CHAPTER 1

1

General introduction

Univentricular heart disease

The normal heart consists of both a right- and left atrium and ventricle. The right side of the heart actively pumps oxygen-poor blood (blue) towards the lungs for oxygenation, while the left side of the heart pumps the oxygen-rich blood (red) towards the rest of the body (**Figure 1, left**). Approximately one percent of children are born with a congenital heart disease, characterized by structural defects in one or multiple parts of the heart and/or great vessels.[1] Patients born with a univentricular heart defect represent the most severe end of the spectrum of congenital heart disease, having only one functional ventricle that excludes a successful biventricular surgical repair. Typical univentricular heart defects include tricuspid atresia, double-inlet left ventricle and hypoplastic left heart syndrome (**Figure 1, right**).

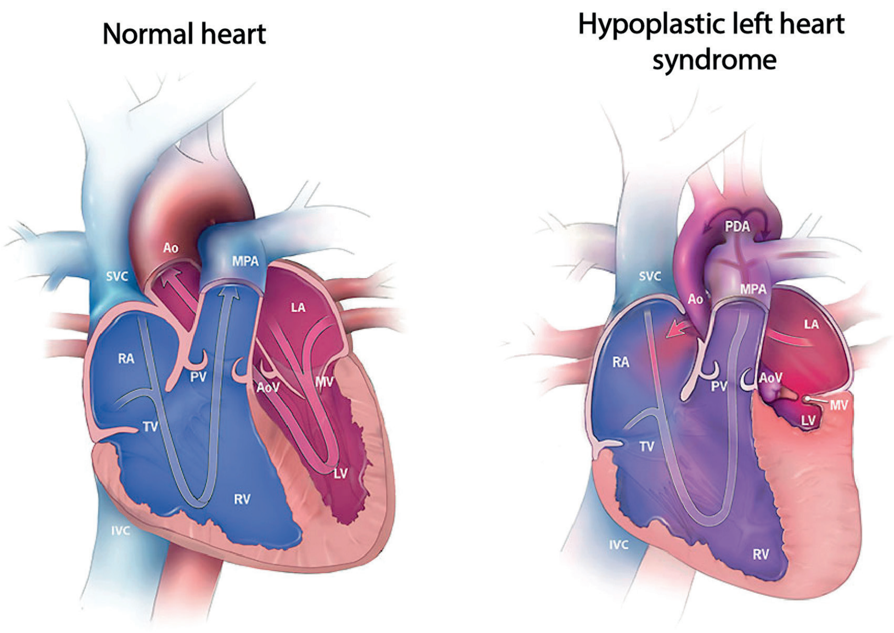

Figure 1. Example of a normal heart and a patient with a hypoplastic left heart syndrome. *Reproduced from Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities.*

RA/LA; right/left atrium, RV/LV; right/left ventricle, IVC/SVC; inferior/superior vena cava, TV; tricuspid valve, MV; mitral valve, AoV, aortic valve, PV; pulmonary valve, MPA; main pulmonary artery, Ao; aorta, PDA; patent ductus arteriosus

Fontan procedure

Firstly performed in 1968, the Fontan procedure is the current gold standard palliative approach for patients with a univentricular heart defect.[2] The Fontan procedure nowadays includes a series of operations with the end goal to completely bypass the subpulmonary ventricle from the pulmonary circulation: the Fontan circulation. As a first step, various operations are usually needed in the first weeks of life to obtain a balanced pulmonary and systemic circulation with an unobstructed systemic outflow tract. At the age of 6-12 months, the superior vena cava is disconnected from the right atrium and directly connected with the pulmonary artery (PA), the so-called bidirectional Glenn shunt. When the child is 2-4 years old and approximately 15kg, the Fontan circulation is completed by connecting the inferior vena cava (IVC) with the PA, which can be performed using multiple different surgical techniques that have evolved over time (**Figure 2**)[3]. The atriopulmonary connection technique directly connects the right atrium auricle with the PA, since the inclusion of the right atrial contraction was considered necessary for maintaining adequate pulmonary blood flow **(Figure 2A)**. This technique, however, is associated with progressive dilatation of the right atrium leading to arrythmias, thrombus formation and inefficient blood flow and has now been abandoned.[4] Nowadays, the total cavopulmonary connection (TCPC) technique is used to direct inferior vena cava blood towards the PA and can be performed in two ways: the lateral tunnel and the extracardiac conduit technique. The main goal of these techniques is to exclude (most) of the right atrium from the Fontan circulation and thereby avoid the complications observed in patients with an atriopulmonary Fontan connection **(Figure 2A)**. The lateral tunnel technique uses an intra-atrial patch to streamline blood flow from the inferior vena cava towards the PA, thereby excluding part of the atrium from the systemic venous return.[5] The main advantage is the growth potential of the Fontan tunnel, since part of the tunnel is made from atrial tissue. The extracardiac conduit technique uses a synthetic (Gore-Tex) conduit to connect the inferior vena cava with the PA, thereby fully excluding the right atrium from the systemic venous return.[6] This technique is now the preferred approach in most centers worldwide and in Leiden since 2000. However, the lack of growth potential of the synthetic conduit remains concerning, and long-term data regarding conduit size adequacy for older Fontan patients is currently lacking. As a result, the most optimal technique (lateral tunnel or extracardiac conduit) is still a matter of debate.[7]

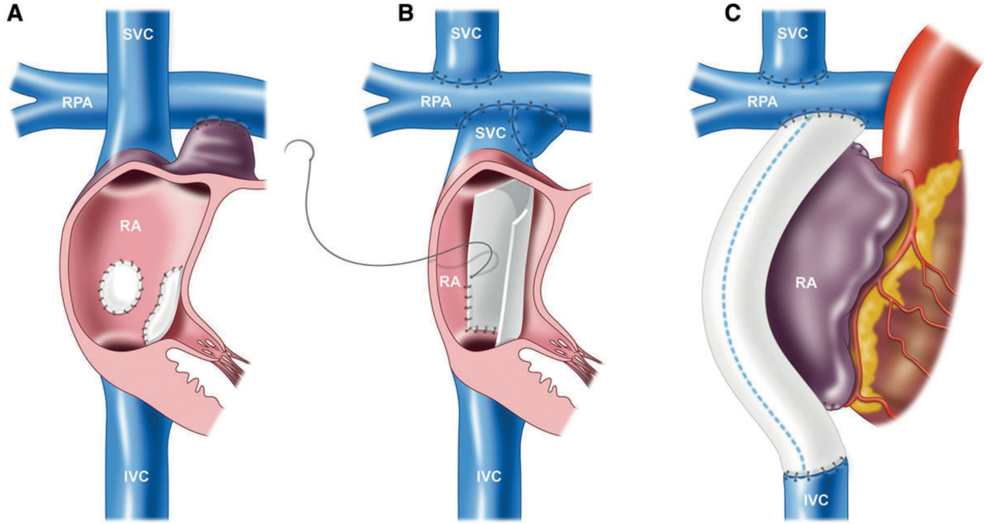

Figure 2. The different surgical techniques for completing the Fontan circulation are shown, including the atriopulmonary connection (A), the lateral tunnel technique (B) and the extracardiac conduit technique (C). *Reproduced with permission from D´Udekem et al.*[3]

RA; right atrium, RPA; right pulmonary artery, IVC/SVC; inferior/superior vena cava.

Fontan physiology

In a normal biventricular circulation, the right ventricle creates the driving force for pulmonary blood flow to overcome the resistance in the pulmonary vascular bed. During exercise, the right ventricular work increases in order to augment cardiac output.[8] In the Fontan circulation, however, blood flow towards the pulmonary circulation is relatively passive, as no subpulmonary ventricle is present that actively pumps blood towards the lungs. Consequently, a chronically elevated venous pressure (CVP) is required to overcome the resistance and associated pressure drop in the TCPC and the pulmonary vascular bed. During exercise, further increase in CVP is needed to augment cardiac output. However, the chronic elevation of CVP that is clinically tolerated and the subsequent increase in CVP during exercise are both limited[9-11], resulting in reduced preload towards the single ventricle and thus reduced cardiac output.

Outcome

The introduction of the Fontan procedure has dramatically improved survival rates for children born with a single ventricle. Nowadays, approximately 70.000 patients worldwide are estimated to be alive and this population is expected to double in the next 20 years. Today, the majority of children with a single ventricle are expected to survive well into adulthood, with an estimated survival of 85% after 30 years for Fontan patients operated in the current era.[12] However, the vulnerable Fontan physiology results in significant morbidity over time, including the occurrence of protein losing enteropathy, liver fibrosis/cirrhosis to even hepatocellular carcinoma, brady- and tachyarrhythmias, systolic and diastolic heart failure, significantly reduced exercise capacity and eventually failure of the Fontan circulation. However, great variability in clinical condition exists between patients and there is an unmet need for a better understanding which patients are prone to worse outcome.[12] Characteristic of the Fontan circulation, the chronically elevated CVP and reduced cardiac output are both important pathophysiologic mechanisms of frequently observed morbidity in Fontan patients. For example, elevated CVP is associated with the formation of liver fibrosis/cirrhosis[13] and reduced stroke volume is one of the most important factors responsible for impaired exercise capacity.[14] Therefore, unobstructed blood flow with minimal resistance from the systemic veins towards the lungs is critical to ensure efficient blood flow with optimal hemodynamics. In this thesis a focus is placed on evaluation of blood flow efficiency in the TCPC, an area that can potentially be optimized at the initial Fontan procedure or during follow-up by reintervention.

Evaluation of blood flow in the TCPC

Magnetic resonance imaging

Currently, evaluation of the Fontan circulation using MRI is advised every 2-3 years to early detect (subclinical) complications.[12] Magnetic resonance imaging is a non-invasive technique that can be used to evaluate *in vivo* blood flow using various phase-contrast sequences. Conventionally, 2D flow MRI acquisitions are used to determine unidirectional blood flow velocity at multiple predefined planes within the Fontan circulation.[15] In the recent years, however, 4D flow MRI has emerged as a novel tool able to capture three-directional (3D) velocities in a 3D volume of interest for multiple timesteps along the cardiac cycle (4D= three-directional velocities + time). It not only allows for quantification of flow rates at every position within the acquired volume of interest, but also can be used to obtain 3D flow patterns within the TCPC. Abnormal, helical flow patterns can be present in the TCPC resulting in less efficient blood flow that may increase risk for future Fontan failure.[16] Besides visualization of flow patterns with 4D flow MRI, novel in vivo hemodynamic markers such as kinetic energy and viscous energy loss rate (kinetic energy lost due to friction within the blood flow) can be quantified from the acquired 3D velocity field.[17] Therefore, 4D flow MRI evaluation of blood flow in the TCPC may identify novel insights into the presence of adverse flow patterns and associated energetic markers which may be related to adverse clinical outcome.

Computational fluid dynamics

Computational fluid dynamics can be used to simulate in silico blood flow in the TCPC by numerically solving the continuity equation and Navier-Stokes equations for incompressible fluid flows.[18] Using CFD, a three-dimensional time-resolved pressure and velocity field can be obtained based on patient-specific 3D TCPC models coupled with patient-specific MRI-derived boundary conditions. This allows for quantification of high-resolution blood flow patterns and associated hemodynamics including viscous energy loss, pressure gradients and resistance. Furthermore, CFD allows for simulation of different physiologic flow conditions including the effect of respiration and exercise on TCPC flow and energetics. In addition, "virtual surgery" can be performed with CFD models, by adapting the TCPC geometry on the computer and subsequently simulate the effect of the geometry adaptation on flow dynamics.[19]

Outline thesis

The first goal in this thesis is to assess the outcome of Fontan surgery performed in the LUMC in the past 45 years. In order to improve future outcome in Fontan patients, a better understanding of the Fontan physiology and better characterization of the state of the Fontan circulation during follow-up are important gaps in current knowledge.[12] In this thesis, the main focus was to investigate the role of the TCPC in current Fontan circulations, by prospectively evaluating TCPC flow dynamics in a cohort of teenage and adolescent Fontan patients using advanced flow MRI and computational fluid dynamics and assess its relationship with adverse outcome.

In **part I**, long-term outcome of the 45-year experience with the Fontan procedure at the Leiden University Medical Center is described, one of the longest experiences to date including the first procedures performed by Dr Fontan himself (Chapter 2). In chapter 3, long-term outcome of the direct relief of subaortic stenosis in single ventricle patients is described, as a relatively simple alternative to the most commonly used indirect relief methods (e.g. Norwood or Damus-Kaye-Stansel).

Part II of this thesis is focused on the assessment of in vivo flow dynamics in the TCPC using multiple different MRI flow imaging modalities. Chapter 4 reviews the role of the cardiac and respiratory cycle on blood flow in the TCPC and its relevance for interpreting the different imaging modalities. Since no subpulmonary ventricle is present, blood flow pulsatility along the cardiac cycle in the TCPC is minimal. To exploit this fact, in chapter 5 a novel scan technique was developed (cardiac-cycle averaged 3D flow MRI) and compared with cardiac-cycle resolved 2D flow MRI and 4D flow MRI. In chapter 6, 4D flow MRI derived energetics in segments of the TCPC are investigated. While previous studies focused on blood flow in the TCPC from the level of the Fontan conduit, blood flow patterns and energetics at the level where the IVC, hepatic veins and Fontan conduit join (IVC-conduit junction) are evaluated with 4D flow MRI in this study. Finally, a case-report illustrates novel insights that can be derived by evaluating TCPC hemodynamics using 4D flow MRI with possible consequences for clinical care.

In chapter 7, the adequacy of the 16-20mm synthetic extracardiac Gore-Tex conduit along the respiratory cycle is assessed using realtime 2D flow MRI, allowing to separate flow measurements in both inspiration and expiration. A case-report shows the effect of an undersized extracardiac conduit on local flow patterns and associated energetics in the TCPC derived from 4D flow MRI.

Chapter 8 describes the correlation between in vivo 4D flow MRI derived energetics (kinetic energy and viscous energy loss rate) in the TCPC with exercise capacity and iron-corrected liver T1 mapping as a marker of liver fibrosis/venous congestion.

Part III is focused on the application of CFD for assessment of TCPC flow dynamics. Chapter 9 reviews the role of flow derived energetics in cardiovascular disease, highlighting the important insights gained using CFD in Fontan patients. In general, the performance of the TCPC as assessed by CFD is evaluated based on power loss and the distribution of hepatic venous flow towards both lungs (hepatic flow distribution). In chapter 10, the assumption of uniform distribution of hepatic venous flow at the level of the Fontan conduit is tested using patient-specific CFD models, for the first time directly including the hepatic veins. In chapter 11, the hemodynamic performance of conventionally used 16-20mm extracardiac conduits is assessed in teenage and adolescent patients using patient-specific CFD models during both rest and simulated exercise conditions, separated into inspiratory and expiratory phases. Finally, in chapter 12 the results of the studies in this thesis are discussed and future perspectives are provided. In chapter 13 a summary in Dutch is provided.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C and Fuster V. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76:2982-3021.
2. Fontan F and Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240-8.
3. d'Udekem Y, Iyengar AJ, Cochrane AD, Grigg LE, Ramsay JM, Wheaton GR, Penny DJ and Brizard CP. The Fontan procedure: contemporary techniques have improved long-term outcomes. *Circulation*. 2007;116:I157-64.
4. Poh C, Zannino D, Weintraub RG, Winlaw DS, Grigg LE, Cordina R, Hornung TS, Bullock A, Justo R, Gentles TL, Verrall CE, du Plessis K, Celermajer DS and D'udekem Y. Three decades later: The fate of the population of patients who underwent the Atriopulmonary Fontan procedure. *International journal of cardiology*. 2017;231:99-104.
5. de Leval MR, Kilner P, Gewillig M and Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. *J Thorac Cardiovasc Surg*. 1988;96:682-95.
6. Marcelletti C, Corno A, Giannico S and Marino B. Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass. *J Thorac Cardiovasc Surg*. 1990;100:228-32.
7. Daley M and d'Udekem Y. The optimal Fontan operation: Lateral tunnel or extracardiac conduit? *J Thorac Cardiovasc Surg*. 2021;162:1825-1834.
8. Gewillig M and Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart*. 2016;102:1081-6.
9. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M and Budts W. Sildenafil improves exercise hemodynamics in Fontan patients. *Circ Cardiovasc Imaging*. 2014;7:265-73.
10. Gewillig M and Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart*. 2016;102:1081-6.
11. Schmitt B, Steendijk P, Ovroutski S, Lunze K, Rahmanzadeh P, Maarouf N, Ewert P, Berger F and Kuehne T. Pulmonary vascular resistance, collateral flow, and ventricular function in patients with a Fontan circulation at rest and during dobutamine stress. *Circ Cardiovasc Imaging*. 2010;3:623-31.
12. Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, Hsia TY, Hsu DT, Kovacs AH, McCrindle BW, Newburger JW, Pike NA, Rodefeld M, Rosenthal DN, Schumacher KR, Marino BS, Stout K, Veldtman G, Younoszai AK, d'Udekem Y, American Heart Association Council on Cardiovascular Disease in the Y, Council on C and Stroke N. Evaluation and Management of the Child and Adult With Fontan Circulation: A Scientific Statement From the American Heart Association. *Circulation*. 2019.

13. Emamaullee J, Zaidi AN, Schiano T, Kahn J, Valentino PL, Hofer RE, Taner T, Wald JW, Olthoff KM, Bucuvalas J and Fischer R. Fontan-Associated Liver Disease: Screening, Management, and Transplant Considerations. *Circulation*. 2020;142:591-604.
14. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li JS, Margossian R, Mital S, Russell J and Rhodes J. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. *J Am Coll Cardiol*. 2008;52:99-107.
15. Fratz S, Chung T, Greil GF, Samyn MM, Taylor AM, Valsangiacomo Buechel ER, Yoo SJ and Powell AJ. Guidelines and protocols for cardiovascular magnetic resonance in children and adults with congenital heart disease: SCMR expert consensus group on congenital heart disease. *J Cardiovasc Magn Reson*. 2013;15:51.
16. Houtzager JH, Westenberg JJ, de Koning PJ, Hazekamp MG and Roest AA. Helical flow pattern in the right pulmonary artery after Fontan palliation. *Eur Heart J Cardiovasc Imaging*. 2014;15:1183.
17. Elbaz MS, van der Geest RJ, Calkoen EE, de Roos A, Lelieveldt BP, Roest AA and Westenberg JJ. Assessment of viscous energy loss and the association with three-dimensional vortex ring formation in left ventricular inflow: In vivo evaluation using four-dimensional flow MRI. *Magn Reson Med*. 2017;77:794-805.
18. Gerrah R and Haller SJ. Computational fluid dynamics: a primer for congenital heart disease clinicians. *Asian Cardiovasc Thorac Ann*. 2020;28:520-532.
19. Trusty PM, Slesnick TC, Wei ZA, Rossignac J, Kanter KR, Fogel MA and Yoganathan AP. Fontan Surgical Planning: Previous Accomplishments, Current Challenges, and Future Directions. *J Cardiovasc Transl Res*. 2018;11:133-144.