventricular volume-overload, at the expense of living without a subpulmonary ventricle to support the pulmonary blood flow. This unique type of circulation has become known as the Fontan circulation.

Over the past decades, the Fontan operation has been subjected to changes in patient selection criteria as well as various modifications in the operative technique. The ten commandments for ideal patient selection, initially proposed by Choussat et al. in 1978, are displayed in table 1.
These commandments have gradually been adapted over the years, in particular the age criterion has been modified. Furthermore, the classic Fontan operation was performed in patients with tricuspid atresia, but gradually more univentricular cardiac defects were referred for a Fontan correction, including double inlet ventricles, pulmonary atresia with intact ventricular septum, hypoplastic left heart syndrome, and other complex congenital cardiac defects that are not suitable for biventricular repair. These changes in patient selection have resulted in a very heterogeneous group of Fontan patients, in which different cardiac diseases carry different risks and ask for different approaches prior to the Fontan surgery. Finally, the surgical techniques have evolved over time. Fontans’ classic atriopulmonary connection (APC) involved a valved conduit between atrial tissue and pulmonary artery. Later on, a direct atriopulmonary connection and a right atrium- to right ventricular connection emerged as a response to the high incidence of valvular dysfunction. In 1987, the first total cavopulmonary connection (TCPC) was performed to provide better streamlining and lower energy loss in the Fontan conduit. The TCPC consisted of an intra-atrial tunnel incorporating the right atrial posterior wall and a Goretex patch or pericardial baffle to tunnel the inferior caval vein (VCI) to the pulmonary artery. This has become known as the TCPC with a lateral tunnel. Furthermore, a lateral tunnel using only autologous tissue, totally created from the right heart auricle, was described. Finally, the TCPC with an extracardiac tunnel was developed, in which the inferior caval flow is directed to the pulmonary artery through a synthetic (PTFE) conduit externally of the heart. The extracardiac tunnel has theoretical advantages in reducing suture lines in the right atrium and relieving it from high systemic pressures, potentially reducing the incidence of arrhythmias.

In the early decades of TCPC surgery, the early postoperative mortality was high. Rapid changes in ventricular geometry due to volume-unloading during Fontan surgery were thought to alter diastolic function and attribute to the mortality rates. Therefore, a stepwise Fontan procedure was introduced, using a bidirectional Glenn procedure (BDG) to achieve early volume-unloading. With the BDG, the superior caval vein is directly anastomosed to the pulmonary artery. Nowadays, the energetically favorable lateral tunnel and extracardiac

| 1. | Minimum age 4 years |
| 2. | Sinus rhythm |
| 3. | Normal caval drainage |
| 4. | Right atrium of normal volume |
| 5. | Mean pulmonary artery pressure ≤ 15 mm Hg |
| 6. | Pulmonary arterial resistance < 4 U/m2 |
| 7. | Pulmonary artery to aorta diameter ratio ≥ 0.75 |
| 8. | Normal ventricular function (ejection fraction > 0.60) |
| 9. | Competent left atrioventricular valve |
| 10. | No impairing effects of previous shunts |

Table 1. Primary selection criteria for patients with tricuspid atresia for the Fontan operation ('the ten commandments')
conduits are the most commonly applied Fontan techniques. The BDG is usually performed when the patient is around 3 to 6 months of age and can be considered the first stage of the Fontan procedure.21,22

Characteristics of a Fontan circulation

The common denominator of all Fontan techniques is the pulmonary flow depending on a non-pulsatile driving pressure due to the lack of a sub-pulmonary pump. This so-called passive pulmonary blood flow and the serial (instead of parallel) connection of the pulmonary and systemic circulations result in several adverse characteristics inherent to the Fontan circulation. Firstly, due to the absence of a subpulmonary pump to overcome the pulmonary vascular resistance (PVR), the central venous pressure, together with the muscular and ventilatory pump, becomes the driving force of pulmonary blood flow. Consequently, central venous pressure increases up to 2 to 4 times of normal23 and the patients suffer from chronic systemic venous congestion. Secondly, the preload of the single ventricle becomes dependent on the passive pulmonary blood flow24. In the Fontan circulation, the ventricular preload is thought to be limited to 60-80% of normal for body surface area, and possibly even less when normalized to ventricular size, with potentially limited ability to increase during exercise25. Thirdly, an increased afterload of the heart is caused by the serial arrangement of the systemic and pulmonary circulation, resulting in three resistances: the systemic vascular bed, the Fontan conduit and the pulmonary vascular bed26,27. Together, the increased afterload and decreased preload result in a restricted cardiac output, particularly during exercise.

Sequelae of the Fontan circulation

Due to its unphysiologic characteristics, the Fontan circulation is associated with gradual attrition and multiple adverse sequelae. Despite all adjustments in the past decades, the Fontan operation thus remains a palliative procedure and is associated with a reduced life expectancy.8,10,28,29. This reduced life expectancy is caused by both early/peri-operative (within 30 days of Fontan surgery) and late mortality. Various strategies have been tried and tested to improve the early survival after cardiothoracic surgery in general and Fontan patients in particular. In addition to the different operation techniques and changes in patient selection described above, these strategies included changes in the peri-operative management and advances in anesthetic care. Previous studies investigating survival after the Fontan surgery found that the early and overall survival after the Fontan operation has improved over the past decades, with only a 2-5% early mortality rate in the most recent era.8,10,28-30. The few reports addressing late mortality show the same trend29,31 However, it is important to bear in mind that the more recent Fontan procedures are commonly performed in two stages (first a BDG procedure followed by a Fontan completion). Previous studies on outcome have mostly disregarded the mortality associated with the BDG procedure and the interstage period. This might have underestimated the mortality associated with newer Fontan techniques.
With improving early survival rates, long-term sequelae of the abnormal circulation are more commonly observed. These sequelae include (continuation of) impaired exercise tolerance, cardiac dysfunction, restricted pulmonary function, intestinal- and hepatic complications and a gradual increase in pulmonary vascular resistance. Eventually, gradual attrition of the circulation can lead to a life-threatening failure of the Fontan circulation. These issues will be consecutively addressed in the sections below.

Firstly, let us address the exercise tolerance in Fontan patients. The peak exercise tolerance, described as peak VO$_2$ index, is around 53- to 65% of predicted in Fontan patients compared to healthy individuals$^{32-36}$. Despite the impaired exercise capacity, most Fontan patients ostensibly live a nearly normal life and are in New York Heart Association-Functional Class (NYHA-FC) I or II at a mean follow-up of 5 years$^{10}$. Importantly, both NYHA-FC and peak VO$_2$ index seem to deteriorate with increasing interval since the Fontan operation$^{10,32,34-38}$. This has been regarded as indicator of Fontan attrition and associated with increased risk of mortality$^{35}$. The underlying mechanisms for the impaired exercise tolerance in Fontan patients are assumed to be a limited ability to increase cardiac output during exercise and the restricted pulmonary function of Fontan patients.

Secondly, the unphysiologic circumstances of the Fontan circulation affect the cardiac function. The single ventricle in the Fontan circulation is subjected to abnormal loading conditions, including a decreased ventricular preload and increased ventricular afterload. The preload depletion is suggested to be associated with systolic and diastolic ventricular dysfunction, and results in a limited ability to increase stroke volume during exercise$^{39}$. The increased afterload increases workload for the single ventricle and reduces the ventricular efficiency, requiring more power to forward flow$^{26,27}$. Furthermore, Fontan patients are prone to develop arrhythmias due to atrial myocardial scarring from surgery and progressive atrial dilatation when the atrium is exposed to the higher systemic venous pressure$^{34}$. The progressive atrial dilatation predisposes Fontan patients to atrioventricular valve dysfunction$^{40}$ and, in combination with the sluggish blood flow and high incidence of coagulation disorders, to a higher incidence of thromboembolic events$^{41}$. Together, the reduced preload, increased afterload, arrhythmias and atrioventricular valve regurgitation all contribute to a limited cardiac output in Fontan patients, leading to potential deterioration over time and eventually Fontan failure$^{42}$.

A biomarker to monitor the cardiac function and circulatory performance over time would be extremely valuable in the Fontan circulation. The N-terminal pro natriuretic peptide (NT-proBNP), which is released from the cardiac tissue in response to increased wall-stress due to volume- or pressure load, is a potential candidate. In patients with biventricular hearts, NT-proBNP is essential in the recognition and monitoring of cardiac dysfunction and congestive heart failure$^{43}$. However, the unique cardiac characteristics in the Fontan circulation hamper the extrapolation of studies on NT-proBNP in biventricular patients to univentricular patients. Therefore, studies aiming at investigating the value of NT-proBNP in the evaluation of cardiac function and circulatory performance of the Fontan circulation are needed.
Thirdly, previous studies have shown that pulmonary function is impaired in almost all Fontan patients. The forced vital capacity, a measure of the pulmonary volume available for ventilation, is generally 80-90% of normal and the pulmonary diffusion capacity, indicating diffusion capacity for oxygen through the alveolar membrane to the blood vessels, is around 70-80% of normal. The reason for the restricted pulmonary function presumably lies in an impaired pulmonary development and repeated thoracic surgeries.

Furthermore, patients with a Fontan circulation can develop protein losing enteropathy (PLE), which is a debilitating intestinal complication, occurring with a reported incidence of 3-18% years in late survivors. It is caused by a break in the mucosal integrity of the intestinal mucosa, and results in protein loss and nutrient malabsorption. The exact cause of the break in the mucosal integrity is unknown, but inflammation and abnormal elevation in mesenteric vascular resistance due to the chronic systemic venous congestion are thought to play a role. Clinical signs of PLE are ascites, diarrhea, peripheral edema and, when PLE has started prior to adolescence, delayed growth and development. It is one of the most life-threatening complications, with a five-year survival after its onset of less than 60%.

Hepatic fibrosis is increasingly recognized in Fontan patients and hepatic cirrhosis is seen in up to 55% of adult Fontan survivors. Potential drivers of Fontan associated hepatic disease appear to be the chronic systemic venous congestion, limited cardiac output and thrombo-embolic insults. Fontan associated hepatic disease can result in liver failure, gastrointestinal bleeding, hepatic encephalopathy and even hepatocellular carcinomas, which have an estimated incidence of 1.5-5.0% per year in Fontan patients. These adverse hepatic events are associated with significant morbidity and mortality, independent of the time since the Fontan operation. Unfortunately, the evaluation of hepatic fibrosis and cirrhosis in Fontan patients is difficult, because a liver biopsy, often considered the golden standard, is hazardous in Fontan patients due to coagulation disorders and hepatic congestion. One of the potential alternatives for a liver biopsy is the diffusion-weighted magnetic resonance imaging (DWI), which might be promising in Fontan patients due to its ability to distinguish microperfusion components (congestion) from cellular diffusion (associated with hepatic fibrosis/cirrhosis). However, its relation with hepatic and functional parameters of the Fontan circulation has not yet been described.

Finally, the pulmonary vascular resistance is an important issue in the Fontan circulation. A low pulmonary vascular resistance (PVR) is essential in the Fontan circulation for the systemic venous return to flow passively through the pulmonary vasculature. Even small increases in PVR will significantly reduce the cardiac preload and cardiac output, and will further increase the central venous pressure. An increase in pulmonary vascular resistance might result from adverse pulmonary vascular remodeling. There are two potential underlying mechanisms of pulmonary vascular remodeling in the Fontan circulation. The first mechanism includes microemboli in the pulmonary vascular bed which occur with an increased incidence in Fontan patients due to the hypercoagulable state. Secondly, the
non-pulsatile pulmonary flow results in changes in circumferential strain and shear stress in the vessel, and is demonstrated to cause endothelial dysfunction, vascular remodeling and an increase in PVR in animal models. Studies exploring the changes in pulmonary vasculature have primarily focused on the peri-operative period, whereas data on the long-term changes in pulmonary vasculature are currently lacking.

Despite the restricted exercise tolerance and other adverse sequelae, previous reports have shown that patients with a Fontan operation have a relatively good quality of life. However, they do seem to score lower on physical functioning, mental health and general health than their healthy peers, and worry about their health, job employment, ability to work and living independently. Previous reports pointed out that worse quality of life in Fontan patients is related to respiratory problems and protein losing enteropathy, but not with exercise tolerance. One important aspect of quality of life is sexual wellbeing. Previous studies demonstrated patients with congenital cardiac diseases to have increased concerns regarding fertility, inheritability and pregnancy, may experience a broad range of sexual problems and might lag behind in psychosexual development. Although these studies have included a variety of congenital cardiac disease, no patients with a Fontan circulation were included. This is unfortunate because the restricted cardiac output and exercise tolerance, the chronic systemic venous congestion, the operations at a young age, frequent hospital visits, previously reported menstrual cycle disorders and fertility problems, and impaired life expectancy might affect patients’ development and wellbeing.

Eventually, dysfunction of several end-organs can occur and the Fontan patient enters a clinical state called “Fontan failure.” The pathophysiology of Fontan failure is distinct from the classical congestive heart failure in biventricular hearts; In biventricular hearts, failure is mainly characterized by a decreased contractility of the heart, whereas in univentricular hearts various factors play a role, including hepatic, gastro-intestinal, pulmonary or cardiac complications. A failing Fontan, with an estimated incidence of 2-13%, has a very poor prognosis and therapeutic options are few. Nowadays, three surgical options are embraced worldwide: Fontan takedown, Fontan conversion from an atriopulmonary connection to an energetically more favorable connection (i.e. lateral tunnel or extra-cardiac conduit), and heart transplantation (HTX). A Fontan takedown is usually performed as a bailout option for early Fontan failure, which occurs after 2-6% of the Fontan operations. An Australian- and New Zealand series reported a 75% hospital survival after Fontan takedown surgery. Early mortality rates after Fontan conversion or a heart transplantation vary substantially: ranging from 0.9% to 13% for Fontan conversion, and 4-30% for heart transplantation. Very limited data is available on long-term outcome of failing Fontan surgery and there are no reports comparing survival after the different surgical options for the failing Fontan circulation.
Aims of this thesis

In summary, the Fontan operation is currently the treatment of choice for patients who are born with a univentricular heart. The Fontan operation results in a unique, unphysiologic circulation characterized by the absence of a subpulmonary ventricle, chronic systemic venous congestion and abnormal cardiac loading conditions. The literature discussed above showed that the Fontan circulation has many adverse sequelae that affect the patients’ health. However, it also demonstrated that there are considerable gaps in our knowledge regarding multiple aspects of the Fontan physiology. Therefore, the aims of this thesis are to investigate survival and functional outcome after the Fontan operation, to gain better understanding and identify potential markers of the Fontan attrition and to evaluate different treatment strategies for a failing Fontan circulation. To elucidate these issues, we addressed the following topics in the subsequent chapters of this thesis:

1. To characterize survival of Fontan patients over the four decades in which the Fontan operation is performed
   Although previous studies have reported an improved survival after the Fontan operation over the past decades, they usually disregard the mortality related with the first stage of the Fontan procedure. In a scientific letter introducing chapter 2, we highlighted the difficulties faced when evaluating survival after the Fontan procedure and the importance of starting the retrospective survival analyses at the initiation of the Fontan procedure, which is the bidirectional Glenn operation or one-stage Fontan operation. Subsequently, we performed a retrospective study to investigate the early and late mortality and its determinants after the Fontan procedure, including the bidirectional Glenn through Fontan completion.

2. To determine the functional outcome of Fontan patients after mid- to long-term follow-up
   It is believed that the functional outcome progressively deteriorates with longer time after the Fontan operation. The nature of the impaired functional status is far from unraveled, and variation in functional outcome might be affected by cardiac and pulmonary function. Unfortunately, few studies have included both cardiac and pulmonary parameters to investigate determinants of exercise tolerance. Furthermore, most studies reported the absolute value of peak oxygen uptake (VO₂index) during exercise, whereas the peak VO₂ as percentage of predicted could provide important information on how functional performance of the Fontan patients over time compares to healthy individuals. This is addressed in chapter 3.

3. To investigate NT-proBNP as a biomarker in the assessment of the Fontan circulation
   The peptide NT-proBNP is an important biomarker in the clinical evaluation of patients with biventricular congestive heart failure. However, the value of NT-proBNP in the evaluation of cardiac function and circulatory performance of the Fontan circulation is still unknown. Chapter 4 is introduced by our editorial on the challenges regarding the interpretation of NT-proBNP serum levels in the Fontan circulation. Thereafter, we address in the value of NT-proBNP as a marker of cardiac function or circulatory performance of the Fontan circulation in a cross-sectional cohort study.
4. To address the hepatic function in Fontan patients and its relation with functional parameters
Patients with a Fontan circulation tend to develop hepatic diseases as a consequence of the unphysiologic circumstances of this circulation. In chapter 5 and 6 we display the diffusion-weighted imaging technique, newly applied in the assessment of hepatic fibrosis and cirrhosis, and its relation with the functional parameters of the Fontan circulation.

5. To identify whether the Fontan circulation is associated with adverse pulmonary vascular remodeling and to characterize this potential pulmonary vascular remodeling.
Pulmonary vascular remodeling might be one of the underlying causes of Fontan attrition. In chapter 7, we describe the histomorphometric and immunohistochemical characteristics of pulmonary vessels in Fontan patients, and compare the vascular characteristics of the patients who died peri-operatively, with the characteristics of the patients who died more than 5 years after the Fontan operation.

6. To explore quality of life and sexual wellbeing in Fontan patients
Quality of life is an important measure to assess the self-perceived health status. Sexual development and wellbeing is an underexposed aspect of quality of life, but may be considerably affected by the Fontan operation. A qualitative pilot study concerning quality of life and sexual wellbeing is presented in chapter 8.

7. To investigate the outcome of surgical interventions after failing of the Fontan circulation
Attrition of the Fontan circulation can lead to life-threatening Fontan failure. There are three main options for Fontan failure surgery; the Fontan takedown, the Fontan conversion and a heart transplantation. To determine the long-term outcome of failing Fontan surgery and to compare the outcome after these different surgical options for the failing Fontan circulation, we performed a multicenter study (chapter 9). Furthermore, in chapter 10 we present our multi-institutional retrospective analyses aiming to identify predictors of outcome after heart transplantation after failure of the Fontan circulation.

Finally, in chapter 11 the main findings of this thesis are summarized and discussed, followed by a section on future perspectives.
References


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Introduction