Outcome, Hemodynamic and Genetic Assessment in Patients with Functionally Univentricular Hearts after the Fontan Operation at Young Age

Daniëlle Robbers-Visser

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Uitkomst, hemodynamische en genetische bepalingen
bij patiënten met een functioneel univentriculair hart
na Fontan operatie op jonge leeftijd

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Chapter 1

General introduction and outline of the thesis

The incidence of CHD is about 0.8%, meaning 12.5 cases per 1000 life births [1]. Errors in the morphogenesis of a normal four-chambered heart result in congenital heart disease (CHD), the most common form of birth defects. Heart formation is a complex morphogenetic process that requires correct function of 1) various embryological developmental regions (including the heart fields and the neural crest); 2) complex looping patterns resulting from selective growth and cell death, and 3) numerous regulatory and structural genes [2]. Disruption of these processes cumulates in various forms of CHD. In the minority of cases of CHD, there is a chromosomal or monogenetic defect. The majority of cases of CHD, however, are of multifactorial origin, meaning a complex interplay of genetic and environmental factors (i.e. a polygenic model).

Up until now, several candidate genes have been identified in patients with defects of cardiac septation, conotruncal anomalies and/or underdevelopment of one of the ventricles [3]. In patients with a so called functionally univentricular heart, all these defects can be combined in one heart. Data on the embryological development of univentricular lesions are scarce, as are candidate genes [4]. Inheritance seems to be comparable to other types of congenital heart defect [5, 6], with 2-5% of siblings affected. Hypoplastic left heart syndrome is an exception with an overrepresentation of familial congenital heart disease, with 19-33% of siblings affected [7-9].

About ten percent of children with CHD have functionally univentricular hearts. The exact assessment of the incidence of functionally univentricular hearts is hampered by the complexity of the lesions combined in this group. In epidemiologic studies, lesions like atrioventricular valve defects, aortic stenosis, pulmonary atresia, double outlet right ventricle and Ebstein's anomaly may all include patients with an anatomy that does not allow biventricular repair. It is common to classify hypoplastic left heart syndrome, hypoplastic right heart syndrome and tricuspid atresia among the 'single ventricle' lesions. Combined, the estimate of these lesions is ± 650 per million [1]. In the Netherlands, this comes to about 120 new patients per year.

In the normal heart, the right ventricle supports the pulmonary circulation and the left ventricle supports the systemic circulation. This results in two closed circuits, thereby preventing de-oxygenated blood to enter the systemic circulation without passing through the lungs for oxygenation (figure 1, right panel). In patients with a functionally univentricular heart, there is only one ventricle capable of sustaining both circulations (figure 1, left panel). Therefore, both the systemic venous return and pulmonary venous return enter this single ventricle. Mixing of systemic venous blood with pulmonary venous blood causes arterial desaturation. Furthermore, the single ventricle, receiving both venous returns, suffers a volume overload and has to support both the pulmonary and systemic circulation.

Various forms of CHD are clustered in the group of patients with functionally univentricular hearts. Some patients have an underdeveloped right ventricle (e.g. patients with tricuspid atresia, pulmonary atresia/intact ventricular septum) and others have an underdeveloped left ventricle (e.g. hypoplastic left heart syndrome). In many cases, underdevelopment of the ventricles is accompanied by septation defects (double inlet left ventricle, atrioventricular septal defect) or conotruncal anomalies (double outlet right ventricle, transposition of the great arteries). All these forms of CHD have in common that biventricular repair is not possible (hence the name "functionally univentricular"). Palliation is the best available surgical option. In 1971, Francis Fontan described a surgical concept for patients with tricuspid atresia [10]. Although his original solution for connecting the systemic venous return directly to the pulmonary arterial circulation has been abandoned nowadays, his concept is the base of the surgical palliation that is currently being performed.

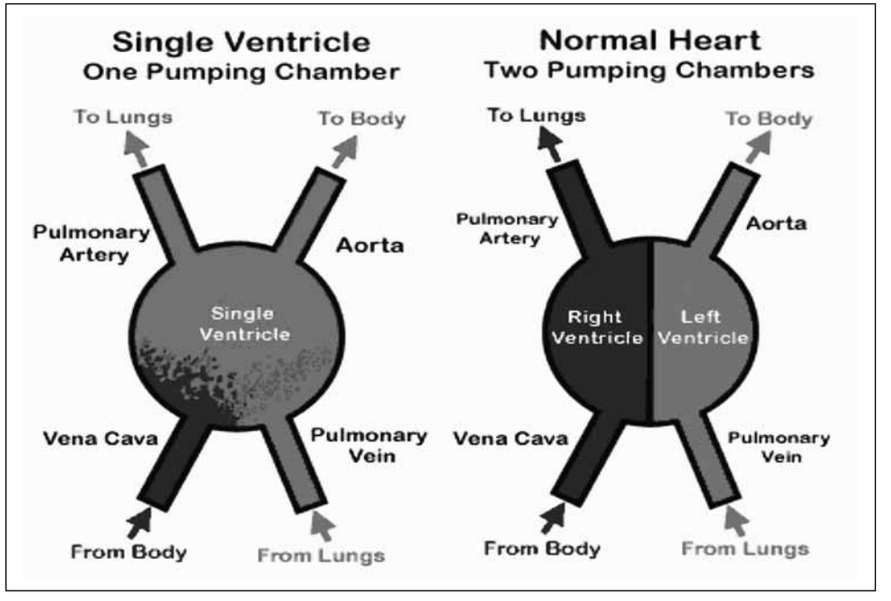

Figure 1. Right panel represents schematically the normal circulation, with two functional ventricles. The left panel represents the circulation in patients with a functionally univentricular heart.

The Fontan operation

If left untreated the prognosis of patients with functionally univentricular hearts is poor, but variable, depending on the anatomical and functional details of individual heart malformations [11, 12]. Without surgical intervention only 10% of patients with tricuspid atresia survived beyond the first year of life [12]. Moodie et al. reported a survival of 50% of patients with left ventricular mor-

phology of the single ventricle at the age of fourteen years. In other types of morphology, survival may be as poor as 50% at the age of four years. Other factors affecting the natural history include the position of the great arteries and the extent of outflow tract obstruction [11].

Before Fontan's publication "Surgical repair of tricuspid atresia" [10], there were few surgical options for patients with functionally univentricular hearts. The main options were ensuring adequate pulmonary blood flow (by creating a shunt from the systemic circulation to the pulmonary circulation) or preventing excessive pulmonary blood flow (by pulmonary artery banding). Regulation of pulmonary blood flow lead to a substantial improvement of survival ranging from 70% at five-year follow-up to 50% at the age of fifteen years [12, 13]. Separation of the systemic venous return and pulmonary venous return was not achieved and therefore these patients suffered from the consequences of long-term desaturation and volume loading of the single ventricle.

The concept of the Fontan operation is separation of the pulmonary and systemic circulation by directly connecting the systemic venous return to the pulmonary arterial circulation, thus without interposition of a subpulmonary ventricle. This results in normalization of arterial saturation and in volume unloading of the single ventricle. Blood flow to the pulmonary arterial circulation, however, now depends on post-capillary energy that has to provide the impelling force for the systemic venous return [14].

Throughout the years, the means by which to connect the systemic venous return to the pulmonary arterial circulation have changed substantially. In his original paper, Fontan described the use of a valved conduit from the right atrium to the pulmonary artery [10]. Valved conduits were soon abandoned, since their use was complicated by calcification of the valves. It was thought that inclusion of the right atrium in the circuit (i.e. an atriopulmonary connection, figure 2A), with maintenance of some contractility, would be beneficial for adequate pulmonary blood flow. However, the increased systemic venous pressure in this circulation eventually caused right atrial dilatation, with loss of flow efficiency, increased risk of thrombo-embolism and atrial arrhythmias. Therefore postoperative mortality of the initial Fontan operations was high and long-term survival was poor [15].

In 1988, de Leval and coworkers described the total cavopulmonary connection (TCPC, figure 2B) as a logical alternative to the atriopulmonary connection for patients with functionally univentricular hearts [16]. In the TCPC the superior caval vein is directed to the pulmonary artery with an end-to-side connection (a so called bidirectional Glenn anastomosis). The inferior caval vein is tunneled through the right atrium to the pulmonary artery (intra-atrial lateral tunnel ILT). This tunnel consists of right atrial free wall and prosthetic material that is sutured into the right atrium. Because this tunnel has a smaller diameter than the right atrium, energy loss is limited compared to the atriopulmonary connection [16]. In 1990, Marceletti et al. described the extracardiac conduit (ECC, figure 2C) as a new form of total cavopulmonary connection [17]. In this modification, the inferior caval vein is directed to the pulmonary artery by means of an extracardiac, completely prosthetic, conduit.

Since the 1990's the Fontan operation has increasingly been done in two stages [18]. In the first stage the superior caval vein is connected to the pulmonary artery (i.e. a partial cavopulmonary connection or PCPC). In the second stage the inferior caval vein is directed to the pulmonary artery (resulting in a TCPC), hereby restoring the pulmonary and systemic circulation functioning as two closed circuits.

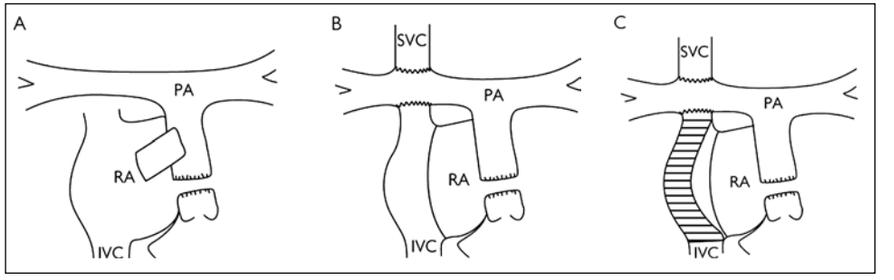

Figure 2. Panel A, atriopulmonary connection, with a direct connection between the right atrium (RA) and the pulmonary artery (PA). Panel B, total cavopulmonary connection, intra-atrial lateral tunnel, SVC = superior caval vein, IVC = inferior caval vein. Panel C, total cavopulmonary connection, extra cardiac conduit.

In 1977, Choussat et al. described their "ten commandments" a patient should met to be considered a suitable Fontan candidate [19]. In the current era criteria to opt for Fontan operation have been revised and include an unobstructed flow from the single ventricle to the aorta, balanced pulmonary and systemic flow and unobstructed venous return to the ventricle [14]. This may require additional procedures, for example to ensure or limit pulmonary blood flow by creating a systemic to pulmonary artery shunt or by pulmonary artery banding, or to ensure an unobstructed single ventricular outflow tract (by performing a Damus-Kaye-Stansel procedure (usually as part of the Norwood operation for hypoplastic left heart syndrome) or a hemi-arterial switch operation).

Long-term outcome after Fontan operation

The Fontan procedure has dramatically increased life expectancy of patients with functionally univentricular hearts, and is accepted as the best palliative option for these patients. In a recent cohort study from Belgium, ± 90% of all patients with hypoplastic left heart syndrome or univentricular physiology underwent PCPC or TCPC in a five-year follow-up after birth [20]. The period before the PCPC is characterized by volume overload and altered afterload of the single ventricle [14, 21], combined with a varying degree of hypoxaemia. This may result in abnormalities in ven-

tricular systolic and diastolic function, incoordinate wall motion, increased ventricular wall stress, accompanied by increased myocardial oxygen consumption and increased coronary blood flow, and ventricular hypertrophy [14, 22-24]. The combination of hypoxaemia and abnormal loading conditions may have important long-term consequences for ventricular function, that extent beyond the period these abnormalities exist.

Contemporary techniques have improved long-term outcome, but medical complications still frequently occur. Survival has improved with the switch from atriopulmonary to TCPC: d'Udekem et al. reported a fifteen year survival in patients with atriopulmonary connection of 81% compared to 94% in patients after TCPC [25]. The most common factors related to death are: heart failure, thrombo-embolism and sudden death [25-27].

After the Fontan operation severe functional decline, including decline of aerobic fitness and heart failure, is common [27-31]. In a recent survey in patients aged 6-18 years of contemporary outcomes of the Fontan operation (85% of 546 patients after TCPC), stroke and/or thrombosis occurred in 8% of patients, and 33% had non-sinus rhythm. Twenty-five percent of patients had a ventricular ejection fraction <50%, and 72% had abnormal diastolic function. Predicted maximum oxygen uptake was 65 ± 16% of normal and 58% used ACE inhibitors [32]. Important deficits in health status, a measure of health related quality of life, were noted, particularly in physical functioning. Poor health status was explained by non-cardiac conditions and by current medical problems, including arrhythmias occurring during follow-up, and the number of current medications [33].

Advances in pediatric cardiac care have resulted in an increasing number of adults with complex congenital heart disease being followed up in tertiary care centers. Marelli et al., studying the prevalence and age distribution of congenital heart disease from 1985 to 2000, reported the number of adults with complex congenital heart disease to increase with time: in the year 2000 the number of adults already equalled the number of children with severe congenital heart disease [34]. Further increases in the adult population are to be expected since the largest reduction in mortality rates in children have been achieved over the past years [35]. As the population of adults with complex congenital heart disease and Fontan physiology increases, so does the occurrence of highly morbid and mortal outcomes, including heart failure and thrombo-embolism [36].

Poor outcome in patients has been related to pre-operative factors, including the balance between systemic and pulmonary flow, ventricular volume before cavopulmonary connections, timing and staging of the operation, heart rate and rhythm and to factors inherent to the Fontan circulation. These include: a.) limited venous capacitance b.) energy loss from non-laminar flow in the Fontan pathway, c.) abnormal growth and compliance of the pulmonary artery resulting from the abnormal, non-pulsatile flow pattern after the PCPC, d.) impaired diastolic ventricular function, all of which factors (a-d) may contribute to impaired ventricular filling, e.) the ventricular

dominancy of the single ventricle, and f.) abnormal regional and global ventricular function [14, 37-42].

The abnormal performance of the functionally univentricular heart results in activation of circulatory and myocardial adaptive mechanisms to stress [43]. Few data exist on the role of neuro-hormonal activation in children and young adults after Fontan operation treated according to current treatment strategies. The long-term effects of the abnormal, non-pulsatile flow pattern on pulmonary artery growth and function are a matter of concern. Several groups have studied the effects of a bidirectional Glenn or Fontan pathway on pulmonary artery growth and diameters but have shown equivocal results [44-46]. It has become increasingly clear that the transport function of the intra-atrial lateral tunnel or the extracardiac conduit as well as that of the pulmonary circulation is important for ventricular performance, exercise function, and the long-term outlook of patients after the Fontan operation [14, 47-49]. Consequently, studies of ventricular function, atrial level transport and of the pulmonary arteries in the Fontan circulation might benefit from studies during stress.

Outcome studies in patients with congenital heart disease are often limited by an insufficient number of patients included to provide adequate statistical power and by absence of a primary outcome that can be observed in a reasonable period [50]. However, with an increasing patient population it becomes important to identify patients at risk for adverse outcome. Secondary outcome variables, reliably predicting primary outcome – such as mortality – and occurring more frequently are needed in the follow-up of patients with complex congenital heart disease. Therefore, there is an increasing need of easily accessible and accurate assessment of hemodynamics in the search for parameters that give prognostic information in this patient population.

Cardiovascular magnetic resonance imaging

From 1984, cardiac magnetic resonance (CMR) imaging is used to study the cardiovascular system [51]. It has proven to be a valuable, additional imaging modality in the study of the anatomy and function of the heart and great vessels [52]. CMR imaging is not hampered by the anatomic orientation in the thorax that is one of the limitations of echocardiography. It is therefore capable of providing adequate analysis of right and left ventricular function, even in complex congenital heart disease.

CMR imaging is considered the gold-standard for assessment of global ventricular function [52]. In patients with Fontan physiology it is an important tool to evaluate cardiac and pulmonary artery function. CMR imaging has been used for the assessment of ventricular performance in congenital heart disease for at least fifteen years now. Clinical indications for CMR assessment of global ventricular and vascular function become relevant in children aged eight years and older. Although CMR imaging is increasingly being implemented in the follow-up of pediatric patients

with congenital and acquired heart disease, normative data on ventricular volumes, function, and mass for this population are lacking. Normal values from small studies, employing gradient-echo MRI sequences are used [53, 54]. In recent years, however, steady-state free precession (SSFP) gradient echo sequences have become the standard method for assessment of ventricular function and volumetric parameters with CMR imaging [52]. Compared to the previously used spoiled gradient-echo sequences, SSFP provides better blood-myocardial contrast, higher image quality and faster acquisition times [55]. Better blood-myocardial contrast in SSFP imaging results in statistically significantly higher end-diastolic volumes, and end-systolic volumes, lower mass and lower ejection fraction [56, 57]. Therefore, SSFP derived data cannot be compared to data obtained with spoiled gradient echo sequences.

In addition, SSFP has a lower interobserver variability and better reproducibility compared to gradient-echo [56-58]. Therefore, it has been suggested that this technique allows considerable reduction in subject numbers to prove a hypothesis in research studies and study groups can be up to 90% smaller than with echocardiography for establishing significant differences [59, 60]. The reproducibility of CMR imaging in patients with congenital heart disease has only been tested in a limited number of studies, generally including few patients.

Stress imaging

Studies of cardiac anatomy and function in patients with congenital heart disease are generally performed at rest. Exercise results in the combined activation of cardiac, pulmonary, vascular, neurohormonal, muscular and metabolic systems. Combined, this will result in important changes in contractility and loading conditions that may directly affect cardiac function. Therefore, it has been questioned if the function of the heart at rest is an adequate predictor for cardiac function with exercise, particularly in patients who have undergone complex repair of congenital heart disease. Assessment of the contractile reserve, i.e. the change of cardiac function with exercise, has been shown to have prognostic value in several types of acquired heart disease [61-65].

CMR imaging combined with pharmacological stress was introduced in 1992 [66], and has proven to be a valuable tool to detect ischemia in patients with known or suspected coronary arterial disease [67, 68]. Dobutamine stress CMR imaging can assess wall motion abnormalities, contractile reserve, abnormalities of diastolic function, and vascular function. There is extensive experience with stress CMR imaging in adults using pharmacological stress. Experience with CMR imaging combined with stress in patients with congenital heart disease is limited. A few groups have reported on the use of this modality to evaluate the reaction of the cardiovascular system in congenital heart disease patients under pharmacological stress conditions [69-76]. These studies have shown abnormal systolic function, abnormal diastolic function, and abnormal vascular responses to stress in these patients that help understand the pathophysiological processes. An important advantage of dobutamine stress CMR imaging is that all these parameters can be obtained in one single study. A few studies have been performed using physical stress [48, 77-80] in older children and young adults, but practical limitations have prevented the widespread use of this technique. In congenital heart disease, dobutamine is the most commonly used pharmacological stressor. Dobutamine increases the myocardial demand for oxygen similar to physical exercise, and is used to study contractile reserve and abnormalities of ventricular wall motion. Dobutamine also enhances diastolic function, and decreases preload and afterload. Studies in patients with congenital heart disease have used low dose dobutamine, with doses ranging from 5.0 to 20 µg/kg/min [69, 81]. Few studies have been done in children. As with CMR studies at rest, safety and variability of stress CMR imaging have not been tested in patients with congenital heart disease.

Outline of the thesis

The aim of this thesis was to study outcome in patients with functionally univentricular hearts after Fontan operation at young age. Main objectives of the studies in this thesis were:

- To compare morbidity and mortality in patients after two contemporary modifications of the Fontan operation, i.e. the intra-atrial lateral tunnel and the extracardiac conduit
- To study clinical and hemodynamic parameters in a subgroup of patients after Fontan operation at young age, with a special emphasis on the use of CMR imaging
- To compare the CMR results of Fontan patients with matched healthy controls by assessing normal values of biventricular function, volumes, and mass
- To study the safety and reproducibility of CMR imaging at rest and during low-dose dobutamine stress in patients with complex CHD
- To explore the role of some candidate genes for development of univentricular hearts in an unselected clinical population after the Fontan operation

In **chapter 2** we describe a multicenter comparative study on morbidity and mortality after two currently used modifications of the Fontan operation: the intra-atrial lateral tunnel and the extracardiac conduit.

In **chapter 3 to 5** we report our results on clinical outcome and hemodynamic assessment of ventricular and pulmonary arterial function in up to 40 patients after staged Fontan operation, completed at young age. In **chapter 3** a detailed assessment of the clinical state at mid-term to long-term follow-up after TCPC – predominantly intra-atrial lateral tunnel technique – performed in at least two stages is described. **Chapter 4** shows our results of global ventricular function at rest and during low-dose dobutamine stress. In **chapter 5** we explore pulmonary artery size and function at rest and during low-dose dobutamine stress in selected Fontan patients.

In **chapter 6** we describe the results of CMR assessment of biventricular function, volumes, and mass in 60 healthy children aged 8-17 years. Adequate normal values as assessed with currently used CMR imaging settings were missing in the literature and hampered comparison of our results acquired in Fontan patients.

Chapter 7 and 8 describe the safety, feasibility and intra-observer and interobserver variability of CMR assessment of biventricular function, volumes, and mass in patients with complex CHD. In **chapter 7** we report our results during CMR studies at rest. **Chapter 8** describes the results of these parameters during low-dose dobutamine stress. **Chapter 9** provides an overview of stress imaging studies that have been performed in children with cardiac disease and adults with congenital heart disease, focusing on studies using echocardiography or cardiac magnetic resonance imaging.

Chapter 10 studies genetic factors that may play a role in the development of functionally univentricular hearts. The results of the aforementioned studies are discussed in **chapter 11**.

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Chapter 2

Results of staged total cavopulmonary connection for functionally univentricular hearts. Comparison of intra-atrial lateral tunnel and extra-cardiac conduit.

Daniëlle Robbers-Visser[a]; Martijn Miedema[b]; Aagje Nijveld[c]; Eric Boersma[d]; Ad J.J.C. Bogers[e]; Felix Haas[f]; Willem A. Helbing[a]; Livia Kapusta[g]

[a] Department of Pediatrics, division of Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Pediatric Cardiology, University Medical Center Utrecht – Wilhelmina Children's Hospital, Utrecht, the Netherlands

[c] Department of Cardiothoracic Surgery, UMC St Radboud, Nijmegen, the Netherlands

[d] Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands

[e] Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, the Netherlands

[f] Department of Pediatric Cardiac Sugery, University Medical Center Utrecht – Wilhelmina Children's Hospital, Utrecht, the Netherlands

[g] Children's Heart Center, UMC St Radboud, Nijmegen, the Netherlands

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Abstract

Objective: to compare the outcome of two contemporary techniques for total cavopulmonary connection (TCPC): the intra-atrial lateral tunnel (ILT) and extracardiac conduit (ECC).

Methods: we included 209 patients after staged TCPC (102 ILT, 107 ECC), operated on between 1988 and 2008. Medical records, and surgical records were reviewed for (1) patient demographics and cardiac anatomy; (2) pre-Fontan procedures; (3) pre-Fontan hemodynamics and cardiac functional status (4) operative details; (5) post-operative hospital course; (6) follow-up information on arrhythmias, and thrombo-embolic events; (7) post-Fontan interventions; (8) clinical status at last follow-up until June 2008.

Results: median follow-up duration was 4.3 years (interquartile range 1.5-7.4). At 6 year follow-up freedom from Fontan failure (i.e. mortality or re-operations for Fontan failure) was 83% for the ILT, and 79% for the ECC ($p = 0.6$), freedom from late re-operations (other than re-operations for Fontan failure) was 79% for the ILT and ECC and freedom from arrhythmias was 83% for the ILT, and 92% for the ECC ($p = 0.022$). Multivariable Cox regression analysis identified intensive care unit stay and cardiopulmonary bypass time as risk factors for Fontan failure, but they were not strong predictors. Right ventricular morphology was identified as risk factor for arrhythmias. The occurrence of thrombo-embolic events was low with no difference between the ILT and ECC group, and irrespective of the post-operative use of anticoagulant or anti-platelet aggregation therapy. At most recent follow-up sinus rhythm was present in 70% of patients; in 23% of patients ventricular function was moderately or severely impaired at echocardiography.

Conclusions: outcome after staged ILT and ECC-type Fontan operations is good, with comparable freedom from late re-operations and freedom from Fontan failure at 6 year follow-up. The incidence of arrhythmias was significantly lower in the ECC-group. Right ventricular morphology was identified as risk factor for arrhythmias.

Introduction

The Fontan operation is a palliative procedure for patients in whom biventricular repair of their complex congenital heart defect – resulting in a functionally univentricular heart – cannot be performed. In 1988, De Leval and coworkers described the total cavopulmonary connection (TCPC) as a modified approach to Fontan reconstruction [1], a modification with superior hydrodynamic characteristics compared to the previously used atriopulmonary connection. In this reconstruction, systemic venous return is directed to the pulmonary arterial circulation by means of a bidirectional Glenn anastomosis (BDG), connecting the superior caval vein to the pulmonary artery, and a connection from the inferior caval vein to the pulmonary artery. The latter can be done by either an intra-atrial lateral tunnel (ILT), according to the report by De Leval [1], or by an extracardiac conduit (ECC) [2]. TCPC results in separation of the systemic and pulmonary venous return and in volume unloading of the systemic ventricle. Nowadays, this is performed as a staged procedure since volume unloading with a BDG prior to TCPC improves outcome and ventricular energetics after TCPC [3-5]. The BDG is usually performed in the first year of life and completion with an ILT or ECC usually takes place in the third or fourth year of life [6,7].

Since the introduction and implementation of the TCPC in the late 1980s, morbidity and mortality have decreased significantly as compared to outcome after atriopulmonary connection [7,8]. Recent survival cohorts of Fontan patients have shown improved survival, but most of these studies also included patients with older Fontan types (right atrium to right ventricle conduit, atriopulmonary connection) [5,8,9]. It is of importance to study the outcome of Fontan patients operated on according to current treatment strategies, and to compare the outcome of patients with an ILT and ECC. The current survival reports that include patients with a TCPC have limited patient numbers (especially for comparison of ILT and ECC), or include patients with and without staging, or have a limited follow-up duration [9-12]. The objective of our study was to compare the outcome of staged ILT and staged ECC.

Materials and Methods

Patients

We searched for patients after TCPC, operated on between January 1988 and January 2008, in the surgical databases of three tertiary referral centers for pediatric cardiac surgery and cardiology. The following patients were excluded: (1) patients who had undergone conversion of a right atrium to right ventricle conduit or atriopulmonary connection into a TCPC; (2) patients who did not have a preceding BDG anastomosis; (3) patients who had undergone a Kawashima operation for functionally univentricular hearts with azygos continuation of the inferior caval vein.

Data inclusion

Medical records, and surgical records of all patients were reviewed for the following data: (1) patient demographics and cardiac anatomy; (2) pre-Fontan procedures; (3) pre-Fontan hemodynamics and cardiac functional status from cardiac catheterization, echocardiography, and electrocardiography reports; (4) operative details; (5) post-operative hospital course; (6) follow-up information on occurrence and treatment of arrhythmias, and thrombo-embolic events; (7) post-Fontan interventions; (8) clinical status at last follow-up from medical history, physical examination, echocardiography, and electrocardiography reports. These data were included until June 2008.

Definitions

Early sequelae were defined as complications within 30 days after Fontan completion. All other complications were considered late. The primary endpoint was Fontan failure, defined as death, or re-operation for revision of the Fontan circulation. Fontan takedown or heart transplantation has not been performed in this cohort. Secondary endpoints were arrhythmias, and late re-operations other than re-operations for Fontan failure. Arrhythmias were defined as documented bradyarrhythmias or tachyarrhythmias that required intervention.

Statistical analysis

Continuous data were tested for normality using the Kolmogorov-Smirnov test. Data with a normal distribution are expressed as mean value ± one standard deviation (SD), whereas the median (interquartile range, 25^{th} and 75^{th} percentile) is shown for data with a non-normal distribution. Dichotomous data are presented as counts and percentages, and differences between groups of patients were evaluated by chi-square tests or Fischer's exact tests, as appropriate. A p-value < 0.05 (two-sided test) was considered to indicate statistical significance.

The incidence of the primary and secondary endpoints over time was evaluated according to the Kaplan-Meier method. Follow-up time was defined as the time from Fontan surgery to the endpoint event or last follow-up visit. Differences in the incidence of the endpoints between the two Fontan types were evaluated by the log-rank test.

Predictors of Fontan failure or arrhythmias were explored in univariable Cox regression models. Variables with a p-value < 0.15 were entered in a stepwise multivariable Cox regression model, that was corrected for the participating centers, and for the year of operation. Variables with skewed distributions (intensive care stay, cardiopulmonary bypass time) were entered in the model as a single term and as a quadratic term to test for possible non-linear contributions. The quadratic terms for these two variables were not significant in a multivariable model, implying a linear relationship between the risk factor and outcome. A p-value < 0.05 was required for a variable to be retained in the equation.

Results

Demographics and anatomy

From 1988 to 2008, 277 patients had undergone a TCPC in the three institutions. The following patients were excluded: 1) fifteen patients for a previous atriopulmonary connection (n = 13) or right atrium to right ventricle conduit; 2) 41 patients did not have a preceding BDG anastomosis; 3) twelve patients for a Kawashima type operation. In this study, 209 patients (118 men) were included. Characteristics of the study population are listed in table 1.

Table 1. Characteristics of the study population

Variable	ILT	ECC
Number (males)	102 (62)	107 (56)
Ventricular morphology		
Right ventricle (n)	48	44
Hypoplastic left heart syndrome (n)	15	29 †
Left ventricle (n)	52	62
Tricuspid atresia (n)	16	38 †
Indeterminate (n)	2	1

Abbreviations: ECC = extracardiac conduit; ILT = intra-atrial lateral tunnel. † Statistically significantly different from ILT.

Six patients were lost to follow-up. Three patients returned to their home country immediately after hospital discharge. Another three patients moved after 1.7 to 2.7 years of follow-up and were censored at that time. These six patients and 26 patients who died after Fontan completion were excluded from the assessment of current clinical status. Median follow-up duration of the remaining patients was 4.3 years (1.5-7.4). Median age at most recent follow-up visit and follow-up duration were significantly longer in patients with an ILT (table 2).

Surgical procedures

Before Fontan completion, 502 procedures were performed in 209 patients. Subtypes of pre-Fontan procedures are displayed in table 3. Of note, five patients received a pacemaker before the TCPC. Two of these patients had a congenital complete atrioventricular block. The other three patients developed complete atrioventricular block or symptomatic bradycardia during the pre-Fontan period. Median age at BDG anastomosis and the median interval between BDG and TCPC were comparable in patients with an ILT or ECC. The BDG was bilateral for persisting left superior vena cava in nineteen patients. There was no difference in pre-Fontan hemodynamics and variables of cardiac function for the two subgroups (table 3, cardiac catheterization reports available in 97%, echocardiography reports available in 93% of patients). Between 10 and 15% of patients had moderately or severely impaired ventricular function or moderate to severe atrioventricular valve insufficiency on pre-Fontan echocardiography.

The first staged TCPC (ILT) in this study was performed in 1990. Before this year, staged volume unloading with a BDG was not performed. The first staged ECC in this study was performed in 1996. An ILT or an ECC was performed according to the surgeon's preference. Age and weight at the time of Fontan completion were comparable in the two groups (table 4). In both groups, circulatory arrest was performed in only one patient. In the ECC-group, the majority of operations (76%) were performed with continuous coronary perfusion. Seventeen patients received a 16 mm Vascutek conduit, one patient had a 16 mm Goretex conduit, 33 had an 18 mm Goretex conduit, and in 56 patients the Goretex conduit diameter was at least 20 mm. Fenestrations were performed on hemodynamic indications (table 4).

Table 2. Follow-up details

Variable	ILT (n = 83)	ECC (n = 94)
Age at most recent follow-up visit (years)	10.7 (7.0-14.3)	7.5 (5.0-9.5)†
Follow-up time since Fontan completion (years)	7.4 (4.3-10.0)	3.8 (1.6-5.6) †
Medication: none (n)	1	13†
Angiotensin converting enzyme inhibitors (n)	14	22
Anti-arrhythmics (n)	2	0
Platelet inhibition (n)	11	64
Anticoagulants (n)	70	13
Rhythm status: sinus rhythm (n)	61	59
Atrial rhythm (n)	11	26
Pacemaker implantation	8	4
Moderately/severely impaired ventricular function (n)	22	14
Moderate/severe atrioventricular valve insufficiency (n)	12	7
Moderate/severe (neo-) aortic insufficiency (n)	5	4
Post-Fontan procedures		
Closure of right-to-left connections (n)	14	5
Atrioventricular valve repair (n)	1	2
Damus-Kaye-Stansel anastomosis (n)	1	1
Mechanical aortic valve prosthesis (n)	2	0
Graft replacement of aortic valve and ascending aorta (n)	1	0
Recoarctation repair (n)	0	1
Left pulmonary artery repair (n)	2	2

Abbreviations: ECC = extracardiac conduit; ILT = intra-atrial lateral tunnel. † Statistically significantly different from ILT.

In 35 patients (19 ILT, 16 ECC) 54 late procedures were performed after Fontan completion other than re-operations for Fontan failure (table 2). The Kaplan-Meier estimates of freedom from re-operation were (figure 1a): (1) ILT: 1 year 98% (SE 2%); 3 years 92% (SE 3%); 6 years 79% (SE 5%); (2) ECC: 1 year 94% (SE 3%); 3 years 82% (SE 4%); 6 years 79% (SE 5%) (log rank test p = 0.6).

Fontan failure

Thirty-day mortality was 4% (4 ILT, 5 ECC). Late mortality occurred in 10% (13 ILT, 5 ECC). Twelve patients required a re-operation of the Fontan circulation (2 ILT, 10 ECC). These included seven early interventions, one of who died shortly after re-operation: creation or enlargement of a fenestration (n = 3), shortening of the ECC for distortion (n = 1), stenting of the superior caval vein for obstruction (n = 1), ECC replacement and fenestration for thrombosis of the conduit (n = 1), and extracorporeal membrane oxygenation for severe pulmonary hypertension (n = 1). Two

Table 3. Pre-Fontan variables

Variable	ILT		ECC	
Pre-Fontan procedures				
Modified BT-shunt (n)	34		19 †	
Central shunt (n)	6		17 †	
Pulmonary artery banding (n)	26		24	
Atrioseptectomy	26		37	
Norwood (BT-shunt/RV-PA conduit) (n)	15	(10/4)	32	(25/7)†
Systemic atrioventricular valve repair (n)	2		3	
Branch pulmonary artery repair (n)	19		25	
Pacemaker implantation (n)	1		5	
Age at BDG (years)	0.9	(0.6-1.8)	0.7	(0.5-1.3)
Interval between BDG and TCPC (years)	1.8	(1.3-2.4)	2.2	(1.7-3.0)
Pre-Fontan hemodynamics/cardiac function				
End-diastolic pressure (mm Hg)	9.0	(8.0-11.0)	9.4	(8.0-12.0)
Mean pulmonary artery pressure (mm Hg)	11.2	(10.0-13.0)	11.0	(9.0-12.0)
Mildly/moderately impaired ventricular function (n)	14		11	
Moderate/severe AV valve insufficiency (n)	12		13	
Sinus rhythm (n)	87		84	
Room-air oxygen saturation (%)	83	(79-87)	83	(79-85)

Abbreviations: AV = atrioventricular; BDG = bidirectional Glenn anastomosis; BT = Blalock-Taussig; ECC = extracardiac conduit; ILT = intra-atrial lateral tunnel; RV-PA = right ventricle to pulmonary artery; TCPC = total cavopulmonary connection. † Statistically significantly different from ILT.

Table 4. Characteristics of the Fontan completion

Variable	ILT		ECC		
Age at TCPC (years)	3.0	(2.5-3.9)	3.2	(2.5-4.1)	
Weight at TCPC (kg)	14.0	(12.1-15.9)	14.0	(12.2-15.8)	
Cardiopulmonary bypass time (minutes)	107	(90-138)	141	(97-204)	†
Aortic cross-clamp time (minutes)	61	(49-74)	42	(19-62)	†; n = 26
Minimal temperature (°C)	28	(26-29)	31	(28-32)	†
Chest tube drainage (days)	11	(7-18)	13	(8-22)	
Intensive care unit stay (days)	6	(3-12)	4	(2-7)	†
Total hospital stay (days)	17	(12-27)	21	(14-32)	
Concomitant procedures at TCPC					
Branch pulmonary artery repair (n)	8		12		
Atrioventricular valve repair (n)	5		4		
Relief of subaortic obstruction (n)	4		1		
Fenestration (n)	19		15		

Abbreviations: ECC = extracardiac conduit; ILT = intra-atrial lateral tunnel; TCPC = total cavopulmonary connection. † Statistically significantly different from ILT.

patients with thrombosis in the Fontan circulation and pulmonary hypertension were treated with sildenafil post-operatively. In five patients the ECC had to be revised or replaced during follow-up 0.3 to 9.5 years after Fontan completion. Four of these were 16 mm conduits that are not being used nowadays. The Kaplan-Meier estimates for freedom from Fontan failure were (figure 1b): (1) ILT: 1 year 86% (SE 4%); 3 year 85% (SE 4%); 6 year 83% (SE 4%); (2) ECC: 1 year 88% (SE 3%); 3 year 88% (SE 3%); 6 year 79% (SE 6%) (log rank test p = 0.93). Table 5 shows the variables identified as risk factors for Fontan failure by univariable Cox regression analysis. In a multivariable model intensive care unit stay and total cardiopulmonary bypass time were statistically significant predictors of Fontan failure, however both hazard ratios were only minimally over 1.0.

Table 5. Predictors of Fontan failure

Risk factor	Hazard Ratio	95% CI	p-value
Univariable			
Right ventricular morphology	2.5	1.2 – 5.4	0.014
Pre-Fontan moderate/severe AVV insufficiency	2.4	1.0 – 5.7	0.05
Total CPB time	1.009	1.005 – 1.012	<0.001
Intensive care unit stay	1.04	1.02 – 1.06	<0.001
Multivariable			
intensive care unit stay	1.04	1.02 – 1.06	<0.001
Total CPB time	1.008	1.005 – 1.012	<0.001

Abbreviations: AVV = atrioventricular valve; CPB = cardiopulmonary bypass.

Table 6. Predictors of arrhythmias

Risk factor	Hazard Ratio	95% CI	p-value
Univariable			
Right ventricular morphology	3.5	1.3 – 9.3	0.011
ILT	5.1	0.97 – 27	0.054
Pre-Fontan AVV repair	5.5	1.2 – 24.7	0.028
Pre-Fontan moderate/severe AVV insufficiency	2.3	0.8 – 7.1	0.135
Multivariable			
Right ventricular morphology	4.3	1.5 – 11.9	0.006

Abbreviations: AVV = atrioventricular valve; ILT = intra-atrial lateral tunnel.

Arrhythmias

Early post-operative arrhythmias occurred in fifteen patients (twelve ILT, three ECC). Six patients received a (temporary) pacemaker for bradyarrhythmias, nine patients experienced tachyarrhythmias. Late arrhythmias occurred in sixteen patients (thirteen ILT, three ECC). New atrial tachyarrhythmias were documented in six patients, two of who were on anti-arrhythmic medication at last follow-up. Two patients received a pacemaker. One patient had ventricular fibrillation and died. Bradyarrhythmias were diagnosed in nine patients, six of who received a pacemaker. The Kaplan Meier estimates of freedom from arrhythmias were (figure 1c): (1) ILT, 1 year 87% (SE 4%); 3 years 87% (SE 4%); 6 years 83% (SE 4%); (2) ECC, 1 year 96% (SE 2%); 3 years 96% (SE 2%); 6 years 92% (SE 4%) (log rank test p = 0.022). In a multivariable model right ventricular morphology was a predictor for arrhythmias (table 6).

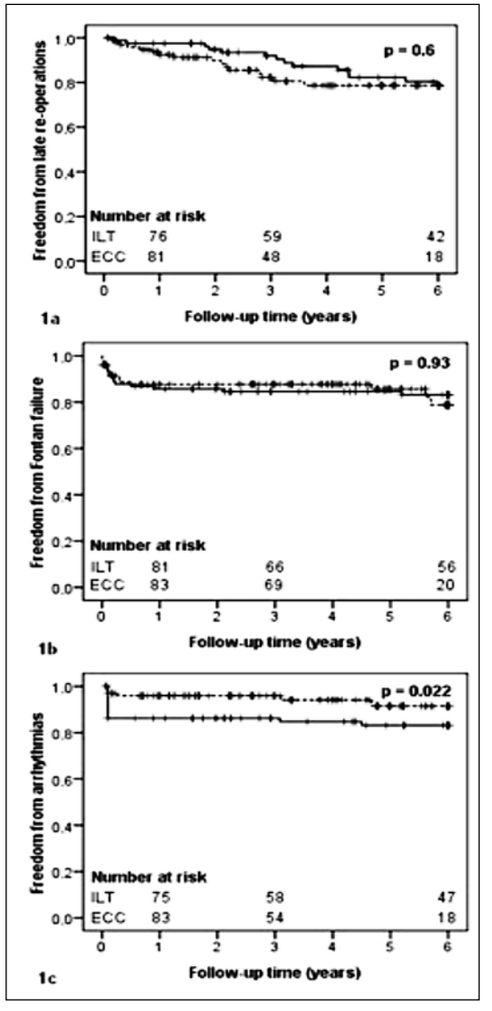

Figure 1. Kaplan-Meier estimates of freedom from late re-operation (A), freedom from Fontan failure (B), and freedom from arrhythmias (C). The straight line represents the intra-atrial lateral tunnel; the dotted line represents the extracardiac conduit. The hatch marks on each curve represent the patients censored at end of follow-up.

Thrombo-embolic events

Early thrombo-embolic complications occurred in thirteen patients (five ILT, nine ECC), five of who were on routine anticoagulation after TCPC. These included thrombosis of the ECC (n = 3), or ILT (n = 1), branch pulmonary arteries (n = 2), inferior caval vein/hepatic veins (n = 2); pulmonary embolisms (n = 2), and cerebrovascular accidents (n = 3). Late thrombo-embolic events occurred

in three patients (two ILT, one ECC), 0.2-10.1 years after Fontan completion: complete thrombosis of the 16 mm Vascutek ECC 4 months after Fontan operation; multiple pulmonary embolisms and veno-occlusive disease; and a transient ischemic attack. The first patient was on platelet aggregation inhibition; the latter two patients were on oral anticoagulation. Evaluation of hemostasis did not reveal any abnormalities.

Clinical status at last follow-up

Median room air oxygen saturation was 95% (92-97). Echocardiographic or angiographic evidence of persistent right-to-left connections was present in 29 patients: in 25 patients (21 ILT (8 after fenestrated Fontan), 4 ECC; $p < 0.001$) there was a connection through the intra-atrial baffle; in four patients (one ILT, three ECC) there were veno-venous collaterals.

Rhythm status is displayed in table 2 and was available in 171 patients (97%). Sinus rhythm was present in 70%, thirteen (8%) patients had a pacemaker. Atrial rhythm was present in 22%, and only two patients had a junctional rhythm (1%). A summary of the medication used is displayed in table 2. The difference in anti-platelet and anti-coagulant therapy between the ILT and ECC group is explained by the fact that two institutions are performing ECC Fontan operations nowadays and prefer platelet aggregation inhibition at least during childhood. The third institution performs ILT Fontan operations and prefers oral anticoagulants as antithrombotic prophylaxis. One patient was on sildenafil therapy for pulmonary hypertension.

Echocardiography at most recent follow-up was available in 158 patients (89%) (table 2). Global ventricular function was moderately or severely reduced in 23% of patients, the majority having had an ILT. Moderate or severe atrioventricular valve insufficiency was present in 12% of patients and moderate or severe (neo-)aortic insufficiency in 6% of patients.

Discussion

In this paper, we describe a cohort of Fontan patients who were all operated on according to current techniques; i.e. TCPC preceded by BDG. Shortly after De Leval's publication on the ILT [1], Marcelletti and coworkers reported on the use of the ECC for completion of the TCPC [2]. The latter technique was proposed for patients with complex anomalies of the atrioventricular valve, and the pulmonary or systemic venous return. Advantages of the ECC are the possibility to perform the Fontan completion without aortic cross-clamping, and possible reduction of the incidence of arrhythmias compared to the ILT. However, there are concerns on the incidence of thromboembolic complications and late re-operations. In this study, we compared the outcome between 102 patients with an ILT and 107 patients with an ECC.

Fontan failure

Thirty-day mortality was 4% in this cohort and late mortality was 10%. At six years of follow-up there was no significant difference in Fontan failure between the ILT and the ECC (figure 1b). We identified two risk factors for Fontan failure with multivariable Cox regression analysis; intensive care stay and total cardiopulmonary bypass time. The hazard ratios of intensive care stay and total cardiopulmonary bypass time were only marginally over 1.0. Both variables were not strong predictors of Fontan failure in this study. Others have identified right ventricular morphology as a risk factor for early mortality [13] and Anderson et al. recently demonstrated that right ventricular morphology is associated with poorer mid-term ventricular and valvular function [14]. However, we recently reported preserved contractile reserve with low-dose dobutamine stress-testing in patients with a dominant right ventricle at a median follow up time of 8.1 years after TCPC [15].

Re-operations for Fontan failure were more frequent in the ECC-group. Most of the late re-operations included replacement of conduits with a diameter of 16 mm, which are not being used nowadays. Excluding these patients from the analysis, resulted in a non-significant comparison of re-operations between the ILT-group and ECC-group. Recently, Lee et al. [16] showed that even at only three years of follow-up, extracardiac conduit diameter decreased with about 14% irrespective of the original conduit diameter. The ideal conduit diameter still has to be assessed at long-term follow-up.

Arrhythmias

Early and late arrhythmias occurred in 7% and 9% of patients respectively. Freedom from arrhythmias was significantly higher in patients with an ECC, analyzed up to six years after Fontan completion. In our study, right ventricular morphology was identified as a risk factor for arrhythmias in a multivariable model.

The incidence of late arrhythmias in our study is slightly lower than in a large cohort from the Pediatric Heart Network [17], but the North-American cohort also included some patients with an atriopulmonary connection. In comparison with the atriopulmonary connection, the incidence of atrial arrhythmias is lower in patients with an ILT [5,18], but can still run up to 20% during follow-up [7,19]. In patients with an ECC, the incidence of arrhythmias has been reported up to 15%, at a follow-up duration of fifteen years [20,21]. There are only a few studies comparing the incidence of arrhythmias in ILT and ECC-groups [10-12]. Fiore et al. did not find any difference in arrhythmias between their ILT and ECC group. In the study by Kumar et al. sinus node dysfunction occurred more frequently in patients with an ECC [12]. They concluded that staging with a BDG, as opposed to performing a hemi-Fontan, was a risk factor for developing sinus node dysfunction. Azakie et al. identified the ILT as a risk factor for mid-term arrhythmias (up to six years of follow-up) and found a higher incidence of atrial rhythm in the ILT group [11]. In our cohort after staging

with a BDG, there was a clear difference in the incidence of arrhythmias, with a low incidence of 3% in the ECC-group up to six years after TCPC. However, in a multivariable model corrected for year of Fontan operation, the ILT was not identified as a risk factor for arrhythmias. Possibly, in our study, evolution of operation techniques was an important factor in the incidence of arrhythmias throughout follow-up.

At most recent follow-up, the majority of our patients was in sinus rhythm, with comparable proportions in the ILT and ECC- groups, and a comparable percentage to other reports [14]. Surprisingly, more patients in the ECC-group had an atrial rhythm. This difference could not be explained by a differences in atrioseptectomies or staging procedures between the two groups. The above mentioned studies do not show a superiority of one Fontan modification over the other in the incidence of arrhythmias. However, different studies use different definitions of arrhythmias and all studies have been retrospective. This underlines the need for longer follow-up to study the incidence of arrhythmia and preservation of sinus rhythm using uniform definitions.

Thrombo-embolic events

In theory, the ECC can be a risk factor for the development of thrombo-embolisms. In our study, as in other reports [20,21], there was no difference in the incidence of thrombo-embolic events between the ILT and ECC group. The incidence of early events was 6%, late incidence was only 2%. This is considerably lower than earlier studies that reported incidences of up to 20% [22-24].

There is still much debate on the appropriate antithrombotic therapy after Fontan operation. In our study, two institutions preferred platelet aggregation inhibition at least during childhood, with oral anticoagulants in selected cases. The third institution preferred oral anticoagulant therapy as the standard. Up until now, neither of these two options has proven to be superior to the other in the prevention of late thrombo-embolic events [23,24]. Seipelt et al. recommended the use of anticoagulants in the early follow-up, since they saw a peak incidence of thrombo-embolisms in the first post-operative year [23]. Although there were more early thrombo-embolic complications in our study than late complications, the preventive effect of anticoagulants was not evident.

Cardiac functional status at last follow-up

A considerable proportion of patients (23%) had moderately or severely reduced ventricular function as assessed with conventional echocardiography. The majority of these patients had an ILT and a longer follow-up time than the patients with an ECC. In a recent large cohort from the Pediatric Heart Network [14], average ejection fraction was preserved even in patients over fifteen years of age and ten years after Fontan completion. However, from these data one can also calculate that 25% of patients had an ejection fraction <50% and diastolic dysfunction was present

in >70% of patients. Deterioration of systolic and diastolic ventricular function is an important complication that is inherent to both the underlying cardiac anatomy and to Fontan physiology. In addition, we recently reported reduced preload at rest and during stress [15], which is an important limiting factor in this process and should be the target of therapeutic interventions for preservation of adequate ventricular function on the long term.

Study limitations

This study is limited by its retrospective nature. Operations took place from 1990 to 2008, leading to differences in peri- and post-operative care throughout time. We corrected for this time-related bias by including year of Fontan completion in the multivariable analyses. Exclusion of patients with a Kawashima-type operation for abnormal systemic venous return in patients with heterotaxy might have influenced our outcome, since others have identified heterotaxy as a risk factor [9,25]. Currently, MRI is the technique of choice for prospective evaluation of the single ventricular circulation. For logistic reasons this technique was not available to all patients in this study, as has been the case in other recent cohort studies [14].

Conclusions

Outcome after staged ILT and ECC-type Fontan operations is good, with comparable freedom from late re-operations and freedom from Fontan failure at 6 year follow-up. The incidence of arrhythmias was significantly lower in the ECC-group. Right ventricular morphology was identified as a risk factor for arrhythmias.

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Chapter 3

Clinical outcome 5 to 18 years after Fontan operation under 5 years of age

Daniëlle Robbers-Visser, MD[a, b]; Livia Kapusta, MD, PhD[c]; Lennie van Osch-Gevers, MD, PhD[a]; Jan L.M. Strengers, MD, PhD[d]; Eric Boersma, PhD[e]; Yolanda B. de Rijke, PhD[f]; Frans Boomsma, PhD[g]; Ad J.J.C. Bogers, MD, PhD[h]; Willem A. Helbing, MD, PhD [a, b]

[a] Department of Pediatrics, Division of Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

[c] Children's Heart Center, UMC St Radboud, Nijmegen, the Netherlands

[d] Department of Pediatric Cardiology, University MC Utrecht – Wilhelmina Children's Hospital, Utrecht, the Netherlands

[e] Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands

[f] Department of Clinical Chemistry, Erasmus MC, Rotterdam, the Netherlands

[g] Department of Internal Medicine, Erasmus MC, Rotterdam, the Netherlands

[h] Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, the Netherlands

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Abstract

Objective: to assess the clinical condition at mid-term follow-up after total cavopulmonary connection for a functionally univentricular heart under five years of age.

Methods: 34 patients (median age 10.4 (range 6.8-20.7) years; 22 boys; median follow-up time 7.8 (5.0-17.8) years) underwent electrocardiography, Holter monitoring, bicycle exercise-testing, cardiac magnetic resonance imaging, and NT-pro-BNP analysis.

Results: 23 (68%) patients were in sinus rhythm. Holter monitoring demonstrated normal mean heart rate, low maximal heart rate, and no clinically significant arrhythmias, or sinus node dysfunction. With maximal bicycle ergometry (n = 19), maximum workload (60% of normal), maximum heart rate (90% of normal), and VO2max (69% of normal) were all significantly lower in Fontan patients compared to controls ($p < 0.001$). Variables of submaximal exercise indicated less efficient oxygen uptake during exercise in all Fontan patients. Ejection fraction was lower than in controls (59 (13)% vs 69 (5)%, $p<0.001$). Mean end-diastolic volumes, end-systolic volumes and ventricular mass were higher compared to controls ($p<0.001$). Mean values of NT-pro-BNP were increased compared to normal values, but only 8 patients had NT-pro-BNP levels above the upper limit of normal.

Conclusions: mid-term after Fontan operation under five years of age, patients are in acceptable clinical condition with preserved global ventricular function, moderately decreased exercise capacity, and NT-pro-BNP levels within the normal range. However, systemic ventricular mass is elevated after Fontan operation, pointing towards contractility-afterload mismatch. The long-term consequences of this phenomenon for ventricular function need further investigation.

Introduction

The Fontan operation is a palliative procedure for patients in whom their congenital heart defect precludes biventricular repair. Nowadays, it is performed as a staged procedure resulting in re-direction of the systemic venous return to the pulmonary circulation, without interposition of a subpulmonary ventricle. There have been important modifications of the original concept, aimed at improving systemic venous and pulmonary artery hemodynamics, and preventing late sequelae [1]. Currently, total cavopulmonary connection (TCPC), with either an intra-atrial lateral tunnel or an extracardiac conduit to connect the inferior caval vein to the pulmonary artery, is the procedure of choice.

Morbidity and mortality have improved significantly in recent years [2]. However, information on mid-term and long-term outcome after Fontan operation according to current techniques is sparse, since these patients are only just reaching adolescence and adulthood. Although there are several reports on clinical outcome in Fontan patients [2-4] most of these retrospective studies include relatively heterogeneous patient groups, with heterogeneous treatment strategies. Hence, the results that are observed in these reports might not be applicable to patients who have their Fontan completion in the present era. Today's policy, for example, is to perform the TCPC at increasingly younger ages.

The objective of this study was to assess clinical condition in a cohort of patients from five years after TCPC at young age, i.e. Fontan completion ≤ five years of age. For this purpose, we performed electrocardiography, bicycle exercise-testing, assessment of ventricular function with magnetic resonance imaging (MRI), and assessment of NT-pro-BNP. The latter is known to identify pediatric patients with cardiac disease, and closely correlates to ventricular function [5].

Materials and Methods

Patients

A cross-sectional study of patients after Fontan completion was performed. The following inclusion criteria were used: 1) patients after initial Fontan completion (TCPC), operated on between 1988 and 2001, who were seen for regular follow-up at three tertiary pediatric referral centers, 2) age at Fontan completion ≤ five years, 3) duration of follow-up since Fontan completion ≥ five years. Exclusion criteria were: 1) contra-indications for MRI or bicycle exercise testing, 2) inadequate communication, either because of mental retardation or because of a language barrier. Medical records were reviewed for patient characteristics, anatomical, and operative details. The study was approved by the Dutch Central Committee on Research involving Human Subjects and institutional review boards. All subjects and/or their parents (if required) gave informed consent.

Electrocardiography

A standardized 12-lead electrocardiogram was obtained in all patients to obtain rhythm status, QRS duration (ms), and QT-interval corrected for heart rate (QTc (ms)). A 24-hour Holter monitoring was performed in all patients on a day with usual activities.

Bicycle exercise-testing

A Jaëger Oxycon Champion System (Viasys Healthcare, Hoechberg, Germany), allowing breath-by-breath ergometry, was used for maximal exercise testing. Subjects were continuously monitored with a 12-lead electrocardiogram and blood pressure measurements. Workload increased stepwise with 10-20 Watts/minute. For bicycle exercise testing, a group of 32 gender- and height-matched controls was selected. Patients and controls were encouraged to perform until exhaustion, defined as a respiratory quotient (RQ) at peak exercise of ≥ 1.05. Twenty-eight controls and nineteen Fontan patients managed to perform until RQ ≥ 1.05. Eight patients with a submaximal exercise test did have a RQ ≥ 1.00. The patients with a RQ < 1.05 were younger than the patients with a RQ ≥ 1.05 (10.0 (2.5) years vs. 13.2 (3.7) years; p = 0.011). In the control group subjects with a RQ < 1.05 were also younger than subjects with a RQ ≥ 1.05 (8.9 (0.8) years vs. 12.7 (3.4) years, p < 0.001).

In all patients and controls, two variables of submaximal exercise were assessed: 1) the slope of oxygen uptake versus exercise intensity according to the method of Reybrouck et al [6]; 2) the oxygen-uptake efficiency slope (OUES) according to the method of Baba et al., i.e. the linear relation between log VE and VO2 [7]. These two variables are a measure of the efficiency of the system to extract oxygen during exercise and use in the periphery. A higher slope indicates a more efficient oxygen uptake. Since Giardini et al. recently reported non-linearity of the relation between log VE and VO2 throughout the exercise test for hypoxemic Fontan patients [8], we first validated the linearity of this relation in patients who performed a maximal exercise test. Maximum workload (Watts), maximum heart rate (beats per minute) and maximum oxygen consumption (VO2max in ml/kg/min) were obtained in patients and controls with a RQ ≥ 1.05.

MRI

Cardiac MRI was performed in all patients on a Signa 1.5 Tesla whole-body MRI system (General Electric, Milwaukee, WI, USA). Dedicated phased-array cardiac surface coils were placed over the thorax. Patients were monitored by vector cardiogram gating and blood pressure monitoring.

A multi-phase, multi-slice volumetric data set was acquired using a fast 2-dimensional cine scan employing steady-state free precession. Ten to twelve contiguous slices were planned parallel to the atrioventricular valve plane of the systemic ventricle to cover the heart from base to apex. Imaging parameters: slice thickness 7 to 10 mm, inter-slice gap 0 mm, field of view 280-370 mm, phase field of view 0.75, matrix 160 x 128 mm, repetition time 3.5 ms, echo time 1.5

ms, flip angle 45°, mean in-plane resolution 2 mm^2. All images were acquired without breath-hold and built up during multiple heartbeats to eliminate the effects of respiration on caval vein and pulmonary artery flow dynamics, using three signal-averages.

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA). The ventricular volumetric data set was quantitatively analyzed using the AW 5.1 version of the MR Analytical Software System (Medis Medical Imaging Systems, Leiden, the Netherlands). Using manual detection of endocardial and epicardial borders in end-systole and end-diastole, the following parameters were calculated: end-diastolic and end-systolic volume indexed for body surface area (EDVI and ESVI respectively), stroke volume index (SVI), ejection fraction (EF), and mass index of the systemic ventricle. Ventricular volumes and mass were defined as the sum of the volumes and mass of the systemic ventricle and a hypoplastic chamber, if present. Data were compared with reference data from 60 healthy children, aged 8-17 years [9].

NT-pro-BNP analysis

Blood samples were taken from a peripheral vein after 30 minutes rest in supine position. Plasma and serum were separated immediately after sample collection and stored at -80°C. NT-pro-BNP was measured with the Elecsys electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). We preferred the determination of NT-pro-BNP for its stability in whole blood, its independency of exercise and position, and its longer half-life in serum than BNP [10]. Data were compared to reference data from a study using an identical analysis method [10, 11]. Expected mean values were calculated according to the equation: NT-pro-BNP = -0.3707*age + 12.346 [10]. The upper limit of normal was defined as the 97.5th percentile from the study of Albers et al [11].

Statistical analysis

Continuous data were tested for normality using the Kolmogorov-Smirnov test. Values of NT-pro-BNP were log10-transformed to obtain approximately normal distribution. Data with a normal distribution are expressed as mean value ± one standard deviation (SD), whereas the median (range) is shown for data with a non-normal distribution. Differences in continuous data between groups of patients were evaluated by Student's T-test or non-parametric tests in case of small subgroups. Dichotomous data are presented as counts and percentages, and differences between groups of patients were evaluated by chi-square tests or Fischer's exact tests, as appropriate.

Univariable regression analyses were performed to study the interrelation of NT-pro-BNP with 1) demographic variables, 2) measures of systemic ventricular function, and volumes acquired with CMR imaging, and 3) physical exercise response, and to study the interrelation of ventricular mass and EF.

Analyses were performed using the SPSS-PC statistical software package version 14.0 (SPSS, Chicago, Ill, USA). A p-value < 0.05 (two-sided test) was considered to indicate statistical significance.

Results

Patients

We identified 100 patients who had undergone a TCPC in the period between 1988-2001 and were alive at the start of the study. The following patients were excluded: 1) 23 patients with Fontan completion at age > five years; 2) eight patients with a pacemaker; 3) five patients with hemi- or quadriplegia; 4) ten patients for inadequate communication. Of 54 eligible patients, 34 patients (22 boys) participated in this study. There was no difference between participants and non-responders in patient, procedural, and follow-up characteristics.

Median age was 10.4 (6.8-22.2) years. Mean age at Fontan completion was 3.0 (1.1) years, median weight 13.9 (8.9-22.0) kg. Median follow-up time after Fontan completion was 7.8 (5.0-17.1) years. Twenty-seven patients had an intra-atrial lateral tunnel, seven patients had an extracardiac conduit. The majority of patients (n = 28; 82%) had had staged procedures, with a bidirectional Glenn anastomosis before completion of the Fontan circulation at a median age of 1.0 (0.2-3.8) years. Median interval between bidirectional Glenn and Fontan completion was 1.7 (0.5-3.3) years. Four patients had a fenestrated TCPC on hemodynamic indications. In one patient, the fenestration closed spontaneously, one other patient underwent catheter-based closure of the fenestration.

The dominant ventricle was of right ventricular (RV) morphology in sixteen patients, six of who had hypoplastic left heart syndrome. The dominant ventricle was of left ventricular (LV) morphology in seventeen patients, seven of who had tricuspid atresia. In one patient ventricular morphology could not be determined. There was one patient with right isomerism, and one patient with left isomerism, with normal systemic venous connections.

The majority of patients (n = 21) had a normal resting oxygen saturation ≥ 95%; ten patients were mildly hypoxemic (oxygen saturation between 90-94%). Three patients had oxygen saturations below 90%; two after a fenestrated intra-atrial lateral tunnel, the other patient had a baffle leak after unfenestrated Fontan. The New York University pediatric heart failure index [12] was between 4 and 9 in this patient group (score of 0 meaning no heart failure, score of 30 meaning severe heart failure). Five patients were taking ACE inhibitors, and no patients were on diuretics or anti-arrhythmic medication.

Electrocardiography

Twenty-three patients were in sinus rhythm. Nine patients had a supraventricular rhythm, and in two patients the rhythm was of atrioventricular nodal origin. Mean QRS duration was 100 (13) ms. Mean QTc duration was 419 (26) ms. There was no difference in QRS duration and QTc duration between patients with a dominant RV and dominant LV.

None of the patients experienced any complaints during 24-hour Holter monitoring. Thirty patients showed sinus rhythm, with frequent episodes of supraventricular rhythm in two patients, and occasional episodes of supraventricular rhythm in twelve patients. Two patients had occasional episodes with a junctional rhythm. Mean heart rate was 79 (12) beats per minute. Mean maximum heart rate was 168 (SD 18; range 128-200) beats per minute; mean minimum heart rate was 46 (SD 9; range 33-67) beats per minute. There was no difference between patients with a lateral tunnel and patients with an extracardiac conduit (table 1). There were no cardiac pauses of more than 1.9 seconds. Only one patient (age 17 years; 16 years after Fontan completion for hypoplastic left heart syndrome) experienced frequent premature atrial contractions. Shortly after the investigations for this study, he presented with atrial flutter.

Table 1. Comparison of outcome variables in different Fontan types

Variable	ILT		ECC		p-value
Age (years)	10.3	(6.8-20.7)	10.3	(8.0-14.1)	NS
Age at Fontan completion (years)	2.9	(1.0-5.0)	2.8	(2.3-4.1)	NS
Follow-up time (years)	7.7	(5.0-17.1)	7.9	(5.2-10.0)	NS
Oxygen saturation at rest (%)	95	(87-100)	97	(95-98)	NS
Systolic blood pressure at rest (mm Hg)	110	(7)	133	(9)	0.013
Diastolic blood pressure at rest (mm Hg)	77	(15)	73	(6)	NS
NT-pro-BNP (pmol/l)	13	(3-57)	7	(4-37)	0.006
OUES	1.55	(0.52)	1.66	(0.37)	NS
O_2 uptake - exercise intensity slope	8.8	(1.3)	10.0	(1.2)	NS
EDVI (ml/m^2)	78	(15)	79	(16)	NS
ESVI (ml/m^2)	36	(17)	24	(6)	NS
Mass (gr/m^2)	70	(16)	73	(7)	NS
EF (%)	56	(14)	69	(4)	0.019
Mean heart rate (beats per minute)	77	(13)	79	(14)	NS
Maximum heart rate (beats per minute)	161	(16)	175	(9)	NS
Minimum heart rate (beats per minute)	46	(10)	47	(8)	NS

Abbreviations: ECC = extra-cardiac conduit; EDVI = end-diastolic volume indexed for body surface area; EF = ejection fraction; ILT = intra-atrial lateral tunnel; OUES = oxygen-uptake efficiency slope.

Bicycle exercise-testing

Bicycle exercise-testing was successfully performed in 32 patients and all controls. One patient (aged 6.8 years, height 117 cm) was too small for our ergometer. Breath-by-breath analysis failed because of a technical problem in the other patient.

When compared to the control group (n =28), Fontan patients (n = 19) reached a lower maximum workload (60% of controls; 146 (61) vs. 87 (30) Watts, or 3.2 (0.6) vs. 2.1 (0.5) Watts/kg, $p < 0.001$), and lower maximum heart rate (90% of controls; 184 (12) vs. 166 (15) beats per minute, $p = 0.001$). VO2max was significantly lower in Fontan patients (69% of controls; 48 (7) vs. 33 (8) ml/min/kg, $p < 0.001$).

In patients who performed a maximal exercise test (n = 19), there was no difference between OUES for the entire exercise test, and OUES during the second half of the test (1.57 (0.38) and 1.50 (0.57) respectively; $p = 0.38$). OUES during the first half of the test (1.46 (0.38)) was lower than OUES of the entire test ($p = 0.046$). In hypoxemic patients, this comparison of OUES yielded the same results. The relation between log VE and VO2 was not considered linear, but OUES of the second half of the test was considered to be representative of the OUES of the complete test.

Both variables of submaximal exercise were higher in controls (n = 32) than in patients (n = 32): 1) the OUES was 2.00 (0.66) in controls, and 1.50 (0.44) in patients ($p = 0.002$); 2) the slope of oxygen uptake versus exercise intensity was 9.7 (0.9) in controls, and 8.9 (1.3) in Fontan patients ($p = 0.004$).

There was no difference in variables of maximal exercise (eight RV, ten LV) and submaximal exercise (fourteen RV, seventeen LV) between patients with a dominant RV and patients with a dominant LV. There were also no differences between different Fontan types.

MRI

Mean EDVI was 77 (16) ml/m^2, mean ESVI was 33 (14) ml/m^2, mean EF was 59 (12) %, and mean mass was 71 (19) g/m^2. EF tended to be lower in patients with a dominant RV, when compared to patients with a dominant LV (RV EF 54 (14) %, LV EF 64 (9) %, $p = 0.053$). EF was significantly higher in the patients with an extracardiac conduit (table 1). There was no difference in volumes and mass between RV and LV morphology. RV ESVI tended to be higher than LV ESVI, but this difference was not statistically significant ($p = 0.17$).

When compared to reference data for ventricular volumes, and mass [9], end-diastolic volume (96 (35) ml vs. 87 (31) ml, $p = 0.017$), end-systolic volume (41 (26) ml vs. 24 (11) ml, $p < 0.001$) and systemic ventricular mass (91 (48) g vs. 72 (33) g, $p < 0.001$) were higher in patients than in the reference population. EF was lower in patients than in controls (systemic ventricle EF 59 (12) % vs. LV EF 69 (5) %, $p < 0.001$). In patients, the higher the mass was, the poorer was the EF ($p = 0.027$; $\beta = -0.11$).

NT-pro-BNP

Blood sample collection was successful in 28 patients. Median level of NT-pro-BNP was 11.5 (2.9-57.0) pmol/l. Compared to reference studies for NT-pro-BNP using an identical analysis method [10, 11], mean NT-pro-BNP levels were higher than to be expected from these normative data (mean NT-pro-BNP in Fontan patients 18.0 (15.2) pmol/l, expected mean NT-pro-BNP 8.1 (1.4) pmol/l, p = 0.002). Eight Fontan patients (29%) had an NT-pro-BNP level above the upper limit of normal (seven lateral tunnel TCPC, one extracardiac conduit TCPC). Age and follow-up time of these eight patients did not differ from age and follow-up time of the patients with NT-pro-BNP within the normal range. There was no difference in exercise response (maximum workload, maximum heart rate, VO2max, OUES, oxygen uptake versus exercise intensity slope), or systemic ventricular volumes, function, and mass between patients with NT-pro-BNP above the 97.5th percentile and the remaining group.

NT-pro-BNP levels did not differ between patients with a dominant RV and patients with a dominant LV. NT-pro-BNP was lower in patients with an extracardiac conduit (table 1). Univariable regression analysis did not identify a significant relation between NT-pro-BNP and age, follow-up time, variables of exercise testing (heart rate increase, maximum workload, VO2max, OUES, or oxygen uptake versus exercise intensity slope), or MRI variables (EDVI, ESVI, EF, mass).

Discussion

The results of this study show acceptable clinical condition in a patient group five to eighteen years after Fontan completion under five years of age. In this patient cohort all patients had a TCPC, and therefore this study group is representative of the current treatment policy.

In our study, 68% of patients were in sinus rhythm and no patients were on anti-arrhythmic medication. Only one patient experienced frequent premature atrial contractions (and presented with atrial flutter shortly after this investigation), and no patients showed signs of clinically relevant sinus node dysfunction. Although patients with a pacemaker were excluded in this study, they comprised only 7% of the complete cohort. The prevalence of arrhythmias after Fontan operation varies with the type of modification. Several groups identified the atriopulmonary connection as a risk factor [2, 13] with a prevalence of atrial tachyarrhythmias at long-term follow-up of 29% in these patients [13]. Prevalence of atrial tachyarrhythmias in lateral tunnel type TCPC is about 15-20% at mid- to long-term follow-up [2, 4, 13]. Although, in theory, atrial tachyarrhythmias should be less frequent in extracardiac conduit TCPC, prevalence has been reported to be up to 11% in a large cohort at mid-term follow-up [3]. Other risk factors for developing atrial tachyarrhythmias are older age at Fontan completion, longer duration of follow-up, and early post-operative atrial tachyarrhythmias [4, 13]. In this study, all patients underwent Fontan completion under five years of age, a possible explanation for the absence of arrhythmias in this study group. However, further follow-up is necessary to determine the prevalence of arrhythmias long-term after Fontan completion.

Although global ventricular function was good in this study, maximal exercise capacity was only 60% of normal. This is comparable to outcome of maximal exercise capacity in 166 Fontan patients in a recent study from the Pediatric Heart Network [14]. Maximal oxygen consumption and peak heart rate in this study and our study were also comparable. The cause for impaired exercise capacity can be of cardiac, pulmonary, or muscular origin. Recently, we demonstrated an impaired preload reserve and an inadequate reaction of the pulmonary vasculature in Fontan patients with magnetic resonance imaging combined with low-dose dobutamine stress-testing [15, 16]. The resultant inability to increase stroke volume with stress-testing could, in part, be responsible for the well known impaired exercise capacity. In contrast to others [17], we did not identify a difference in exercise capacity between patients with a dominant LV or RV, but subgroups were small.

The OUES and the oxygen uptake versus exercise intensity slope are two measures of submaximal exercise that integrate the contributions of the cardiovascular, pulmonary and muscular systems to exercise capacity. Because of their linearity, they are good indicators of maximal exercise capacity, even when maximal exercise is not possible or wanted. The OUES and oxygen uptake versus exercise intensity slope both indicate how effectively oxygen is extracted and utilized in the body [6, 7]. The steeper the slope, the better the cardiovascular, pulmonary, and muscular systems work during exercise. The results in this study indicated a decreased efficiency of the system to extract oxygen, as has been demonstrated by others in a small group of Fontan patients [8]. As in the study by Giardini and coworkers [8], the relation between log VE and VO2 was not linear throughout the exercise test, but only for the second half of the exercise test. Therefore, the OUES is not a good indicator of maximal exercise capacity in patients who manage to perform the exercise test only very shortly (which was not the case in our study). Giardini et al. hypothesized that hypoxemia might be the cause for this non-linear relationship [8].

There are a limited number of studies on global ventricular function, and volumes in patients after Fontan operation, as assessed with MRI. Recently, the Pediatric Heart Network [4] reported on a large cohort of children after Fontan operation. In this study, a subgroup of 161 children underwent MRI. Data in the Network study are not easily comparable to other data, since they were indexed to BSA1.3 and a reference group is lacking. Anderson et al. showed a decrease in end-diastolic volume with increasing age, and an increase in mass/volume ratio [4]. There was no increase in ventricular mass over time as assessed with MRI. Echocardiographic data in that study suggest that the end-systolic volume is relatively large compared to end-diastolic volume [4], which is in accordance with our findings. Eicken et al. reported normal volumes, normal mass, and decreased EF in patients ten years after Fontan completion (atriopulmonary connection, right atrium to RV conduit, or TCPC) [18]. After Fontan completion, dramatic changes in

ventricular geometry occur [19, 20]. In the early post-operative period, there is a decrease in ventricular dimensions and an inappropriate degree of ventricular hypertrophy. Although others have shown normalization of ventricular volumes and mass with increasing follow-up time [18, 20], we demonstrated higher end-diastolic volumes, higher end-systolic volumes, higher ventricular mass, and lower EF than in the control group. Our observations that the ventricle operates at an increased end-systolic volume with normal systolic blood pressure suggest that arterial elastance is increased. Recently, Senzaki et al. found a higher ventricular afterload in Fontan patients compared to patients with a two-ventricle circulation [21]. These observations support experimental data from Szabo et al., who demonstrated contractility-afterload mismatch in an animal model of the Fontan circulation [22]. Earlier, we demonstrated well-preserved contractility with stress-testing [15]. This might explain the increase in ventricular mass (and increase in mass/volume ratio compared to controls) we found in this group. As in patients with aortic valve stenosis, we found an inverse correlation of ventricular mass with EF [23]. In isolated aortic valve stenosis, increased LV mass predicts the presence of systolic dysfunction and heart failure, and LV hypertrophy as a reaction to increased afterload may be maladaptive rather than beneficial [23]. Penny et al. linked ventricular hypertrophy to diastolic dysfunction in Fontan patients, with evidence for the development of incoordinate ventricular relaxation [24]. The effects of increased ventricular mass and the effects of contractility-afterload mismatch on the long-term function of the single ventricle have to be investigated. Furthermore, together with the study by Senzaki et al. [21], the present study provides data that suggests further clinical trials are required to investigate the effects of long-term afterload reduction on systemic ventricular function in the Fontan circulation.

Several groups have investigated BNP or NT-pro-BNP levels at short-term to mid-term follow-up after Fontan operation [25-29]. In these studies, levels were increased compared to control groups, but there seemed to be low clinical value of BNP or NT-pro-BNP for diagnostic or prognostic purposes [27]. Only Hjortdal et al. found normalization of neurohormones late after Fontan operation [29]. Law et al. concluded that BNP could discriminate between patients with systemic ventricular failure (elevated BNP) and isolated cavopulmonary failure (BNP not elevated) [28]. Man and Cheung found a correlation between BNP and variables of diastolic function (the majority of patients had had an atriopulmonary connection) [25].

Under pathological conditions, production of BNP rises strongly in both atria and ventricles. In our study group systemic ventricular EDVI was only slightly higher than in the control group. Therefore, BNP release from ventricular myocardial stretch is not to be expected. In this study, the number of patients with an NT-pro-BNP level above the upper limit of normal was small, preventing us from proper analysis of NT-pro-BNP usefulness for risk stratification in Fontan patients.

Study limitations

This study is limited by the size and characteristics of the study group. Due to small numbers, comparisons between different Fontan types, or between different systemic ventricular morphologies should be made with caution. As in most studies in Fontan patients, the study group is heterogeneous and therefore conclusions might not be applicable to all categories of patients. This group is not a representative random sample of the entire TCPC population, since we have excluded patients with a pacemaker and patients with neurologic complications. This prevents us from making firm conclusions on the rhythm status of this patient group.

Conclusions

Mid-term after Fontan operation under five years of age, patients are in acceptable clinical condition with preserved global ventricular function, moderately decreased exercise capacity, and NT-pro-BNP levels within normal range. However, systemic ventricular mass is elevated after Fontan operation, pointing towards contractility-afterload mismatch. The long-term consequences of this phenomenon for ventricular function need further investigation.

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Chapter 4

Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after Fontan operation at young age

Daniëlle Robbers-Visser, MD[a, b]; Derk Jan ten Harkel, MD, PhD[a]; Livia Kapusta, MD, PhD[c]; Jan L.M Strengers, MD, PhD[d]; Michiel Dalinghaus, MD, PhD[a]; Folkert J. Meijboom, MD, PhD[e]; Peter M. Pattynama, MD, PhD[b]; Ad J.J.C. Bogers, MD, PhD[f]; Willem A. Helbing, MD, PhD[a, b]

[a] Department of Pediatric Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands
[b] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands
[c] Children's Heart Center, UMC St Radboud, Nijmegen, the Netherlands
[d] Department of Pediatric Cardiology, University MC Utrecht – Wilhelmina Children's Hospital, Utrecht, the Netherlands
[e] Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands
[f] Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, the Netherlands

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Abstract

Objective: to study factors leading to decreased global ventricular performance with stress after Fontan operation, the stress response of functionally univentricular hearts was assessed at rest and during low-dose dobutamine stress using cardiovascular magnetic resonance (CMR) imaging.

Methods: thirty-two patients after Fontan completion at young age were included (27 total cavopulmonary connection, 5 atriopulmonary connection, mean age 13.3 (range 7.5 – 22.2) years, 23 boys, median follow-up after Fontan operation 8.1 (range 5.2-17.8) years). A multiphase short axis stack of ten to twelve contiguous slices of the systemic ventricle was obtained at rest and during low-dose dobutamine stress CMR imaging (7.5 μg/kg/min maximum).

Results: with stress-testing, heart rate, ejection fraction (EF), and cardiac index increased adequately ($p < 0.001$). There was an abnormal decrease in end-diastolic volume and an adequate decrease in end-systolic volume ($p < 0.001$). Stroke volume did not change with stress-testing ($p = 0.15$). At rest dominant left ventricles had a higher EF than dominant right ventricles ($p = 0.01$), but this difference disappeared with stress-testing.

Conclusions: the functionally univentricular heart after Fontan completion at young age has an adequate increase in EF with beta-adrenergic stimulation. However, as a result of impaired preload with stress, only an increase in heart rate can increase cardiac output.

Introduction

It is well known that patients after Fontan operation have a diminished exercise capacity [1-4]. Impairment in preload reserve is thought to be an important factor contributing to this impairment, and has been demonstrated with exercise testing and invasive methods [1, 2, 5, 6]. A decrease in global ventricular function has been reported as another important determinant of the impaired exercise capacity in Fontan patients [7, 8]. Cardiovascular magnetic resonance (CMR) imaging has proved to be a valuable tool in the follow-up of patients with complex congenital heart disease and is the gold standard for assessing global ventricular function [9]. Furthermore, CMR has shown its ability to detect an abnormal ventricular stress response with physical or pharmacological stress-testing in patients with congenital heart disease [10, 11]. Global ventricular function and contractility at rest and with stress-testing have not been studied in patients at mid-term follow-up after Fontan operation at young age, operated on according to current treatment strategies. Therefore CMR imaging combined with low-dose dobutamine was used to study the effects of pharmacological stress on global ventricular function in patients mid-term after atriopulmonary or total cavopulmonary connection at young age.

Materials and Methods

Patients

A cross-sectional study of patients after Fontan completion was performed. The following inclusion criteria were used: 1) patients after initial Fontan completion, who were seen for regular follow-up at three tertiary referral centers, 2) age at Fontan completion ≤ seven years, 3) duration of follow-up since Fontan completion ≥ five years. Exclusion criteria: 1) contra-indications for CMR imaging, 2) mental retardation. Medical records were reviewed for patient characteristics, anatomical, and operative details. The study was approved by the Dutch Central Committee on Research involving Human Subjects and institutional review boards. All subjects and/or their parents (if required) gave informed consent.

MRI

A Signa 1.5 Tesla whole-body MR imaging system was used (General Electric, Milwaukee, WI, USA). Dedicated phased-array cardiac surface coils were placed over the thorax. Patients were monitored by vector cardiogram gating and blood pressure monitoring.

A multi-phase, multi-slice volumetric data set was acquired using a fast 2D cine scan employing steady-state free precession. Ten to twelve contiguous slices were planned parallel to the atrioventricular valve plane of the systemic ventricle to cover the heart from base to apex. Imaging parameters: slice thickness 7 to 10 mm, inter-slice gap 0 mm, field of view 280-370 mm, phase field of view 0.75, matrix 160 x 128 mm, repetition time 3.5 ms, echo time 1.5 ms, flip angle 45°, mean in-plane resolution 2 mm^2. All images were acquired without breath-hold and built up during multiple heartbeats to eliminate the effects of respiration on caval vein and pulmonary artery flow dynamics, using three signal-averages. Two short-axis stacks were obtained: during rest and during low-dose dobutamine stress.

For internal validation of ventricular stroke volume at rest and during stress, flow measurements were done in the ascending aorta with velocity-encoded phase-contrast imaging (2D fast spoiled gradient echo, repetition time =5-6 ms, echo time =3 ms, flip angle=20°, 7 mm slice thickness, 6 views/segment, scanning matrix of 256 *128, 3 signal-averages, no breath-hold). To evaluate the effect of dobutamine stress on systemic venous return index, flow measurements in both caval veins were done, using the flow imaging parameters specified. Duration of the total scan protocol was 60-75 minutes.

When the study protocol had been completed at rest, dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) was administered by continuous infusion into a large antecubital vein at 7.5 µg/kg/min. This dosage was chosen since it is known from studies in healthy children that important changes in systolic function, diastolic function, and afterload occur from 5 µg/kg/min, and that the incidence rate of adverse symptoms increases significantly from 10 µg/kg/min [12, 13]. When a steady state in heart rate and blood pressure had been obtained, a second short-axis stack and flow measurements were acquired using the imaging parameters specified above. Dobutamine infusion was lowered to 5 µg/kg/min if any of the following events occurred: a rise in heart rate, systolic, or diastolic blood pressure of more than 50%; or a decrease in heart rate, systolic, or diastolic blood pressure of more than 20%. The test was discontinued if the patient suffered significant discomfort.

Analysis was performed on a commercially available Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA). The ventricular volumetric data set was quantitatively analyzed using the AW 5.1 version of the MR Analytical Software System (Medis Medical Imaging Systems, Leiden, the Netherlands). Using manual detection of endocardial and epicardial borders in end-systole and end-diastole, the following parameters were calculated: end-diastolic and end-systolic volume indexed for body surface area (EDVI and ESVI respectively), stroke volume index (SVI), ejection fraction (EF), cardiac index and mass index of the systemic ventricle [14]. Ventricular volumes and mass were defined as the sum of the volumes and mass of the systemic ventricle and a hypoplastic chamber, if present. Flow images were quantitatively analyzed using the Flow analysis software package V3.1 (Medis Medical Imaging Systems, Leiden, the Netherlands).

Calculations

Stress response of the systemic ventricle was defined as the relative change in EDVI ((EDVIrest – $EDVI_{stress}$)/$EDVI_{rest}$ * 100%), and EF ((EF_{rest} – EF_{stress})/EF_{rest} * 100%) with stress-testing. To estimate the effect of low-dose dobutamine stress-testing on contractility and afterload, the following approximations were used: contractility ≈ mean arterial pressure / ESVI [15], and afterload ≈ mean arterial pressure / CI [16].

Echocardiography

For assessment of diastolic function at rest, systemic atrioventricular flow and pulmonary venous flow were obtained with conventional Doppler echocardiography on an iE33 echocardiography system (Philips Medical Systems, Bothell, WA, USA) or System Five model (GE/Vingmed Inc., Horton, Norway). Pulmonary venous flow was recorded in the orifice of the right upper pulmonary vein using the apical 4-chamber view, placing the sample volume within 1 cm of the venoatrial junction. We measured the peak velocity of the antegrade systolic wave and early diastolic wave, and the peak velocity of the late diastolic retrograde wave. Systemic atrioventricular flows were obtained with pulsed wave Doppler at the leaflet tips. We measured E and A wave velocities, and E to A wave (E/A) ratio. Patient data were compared to data of 152 healthy children from our department database (mean age 12 (range 8-18) years).

Statistical analysis

Results are expressed as frequencies, mean (standard deviation) or as median (range). Paired data analysis was performed using the paired t-test. Comparisons between two groups were performed using the student t-test or the Mann-Whitney U test when appropriate. Linear regression analysis was performed for comparison of ventricular SVI, and aortic SVI, and systemic venous return per cardiac cycle. Variability between ventricular SVI,aortic SVI, and systemic venous return per cardiac cycle was expressed relative to the ventricular SVI ± two standard deviations by Bland-Altman analysis [17]. Twenty-five percent randomly selected rest and stress short axis sets were re-analyzed for assessment of intra- and interobserver variability and a coefficient of variation was calculated. Univariable analysis was performed to study the association of operation and follow-up details and ventricular stress response. A p-value < 0.05 was considered to indicate statistical significance.

Results

Patients

Sixty-eight patients were eligible for participation in this study. Thirty-two patients gave informed consent. Statistical analysis did not show any differences between participants and non-responders when compared for patient characteristics and clinical status at most recent follow-up. Characteristics of the 32 patients are summarized in table 1. At the latest follow-up before this study, none of the patients had a residual outflow tract obstruction on echocardiography.

Table 1. Patient characteristics

Male/female	25/9	
Age (years)	13.4	(4.2, range 7.5-22.2)
Follow-up time since Fontan completion (years)	8.2	(5.2-17.8)
Oxygen saturation at follow-up (%)	95	(3.4)
Age at Fontan (years)	3.5	(1.5)
Dominant ventricle		
Right ventricle	11	
Left ventricle	18	
Undefined	3	
Fontantype		
Total cavopulmonary connection	27	
Lateral tunnel	22	(3 fenestrated)
Extracardiac conduit	5	
Atriopulmonary connection	5	
Pre-Fontan surgery		
Pulmonary artery banding	8	
Blalock-Taussig shunt	15	
Norwood	4	
Bidirectional Glenn	24	
Post-Fontan intervention		
Extracardiac conduit replacement	1	
Atrial level shunt closure	2	
Closure of tricuspid valve	1	
Damus-Kaye-Stansel anastomosis	1	
Graft replacement of ascending aorta and aortic valve	1	

MRI

CMR scanning was well tolerated by all patients and none of the subjects experienced any discomfort necessitating termination of the study. Dobutamine was administered safely to all subjects

with no side-effects, apart from one patient with a minor headache. In eight patients, dobutamine was lowered to 5 µg/kg/min because of an increase in heart rate of > 50%. The 32 datasets were of sufficient quality to be included in the study. Results of the study are summarized in table 2. With dobutamine stress-testing, mean heart rate increase was 33 ± 19% . There was a decrease in EDVI in all patients when compared to rest (figure 1a). SVI did not change with stress-testing (figure 1c). The increase in EF was 22 ± 12% (figure 1b).

Coefficients of variation for intra-observer variability at rest were: EDV 4.9%, EF, 5.9%, and mass 5.4%. With stress-testing, these coefficients were: EDV 3.4%, and EF 2.1%. Coefficients of variation for interobserver variability at rest were: EDV 4.8%, EF, 4.7%, and mass 8.5%. With stress-testing, these coefficients were: EDV 11.1%, and EF 4.6%.

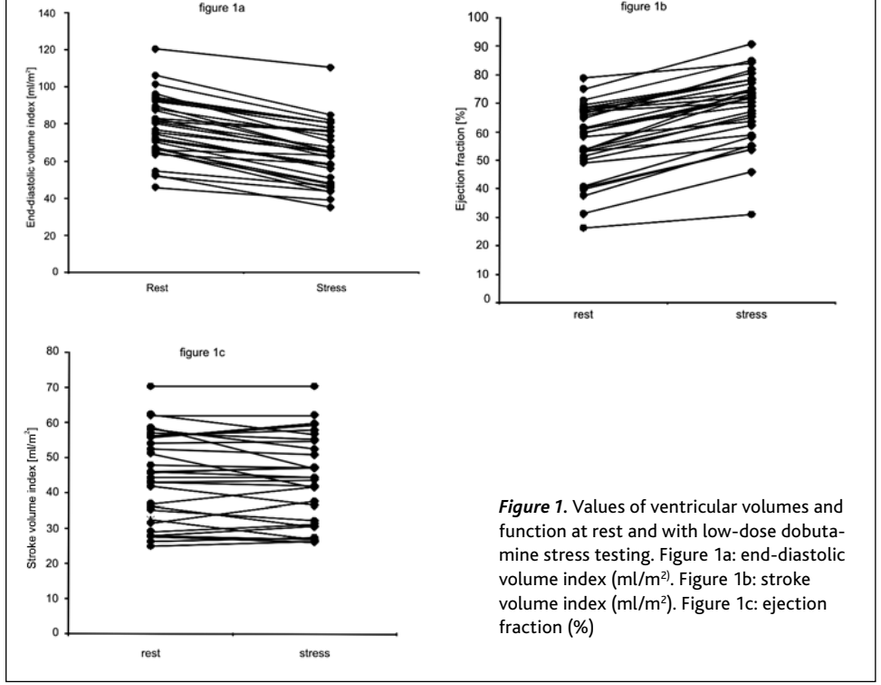

Figure 1. Values of ventricular volumes and function at rest and with low-dose dobutamine stress testing. Figure 1a: end-diastolic volume index (ml/m$^{2)}$. Figure 1b: stroke volume index (ml/m^2). Figure 1c: ejection fraction (%)

Aortic flow measurements were successful in 28 patients. Flow measurements failed because of technical problems with the CMR scanner (n = 2), graft replacement of the ascending aorta and aortic valve (n = 1), unknown cause (n = 1). Linear regression analysis showed a good correlation between SVI in the aorta and SVI measured with the ventricular volumetric data set (R = 0.95; y = 0.93x + 3.1, standard error of estimate = 4.1 ml). The limits of agreement analysis demonstrated a mean difference of 0.20 (4.1) ml.

Table 2. Ventricular volumetric results of the systemic ventricle at rest and during dobutamine stress

Variables	Rest	Dobutamine stress	p-value
Heart rate (beats/min)	71 (12)	94 (17)	< 0.001
Mean arterial pressure (mm Hg)	80 (9)	92 (9)	< 0.001
End-diastolic volume index (ml/m^2)	78 (17)	64 (16)	< 0.001
End-systolic volume index (ml/m^2)	34 (15)	20 12)	< 0.001
Stroke volume index (ml/m^2)	44 (13)	43 (12)	0.0153
Ejection fraction (%)	57 (13)	69 (13)	< 0.001
Cardiac index (l/min/m^2)	3.0 (0.7)	3.9 (0.8)	< 0.001
Mass index (gr/m^2)	73 (19)		
Contractility (mm Hg/ml/m^2)	2.8 (1.2)	5.9 (2.9)	< 0.001
Afterload (mm Hg/l/min/m^2)	29 (9)	25 (6)	0.002

We compared patients with a dominant right ventricle (n = 11) to patients with a dominant left ventricle (n = 18). Three patients with an undefined systemic ventricle were not included in this analysis. Results of the comparison are displayed in table 3. In summary, at rest, patients with a dominant right ventricle had a higher ESVI and a lower EF than patients with a dominant left ventricle. With stress-testing, the relative increase in EF was higher in patients with a dominant right ventricle (p = 0.033). Both at rest and during stress, there was a statistically significant difference in contractility in favor of dominant left ventricles.

At rest, flow measurements of both caval veins were successful in 24 patients. Flow measurements failed because of technical problems with the CMR scanner (n = 2), flow artifacts (n = 2), or unknown cause (n = 4, significant underestimation of the flow volume). The latter could be explained by the fact that 2D flow measurements were performed in an area with non-laminar flow. Seven of the younger patients did not complete the full protocol at stress because of the long total scan time, resulting in seventeen flow measurements in both caval veins with stress-testing. There was a good correlation between ventricular SVI and systemic venous return per cardiac cycle (R = 0.95; y = 1.1x – 2.8; standard error of estimate = 4.2 ml). The limits of agreement analysis demonstrated a mean difference of 0.33 (3.9) ml. Both at rest and during stress, superior vena cava flow accounted for 40% of the systemic venous return. With dobutamine stress-testing, systemic

venous return per cardiac cycle did not change. Total systemic venous return increased from 2.8 (0.6) l/min/m² to 3.5 (0.7) l/min/m² (p < 0.001).

Table 3. Comparison of volumetric data and stress response of dominant right and left ventricles

	Variables	Right ventricle	Left ventricle	p-value
Rest	Heart rate (beats/min)	74 (13)	68 (12)	NS
	End-diastolic volume index (ml/m²)	82 (17)	77 (17)	NS
	End-systolic volume index (ml/m²)	42 17)	30 (12)	0.014
	Stroke volume index (ml/m²)	40 (14)	48 (12)	NS
	Ejection fraction (%)	50 (14)	62 (11)	0.011
	Cardiac index (l/min/m²)	2.9 (0.6)	3.2 (0.8)	NS
	Mass index (gr/m²)	74 (14)	71 (23)	NS
	Contractility (mm Hg/ml/m²)	2.1 (0.6)	3.1 (1.2)	0.02
	Afterload (mm Hg/l/min/m²)	30 (8)	28 (8)	NS
Stress	Heart rate (beats/min)	100 (24)	90 (12)	NS
	End-diastolic volume index (ml/m²)	65 (15)	63 (17)	NS
	End-systolic volume index (ml/m²)	24 (14)	17 (9)	NS
	Stroke volume index (ml/m²)	40 (13)	46 (13)	NS
	Ejection fraction (%)	63 15)	73 (10)	NS
	Cardiac index (l/min/m²)	3.7 (0.3)	4.0 (1.0)	NS
	Contractility (mm Hg/ml/m²)	4.7 (2.0)	7.0 (3.1)	0.02
	Afterload (mm Hg/l/min/m²)	25 (4)	25 (7)	NS
	Decrease in end-diastolic volume index (%)	21 (6)	18 (10)	NS
	Increase in ejection fraction (%)	29 (11)	19 (12)	0.01

Echocardiography

Pulmonary venous flow and systemic atrioventricular flow velocity data were available in 29 patients. In three patients, analysis was not possible due to inferior image quality. In Fontan patients, mean atrial reversal flow velocity was 0.28 m/s (0.05), mean systolic flow velocity was 0.55 m/s (0.15), and mean diastolic flow velocity was 0.64m/s (0.26). In the reference population these data were 0.22 m/s (0.09), 0.50 m/s (0.11), and 0.64 m/s (0.12) respectively (p = non significant for all variables). Systemic atrioventricular E-wave velocity, A-wave velocity, and E/A-ratio were statistically significantly different in the patient population. In patients, E-wave velocity was lower (0.81 (0.20) vs. 1.00 (0.16) m/s in controls), A-wave velocity was higher (0.57 (0.17) vs. 0.48 (0.13) m/s in controls), and E/A ratio was lower (1.50 (0.46) vs. 2.22 (0.59) in controls) than in healthy controls.

Univariable analysis did not identify any factors in patient characteristics or the patient's medical history that were of influence on the stress response (the relative decrease in EDVI and the relative increase in EF) of the systemic ventricle. The following variables were included in this analysis: 1.

for pre-Fontan procedures: age; pre-Fontan volume unloading (yes/no); hemoglobin level; duration of intensive care stay; duration of total hospital stay; 2. for Fontan completion: systolic pressure, and end-diastolic pressure of the systemic ventricle, and systolic, diastolic and mean aortic pressure at pre-Fontan catheterization; age; hemoglobin level; oxygen saturation; aortic cross-clamp time; total bypass time; duration of thoracic drainage; duration of intensive care stay; duration of total hospital stay; 3. post-Fontan: age at follow-up; follow-up time after Fontan completion.

Discussion

The results of this study of patients having had a Fontan operation for a univentricular heart at young age show that – with low-dose dobutamine stress-testing – EF increases adequately, demonstrating a good contractile capacity, and SVI does not change. This is caused by an abnormal decrease in EDVI with stress, while ESVI decreases adequately. Consequently, the systemic ventricle increases its output only by increasing heart rate. The normal response to low-dose dobutamine stress in children, and young adults, studied with echocardiography and CMR imaging shows no change in EDVI, a decrease in ESVI, and an increase in SVI [12, 13, 18].

In Fontan patients, reduced preload reserve with dobutamine stress-testing could be responsible for the abnormal stress response. The concept of impaired preload reserve in the Fontan circulation is well known [1, 2, 5, 6]. Senzaki et al. demonstrated a limited preload reserve with low-dose dobutamine stress-testing, by analyzing ventricular performance and hemodynamics in Fontan patients during cardiac catheterization [5, 6]. During stress, parameters of preload decreased, cardiac index increased, and afterload did not change. In multivariate analysis, the limited stress response could only be attributed to limited preload reserve [6]. The design of these studies did not allow further analysis of the causes of impaired preload reserve. Apart from the lack of a subpulmonary ventricle, pathophysiological explanations for this reduced reserve can be sought in alterations in either a) ventricular diastolic function b) venous capacitance vasculature, c), caval vein and pulmonary artery flow dynamics, d) function of the atrial baffle in case of TCPC, or e) combinations of these factors.

Echocardiographic indices of diastolic function are abnormal after Fontan operation, compatible with reduction of ventricular compliance in addition to persisting abnormalities of relaxation [19]. In our patient group, echocardiographic indices of systemic atrioventricular flow indicated impairment in relaxation. However, we do not consider this diastolic dysfunction of great importance for the observed decrease in EDVI with stress-testing, since others have shown that the effect of diastolic dysfunction on ventricular filling during dobutamine stress-testing is negligible [5, 6]. Furthermore, low-dose dobutamine is considered to improve diastolic relaxation [20].

With regard to the peripheral vasculature Kelley et al. found evidence of an increased venous tone in Fontan patients [21]. This led to limitations in the ability to mobilize blood from

capacitance vessels with exercise testing. Two other studies demonstrated the effect of supine leg exercise and respiration on systemic venous flow dynamics in patients without evidence of residual obstruction in the Fontan connection [22, 23]. An increase in total systemic venous return was mainly attributable to the increase in heart rate with exercise testing [22]. Inferior vena cava flow increased more than superior vena cava flow with supine leg exercise, and it was concluded that the peripheral pump is probably the most important factor for increasing systemic venous return [23]. However, from the same data, it could also be concluded that only redistribution of cardiac output to the lower body half was the cause of the increase in inferior vena cava flow. In our study with pharmacological stress, systemic venous return also increased despite the lack of physical exercise and was solely caused by the increase in heart rate.

Recently, Whitehead et al. studied the effects of increased inferior vena cava flow on power losses in the total cavopulmonary connection with computational fluid dynamics [24]. In their study, power loss increased in a nonlinear fashion with physiologic increases in inferior vena cava flow (as with lower limb exercise), and there was a dramatic increase in resistance index in the total cavopulmonary connection, These observations point towards another potential contribution to impaired preload reserve, which is the inability to increase flow through the atrial baffle with stress-testing.

In our study, there was an adequate decrease in ESVI with stress-testing, implicating that systemic ventricular failure is not the underlying mechanism of the abnormal stress response. EF at rest was slightly higher than in a recent study by Eicken et al (57% and 51% respectively) [25]. In our study, however, patients were younger, age at Fontan completion was lower, and the majority of the patients had had a total cavopulmonary connection, all possible explanations for this difference in EF. We observed a statistically significant difference in global ventricular performance and contractility in favor of dominant left ventricles. Heart rate, afterload, and stroke volume did not differ between dominant right and left ventricles, suggesting a difference in loading conditions between these two groups. Interestingly, dominant right ventricles had a more pronounced increase in EF during stress-testing, whereby the difference in EF between dominant left and right ventricles disappeared. In general, it can be concluded from our results, that almost ten years after Fontan completion, the systemic ventricle has a good contractile response with stress-testing and that the reported disadvantage of having a dominant right ventricle could not be demonstrated [26, 27].

Study limitations

This study was limited by the conditions inherent to CMR imaging. CMR imaging is not suitable for patients with anxiety, claustrophobia or implantable devices. Our preference to perform this study in non-sedated children, limited the inclusion to patients over seven years of age. Another limitation of this study was the small size of the study group. However, all patients showed the same reaction to dobutamine stress (figure 1), but it was not possible to distinguish between patients with different types of Fontan operations.

Since our CMR scanner is not suitable for supine leg exercise, the effects of exercise on ventricular systolic function and systemic venous return had to be simulated with pharmacological stress. Parameters on contractility and afterload could only be estimated, as is a limitation of every non-invasive study. It could be argued that the non-physiologic form of stress of this study contributed to the impaired preload. However, both Gewillig et al. and Kondoh et al. also found that stroke volume did not increase with supine bicycle exercise testing [1, 2], implicating that the contribution of respiration and the peripheral muscle pump to maintaining preload is negligible.

Conclusions

The functionally univentricular heart after Fontan completion at young age has an adequate increase in EF with beta-adrenergic stimulation. However, as a result of impaired preload with stress, only increasing heart rate can increase cardiac output.

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Chapter 5

Pulmonary artery size and function after Fontan operation at young age

Daniëlle Robbers-Visser, MD[a, b]; Frank Helderman, MSc[c]; Jan L. Strengers, MD, PhD[d]; Lennie van Osch-Gevers, MD, PhD[a]; Livia Kapusta, MD, PhD[e]; Peter M. Pattynama, MD, PhD[b]; Ad J. Bogers, MD, PhD[f]; Rob Krams, MD, PhD[c]; Willem A. Helbing, MD, PhD[a, b]

[a] Department of Pediatrics, Division of Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

[c] Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands

[d] Department of Pediatric Cardiology, University MC Utrecht – Wilhelmina Children's Hospital, Utrecht, the Netherlands

[e] Children's Heart Center, UMC St Radboud, Nijmegen, the Netherlands

[f] Department of Cardiothoracic Surgery, Erasmus MC, Rotterdam, the Netherlands

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Abstract

Objective: To assess pulmonary artery size (PA), flow variables, and wall shear stress (WSS) in patients after Fontan operation at young age.

Methods: Flow in the branch PA was obtained with phase contrast velocity-encoded cardiovascular magnetic resonance imaging in fourteen patients before and after low-dose dobutamine stress (7.5 μg/kg/min) and in seventeen healthy controls at rest.

Results: At rest, stroke index, total flow, average, and peak flow rate were all statistically significantly lower in patients than in controls ($p<0.001$). With stress-testing, all variables increased in patients ($p<0.001$), apart from stroke index, that did not change. At rest, branch PA area did not differ between patients and controls. Distensibility was lower in patients than in controls ($p<0.001$). With stress-testing, area, and distensibility did not change. At rest, WSS was lower in patients than in controls ($p<0.001$). WSS increased with stress-testing ($p<0.001$), but not to the same levels as during resting conditions of the control group.

Conclusion: PA size is normal long-term after Fontan operation at young age. Flow variables, distensibility, and WSS are significantly lower compared to healthy controls, and do not show adequate reactions with stress-testing, which is suggestive of pulmonary artery endothelial and/or vascular dysfunction.

Introduction

After Fontan completion for a functionally univentricular heart, the systemic venous return is directly connected to the pulmonary arteries (PA's), resulting in substantial or total loss of pulsatile flow into the lung [1-4]. The long-term effects of this abnormal flow pattern on PA growth and function are a matter of concern. Several groups have studied the effects of a bidirectional Glenn or Fontan pathway on PA growth and diameters [5-7], but have shown equivocal results.

Wall shear stress (WSS), the force per unit area induced by the relative movement of blood and endothelium, is an important determinant of vascular function [8], and altered levels of WSS are associated with a variety of disease processes [9-11]. WSS is inversely related to vessel diameter and alterations in WSS induce vascular remodeling [9]. After Fontan operation, increased WSS was found in one study [12] and endothelial dysfunction has been reported that may interfere with the normal remodeling process of the PA [2, 13, 14].

Recent studies on the effects of exercise on caval vein and pulmonary artery flow after Fontan operation have emphasized the need for evaluation of the Fontan circulation under exercise conditions [15, 16]. In Fontan patients, PA flow has been studied directly after supine bicycle exercise with magnetic resonance imaging [16]. However, this study did not look into the reaction of the PA's on an increase in flow. Therefore, the objectives of this study were: 1. to assess the size of a branch of the PA, its local flow pattern, and the local WSS after Fontan operation performed at young age using phase contrast velocity-encoded cardiovascular magnetic resonance imaging; 2. to simulate the effects of exercise on the PA's with low-dose dobutamine stress.

Materials and Methods

Subjects

Fourteen patients were included in this study (table 1). All patients had been subject to an atriopulmonary connection (APC) or to a total cavopulmonary connection (TCPC), completed before seven years of age. Follow-up time after Fontan completion was at least five years. In two patients, the initial TCPC was fenestrated, but the fenestration had been interventionally closed during follow-up. Patients did not have contra-indications for magnetic resonance imaging or dobutamine administration. Medical records were reviewed for anatomical and operative details. Mean PA pressure before Fontan completion was 10.0 mm Hg (7-14 mm Hg, n = 12). Mean PA pressure after Fontan completion was 10.5 mm Hg (6-16 mm Hg, n = 8). These invasive measurements were obtained 2.3 (1.2-5.6) years after Fontan completion and 4.9 (2.0-13.4) years before participation in this study. The post-operative measurements were part of standard invasive investigations at least one year after Fontan completion.

Seventeen healthy children (nine boys) were included as controls for this study. Mean age was 13.3 (2.3) years, mean body surface area (BSA) was 1.54 (0.20) m². There was no statistically significant difference between the controls and patients in age, gender and BSA. The study was approved by institutional review boards and by the Dutch Central Committee on Research involving Human Subjects. All subjects and/or their parents (if required) gave informed consent.

Table 1. Characteristics of the patients

		Patients	
Total (male)		14	(9)
Age (years)		11.9	(7.5-20.1)
BSA (m^2)		1.35	(0.93-2.09)
Follow-up after Fontan completion (years)		8.2	(5.4-16.8)
Age at Fontan completion (years)		3.5	(1.0-6.8)
Fontan type:	APC	3	
	TCPC, lateral tunnel	8	
	TCPC, extracardiac conduit	3	
Dominant ventricle:	Right	4	
	Left	10	
Pre-Fontan procedures:	BT-shunt	6	
	PA-banding	2	
	Norwood	1	
	Glenn anastomosis	9	
	Branch pulmonary artery augmentation	2	
Post-Fontan procedures:	Bentall procedure	1	
	Atrial level shunt closure	2	
	Extracardiac conduit replacement	1	

Data are given as frequencies, or median (range). Abbreviations: APC = atriopulmonary connection, BT-shunt = Blalock-Taussig shunt, PA-banding = pulmonary artery banding, TCPC = total cavopulmonary connection.

Magnetic resonance imaging

A Signa 1.5 Tesla whole-body MR imaging system was used (General Electric, Milwaukee, WI, USA) for all patients, in combination with a dedicated phased-array cardiac surface coil that was placed over the thorax. All patients were monitored by vector cardiogram gating and blood pressure monitoring.

The PA's were localized on an axial set through the thorax, using a steady-state free precession sequence. On this axial localizer, the PA's were cut longitudinally (figure 1a). The subsequent image together with the axial localizer was used to plan a flow measurement perpendicular to the flow, using phase-contrast velocity-encoded imaging. The imaging plane was set halfway between the origin (i.e. point of the Fontan anastomoses in patients) and the first branching point of the PA (figure 1b). The branching points could be well visualized and there was no evidence of proximal PA stenosis on this double-oblique localizer. Flow measurements were obtained over one

cardiac cycle, and were divided in 24 phases. Imaging parameters were TR=5-6 ms, TE=3 ms, flip angle=20°, 7 mm slice thickness, 6 views/segment, scanning matrix of 256 *128.

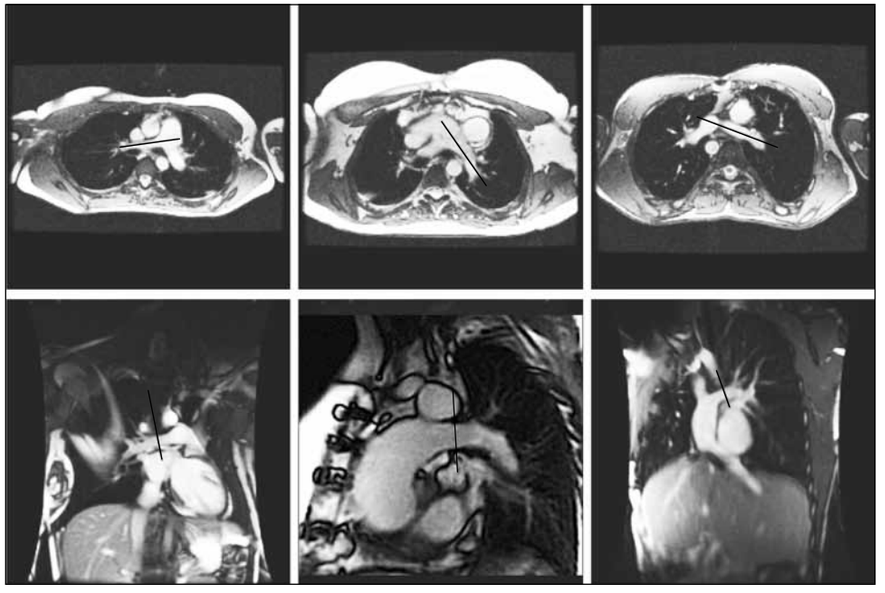

Figure 1. SSFP images of the PA's on an axial localizer (1a) of a healthy control (left), patient with an APC (middle), and patient with a TCPC (right). The line indicates the imaging plane in the RPA (left panel), and LPA (middle and right panel) for the subsequent localizer (1b). On this double oblique image, the flow measurements were planned halfway the origin of the PA and the first branching point (line).

It is known that the better the velocity encoding matches the real velocity in the region of interest, the more precise the measurement becomes [17]. In patients, unidirectional velocity encoding was set at 30 cm/s and adjusted in case of aliasing. The maximal velocity encoding used was 80 cm/s. To minimize the effect of breathing, flow measurements were made without breath-hold, using three signal-averages. When the study protocol had been completed, dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) was administered by continuous infusion into an antecubital vein at 7.5 µg/kg/min. After fifteen minutes, when a new steady state in heart rate and blood pressure had been obtained, a second flow measurement was acquired using the imaging parameters specified above. Dobutamine infusion was lowered to 5 µg/kg/min if any of the following events occurred: a) heart rate, systolic, or diastolic blood pressure of more than 150% baseline; b) heart rate, systolic, or diastolic blood pressure of less than 80% baseline [18].

In healthy controls, flow measurements in the PA's were performed as part of another study protocol. In this study, unidirectional velocity encoding was 150 cm/s and acquisitions were taken with breath-hold in end-expiration. Flow measurements were done at rest only. Difference in acquisition parameters between the patient and control group were accepted, since others have demonstrated clinically non-significant differences in absolute blood flow and peak velocity in the branch PA's between expiratory breath-hold versus free-breathing acquisitions [19, 20].

Image analysis

CMR studies were analyzed on a commercially available Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA) using the Flow analysis software package V3.1 (Medis Medical Imaging Systems, Leiden, the Netherlands). The following variables were determined: time averaged intraluminal area; maximal and minimal intraluminal area; peak flow rate, minimal and time averaged flow rate; stroke index (stroke volume divided by BSA), and total flow per minute indexed for BSA.

Calculations

To compare our results to the results of a previous study [12], distensibility of the PA was approximated by the formula: (maximal area – minimal area)/maximal area.

WSS determination

WSS was determined according to the method of Wentzel et al [10]. All 24 phases of the velocity measurement were processed to obtain WSS data. We applied a moving average filter (3 x 3) to reduce noise. Shear rate, being the change in velocity per unit distance, was calculated according to the following method: for each pixel the velocity value of the left and right neighbor pixel, and the upper and lower neighbor pixel were taken and half of the velocity difference was divided by the pixel size. This resulted in a velocity gradient in two orthogonal directions for each pixel. Those two velocity gradients were squared. The final shear rate for each pixel was taken as the square root from the squared sum of these values. To determine the shear rate at the vessel wall, we separated the wall in twelve parts. Each part was determined by the outer 10% of the vessel radius and 30° in the circumferential direction. The highest shear rate found in each part was considered representative for the wall shear rate in the corresponding part. The wall shear rate (s^{-1}) was multiplied with the viscosity (3 N·s/m²) to get the WSS (N/m^2). Average WSS per cardiac phase was the arithmetic mean from the WSS of the twelve parts. Mean WSS of the whole cardiac cycle was the arithmetic mean from the average WSS of all 24 phases.

Statistical analysis

Data are expressed as frequencies, mean (standard deviation), or median (range) as appropriate. Comparisons between groups were made using the appropriate t-test. A p-value < 0.05 was considered to indicate statistical significance.

Results

The study protocol was well tolerated and completed by all subjects. In three patients, dobutamine infusion was lowered to 5 µg/kg/min, since heart rate was > 150% baseline with a dosage of 7.5 µg/kg/min, although this was well tolerated.

In patients, flow measurements in the right pulmonary artery (RPA) were not always possible due to the short distance between the connection with the superior vena cava and the first branching point. Therefore, all flow measurements were additionally performed in the left pulmonary artery (LPA). In eight patients, there was an adequate flow measurement in the RPA. Statistical analysis of flow variables did not show any difference between the RPA and LPA (table 2).

In the control group, the first branching point of the LPA was closer to the bifurcation than the branching point of the RPA. This led to difficulties with WSS determination in half of the controls, since – because of vessel movement during the cardiac cycle – the flow signal of the LPA was disturbed by flow signals of branch vessels. Therefore, all flow measurements were done in the RPA. Statistical analysis of flow variables in the RPA and LPA of the controls also did not show any difference (table 2). In table 3, the results of measurements in a branch PA are shown (i.e. the RPA for healthy controls and the LPA for Fontan patients).

Flow measurements

At rest, stroke index, total flow, average flow rate, and peak flow rate were statistically significantly higher in controls than in Fontan patients (table 3). With dobutamine stress-testing in Fontan patients, stroke index did not change. Total flow per minute increased significantly with increased heart rate (table 3). However, all variables remained below the levels of controls during rest.

Pulmonary artery area and distensibility

At rest, average area of the branch PA halfway the origin and the first branching point did not differ between patients and controls. In contrast, there was a statistically significantly higher maximal area in the controls compared to patients, which was partly related to a higher distensibility in the control group (table 3). With stress-testing in patients, area and distensibility did not change, despite an increase in blood flow (table 3).

WSS determination

At rest, WSS was significantly lower in the patient group compared to controls. When the spatial average WSS per cardiac phase was plotted against cardiac phase, three distinct patterns were visible in controls, TCPC patients and APC patients, in agreement with the flow patterns in these groups (figure 2). In controls, peak WSS occurred at peak systole, while in TCPC patients, there was only little variation in WSS throughout the cardiac cycle. In contrast, in APC patients, there was an increase in WSS in late diastole, coinciding with atrial contraction. When WSS was plotted against area of the branch PA, Fontan patients showed a WSS that was too low for the area (figure 3). With stress-testing in patients, WSS increased but not to the level of the controls at rest (table 3).

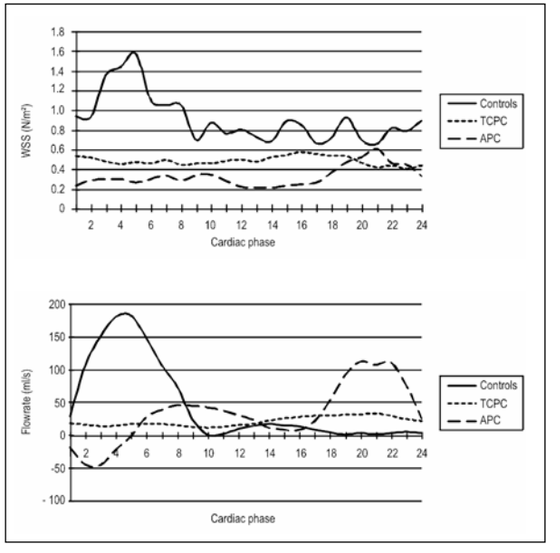

Figure 2. WSS (2a) and flow rate (2b) throughout the cardiac cycle of representative study subjects.
Abbreviations: APC = atriopulmonary connection, TCPC = total cavopulmonary connection, WSS = wall shear stress.

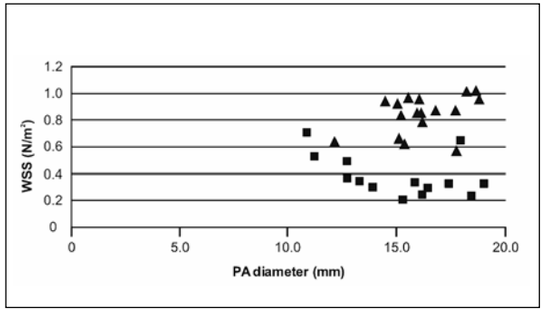

Figure 3. WSS versus branch PA diameter. Triangles represent the control group, squares the Fontan group.
Abbreviations: PA = pulmonary artery, WSS = wall shear stress.

Table 2. Comparison of flow results in the RPA and LPA

	Controls (n = 9)			Patients (n = 8)		
	RPA	**LPA**	**p-value**	**RPA**	**LPA**	**p-value**
Average area (mm²)	197 (45)	216 (29)	0.184	203 (61)	210 (57)	0.401
Maximal area (mm²)	253 (58)	267 (40)	0.473	229 (70)	232 (63)	0.674
Average flow (ml/s)	52 (12)	46 (13)	0.641	28 (8)	29 (8)	1.000
Peak flow (ml/s)	177 (31)	171 (32)	0.110	59 (40)	59 (36)	0.726
SVI (ml/m²)	29 (5)	25 (4)	0.092	19 (6)	20 (9)	1.000
Total flow (ml/min/m²)	2007 (383)	1761 (395)	0.100	1243 (182)	1284 (285)	1.000

Data are given as mean (SD). Abbreviations: LPA = left pulmonary artery, RPA = right pulmonary artery, SVI = stroke volume indexed for body surface area.

Table 3. comparison of branch pulmonary flow variables in patients (LPA results) and controls (RPA results)

Variables	**Controls**	**Patients (rest)**	**Patients (stress)**	**p-value (patients vs controls)**	**p-value (rest vs stress)**
Heart rate (beats/min)	72 (12)	69 (12)	93 (17)	NS	<0.001
Stroke index (ml/m²)	31 (7)	19 (7)	19 (7)	<0.001	NS
Total flow (ml/min/m²)	2189 (463)	1244 (274)	1705 (308)	<0.001	<0.001
Average flow (ml/s)	56 (15)	28 (6)	39 (13)	<0.001	<0.001
Peak flow (ml/s)	187 (48)	55 (31)	71 (44)	<0.001	<0.001
Average area (mm²)	207 (42)	183 (63)	186 (66)	NS	NS
Maximal area (mm²)	263 (59)	206 (70)	209 (78)	0.02	NS
Distensibility	0.41 (0.09)	0.22 (0.06)	0.20 (0.07)	<0.001	NS
Average WSS (N/m²)	0.84 (0.14)	0.38 (0.15)	0.50 (0.18)	<0.001	<0.001

Data are given as mean (SD). Abbreviations: LPA = left pulmonary artery, NS = not significant, RPA = right pulmonary artery, WSS = wall shear stress

Discussion

In this study, we have demonstrated that normal PA areas after Fontan operation coincide with a decreased distensibility, and WSS. Furthermore, pulsatility of different parameters (flow, WSS) has been reduced considerably. We propose that these observations are suggestive of endothelial and/or vascular dysfunction in Fontan patients.

In the present study, loss of pulsatility was demonstrated by the flow curves and WSS curves as presented in figure 2. Loss of pulsatility has been linked to pulmonary endothelial dysfunction in a few recent studies [2, 4]. After a bidirectional Glenn procedure, Kurotobi et al. [2] found a significant correlation between loss of pulsatility and significantly impaired endothelium-dependent relaxation (by acetylcholine) in the lower lobe PA. Others have observed an abnormal pulmonary vascular response to exogenous nitric oxide in Fontan patients, in some part related to lack of pulsatility in the pulmonary circulation [13].

The long-term effects of total or substantial loss of pulsatility of flow in the PA's after Fontan operation remain unclear. Results from a few studies focusing on the pulmonary vasculature in Fontan patients are suggestive of pulmonary endothelial dysfunction, particularly in the nitric oxide pathway. Pulsatile stretch and WSS are important for the release of nitric oxide by the endothelium [21, 22]. Nitric oxide, a locally acting vasodilator, contributes to the maintenance of low pulmonary vascular resistance in healthy children [23]. Low pulmonary vascular resistance might be essential for optimal functioning of the Fontan circulation.

Previous studies have measured decreased PA sizes after Fontan operation [5-7, 12]. However, in these studies, PA size was determined at different locations than in the present study. Furthermore, Reddy [5], Buheitel [6], and Tatum [7] determined maximal PA diameter on angiograms, Morgan [12] determined maximal PA area on CMR flow measurements (perpendicular to the axial axis of the vessel). It is known that the cross-sectional area of a PA is not a perfect circular shape, but rather oval shaped. Determination of the diameter on angiograms in postero-anterior projections can therefore give an inaccurate estimate of the real diameter or area of the vessel. In our study, we used the average and maximal cross-sectional area of the branch PA (halfway between the origin and the first branching point) on CMR flow measurements. Although there was a statistically significant difference in maximal area, time averaged area did not differ between patients and controls. In our opinion, average PA area is a more representative measure of PA size. Pulmonary artery flow, in Fontan patients, is not primarily in systole, but continuously throughout the cardiac cycle. Although pressure was not measured, it is to be expected that this signal will follow the flow signal. Hence, a lower maximal area of a PA in a Fontan patient reflects the lack of pulsatility of pressure and an impaired distensibility of the vessel, but does not necessarily mean the vessel is too small. Therefore, we did not calculate the McGoon ratio or the Nakata index in this study group, since both these parameters use maximal PA diameter.

In our study, lower distensibility in Fontan patients at rest might be explained by the decreased pressure range after the Fontan operation. Distensibility is, however, not only affected by pulse pressure but also by properties of the vessel wall. Hence, the current findings might also be explained by altered muscle mechanics due to different tone of the smooth muscle cells. Tone of the smooth muscle cells is partly determined by the blood flow. However, with an increase in blood flow during low-dose dobutamine stress, distensibility did not change, arguing against an important effect of blood flow on distensibility. In healthy adults, pulmonary arteries distend ≈ 2% of their initial diameter with every millimeter mercury increase in transmural pressure with increased flow during exercise [24]. Possibly, the PA is already maximally dilated at rest to ensure adequate pulmonary blood flow and cannot expand with increased flow. A second explanation might be endothelial dysfunction, preventing the vessel from dilating. This might explain the inability to increase stroke index with stress-testing and therefore, cardiac index can only be increased by increasing heart rate.

In our study, time and spatially averaged WSS was significantly lower in the Fontan patients than in the control group, which is consistent with a reduced blood flow at rest, while vessel area was normal. Throughout the cardiac cycle, distinct WSS-patterns were seen in healthy controls, TCPC patients and APC patients, comparable with the flow curves in these groups (figure 2). Physiologic and pulsatile WSS constitutes the most potent stimulus for continuous production of nitric oxide by the endothelium [11]. Low WSS reduces the bioavailability of nitric oxide by decreasing expression of nitric oxide synthase. This will lead to an increase in pulmonary vascular resistance, as has been demonstrated in patients late after Fontan-type operation by Khambadkone et al [13]. Levy et al. demonstrated weak expression of nitric oxide synthase in Fontan patients with a good surgical outcome, but over expression of nitric oxide synthase in patients after Fontan failure [14]. They hypothesized that this over expression could be due to an attempt to improve the pulmonary vascular resistance and facilitate the Fontan circulation. The mechanism, however, cannot be explained by the low WSS in this circulation and warrants further investigation.

Recently, Cheng et al. postulated that average WSS is not constant throughout the vascular tree – as has been assumed – but is inversely related to the vessel diameter [9]. This new theory explains the variation in average WSS observed in vessels of varying sizes. In our study group, average WSS in Fontan patients was too low for the corresponding area when compared to controls (figure 3). According to the theory of Cheng, WSS in these Fontan patients should either be higher, or vessel area should be larger. The mismatch between blood flow and area may indicate a lack of appropriate vascular remodeling by WSS.

When comparing our results to the results of the study of Morgan, also investigating PA size, blood flow, and WSS in Fontan patients [12], we found: 1) a higher total flow and branch PA flow in controls and patients, 2) no difference in PA area between patients and controls, 3) sig-

nificantly lower distensibility in patients, 4) lower WSS in patients at rest and even during stress with different WSS patterns. The findings by Morgan et al. are somewhat unexpected and counterintuitive in light of the current knowledge on the pulmonary circulation after Fontan operation. Important differences in study group and methods might explain these discrepant findings. In our study, patients were younger at Fontan completion, follow-up age was lower, and follow-up time after Fontan completion was longer. Flow measurements were planned on a double-oblique cross-section of the PA – halfway between the origin and the first branching point – to plan the measurements perpendicular to the flow, and to limit influences of bifurcations on the flow pattern. In the study by Morgan [12], WSS was determined immediately after the bifurcation of the main PA, which is an area with swirling flow, possibly responsible for the increase in WSS they found.

In our group of patients, all after Fontan completion at young age and in which the majority has had a TCPC, average PA area is normal; an important finding for patients operated on according to this treatment strategy nowadays. The implications of the results that are suggestive of PA endothelial dysfunction and inappropriate vascular remodeling should be made with caution. The inability of the pulmonary vascular bed to expand with increasing blood flow might be an important limitation for maintenance of adequate ventricular preload on the long-term. However, more information is needed on the long-term effects of this pulmonary vascular dysfunction, e.g. the effects on the peripheral pulmonary vasculature and resistance, and will require serial follow-up. CMR imaging is a safe, non-invasive, and easily applicable modality for this assessment of PA size and function in selected patients.

Study limitations

This study is limited by the small size and inhomogeneity of the study group, preventing us from analyzing the effects of diagnosis, pre-Fontan procedures, and Fontan type on the measured variables. In theory, endothelial function can be different in patients with an APC, because of the different flow profile and higher energy losses. Our results are not applicable to patients with different operative courses (e.g. Fontan completion at older age). Although there was no clinical evidence of increased PA pressure or resistance, this has not been assessed invasively.

Acquisition parameters were different between patients and controls. This could introduce an error in the comparison of WSS in patients and controls. However, studies have shown differences of only 1 to 10% in flow velocity between free breathing and breath-hold acquisitions [19, 20]. Since the error in WSS is proportionate to the error in flow velocity, and differences in flow velocity between patients and controls were much higher in this study, we consider this error negligible.

Adenosine, a vasodilator commonly used for myocardial perfusion imaging in patients with coronary artery disease, may be a better pharmacological agent to test a vessel's distensibility. However, since our objective was to simulate physical exercise, we chose to use dobutamine for its positive inotropic and chronotropic effects.

Velocity-encoding in three directions might be more accurate and informative on the flow pattern. All flow measurements were planned in the branch PA before the first branching point. The smaller peripheral pulmonary vasculature was not visualized and therefore absence of stenosis in this area cannot be excluded, even as possible effects on blood flow and endothelial function in the proximal branch PA. Temporal resolution of the flow measurements can be improved and results in more accurate measurements [25]. However, this also increases acquisition time. Depending on the study subject, an acceptable balance between temporal and spatial resolution and acquisition time should be sought.

Conclusions

Long-term after Fontan completion at young age, patients have a normal average PA size when compared to controls. However, pulmonary blood flow, distensibility, and WSS are all decreased in these patients and do not show adequate reactions with low-dose dobutamine stress testing, suggesting endothelial and/or vascular dysfunction.

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Chapter 6

Normal biventricular function, volumes, and mass in children aged 8 to 17 years

Daniëlle Robbers-Visser, MD[a, b]; Eric Boersma, PhD[c]; Willem A. Helbing, MD, PhD[a, b]

[a] Department of Pediatric Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

[c] Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands

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Abstract

Objective: to assess normal values for biventricular function, volumes, and mass with current CMR imaging sequences in children.

Methods: inclusion of 60 healthy children aged 8-17 years. A short axis set of contiguous slices was acquired with CMR imaging employing steady-state free precession. Biventricular end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and mass were determined. Uni- and multivariable linear regression analyses were performed to study the interrelation of age, gender, and body surface area (BSA) on biventricular volumes and mass. The coefficient of variation was calculated for intra- and interobserver variability.

Results: EF did not differ between boys and girls (mean LV-EF 69 ± 5 (SD) %, mean RV-EF 65 ± 5 %). BSA had good (EDV, mass) and modest (ESV) correlation with biventricular measurements. Gender appeared a significant modifier of these relations, whereas age had no independent contribution. The intra-and interobserver coefficient of variation was in the range 2.1 to 13.9% for biventricular EDV, ESV, and mass.

Conclusions: this study reveals gender-specific normative data for biventricular function, volumes, and mass in children aged 8-17 years that can be used as reference data in the follow-up of pediatric cardiac patients.

Introduction

Assessment of global ventricular function is important in the follow-up of patients with congenital and acquired heart disease. Cardiovascular magnetic resonance (CMR) imaging is an accurate, reproducible, and non-invasive method for the assessment of both right and left ventricular function, which has been validated extensively [1]. In congenital heart disease, it is the only non-invasive technique that allows adequate measurement of right ventricular size and function [2]. CMR imaging contributes to decision-making and timing of (re) interventions, and as such has become an internationally accepted and widely used clinical tool, for which clear guidelines have been established [1].

Although CMR imaging is increasingly being implemented in the follow-up of pediatric patients with congenital and acquired heart disease, normative data on ventricular volumes, function, and mass for this population are lacking. Currently, normal values from small studies, employing gradient-echo MRI sequences are used [2, 3]. In recent years, however, steady-state free precession (SSFP) gradient echo sequences have become the standard method for assessment of ventricular function and volumetric parameters with CMR imaging [1]. Compared to the previously used spoiled gradient-echo sequences, SSFP provides better blood-myocardial contrast, higher image quality and faster acquisition times [4]. Better blood-myocardial contrast in SSFP imaging results in statistically significantly higher end-diastolic volumes (EDV) and end-systolic volumes (ESV), lower mass and lower ejection fraction (EF) [5, 6]. Therefore, SSFP derived data cannot be compared to data obtained with spoiled gradient echo sequences. In addition, SSFP has a lower interobserver variability and better reproducibility compared to gradient-echo [4-7]. Therefore, it has been suggested that this technique allows considerable reduction in subject numbers to prove a hypothesis in research studies and study groups can be up to 90% smaller than with echocardiography for establishing significant differences [8, 9]. Although SSFP has become the method of choice for CMR imaging at 1.5T, spoiled gradient echo sequences are more useful at 3T, where SSFP yields more artefacts [10].

Besides different MRI sequences, the few studies measuring ventricular function, volumes, and mass in small groups of healthy children have used different acquisition techniques (free breathing instead of breath hold techniques, different image orientation) then are commonly used in a clinical setting nowadays [2, 3].

Lack of adequate normative data in the pediatric population limits optimal use of this imaging modality in the follow-up of patients with congenital and acquired heart disease throughout childhood. Although a study of Lorenz [3] demonstrated no difference between adults and children in biventricular volumes, function, and mass indexed for body surface area (BSA), this study group comprised only eight children in the age range seven to twenty years. The assumption that adult normal values indexed for BSA can be used as reference data for the pediatric population needs further investigation. Therefore, the objective of this study was to obtain normal values for biventricular function, volumes, and mass in healthy children using CMR imaging employing a steady-state free precession gradient echo sequence, and to evaluate their relationship with age, gender, and body size.

Materials and Methods

Subjects

Sixty healthy children (30 boys), aged 8-17 years, were included in this study. Health status was evaluated by questionnaire and physical examination. All children under the age of thirteen underwent echocardiography as part of another study protocol prior to the CMR study. The participants were divided in three groups of twenty children (ten boys): 8 to 11 years (group A), 12 to 14 years (group B), and 15 to 17 years of age (group C). The age distribution of our study group was representative of the age distribution of patients in whom CMR imaging was requested in our daily clinical practice. The number of twenty children per group was based on the study by Bellenger et al. (8) who calculated a minimal sample size of ten to fifteen subjects to detect clinically relevant changes in ventricular volumes, function, and mass with CMR imaging. All children performed less than six hours of structured exercise per week. The study was approved by the institutional review board, and all subjects and their parents gave written informed consent.

CMR study

CMR imaging was performed using a Signa 1.5 Tesla whole-body MR imaging system (General Electric, Milwaukee, WI, USA). Dedicated phased-array cardiac surface coils were placed over the thorax. All patients were monitored by vector cardiogram gating and respiratory monitoring.

All studies were obtained by a single experienced operator. Standard scout images were made to obtain a four chamber view of the heart. A multi-phase, multi-slice volumetric data-set was acquired using a fast 2-dimensional cine scan employing SSFP. The first slice was positioned at and parallel to the atrioventricular valve plane of the left ventricle in end-diastole, perpendicular to the long axis of the left ventricle. Ten to twelve slices were planned from base to apex, covering the entire ventricles in end-diastole. Depending on heart size, slice thickness varied to obtain a comparable number of slices in all subjects. The field of view was chosen as the minimum field of view that did not lead to phase wrap in the region of interest. The imaging parameters were: repetition time 3.5 ms, echo time 1.5 ms, flip angle 45°, bandwidth 111 Hz, slice thickness 7 to 10 mm, inter-slice gap 0 mm, field of view 280-370 mm, phase field of view 0.75, matrix 160 x 128 mm, 1 signal average. All images were obtained during breath-hold in end-expiration. Respiration was monitored during acquisition. In case of unsuccessful breath-hold, the image was repeated.

CMR analysis

The CMR studies were analyzed on a commercially available Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA). The ventricular volumetric data set was quantitatively analyzed using the AW 5.1 version of the MR Analytical Software System (Medis Medical Imaging Systems, Leiden, the Netherlands). Currently, there are no programs that can adequately perform automated right ventricular contour detection, and therefore we used manual detection of endocardial and epicardial borders in end-systole and end-diastole. The following parameters were calculated: biventricular EDV, ESV, stroke volume (SV), EF, and mass [11].

End-diastole and end-systole were visually defined on multiple midventricular slices. When there was any doubt on the exact phase, multiple adjacent phases were used for border detection and the calculated largest and smallest volumes were chosen as the EDV and ESV respectively. Major papillary muscles were outlined separately [5-7, 12, 13]. The interventricular septum was included in the left ventricular mass. In the basal slices, the following criteria for inclusion in the ventricular volume were used: 1) when the cavity was only partially surrounded by ventricular myocardium in end-systole or end-diastole, only the part up to the junction with atrial tissue was included in the ventricular volume [6]; 2) when the pulmonary or aortic valve was visible in the basal slice, contours were drawn up to the junction with the semilunar valves [6, 13]. In the apical area, major trabeculations and the moderator band were included in the left or right ventricular mass [13].

Ventricular volume was calculated as the sum of the ventricular cavity areas multiplied by the slice thickness. Ventricular mass was calculated as the difference between the epicardial and endocardial contours multiplied by the slice thickness and a specific gravity of ventricular mass of 1.05 g/ml [14]. Papillary muscles were excluded from the ventricular volumes and included in the ventricular mass.

All data sets were analyzed by one experienced observer. For intra-observer variability, fifteen randomly selected studies were reanalyzed after a minimal period of four weeks. For interobserver variability, a second experienced observer analyzed another fifteen randomly selected studies and measured the aforementioned parameters independently and blinded to previous results.

Statistical analysis

Data are expressed as frequencies, or mean ± standard deviation. Group comparisons were performed using chi-squared tests for categorical variables and analysis of variance for continuous variables. Uni- and multivariable linear regression analyses were performed to study the interrelation of age, gender, BSA, height and weight on biventricular EDV, ESV, and mass. Gender was also studied as an effect modifier of these relations. We report R^2, i.e. the percentage of the variability of the data that is explained by the association between variables. Intra- and interobserver variability was assessed using the method of Bland-Altman [15]. The coefficient of variation, i.e. the standard deviation of the difference of the two measurements divided by the mean of the two measurements, and multiplied by 100%, was calculated to study the percentage of variability of the measurements.

Results

Characteristics of the study population are listed in table 1. In each age group, there was an even distribution of boys and girls. As can be expected, there was a statistically significant difference in anthropometric variables between age groups. In girls, this difference was most pronounced between group A and B. In boys, this difference was also evident between group B and C.

EF did not differ between boys and girls in all age groups (mean LV-EF 69 ± 5 (SD)%, mean RV-EF 65 ± 5 %). Univariable linear regression analysis demonstrated a good correlation of BSA with biventricular EDV and left ventricular mass (R^2 0.65 to 0.72, table 2). BSA had a modest correlation with biventricular ESV and right ventricular mass (R^2 0.48 to 0.53) (table 2). Gender appeared a significant modifier of these relations ($p<0.005$), whereas age had no independent contribution (0.304). When height and weight were separately introduced in the regression model, R2 of biventricular volumes were higher than in a model with BSA (table 2, outer right columns). R^2 for biventricular mass, however, was slightly lower for height and weight separately.

Gender-specific regression lines with 95% confidence bands for the mean values, and 95% prediction bands for the absolute values of biventricular volumes and mass are displayed in figures 1 to 3. The model containing gender and BSA was used for reference data, since 1) this model has a good R^2; 2) calculating BSA is common practice in pediatrics; 3) the model can be displayed in a two dimensional plot (when compared to the model containing height and weight separately). The regression equations representing the lines in figures 1-3 are given in table 2.

In table 3, indexed values for biventricular EDV, ESV and mass are displayed for the three age groups and for gender. When comparing the age groups, the only statistically significant differences where found for LV mass index (group A vs group C, $p = 0.027$) and for RV mass index (group A vs group B, $p = 0.035$). For all variables, except for left ventricular ESVI ($p = 0.060$), there was a statistically significant difference between boys and girls. Indexed values showed a good correlation with gender ($p = 0.002$) and weight ($p = 0.007$). Therefore, when indexing only for BSA, as is commonly used, one should realize that there is an insufficient correction for weight.

Intra-observer agreement was good with the highest variation in measurements in left and right ventricular ESV and right ventricular mass (table 4). Interobserver agreement demonstrated more variation for all variables, and, again, the highest variation was found in measurements of left and right ESV, and left and right ventricular mass.

Table 1. Characteristics of the study population

	8-11 years		12-14 years		15-17 years	
Variables	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
number	10	10	10	10	10	10
Height (cm)	145 ± 9	146 ± 10	169 ± 9	163 ± 5	178 ± 6	168 ± 5
Weight (kg)	38 ± 7	38 ± 6	53 ± 9	51 ± 6	66 ± 7	58 ± 9
BSA (m^2)	1.23 ± 0.14	1.24 ± 0.13	1.58 ± 0.17	1.52 ± 0.10	1.81 ± 0.13	1.64 ± 0.14
Heart rate (beats/min)	81 ± 13	83 ± 8	84 ± 11	78 ± 8	73 ± 16	77± 16

Abbreviation: BSA = body surface area

Table 2. Outcome of univariable and multivariable regression analysis

	Boys	**Girls**	**R^2**	**R^2**	**R^2**
			BSA	***BSA and gender***	***Gender, height, and weight***
LV-EDV (ml)	= -49 + 110 * BSA (92-128)	= -10 + 78 * BSA (54-102)	0.72	0.79	0.81
LV-ESV (ml)	= -20 + 37 * BSA (27-47)	= -5 + 19 * BSA (6-32)	0.48	0.56	0.60
LV-mass (gr)	= -83 + 126 * BSA (107-145)	= -3 + 60 * BSA (35-85)	0.65	0.81	0.80
RV-EDV (ml)	= -59 + 123 * BSA (101-145)	= -15 + 84 * BSA (56-112)	0.68	0.78	0.82
RV-ESV (ml)	= -31 + 50 * BSA (37-63)	= -0.7 + 25 * BSA (9-41)	0.50	0.66	0.70
RV-mass (gr)	= -23 + 38 * BSA (29-47)	= -0.6 + 20 * BSA (8-32)	0.53	0.64	0.61

The reported equations for boys and girls are the regression equations of the models containing BSA and gender . The numbers between parentheses are the 95% confidence intervals of the slopes of the equations. Abbreviations: BSA = body surface area; EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricular; RV = right ventricular; R^2 = percentage explained variance of the regression model.

Table 3. Indexed biventricular volumes, and mass per age group or gender

	Group A	**Group B**	**Group C**	**All boys**	**All girls**
Variable	8 - 11 years	12-14 years	15-17 years	8 - 17 years	8 - 17 years
Left ventricular EDV (ml/m^2)	71 ± 8 (58-87)	78 ± 9 (66-97)	77 ± 12 (62-102)	79 ± 11 (64-102)	71 ± 8 (58-87)
Left ventricular ESV (ml/m^2)	22 ± 5 (15-33)	24 ± 5 (16-34)	25 ± 6 (18-39)	25 ± 6 (16-39)	22 ± 4 (15-33)
Left ventricular mass (g/m^2)	59 ± 8 (44-84)	66 ± 11 (54-87)	70 ± 17 (42-98)	72 ± 13 (52-98)	58 ± 9 (42-84)
Right ventricular EDV (ml/m^2)	76 ± 8 (60-91)	82 ± 12 (61-103)	82 ± 15 (64-108)	86 ± 12 (61-108)	73 ± 9 (60-99)
Right ventricular ESV (ml/m^2)	27 ± 5 (18-40)	28 ± 7 (19-43)	30 ± 8 (21-47)	32 ± 7 (21-47)	25 ± 5 (18-40)
Right ventricular mass (g/m^2)	19 ± 3 (13-25)	23 ± 5 (17-38)	21 ± 5 (12-32)	23 ± 5 (12-38)	19 ± 3 (14-27)

Reported data are mean ± SD (range). Abbreviations: EDV = end-diastolic volume; ESV = end-systolic volume.

Table 4. Intra-observer and interobserver variability analysis

	LV-EDV	**LV-ESV**	**LV-SV**	**LV-EF**	**LV-mass**	**RV-EDV**	**RV-ESV**	**RV-SV**	**RV-EF**	**RV-mass**
Intra-observer variability										
Mean difference	0.5	-0.07	0.6	0.01	-1.9	0.9	0.4	0.5	0.05	-0.9
Limits of agreement	-3.9 to 5.0	-3.8 to 3.7	-3.2 to 4.4	-3.0 to 3.0	-9.3 to 5.5	-3.6 to 5.5	-4.3 to 5.1	-3.0 to 4.1	-3.3 to 3.5	-5.1 to 3.3
coefficient of variation	2.1%	5.8%	2.6%	0.01%	3.9%	2.1%	6.0%	2.5%	0.08%	6.2%
Inter-observer variability										
Mean difference	-5.1	-3.6	-1.5	1.6	3.2	-5.9	-3.6	-2.3	1.3	0.4
Limits of agreement	-17.7 to 7.5	-14.2 to 7.0	-6.7 to 3.8	-3.2 to 6.4	-8.2 to 14.6	-14.5 to 2.7	-10.4 to 3.2	-9.5 to 4.9	-3.9 to 6.5	-4.8 to 5.6
Coefficient of variation	5.3%	13.9%	3.3%	2.3%	6.1%	3.4%	7.6%	4.5%	2.0%	8.9%

Volumetric variables in milliliters, mass variables in grams. Abbreviations: EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; RV = right ventricular; SV = stroke volume.

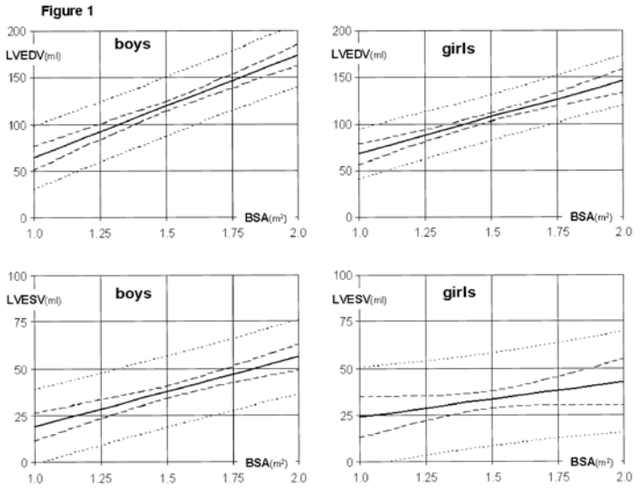

Figure 1. Gender-specific regression lines (bold lines) with 95% confidence bands (dashed lines), and 95 % prediction bands (dotted lines) for left ventricular volumes. Abbreviations: BSA = body surface area; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

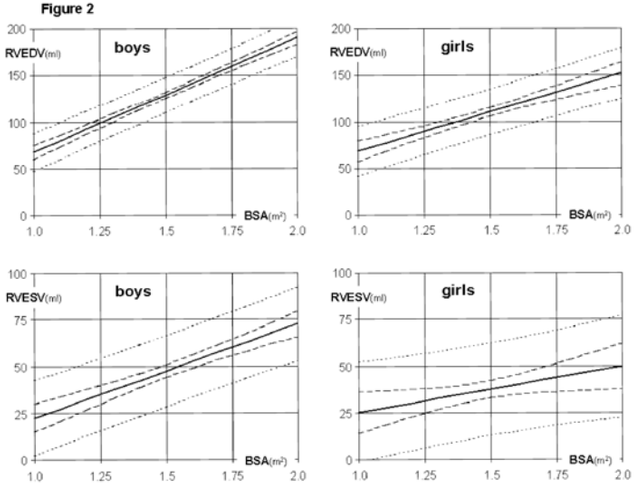

Figure 2. Gender-specific regression lines (bold lines) with 95% confidence bands (dashed lines), and 95 % prediction bands (dotted lines) for right ventricular volumes. Abbreviations: BSA = body surface area; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume.

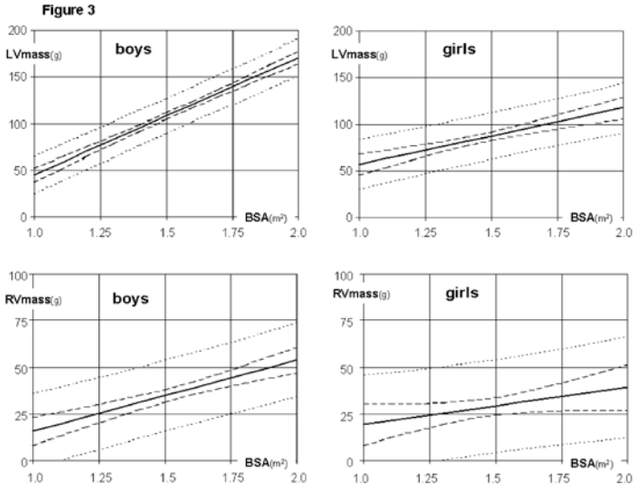

Figure 3. Gender-specific regression lines (bold lines) with 95% confidence bands (dashed lines), and 95 % prediction bands (dotted lines) for left (upper panels) and right (lower panels) ventricular mass. Abbreviations: BSA = body surface area; LV = left ventricular; RV = right ventricular.

Discussion

In our study biventricular EF, as a global measure for ventricular function, remained constant throughout growth and was not gender-specific. In the BSA range from 1.0 to 2.0 m^2, there was a linear relation between biventricular volumes and mass that was significantly modified by gender.

Up until now, normal values from very small pediatric study groups or from adult studies have been used in pediatric CMR imaging. When compared to the studies from Lorenz (3) and Helbing et al [2], biventricular volumes indexed for BSA were between 9 and 33% higher in our study (table 5). These two studies used older gradient echo sequences, or different image orientations, and did not identify the gender difference, and therefore cannot be used for reference data nowadays. Studies with spoiled gradient echo sequences can be used as reference data for studies using the same sequences, for example with acquisition at 3T.

Compared to studies in young adults [6, 12, 16, 17], mean values for indexed volumes, and mass were almost always lower in our study. Compared to the study by Tandri [16], however, right ventricular indexed volumes were higher in our study (table 5).

The results of our study show significant and clinically relevant gender differences in biventricular volumes and mass with increasing BSA, as has been demonstrated by other in adults [6, 12, 13, 17]. The effects of gender on cardiac size have also been assessed with 2-dimensional

Table 5. Comparison of study results for biventricular volumes and mass

	LV-EDV (ml/m²)		LV-ESV (ml/m²)		LV-mass (g/m²)		RV-EDV (ml/m²)		RV-ESV (ml/m²)		RV-mass (g/m²)	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Present study	79 ± 11	71 ± 8	25 ± 6	22 ± 4	72 ± 13	58 ± 9	86 ± 12	73 ± 9	32 ± 7	25 ± 5	23 ± 5	19 ± 3
Helbing[2]		*69 ± 10*		*20 ± 5*				*70 ± 9*		*21± 5*		
Lorenz[3]		*67 ± 9*				*81 ± 13*		*75 ± 13*				*26 ± 3*
Alfakih[6]	88 ± 15	83 ± 12			68 ± 11	56 ± 8						
Tandri[12]							82 ± 16.2	69 ± 14.0	31 ± 9.2	22 ± 7.5		
Maceira[16, 17]	86 ± 9	82 ± 8.7	30 ± 5.5	28 ± 4.7	76 ± 8.5	62 ± 7.5	91 ± 11.7	84 ± 9.4	35 ± 7.4	32 ± 6.6	36 ± 6.8	32 ± 5.2

Abbreviations: EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricular; RV = right ventricular

and 3-dimensional echocardiography [18, 19]. Gender differences in left ventricular mass are apparent from puberty, with higher masses in boys than in girls. This difference continues to exist in adulthood [20]. It has been suggested that the effect of sexual maturation on left ventricular mass is mediated through hormonal changes that also influence body size, particularly acquisition of fat free mass [21]. The effects of gender on right ventricular measurements have been assessed in adults [16, 17], but not in subjects less than eighteen years of age. Gender differences in RV volumes are apparent in subjects up to 80 years of age, with higher volumes in men than in women [16, 17].

The best means by which to adjust for the impact of body size on the size of cardiovascular structures remains unclear. Several groups have studied the correlation of vascular or ventricular size with BSA or functions of BSA [22-24]. Recently, Sluysmans and Colan demonstrated that indexing dimensions of vascular structures for BSA does not adequately account for the dependence of vascular size on BSA [22]. In their analysis, indexing with the square root of BSA fully accounted for the variance in aortic root annulus. However, others have shown good correlations of vascular and ventricular dimensions with a cube root function of BSA [24]. These analyses did not include gender in their model.

In our study, we demonstrated a linear relation between BSA (in the range 1.0 to 2.0 m^2) and biventricular volumes and mass that is modified by gender. We also demonstrated that when indexing for BSA, there is an insignificant correction for weight in the model. A model correcting for BSA and gender, however, is easily applicable and explains up to 81% of the variability of the variables.

Outside the BSA range 1.0 to 2.0 m^2, the relation between BSA and volumes and mass is probably different from the one we found in our study (especially in children with a BSA < 1.0 m^2). This has to be investigated, but is hampered by the need of performing CMR studies under general anaesthesia in very young, healthy children. The reason we studied children aged 8-17 years, is that the majority of our patients in whom clinical CMR imaging becomes relevant is in this age range. We believe that our reference data with gender-specific regression lines are easily applicable in the follow-up of pediatric cardiac patients since calculating BSA is standard practice in pediatrics and no further calculations are needed.

Intra-observer variability for the absolute values of clinically relevant variables was good, with the smallest variations in both left and right ventricular EDV, SV, and EF. These variables also showed the smallest variation for interobserver variability. The results of intra- and interobserver variability analysis in this study are comparable to the results of other studies with SSFP for all variables [6, 25-28]. Therefore, CMR imaging is an accurate and reliable method for follow-up of these variables and can adequately assess changes in ventricular size and global ventricular performance.

For intra-observer variability, the largest amount of variation was found in biventricular ESV and right ventricular mass. Although two observers extensively discussed criteria for border detection beforehand, these variables together with left ventricular mass showed the largest variation in interobserver variability analysis. When critically reviewing the individually traced contours afterwards, the variation could be explained by different interpretations in the basal slice and in the apical slices.

In the basal area, even small differences in inclusion or exclusion of certain areas can result in large differences in absolute volumes and remains an area in which there may be much discussion if image acquisition in the short axis plane is used. For the right ventricle, assessment in the short axis orientation complicates identification of the position of the pulmonary and tricuspid valves. The axial orientation facilitates detection of the atrioventricular valve border and has a lower intra-observer and interobserver variability than the short axis method [27]. However, acquisition in short axis orientation has two advantages: (1) only one data set is required for biventricular measurements; (2) there is less partial volume effect of blood and myocardium on the inferior wall of the RV compared to the axial orientation [27].

Three-dimensional volumetric analysis, also using the vertical and horizontal long axis planes for adequate delineation of the atrioventricular valve plane, will facilitate border delineation in the basal area [29], even more so in patients with complex congenital heart disease. In the apical area, trabeculations complicate exact border delineation between blood and myocardium. In patients with congenital heart disease, edge detection can be even more complicated. Variations within and between observers will remain an important issue to be taken into consideration when evaluating follow-up data of myocardial mass. Despite these shortcomings, follow-up studies in patients with congenital heart disease are feasible when side-by-side comparisons are made to ascertain identical image analysis.

The results of our study show acceptable 95% confidence intervals for the mean values of biventricular volumes and mass, and wide 95% prediction intervals for the absolute values of biventricular volumes or mass (figures 1 to 3). This could be due to the relatively small sample size of this study. However, when comparing our results to adult CMR studies with larger sample sizes [12, 16, 17], e.g. 120 and 487 subjects, the range of biventricular volumes and mass is comparable. Therefore, we consider our results representative normal values for this age group.

For biventricular volumes and mass, the regression lines for the mean values can be used to predict the values for individuals and are helpful in follow-up studies. For a given BSA, volumes or mass should be within the 95% prediction bands (presented in figures 1-3) to be considered normal. During follow-up, with a higher BSA, the 95% prediction interval changes. The slope of the line connecting two measurements can be compared with the given slope of the regression line. If the slope of a line connecting two measurements from a patient differs from the slope (and its 95% confidence interval) as presented in table 2, this can be considered a significant increase or decrease of the variable with increasing BSA. This interpretation might be helpful in timing of (re) interventions.

Study limitations

The imaging parameters used in this study have been implemented because of the combination of acceptable scanning time per image and acceptable spatial resolution, and are therefore applicable in daily clinical practice with pediatric patients. Spatial resolution, however, can be improved and yield better contrast between blood and myocardium and less variability in study results. The results of this study are, thus, applicable to studies with comparable imaging parameters. When comparing results from different studies, special attention should be made to the image analysis, since there are many different criteria used for border detection (selection of the basal slice, inclusion or exclusion of trabeculae, papillary muscles, etc.).

Conclusions

Assessment of biventricular volumes, function, and mass in 60 healthy children aged 8-17 years, reveals normative data for this group with good intra-observer and interobserver variability. Gender is a significant modifier of the relation between BSA and biventricular volumes and mass in children.

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Chapter 7

Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging

Saskia E. Luijnenburg, MD[a-d]; Daniëlle Robbers-Visser, MD[a, b]; Adriaan Moelker, MD, PhD[b]; Hubert W. Vliegen, MD, PhD[c]; Barbara J.M. Mulder, MD, PhD[d, e]; Willem A. Helbing, MD, PhD[a, b]

[a] Department of Paediatrics, Division of Cardiology, Erasmus Medical Center - Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Radiology, Erasmus Medical Center, Rotterdam, the Netherlands

[c] Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

[d] Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands

[e] Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands

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Abstract

Objective: to assess intra-observer and interobserver variability of biventricular function, volumes and mass in a heterogeneous group of patients with CHD using CMR imaging.

Methods: Thirty-five patients with CHD (7 – 62 years) were included in this study. A short axis set was acquired using a steady-state free precession pulse sequence. Intra-observer and inter-observer variability was assessed for left ventricular (LV) and right ventricular (RV) volumes, function and mass by calculating the coefficient of variability.

Results: Intra-observer variability was between 2.9% and 6.8% and interobserver variability was between 3.9% and 10.2%. Overall, variations were smallest for biventricular end-diastolic volume and highest for biventricular end-systolic volume.

Conclusions: Intra-observer and interobserver variability of biventricular parameters assessed by CMR imaging is good for a heterogeneous group of patients with CHD. CMR imaging is an accurate and reproducible method and should allow adequate assessment of changes in ventricular size and global ventricular function.

Introduction

Assessment of ventricular function is important in the follow-up of patients with congenital and acquired heart disease. Cardiovascular magnetic resonance (CMR) imaging is frequently used for the assessment of both left ventricular (LV) and right ventricular (RV) size and function, because it is an accurate and non-invasive method, which has been validated extensively [1].

Reproducibility of CMR measurements plays an important role in establishing the feasibility of CMR imaging in clinical practice. Whether differences in measurements are caused by progression of disease or could be explained by intra-observer or interobserver variability is of crucial importance, because CMR imaging has a main contribution to decision making and timing of (re) interventions.

There are several reports on the reproducibility of CMR measurements, but most have been done in healthy patients or patients with acquired heart disease [2-11]. Only a few studies measured reproducibility in patients with CHD [12-15]. These studies were performed using gradient echo imaging pulse sequences [12] or only examined a selected group of patients (tetralogy of Fallot (TOF), atrial septal defect (ASD) or systemic RV) [13-15]. Intra-observer and interobserver variability has never been studied in a heterogeneous group of patients with CHD, representative for the total spectrum in a clinical program.

In patients with CHD, the RV is often involved in the disease process. The geometric shape of the RV can be altered by abnormal volume- and/or pressure loading conditions, e.g. caused by pulmonary regurgitation in patients with TOF, or due to extensive trabeculation with hypertrophy, as in patients with intra-atrial correction of transposition of the great arteries (TGA). In theory, the complex geometry of the RV in patients with CHD can potentially lead to higher intra-observer and interobserver variability, compared to measurements in healthy volunteers.

The objective of this study was to assess intra-observer and interobserver variability of biventricular function, volumes and mass in a heterogeneous group of patients with CHD using CMR imaging.

Material and Methods

Subjects

Thirty-five patients with CHD (26 males, 9 females; mean age 22 ± 13 years, range 7 – 62 years) were included in this study. The subjects were selected from the total group of patients with CHD in whom CMR imaging was requested in daily clinical practice in 2007. The study was approved by the institutional review board.

The characteristics of the study population are displayed in table 1. The distribution of diagnoses in our study group was representative of the distribution of diagnoses in the total group of subjects with CHD undergoing CMR imaging in 2007.

Table 1. Characteristics of the study population

Characteristic	Value	
Gender (male / female)	28/9	
Age (years)	22.2 ± 13.2	(6.8 – 61.6)
Heart rate (beats per minute)	76 ± 11	(62 – 101)
Diagnosis		
- Aortic stenosis (repaired/unrepaired)	n = 5	(4/1)
- ASD (unrepaired)	n = 1	
- ccTGA, PA, VSD (repaired)	n = 1	
- DORV, VSD, coarctation (repaired)	n = 1	
- Fontan circulation (dominant RV/dominant LV)	n = 10	(3/7)
- Intra-atrial correction of TGA	n = 3	
- PA, VSD (repaired)	n = 3	
- Pulmonary stenosis (repaired)	n = 1	
- Tetralogy of Fallot (repaired)	n = 8	
- VSD (unrepaired)	n = 2	

Reported data are expressed as mean ± SD (range). Abbreviations: ASD = atrial septal defect; ccTGA = congenitally corrected transposition of the great arteries; PA = pulmonary atresia; VSD = ventricular septal defect; DORV = double outlet right ventricle; RV = right ventricle; LV = left ventricle; TGA = transposition of the great arteries.

CMR image acquisition

CMR imaging was performed using a Signa 1.5 Tesla whole-body MR imaging system (General Electric, Milwaukee, WI, USA). An 8-channel phased-array cardiac surface coil was placed on top and beneath the chest. All patients were monitored by vector cardiogram gating and respiratory monitoring. Studies were performed by experienced MR-technicians, supervised by one of the four physicians (SEL, DR-V, AM, WAH), or by the physicians themselves. Standard scout images were made to obtain a four-chamber view of the heart. A short axis set, using steady-state free precession (SSFP) cine imaging, was acquired from base to apex. An average of thirteen contiguous slices were planned on the four-chamber image, parallel to the atrioventricular valve plane of the LV in end-diastole. Typical imaging parameters were: repetition time 3.4 ms, echo time 1.5 ms, flip angle 45°, receiver bandwidth 125 kHz, slice thickness 7–10 mm, inter-slice gap 0–1 mm, field of view 380 x 380 mm, phase field of view 0.75 and matrix 164 × 128 mm. All images were obtained during breath-hold in end-expiration.

CMR analysis

The CMR studies were analyzed on a commercially available Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA), equipped with Q-mass (version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands).

The ventricular volumetric data set was quantitatively analyzed using manual outlining of endocardial and epicardial borders in end-systole and end-diastole. The following parameters were calculated: biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and mass. Criteria for border detection were used as described by Robbers-Visser et al. [11] Specifically: end-diastole and end-systole were visually defined on multiple midventricular slices. In the basal slices, the following criteria were used: 1) when the cavity was only partially surrounded by ventricular myocardium, only the part up to the junction with atrial tissue was included in the ventricular volume; 2) when the pulmonary or aortic valve was visible in the basal slice, contours were drawn up to the junction with the semilunar valves [16]. The interventricular septum was included in the left ventricular mass. Major papillary muscles and trabeculations were excluded from the ventricular volumes and included in the ventricular mass [17].

Ventricular volume was calculated as the sum of the ventricular cavity areas multiplied by the slice thickness. Ventricular mass was calculated as the difference between the epicardial and endocardial contours multiplied by the slice thickness and a specific gravity of the myocardium of 1.05 g/ml. [18]

All data sets were analyzed by one observer (SEL). For intra-observer variability, studies were reanalyzed after an average period of six months. For interobserver variability, a second observer (DR-V) analyzed all studies and measured the aforementioned parameters independently and blinded to previous results.

Statistical analysis

Data are expressed as frequencies, or mean ± standard deviation. Intra- and interobserver variability was assessed using the method of Bland-Altman [19]. The coefficient of variability, i.e. the standard deviation of the difference of the two measurements divided by the mean of the two measurements, and multiplied by 100%, was calculated to study the percentage of variability of the measurements. A p-value < 0.05 was considered statistically significant.

Results

The intra-observer and interobserver variability data are displayed in table 2. Intra-observer variability was between 2.9% and 6.8%, with the smallest variation in measurements of LV and RV EDV (2.9% and 3.0% respectively). The highest variation was found in LV ESV (6.8%) and RV mass (5.7%). Interobserver agreement demonstrated more variation for all variables and was between

Table 2. Intra-observer and interobserver variability analysis

	LV-EDV	LV-ESV	LV-SV	LV-EF	LV-mass	RV-EDV	RV-ESV	RV-SV	RV-EF	RV-mass
Intra-observer										
Mean difference ± SD	1.6 ± 3.9	1.9 ± 3.4	-0.4 ± 3.4	-0.9 ± 2.3	0.6 ± 4.1	0.9 ± 5.3	3.4 ± 3.4	-2.5 ± 4.4	-1.6 ± 1.9	0.1 ± 4.7
Limits of agreement	-6.3 to 9.4	-4.9 to 8.8	-7.2 to 6.5	-5.6 to 3.7	-7.6 to 8.9	-9.7 to 11.5	-3.3 to 10.2	-11.4 to 6.4	-5.4 to 2.1	-9.3 to 9.5
Mean value ± SD	134.9 ± 42.5	50.3 ± 19.2	84.7 ± 27.8	62.9 ± 6.4	125.2 ± 47.3	179.3 ± 84.8	86.9 ± 51.9	92.3 ± 37.2	53.8 ± 9.5	81.8 ± 44.6
Coefficient of variability	2.9%	6.8%	4.1%	3.7%	3.3%	3.0%	3.9%	4.8%	3.5%	5.7%
Inter-observer										
Mean difference ± SD	0.3 ± 5.8	1.6 ± 5.1	-1.1 ± 4.4	-0.9 ± 2.5	-0.3 ± 7.5	4.0 ± 7.1	6.8 ± 6.4	-2.6 ± 5.2	-2.7 ± 3.0	2.4 ± 5.0
Limits of agreement	-11.2 to 11.9	-8.6 to 11.8	-9.9 to 7.6	-5.9 to 4.1	-15.3 to 14.8	-10.2 to 18.1	-6.1 to 19.6	-13.0 to 7.8	-8.7 to 3.4	-7.5 to 12.4
Mean value ± SD	135.0 ± 41.6	49.7 ± 18.9	85.4 ± 28.0	63.5 ± 6.9	125.3 ± 47.6	177.6 ± 83.7	83.8 ± 50.9	93.9 ± 37.4	55.2 ± 9.8	80.6 ± 45.6
Coefficient of variability	4.3%	10.2%	5.1%	3.9%	6.0%	4.0%	7.7%	5.5%	5.5%	6.2%

Reported data are expressed as mean ± SD. Coefficient of variability: expressed as a percentage of the SD of the difference divided by the mean of the two measurements. Volumetric variables in milliliters, mass variables in grams. Abbreviations: LV = left ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; RV = right ventricle.

3.9% and 10.2%. The smallest variation was found in LV EF (3.9%) and RV and LV EDV (4.0% and 4.3% respectively). The highest variation was found in measurements of LV and RV ESV (10.2% and 7.7% respectively) and LV and RV mass (6.0% and 6.2% respectively).

Discussion

In our study, intra-observer and interobserver variability for all variables was good. Overall, the variations were smallest for biventricular EDV and highest for biventricular ESV. Although we expected higher intra- and interobserver variability in the RV, because of its complex shape and heavy trabeculations, we did not find a difference in results for both ventricles. Our results are comparable to those of other studies who reported on reproducibility with SSFP CMR imaging [3-4, 6-8, 10-11, 13, 15] (table 3 and table 4).

Recently, Mooij et al. [13] reported on reproducibility in patients with RV dilation (unrepaired ASD (n = 20); TOF (n = 20)) and in a normal RV group (n = 20). Variability for all patients ranged from 3.6% – 13.0%. Mooij et al. examined a selected group of patients, whereas our study population consisted of a more heterogeneous group of patients with CHD, representative for the total spectrum in a clinical program. Valsangiacomo – Buechel et al. [14] reported that observer variability, in ten children with TOF, ranged from < 1 to 5% for intra-observer analysis and from < 1 to 13% for interobserver analysis. Although we cannot compare all our reported results to theirs, this seems comparable to our results.

Similar to our results, other authors found the largest amount of intra-observer or interobserver variation in biventricular ESV [4, 8, 10, 13]. One of the possible explanations is the smaller absolute value of ESV. Similar absolute measurement errors will therefore lead to higher observer variation in ESV, compared to for example EDV. Another source of error is the endocardial border detection, which is more difficult in end systole due to more densely packed trabeculations and papillary muscles [15].

Image analysis

A critical review of contours traced revealed that the interobserver variation for both ventricles was mainly caused by different interpretations in the basal slice and in the apical slices. Guidelines for image analysis might be helpful, but are still a subject of debate. Most authors agree on criteria on how to draw contours in the basal slice [4, 6, 9, 16, 20]. However, there is less consensus about inclusion or exclusion of papillary muscles and trabeculations [3, 6, 15-16]. It is important that the used criteria for border detection are described in reports, because inclusion or exclusion of papillary muscles and trabeculations cause differences in measurements of biventricular dimensions and function [15]. To reduce observer variability, it is important to have clear guidelines for methods of delineation in routine clinical practice as well as in research projects, since different observers may develop slightly different habits.

Table 3. Reports assessing intra-observer variability of biventricular parameters by SSFP CMR imaging

Study	Population / Diagnosis	M/F	Age (yrs)	Statistics	LV					RV				
					EDV	ESV	SV	EF	Mass	EDV	ESV	SV	EF	Mass
This study	n = 35 CHD	26/9	22 ± 13 (7-62)	CoV n = 35	2.9%	6.8%	4.1%	3.7%	3.3%	3.0%	3.9%	4.8%	3.5%	5.7%
Catalano [3]	n = 45 Acquired / Healthy	33/12	49 ± 20 (8-83)	CoV n = 45						7%	9%		10%	12%
Clay [4]	n = 20 Acquired / Healthy	14/6	30	CoV n = 20	5.2%	6.5%		2.9%	4.7%					
Hudsmith [6]	n = 108 Healthy	63/45	38 ± 12 (21-68)	CoV* n = 12	5.6%			2.3%	6.1%	9.0%			5.3%	
Maceira [8]	n = 120 Healthy	60/60	(20-80)	CoV n = 10						3.6%	6.5%	5.9%	4.0%	5.7%
Plein [10]	n = 41 Acquired / Healthy	23/18	53 (32-77)	CoV n = 10	2.8%	10.1%	3.4%	5.2%	3.9%					
Robbers-Visser [11]	n = 60 Healthy	30/30	(8-17)	CoV n = 15	2.1%	5.8%	2.6%	0.01%	3.9%	2.1%	6.0%	2.5%	0.08%	6.2%
Winter [15]	n = 29 Systemic RV	20/9	35 ± 12	CoV n= 20						6.1%	6.7%	9.4%	5.8%	

Reported data are expressed as mean ± SD (range). * CoV, indexed for body surface area (BSA). Abbreviations: CHD = congenital heart disease; Acquired = acquired heart disease; Healthy = healthy controls; M = male; F = female; CoV = coefficient of variability; LV = left ventricle; RV = right ventricle; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction.

Table 4. Reports assessing interobserver variability of biventricular parameters by SSFP CMR imaging

Study	Population / Diagnosis	M/F	Age (yrs)	Statistics	LV					RV			
					EDV	ESV	SV	EF	Mass	EDV	ESV	SV	EF	Mass
This study	n = 35 CHD	26/9	22 ± 13 (7-62)	CoV n = 35	4.3%	10.2%	5.1%	3.9%	6.0%	4.0%	7.7%	5.5%	5.5%	6.2%
Catalano[3]	n = 45 Acquired / Healthy	33/12	49 ± 20 (8-83)	CoV n = 45						8%	11%		12%	13%
Clay[4]	n = 20 Acquired / Healthy	14/6	30	CoV n = 20	3.3%	6.8%		4.6%	3.7%					
Hudsmith [6]	n = 108 Healthy	63/45	38 ± 12 (21-68)	CoV* n =12	2.7%			3.3%	5.2%	9.6%			10.7%	
Karamitsos [7]	n = 10 Healthy	5/5	34 ± 14	CoV n = 10	2.6%	6.9%	3.4%	2.9%	5.8%					
Maceira[8]	n = 120 Healthy	60/60	(20-80)	CoV n = 10						6.3%	8.6%	7.0%	4.4%	7.8%
Mooij[13]	n = 60 ASD / TOF / Healthy	34/26	21 ± 13	CoV* n = 60	3.6%	10.5%	6.6%	5.8%	5.3%	6.4%	13.0%	11.8%	8.0%	11.3%
Plein[10]	n = 41 Acquired / Healthy	23/18	53 (32-77)	CoV n = 41	4.3%	9.4%	9.5%	6.0%	6.0%					
Robbers-Visser[11]	n = 60 Healthy	30/30	(8-17)	CoV n = 15	5.3%	13.9%	3.3%	2.3%	6.1%	3.4%	7.6%	4.5%	2.0%	8.9%
Winter[15]	n = 29 Systemic RV	20/9	35 ± 12	CoV n= 20						10.0%	12.7%	12.2%	7.5%	

Reported data are expressed as mean ± SD (range). * CoV, indexed for BSA. Abbreviations: ASD = atrial septal defect; TOF = tetralogy of Fallot. Other abbreviations as in table 3.

The basal slice will remain an area in which there may be discussion if image acquisition in the short axis plane is used, particularly for the RV. Alternative imaging orientations have been studied, as well as methods to improve image analysis and assessment of volumes and mass. For example, Alfakih et al. [2] found that observer variability for RV measurements in the axial orientation was slightly lower compared to results of the short axis orientation. Strugnell et al. [21] reported on a modified RV short axis orientation, which is aligned to the outflow of the RV. This method demonstrated a closer agreement between the RV and LV stroke volumes compared to the current method. However, observer variability analysis was not performed and should be assessed to establish the real advantage of this new method. Both the axial orientation as well as the modified RV short axis orientation makes detection of the atrioventricular valve border easier. However, the major advantage of the use of the short axis orientation is that only one data set is required for both LV and RV measurements. Furthermore, in the axial orientation, the partial volume effect of blood and myocardium on the inferior wall of the RV can make it difficult to identify the blood / myocardial boundary [2].

Kirschbaum et al. [22] have reported that identification of the mitral valve plane and apex on long-axis images in addition to short axis contours reduces the interstudy variability for all parameters in LV functional assessment, when compared with using short axis images alone. This method might be applicable for the RV as well.

Van der Geest et al. [20] suggested that semiautomated contour detection is less hampered by random variabilities. At present, semiautomatic contour detection algorithms are only available for the LV and still require manual correction in a significant number of slices [10, 20]. Further analysis and improvement of these algorithms is needed to demonstrate a reduction in observer variation.

Catalano et al [23]. and Corsi et al. [24] reported on a technique for volumetric surface detection (VoSD) and quantification of biventricular volumes without tracing and geometric approximations. The VoSD method showed lower observer variation for all parameters compared to the short axis method. Although limitations clearly exist, this technique might improve reproducibility of biventricular assessments [23-24].

Study limitations

The size and variation of our population prevented subgroup analysis. The amount and size of trabeculations and papillary muscles might be a cause of differences in variation between subgroups. In theory, the extensive trabeculations and large papillary muscles in patients with intra-atrial correction of TGA can potentially lead to higher observer variability compared to patients, in whom the shape of the RV is less altered by abnormal loading conditions. In patients after Fontan operation, the interpretation of the basal slice might be more difficult due to the abnormal

anatomy, which can potentially lead to higher observer variability too.

Another issue that should be taken into consideration when evaluating follow-up data, is that variation in CMR measurements could also be caused by interoperator variation, introduced during CMR planning, as reported by Danilouchkine et al. [25]. In research protocols it is favourable to have all studies carried out by the same operator, but in routine clinical practice, this is more difficult to achieve. In our center, image acquisition is perfomed according to a standard protocol and studies are carried out by experienced technicians, under direct supervision of an experienced CMR cardiologist / radiologist, to reduce operator variability.

Conclusions

Variations within and between observers and operators will remain an important issue to be taken into consideration when evaluating follow-up data of MRI measurements, especially in patients in whom CMR imaging contributes to decision-making and timing of (re) interventions as in patients with CHD. Our results show that intra-observer and interobserver variability of biventricular parameters assessed by CMR imaging, using SSFP, is good in a heterogeneous group of patients with CHD. CMR imaging is an accurate and reliable method for follow-up of biventricular function and mass and should allow adequate assessment of changes in ventricular size and global ventricular function.

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Chapter 8

Safety and observer variability of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with complex congenital heart disease

Daniëlle Robbers-Visser, MD[a, b]; Saskia E. Luijnenburg, MD[a, b]; Jochem van den Berg, MD, PhD[a, b]; Jolien W. Roos-Hesselink MD, PhD[c]; Jan L. Strengers MD, PhD[d]; Livia Kapusta MD, PhD[e]; Adriaan Moelker, MD, PhD[b]; Willem A. Helbing, MD, PhD[a, b]

[a] Department of Paediatrics, Division of Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

[c] Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands

[d] Department of Pediatric Cardiology, University MC Utrecht – Wilhelmina Children's Hospital, Utrecht, the Netherlands

[e] Children's Heart Center, UMC St Radboud, Nijmegen, the Netherlands

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Abstract

Objective: to report our experiences regarding safety and intra-observer and interobserver variability of low-dose DCMR in complex CHD.

Methods: In 91 patients, 110 low-dose DCMR studies were performed with acquisition of a short axis set at rest, and during dobutamine administration (7.5 µg/kg/min maximum). We assessed biventricular end-diastolic volumes, end-systolic volumes, stroke volumes, ejection fraction and ventricular mass. Intra- and interobserver variability for all variables was assessed by calculating the coefficient of variation (%), i.e. the standard deviation of the difference divided by the mean of 2 measurements multiplied by 100%.

Results: In three patients minor side effects occurred (vertigo, headache, bigeminy). Ten patients experienced an increase in heart rate of >150% from baseline, although well tolerated. For all variables, intra-observer variability was < 10% at rest and during stress. At rest, interobserver variability was 10.5% maximal. With stress-testing, only variability of biventricular end-systolic volumes (ESV) exceeded 10%.

Conclusions: In patients with complex CHD low-dose DCMR is feasible, and safe. Intra-observer variability is low for rest and stress measurements. Interobserver variability of biventricular ESV is high with stress-testing. Whether this limits the potential usefulness of DCMR for risk assessment during follow-up has to be assessed.

Introduction

Assessment of ventricular function with stress-testing is safe and widely applied in adult patients with coronary artery disease [1]. It is used to study wall motion abnormalities under stress conditions. Stress-testing is able to reveal symptoms not apparent at rest, and can give information on prognostic factors [1-3]. Dobutamine stress echocardiography has been widely used for this purpose, and its use has been extended to pediatric patients with coronary artery abnormalities, e.g. patients after Kawasaki disease or after arterial switch operation for transposition of the great arteries [4,5]. Stress echocardiography has several limitations, such as poor acoustic windowing, high interobserver variability, and high interoperator variability [6]. Cardiovascular magnetic resonance (CMR) imaging combined with dobutamine stress (DCMR) can overcome these limitations and has a higher sensitivity and specificity for identifying coronary artery disease as compared to dobutamine stress echocardiography [7].

In patients with complex congenital heart disease (CHD) several groups have studied the stress response of the heart, predominantly looking at the change in ventricular volumes and ejection fraction during stress-testing. Wall motion analysis is of lesser importance in this patient group with few coronary artery abnormalities. In several small studies abnormal stress responses of ventricular and vascular function have been reported [8-18]. These abnormal stress responses are of special interest since they are potential surrogate markers related to primary endpoints relevant for assessment of long-term outcome, such as death or functional impairment.

Although the clinical usefulness of the abnormal stress responses in patients with complex CHD with DCMR imaging still has to be assessed in follow-up studies, it is important to know the reliability of the measurements and the safety of the technique. The intra-observer and interobserver variability of CMR measurements of biventricular function, volumes, and mass have been assessed in patients and controls at rest and multiple studies have shown a good reproducibility of these measurements [19,20]. Reproducibility of these measurements obtained during stress-testing in patients with complex CHD has only been assessed in one study [9]. The objective of this study was to assess the intra-observer and interobserver variability, and, in addition, to report on the adverse effects of low-dose DCMR imaging in pediatric and adult patients with complex CHD.

Materials and Methods

Patients

We included 91 patients who had undergone 110 low-dose DCMR studies between September 2002 and August 2008. Most of these studies were performed in research protocols and the results of ventricular and vascular responses have been previously published [8-11]. Low-dose DCMR studies that were performed for research purposes conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Dutch Central Committee on Research involving Human Subjects and the institutional review board. All subjects and/or their parents (if required) gave written informed consent. The study group included 54 patients after repair of tetralogy of Fallot, and 37 patients with a functionally univentricular heart after Fontan operation [8-11]. Characteristics of the study population are displayed in table 1 and 2. Median age at study was 14.2 (6.8-25.5) years. We obtained patient demographics, diagnosis, maximal dobutamine dosage, and occurrence of adverse effects.

Table 1. Patient and study characteristics

Characteristic	Patients	
Number (male)	91	(63)
Tetralogy of Fallot/Fontan (n)	54/37	
Age at 1st study (years)	14.2	(6.8-25.5)
Follow-up since repair/palliation (years)	12.5	(5.1)
Repeat studies (n)	19	
Interval 1st and 2nd study (years)	5.0	(0.3)
Systolic blood pressure rest (mm Hg)	115	(9)
Systolic blood pressure stress (mm Hg)	133	(14)
Heart rate rest (beats per minute)	75	(13)
Heart rate stress (beats per minute)	91	(17)
Adverse effects (n)	3	
Vertigo (n)	1	
Bigeminy (n)	1	
Minor headache (n)	1	
Studies discontinued (n)	2	
Dobutamine lowered to 5 µg/kg/min (n)	10	

Data are given as frequencies, median (range), or mean (standard deviation) as appropriate.

Table 2. Diagnoses in patients after Fontan operation

Diagnosis	Number
Tricuspid atresia	10
Pulmonary atresia/intact ventricular septum	3
Double inlet left ventricle	6
Double outlet right ventricle	7
Hypoplastic left heart syndrome	5
Other complex CHD	6

CMR study

The study protocol and image analysis have been previously reported [8-11]. In summary, all patients underwent CMR imaging at a Signa 1.5 Tesla whole-body MR imaging system (General Electric, Milwaukee, WI, USA). A multi-phase, multi-slice volumetric data set was acquired using a fast 2D cine scan employing steady-state free precession. Contiguous slices were planned starting at and parallel to the atrioventricular valve plane of the systemic ventricle to cover the heart from base to apex. Imaging parameters: slice thickness 7 to 10 mm, inter-slice gap 0 mm, field of view 280-370 mm, phase field of view 0.75, matrix 160 x 128 mm, repetition time 3.5 ms, echo time 1.5 ms, 12 views/segment, flip angle 45°, mean in-plane resolution 2 mm^2, range of temporal resolution 22-37 ms. When the study protocol had been completed at rest, dobutamine-hydrochloride (Centrafarm Services, Etten-Leur, the Netherlands) was administered by continuous infusion into a large antecubital vein at 7.5 µg/kg/min. In healthy children important changes in systolic function, diastolic function, and afterload occur from 5 µg/kg/min, and the incidence rate of adverse symptoms increases significantly from 10 µg/kg/min [21,22]. Therefore, a dobutamine dosage of 7.5 µg/kg/min was considered safe and effective. When heart rate and blood pressure were at steady state, a second short-axis stack was acquired. Dobutamine infusion was lowered to 5 µg/kg/min whenever heart rate, systolic blood pressure, or diastolic blood pressure increased to more than 150% from baseline or decreased to less than 80% from baseline. The test was discontinued in the event of arrhythmias or significant patient discomfort. Dobutamine was administered for ten minutes to reach a new steady state and another ten minutes for image acquisition.

Image analysis

From the short-axis set biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF), and mass were assessed with manual contour detection. Criteria for border detection have been previously described [23]. For intra-observer variability, 25 randomly selected studies (15 tetralogy of Fallot, 10 Fontan studies) were reanalyzed after a mean period of eleven months (SD 11, range 1-38 months). For interobserver variability, a second experienced observer analyzed these 25 studies and measured the aforementioned parameters independently and blinded to previous results. The two observers who were involved in these analyses (DR-V and SEL) have 3.5 years and 1.5 years CMR experience in patients with complex CHD respectively.

Statistical analysis

Data with a normal distribution are expressed as mean value ± one standard deviation, whereas the median (range) is shown for data with a non-normal distribution. Dichotomous data are presented as counts and percentages. Intra- and interobserver variability were assessed using the method of Bland-Altman [24]. The coefficient of variation, i.e. the standard deviation of the difference of the two measurements divided by the mean of the two measurements, and multiplied by 100%, was calculated to study the percentage of variability of the measurements. A p-value < 0.05 was considered to indicate statistical significance.

Results

Minor side effects occurred in three patients. In one patient with vertigo, the CMR study was discontinued subsequently. Another patient with bigeminy completed the first study. Due to inadequate triggering during the bigeminy, images were of insufficient quality for analysis. She experienced the same side effect during a repeat study five years later and the study was discontinued for this reason. One patient with minor headache completed the whole study. All side effects disappeared shortly after discontinuation of dobutamine administration. In ten Fontan patients, dobutamine was lowered to 5 µg/kg/min because of an increase in heart rate of more than 150% from baseline, although this was well tolerated. In conclusion, of 110 studies two studies were discontinued because of minor side effects, only one study was of insufficient image quality.

Table 3 and 4 show the intra-observer and interobserver variability for the rest and stress measurements. At rest intra-observer variability was good with the coefficient of variation between 2.3 and 8.7 %. During stress-testing, intra-observer variability was between 3.0 and 7.0%. The highest variation was found in biventricular ESV and mass. At rest, interobserver variability was between 3.6 and 10.5% and again, the highest variation in biventricular ESV and mass. With stress-testing, the coefficient of variation of all variables stayed $< 10\%$, except for biventricular ESV. The latter increased to $\geq 14.9\%$, which was significantly higher compared to the rest measurements ($p = 0.04$ for intra-observer variability, $p = 0.004$ for interobserver variability).

Table 3. Intra- and interobserver variability analysis of rest measurements

	LV-EDV	LV-ESV	LV-SV	LV-EF	LV-mass	RV-EDV	RV-ESV	RV-SV	RV-EF	RV-mass
Intra-observer variability										
Mean value	87 (25)	37 (13)	51 (14)	58 (7)	69 (20)	133 (28)	65 (17)	69 (15)	52 (6)	25 (6)
Mean difference	1.2 (3.4)	1.2 (3.0)	-0.1 (1.6)	-0.7 (2.4)	-0.5 (5.2)	-1.2 (4.2)	0.9 (2.8)	-2.1 (2.2)	-1.2 (1.2)	0.5 (1.9)
Limits of agreement	-5.6 to 8.0	-4.8 to 7.2	-3.3 to 3.1	-5.5 to 4.1	-10.9 to 9.9	-9.6 to 7.2	-4.7 to 6.5	-6.5 to 2.3	-3.6 to 1.2	-3.3 to 4.3
Coefficient of variation	4.3%	8.7%	3.3%	4.1%	6.6%	3.2%	3.9%	4.0%	2.3%	7.3%
Inter-observer variability										
Mean difference	-0.4 (3.8)	0.5 (3.4)	-1.0 (2.7)	-0.8 (3.3)	0.9 (6.1)	3.7 (4.7)	3.7 (4.1)	-0.09 (4.1)	-2.0 (3.5)	0.6 (2.2)
Limits of agreement	-10.8 to 10.4	-10.2 to 12.6	-10.2 to 7.4	-7.4 to 6.6	-20.3 to 20.9	-8.8 to 22.4	-8.4 to 22.4	-15.3 to 14.7	-9.0 to 5.0	-6.1 to 8.7
Coefficient of variation	4.1%	10.5%	5.9%	5.7%	10.5%	3.6%	7.3%	6.9%	6.7%	9.0%

Data are given as mean (standard deviation). Volumetric variables in milliliters/m^2, mass in grams/m^2. Abbreviations: LV = left ventricular; RV = right ventricular .

Table 4. Intra- and interobserver variability analysis of stress measurements

	LV-EDV	LV-ESV	LV-SV	LV-EF	RV-EDV	RV-ESV	RV-SV	RV-EF
Intra-observer variability								
Mean value	78 (26)	23 (10)	55 (19)	71 (7)	121 (27)	44 (13)	76 (18)	64 (6)
Mean difference	0.8 (2.4)	0.6 (1.3)	0.2 (1.9)	-0.8 (2.1)	-0.5 (4.6)	-0.2 (2.4)	-0.4 (4.2)	-0.2 (2.0)
Limits of agreement	-4.0 to 5.6	-2.0 to 3.2	-3.7 to 4.0	-5.0 to 3.4	-9.7 to 8.7	-5.0 to 4.6	-8.8 to 8.0	-4.2 to 3.8
Coefficient of variation	3.4%	7.0%	3.6%	3.0%	3.8%	5.4%	5.4%	3.1%
Inter-observer variability								
Mean difference	-0.7 (5.2)	-0.4 (4.1)	-0.2 (2.9)	0.06 (3.4)	-0.5 (5.4)	-0.3 (5.6)	-0.2 (3.2)	-0.3 (4.4)
Limits of agreement	-11.1 to 9.7	-8.6 to 7.8	-6.0 to 5.6	-6.8 to 6.8	-11.3 to 10.3	-11.5 to 10.9	-6.6 to 6.2	-9.1 to 8.5
Coefficient of variation	6.6%	17.4%	6.3%	4.8%	5.3%	14.9%	5.0%	6.9%

Data are given as mean (standard deviation). Volumetric variables in milliliters/m^2, mass in grams/m^2. Abbreviations: LV = left ventricular; RV = right ventricular .

Discussion

Although the first report on stress imaging in patients with CHD involved echocardiography [25], its implementation has been largely hampered by the limitations of the acoustic window that occur in this patient group. Suboptimal image acquisition and suboptimal image quality are common in patients with complex cardiac anatomy. Combined with an abnormal orientation of the heart and great vessels in the chest, and the problems encountered in imaging the single and right ventricle [26,27], this has led to limited use of stress echocardiography in CHD. CMR imaging overcomes these limitations in this patient gro up. In this report, we demonstrated the feasibility of low-dose DCMR imaging in selected pediatric and adult patients with complex CHD. Intra-observer and interobserver variability for biventricular function, volumes, and mass were good. In addition, low-dose DCMR imaging was safe, with a low incidence of minor adverse effects.

In this study, the incidence of adverse effects was 4%. The reported effects (bigeminy, headache, vertigo) were not severe, and all disappeared shortly after discontinuation of dobutamine administration. Major side effects, such as ventricular arrhythmias or even death, have been described in adult patients with coronary artery disease, receiving high doses of dobutamine of up to 40 µg/kg/min [1,2]. High-dose dobutamine stress imaging is rarely used in children and patients with CHD [13,28-30]. It is usually performed to induce wall motion abnormalities in patients with coronary artery abnormalities [4,13]. In both echocardiographic and CMR studies, no major side effects have been reported in pediatric patients using high-dose dobutamine. However, minor side effects, such as headache, nausea, has been reported in up to 20% [4]. DCMR imaging has been combined with low-dose dobutamine stress-testing in patients with complex CHD in most studies [8-12,14-18].

In other studies performing low-dose dobutamine stress imaging in patients with CHD, the reported incidence of arrhythmias is low. Of these, all occurred with a dobutamine dosage of ≥ 10 µg/kg/min, as has been demonstrated in healthy children [12,16,21,22,28]. In the study by Fratz et al. three of 23 patients experienced arrhythmias at 10 µg/kg/min that disappeared at 5 µg/kg/min [12]. In another study, the reported arrhythmia occurred at a dobutamine dosage 15 µg/kg/min necessitating termination of that particular DCMR study [16]. At a dobutamine dosage of 20 µg/kg/min, one of 21 patients with tetralogy of Fallot had a monomorphic non-sustained ventricular tachycardia of fifteen beats [28].

Different dobutamine dosages are used in other studies performing low-dose DCMR imaging in patients with CHD, ranging from 5 to 15 µg/kg/min[12,14-18]. In our experience, a dobutamine dosage of 7.5 µg/kg/min is safe, with a low incidence of only minor adverse effects. It is high enough to elicit a significant cardiovascular response and to demonstrate abnormal stress responses in patients with CHD [8-11]. Although in 27% of Fontan patients dobutamine was lowered to 5 µg/kg/min because of an increase in heart rate of > 150% from baseline, we do not think this

is a contra-indication for this dosage in these patients since it was well tolerated without patient discomfort. Standardization of low-dose dobutamine stress protocols will facilitate comparison of different stress responses in different types of CHD.

Intra-observer and interobserver variability of biventricular function, volumes and mass with CMR imaging at rest have been reported in healthy subjects and in patients with tetralogy of Fallot [19,20,23]. The results of these studies are comparable to our results in table 3. When comparing intra-observer variability of rest and stress measurements, in general, the variability of LV measurements was lower during stress-testing, and the variability of RV measurements was somewhat higher during stress-testing, but still <10%. Interobserver variability of biventricular SV and EF improved with stress-testing or was comparable to the rest measurements. Interobserver variability of biventricular EDV and ESV was higher with stress-testing, with the highest increase in the variability for biventricular ESV (table 3 and 4). This was an unexpected finding as we observed a better blood-myocardial contrast in end-systole during stress-testing when compared to rest. This could be explained by the fact that with increased heart rates during stress-testing, there is a faster inflow of unsaturated blood into the region of interest which will yield more signal during acquisition. However, during stress-testing, biventricular ESV decreased significantly, so that small differences in consecutive measurements (with a comparable standard deviation of the difference for LV ESV at rest and during stress), result in an increase in the coefficient of variation. For clinical evaluation, EDV and EF are important parameters to study cardiac functional status with MRI in patients with CHD [31,32]. Therefore, with the current experiences, we do not think the higher variability of biventricular ESV during stress-testing limits the potential clinical usefulness of low-dose DCMR imaging. However, as stated before, the clinical usefulness of the abnormal stress responses in patients with complex CHD with DCMR imaging still has to be assessed and it might be possible that the stress response of RV ESV or LV ESV turns out to be an interesting parameter. The use of reliable automatic contour detection, that is not available for complex CHD up until now, will be an important improvement in diminishing observer variability.

Conclusions

In patients with complex CHD CMR imaging combined with low-dose dobutamine stress-testing is feasible, safe, and can be performed in selected pediatric and adult patients. Intra-observer variability is low for both rest and stress measurements. With stress-testing, interobserver variability of biventricular ESV increases significantly. Whether this limits the potential usefulness of DCMR imaging for risk assessment during follow-up has to be assessed.

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Chapter 9

Stress imaging in congenital heart disease

Daniëlle Robbers-Visser[a, b]; Saskia E. Luijnenburg[a, b]; Jochem van den Berg[a, b]; Adriaan Moelker[b]; Willem A. Helbing[a, b]

[a] Department of Paediatrics, Division of Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Radiology, Erasmus MC, Rotterdam, the Netherlands

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Abstract

In patients with coronary artery disease, stress imaging is able to demonstrate wall motion abnormalities and coronary perfusion abnormalities not apparent at rest, and it can provide information on prognostic factors. In patients with congenital heart disease, stress imaging is used to determine contractile reserve, wall motion abnormalities, and global systolic function, but also to assess diastolic function, and vascular function. In these patients the majority of studies induced stress using pharmacological agents, mainly low-dose to high-dose dobutamine. The clinical usefulness of abnormal stress responses found in patients with congenital heart disease has to be addressed in follow-up studies. The abnormal stress responses might serve as surrogate endpoints, predicting primary endpoints at an early stage, that are useful for risk stratification in this growing patient population. This review describes the stress imaging studies performed in patients with congenital heart disease so far, with a special emphasis on echocardiography and cardiac magnetic resonance imaging.

Introduction

In 1979, Wann et al. identified exercise-induced wall motion abnormalities with 2-dimensional echocardiography in patients with ischemic heart disease [1]. From then on assessment of ventricular function with stress imaging has been widely applied in patients with coronary artery disease [2]. In these patients, stress imaging is able to demonstrate wall motion and coronary perfusion abnormalities not apparent at rest, and can provide information on risk factors and prognostic factors [2-4]. The use of stress imaging has been extended to patients with dilated or hypertrophic cardiomyopathy, valvular heart disease and congenital heart disease. In patients with dilated or hypertrophic cardiomyopathy, stress imaging is used to assess wall motion abnormalities, outflow tract pressure gradients, and contractile reserve, i.e. the change in ventricular ejection fraction with stress-testing [5]. In patients with congenital heart disease, stress imaging is used to determine contractile reserve, wall motion abnormalities, and global systolic function, but also to assess diastolic function, and vascular function. In this review, we will discuss the use, limitations, and future applications of stress imaging in patients with congenital heart disease with an emphasis on echocardiography and cardiovascular magnetic resonance imaging.

Stressors

Physical exercise

Physical exercise is the 'ideal' stressor. It results in the combined activation of cardiac, pulmonary, vascular, neurohormonal, muscular, and metabolic systems involved in the adaptations to stress. Common tools to perform physical exercise during imaging procedures are the treadmill, bicycle ergometer, or handgrip. Specific magnetic resonance-compatible supine or upright bicycle ergometers have been used for exercise testing in combination with magnetic resonance imaging. It is of importance to consider the posture of the patient during stress-testing, since this has a significant effect on central hemodynamics, with lower cardiac output, higher stroke volumes, and lower heart rates in supine compared to upright position [6].

Different stress protocols have been described during stress imaging in patients with congenital heart disease. Examples are: 1) exercise to a certain percentage of their maximal exercise capacity or oxygen consumption [7-9]; 2) symptom-limited exercise [10-12]; 3) exercise at 0.5 and 2.5 W/kg [13-16]. Physical exercise has several limitations. Maximal physical stress is dependent on the patient's motivation and cooperation, and cannot be attained in patients with certain neurologic or orthopedic co-existing diseases. Hyperventilation during physical exercise hinders breath-hold during image acquisition. In combination with echocardiography, image acquisition during physical exercise is difficult and therefore acquisition usually takes place directly after exercise. This is applicable to magnetic resonance imaging specifically [8, 9, 16-18], although with real-time imaging this limitation has been overcome and scanning during rapid breathing is feasible, even in patients with complex congenital heart disease [14, 15].

Pharmacological stress

During the 1980's pharmacological agents were introduced to overcome the limitations of physical exercise [19, 20]. Pharmacological stressors have extended the use of stress imaging to patients with constraints that preclude adequate exercise. The most commonly used drugs are adenosine, dipyridamole, and dobutamine.

Adenosine and dipyridamole are coronary vasodilators that generate a reduced oxygen supply in myocardial areas supplied by stenotic coronary arteries, and are used for coronary perfusion imaging. Adenosine is a naturally occurring substance in the body that causes coronary vasodilatation through activation of A2-receptors. This results in increased blood flow in normal coronary arteries compared to stenotic coronary arteries ("steal phenomenon"), resulting in a perfusion mismatch. It does not necessarily cause ischemia. Adenosine has a very short half-life of only two seconds and therefore needs to be administered through continuous intravenous infusion. The adenosine dose rate used for stress-testing is 0.14 mg/kg/min over six minutes or until significant patient discomfort, whichever comes first. Common side effects are flushing, dyspnea, chest pain, gastro-intestinal discomfort, headache, and light-headedness. Most side effects disappear shortly after discontinuation of adenosine administration and do not require medical treatment. Adenosine is contra-indicated in patients with active restrictive airway disease, second or third degree atrioventricular block, and in patients taking dipyridamole. Since theophylline and caffeine are adenosine receptor antagonists, abstention of these substances is required 24-48 hours before stress testing with adenosine or dipyridamole. In patients with congenital heart disease, adenosine has been rarely used for stress imaging, since coronary artery abnormalities are not common.

Dipyridamole inhibits reuptake of adenosine by vascular endothelial cells and indirectly causes coronary vasodilatation. Dipyridamole has a considerably longer half-life than adenosine and hemodynamic effects can persist up to 30 minutes. Dipyridamole is administered in a dose rate of 0.56 mg/kg over four minutes. Side effects and contraindications for the use of dipyridamole are similar to those of adenosine.

Dobutamine increases myocardial oxygen demand similar to physical exercise, and is used to study contractile reserve and wall motion abnormalities. Dobutamine is a synthetic catecholamine with positive inotropic and, to a lesser extent, chronotropic effects. In healthy children, positive inotropic effects occur from 1 to 2 µg/kg/min with dose-dependent increases in measures of systolic ventricular function [21], while chronotropic effects are seen from 5 to10 µg/kg/min [22]. Dobutamine is also known to enhance diastolic function and to decrease preload and afterload [23]. In normal subjects, during dobutamine infusion, stroke volume increases, end-diastolic

volume does not change, end-systolic volume decreases, and ejection fraction increases [24]. The half-life of dobutamine is only two minutes and therefore it should be given through continuous intravenous infusion. In patients with congenital heart disease, different dosages are used to answer different research questions. Low-dose or moderate-dose dobutamine is used to assess cardiac contractile reserve. Dobutamine infusion is started at 2.5 or 5 μg/kg/min, and increased every three to five minutes with 2.5 or 5 μg/kg/min to 5 to 20 μg/kg/min. High-dose dobutamine is used to detect wall motion abnormalities in patients with coronary artery abnormalities, as in patients after Kawasaki disease or after arterial switch operation for transposition of the great arteries. Infusion rates usually start at 10 μg/kg/min, and are increased every three to five minutes with 10 μg/kg/min until the heart rate is 85% of the maximal predicted heart rate for age or to 40 μg/kg/min maximum. If 85% of the maximal predicted heart rate for age is not reached at 40 μg/kg/min, atropine can be administered in conjunction with dobutamine to reach the target heart rate. Heart rate, blood pressure, and (if possible) heart rhythm are continuously monitored during dobutamine stress-testing. Common minor side effects, such as headache, nausea, hypertension, hypotension, and hemodynamically insignificant arrhythmias, can occur in up to 20% of children [25]. Major side effects have not been reported in patients with congenital heart disease. Side effects of atropine are dry mouth, tachycardia, and hallucinations. Side effects of both dobutamine and atropine can be treated with β-blockers or calcium antagonists that should be readily available during stress-testing. Dobutamine administration is contra-indicated in patients with a mechanical obstruction of systemic ventricular filling or ejection, in patients with second or third degree atrioventricular block, and in patients with a history of sustained ventricular tachycardia.

The majority of studies with stress imaging in patients with congenital heart disease has been performed with pharmacological stress, almost exclusively using dobutamine. Only one study reported on the safety and feasibility of adenosine-stress cardiovascular magnetic resonance imaging in pediatric patients with congenital aortic stenosis or after arterial switch operation for transposition of the great arteries [26]. High-dose dobutamine stress imaging has only been performed in a limited number of studies with congenital heart disease patients [27-30]. In studies performing low-dose dobutamine stress imaging, different dobutamine dosages are used, ranging from 5.0 to 20 μg/kg/min. In our experience, a dobutamine dosage of 7.5 μg/kg/min is safe, with a low incidence of only minor adverse effects. Furthermore, it is sufficiently high to elicit a significant cardiovascular stress response in patients [31-34]. Arrhythmias are side effects of special concern in this group of patients with congenital heart disease. Although the incidence of arrhythmias is low in the studies performed so far, most occurred with a dobutamine dosage of at least 10 μg/kg/min [35-38]. In patients after Fontan operation for a functionally univentricular heart, dobutamine administration at 7.5 μg/kg/min provoked an increase in heart rate of more than 150% from baseline in 10 of 37 patients [34]. This was well tolerated and lowering the dobutamine dosage to 5 μg/kg/min was sufficient to decrease the heart rate and successfully complete the study protocol, i.e. with images adequate for analysis.

Imaging modalities

Radionuclide myocardial perfusion imaging

Positron emission tomography and single-photon emission computed tomography allow evaluation of myocardial perfusion and the effects of myocardial hypoperfusion on metabolic activity and myocardial contractility [39]. Positron emission tomography and single-photon emission computed tomography cameras capture the photons emitted by radiopharmaceuticals (e.g. nitrogen-13 labeled ammonia, and technetium-99m tetrophosmin or sestamibi) and translate the information into digital data representing the magnitude and location of the emission in the heart. Positron emission tomography has a better performance on spatial and temporal resolution, with less attenuation of the emitted signal than single-photon emission computed tomography. In children and patients with congenital heart disease, positron emission tomography and single-photon emission computed tomography are rarely used and predominantly in patients with coronary artery disease [40-45]. These studies assessed myocardial perfusion and coronary flow reserve at rest and during adenosine or dipyridamole infusion. Although these studies have shown signs of coronary damage or decreased coronary vasoreactivity, use of these imaging modalities is limited because of concerns on radiation exposure in young children. Furthermore, coronary artery abnormalities can also be assessed with radiation-free imaging modalities, such as echocardiography and cardiovascular magnetic resonance imaging.

Echocardiography

Conventional echocardiography, M-mode, Doppler and tissue Doppler imaging have all been performed in combination with stress in patients with various forms of congenital heart disease [7, 10-13, 27-29, 35, 36]. Although the first report on stress imaging in patients with congenital heart disease involved echocardiography, its implementation has been largely hampered by the limitations of the acoustic window that occur in this patient group. Suboptimal image acquisition and suboptimal image quality are common in patients with complex cardiac anatomy. Combined with an abnormal orientation of the heart and great vessels in the chest, and the problems encountered in imaging the single and right ventricle [46, 47], this has led to limited use of stress echocardiography in congenital heart disease.

Magnetic resonance imaging

In patients with coronary artery disease, echocardiography was the imaging modality of choice for stress imaging up until the early 1990's. In 1992 the use of dobutamine stress cardio-

vascular magnetic resonance imaging was introduced [48], and has proven to be a valuable tool to detect ischemia in patients with known or suspected coronary artery disease [3, 49]. Dobutamine stress cardiovascular magnetic resonance imaging can assess wall motion abnormalities, contractile reserve, abnormalities of diastolic function, and vascular function. It has a sensitivity and specificity comparable to dobutamine stress echocardiography for identifying coronary artery disease [49]. Cardiovascular magnetic resonance imaging overcomes the limitations of echocardiography in selected patients with congenital heart disease [50]. A few groups have reported on the use of this modality to evaluate the reaction of the cardiovascular system in congenital heart disease patients under stress conditions [8, 9, 14-16, 18, 26, 30-34, 37, 38, 50-54]. These studies have shown abnormal systolic, and diastolic function, and abnormal vascular responses to stress in these patients that help understand the pathophysiological processes. An important advantage of dobutamine stress cardiovascular magnetic resonance imaging is that all these parameters can be obtained in one single study. Disadvantages of cardiovascular magnetic resonance imaging are the exclusion of patients with claustrophobia, severe obesity, and magnetic resonance-incompatible devices, and the need for sedation or general anaesthesia in young children (usually under five to six years of age).

Stress imaging in children and patients with congenital heart disease

Stress echocardiography

The first report of stress-testing (supine exercise) combined with echocardiography in children with left-sided cardiac disease was published in 1980 [7]. Thereafter stress echocardiography combined with dobutamine was used to assess contractile reserve in children with thalassemia major, children after Kawasaki disease, after chemotherapy for childhood cancer, or heart transplantation [24, 25, 55-58]. These studies showed that dobutamine stress echocardiography might reveal important information on subclinical global ventricular dysfunction or coronary artery disease in these patients.

Only a few studies have reported on stress echocardiography in patients with congenital heart disease. More recently, this technique has also been applied to patients with complex congenital heart disease, e.g. patients after atrial correction or arterial switch operation for transposition of the great arteries, or after Fontan operation, and patients with tetralogy of Fallot [10-13, 27-29, 35, 36]. The results of these studies are summarized in table 1. Half of these studies have been performed in combination with physical exercise. The other 50% has been performed using dobutamine stress-testing, with dosages ranging from 20 to 40 µg/kg/min. With dobutamine infusions of at least 20 µg/kg/min no major side effects have been reported. Hui et al. reported a high incidence of hypertension (in 23 of 31 patients) [35]. However, their definition of hypertension was an increase in systolic blood pressure of > 30% from baseline, while others defined hypertension as an increase in systolic blood pressure of > 50% from baseline [24].

Outcomes of these studies cannot be easily compared. There is a wide variety in patient age, diagnoses, type of measurements with echocardiography, and type of stressor. All studies demonstrated abnormal ventricular and/or vascular responses with stress-testing. Some studies identified these abnormal responses as predictors of exercise capacity [11, 27]. In general, the clinical relevance of these abnormal findings with stress-testing is unknown. Standardized studies using identical stressors and identical methods of measurement are needed to determine the clinical relevance in patients with congenital heart disease. Furthermore, the combination of new techniques, such as 3-dimensional echocardiography, with its capability for assessment of ventricular volumes and dyssynchronicity, and of tissue Doppler and speckle tracking techniques with stress imaging need further exploration.

Stress cardiovascular magnetic resonance imaging

A few groups have performed stress cardiovascular magnetic resonance imaging in patients with congenital heart disease. Table 2 is an overview of the stress cardiovascular magnetic resonance studies that have been performed in patients with different types of congenital heart disease. In more than 200 patients, these studies showed the feasibility and safety of stress cardiovascular magnetic resonance imaging. Unfortunately, as in stress echocardiography studies, differences in patient groups, age ranges, measurement types, and stress protocols preclude direct comparison of outcomes of these studies.

Stress cardiovascular magnetic resonance studies in congenital heart disease have been performed predominantly in three patient groups: 1) patients with a pressure overloaded right ventricle (congenitally corrected transposition of the great arteries , pulmonary artery stenosis, Eisenmenger syndrome) [8, 37, 38, 50-54]; 2) patients with a volume overloaded right ventricle (after correction for tetralogy of Fallot) [9, 31, 32, 54]; and 3) patients with a potentially impaired ventricular preload as a result of atrial baffle reconstruction (after Fontan operation or atrial correction for transposition of the great arteries) [14-16, 33, 34, 38, 50, 51, 53].

In patients with a pressure overloaded right ventricle, dobutamine stress cardiovascular magnetic resonance imaging demonstrated abnormal responses of the systemic right ventricle. In patients with congenitally corrected transposition of the great arteries, different stress responses of the systemic right ventricle have been reported, according to the type of repair. In studies by Tulevski et al. and Dodge-Khatami et al. stroke volume did not increase with dobutamine stress cardiovascular magnetic resonance imaging [38, 52]. The latter study did report a normal stress response (with an increase in stroke volume) in unoperated patients with congenitally corrected transposition of the great arteries compared to patients after physiologic repair. Fratz et al. also demonstrated an increase in stroke volume with dobutamine stress cardiovascular magnetic resonance imaging in unoperated patients with congenitally corrected transposition of the great arteries [37]. Dodge-Khatami

Table 1. Stress echocardiography in congenital heart disease

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Alpert [7]	Supine bicycle exercise	19 patients with LV pressure and/or LV volume overload 1 patient with cardiomyopathy 1 patient s.p. LVOTO resection	8-19 years	None	M-mode echocardiography combined with cardiac catheterization: mean Vcf, peak meridional wall stress	Feasibility and safety of the technique. With exercise the change in Vcf and peak wall stress discriminated between different patient groups and indicate functional reserve.
Oyen [13]	Supine bicycle exercise	35 patients with AS, or AVR, or coarctation, or VSD, or AR, or HOCM	6-14 years	None	LV end-diastolic and end-systolic diameter, fractional shortening, and Vcf	Frequency corrected Vcf indicated a disproportion in heart rate increase and LV contraction and could discriminate LV reaction between patients and controls.
Cyran [12]	Upright treadmill exercise	24 patients after coarctation repair	5-19 years	None	Ascending and descending aortic systolic velocities	Identification of descending aortic systolic velocity ab-normalities as a determinant of systolic blood pressure
Kaplan [11]	Supine bicycle exercise	27 patients with TOF, or ASD, or VSD, or TGA, or ccTGA, or Ebstein's anomaly.	17-63 years	None	Biventricular systolic function, peak velocity of tricuspid regurgitation jet, pulmonary valve gradients	Poor exercise tolerance associated with 1) abnormal responses of PA pressure during exercise; 2) abnormal LV systolic function
Hauser [10]	Maximal exercise	21 patients after ASO for TGA 9 patients after Ross procedure	12 (2) years 19 (8) years	None	Conventional, Doppler, and M-mode echocardiography, analysis of WMA	Stress-induced dyskinetic areas in 2 patients after ASO
Li [27]	Dobutamine stress, 40 µg/kg/min max	27 patients after atrial switch for TGA	29 (7) years	Shortness of breath (n = 1) Lightheadedness (n = 1)	Biventricular function applied to the long axis of the heart with conventional echocardiography, Doppler, M-mode and TDI	Depressed RV ventricular long-axis function with stress. Excursion of the RV free wall (at rest or during stress) predicts exercise capacity.
Hui [35]	Dobutamine stress, 20 µg/kg/min max	31 patients after ASO for TGA	7-14 years	Hypertension (n = 23) , arrhyth-mia (n = 7), tachycardia (n = 6), chestpain (n = 3), hypotension (n = 1), headache (n = 1)	2D echocardiography: apical 2 and 4 chamber, parasternal long and short axis for analysis of WMA	Stress induced WMA in 23 patients

Table 1. Continued

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Apostolopulou [28]	Dobutamine stress, 40 µg/kg/min max	25 patients after TOF repair	6-27 years	None	RVOT pulsed Doppler, tricuspid valve continuous Doppler, TDI at the lateral corner of the tricuspid valve annulus	Decreased TDI indices at rest, with a significant gradual increase during dobutamine. TDI indices correlate with functional RV parameters.
Brili [29]	Dobutamine stress, 40 µg/kg/min max	10 patients after Fontan operation	28 (5) years	None	2D and Doppler echocardiography: LVOT diameter and VTI, LV EDV, LV ESV, LV EF, LV SV, CO, WMA	Feasibility and safety of the technique for assessment of global hemodynamics, propensity to arrhythmia and cardiac reserve.
Brili [36]	Dobutamine stress, 20 µg/kg/min max	21 patients after TOF repair	19-48 years	Non-sustained monomorphic VT of 15 beats at 20 µg/kg/min (n = 1)	TDI of the tricuspid valve annulus	Lower TDI indices at baseline and during dobutamine. TDI predicts RV contractile reserve at rest.

Ages are given as ranges, or mean (standard deviation). Abbreviations: AR = aortic regurgitation, AS = aortic stenosis, ASD = atrial septal defect, ASO = arterial switch operation, AVR = aortic valve replacement, ccTGA = congenitally corrected transposition of the great arteries, CO = cardiac output, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, HOCM = hypertrophic obstructive cardiomyopathy, LV = left ventricle, LVOT = left ventricular outflow tract, LVOTO = LVOT obstruction, PA = pulmonary artery, RV = right ventricle, RVOT = right ventricular outflow tract, SV = stroke volume, TDI = tissue Doppler imaging, TGA = transposition of the great arteries, TOF = tetralogy of Fallot, VSD = ventricular septal defect, VT = ventricular tachycardia, VTI = velocity time integral, WMA = wall motion abnormalities.

Table 2. Stress cardiovascular magnetic resonance imaging in congenital heart disease

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Tulevski [50]	Dobutamine, 15 µg/kg/min max	12 patients after atrial switch for TGA	18-28 years	None	Biventricular volumes, function	No increase in RV SV and decrease in LV SV with stress-testing.
Roest [8]	Supine bicycle exercise	10 patients after atrial switch for TGA	17-31 years	None	Biventricular volumes, function Ascending aorta flow	Prolonged SV recovery after supine bicycle exercise in patients after atrial switch for TGA.
Dodge-Khatami [52]	Dobutamine, 15 µg/kg/min max	13 patients with ccTGA	28 (12) years	None	Biventricular volumes, function	No increase in RV SV with DCMR. Five asymptomatic, unoperated patients had near normal volumes and adequate response to stress-testing.
Roest [9]	Supine bicycle exercise	15 patients after TOF repair	14-24 years	None	Pulmonary regurgitation Biventricular volumes, function	Decrease in pulmonary regurgitation with supine bicycle exercise. Abnormal RV response, normal LV response to exercise.
Tulevski [38]	Dobutamine, 15 µg/kg/min max	47 patients with RV pressure overload	26 (5) years	Dizziness, nausea (n = 3). Arrhythmia (n = 1)	Biventricular volumes, function	Clear heterogeneity in response to DCMR between different groups with chronic pressure overloaded RV.
Pedersen [16]	Supine bicycle exercise	11 patients after Fontan operation	11 (5)	None	Branch pulmonary artery and caval vein flow	During exercise: Unchanged flow distribution to the branch pulmonary arteries Increase in cardiac output predominantly by increase in heartrate.
Hjortdal [15]	Supine bicycle exercise	11 patients after Fontan operation	12 (5)	None	Real-time aorta and IVC and SVC flow	Feasibility of the technique. Aortic and IVC flow increase with supine leg exercise. Inspiration facilitates IVC flow at rest, less during exercise.
Tulevski [54]	Dobutamine, 5 µg/kg/min	13 patients with RV pressure overload 9 patients with RV pressure + volume overload	27 (7) years	None	RV volumes, function	During DCMR: significant decrease in RV EDV and RV SV, no increase in EF. Impaired RV filling during stress in asymptomatic or minimally symptomatic patients.

Table 2. Continued

Study	Stressor	Patients	Age	Adverse effects	Measurements	Outcome
Van der Zedde [53]	Dobutamine, 15 µg/kg/min max	13 patients with ccTGA 17 patients after atrial switch for TGA	17-65 years	None	Segmental and global ventricular function and volumes	At rest: TGA-patients have diminished segmental and global ventricular function During stress: ccTGA-patients no increase in segmental and global ventricular function.
Oosterhof [51]	Dobutamine, 15 µg/kg/min max Supine bicycle exercise	39 patients after atrial switch for TGA:	25 (4) years	None	Segmental and global ventricular function and volumes	Dobutamine stress and physical exercise not interchangeably for assessment of systolic and diastolic function in patients with after atrial switch for TGA.
Taylor [26]	Adenosine, 0.14 mg/kg/min	15 patients with congenital AS 2 patients after ASO for TGA	9-17 years	None	Biventricular volumes, function	Feasibility of adenosine stress-testing for assessment of biventricular function during single breath-hold cine CMR
Van den Berg [32]	Dobutamine, 7.5 µg/kg/min max	36 patients after TOF repair	7-23 years	Bigeminy (n = 1)	Biventricular volumes, function Pulmonary artery, tricuspid, and IVC flow	Abnormal relaxation with stress-testing in patients with end-diastolic forward flow
Van den Berg [31]	Dobutamine, 7.5 µg/kg/min max	51 patients after TOF repair	7-26 years	None	Biventricular volumes, function Pulmonary artery and tricuspid flow	Biventricular functional reserve preserved in TOF repaired at young age, irrespective of RV volume
Hjortdal [14]	Supine bicycle exercise	14 Fontan patients	9 (5) years	None	Aortic and caval vein flow	A similar increase in flow rates in Fontan patients as in healthy controls.
Fratz [37]	Dobutamine, 10 µg/kg/min max	12 patients after atrial switch for TGA 11 patients with ccTGA	15-28 years	Arrhythmias (n = 3)	Biventricular function, mass Aortic flow	Non increase in SV during dobutamine stress in patients after atrial switch for TGA. Increased SV in patients with ccTGA.
Robbers-Visser [34]	Dobutamine, 7.5 µg/kg/min max	32 patients after Fontan operation	8-22 years	Minor headache (n = 1)	Systemic ventricular volumes, function. Aortic and IVC flow	Abnormal decrease in EDV with stress-testing, adequate decrease in ESV and increase in EF
Robbers-Visser [33]	Dobutamine, 7.5 µg/kg/min max	14 patients after Fontan operation	8-20 years	None	Branch pulmonary artery flow	Flow variables, distensibility, and wall shear stress lower compared to controls; abnormals reaction to stress.
Strigl [30]	Dobutamine,atropine 40 µg/kg/min max	28 patients with (suspected) coronary artery abnormalities	0.8-22 years	None	Wall motion abnormalities	Feasibility of the technique with high observer agreement for test positivity (κ 1.0) and wall motion analysis (κ 0.72).

Ages are given as ranges, or mean (standard deviation). Abbreviations: AS = aortic stenosis, ASO = arterial switch operation, CMR = cardiovascular magnetic resonance, ccTGA = congenitally corrected transposition of the great arteries, DCMR = dobutamine CMR; EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, IVC = inferior caval vein, LV = left ventricle, RV = right ventricle, SV = stroke volume, SVC = superior caval vein, TGA = transposition of the great arteries, TOF = tetralogy of Fallot

suggested that unoperated patients, with a favorable anatomy, may never require an operation and that dobutamine stress cardiovascular magnetic resonance imaging might be helpful in identifying patients who will need anatomic correction [52]. In patients with pulmonary artery stenosis and in those with Eisenmenger syndrome, end-diastolic volume was significantly larger compared to controls, but ejection fraction was normal at rest. With stress-testing, end-diastolic volume, end-systolic volume, and stroke volume all decreased, and ejection fraction did not change, clearly demonstrating the highly abnormal response of these right ventricles to stress [38].

Several studies have reported on the biventricular stress response in patients with a volume overloaded right ventricle. In a study by Roest et al. supine bicycle exercise demonstrated a decrease in pulmonary regurgitation with stress-testing, and a normal left ventricular stress response in patients with tetralogy of Fallot [9]. Van den Berg and coworkers reported on the results of low-dose dobutamine stress cardiovascular magnetic resonance imaging in patients after contemporary repair of tetralogy of Fallot [31, 32]. They showed well-preserved functional reserve in all patients despite important pulmonary regurgitation and right ventricular dilatation as well as an abnormal relaxation with stress-testing in patients with end-diastolic forward flow, that was not appreciated at rest. Many of these patients with normal contractile reserve had right ventricular volumes that would have made them candidates for pulmonary valve replacement according to right ventricular volume criteria [31, 59]. This demonstrates the potential added value of stress imaging in clinical decision-making.

In patients with an impaired ventricular preload as a result of atrial baffle reconstruction, several study groups have performed various stress cardiovascular magnetic resonance studies. Pedersen, Hjortdal, and Robbers-Visser and coworkers studied the systemic venous return, pulmonary arterial circulation, and systemic ventricular function [14-16, 33, 34]. Pedersen and Hjortdal performed branch pulmonary artery and caval vein flow measurements immediately after exercise or during exercise using real-time cardiovascular magnetic resonance imaging [14-16]. In these studies, the technique was feasible and all children (mean age between nine and twelve years old) were able to perform and complete the protocol. They demonstrated that an increase in cardiac output with exercise is predominantly caused by an increase in heart rate and that the influence of inspiration on systemic venous return is less pronounced during exercise.

Using pharmacological stress with dobutamine at 7.5 μg/kg/min, Robbers-Visser et al. demonstrated an abnormal decrease in end-diastolic volumes and no increase in stroke volumes with stress-testing in patients after Fontan operation at young age [34]. Secondly, they showed abnormal reactions of flow variables, distensibility, and wall shear stress with stress-testing in the branch pulmonary arteries in Fontan patients [33]. These results demonstrate that low-dose dobutamine stress cardiovascular magnetic resonance imaging revealed abnormal findings that were not apparent at rest and that could help in understanding the pathophysiology of this group

of congenital heart disease and the progression of dysfunction during follow-up in these patients.

In patients after atrial switch operation for transposition of the great arteries stroke volume did not increase with pharmacological stress-testing [37, 38, 50, 51]. Roest and coworkers demonstrated a smaller increase in stroke volume in patients after atrial switch when compared to healthy subjects, and a prolonged stroke volume recovery using supine bicycle exercise testing [8]. In patients after intra-atrial correction for transposition of the great arteries, heart rate increase is significantly higher when compared to patients with congenitally corrected transposition of the great arteries or healthy subjects, probably as a compensatory mechanism for the lack of increase in stroke volume with stress-testing [37, 38].

Recently, Strigl et al. were the first to publish their data on the feasibility of high-dose dobutamine stress cardiovascular magnetic resonance imaging in pediatric patients and young adults with (suspected) coronary artery abnormalities, looking at wall motion abnormalities [30]. In 28 patients, they reported no major adverse effects and high-quality imaging of all ventricular wall segments in patients from less than one year of age. However, only one patient had an inducible wall motion abnormality, and they recommended further exploration of high-dose dobutamine stress cardiovascular magnetic resonance in pediatric patients.

The type of stressor should be taken into account when comparing the results of stress studies. Coma-Canella et al. showed a different response in healthy volunteers to physical exercise and to dobutamine stress [60]. Global and regional ejection fraction increased more with dobutamine than with physical exercise. Oosterhof et al. demonstrated a discrepancy in response to physical exercise and low-dose dobutamine stress in patients after intra-atrial correction for transposition of the great arteries, whilst in controls the response to both stressors was comparable [51]. They suggested that this disagreement was the result of differences in preload and afterload. However, both dobutamine and physical exercise increase contractility, and decrease preload and afterload [22, 61]. Secondly, there are some differences in acquisition parameters between the dobutamine and physical exercise studies that might explain discrepancies. Furthermore, the results are based on only 5 patients and additional studies are needed to clarify this phenomenon.

Although the aforementioned studies showed pathophysiologically relevant observations in patients with various types of congenital heart disease, the clinical significance of these abnormal responses still has to be assessed. In congenital cardiology, surrogate endpoints for clinical trials are necessary. Primary endpoints (such as death and major complications) are rare, requiring large study populations or prolonged study length to acquire adequate statistical power, while the patient population is relatively small [62]. Surrogate endpoints are expected to predict a primary endpoint, and have a higher incidence in the patient population under investigation. Thus, surrogate endpoints facilitate clinical trials in congenital cardiology by reducing the numbers of subjects needed and by reducing the length of the study. The abnormal stress responses found in

patients with congenital heart disease are potential surrogate endpoints for this purpose and their clinical usefulness has to be addressed in follow-up studies.

Future applications

As for echocardiography, standardized dobutamine stress cardiovascular magnetic resonance studies using identical stressors and identical methods of measurement are needed to determine the clinical relevance of the abnormal stress responses in patients with congenital heart disease. Future applications of dobutamine stress cardiovascular magnetic resonance imaging in patients with congenital heart disease might involve the assessment of pressure-volume loops. Pressure-volume loops give information on myocardial contractility, ventricular pump function, and ventriculo-arterial coupling, that might help explain the pathophysiological processes in cardiac function in patients with congenital heart disease [63]. Kuehne and co-workers demonstrated the feasibility of magnetic resonance-derived pressure volume loops in the right ventricle of patients with chronic pressure overload [64].

Magnetic resonance tissue-tagging with radiofrequency signals destroys the spins in a selected plane, resulting in a line or grid of signal void on the image [65]. These lines or grids deform with ventricular contraction and relaxation and this allows quantification of strain, i.e. the deformation of an object normalized to its original shape, as a measure of regional myocardial function. In combination with stress-testing, this technique could reveal important regional functional information in patients with complex congenital heart disease. In patients with coronary artery disease the response of systolic strain to low-dose dobutamine has a significant promise in discriminating between viable and non-viable myocardium [66].

Lastly, in pathways with complex flow patterns, e.g. in the Fontan circulation, or intra-atrial baffles, three-directional flow measurements can give important additional information on shear stress and energy dissipation and the influence of increased flow during stress on these variables.

Conclusions

Stress imaging is a tool that has been used in patients with congenital heart disease in a limited way, compared to its implementation in patients with coronary artery disease. Several studies have shown its feasibility and safety. Stress imaging is able to assess systolic, diastolic, and vascular responses in patients with various types of complex congenital heart disease. At present, magnetic resonance imaging has been used more often for this purpose than echocardiography. The clinical relevance of these findings needs to be investigated in standardized study protocols. The abnormal stress responses can potentially be used for risk assessment in the follow-up of patients with congenital heart disease.

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Chapter 10

NKX2-5 and *GATA4* analysis in patients with a functionally univentricular heart

Daniëlle Robbers-Visser[a]; Marja Wessels[b]; Livia Kapusta[c]; Jolien Roos-Hesselink[d]; Willem Helbing[a]; Dennis Dooijes[b]

[a] Department of Pediatrics, division of Cardiology, Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands

[b] Department of Clinical Genetics, Erasmus MC, Rotterdam, the Netherlands

[c] Children's Heart Center, UMC St Radboud, Nijmegen, the Netherlands

[d] Department of Cardiology, Erasmus MC, Rotterdam, the Netherlands

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Abstract

Objective: to assess the incidence of mutations in *NKX2-5* and *GATA4* in patients with functionally univentricular hearts.

Methods: we included 38 non-related patients with non-syndromic functionally univentricular hearts, irrespective of their cardiac anatomy. Direct sequence analysis of all coding regions and intron-exon boundaries of the *GATA4* and *NKX2-5* genes was performed in each patient.

Results: no sequence variants in *NKX2-5* were observed. In two patients mutations in *GATA4* were found. Both patients had right ventricular hypoplasia. In the first patient *GATA4* analysis revealed two missense variants: 1) p.Val380Met (c.1138G>A, *GATA4* exon 5); and 2) p.Pro407Gln (c.1220C>A, *GATA4* exon 6). In the second patient *GATA4* analysis resulted in the identification of the synonymous c.822C>T nucleotide change (p.=) in exon 3. In both cases, the mutations/sequence variants were also identified in the mothers, who had a normal cardiac phenotype. One of these mutations, p.Pro407Gln, was predicted to alter protein function.

Conclusions: P.Pro407Gln is probably a pathogenic mutation with intermediate penetrance. Further investigation of *GATA4* and *NKX2-5* mutations in larger cohorts of patients with ventricular hypoplasia will contribute to elucidate the role of these genes in ventricular cardiogenesis.

Introduction

Congenital heart disease (CHD) is the most common type of birth defect, and is the leading non-infectious cause of death during the first year of life. The incidence of CHD is 0.8% and about 10% of these patients have functionally univentricular hearts [1]. Patients with functionally univentricular hearts comprise a heterogeneous patient population who all have in common that their type of CHD precludes biventricular repair. Hypoplasia of the right or left ventricle is accompanied by anomalies of the atrioventricular valve apparatus and/or ventricular outflow tract.

Although the etiology of cardiac malformations is still largely unknown, great progress in the identification of genetic factors has been made during the last decade as more than 40 different genes have already been identified in human non-syndromic CHD. Several of these genes encode transcription factors involved in cardiac development. *NKX2-5*, a homeodomain containing transcription factor known to be involved in left ventricular development, contributes to various cardiac developmental pathways through interaction with a network of transcriptional regulators of heart morphogenesis, including *GATA4*, TBX5 and TBX20 [2-4].

In 1998 Schott et al. identified *NKX2-5* as the first gene involved in human non-syndromic CHD [5]. Mutations in *NKX2-5* cause a spectrum of CHD; from cardiac conduction abnormalities to cardiac septation defects, and ventricular outflow tract anomalies [6-9]. Although most *NKX2-5* mutations are found in familial atrioventricular block with atrial septal defect [5, 9, 10] and tetralogy of Fallot [5, 6], association with hypoplasia of the left ventricle has also been described [6, 8].

GATA4 is a zinc finger transcription factor that interacts with multiple nuclear proteins, including *NKX2-5*, and regulates expression of other regulatory proteins, as well as downstream targets such as cardiac contractile protein genes [2]. *GATA4* is also known to be involved in various types of human CHD, including septation defects, and right ventricular hypoplasia [3, 11-14].

The incidence of *NKX2-5* and *GATA4* mutations is low in several reports including relatively large groups of patients with various types of CHD [6, 8, 14]. These studies, however, included no or only limited numbers of patients with functionally univentricular hearts. Both *NKX2-5* and *GATA4* are known to be involved in left and right ventricular morphogenesis respectively [13, 15]. In addition, cardiac septation and outflow tract anomalies are common in this patient population. Therefore, we hypothesized an increased incidence of mutations in *NKX2-5* and *GATA4* in patients with a functionally univentricular heart.

Materials and Methods

Patients

We included 38 non-related patients with non-syndromic functionally univentricular hearts and no known CHD in the family, irrespective of their cardiac anatomy. Cardiac anatomy was confirmed from echocardiography reports, cardiac catheterization reports and surgical reports if applicable. Figure 1 shows the details of the cardiac anatomy. There were fifteen patients with hypoplasia of the left ventricle, and twenty patients with hypoplasia of the right ventricle. In three patients, ventricular dominancy could not be determined. Parental DNA was analyzed when mutations were identified, and parents underwent cardiac screening, including physical examination, electrocardiogram and echocardiography, for analysis of their cardiac phenotype. The study was approved by the Dutch Central Committee on Research involving Human Subjects and institutional review boards. All subjects and/or their parents (if required) gave informed consent.

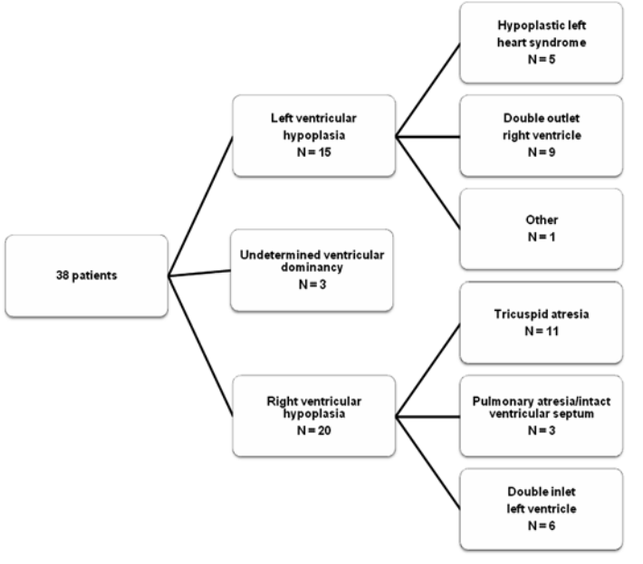

Figure 1. Anatomic subgroups of the patient population

Genetic analyses

Direct sequence analysis of all coding regions and intron-exon boundaries of the *GATA4* (genbank reference NM_002052.2) and NKX2.5 (genbank reference NM_004387.2) genes was performed in each patient. Sequence analysis of M13-tagged PCR products was carried out on an ABI3730xl capillary sequencer using Big-Dye Terminator v 3.1 chemistry (Applied Biosystems) (Details of methods and primer sequences available on request.) Analysis of sequence data was performed using SeqScape analysis software (v2.5, Applied Biosystems). In addition to sequence analysis, quantitative PCR analysis (Q-PCR) of both coding exons of the NKX2.5 gene was carried out to detect possible genomic rearrangements.

Mutations were considered pathogenic when they were either truncating of splice-site mutations or when they segregated with disease in a family, were predicted to affect protein function according to protein analysis software (SIFT (Sorting Intolerant From Tolerant) [16] and PolyPhen [17]. Mutation nomenclature according to www.HGVS.org with the translation initiation ATG codon in exon1.

Results

No sequence variants in *NKX2-5* were observed. In two of 38 patients (5.3%) mutations in *GATA4* were found. The first patient was diagnosed with tricuspid atresia, ventricular septal defect, and transposition of the great arteries. *GATA4* analysis revealed two missense variants: 1) p.Val380Met (c.1138G>A, *GATA4* exon 5); and 2) p.Pro407Gln (c.1220C>A, *GATA4* exon 6). *GATA4* analysis of the mother identified the presence of the c.1138G>A and c.1220C>A mutations, indicating that both variants are most likely on the same *GATA4* allele. Both variants were absent in DNA from the father. Cardiac evaluation (physical examination, electrocardiography, and echocardiography) revealed no signs of a congenital heart defect in the mother.

The second patient had pulmonary atresia, intact ventricular septal defect, with coronary and aorta fistulae to the right ventricle. *GATA4* analysis resulted in the identification of the synonymous c.822C>T nucleotide change (p.=) in exon 3. DNA analysis of the parents showed that the c.822C>T nucleotide change was also present in the mother. Analysis of paternal DNA showed absence of the variant. Cardiac evaluation of both parents (physical examination, electrocardiography, and echocardiography) showed no abnormalities.

Discussion

The current study sought to investigate the incidence of mutations in *NKX2-5* and *GATA4* in patients with functionally univentricular hearts. We did not identify mutations in *NKX2-5*. We found three mutations in *GATA4*, in two of 38 patients, that have been previously described in heterogeneous cohorts of patients with CHD, [11, 14, 18] but not in patients with functionally univentricular hearts. As in other studies, we demonstrated a low incidence of non-synonymous sequence variants of *GATA4* in patients with non-syndromic CHD.

The p.Pro407Gln mutation, found in a patient with tricuspid atresia, ventricular septal defect and transposition of the great arteries, has previously been described in a patient with tetralogy of Fallot out of 486 Chinese Han patients with various types CHD, [11] and in one patient with tetralogy of Fallot out of 62 Chinese Uygur CHD patients [19]. Our study is the first to describe the p.Pro407Gln mutation in a patient with tricuspid atresia and transposition of the great arteries. Using prediction algorithms, this mutation is expected to alter protein function [16, 17], confirming the conclusion from other studies [11, 19]. Although the mother of the patient is a healthy carrier of the mutation, this does not exclude a possible pathogenic character of this mutation. Missense mutations in sporadic patients with CHD whose unaffected family members also show the DNA variation can be considered as rare variants with intermediate penetrance, although additional functional analyses are necessary to clarify the meaning of these mutations. Furthermore, in our study as well as in other studies, the p.Pro407Gln mutation has not been found in large control panels. Two studies [3, 14] described *GATA4* missense mutations in patients with atrial septal defects, that were also found in unaffected parents, indicating that these mutations have reduced penetrance.

The other non-synonymous amino acid change, p.Val380Met, identified in the same patient and his unaffected mother, is found both in patients with CHD and controls [18]. We conclude that this variant is most likely a polymorphism, that by itself is unlikely to cause CHD, although a contribution to polygenic CHD cannot be excluded.

In one patient with pulmonary atresia, intact ventricular septal defect, with coronary and aorta fistulae to the right ventricle we identified the synonymous c.822T>C mutation. Tomita-Mitchell et al. described this synonymous sequence variant in three patients with tetralogy of Fallot/pulmonary atresia, double outlet right ventricle, and ventricular septal defect respectively [14]. This variant was not found on control chromosomes and is thought to affect an exonic splice enhancer motive [14]. The c.822T>C mutation was also found in patients with hypertrophic cardiomyopathy [20], a disease that is increasingly associated with congenital cardiovascular malformations [21]. In our study this variant was also present in the healthy mother and absent in 185 controls. Although it is unclear whether this variant is disease-related it could be a mutation with intermediate or low penetrance.

In general, the studies on *GATA4* and/or *NKX2-5* analysis in CHD involve only a limited number of patients with functionally univentricular hearts [6, 8, 11, 18, 19, 22, 23]. The focus has been on patients with septation defects and conotruncal anomalies, especially in studies on *NKX2-5*. In a study by Schluterman et al. [18] at least 25 of 157 CHD patients had a functionally

univentricular heart. In this study, the p.Val380Met mutation was also identified in two patients with CHD and three controls. None of the mutations in the study by Schluterman occurred in patients with functionally univentricular hearts. Thus, our study describes the first *GATA4* mutations associated with this type of cardiac malformation.

NKX2-5 mutations have been found in patients with hypoplastic left heart syndrome. McElhinney et al.,including 80 patients with hypoplastic left heart syndrome in their entire cohort of 608 CHD patients, found the p.Arg25Cys mutation in one patient with hypoplastic left heart syndrome [6]. Elliot et al. reported a p.Thr178Met mutation in a patient with hypoplastic left heart syndrome [8]. Furthermore, Hinton et al.[24] demonstrated high heritability of hypoplastic left heart syndrome, suggesting that it is largely determined by genetic factors. Our study included only five patients with hypoplastic left heart syndrome. Analysis of larger cohorts will be necessary to investigate the incidence and role of *NKX2-5* mutations in this patient group.

GATA4 is known to be involved in cases with right ventricular hypoplasia (in the context of double inlet left ventricle) [3, 13]. In our study, the two patients in whom sequence variants were identified both had a hypoplastic right ventricle (tricuspid atresia and pulmonary atresia/ intact ventricular septum). In larger cohorts, one would expect to find more *GATA4* mutations in this patient group, as was also suggested by Rajagopal et al.[3].

Conclusions

We found three *GATA4* mutations in two patients out of 38 patients with functionally univentricular hearts. Both patients had right ventricular hypoplasia confirming the importance of *GATA4* in right ventricular development. One of these mutations, p.Pro407Gln, was predicted to alter protein function, confirming a previous conclusion by others. P.Pro407Gln is probably a pathogenic mutation with intermediate penetrance. From our study we conclude that *NKX2-5* mutations are not a frequent cause of functionally univentricular hearts. Conversely, a relatively high percentage (5.3%) of *GATA4* mutations in this patient population warrants molecular analysis of this gene in patients with a univentricular heart. Further investigation of *GATA4* and *NKX2-5* mutations in larger cohorts of patients with ventricular hypoplasia will contribute to elucidate the role of both genes in ventricular cardiogenesis.

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Chapter 11

Summary, conclusions and future perspectives

Important advances in both operation techniques and peri-operative procedures have been made in the past twenty years in the care for patient with complex congenital heart disease. This means that physicians are increasingly encountering adolescents and young adults with complex congenital heart disease. Physicians, patients and their parents want to be informed on the long-term sequelae after palliation of these serious conditions, how to recognize them at an early stage with the best possible modality and how to intervene. In this thesis we addressed several of these issues, focusing on patients with a functionally univentricular heart, who have been palliated with the Fontan operation in its current modifications. For this purpose the following studies were performed:

- Analysis of morbidity and mortality in a study population of more than 200 patients after total cavopulmonary connection in three Dutch tertiary referral centers for pediatric cardiology and cardiothoracic surgery
- Subgroup analyses in approximately 40 patients on clinical and hemodynamic status from five years after Fontan completion at young age, with a special emphasis on the use of cardiovascular magnetic resonance imaging
- Feasibility and usefulness of cardiovascular magnetic resonance imaging, whether or not in combination with low-dose dobutamine stress for assessing global ventricular function in patients with complex congenital heart disease, including assessment of normal values of biventricular function, volumes, and mass in 60 healthy children aged 8 to 17 years

In this section we will summarize our most relevant findings and our future perspectives on research and patient care after Fontan operation.

Morbidity and mortality after total cavopulmonary connection

In **chapter 2** our objective was to compare the outcome of the 2 co-existing modifications of staged total cavopulmonary connection: the intra-atrial lateral tunnel and extracardiac conduit. Since the introduction of the total cavopulmonary connection in the late 1980s, there is discussion on the superiority of either the intra-atrial lateral tunnel or the extracardiac conduit over the other in terms of long-term sequelae. Special concerns are mortality, and the incidence of arrhythmias, re-operations, and/or thrombo-embolic events. Although there are multiple studies on outcome after Fontan operation, analyses usually include patients with older and currently abandoned modifications of the Fontan operation, and have a limited follow-up duration for total cavopulmonary connection. Since the introduction of the extracardiac conduit in the mid 1990s, follow-up data in this group are limited to a maximum of ten to twelve years. This limits follow-up analysis and comparison with the intra-atrial lateral tunnel.

In our study, we included more than 200 patients with a total cavopulmonary connection, 102 having had an intra-atrial lateral tunnel and 107 with an extra-cardiac conduit. Median follow-up of intra-atrial correction was 7.4 years (interquartile range 4.3-10.0 years), while median follow-up time of the extra-cardiac conduit was 3.8 years (interquartile range 1.6-5.6 years). At six-year follow-up after completion, overall outcome was good and there was no difference in the incidence of Fontan failure – i.e. mortality or re-operation for revision of the Fontan circulation –, late re-operations or thrombo-embolic events between the two groups. Arrhythmias occurred more frequently in the patients with an intra-atrial lateral tunnel: freedom from arrhythmias at 6-year follow-up was 83% in the intra-atrial lateral tunnel group and 92% in the extra-cardiac conduit group. Multivariable Cox regression analysis, corrected for participating center and year of operation, identified only right ventricular morphology as a risk factor for arrhythmias. Arrhythmia may be a potential drawback of the intra-atrial lateral tunnel technique. An important limitation of the extracardiac technique is the lack of growth of the communication of the inferior caval vein and pulmonary artery [1]. Longer follow-up is required to determine the best option in these patients.

Clinical and hemodynamic status after Fontan operation

In **chapter 3** we assessed the clinical condition in a group of 34 patients (aged 6.8 to 20.7 years) who had undergone a total cavopulmonary connection at young age (i.e. under 5 years of age) and who were at least five years after Fontan completion (median follow-up time 7.8 years, range 5.0-17.8 years). Intra-atrial tunnel was performed in 27 patients; seven patients had an extracardiac conduit. These patients underwent a 12-lead electrocardiogram, 24-hour ECG-monitoring, bicycle exercise testing, cardiac magnetic resonance imaging, and NT-pro-BNP analysis. The latter is known to be increased in adult patients with heart failure, and closely correlates with ventricular function. Almost 70% of patients had preservation of sinus rhythm and 24-hour ECG-monitoring did not show signs of clinically significant arrhythmias or sinus node dysfunction. Global ventricular function – assessed with cardiac magnetic resonance imaging – was preserved, expressed by an ejection fraction of 59% compared to 69% in age and sex-matched controls. Exercise capacity was considerably lower in Fontan patients, with a maximal workload of 60% compared to height and sex-matched controls. NT-pro-BNP levels were within the normal range. However, ventricular mass was elevated compared to controles, pointing towards contractility-afterload mismatch.

The usefulness of cardiac magnetic resonance imaging was further explored in **chapter 4**, combining it with low-dose dobutamine stress-testing. In this thesis, we demonstrated preserved ventricular function and contractile reserve with low-dose dobutamine stress testing in 32 patients from five years after Fontan completion (mean age 13.3 (range 7.5-22.2 years), median follow-up time 8.1 (range 5.2-17.8 years). There was an adequate increase of ejection fraction and heart rate, and an adequate decrease of end-systolic volumes. However, with stress-testing, end-diastolic volume could not be maintained and stroke volume did not increase. As is known from earlier

studies by others, low-dose dobutamine stress-testing in control subjects causes an increase in stroke volume and maintenance of end-diastolic volume. Our results in Fontan patients indicate that, with stress-testing, cardiac index can only be increased by increasing heart rate as a result of impaired preload.

The cause for the abnormal stress response in Fontan patients is multifactorial, but the pulmonary circulation is thought to be an important determinant of the long-term functioning of the single ventricle circulation. In **chapter 5**, we assessed pulmonary arterial function in fourteen patients at rest and during low-dose dobutamine stress-testing with cardiac magnetic resonance imaging. We determined pulmonary artery size, flow variables and wall shear stress. We compared the outcomes of the variables at rest with matched healthy controls. At rest, stroke index, total flow, average flow, and peak flow rate were all statistically significantly lower in patients than in controls. With stress-testing, all variables increased in patients ($p<0.001$), apart from stroke index, that did not change. At rest, branch pulmonary artery area did not differ between patients and controls. Distensibility was lower in patients than in controls ($p<0.001$). With stress-testing, average pulmonary artery area and distensibility did not change despite an increase in flow volume. At rest, wall shear stress was lower in patients than in controls ($p<0.001$). Although wall shear stress increased with stress-testing ($p<0.001$), it did not reach the levels of the control group at rest. We concluded that pulmonary artery size is normal long-term after Fontan operation at young age. Flow variables, distensibility, and WSS are significantly lower compared to healthy controls, and do not show adequate reactions with stress-testing, which is suggestive of pulmonary artery endothelial and/or vascular dysfunction.

Cardiac magnetic resonance imaging in congenital heart disease

Cardiac magnetic resonance imaging is considered the gold standard for assessment of ventricular function. In preparation of the studies on clinical and hemodynamic status in Fontan patients we encountered important missing data for proper use of cardiac magnetic resonance imaging in patients with congenital heart disease. First of all, we missed normal values for ventricular volumes, function and ventricular mass in children and adolescents, assessed according to currently used MRI techniques. Secondly, there were no adequate studies on the intra-observer and interobserver variability for CMR assessment of ventricular volumes, function, and mass in patients with congenital heart disease.

In **chapter 6** we describe normal values in 60 healthy children, aged 8-17 years. We assessed biventricular volumes, ejection fraction and biventricular mass and we studied the interrelation of age, gender and body surface area on these parameters. We published gender-specific normative data, adjusted for body surface area in the range of 1.0 – 2.0 m^2. Furthermore, we calculated coefficients of variation for intra-observer and interobserver variability, with good to acceptable results for clinical practice.

Chapter 7 shows our results for intra-observer variability and interobserver variability of ventricular volumes, function and mass assessed in a heterogeneous population with congenital heart disease. Again, we calculated coefficients of variation for biventricular end-diastolic volume, end-systolic volume, ejection fraction and biventricular mass. Intra-observer variability and interobserver variability were good (between 2.9-6.8% and 3.9-10.2% respectively), with the smallest variations in end-diastolic volumes and ejection fraction. The largest variations were found for end-systolic volumes and mass. We do not think the magnitude of the variabilities limits detection of changes in ventricular volumes and global ventricular function over time.

Chapter 8 describes the safety and intra-observer variability and interobserver variability of assessment of ventricular function, volumes and mass of cardiac magnetic resonance imaging combined with low-dose dobutamine stress-testing in patients with congenital heart disease. In a series of more than 100 low-dose dobutamine stress studies in 91 patients minor side effects occurred in only three patients. Intra-observer and interobserver variability were good, with the largest variability in end-systolic volumes, as described in chapter 6 and 7.

Chapter 9 reviews the use and results of stress imaging in patients with congenital heart disease. We discuss the use of different types of stressors and imaging modalities and the results of stress studies (in combination with echocardiography and cardiac magnetic resonance imaging) in patients with congenital heart disease.

Future perspectives

The genetic basis of congenital heart disease

The genetic basis of congenital heart disease is still merely unknown. Most likely, a complex interplay of genetic predisposition, timing and location of expression of genes contributing to heart formation and environmental factors contributes to non-syndromic congenital heart disease [2]. **Chapter 10** previews to an issue, that is only starting to become a topical subject: to identify the underlying genetic abnormality or abnormalities in (complex) congenital heart disease and its implications for the individual patient and his or her family. In the last decade great progress has been made in the identification of genetic factors. Up until now, more than 40 candidate genes have been identified in human non-syndromic congenital heart disease. *NKX2-5* and *GATA4* are two transcription factors known to be involved in right and left ventricular morphogenesis. As

such, they may be considered candidate genes in the origin of functionally univentricular hearts with left or right ventricular hypoplasia. We explored the incidence of mutations in these two transcription factors in 38 patients with a functionally univentricular heart. We did not find mutations in *NKX2-5*. Three *GATA4* mutations were found in two patients with right ventricular hypoplasia, confirming the importance of *GATA4* in right ventricular development. Pathogenicity of these mutations requires further confirmation. However, one of the mutations is predicted to alter corresponding protein function and might be pathogenic.

Optimizing the total cavopulmonary connection

Intra-atrial lateral tunnel or extracardiac conduit?

The Fontan operation is a palliative procedure that has prolonged the life-span of patients with a functionally univentricular heart considerably [3]. Technical surgical preference and theoretical considerations with regard to long-term outcome dictate institutional choice for either of the current modifications of the Fontan technique. More follow-up time is needed to answer the question if one of the two current modifications is superior to the other in terms of morbidity and mortality. Special interest concerning complications are the incidence of arrhythmias [4], thrombo-embolic events and need for re-operations for the intra-atrial lateral tunnel and for the extracardiac conduit [5]. Furthermore, assessment of hydrodynamic efficiency of the intra-atrial lateral tunnel and extracardiac conduit in vivo is needed to adequately compare these two techniques [6]. Lastly, another issue to address is the influence of either modification on the function of the pulmonary circulation.

Function of the pulmonary vascular system

Reduced exercise capacity in Fontan patients is primarily caused by limitations in preload reserve. Contractile reserve, as was shown in this thesis, is intact in the majority of patients in the paediatric and young adult age range. The inability of the pulmonary vascular system to augment blood flow during exercise prevents the increase in stroke volume. Combined with possible diastolic dysfunction and the high incidence of chronotropic incompetence, augmentation of cardiac output is limited during exercise. Exploring what happens in the pulmonary circulation during exercise seems to be a pivotal issue in understanding the pathophysiology of the Fontan circulation [7] and will guide future interventions and/or medical therapy with – for example – phosphodiesterase inhibitors [8, 9]. Cardiac magnetic resonance imaging can play an important role in this area of research, and has already proven to generate information on flow dynamics in the total cavopulmonary connection acquired non-invasively [10, 11]. However, invasive studies, preferably in a limited number of patients, using cardiac catheterization are probably needed to verify the data acquired during cardiac magnetic resonance imaging [12].

Search for early signs of the failing Fontan

Improvement of care for patients with a functionally univentricular heart includes early recognition of those patients at risk for decline of function or adverse events. Ideally, this is a marker that can be obtained at a pre-symptomatic stage. In this thesis, we explored the feasibility, safety and variability of cardiac magnetic resonance imaging (at rest and during low-dose dobutamine stress) in patients with various types of congenital heart disease. Abnormal stress response assessed with cardiac magnetic resonance imaging in serial measurements might be a marker that can be used to identify patients with a predisposition for Fontan failure. This includes assessment of ventricular size – which relates to loading conditions, contractility and afterload – , and also for assessment of pulmonary artery function. Future studies should also include assessment of optimal dobutamine dose. Although physical stress might be the preferred stressor, particularly since this may result in the inclusion of the effects of respiration on ventricular and (pulmonary) vascular function, technical limitations with regard to (magnetic resonance) imaging techniques need to be solved for physical stress to be a feasible option.

In various disease states, biomarkers have been suggested to contribute to early detection of clinically relevant problems [13, 14]. In this study the biomarker NT-pro BNP was not affected in our relatively small and homogeneous study population. Larger studies and markers including various pathways involved in functional failure of the Fontan circulation are required to explore the options of the use of biomarkers in this population.

Improvement of care for Fontan patients

The long-term outcome of patients with functionally univentricular hearts should be considered relatively unexplored territory. Although various studies have contributed to our knowledge of this problem, it should be acknowledged that treatment strategies have varied widely since the introduction of the original Fontan technique. This includes differences in indications, staging, age of completion of the Fontan operation and medical strategies to optimize outcomes. Most of the drug regimens used in clinical practice is not based on sound evidence with regard to their mechanism of action in these patients, have not been well studied or have even been proven ineffective. An important outcome measure is quality of life. Often, this parameter is not included or not well defined in study designs. Numbers of patients in single institutions are often very small. Multicenter, detailed, standardized and well-monitored long-term follow-up is required to answer the important questions of patients, their parents and providers of care.

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SAMENVATTING

Samenvatting in het Nederlands

In de afgelopen twintig jaar zijn belangrijke vooruitgangen geboekt in zowel operatietechniek als in peri-operatieve zorg bij patiënten met complex aangeboren hartafwijkingen. Dit betekent dat artsen in toenemende mate te maken kunnen krijgen met adolescenten en jong volwassenen met een complex cor vitium. Zowel artsen, patiënten en hun ouders willen informatie over de lange termijn gevolgen na palliatie van deze ernstige aangeboren afwijkingen. Daarnaast is het belangrijk te weten hoe deze gevolgen zo vroeg mogelijk kunnen worden herkend met de beste onderzoeksmodaliteit en wat vervolgens de beste interventie is. In dit proefschrift hebben we enkele van deze aspecten onder de loep genomen bij patiënten met een complexe aangeboren hartafwijking en in het bijzonder bij patiënten met een functioneel univentriculair hart die een Fontan operatie hebben ondergaan zoals die tegenwoordig wordt uitgevoerd. De volgende studies zijn uitgevoerd en beschreven:

- analyse van morbiditeit en mortaliteit in een onderzoekspopulatie van meer dan 200 patiënten na totale cavopulmonale connectie in drie Nederlandse tertiaire centra voor kindercardiologie en cardiothoracale chirurgie
- subgroepanalyses in ongeveer veertig patiënten betreffende klinische en hemodynamische parameters vanaf vijf jaar na completering van de Fontan operatie op jonge leeftijd, bij wie in het bijzonder gebruik is gemaakt van cardiovasculaire MRI.
- onderzoek naar de uitvoerbaarheid en toepasbaarheid van cardiovasculaire MRI, al dan niet gecombineerd met lage dosering dobutamine stress, voor het bepalen van globale hartkamerfunctie in patiënten met complexe aangeboren hartafwijkingen. Voor optimaal vergelijk werden tevens normaalwaarden voor biventriculair volume, massa en functie bepaald in 60 gezonde kinderen in de leeftijd van acht tot en met zeventien jaar.

In dit hoofdstuk vindt u een samenvatting van onze belangrijkste bevindingen en onze gedachten over toekomstige onderzoeksmogelijkheden en patiëntenzorg na de Fontan operatie.

Morbiditeit en mortaliteit na totale cavopulmonale connectie

In **hoofdstuk 2** beschrijven wij ons onderzoek naar het vergelijken van de uitkomst van twee naast elkaar bestaande modificaties van de totale cavopulmonale connectie: de intra-atriale laterale tunnel en de extra-cardiale conduit. Eind jaren tachtig werd de totale cavopulmonale connectie voor het eerst beschreven en sindsdien is er discussie of een van beide modificaties superieur is wat betreft gevolgen op de lange termijn. Hierbij wordt met name gedacht aan mortaliteit, het vóórkomen van ritmestoornissen en trombo-embolieën en re-operaties. Er zijn weliswaar reeds meerdere studies gepubliceerd over de uitkomsten na Fontan operatie, maar deze studies hebben meestal ook patiënten geïncludeerd die volgens inmiddels verlaten technieken zijn geopereerd.

Daarnaast is de follow-up duur van patiënten met een totale cavopulmonale connectie beperkt. De extra-cardiale conduit, als modificatie van de totale cavopulmonale connectie, werd in het begin van de jaren negentig geïntroduceerd. De follow-up duur van patiënten met deze modificatie is beperkt tot tien tot twaalf jaar. Hierdoor is een goed vergelijk met de intra-atriale laterale tunnel, welke enkele jaren langer "in gebruik" is, beperkt.

In onze studie zijn meer dan 200 patiënten geïncludeerd die een totale cavopulmonale connectie hebben ondergaan: 102 na intra-atriale laterale tunnel, 107 na extra-cardiale conduit. De mediane follow-up duur van patiënten met een intra-atriale laterale tunnel was 7.4 jaar (interquartile range 4.3-10.0 jaar). De mediane follow-up duur van patienten met een extra-cardiale conduit was 3.8 jaar (interquartile range 1.6-5.6 jaar). Zes jaar na Fontan completering was de algemene uitkomst goed en er was geen verschil in de incidentie van Fontan falen, gedefinieerd als mortaliteit of een re-operatie voor revisie van de Fontan circulatie, re-operatie voor andere indicaties of het vóórkomen van trombo-embolieen bij vergelijk van patiënten met een intra-atriale laterale tunnel en patienten met een extra-cardiale conduit. Ritmestoornissen kwamen vaker voor bij patienten met een intra-atriale laterale tunnel dan bij patienten met een extracardiale conduit: afwezigheid van ritmestoornissen 6 jaar na completering van de Fontan circulatie was 83 % respectievelijk 92%. Bij multivariate Cox regressie analyse, gecorrigeerd voor de deelnemende centra en jaar van operatie, werd een systeemkamer van het rechter kamertype geïdentificeerd als risicofactor voor ritmestoornissen. Het optreden van ritmestoornissen is een belangrijke factor die in overweging moet worden genomen wanneer men kiest voor een intra-atriale laterale tunnel. De extra-cardiale conduit heeft als beperking dat er geen groeipotentiaal is van de aansluiting met de vena cava inferior en de longslagader [1]. Langere follow-up duur is nodig om duidelijkheid te krijgen welke van de twee huidige modificaties de beste keus is voor patiënten.

Klinische en hemodynamische status praesens na Fontanoperatie

In **hoofdstuk 3** is de klinische conditie bekeken van 34 patiënten (in de leeftijd van 6.8 tot 20.7 jaar) die allemaal op jonge leeftijd (maximaal vijf jaar oud) een totale cavopulmonale connectie hebben gekregen (mediane follow-up duur 7.8 jaar, range 5.0-17.8 jaar). Bij 27 patiënten was een intra-atriale laterale tunnel aangelegd, bij de overige zeven een extra-cardiale conduit. Bij deze patiënten was een 12-afleidingen ECG gemaakt en een 24-uurs ECG analyse. Verder voerden zij een fietstest uit, werd naar hartfunctie gekeken met cardiale MRI en werd het NT-pro-BNP bepaald. NT-pro-BNP is verhoogd in volwassen patiënten met hartfalen en heeft een nauwe correlatie met ventrikelfunctie. Bijna 70% van de patiënten had sinusritme op moment van follow-up en bij 24-uurs ECG analyse werden geen belangrijke ritmestoornissen of sinusknoopdysfunctie gezien. Globale kamerfunctie – zoals bepaald met cardiale MRI – was behouden met een ejectiefractie van

59% bij patiënten in vergelijking met een ejectiefractie van 69% bij controles die waren gematcht op leeftijd en geslacht. Inspanningscapaciteit was duidelijk lager bij patiënten, de maximale belasting was 60% vergeleken met een controlepopulatie die was gematcht op lengte en geslacht. NT-pro-BNP waarden vielen binnen de normaalwaarden. Bij cardiale MRI werd gevonden dat de massa van de hartkamers verhoogd was vergeleken met een controlepopulatie, duidend op een mismatch tussen contractiliteit en afterload.

Het nut van het gebruik van cardiale MRI bij patiënten na Fontan operatie werd verder onderzocht in **hoofdstuk 4**, waarin cardiale MRI tijdens een lage dosering dobutamine stress werd uitgevoerd. In dit proefschrift hebben we laten zien dat er een behouden functie van de hartkamer is en een behouden contractiele reserve tijdens dobutamine stress. Dit onderzoek werd uitgevoerd bij 32 patiënten van gemiddeld 13.3 jaar oud (range 7.5-22.2 jaar) en bij een mediane follow-up duur van 8.1 jaar (range 5.2-17.8 jaar). Tijdens lage dosering dobutamine stress trad een adequate toename van de hartfrequentie en ejectiefractie op, en was er een adequate afname van het eind-systolisch volume in vergelijking met de waarden tijdens rust. Echter, tijdens dobutamine stress trad een abnormale afname van het eind-diastolisch volume op en was er geen toename van het slagvolume. In eerdere studies is reeds aangetoond dat tijdens lage dosering dobutamine stress bij gezonde personen een toename van slagvolume optreedt en dat er behoud is van eind-diastolisch volume. Onze resultaten bij Fontan patiënten laten zien dat tijdens stress toename van het hartminuutvolume alleen kan worden bewerkstelligd door een toename van de hartfrequentie bij een beperking van de preload.

De oorzaak voor de abnormale reactie op stress bij Fontan patiënten is multifactorieel, maar aangenomen wordt dat de longcirculatie een belangrijke factor is voor het functioneren van de systeemkamer van een functioneel univentriculair hart op lange termijn. In **hoofdstuk 5** hebben we gekeken naar het functioneren van de arteriële longcirculatie met cardiale MRI, opnieuw zowel in rust als tijdens lage dosering dobutamine stress. Bij veertien patiënten hebben we gekeken naar afmeting van de longslagaders, bloedstroomvariabelen en shear stress. Voor vergelijk van de waarden in rust werd gebruik gemaakt van een gezonde controlepopulatie. In rust waren variabelen van de bloedstroom (een afgeleide van het slagvolume, de totale hoeveelheid flow per minuut, de gemiddelde flow en de piekstroomsnelheid) allemaal significant lager bij patiënten dan bij controles. Tijdens dobutamine stress namen al deze variabelen toe bij de patiënten, behalve de afgeleide van het slagvolume. Deze laatste bleef onveranderd. In rust was er geen verschil tussen de oppervlakte van een doorsnede van de longslagader van patiënten en controles. Met dobutamine stress veranderde de oppervlakte en distensibiliteit van de longslagader niet bij patiënten, alhoewel het flow volume toenam. In rust was de waarde van shear stress – de wrijving tussen het stromende bloed en de vaatwand – bij patiënten lager dan bij controles. Tijdens dobutamine stress nam de shear stress toe bij patiënten, maar kwam zelfs niet op de waarde die bij controles in rust werd gemeten. De conclusies waren dat de afmeting van de longslagaders normaal is na Fontan operatie op jonge leeftijd. Echter variabelen van de bloedstroom, distensibiliteit en van shear stress zijn significant lager bij Fontan patiënten dan bij controles. Tevens is de reactie tijdens dobutamine stress abnormaal, hetgeen suggereert dat er sprake kan zijn van ofwel endotheeldysfunctie ofwel vaatwanddysfunctie.

Cardiale MRI bij aangeboren hartafwijkingen

Cardiale MRI wordt beschouwd als de gouden standaard voor het bepalen van hartkamerfunctie. Bij de voorbereidingen van de onderzoeken bij Fontan patiënten liepen we tegen het probleem aan dat er tot dan toe geen goede controledata in de literatuur voorhanden waren om cardiale MRI bij patiënten met een aangeboren hartafwijking goed te kunnen gebruiken. Ten eerste waren er geen normaalwaarden voor globale hartkamerfunctie, hartkamervolumes en hartkamermassa die waren bepaald bij kinderen en jong volwassenen met de huidige MRI technieken. Ten tweede ontbraken gegevens over intra-observer en interobserver variabiliteit van bepaling van eerder genoemde parameters met cardiale MRI bij patiënten met aangeboren hartafwijkingen.

In **hoofdstuk 6** beschrijven we normaalwaarden zoals bepaald bij 60 gezonde kinderen in de leeftijd van 8-17 jaar. We hebben gekeken naar het volume van beide hartkamers, massa van beide hartkamers en ejectiefractie. Daarnaast hebben we gekeken naar de relatie tussen deze waarden en leeftijd, geslacht en lichaamsoppervlakte. Met deze studie hebben we normaalwaarden gepubliceerd voor jongens en meisjes en aangepast aan lichaamsoppervlakte in de waarden van 1.0-2.0 m^2. Bovendien hebben we de variatiecoefficiënt berekend bij de bepaling van intra-observer en interobserver variabiliteit, waaruit bleek dat de mate van variabiliteit acceptabel is voor een goed gebruik in de dagelijkse, klinische, praktijk.

Hoofdstuk 7 laat de resultaten zien van de bepaling van intra-observer en interobserver variabiliteit voor hartkamervolume, -massa en –functie bij aangeboren hartafwijkingen. Opnieuw werden variatiecoefficiënten berekend voor biventriculair eind-diastolisch volume, eind-systolisch volume, ejectiefractie en massa. De mate van variabiliteit was het kleinst bij de bepaling van het eind-diastolisch volume en ejectiefractie. De grootste mate van variabiliteit werd gevonden bij de bepaling van eind-systolisch volume en massa. In het algemeen waren intra-observer en interobserver variabiliteit acceptabel (respectievelijk 2.9-6.8% en 3.9-10.2% voor de verschillende parameters), waarbij wij denken dat de mate van variabiliteit geen belemmering is voor het detecteren van klinisch relevante veranderingen hartkamervolume en –functie in de tijd.

In **hoofdstuk 8** zijn de resultaten weergegeven van een studie naar de veiligheid en intra- en interobserver variabiliteit bij het bepalen van hartkamervolume, -massa en ejectiefractie middels cardiale MRI in combinatie met een lage dosering dobutamine stress bij patiënten met een aangeboren hartafwijking. Meer dan 100 MRI-onderzoeken werden uitgevoerd bij 91 patiënten met een lage dosering dobutamine stress en bij slechts drie patiënten traden geringe bijwerkingen op (van hoofdpijn tot ventriculaire bigeminie). Intra- en interobserver variabiliteit waren goed met de grootste mate van variabiliteit bij het bepalen van het eind-systolisch volume, zoals beschreven in hoofdstuk 6 en 7.

Hoofdstuk 9 laat een overzicht zien van het gebruik en de resultaten van cardiale beeldvorming in combinatie met fysieke of farmacologische stress bij patiënten met een aangeboren hartafwijking. Wij bespreken de verschillende manieren van stress, verschillende beeldvormingsmodaliteiten en de resultaten van de studies met echocardiografie en cardiale MRI bij patiënten met een aangeboren hartafwijking zoals die tot dan toe waren gepubliceerd.

Toekomstperspectieven

De genetische basis van aangeboren hartafwijkingen

De genetische basis van aangeboren hartafwijkingen is tot op heden nog grotendeels onbekend. Meest waarschijnlijk is er sprake van een complex samenspel van genetische predispositie, omgevingsfactoren en expressie en lokatie van genen die betrokken zijn bij de vorming van het hart dat leidt tot niet-syndromale aangeboren hartafwijkingen [2]. **Hoofdstuk 10** blikt vooruit op een onderwerp dat nog in de kinderschoenen staat, maar mogelijk in de toekomst belangrijk gaat worden: het identificeren van de onderliggende genetische afwijking(en) bij (complexe) aangeboren hartafwijkingen en de implicaties hiervan voor de individuele patiënt en zijn/haar familie. In de laatste tien jaar is er veel vooruitgang geboekt bij het identificeren van genetische factoren.

Tot op heden zijn meer dan 40 kandidaatgenen geïdentificeerd die betrokken zijn bij het ontstaan van niet-syndromale aangeboren hartafwijkingen bij mensen. *NKX2-5* en *GATA4* zijn twee transcriptiefactoren die betrokken zijn bij de morfogenese van de linker en rechter hartkamer. Ze kunnen beschouwd worden als kandidaatgenen voor het ontstaan van een functioneel univentriculair hart met onderontwikkeling van de rechter of linker hartkamer. Wij hebben gekeken naar de incidentie van mutaties van deze twee transcriptiefactoren bij 38 patiënten met een functioneel univentriculair hart. Er werden geen mutaties gevonden van *NKX2-5*. Bij twee patiënten werden in totaal drie *GATA4* mutaties gevonden. Beide patiënten hadden een onderontwikkeling van de rechter hartkamer, een bevestiging van de betrokkenheid van *GATA4* bij de morfogenese van de rechter kamer. Hoe pathogeen deze mutaties zijn, kan uit onze studie niet worden bepaald. Een voorspellingsalgoritme gaf echter aan dat één van de mutaties leidt tot een verandering van het corresponderende eiwit en zou in theorie een pathogene mutatie kunnen zijn.

Optimaliseren van de totale cavopulmonale connectie

Intra-atriale laterale tunnel of extracardiale conduit?

De Fontan operatie is een palliatieve operatie die de levensduur van patiënten met een functioneel univentriculair hart aanzienlijk heeft verlengd [3]. De keuze voor een van beide hedendaagse modificaties van de Fontan operatie wordt bepaald door chirurgische voorkeur van techniek en theoretische overwegingen met betrekking tot de lange termijn resultaten. Er is meer follow-up tijd nodig om te kunnen bepalen of een van beide modificaties uiteindelijk superieur is wat betreft morbiditeit en mortaliteit. Hierbij wordt met name gekeken naar de incidentie van ritmestoornissen [4], thrombo-embolische complicaties en de noodzaak tot re-operatie van zowel de intra-atriale laterale tunnel als van de extracardiale conduit [5]. Daarnaast is het van belang om te kijken naar de hydrodynamische efficiëntie van beide modificaties in vivo [6]. Dit zal waarschijnlijk ook meer inzicht geven in de invloed van beide modificaties op het functioneren van de longcirculatie.

Functie van het pulmonale vaatbed

Verminderde inspanningscapaciteit bij Fontan patiënten wordt voornamelijk veroorzaakt door een beperking van de preload bij stress. De contractiele reserve, zoals in dit proefschrift is beschreven, is normaal in de meerderheid van de onderzochte patiënten op de kinderleeftijd en op jong volwassen leeftijd. Het onvermogen van het longvaatbed om de bloedstroom tijdens inspanning te vergroten verhindert een toename van het slagvolume. In combinatie met mogelijk diastolische dysfunctie en de hoge incidentie van chronotrope incompetentie is toename van het hartminuutvolume tijdens inspanning beperkt. Om de pathofysiologie van de Fontancirculatie beter te begrijpen moet duidelijk worden wat er in de longcirculatie gebeurt tijdens inspannning [7]. Deze kennis zal belangrijk zijn bij het vaststellen van toekomstige interventies en/of medicatie, zoals behandeling met fosfodiesterase remmers [8, 9]. Cardiale MRI kan een belangrijke rol spelen op dit onderzoeksgebied. Het is al aangetoond dat met cardiale MRI op een niet invasieve manier informatie kan worden verkregen over bloedstroom dynamiek in de totale cavopulmonale connectie [10, 11]. Om deze data te verifiëren zullen echter invasieve metingen met hartcatheterisatie nodig zijn, vanzelfsprekend in een zo klein mogelijke patiëntengroep [12].

Vroege tekenen van Fontan falen

Om de zorg voor patienten met een functioneel univentriculair hart te verbeteren is het belangrijk om patiënten met een hoog risico op (acute) achteruitgang van klinische conditie in een vroeg stadium te herkennen. Idealiter kan dit worden bepaald met een marker die al in een pre-sympto-

matisch stadium wordt verkregen. In dit proefschrift hebben we gekeken naar de uitvoerbaarheid, veiligheid en meetvariabiliteit van cardiale MRI (zowel in rust als tijdens lage dosering dobutamine stress) uitgevoerd bij patiënten met verschillende soorten aangeboren hartafwijkingen. Een abnormale reactie op lage dosering dobutamine stress bij cardiale MRI en de mogelijke veranderingen in deze reactie bij seriële metingen zou zo'n marker kunnen zijn die patiënten identificeert met een verhoogde kans op Fontan falen. Hierbij kan gekeken worden naar het volume van de hartkamer – een afgeleide van preload, contractiliteit en afterload van de hartkamer – en bijvoorbeeld naar metingen van de functie van het longvaatbed. In de toekomst zal bepaald moeten worden wat de optimale dosering van dobutamine is om deze parameters te bepalen. Alhoewel fysieke stress de beste stressor is voor het testen van het gehele samenwerkende systeem van respiratie en circulatie, is het niet goed mogelijk om dit in combinatie met cardiale MRI uit te voeren.

Bij verschillende soorten aandoeningen zijn biomarkers nuttig om klinische relevante problemen (in een vroeg stadium) aan te tonen [13, 14]. In onze studie is gekeken naar de mogelijk waarde van het bepalen van de biomarker NT-pro BNP. In onze kleine en diverse studiepopulatie gaf NT-pro-BNP echter geen toegevoegde waarde. Grotere studies met inbegrip van meerdere markers moeten uitmaken wat de mogelijkheden zijn voor het gebruik van biomarkers bij patiënten na Fontan operatie.

Verbetering van de zorg voor Fontan patiënten

De lange termijn resultaten van de Fontan operatie voor patiënten met een functioneel univentriculair hart zijn nog relatief onbekend. Studies waarin is gekeken naar lange termijn resultaten zijn veelal uitgevoerd bij patiënten die geopereerd zijn volgens inmiddels verouderde Fontan modificaties. Sinds de introductie van de Fontan operatie zijn er veel aanpassingen geweest in bijvoorbeeld de indicatiestelling, het gestageerd uitvoeren van de operatie en de leeftijd waarop operatie plaatsvindt. Daarnaast zijn er veranderingen in medicamenteuze therapie, alhoewel deze niet gestoeld zijn op evidence based medicine. Een belangrijke uitkomstmaat is kwaliteit van leven, een parameter die vaak ofwel niet is bepaald, ofwel niet goed is gedefinieerd. Veel studies die zijn gedaan bij patiënten na Fontan operatie zijn uitgevoerd in kleine patiëntengroepen. Voor de toekomst is het belangrijk om gedetailleerd, gestandaardiseerd en goed gemonitorde follow-up uit te voeren om de lange termijn resultaten en hun implicaties te verduidelijken. Multicenter onderzoek is hierbij van cruciaal belang teneinde de patiëntenaantallen in toekomstige studies te vergroten.

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DANKWOORD

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CURRICULUM VITAE

Daniëlle Robbers-Visser is geboren op 8 april in 1977 in Huizen. Zij ging naar de middelbare school van 1989 t/m 1995; het christelijk college Stad en Lande dat in het eindexamen jaar werd omgedoopt naar het Erfgooierscollege. In oktober 1995 werd zij nageplaatst voor de studie geneeskunde aan de Universiteit Utrecht. In het 4e jaar deed zij haar wetenschappelijke stage bij de afdeling kindercardiologie (begeleider Prof.dr. E.J. Meijboom) naar de waarde van CK-MB na de arteriële switch operatie. Voor zij met haar co-schappen begon, ging zij voor 3 maanden naar the Children's Hospital of Philadelphia, afdeling kindercardiologie, voor onderzoek naar de groei van de neo-aorta na palliatie van het hypoplastisch linker hart syndroom (begeleider Prof.dr. G. Wernovsky). De co-schappen werden afgerond met een keuze co-schap bij de afdeling kindercardiologie van the Royal Children's Hospital in Melbourne, Australië (begeleider Prof.dr. D.J. Penny). Na het behalen van het artsendiploma eind 2002 werkte zij kort als poortarts in het IJsselmeerziekenhuis in Lelystad en daarna als ANIOS kindergeneeskunde in het Gelre ziekenhuis in Apeldoorn (opleider Dr. G.T. Heikens). In 2004 startte zij met onderzoek bij de afdeling kindercardiologie/radiologie van het Erasmus Medisch Centrum (promotoren Prof.dr. W.A. Helbing en Prof.dr. G.P. Krestin), de basis voor dit proefschrift. In 2009 werkte zij enkele maanden als ANIOS cardiologie in het UMC St Radboud te Nijmegen (opleider Prof.dr. J.L.R.M. Smeets) alvorens in augustus vanuit dit centrum met de opleiding tot cardioloog te beginnen. Inmiddels is de vooropleiding interne geneeskunde afgerond in het Meander Medisch Centrum te Amersfoort (opleider Prof.dr. C.A.J.M Gaillard) en is zij begonnen met het B-jaar cardiologie in ditzelfde opleidingsziekenhuis (opleider Dr. P.J. Senden). Daniëlle is getrouwd met Maarten Robbers. Zij hebben drie prachtige kinderen: Matthijs (2004), David (2007) en Amanda (2010).

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- *2e Posterprijs, 43rd meeting of the Association for European Pediatric Cardiology, Venetië, mei 2008*

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- *Posterpresentatie, 2nd symposium on biomechanics in cardiovascular disease: shear stress in vascular biology. Rotterdam, april 2007*
- *Presentatie, 42nd meeting of the Association for European Pediatric Cardiology, Warschau, mei 2007*
- *Posterprijs, Sophia Kindergeneeskunde Onderzoeksdag, Rotterdam, oktober 2007*
- *Posterpresentatie, 11th annual scientific sessions of the Society of Cardiovascular Magnetic Resonance, Los Angeles, februari 2008*
- *Presentatie, 30e congres "Nederlandse Vereniging voor Kindergeneeskunde", Veldhoven, november 2008*

Robbers-Visser D, ten Harkel ADJ, Strengers JLM, Kapusta L, Meijboom FJ, Pattynama PMT, Bogers AJJC, Helbing WA. *Cardiac MRI combined with low-dose dobutamine stress reveals an abnormal stress response in children and young adults after Fontan operation at young age.* J Cardiovasc Magn Res 2007;9:115.

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PhD portfolio

Name PhD Student	Daniëlle Robbers-Visser
Erasmus MC Department	Pediatrics, division of Cardiology
	Radiology
Research School	COEUR
PhD period	August 2004 – December 2008
Promotors	Prof.dr. W.A. Helbing
	Prof.dr. G.P. Krestin
Co-promotor	Dr. L. Kapusta

	Year	Workload (CME/ECTS)
General academic skills		
Classical methods of data analysis	2005	5.7
Biomedical English writhing and communication	2006	4.0
Integrity in Research	2007	1.0
In-depth courses		
Erasmus course cardiovascular MRI with CT correlation	2005	1.5
Pre-conference physician workshop SCMR	2006	8.0
COEUR course congenital heart disease	2008	1.5
Presentations		
Society of Cardiovascular Magnetic Resonance	2007	1.5
Biomechanics in vascular disease	2007	0.5
Association for European Pediatric Cardiology	2007	1.5
Sophia kindergeneeskunde onderzoeksdag	2007	0.5
Society of Cardiovascular Magnetic Resonance	2008	1.5
Association for European Pediatric Cardiology	2008	1.5
Nederlandse Vereniging voor Kindergeneeskunde	2008	0.5
Sophia kindergeneeskunde onderzoeksdag	2008	0.5
COEUR course congenital heart disease	2008	0.5
Committee		
PhD committee, COEUR representative	2006-2008	