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

Harteveld, L.M.

Chapter 9

General discussion and future perspectives

Despite improvement in survival, Fontan patients still have an increased risk of morbidity and mortality (1, 2). However, a clear therapeutic strategy to improve Fontan circulation and prevent Fontan failure is still lacking. While many centres have focused their therapy on treating or preventing ventricular dysfunction using angiotensin converting enzyme (ACE) inhibitors, evidence of their efficacy in these patients is still lacking (3, 4). Accordingly, in this thesis, we studied the effects of ACE inhibition on various cardiovascular and hemodynamic properties of the Fontan circulation of paediatric patients. In addition, to further elucidate the effectiveness of ACE inhibition in Fontan patients and understand the pathophysiology of Fontan failure, we also studied the haemodynamics of the Fontan circulation of paediatric patients. Different pathophysiological mechanisms may influence the Fontan circulation negatively, such as systolic and diastolic ventricular dysfunction, reduced vascular compliance and autonomic failure. Since little is known about the normal development of autonomic function in healthy children, we studied both normal development of autonomic function as well as the autonomic function of paediatric Fontan patients. At last, in this thesis, the literature of plastic bronchitis, a severe complication of the Fontan circulation, was systematically reviewed to evaluate several aspects of plastic bronchitis in Fontan patients.

All different parts of this thesis with associated findings will be discussed below. First the results of cardiac autonomic function in healthy children and paediatric Fontan patients will be discussed. Thereafter, the results of evaluation of the Fontan circulation and effects of ACE inhibition are evaluated. At last, results of the systematic review of plastic bronchitis will be explicated.

Cardiac autonomic nervous activity

The autonomic nervous system (ANS), consisting of the parasympathetic- (PNS) and sympathetic nervous system (SNS), influences the circulation by regulating, e.g., blood pressure and heart rate. The interest in cardiac ANS activity has increased in recent years because of its relevance for cardiovascular disease and mortality (5). However, the normal development of cardiac ANS activity is still not fully understood. Therefore, in this thesis in **chapter 3**, we assessed the maturation of the cardiac PNS and SNS activity by measuring different non-invasive PNS activity parameters, i.e., respiratory sinus arrhythmia and two heart rate variability parameters, and a SNS activity parameter, i.e., pre-ejection period. For this study, cardiac PNS and SNS activity parameters from 5 different studies were combined, resulting in a multi-cohort study of 4820 healthy subjects aged 0.5 to 20 years (6-10). Our study showed that PNS activity increased rapidly after birth, levelled off during middle childhood

(≈11 years), and then decreased into adolescence, while SNS activity showed a linear decrease from early childhood to late adolescence. Such patterns were highly compatible with previously performed studies (11-28). Furthermore, there was a difference in maturation between sexes with PNS activity peaking later in boys than in girls. This later peak in boys is likely due to differences in hormonal changes since girls are known to enter puberty earlier than boys. Although the maturational trends are clear there is a large interindividual variability in absolute ANS parameters. This interindividual variability can be caused by various factors including ethnicity, differences in development of stature, body composition and entering puberty, differences in loading conditions, heart size, sensitivity of the baroreflex and lung stretch reflexes and respiratory behaviours (frequency and tidal volume), adopted lifestyle patterns (smoking, dietary habits, and physical activity), and psychosocial stress exposures. Moreover, even experimental factors can impact absolute values, such as time of day, posture, previous physical activity, and even analytic strategy to quantify SNS and PNS cardiac activity. This may limit the usefulness of individual absolute parameters, although group comparisons can still be valuable.

In **chapter 4**, we compared absolute values of cardiac ANS activity of Fontan patients with healthy controls to get an interpretation of baseline values. While PNS activity was comparable between both groups, the pre-ejection period was increased in Fontan patients suggesting lower SNS activity. This is in contrast with previous studies in adult Fontan patients who showed an impaired autonomic function with decreased PNS- and increased SNS activity (29-31). However, caution is needed with interpretation of pre-ejection period in Fontan patients as it is known to be sensitive to preload and afterload effects, which are both known to be different in Fontan patients. Our findings suggest a preserved ANS function in young Fontan patients being treated in the present era. Future research should consider more invasive parameters to measure SNS activity, as no other good non-invasive alternative exists. Since autonomic dysfunction has been described in adult Fontan patients and autonomic function may play a role in the deterioration of the Fontan circulation, it is interesting for future research to investigate the maturation of cardiac ANS activity in Fontan patients.

Evaluation of the Fontan circulation

Multiple pathophysiological mechanisms may impact the Fontan circulation. A combination of exercise stress testing and the use of acute fluid challenges, either fluid loading or fluid depletion may give more insight in these mechanisms.

Exercise stress testing

During exercise stress testing an adequate increase in cardiac output is mandatory, being influenced by heart rate, preload, contractility, and afterload. In Fontan patients the exercise capacity is known to be impaired. As shown in **chapter 4,** the percentage of predicted exercise capacity can range from 54-72% in one cohort, differing on the parameter used, which is comparable with previous literature (32-37).

The main limiting factor of Fontan circulation is the inability to augment venous return due to the lack of a ventricle for the pulmonary circulation. In our patient population, we observed an adequate increase in heart rate, i.e., a good chronotropic competence, while stroke volume was reduced at peak exercise. We found that decreased diastolic function, influencing preload, and increased arterial stiffness, influencing afterload, were correlated with decreased exercise performance. It is known that diastolic dysfunction and increased arterial stiffness are present in Fontan patients at an early age and that both may worsen over time and therefore may contribute to deterioration of exercise performance (38-42). In contrast to other studies systolic function, i.e., contractility, was not correlated with exercise performance in our study. This may be explained by the selection criteria of our study cohort, excluding patients with significant systolic dysfunction, (1). Although we investigated the relationship between exercise capacity and various cardiovascular parameters we did not study other parameters such as the impact of residual obstructions in the Fontan tunnel or pulmonary arteries or increased pulmonary vascular resistance that will lead to energy loss and reduced pulmonary blood flow (37, 43, 44).

Acute fluid challenges

While acute fluid challenges were previously performed more frequently in invasive (laboratory) studies, in recent decades it has also been performed non-invasively by means of passive leg raising, mimicking fluid loading, and head-up tilt table testing, reflecting acute fluid unloading.

Passive leg raising as a test to evaluate the hemodynamic response to an increase in preload has not been used in Fontan patients. Passive leg raising is a non-invasive, reversible, and reliable test to predict volume responsiveness. In this thesis, in **chapter 5**, hemodynamic reaction to passive leg raising was studied in Fontan patients and healthy controls. Overall, the hemodynamic response of Fontan patients was similar to the response in healthy controls. Moreover, Fontan patients who did not respond with an increase in stroke volume were not more

negatively affected by passive leg raising than controls. However, in a previous catheterization study (45) an increase in preload was related to an increase in end-diastolic pressure, decreasing the transpulmonary gradient and cardiac output in part of the patients. Since the response to an increase in preload may be affected by differences in loading conditions, this can explain the different results from our study as compared to literature.

Head-up tilt testing can be used to test the acute orthostatic stress response. A good reaction to orthostatic stress requires activation of the sympathetic nervous system and concurrent vagal withdrawal to increase heart rate, systemic vasoconstriction, and venous return to be able to maintain adequate blood pressure and cerebral blood flow (46, 47). Previous studies, mostly performed in adult Fontan patients, have shown differing results with overall an impaired cardiac ANS activity and decreased baroreflex sensitivity, resulting in a blunted autonomic response to orthostatic stress (30, 31, 45, 48). In contrast to these studies, in **chapter 6,** we showed that paediatric patients had a sufficient autonomic response during head-up tilt testing while maintaining adequate blood pressure and cardiac output. Sufficient autonomic response was demonstrated by an increase in heart rate and aortic stiffness, both indicative of intact autonomic regulation, as well as by the same degree of decrease in cardiac PNS activity between patients and controls. As previous studies were performed in adult patients, age may have affected the difference in results. Furthermore, cardiac output was maintained which may imply that patients are likely to be able to adapt to the Fontan circulation and to prevent venous pooling while standing and avoid a deleterious drop in central venous pressure. Although paediatric patients seem to adapt, studies in adult Fontan patients show a large decrease in cardiac output in response to tilt, suggesting that the adaptive mechanisms may be falling short on the long-term (48). It is interesting to further investigate both patients who respond well and those who do not, to clarify the difference and to possibly identify risk factors for deterioration of the circulation over time.

ACE inhibition

Since many Fontan patients, even without systolic ventricular dysfunction, are currently treated with ACE inhibition without evidence of efficacy, in this thesis, in **chapters 6 and 7**, we investigated the effect of ACE inhibition on the Fontan circulation. The previously mentioned methods to evaluate the circulation were also used to evaluate the effects of a 3-month treatment with enalapril on the circulation.

We showed that a 3-month enalapril treatment had no effect on the exercise performance of the Fontan patients and did not improve arterial stiffness, diastolic nor systolic ventricular function, which was comparable with the previous two smaller studies performed in Fontan patients (49, 50). Enalapril did, however, lower the systolic blood pressure and NT pro-BNP levels. Lower levels of NT pro-BNP might suggest lower filling pressures, although not directly measured in this study, this effect of enalapril has previously been shown in a small catheterization study in univentricular heart patients (51). Furthermore, although enalapril lowered the blood pressure at rest, it did not lead to orthostatic hypotension or a decrease in cardiac output during head-up tilt testing. During the titration period a large proportion of patients experienced side effects (42%), such as a significant drop in systolic blood pressure, dizziness, and syncope. After the titration period patients were given a stable dosage, which was better tolerated. In other words, ACE inhibition has a vasodilatory effect in Fontan patients leading to lowering the blood pressure, but after the titration period most side effects have disappeared. This habituation is further supported by the good orthostatic tolerance under enalapril treatment.

Although we did not show beneficial effects of enalapril on the short-term, on the long-term cardiac renin-angiotensin-aldosterone system (RAAS) inhibition could limit cardiac remodelling and cardiomyocyte fibrosis (52). However, future studies are warranted to investigate if ACE inhibition or other RAAS inhibition may have beneficial effects in Fontan patients on the long-term.

Plastic Bronchitis

When the Fontan circulation fails in single ventricle patients, plastic bronchitis can manifest as a serious complication. Plastic bronchitis is characterized by the formation of mucofibrinous casts in the tracheobronchial tree, leading to airway obstruction and possible suffocation. Systematically reviewing the literature in **chapter 8** showed that the overall mortality rate in single ventricle patients was 15.2%, with a lower overall mortality rate of 10.5% in cases published after 2012. Mortality was associated with diagnosis of plastic bronchitis within 12 months of the Fontan palliation, which could indicate that early onset of plastic bronchitis may be a manifestation of a poor Fontan circulation. Furthermore, a higher age at Fontan operation was found as an additional risk factor, however, whether this finding has been influenced by other factors could not be determined as many other possible risk factors were often missing from records.

Concerning treatment for plastic bronchitis, we found that most cases received a combination therapy consisting of relief of airway obstruction, inflammatory treatment, and treatment to improve the haemodynamics of the Fontan circulation, which eventually led to the successful management of plastic bronchitis in most cases. Therefore, based on the data from our systematic review, we developed a treatment algorithm in which the acute phase may exist of bronchoscopy for direct cast relief and aerosolized tissue plasminogen activator can be considered, next to diagnostic evaluation. After the acute phase, treatment may best be consisting of a combination of all three treatment strategies. Improving the haemodynamics can consist in this phase of optimizing the Fontan circulation by medical therapy or surgery, anti-arrhythmic therapy and/or inhibition of lymph leakage. When the plastic bronchitis is still not improving, the haemodynamics could be improved by more invasive strategies, i.e., decompression of the circulation by creation of a fenestration or Fontan takedown, and even heart transplantation could be considered. In our case report, presented in this review, a temporary Fontan takedown was lifesaving, and during this period, the plastic bronchitis could resolve, the pulmonary circulation recovered, and the Fontan circulation restored successfully later. Finally, when the plastic bronchitis has resolved, we recommend that patients start prophylactic antibiotics as preventive therapy, as recurrence has been associated with respiratory infections (53).

Although a good overview of alle cases in the literature was given, much data from many cases were lacking to be able to determine more exactly which patients may be at risk for developing plastic bronchitis and which treatment option/strategy will work best. Large multicentre cohort studies are warranted to unravel the exact pathophysiology to determine which patients are at risk for developing plastic bronchitis and which therapeutic strategy is most effective.

Conclusions and future perspectives

In this thesis several aspects of the Fontan circulation were studied in a relatively homogeneous group of paediatric patients, with an extracardiac conduit and moderate to good systolic ventricular function, to evaluate not only the effectiveness and side effects of ACE inhibition, but also study the limitations of exercise capacity and haemodynamic reaction to acute fluid challenges.

We demonstrated that ACE inhibition on the short term does not show positive effects on exercise capacity, cardiovascular and ventricular function, but besides the side effects during the titration period, also had no negative effects on the

circulation itself. When evaluating the circulation itself further, we showed that even relatively healthy young Fontan patients have an impaired exercise capacity which is correlated with diastolic dysfunction and aortic stiffness. During exercise, patients showed a good chronotropic competence, implicating a preserved cardiac autonomic function. Preserved autonomic function could also be conducted from the sufficient response to acute fluid depletion, i.e., orthostatic stress. In contrast to limited exercise capacity, paediatric Fontan patients are still able to respond well to acute fluid changes and seem able to adapt well to the circulation.

As shown in this thesis, future therapeutic strategies should also be aimed at treating and preventing diastolic dysfunction and aortic stiffness in Fontan patients to optimize and hopefully prevent deterioration of the circulation. However, both diastolic dysfunction and increased aortic stiffness are difficult to treat and no single treatment option is yet available. Diastolic dysfunction may be caused by impaired ventriculo-arterial coupling and myocardial fibrosis (54, 55). The optimal treatment would keep ventricular filling pressure low and enhance ventricular pull, however, such an effective lusotropic drug is still lacking. In addition, anti-hypertensive drugs can be prescribed to lower the systemic vascular resistance, such as ACE inhibitors, and they may lower the blood pressure by a vasodilator effect but not effectively improve the aortic compliance and reduce aortic stiffness, as shown in this thesis. Possible treatment for improving aortic stiffness with anti-inflammatory drugs or endothelin-A receptor antagonist have shown some promising but also conflicting results in patients with a biventricular heart circulation (56). However, each treatment may only impact a part of the cause of the aortic stiffness. Future research is needed to first determine the exact pathophysiology and then develop medical therapies that can improve both diastolic function and arterial stiffness.

Furthermore, although we recognized diastolic dysfunction and arterial stiffness as limiting factors, we did not study all possible potential limiting factors and only studied a relatively specific group of patients. For example, the pulmonary circulation, which has been recognized as one of the major limiting factors of Fontan circulation, has not been investigated. Nevertheless, improving the pulmonary circulation by pulmonary vasodilators has been the key focus of some recent large randomized studies and showed a slight increase in exercise capacity after treatment, which is promising (57). Whether this will prevent circulatory deterioration in the long term, however, needs further investigation. In addition, although systolic ventricular function was not a limiting factor in our population, systolic function is known to deteriorate, leading to heart failure on the long term. Therefore, preventing systolic ventricular function to deteriorate and treating systolic heart failure will still be one

of the therapeutic targets. However, from this thesis, we can conclude that there is no beneficial effect of short-term ACE inhibition in Fontan patients with moderate to good systolic ventricular function. If ACE inhibition might play a role in treating patients with significant systolic dysfunction has still to be determined.

As the Fontan population consists of a heterogeneous group of patients, the cause of deterioration of the circulation and eventually Fontan failure can vary between patients. Future studies are needed not only to develop medical therapies for the various possible limiting factors, but also to be able to recognize the limiting factors and determine which patients benefit most from which therapy.

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