The Enigma of the Fontan circulation
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General Discussion
This thesis began with the statement that a heart has the same biventricular design in all mammals. A univentricular cardiac design is the norm in amphibians and fish, but these circulations are sustained with systemic oxygen saturation much lower than in humans. Humans with a Fontan circulation, however, are an exception, and live with a functionally single ventricle to sustain both the pulmonary and systemic circulation. The Fontan circulation is inherently related to unphysiologic characteristics with multiple known and unknown sequelae after the operation. The aims of this thesis were to investigate 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. In this chapter, the main findings of this thesis and future perspectives are discussed.

Survival after the Fontan circulation

Multiple strategies have been tried and tested to improve the outcome after the Fontan operation. Two of the most compelling landmarks in the Fontan evolution are the development of the TCPC technique and the introduction of staging the procedure. Various studies have demonstrated the TCPC to be favorable compared to the APC, in terms of survival and functional outcome, but have frequently not included mortality associated with the first stage of the Fontan procedure (bidirectional Glenn) and the interstage period. With analyses starting at the initiation of the Fontan circulation (the bidirectional Glenn or one-stage Fontan operation), we demonstrated the benefits of the TCPC technique and staging the Fontan procedure. We did this by showing that the one-stage APC and one-stage TCPC are independent risk factors for early mortality. Besides improved early survival, staging with early volume unloading has been suggested to be beneficial for future ventricular function and exercise capacity. This supports the widely accepted current practice of staging the Fontan procedure and performing a bidirectional Glenn operation for early volume unloading around the age of 6 months.

The benefit of early volume unloading of the functionally single ventricle is, however, in contradiction with the “ticking clock” theory. This concept suggests that the Fontan circulation has a limited survival once it has been installed and advocates that the Fontan operation might best be postponed to the latest possible age. However, the incompatibility of the Fontan circulation with a normal life-span is a point of discussion. Our finding that no robust improvement in late survival could be demonstrated over the subsequent decades of Fontan surgery seems to support this “ticking clock” theory. However, patients who were operated upon in the most recent decades accordingly to current strategies inevitably had a shorter follow-up duration. In our latest cohort, mean follow-up duration was only 4 years, whereas Fontan et al. pointed out in 1990 that the hazard ratio of death or functional decline starts to rise 6 years after the operation. Furthermore, another factor than follow-up duration that might play a role is the fact that, with increasing experience with the Fontan operation over the years, the criteria for eligibility for Fontan surgery have been widened. This has led to the allocation of more high risk patients to Fontan surgery, which might have affected survival.
over time9,10. Only future can tell whether the surgical modifications and the new approaches in timing of the operations have improved the long-term survival after the Fontan procedure, and will elucidate whether either early volume unloading or postponement of the surgery is most beneficial to patients. We advocate including the first stage of the Fontan procedure, the bidirectional Glenn, in these future survival analyses to provide better comparison with older Fontan techniques.

Either favoring the ticking clock theory or seeing the benefits of early volume unloading, there is general consensus that the Fontan circulation shows attrition over time. Multiple organ systems and outcome measures are impaired in the Fontan patients and vulnerable for gradual attrition with aging or time since the Fontan operation.

Exercise tolerance

Previous reports have shown that peak exercise capacity, measured by the peak oxygen consumption during exercise (peak VO2index), is low in Fontan patients compared to controls (around 52- to 65% of predicted) and negatively affected by the time since Fontan completion, which is consistent with our own findings11-15. Longitudinal studies showed a progressive decline in exercise tolerance in Fontan patients of 1.25 – 2.6% per year, but these studies are potentially biased by including only patients with ≥ 2 subsequent exercise tests, which, in the absence of the standardized follow-up protocol with yearly or two-yearly exercise tests, favors patients with an advanced exercise intolerance or circulatory deterioration as these are more likely to be referred for a second exercise test14,16. Our analyses, using the peak VO2 as percentage of predicted compared to reference values, showed that exercise capacity of Fontan patients seemed not to deteriorate faster than healthy individuals. It suggested the unphysiologic circumstances after the installment of the Fontan circulation to be the main cause of the exercise limitation, and Fontan patients to show a rate of decline in exercise capacity very similar to those of healthy individuals. This finding might be of great help to identify failing Fontan patients: assuming that they reach the same percentage of peak exercise tolerance compared to normal values throughout their lives, a drop in this percentage could signal the physician that the circulatory performance is deteriorating and potentially failing.

Cardiac function

The single ventricle in a Fontan circulation is subjected to abnormal loading conditions including a decreased ventricular preload and increased ventricular afterload17-19. Together with cardiac complications such as arrhythmias and atrioventricular valve regurgitation, these factors are likely to contribute to a low cardiac output in Fontan patients and result in a limited ability to increase heart rate and stroke volume (determinants of cardiac output) during exercise7,20,21. We demonstrated that this ability to increase cardiac
output during exercise is, together with pulmonary function, an important determinant of exercise capacity in Fontan patients, whereas conventional cardiac measurements, including end-diastolic volume, ejection fraction and cardiac index, were not associated with exercise tolerance. The importance of therapies aiming to increase preload and preserve heart rate reserve in the Fontan circulation is thereby highlighted.

The conventional cardiac measurements are known to be load-dependent. The ventricular loading conditions in patients with a biventricular heart and congestive heart failure are very distinct from those in patients with a Fontan circulation. Congestive heart failure in biventricular patients is characterized by systolic or diastolic ventricular dysfunction and an increased end-diastolic volume or pressure, causing ventricular wall stress. In contrast, in Fontan patients, the serial coupling of both systemic and pulmonary circulation results in a chronically restricted ventricular preload, systemic venous congestion and increased ventricular afterload. Potentially, the abnormal loading conditions in the Fontan circulation cause the conventional cardiac measurements to be less informative on intrinsic (myocardial) cardiac function and circulatory performance in Fontan patients than in patients with biventricular hearts. This is illustrated by our finding that NT-proBNP, an important biomarker of ventricular dysfunction in patients with a biventricular heart, is related to measures of the circulatory performance (namely systemic venous congestion), but is only limitedly related to conventional measures of ventricular function in the Fontan circulation.

We identified, however, that NT-proBNP is not only related to indices of circulatory performance, but also progressively rises along with longer time after the Fontan procedure, suggesting that this peptide might be valuable in the recognition of Fontan failure by signaling a less-optimal circulatory performance of the Fontan circulation.

Despite the potentially limited value of conventional cardiac measurements, cardiac function does affect the Fontan patients when dysfunction is evident. We identified in the intention-to-treat analyses regarding failing Fontan surgery, that poor ventricular function is a risk factor for mortality/HTX after Fontan conversion or heart transplantation (HTX) for Fontan failure. Moreover, in patients with overt ventricular dysfunction, no survival benefit of HTX over Fontan conversion was found, suggesting that poor ventricular function is related to a high patient frailty. Interestingly, poor ventricular function was not a risk factor in the analyses starting at the HTX procedures. Instead, patients with a poor ventricular function had a better outcome than patients with a preserved ventricular function. This difference between the intention-to-treat analyses and the HTX-only analyses is presumably caused by the patients who first underwent Fontan conversion and were then redirected for a HTX. All these patients had an impaired ventricular function prior to the failing Fontan surgery. In the intention-to-treat analyses, these patients reached the primary endpoint (defined as HTX or death) quite early after Fontan conversion (3.7±0.9 years), thereby negatively influencing transplant-free survival for patients with poor ventricular function. After their HTX treatment, none of these patients died, resulting in a better outcome. Previous studies have also recognized a favorable outcome after HTX for patients with a poor ventricular function compared to patients with...
a preserved ventricular function\textsuperscript{28}, consistent with our findings. Potentially, the underlying mode of failure is distinct between these two patient groups, explaining the difference in survival rates.

**Pulmonary function**

Patients with a Fontan circulation generally tend to have a restricted pulmonary function\textsuperscript{29-31}. There are developmental, functional and mechanical explanations for this sequel\textsuperscript{31}. Some patients have a deprived pulmonary perfusion prior to the Fontan operation, which can inhibit alveolar recruitment and subsequent pulmonary development\textsuperscript{31-33}. Furthermore, Fontan patients undergo several thoracic operations in early life, including lateral thoracotomies. The number of thoracotomies is negatively associated with the pulmonary capacity\textsuperscript{34}. Ascites, scoliosis, cardiomegaly and diaphragmatic paralysis, may further limit pulmonary volumes\textsuperscript{31,35,36}. However, the question whether these “hits” in the past (decreased perfusion or thoracotomies) or progressively deterioration with longer follow-up duration since the Fontan operation, are the main determinants of the restricted pulmonary function, remains unanswered. Nevertheless, smaller pulmonary volumes and increased pulmonary air trapping have been associated with reduced exercise tolerance in Fontan patients\textsuperscript{29,31}. To our knowledge, we were the first to demonstrate that pulmonary parameters significantly contribute to a multivariable model including exercise and cardiac parameters to explain variation in exercise tolerance in Fontan patients. These findings implicates that pulmonary function is important in Fontan patients and diagnostics should be directed towards potential impairment of pulmonary function.

**Hepatic fibrosis and -cirrhosis**

Chronic systemic venous congestion is inevitably associated with a Fontan circulation and appears to be related to several severe complications in the longer term, including hepatic disease. Gross structural changes in hepatic architecture are previously recognized in patients with longstanding Fontan circulation and the degree of fibrosis and cirrhosis have been shown to correlate with an increased interval from the Fontan operation to death\textsuperscript{37-40}. Incidences of fibrosis/cirrhosis of up to 58\% are reported\textsuperscript{37,41} and five-year survival after the diagnosis of hepatic cirrhosis is only 35\%\textsuperscript{42}. In search for an alternative for the invasive and hazardous liver biopsy to monitor hepatic damage, we performed the first diffusion-weighted magnetic resonance imaging (DWI) study in Fontan patients, and showed that the apparent diffusion coefficients measured by DWI seem to reflect progressive hepatic damage in Fontan patients. The bi-exponential model demonstrated that this hepatic damage might be associated with chronically decreased microperfusion, probably due to hepatic congestion, and deteriorating cellular diffusion, presumably related to development of hepatic fibrosis/-cirrhosis. This newly applied DWI technique might be a useful, non-invasive technique for longitudinal assessment and early detection of hepatic fibrosis/cirrhosis.
Pulmonary vascular resistance

One of the potential underlying mechanisms of progressive Fontan attrition is progressive pulmonary vascular remodeling that may cause a gradual increase in pulmonary vascular resistance. Previous studies have reported histopathological changes in the pulmonary vasculature of patients undergoing a Fontan operation. These vascular changes included increased wall-thickness due to the muscularization of the medial layer in the intra-acinar pulmonary vessels. Since the studied pulmonary tissue in these studies was obtained either by biopsy during the Fontan operation itself or at autopsy after perioperative mortality, this pattern of vascular remodeling was most probably still related to the pulmonary hemodynamics that had existed pre-operatively. We demonstrated that the long-term Fontan circulation is associated with a completely different pattern of adverse changes in the pulmonary vasculature and that this was related to the interval since the Fontan operation. The pulmonary vascular remodeling we observed after more than 15 years of Fontan circulation comprised a decreased medial thickness and eccentric intimal fibrosis. We hypothesize that this type of pulmonary vascular remodeling is associated with the chronic non-pulsatile pulmonary flow, which reduces circumferential strain and shear stress, and with in-situ thrombosis or multiple microembolic events, of which high rates have been suggested in the Fontan circulation as a result of a frequent hypercoagulable state and sluggish blood flow. Importantly, the observed pattern of pulmonary vascular remodeling in the long term Fontan circulation was completely different from that found in pulmonary arterial hypertension (PAH). Therefore, these observations do not support the concept of PAH-targeted therapy in the failing Fontan circulation. Future studies should focus on the underlying pathogenetic and biological mechanisms of this remodeling. Furthermore, the question whether these pulmonary vascular changes (preferably assessed in vivo) are associated with Fontan hemodynamics, including pulmonary vascular resistance and systemic venous congestion, should be investigated.

In addition, systemic vascular remodeling and resistance are of interest in the Fontan circulation. Chronic systemic venous congestion potentially affects the systemic peripheral vessels and could lead to adaptive changes in order to maintain cardiac output. A reduced venous compliance, reduced basal arterial tone and vasodilator response have been recognized. Altered endothelial dysfunction as well as sympathetic and parasympathetic nerve dysregulation might be underlying causes. The effects of systemic venous congestion on systemic vasculature and its autonomic feedback has to be further elucidated in future studies.

Quality of life and sexual wellbeing

Despite the limited life expectancy, impaired exercise tolerance and further comorbidities of the univentricular circulation, Fontan patients have a generally well preserved self-perceived health related quality of life. Only on physical
functioning and general health, Fontan patients tend to score lower than their healthy peers. In patients with congenital heart diseases, the peak exercise tolerance is associated with the perceived physical functioning and general health, but specifically in Fontan patients, no such relation has been identified. However, we demonstrated that most patients did experience physical limitations during their childhood. These physical limitations often resulted in the feeling of being an outsider and being bullied at school.

To our knowledge, we were the first to show that in Fontan patients, despite them showing a general well preserved sexual wellbeing as a cohort in general, large inter-individual differences existed. The sexual problems described by the Fontan patients, including erectile dysfunction and sexual avoidance due to arrhythmias, are generally comparable to those described in patients with other congenital heart defects. In those patients, the sexual problems significantly affected the quality of life. Whether these issues are more common in Fontan patients due to their unphysiologic circulation, remains to be investigated. The concerns regarding fertility and pregnancy were distinct in women with a Fontan circulation from patients with other congenital heart diseases, and impacted on their self-esteem. Importantly, our findings suggested that sexual function in Fontan patients deteriorates with progressive attrition of the Fontan circulation. Future studies have to be conducted to investigate the social isolation in Fontan children, as well as the prevalence of sexual problems and its relation with attrition of the Fontan circulation.

**Fontan Failure**

Eventually, attrition of the Fontan circulation can lead to the life-threatening Fontan failure. There are two types of Fontan failure: early postoperative failure, occurring in 2-6% in the same hospital admission as the Fontan completion procedure, and late failure, with an estimated incidence of Fontan failure of 2-13%, including “hemodynamic and multi-organ complications of the Fontan circulation which are not reversible by surgical or catheter interventions at acceptable risk”. We demonstrated that the Fontan takedown surgery has predominantly been performed to treat Fontan failure in the early postoperative phase, with a high risk of mortality. Early Fontan failure was also found to be one of the most important predictors of mortality of HTX. Potentially, early failure is associated with a distinct, more fulminant, etiology or the more frail patients fail earlier, exhibiting a higher risk of mortality.

Fontan conversion and HTX have been the main treatment options for late Fontan failure. Ten-year survival after HTX for failing Fontan patients have demonstrated to be around 86%, but a rate of 44% survival after HTX in children with congenital heart diseases has also been reported. Transplant-free survival of 67% following Fontan conversion is described. In our multi-center international cohort of failing Fontan surgeries, we were not able to identify a difference in transplant-free survival after Fontan conversion or HTX to treat late Fontan failure. Future studies should elucidate whether early recognition and treatment
of Fontan failure, for instance prior to the development of ventricular dysfunction, results in better outcome for the patients. Finally, newer surgical treatment options for a failing Fontan, such as the recently suggested Hraška shunt to treat protein losing enteropathy\textsuperscript{68}, late Fontan takedown\textsuperscript{69} or ventricular assist devices\textsuperscript{70} might expand the treatment arsenal for these complex patients in the future.

Conclusions

In conclusion, outcome after the Fontan procedure has improved over the past decades, but patients with a Fontan circulation still face multiple long-term sequelae and an uncertain future. By evaluating functional state, NT-proBNP and hepatic status, relations with the circulatory performance and changes over time became apparent, making these measurements potential markers of Fontan attrition. Treatment for eventual failure of the circulation is associated with considerable mortality, and does not favor one surgical option above another. Future research is necessary to determine how we can improve the outcome for these patients.
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