Cardiac Biomarkers in
Adult Congenital Heart Disease

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Cardiac Biomarkers in
Adult Congenital Heart Disease

Cardiale biomarkers in volwassen patiënten

met een aangeboren hartafwijking

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Voor mijn lieve familie

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Part I

Introduction

Chapter 1

General Introduction

General introduction

Congenital heart disease (ConHD) is the most common congenital abnormality in newborns[1], with a birth prevalence of 9 per 1000 live births.[2] ConHD comprises a number of cardiac abnormalities with varying aetiology which can be divided into simple, moderate and complex disease (Table 1).[3] The eight most common ConHD are ventricular septal defect (34%), atrial septal defect (13%), persistent ductus arteriosus (10%), pulmonary stenosis (8%), tetralogy of Fallot (ToF, 5%), aortic coarctation (5%), transposition of the great arteries (TGA, 5%) and aortic stenosis (4%).[2]

With the introduction of open-heart surgery, and the use of cardiopulmonary bypass (heart-lung machine) life expectancy of ConHD patients has remarkably improved. Before these techniques became available half of the new-borns with ConHD died during the first decade of life. Improvements over the last decades in cardiac surgery, anaesthesia, intensive care and specialized congenital cardiologist care have led to a steadily growing number of adult patients with ConHD, in particular those patients with more complex ConHD. The estimated number of adults with ConHD in the Netherlands is 35.000 currently.[4]

TABLE 1. Complexity of congenital heart disease

Simple ConHD	ConHD with moderate severity	ConHD with great complexity
Congenital aortic valve disease	Coarctation of the aorta	Fontan procedure
Atrial septal defect	Ebsteins anomaly	Mitral atresia
Mild pulmonary stenosis	Tetralogy of Fallot	Cyanotic congenital heart
Repaired ventricular septal defect	Moderate /severe pulmonary Stenosis	Double outlet right ventricle
Isolated persistent oval foramen		Single ventricle
		Transposition of the great arteries
		Eisenmenger syndrome
		Pulmonary atresia

Adapted from Warnes et al.*3*

Congenital heart disease at adult age

It is questionable whether cardiac operations performed at young age are curative. A substantial number of patients have residual lesions. These sequelae as well as the long-term development of the ConHD itself entail an increased risk for late complications.[5, 6] For example, arrhythmias can occur in all ConHD, although they are mainly observed in ConHD with moderate or great complexity.[7] The overall annual incidence of sudden cardiac death in ConHD, mostly caused by ventricular arrhythmias, is estimated at 0.09%.[8] The reported incidence of infective endocarditis in ConHD is 15-140 times higher than in the general population, with a yearly incidence of 0.1% in adult patients and an estimated mortality rate of 4-10%.[9, 10] Furthermore, despite earlier interventions, approximately 5-10% of ACHD patients develop pulmonary arterial hypertension of variably severity.[11] Pulmonary arterial hypertension associated with ConHD entails increased morbidity and mortality.[12]

One of the most common complications is heart failure, which is the main cause of death in adult ConHD.[6] Some investigators even state that all patients with ConHD have heart failure by definition, since all ConHD patients have a cardiac abnormality, a degree of exercise limitation and neurohormonal activation (Figure 1).[13] Whether these last two conditions apply to all patients with ConHD is debatable, because disease severity differs strongly among the various ConHD.
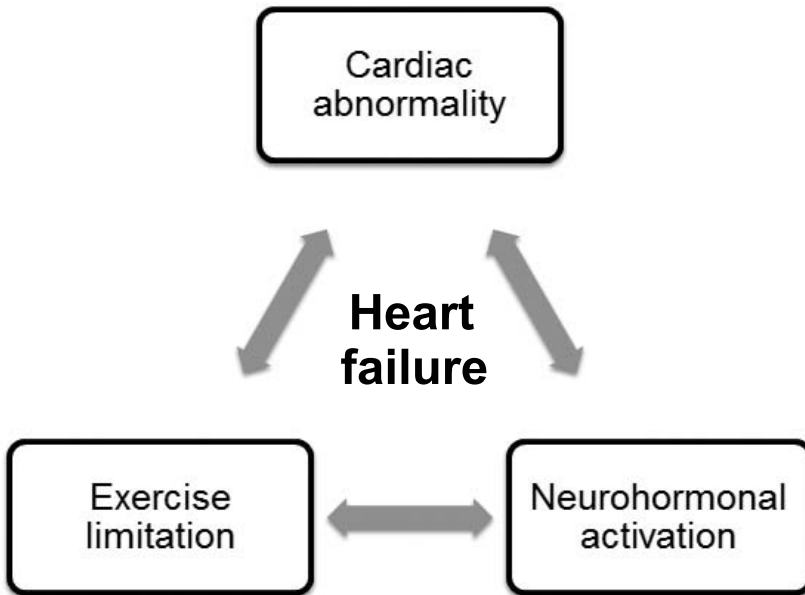
FIGURE 1. Heart failure triad, applicable for all patients with ConHD? (Adapted from: *Bolger et al.[13]*)

The estimated heart failure incidence for adults with ConHD in the Netherlands is 1.2 per 1000 patient-years.[5] These numbers are retrieved from the Dutch CONgenital CORvitia registry (CONCOR), a nation-wide registry of all adult patients with ConHD in the Netherlands. The incidence of heart failure differs among the various congenital heart defects. Heart failure is less often observed in patients with simple lesions, including atrial septal defect and pulmonary stenosis, while highest incidences are reported in patients with more complex disease, such as patients with TGA after Mustard surgery, congenitally corrected TGA, and those with Fontan circulation.

Identification of patients at risk for adverse events

Adequate cardiac function monitoring is crucial to identify adults with ConHD at risk for complications and adverse outcome. Currently used diagnostic techniques such as electrocardiography, conventional echocardiography, cardiac magnetic resonance imaging (CMR), and Holter monitoring are useful to identify cardiac dysfunction or arrhythmias, but fail to address function deterioration in an early (often

asymptomatic) phase. Early detection of cardiac dysfunction could result in a more adequate medical treatment regime or more precise timing of cardiac (re)intervention. This could avoid further deterioration in cardiac function and development of heart failure or life-threatening arrhythmias. Especially in patients with ConHD, the complex cardiac anatomy can be difficult to visualize with conventional imaging techniques. Therefore, quantitative, more sensitive and specific diagnostic tools are warranted. Potentially, cardiac dysfunction can be identified earlier in the process of hemodynamic changes with use of so-called 'biomarkers', including blood markers or novel echocardiographic techniques.

Aims

The aim of this thesis is to evaluate novel, non-invasive diagnostic tools in adult patients with ConDH, including laboratory measurements and advanced echocardiographic parameters, which can contribute to an accurate quantitative assessment of cardiac function and functional capacity.

Transposition of the great arteries

Over the last decades surgical interventions for ConHD have changed and improved dramatically. For example, for patients born with TGA, the first surgical option was the atrial switch procedure as described by Senning in 1959 and Mustard in 1964.[14] At that time, cardiac surgeons in our centre decided to preferentially perform the Mustard procedure over the Senning procedure. During this Mustard procedure, the caval venous blood flow is redirected by a baffle, an artificial tunnel, through the atria to the subpulmonary left ventricle. Consequently, the morphologic RV in the subaortic position has to function as the systemic ventricle (Figure 2). This procedure has reasonably good outcome with a survival of approximately 80% after 25 years,[15] but late sequelae are frequently encountered, including baffle-related problems, arrhythmias and systemic RV dysfunction

FIGURE 2. Mustard procedure[17]

leading to heart failure.[15] Since the mid-1980s, the Mustard procedure has been replaced by the arterial switch operation.[16] But of course, cardiologists continue to see older patients after Mustard repair. Not much is known about the very long-term outcome of these patients. The morphologic RV supporting the systemic circulation remains an important concern and may cause a high burden of morbidity and premature mortality from heart failure or sudden cardiac death due to arrhythmias.

Tetralogy of Fallot

Another large and still growing adult ConHD patient population are patients with tetralogy of Fallot (ToF). This ConHD consists of four cardiac abnormalities: ventricular septal defect, overriding aorta, (sub)valvular pulmonary stenosis and RV hypertrophy (Figure 3). Tetralogy of Fallot is the most common cyanotic heart defect. Survival of patients with ToF has improved considerably since Lillehei performed the first successful corrective surgery in 1954.[18] Despite satisfactory survival results of over 90% 30 years after corrective surgery[19], an increasing number of patients encounter late complications including pulmonary regurgitation with the need for reintervention, right and left ventricular dysfunction, aortic root dilation and arrhythmias. These late complications are an important concern affecting long-term outcome.[20]

FIGURE 3. Tetralogy of Fallot[21]

Cardiac biomarkers

A biomarker generally refers to a measurable indicator of some biological state or condition. Biomarkers can be a hormone, enzyme, biologic substance, but also an echocardiographic feature or other marker that generally refers to a physiological or pathological process. The ideal biomarker in medicine would help to identify those patients who are at risk for adverse outcome, and should meet the criteria as depicted in Figure 4. A good biomarker should have a strong and consistent association with outcome, decision limits should be validated in more than one study, and the biomarker should improve risk stratification. Better risk stratification can enhance identification of high-risk patients who need intensive follow-up, but on the other hand can also improve identification of those patients at relatively low-risk for adverse events who possibly need less frequent follow-up and care. From this point onwards the term 'biomarker' will refer to laboratory serum and plasma measurements. Echocardiographic features will be discussed as a separate topic.

We hypothesize that intracardiac hemodynamic changes can be identified and monitored with use of cardiac biomarkers that are released from the myocardium, before cardiac function deterioration becomes clinically visible. In acquired heart disease cardiac biomarkers already have a well-established diagnostic and prognostic value. For example, natriuretic peptides are well-established markers to exclude alternative causes of dyspnoea from dyspnoea caused by heart failure, and provide prognostic information in patients with acquired heart failure. Whereas in patients with acute coronary syndrome troponins are the gold standard to identify myocardial infarction and are associated with the extent of the myocardial damage.

Consistent associations with outcome		Validated decision limits
Enhances care		Acceptable costs
Additional value	**Ideal biomarker**	Superior performance
Associated risk modifiable with therapy		Accurate and reproducable method
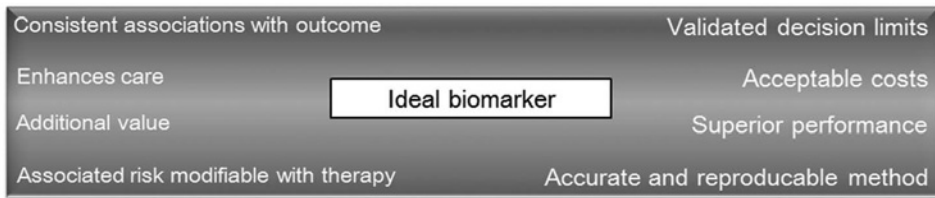
FIGURE 4. Criteria for a novel cardiac biomarker for clinical use (adapted with permission from Morrow et al.[22])

Natriuretic Peptides

The natriuretic peptide family consists of three peptides: atrial natriuretic peptide, brain natriuretic peptide (BNP) and C-type natriuretic peptide. BNP was originally identified in extracts of the porcine brain, from where its name originates. It also present in the human brain but considerably more in the ventricles of the heart.[23] Both the active B-type natriuretic peptide and its amino-terminal propeptide equivalent, N-terminal proBNP (NT-proBNP) are released from the cardiomyocytes in response to ventricular stretch and volume overload. Physiologic actions of the active fragment BNP included increase in natriuresis and diuresis, inhibition of the Renin-Aldosteron-System, inhibition of sympathetic nerve system and vasodilation. In patient with acquired acute and chronic heart failure both BNP and NT-proBNP have proven diagnostic value,[24] can be used to guide therapy [25] and are associated with increased morbidity and mortality[26, 27]. Meanwhile in patients with ConHD, in whom heart failure is a major concern, knowledge of the use of BNP and NT-proBNP is lacking. In this thesis we sought to explore the value of natriuretic peptides in ConHD.

High-sensitive Troponin T

Cardiac troponins are regulatory proteins that control calcium-mediated interaction of actin and myosin. The troponin complex consists of three parts: Troponin I, C and T. Troponin I and T are cardiac-specific and detectable with monoclonal antibody-based assays. Cardiac troponins are released from the cardiomyocyte as a result of irreversible or reversible cell damage. These troponins are the gold standard for the diagnosis of acute myocardial infarction,[28] but elevation of troponin may also occur in other cardiac conditions. Especially with the recent introduction of highly-sensitive assays,[29] smaller amounts of troponin-T are measurable in a subset of patients with various cardiac condition including hypertension, hypertrophic cardiomyopathy, and acute and chronic heart failure.[30, 31] In various cardiac diseases high-sensitive troponin-T (hs-TnT) has shown to be associated with risk stratification and adverse outcome.[31, 32] Cardiac troponin release has been reported in selected subgroups of children with complex ConHD, i.e. hypoplastic left heart syndrome,[33] but information on the release of hs-TnT in adults with ConHD is lacking.

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Speckle-tracking echocardiography

Speckle-tracking echocardiography (STE) is a novel echocardiographic technique that is able to quantify regional and global myocardial function based on frame-to-frame tracking of ultrasonic "speckles" in grey scale 2D images (Figure 5). With STE we can measure strain and strain rate in longitudinal, radial and circumferential directions. Increasing data suggest that myocardial strain imaging with STE provides strong indices of ventricular function in acquired heart disease.[34]

Information about the use of STE for LV and RV function in adults with ConHD is limited. Assessment of RV function with conventional echocardiography is difficult because of its complex geometry and position close behind the sternum. At the moment a reliable, reproducible method for RV function assessment is lacking. The relatively angle- and geometry independence of STE could be a useful advantage in adults with ConHD, with often complex ventricular geometry and varying intrathoracic positions and orientation of the heart.

It has been demonstrated that STE in patients with acquired heart disease is feasible in clinical settings, and that STE parameters may provide useful clinical measurements for early detection of a subclinical state that is likely to progress in heart failure. The feasibility and additional value of STE in adult patients with ConHD is not yet determined and will be addressed in this thesis.
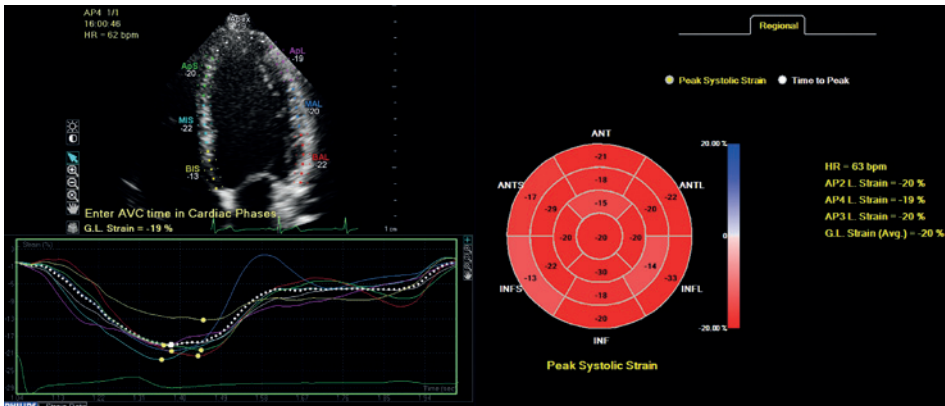

FIGURE 5. Strain imaging.
Longitudinal strain analyses from the apical 4-chamber view.

Outline of the thesis

Patients with TGA after Mustard surgery comprise one of the more complex ConHD with considerable associated morbidity and increased mortality. Results on very long-term outcome of patients after Mustard surgery are lacking. In the first part of this thesis we describe the very long-term outcome of patients after Mustard surgery in a uniquely designed, prospective study, where the patients underwent a thorough in-hospital investigation in 1990, 2001 and 2012. We report outcome up to 40 years and investigate predictors for adverse events in these patients. This study is described in **Chapter 2**.

The second part of this thesis focuses on the use of laboratory cardiac biomarkers in adult ConHD. The exact role of cardiac biomarkers such as natriuretic peptides and troponins in these patients is not yet established. With the studies in this thesis we aim to improve insight in the use of these biomarkers in ConHD. The heart failure biomarkers, natriuretic peptides, are discussed in Chapter 3 to 7. A systematic review of previously published literature on BNP and NT-proBNP in patients with uncorrected and cor-rected atrial and ventricular septal defect is described in **Chapter 3**. Literature on the course of natriuretic peptide release before and after septal defect closure is presented and discussed. **Chapter 4** describes the state of the art on the release, diagnostic and prognostic value of BNP and NT-proBNP in patients with complex ConHD lesions, including patients with ToF, a systemic RV, and univentricular hearts. **Chapter 5** describes the release of NT-proBNP and its relationship with cardiac function and exercise capacity in a cohort of stable adult patients with ConHD. Differences between various congenital heart lesions are discussed. The use of NT-proBNP and associated influences of valvular disease in patients with ToF are described in more detail in **Chapter 6**. In **Chapter 7** we assessed the association between NT-proBNP and the Short-Form Healthy Survey as a measure of quality of life in ConHD patients.

Furthermore, we sought to describe levels of hs-TnT and inflammatory markers hs-CRP and GDF-15 in adults with ConHD, and assess their relationship with cardiac function parameters. **Chapter 8** focuses on the release of hs-TnT and hs-CRP in an outpatient clinic cohort of patients with ConHD. The use of hs-TnT as a marker of cardiac function and differences between various ConHD will be described. Additionally, the possible underlying aetiology and clinical consequences of hs-TnT release in ConHD patients are discussed. In **Chapter 9** the additional value of GDF-15 to monitor ventricular function and functional capacity in patients with ConHD will be assessed.

The third part of this thesis will focus on the use of STE to measure myocardial deformation in ConHD patients. We investigate the use of STE for assessment of RV and LV function in patients with a systemic RV (Mustard patients and congenitally corrected TGA) and in patients with ToF: two patients groups in whom RV dysfunction is a major concern at adult age. We assess the feasibility of STE in these patients, investigate the presence of ventricular-ventricular interaction and determine the relationship of STE with clinical parameters and conventional echocardiography and CMR. The feasibility of STE to assess myocardial deformation for quantification of systolic RV function in patients with a systemic RV will be discussed in **Chapter 10.** Furthermore, we assess the relationship between STE and clinical parameters in these patients. In **Chapter 11** we evaluate the use of myocardial deformation to assess both RV and LV function in patients with ToF, and aim to quantify the presence of ventricular-ventricular interaction. In

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Chapter 12 we address the use of STE to assess LV rotation and twist, and determine its relationship with conventional echocardiography, cardiac magnetic resonance imaging, and exercise capacity in adults with ToF.

The fourth part provides a summary of our work in **Chapter 13**. Finally, in **Chapter 14** the main findings of the studies presented in this thesis are discusses in the light of current literature. Clinical implications and future perspectives are discussed.

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Part II

Late outcome after Mustard surgery

Chapter 2

The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years

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2

Abstract

Aims

To describe long-term survival, clinical outcome and ventricular function in a longitudinally followed cohort of patients after Mustard repair for transposition of the great arteries (TGA). There is serious concern about the long-term outcome after Mustard repair.

Methods and Results

This longitudinal single-center study consisted of 91 consecutive patients, who underwent Mustard repair before 1980, at age<15 years, and were evaluated in-hospital every 10 years. Survival status was obtained of 86 patients. Median follow-up was 35 (IQR 34–38) years. Cumulative survival was 84% after 10 years, 80% after 20 years, 77% after 30 years, and 68% after 39 years. Cumulative survival free of events (i.e. heart transplantation, arrhythmias, reintervention, and heart failure) was 19% after 39 years. Reinterventions were mainly required for baffle-related problems. Supraventricular and ventricular arrhythmias occurred in 28 and 6%of the patients, respectively. Pacemaker and/or ICD implantation was performed in 39%. Fifty survivors participated in the current in-hospital investigation, which included electrocardiography, 2D-echocardiography, cardiopulmonary-exercise testing, NT-proBNP measurement, Holter monitoring, and cardiac magnetic resonance. Right ventricular systolic function was impaired in all but one patient at last follow-up, and 14% developed heart failure in the last decade. NT-proBNP levels [median 31.6 (IQR 22.3–53.2) pmol/L] were elevated in 92% of the patients. Early postoperative arrhythmias were a predictor for late arrhythmias [HR 3.8 (95% CI 1.5–9.5)], and development of heart failure [HR 8.1 (95% CI 2.2–30.7)]. Also older age at operation was a predictor for heart failure [HR 1.26 (95% CI 1.0–1.6)].

Conclusion

Long-term survival after Mustard repair is clearly diminished and morbidity is substantial. Early postoperative arrhythmias are a predictor for heart failure and late arrhythmias.

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Introduction

The survival of patients with transposition of the great arteries (TGA) has improved dramatically after introduction of the atrial switch procedures described by Senning in 1959[1] and Mustard in 1964.[2] At that time, the choice was made in our centre to preferentially apply the Mustard procedure. Although the Mustard procedure has reasonably good outcome during the first two decades of life,[3] late sequelae are frequently encountered including arrhythmias, baffle-related complications, and right ventricular (RV) dysfunction leading to heart failure.[3-5] Since the mid-1980s, the Mustard procedure has been replaced by the arterial switch operation.[6] Nevertheless, cardiologists continue to see older patients after Mustard repair.[4,5] The cumulative survival after atrial switch is approximately 80% after 25 years.[3-5,7,8] The morphologic RV supporting the systemic circulation remains an important concern and may cause a high burden of morbidity and premature mortality from heart failure.[9]

So far, reliable information on outcome beyond 30 years is limited. The aim of this study is to assess survival, occurrence of arrhythmias and systemic ventricular dysfunction, and clinical course over a time span of nearly 40 years. This study is unique by its longitudinal design and extensive in-hospital investigations every 10 years.

Methods

Study population

All 91 consecutive patients who underwent Mustard repair for transposition of the great arteries in our institution between 1973 and 1980, at age <15 years, were included in this longitudinal study.

In 36 patients, additional VSD closure or relief of pulmonary stenosis was performed in the same procedure. These patients are referred to as 'complex TGA'. The cohort was first studied in 1990[10] and the second follow-up was performed in 2001.[3] All patients who were alive and had participated in one or both of the previous studies were invited to participate in the current third study. Survival status was obtained from the Dutch National Population Registry. Patients were invited to participate and were seen at the outpatient clinic of Erasmus Medical Center between April 2011 and March 2012. Detailed information describing the baseline characteristics, surgical procedure, and 10-year and 20-year follow-up results has previously been reported.[3,10] The study protocol was approved by the institutional Medical Ethics Committee (2010-15). Written informed consent was obtained from all study participants.

Adverse events

Survival was compared with the expected survival of the normal, age-matched Dutch population. Major events were defined as: all-cause mortality; heart transplantation (HTx); cardiac reinterventions; symptomatic arrhythmias, or heart failure. Arrhythmias were defined as symptomatic if antiarrhythmic medication was prescribed, cardioversion or catheter-based or surgical ablation had been applied,

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or pacemaker/ICD implantation was performed. Heart failure was defined as hospitalization for heart failure or initiation of heart-failure medication.

Clinical assessment

All participating patients underwent extensive medical examination including history, physical examination, standard 12-lead electrocardiography (ECG), 24 h ambulatory Holter monitoring, 2D-echocardiography, bicycle ergometry with maximum oxygen consumption (VO$_2$ max), NT-proBNP measurement, and if possible cardiac magnetic resonance (CMR) imaging.

If a patient was unwilling or unable to visit the outpatient clinic, an additional questionnaire was sent to obtain information on morbidity, and to receive permission for the use of information from their medical record.

Electrocardiography and 24 h Holter monitoring

Standard 12-lead surface ECGs were analysed for rhythm, PR interval, and QRS duration. A 24 h Holter monitoring was performed with a Cardio Perfect Holter DR180+ three-channel recorder (Welch Allyn Cardio Control, North East Monitoring, Maynard, MA, USA). Sinus node disease (SND) was defined according to the Kugler criteria, as described previously.[10]

Echocardiography

A detailed two-dimensional transthoracic echocardiogram was performed using the commercially available IE33 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions and function were measured according to the current guidelines.[11,12] Right ventricular systolic function was also assessed visually ("eyeballing") to make a comparison with the two previous studies possible. Right ventricular systolic function was graded as normal or mildly, moderately or severely impaired. Additionally, more objective measures including fractional area change (FAC), S' of the tricuspid annulus, and tricuspid annulus plane systolic excursion (TAPSE) were used to quantify RV function. Elevated pulmonary pressure was defined as early diastolic pulmonary regurgitation flow velocity of > 2.5 m/s or, in the absence of (sub)pulmonary obstruction, mitral regurgitation flow velocity > 3.0 m/s. The presence of baffle leakage or stenosis was assessed with colour Doppler echocardiography. All measures were obtained by two independent observers.

Bicycle ergometry

Maximal workload and maximal oxygen consumption (VO$_2$ max) were assessed by bicycle ergometry with gradual workload increment of 20 Watts per minute (Ramp protocol), and compared with that of normal individuals corrected for age, gender, body height, and weight. The ratio of minute ventilation

to carbon dioxide production (VE/VCO2) was assessed at the anaerobic threshold and at maximum workload. Performance was considered maximal when a respiratory quotient (RER) of >1 was reached.

NT-proBNP measurement

Peripheral venous blood samples were collected after 30 min rest. Plasma NT-proBNP levels were determined with the use of the commercially available electrochemiluminesence immunoassay Elecsys (Roche Diagnostics, Basel, Switzerland). The reference value of normal for NT-proBNP in our hospital is <14 pmol/L.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a Signa 1.5-Tesla whole-body scanner (GE Medical Systems, Milwaukee, WI, USA) with dedicated phased-array cardiac surface coils. Details of the used MR sequence have been reported previously.[13] For CMR analyses a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass version 5.2 (Medis Medical Imaging Systems, Leiden, the Netherlands). Ventricular volume was quantified using manual outlining of endocardial borders, excluding large trabeculae and the papillary muscles from the blood volume, in end-systole and end-diastole.

Statistical analysis

For the descriptive data analyses, we used the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean±SD, or median with interquartile range (IQR) depending on data distribution. Categorical variables are presented as frequencies and percentages. For comparison of continuous variables between independent groups, the Student's unpaired t-test was used. For paired groups, the paired Student's t-test or Wilcoxon signed-rank test were performed. Frequencies of unpaired data were compared with use of the Chi^2 test or Fisher's exact test when applicable, and for paired data the McNemar test was used. To quantify correlations between two variables, the Pearson correlation test or Spearman correlation test was used.

For advanced statistical analyses of the longitudinal and survival data, the R software version 3.0.1 package was used (available at www.r-project.org). Univariable and multivariable Cox proportional hazard regression analyses were used to identify predictors for the pre-defined events: all-cause mortality and HTx; arrhythmia or pacemaker implantation; heart failure, and need for reinterventions. The following baseline covariates were included in the models: age at operation, era of Mustard operation (before or after the median, 1977), simple vs. complex TGA, temperature during surgery, and early postoperative arrhythmias, defined as any arrhythmia within 30 days after Mustard repair. Clinical parameters from 1990 and 2001 that were included in the models comprised: QRS duration; exercise capacity; RV systolic function and severity of tricuspid regurgitation on echocardiography; signs of SND, VT or SVT on Holter.

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Due to the low frequencies of the aforementioned events, a penalized likelihood approach was used in the multivariable Cox model.[14] To account for missing covariate data, we used a multiple imputation approach.[15] Wald tests were used to assess which covariates were most associated with the risk of each event. In addition, time-dependent Cox regression analysis was used to assess the effects of the time-dependent covariates QRS duration, exercise capacity, and ECG rhythm on outcome.

Cumulative survival plots and cumulative event incidences for the pre-defined adverse events were calculated using the Kaplan-Meier method. The survival of Mustard patients was compared with the expected survival of the normal Dutch population. The Mantel and Haenszel log-rank test was used to compare survival curves. All statistical tests were two-sided and a *p*-value of <0.05 was considered significant.

Results

Study population

The original study cohort consisted of 91 patients. Baseline characteristics are presented in Table 1. An overview of the patient participation for the current study is presented in Figure 1. Median age at operation was 0.7 [IQR 0.4–2.5] years. Age at current study did not differ significantly between patients operated before and after 1977 (28.0±15.9 vs. 31.1 years, *P*= 0.257). There were no differences in baseline characteristics between the current participating and non-participating patients.

TABLE 1. Baseline characteristics

	Total	1990	2001	2012
	n=91	n=58	n=54	n=50
Male (%)	65%	69%	70%	64%
Age at time of study (years)	--	14.1 [12.8-17.5]	25.8 [24.5-30.1]	35.8 [34.4-40.1]
Age at operation (years)	0.7 [0.3 - 3.2]	0.7 [0.3-2.5]	0.7 [0.3-2.5]	0.7 [0.4-2.5]
Prior palliation (n, %)	83 (91%)	55 (95%)	52 (96%)	47 (94%)
Follow-up since surgery (years)	--	13 [12 – 16]	25 [24 – 28]	35 [34 – 38]
Hypothermia during surgery:				
Temperature <20℃ (n, %)	60 (66%)	44 (76%)	40 (74%)	37 (74%)
Temperature 20-35℃ (n, %)	22 (24%)	11 (19%)	11 (20%)	10 (20%)
Temperature unknown (n, %)	9 (`10%)	3 (5%)	3 (6%)	3 (6%)
Complex TGA (%)	40%	36%	33%	36%
Pacemaker before 1990 (n, %)	12 (13%)	8 (14%)	8 (15%)	6 (12%)

TGA=transposition of the great arteries
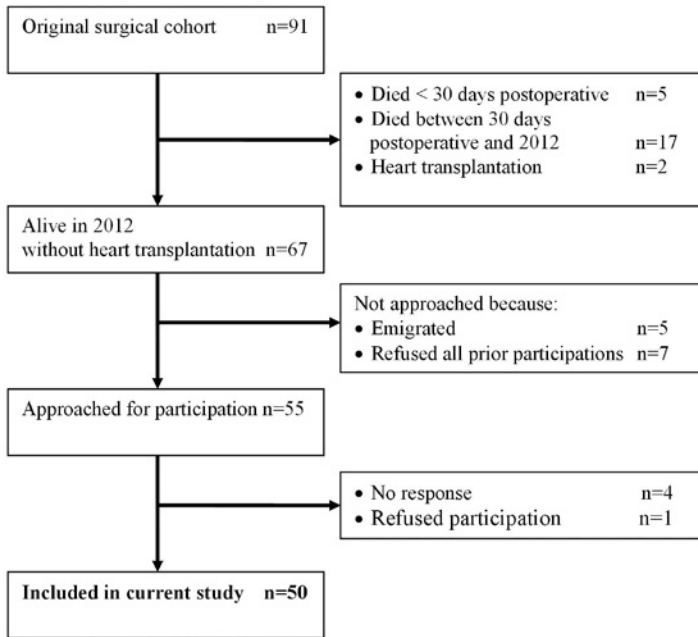
FIGURE 1. Flow chart of the study population

Survival

Survival status was obtained of 86 (95%) patients. Cumulative survival without HTx was 84% at 10 years, 80% at 20 years, 77% at 30 years and 68% after 39 years (Figure 2). Five patients moved abroad and were untraceable. The median postoperative follow-up was 35 [IQR 34 – 38] years. Twenty-two patients died:
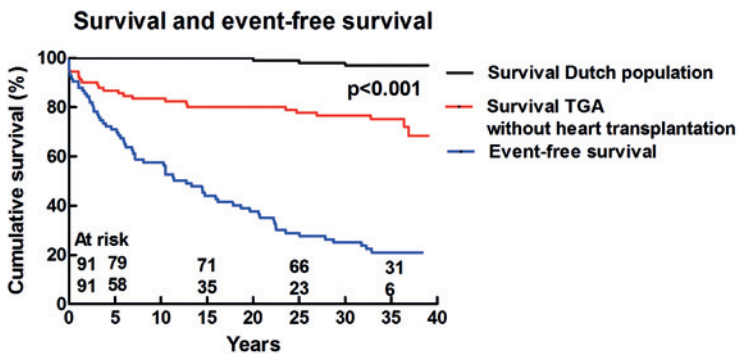
FIGURE 2. Kaplan Meier survival curves for survival without heart transplantation and event-free survival, i.e. free of heart transplantation, cardiac reinterventions, symptomatic arrhythmias, heart failure or death. Survival without heart transplantation was compared to the survival of the Dutch population.

five patients died within 30 days after surgery. Until the first follow-up study in 1990, 13 patients died, 7 of whom suddenly without evidence of prior heart failure or arrhythmias.[10] In the following decade, two patients died of heart failure.[3] In the last decade, two patients died, both of ventricular fibrillation (VF). One patient died of VF during exercise, without previous signs of heart failure. This patient had showed non-sustained VT on Holter in 1990, but never had experienced symptomatic arrhythmias. The other patient developed VF in hospital, shortly after ICD implantation, before threshold testing could be performed. Resuscitation was not successful. He had received the ICD because of severely impaired RV systolic function. No differences in survival and event-free survival between patients with simple or complex TGA were observed (Figure 3). Two patients underwent successful HTx for failure of the systemic RV, respectively 26 and 37 years after Mustard correction.
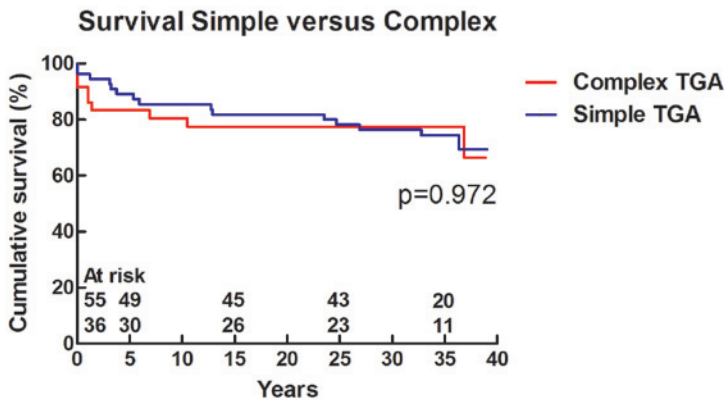
FIGURE 3. Kaplan Meier curves for survival without heart transplantation of patients with complex TGA (n=36) versus simple TGA (n=55).

Adverse events

During total follow-up, 66 patients had at least one of the pre-defined adverse events, with a subsequent cumulative event-free survival of 19% after 39 years (Figure 2).

Reinterventions

In the last decade, three patients (6%) underwent catheter intervention for inferior baffle stenosis. In one of them, reintervention for superior baffle stenosis was performed in the same procedure. One patient had an acute myocardial infarction at the age of 45 years, for which she underwent a successful percutaneous coronary intervention.

During total follow-up, 27 patients (cumulative incidence of 46%) required reintervention, mainly for baffle stenosis or leakage (n=19). The median time between Mustard repair and first baffle reintervention was 14.8 [IQR 10.3 – 20.6] years.

Arrhythmias

In the last decade, two patients (4%) developed atrial fibrillation (AF), two patients (4%) had atrial flutter, one patient (2%) had VF and two (4%) experienced both VT and SVT. The cumulative incidence of SVT was 28% and of VT / VF was 6% during total follow-up. In total, pacemaker implantation was performed in 19 patients (cumulative 33%) and ICD implantation in three patients (6%). One patient received an ICD for primary prevention, and the other two for secondary prevention.

Heart failure

In the last 10 years, 7 patients (14%) developed heart failure of whom five needed hospital admission. During total follow-up, 12 patients (23%) developed heart failure; two of them died and two underwent HTx.

History and clinical evaluation

The median age at the time of the current study was 36 [IQR 34 – 40] years with a median postoperative follow-up of 35 [IQR 34 – 38] years. Median oxygen saturation was 97 [IQR 96 – 99]%. Twenty-six patients (52%) used cardiac medication comprising: ACE-inhibitors (n=16), beta-blockers for heart failure (n=2) or arrhythmia (n=9), digoxin (n=6) or other antiarrhythmic drugs (n=5). One patient was treated for pulmonary arterial hypertension with sildenafil. A total of 22 patients (44%) had at least one hospital admission in the last decade. No paradoxical embolic events occurred.

Seven women had 13 successful pregnancies. Three patients refrained from pregnancy after careful counselling regarding the possible risks posed by their cardiac status.

Electrocardiography and 24 h Holter

The results are summarized in Table 2. The majority of patients were in sinus rhythm (66%). QRS duration increased significantly over time (Figure 4). On Holter, no significant bradycardia (ventricular pauses longer than three seconds) or sustained VTs were observed. None of the patients with non-sustained VT (16%) was symptomatic. There were no differences in the incidence of supraventricular or ventricular arrhythmias between patients with simple and complex TGA (*p*=0.4).

Echocardiography

The systemic RV function deteriorated over time (Table 2). At last follow-up, only one patient (2%) had a good RV systolic function. Right ventricular systolic dysfunction was mild in 11 patients (23%), moderate in 28 (60%) and severe in 7 (15%). Both RV FAC and TAPSE were decreased in the majority of patients (Table 3). TDI S' was below 10 cm/s in all but one patient. Lower RV FAC was correlated with a larger RV annulus dimension (r=-0.35, *p*=0.03). There was no difference in RV systolic function or a difference in deterioration of RV systolic function over time between patients with simple or complex TGA. To investigate the

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TABLE 2. Diagnostic tests

	1990 (10)	2001 (3)	2012	P-value*	
				2012 vs. 1990	2012 vs. 2001
	n = 58	n = 54	n = 50		
12-lead electrocardiogram	n=58	n=54	n=47		
Rhythm					
- Sinus rhythm	40 (69%)	34 (63%)	31 (66%)	0.4	1.0
- Atrial rhythm	6 (10%)	5 (9%)	5 (11%)	0.7	0.7
- Atrial fibrillation / flutter	1 (2%)	0	3 (6%)	0.2	0.2
- Nodal rhythm	7 (12%)	7 (13%)	1 (2%)	0.2	**0.03**
- Pacemaker rhyhtm	4 (7%)	8 (15%)	7 (15%)	0.5	1.0
PR interval (ms)	162±42	165±23	175±43	**< 0.001**	**0.02**
PR interval >200 ms	1 (2%)	1 (3%)	7 (21%)	**0.03**	0.1
QRS duration (ms)	94±11	110±17	117±19	**<0.001**	**0.001**
QRS duration >120 ms	0	11 (25%)	13 (33%)	**0.01**	0.5
RBBB	5 (9%)	9 (17%)	20 (40%)	**<0.001**	**0.001**
24-hour Holter ECG	n=57	n=50	n=37		
Mean heart rate (bpm)	-	-	73±14	-	-
Maximum heart rate (bpm)	-	-	132±28	-	-
Minimum heart rate (bpm)	-	-	44±10	-	-
Sinus node disease	18 (32%)	30 (60%)	19 (51%)	**0.003**	0.3
Paroxysmal AF/flutter	1 (2%)	0	4 (9%)	0.3	0.5
VT 3-10 complexes	3 (5%)	4 (8%)	6 (16%)	0.1	0.5
VT >10 complexes	0	0	0	-	-
Bicycle ergometry	n=49	n=49	n=36		
Maximum workload (%)	84 [74-93]	74 [64-84]	73 [68-87]	**0.001**	1.0
Maximum heart rate (%)	86 [80-90]	87 [79-92]	85 [76-92]	0.2	**0.02**
VO$_2$ max (%)	-	-	69 [54-80]	-	-
RER max	-	-	1.3[1.3-1.4]	-	-
VE/VCO2 - anaerobic threshold			28.3[25.8-33.8]		
VE/VCO2 – max workload			29.3[28.7-38.6]		
Echocardiogram	n=58	n=53	n=47		
RV systolic function normal	40 (69%)	3 (6%)	1 (2%)	**<0.001**	0.3
Valve regurgitation (>trace)					
- Aortic regurgitation	4 (7%)	5 (9%)	7 (15%)	**0.03**	0.2
- Mitral regurgitation	8 (14%)	12 (23%)	11 (23%)	0.3	0.7
- Pulmonary regurgitation	15 (26%)	27 (51%)	27 (57%)	**<0.001**	0.3
- Tricuspid regurgitation	36 (62%)	45 (85%)	43 (92%)	**0.001**	0.2
Severe tricuspid regurgitation	1 (2%)	10 (19%)	17 (38%)	**<0.001**	0.1
Mitral regurgitation vmax (m/s)	2.9	2.5	2.8	0.7	0.4
Pulmonary regurgitation vmax (m/s)	1.9	1.9	2.0	0.1	0.9

bpm: beats per minute, RER: respiratory exchange ratio, SVT: supraventricular tachycardia, vmax: maximum velocity, VT: ventricular tachycardia.

Values are presented as mean±SD, median [IQR] or n (%).

* p-values are displayed only for measured performed in two or all three studies

TABLE 3. Additional diagnostics tests performed only in 2012

Echocardiography			
	Mean±SD	IQR	Abnormal (%)*
MR vmax (m/s)	2.9±0.8	[.2 - 3.4]	50
PR vmax (m/s)	1.9±0,7	[1.4 -2.50	26
RV annulus (mm)	50±7	[45 - 55]	94
RV apex-base (mm)	81±10	[74 - 87]	35
TAPSE (mm)	13±3	[11 - 15]	89
RV FAC (%)	25±10	[19 - 30]	79
TDI S'tricuspid annulus	7.5±1.5	[6.3 - 8.5]	97
IVC collapse > 50% (n, %)	33(77%)		
Cardiac Magnetic Resonance imaging			
	n = 24		
LV EDV/BSA (ml/m^2)	60 [37-89]		
LV ESV/BSA (ml/m^2)	21 [10-46]		
LV EF (%)	63 [43-76]		
RV EDV/BSA (ml/m^2)	93 [50-145]		
RV ESV/BSA (ml/m^2)	41 [17-78]		
RV EF (%)	47 [28-71]		

CMR data are presented as median [IQR]
BSA: body surface area, EDV: end-diastolic volume, EF: ejection fraction, ESV: end-systolic volume, FAC: fractional area change, IVC: inferior vena cava,
LV: left ventricle, MR: mitral regurgitation, RV: right ventricle, PR: pulmonary regurgitation, TAPSE: tricuspid annular plane systolic excursion
* According to the reference values in the guidelines for structural heart disease (11, 12)

impact of pregnancy on deterioration of RV systolic function, we compared changes in RV systolic function between women with and without previous pregnancy. No significant differences were found.

More patients developed regurgitation of the aortic, pulmonary, and tricuspid valve. Severe tricuspid regurgitation was not significantly associated with diminished RV systolic function. Eight patients (16%) had elevated pulmonary arterial pressures. Neither pulmonary nor mitral regurgitation peak velocities
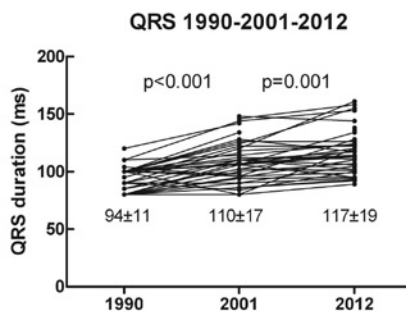
FIGURE 4. QRS duration over time.
The course of QRS duration over time for each participant.

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were related to the severity of RV dilation or RV systolic dysfunction. In 18 patients, residual lesions were found comprising mild obstruction of the inferior baffle (n=4), pulmonary venous baffle (n=4) or both (n=2), pulmonary valve stenosis (n=9), baffle leakage (n=2), residual VSD (n=1), and residual ASD (n=1). All lesions were well tolerated and did not require intervention.

Bicycle ergometry

Maximal exercise capacity was decreased but remained stable over the last t10 years (Table 2). Sixty-nine percent achieved a VO_2 max <85% of the predicted value. During exercise, six patients had an increase in ventricular extrasystoles; in two patients, these were multifocal. No SVT or VT was observed.

NT-proBNP

Median NT-proBNP level was 31.6 [IQR 22.3 – 53.2] pmol/L. An elevated NT-pro-BNP level was observed in 92% of the patients. NT-pro-BNP correlated with age (r=0.5, p=0.01) and there was a trend with RV FAC (r= -0.33, p=0.059) and RV annulus dimension (r=0.30, p=0.063). Patients with pacemaker rhythm or AF had significantly higher NT-proBNP levels than patients with sinus or atrial rhythm (134.3 [IQR 44.4-230.5] vs. 28.6 [IQR 21.9-40.4] pmol/L, p=0.006).

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed in 24 patients (48%). The reasons for not performing CMR in the others were the presence of a pacemaker (n=16), refusal (n=7) and claustrophobia (n=3). The results of CMR are summarized in Table 3. Median RV ejection fraction was 47 [IQR 28 - 71]%. Patients with complex TGA had a higher LVEF (67% vs. 58%, p=0.007) and RVEF (56% vs. 43%, p=0.005) than patients with simple TGA.

Predictor analyses

Results of Cox regression analyses are presented in Table 4. Patients operated before 1977 more often died, but needed fewer reinterventions than patients operated after 1977. Early post-operative arrhythmias were predictive for arrhythmias and for development of heart failure during follow-up. Using a time-dependent Cox regression model, early postoperative arrhythmias were predictive for heart failure independent of changes in QRS duration, exercise capacity, and loss of sinus rhythm over the three study moments. No clinical parameters derived from ECG, echocardiography, Holter, and bicycle ergometry in 1990 and 2001 were predictive for outcome.

TABLE 4. Predictors for clinical endpoints; all-cause mortality, reinterventions, heart failure and arrhythmias

	Univariable model			Multivariable model		
Endpoint	HR	CI	p-value	HR	CI	p-value
All-cause mortality						
Early postoperative arrhythmias	2.04	[0.76 - 5.50]	0.158	1.50	[0.55 - 4.10]	0.432
Temperature during surgery	1.15	[1.04 - 1.26]	**0.004**	1.05	[0.95 - 1.17]	0.328
Complex or simple TGA	0.99	[0.43 - 2.25]	0.972	1,00	[0.44 - 2.30]	0.995
Age at operation	1.11	[0.95 - 1.28]	0.182	0.97	[0.80 - 1.17]	0.738
Operated before 1977	4.26	[1.44 - 12.60]	**0.009**	2.89	[1.00 - 8.33]	**0.049**
Reintervention						
Early postoperative arrhythmias	0.50	[0.12 - 2.09]	0.343	1.23	[0.62 - 0.36]	0.739
Temperature during surgery	0.97	[0.88 - 1.08]	0.589	1.03	[0.90 - 1.18]	0.622
Complex or simple TGA	1.35	[0.64 - 2.86]	0.428	1.33	[0.63 - 2.81]	0.450
Age at operation	0.88	[0.73 - 1.08]	0.239	0.99	[0.77 - 1.28]	0.944
Operated before 1977	0.37	[0.18 - 0.78]	**0.008**	0.34	[0.14 - 0.84]	**0.020**
Heart failure						
Early postoperative arrhythmias	3.00	[0.81 - 11.12]	0.100	8.13	[2.15 - 30.72]	**0.002**
Temperature during surgery	1.02	[0.89 - 1.18]	0.760	0.92	[0.77 - 1.11]	0.393
Complex or simple TGA	0.70	[0.22 - 2.19]	0.695	1.26	[0.38 - 4.19]	0.706
Age at operation	1.23	[1.01 - 1.50]	**0.038**	1.26	[1.01 - 1.56]	**0.041**
Operated before 1977	1.22	[0.39 - 3.86]	0.730	0.57	[0.15 - 2.07]	0.391
Arrhythmias						
Early postoperative arrhythmias	4.62	[1.96 - 10.90]	**<0.001**	3.82	[1.54 - 9.49]	**0.004**
Temperature during surgery	1.11	[1.02 - 1.21]	**0.012**	1.05	[0.95 - 1.17]	0.331
Complex or simple TGA	1.12	[0.53 - 2.36]	0.765	1.42	[0.65 - 3.09]	0.378
Age at operation	1.18	[1.03 - 1.35]	**0.019**	1.09	[0.91 - 1.29]	0.356
Operated before 1977	1.95	[0.96 - 3.98]	0.065	1.10	[0.48 - 2.51]	0.829

CI= 95% Confidence Interval; HR= Hazard Ratio; TGA= Transposition of the great arteries

Discussion

This longitudinal study, evaluating Mustard patients systematically every 10 years for nearly 40 years, shows that patients operated in the 1970s have an acceptable survival and remain in remarkably stable clinical condition despite substantial morbidity and compromised ventricular systolic function. Although ventricular systolic function shows a further decline over time and arrhythmias are often encountered, exercise capacity remains stable.

Survival and major events

Survival in our cohort is clearly worse than in the general Dutch population. So far, results after the arterial switch operation are better, but follow-up in these patients is still inevitably shorter.[16-18] Survival seems comparable to patients after the Senning operation; however, only follow-up of no longer than 20 year has been described for Senning patients.[19] In contrast to findings by Lange et al.,[8] survival rates of patients with

simple and complex TGA were similar in our study. At 25-year follow-up there was a difference in event-free survival between simple and complex TGA. This difference disappeared over the last 10 years.

While in the previous decade, heart failure was the main cause of death, ventricular arrhythmias were the sole cause in the last decade. Ventricular arrhythmias are associated with impaired systemic ventricular systolic function in Mustard patients.[20] One of our patients had VF despite having only mild systolic ventricular dysfunction.

Survival results were not as bad as we expected, based on the findings in this cohort 10 years ago. However, morbidity was substantial. Baffle-related complications are the most frequent cause of reintervention, which has been described by Hörer et al.[7] However, as only three baffle-related reinterventions were performed in the last 10 years, baffle problems seem to have been addressed effectively in the previous decades and new stenosis are not often encountered.

Systemic right ventricular systolic dysfunction

Progressive decline in systemic RV systolic function is confirmed by our study and remains the major concern in Mustard patients. Tricuspid regurgitation increased in line with further deterioration of RV systolic function and dilation of the ventricle. The degree of RV systolic dysfunction was correlated with NT-proBNP levels, a known marker of prognosis in acquired heart failure.[21] Decline in RV systolic function seems to be confirmed by CMR-derived ejection fraction, although normal values for these subaortic RVs are not available. Nevertheless, the median RVEF in our patients is lower than the RVEF measured in the younger patients with systemic RVs described by Dobson et al.[22] As the benefit of conventional heart failure medication for failing subaortic RVs is limited,[23,24] we expect that more patients will qualify for heart transplantation in the future.

Interestingly, patients with complex TGA had a higher LV and RV ejection fraction on CMR than those with simple TGA. Possibly, the presence of a residual LV outflow tract obstruction with subsequent higher systolic LV pressure causing a more favourable position of the interventricular septum improves ventricular interaction and thereby ventricular systolic function. However, regarding our CMR results, our study population was small and data will have to be confirmed by larger studies.

Arrhythmias

In the last decade, the incidence of SVTs has doubled. This is worrisome, as Kammeraad et al showed that SVTs are a predictor of sudden cardiac death.[25] The occurrence of atrial macro-re-entry tachycardia could be related to extensive atrial scar tissue, since patients with a systemic RV without atrial scarring (i.e. congenitally corrected TGA) have significantly less SVTs.[22] Also increase in atrial pressure caused by ongoing decline in RV systolic function could induce AF. Although Holter recordings did not show an increase in ventricular arrhythmias, five patients experienced them and two of them died. This urges the question whether more patients with systemic RV systolic dysfunction should receive an ICD for primary prevention. Decisions on this topic are difficult, because in these young patients inappropriate shocks

are known to occur more often and consequent psychological problems are of major concern.[26,27] Moreover, lead implantation may lead to obstruction in relatively narrow superior systemic venous baffles.[28] Additionally, lead renewal may be necessary over time in these relatively young patients, which has a significant morbidity. On the other hand two patients died because of ventricular fibrillation in the last decade, which probably could have been prevented by an ICD in one.

Sinus-node disease has been a major concern and the main reason for pacemaker implantation in Mustard patients.[29] Although more than half of our patients showed signs of SND on Holter, only two additional pacemakers were implanted for this indication. Moreover, there was no further loss of sinus rhythm on ECG. Therefore, SND appears to be primarily a problem of the earlier decades after surgery.

Functional capacity

Exercise capacity is clearly impaired in our cohort of patients, but remained stable in the last ten years. This impaired exercise capacity and lower VO_2 max are in line with the reference values for patients after atrial switch operation described by Kempny et al.[30] Exercise capacity could be limited by several factors: failure to increase ventricular stroke volume due to impaired myocardial contractile reserve, the inability to augment ventricular filling because of non-compliant baffles or inadequate coronary flow reserve in the hypertrophic RV, and chronotropic incompetence, which is a known problem in Mustard patients.[31] In our patients, the maximum heart rate during exercise testing declined over the last 10 years.

Predictors for late events

Older age at time of Mustard repair was associated with a higher chance of developing heart failure. This emphasizes the importance of early surgery, which became standard in the last era of Mustard repair. In patients who are operated at an older age, the prolonged presence of cyanosis may negatively affect the ventricular myocardium.

Mortality was significantly higher in the patients operated before 1977 than in those patients operated after 1977. This could reflect improvement in experience, in surgical techniques, and in the quality of perioperative care.

Early postoperative arrhythmias predicted the development of late arrhythmias and also the occurrence of heart failure in our cohort. Sakar et al[32] found early post-operative arrhythmias to be associated with late sudden death and childhood junctional rhythm in Mustard patients was a predictor for late SVTs in the study of Puley et al.[33] Possibly, the relation between early and late arrhythmias can be explained by surgical damage to the conduction system and the presence of postoperative scar tissue and fibrosis. The relation between early arrhythmias and heart failure is new and needs attention. As patients with early arrhythmias receive a pacemaker more often, ventricular function could be hampered by longstanding abnormal ventricular activation.[34] Also the use of negative inotropic antiarrhythmic drugs could have had a negative effect on RV function. For example, 20% of our patients used a beta-blocker. On the other hand, perhaps the occurrence of early post-operative arrhythmias is an independent sign

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of a compromised hemodynamic or anatomic situation. Further studies should investigate the exact role and predictive value of these early arrhythmias.

Study limitations and advantages

Although the number of patients in this study is limited, we report the follow-up of a consecutive cohort of operated patients, without selection bias related to disease severity. After a follow-up of nearly 40 years, we gathered medical information on 50 (91%) of the 55 approached patients. We found no significant differences in baseline characteristics between participating and non-participating patients. Therefore, we are confident that there was no selection bias and consider the patients who participated in this study as a non-selected population. Most other studies report on selected patients, still regularly seen at the adult outpatient clinic, while we approached the total patient population operated in the pre-defined time period to visit the hospital.

Assessment of RV function with use of echocardiography is difficult in the normal heart, and even more difficult in Mustard patients.[35] Normal values for subaortic RVs are not available. The same holds for CMR. Cardiac magnetic resonance is an elegant technique to assess RV volume and function, also in Mustard patients. However, a substantial number of the Mustard patients has a pacemaker, which makes it impossible to perform a CMR. Even with the use of MRI compatible pacemakers, the intracardiac leads will continue to cause artefacts in the area of interest and thus accurate assessment of RV function in these patients remains difficult.

Diagnostic methods have been changed inevitably over the last decades. Therefore, for comparison to data of the previous studies, we used the same methods as were used in the past. In addition, we performed and reported all up-to-date diagnostic methods which were available in 2012. We believe that this study provides unique data, because this is the only study to examine the same cohort of Mustard patients longitudinally.

Conclusions

Forty years after Mustard repair, two-third of our original cohort are still alive. There is a progressive decline in RV systolic function and an increasing incidence of arrhythmias and heart failure. However, functional capacity remains stable.

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Part III

Cardiac biomarkers in adult congenital heart disease

Chapter 3

The usefulness of brain natriuretic peptide in simple congenital heart disease: a systematic review

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Abstract

Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide are two well-established markers for cardiac failure in acquired heart disease. Nevertheless, the clinical utility of these markers in patients with congenital heart disease remains unclear. Therefore, the aim of this study was to evaluate the diagnostic and prognostic value of these markers in patients with congenital heart disease. A PubMed and EMBASE literature search was executed with focus on the most common simple congenital heart defects; atrial septal defect and ventricular septal defect. Data on brain natriuretic peptide measurement, cardiac function parameters, and follow-up were collected. In patients with atrial or ventricular septal defect, brain natriuretic peptide levels were mildly increased when compared with healthy age-matched controls. Shunt severity and pulmonary artery pressure correlated strongly with natriuretic peptide levels. A clear association between brain natriuretic peptide and functional class was demonstrated. After closure of the defect, a rise in brain natriuretic peptide levels in the first hours to days was observed. After longer follow-up, natriuretic peptide levels decreased and became comparable to pre-procedural values. In conclusion, this systematic review shows that brain natriuretic peptide levels are mildly increased in patients with unrepaired and repaired atrial or ventricular septal defect. Brain natriuretic peptide measurement might be a useful additional tool in the diagnostic work-up of patients with atrial or ventricular septal defect. Further investigation in a larger, prospective study with long-term follow-up is warranted to elucidate the true prognostic value of natriuretic peptides in patients with simple congenital heart disease.

Introduction

Atrial septal defect and ventricular septal defect are the two most common forms of congenital heart disease that occur as an isolated anomaly with a prevalence of 2.6 and 1.6 per 1000 live births, respectively.[1] These septal defects vary in size, ranging from small defects without hemodynamic significance to large shunts. Pathophysiologically, the intracardiac shunt will impose a hemodynamic burden on the heart, which can lead to atrial and ventricular dilatation and increased pulmonary vascular resistance. Surgical or percutaneous closure of the defect is used as standard treatment when patients with atrial septal defect and ventricular septal defect develop conditions such as intractable chronic cardiac failure, failure to thrive, pulmonary hypertension, or significant left-to-right shunt.

Brain natriuretic peptide and its inactive precursor N-terminal pro-brain natriuretic peptide are cardiac markers that are released into the circulation after pressure overload, volume expansion, and increased myocardial wall stress.[2] The active fragment of brain natriuretic peptide has natriuretic, vasodilatory, and diuretic effects. Both markers have proven their ability to detect cardiac impairment in cardiac failure in the general population.[3]

Although both brain natriuretic peptide and N-terminal pro-brain natriuretic peptide have proven to be useful for assessing cardiac function in acquired heart disease, their role in the diagnostic approach and clinical decision making in patients with simple congenital heart diseases such as atrial septal defect and ventricular septal defect is not well defined.

The aim of this systematic review was to evaluate the recent literature on B-type natriuretic peptide activation in patients with atrial or ventricular septal defects and clarify the relationship of these markers with cardiac function and haemodynamic changes after defect closure.

Methods

Search strategy, selection criteria and data extraction

On January 20th, a systematic literature search using MEDLINE and EMBASE, with focus on atrial septal defect and ventricular septal defect, was executed. The following Medical Subject Headings and text keywords were used: "natriuretic peptide, brain" or "pro-brain natriuretic peptide" and "heart septal defects" or "ventricular septal defect", or "atrial septal defect".

All article titles and abstracts were screened to identify relevant studies. Articles had to be written in English and involved human subjects. Brain natriuretic peptide levels and patients' age at the time of brain natriuretic peptide measurement had to be reported clearly per cardiac diagnosis. Therefore, articles describing brain natriuretic peptide levels for a group of patients with diagnoses of congenital heart disease were excluded. We focused on isolated atrial and ventricular septal defect as these diagnoses are two of the most common congenital heart defects, and especially ventricular septal defect is often associated with cardiac failure at young age. Patients with septal defects as part of a more complex congenital heart disease were excluded because natriuretic peptide levels could be influenced by other

components of the complicated anatomy. Articles on Eisenmenger syndrome due to isolated ventricular septal defect or atrial septal defect were included to provide a complete overview, including this rare but severe complication. In all selected articles, references were cross checked using the same inclusion and exclusion criteria to identify articles missed by the initial search strategy.

We extracted data on the type of congenital heart disease, age, plasma brain natriuretic peptide levels, and brain natriuretic peptide immunoassay method. When reported in the article, plasma brain natriuretic peptide levels of healthy controls, moment of brain natriuretic peptide measurement – when sequential measurement was reported – and correlations between plasma brain natriuretic peptide and cardiac function parameters measured with echocardiography, cardiac magnetic resonance imaging, cardiac catheterization, exercise test, or New York Heart Association classification were collected. For all potentially relevant articles, eligibility was assessed by two authors. Discrepancies were resolved by discussion. Both brain natriuretic peptide and N-terminal pro-brain natriuretic peptide will further be referred to as brain natriuretic peptide in this article, unless a separate use is needed for clarification.

Results

The literature search yielded 193 potential eligible studies (Figure 1). First, 114 articles were excluded as they described topics irrelevant for this systematic review. We excluded 41 articles because of their focus on other congenital heart diseases or congenital heart disease in general. In all, 38 articles met our inclusion criteria. After critical review of the complete article, nine more articles were excluded. In seven studies, brain natriuretic peptide values were not clearly reported. Furthermore, two articles were excluded because patient populations were described for the second time in a subgroup analyses. Eventually, 28 articles were included in this systematic literature review, describing atrial septal defect (n=14), ventricular septal defect (n=8), both atrial septal defect and ventricular septal defect (n=3), and Eisenmenger syndrome (n=3). In 11 articles, longitudinal data were available, describing sequential brain natriuretic peptide measurements before and after septal defect closure.

Atrial septal defect

We included 17 articles reporting data on brain natriuretic peptide values in patients with unrepaired atrial septal defect, describing a total of 429 patients with a mean/median age ranging from 4 to 75.8 years.[4–20] No studies describing brain natriuretic peptide in repaired atrial septal defect patients were found. A significant difference was observed for all ages in brain natriuretic peptide levels between patients with atrial septal defect (mean/median values of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide ranging from 10.6 to 175.9 pg/ml and 35.2 to 240 pg/ml, respectively) and healthy age-matched controls (mean/median values of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide ranging from 5.3 to 32.6 pg/ml and 4.04 to 59 pg/ml, respectively; Figure 2). Symptomatic patients in New York Heart Association class III revealed significantly higher N-terminal
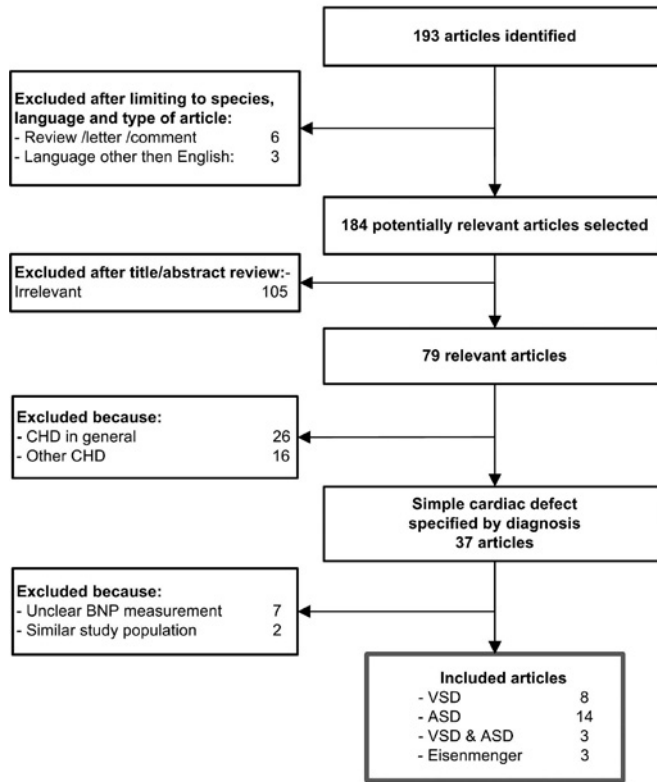
FIGURE 1. Literature search and selection
Numbers of articles for each step of the process are indicated.

pro-brain natriuretic peptide values when compared with asymptomatic patients in New York Heart Association functional class I (142 ± 72 pg/ml versus 285 ± 101 pg/ml, p< 0.05).[16]

A total of 11 articles presented correlations between plasma brain natriuretic peptide and cardiac function parameters measured by echocardiography, cardiac magnetic resonance imaging, and/or cardiac catheterization (Table 1). In five out of seven studies, a positive correlation was observed between brain natriuretic peptide levels and right ventricular end-diastolic dimensions and/or volume.[4,7,9–11,16,18] In contrast, left ventricular end-diastolic dimensions did not relate to brain natriuretic peptide and N-terminal pro-brain natriuretic peptide values.[9,10] In three studies, measures of diastolic dysfunction correlated with brain natriuretic peptide values.[6,7,10] Right ventricular end-diastolic pressure measured during cardiac catheterization also related to brain natriuretic peptide values.[14,16] When focusing on left ventricular end-diastolic pressure this relation was not observed.[14] In three out of four studies, pulmonary artery pressure correlated strongly with natriuretic peptide values.[4,14,16] In contrast, in one study the presence of pulmonary hypertension was not related to brain natriuretic peptide.[5]

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TABLE 1. Atrial septal defect

Baseline characteristics				Natriuretic peptides		BNP / NT-proBNP and cardiac function parameters									
Author	No. of patients	age* (years)	Function assessment	BNP (pg/ml)	NT-proBNP (pg/ml)*	RV function (r)	Qp/Qs (r)	PAP (r)	RVEDV/D (r)† ‡	RAV/P (r)§ ‖	PVR (r)	Diastolic dysfunction (r)	RVEDP (r)	LVESV (r)	ASD size (r)
Attenhofer(7)	21	46±14	Echo	42±46					NS†			+ p=0.007			
Eerola 2007 (10)	24	6.9(2.3-18.5)	Cardiac Catheterization Echo		85(11-245)		NS		NS†			0.68 p<0.001		0.47 p=0.022	
Eerola 2009 (9)	41	6.4(2.3-18.5)	Echo		90(5-458)				0.41† p<0.01					NS	0.35 p<0.05
Jan (5)	34	9.2±5.7	Cardiac Catheterization Echo	10.6±9.3			NS								NS
Kunii (11)	34	5.8±0.7	Cardiac Catheterization Echo	37.6±8.4			0.69 p<0.001		0.81‡ p<0.001						
Masutani (6)	39	27.5±16.3	Echo	48.4±5.2								β= −0.36 p<0.05			
Nagaya (14)	31	45.5±4	Cardiac Catheterization	mean 38			NS	0.73 p<0.001		0.56‖ p<0.01	0.51 p<0.01		0.44 p<0.05		
Schoen (16)	20	43±13	CMR Echo		240±93	NS	0.62 p<0.05	0.75 p<0.01	0.65‡ p<0.05	0.69‖ p<0.05			0.7 p<0.01		NS
Trojnarska(18)	36	44.7±8.2	Echo	60.6±49.9			0.39 p=0.03	0.61 p<0.001	0.38† p=0.03						
Uz (4)	56	22.9±2.0	Echo	42.9±29.4		0.50 p<0.001	0.71 p<0.001	0.61 p<0.001	0.55‡ p<0.001	0.54§ p<0.001					
Wu (20)	17	58.4±17.3	Cardiac Catheterization Echo	28.8±20.4			NS								NS

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β: beta coefficient. (r): correlation coefficient. +: positive correlation, not further specified. CMR: cardiac magnetic resonance imaging. LVESV: left ventricular end-systolic volume. NS: Not significant. PAP: pulmonary artery pressure. PVR: pulmonary vascular resistance. RV-function: right ventricular function. RVEDP: right ventricular end-diastolic pressure. Qp/Qs: pulmonary-to-systemic flow ratio. BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics), IRMA (Shionoria), NT-proBNP was evaluated with ECLIA (Elecsys, Roche Diagnostics). * Values are presented as mean±SD or median(range). † RVEDD: right ventricular end-diastolic diameter. ‡ RVEDV: right ventricular end-diastolic volume.§ RAV: right atrial volume. ‖ RAP: right atrial pressure.
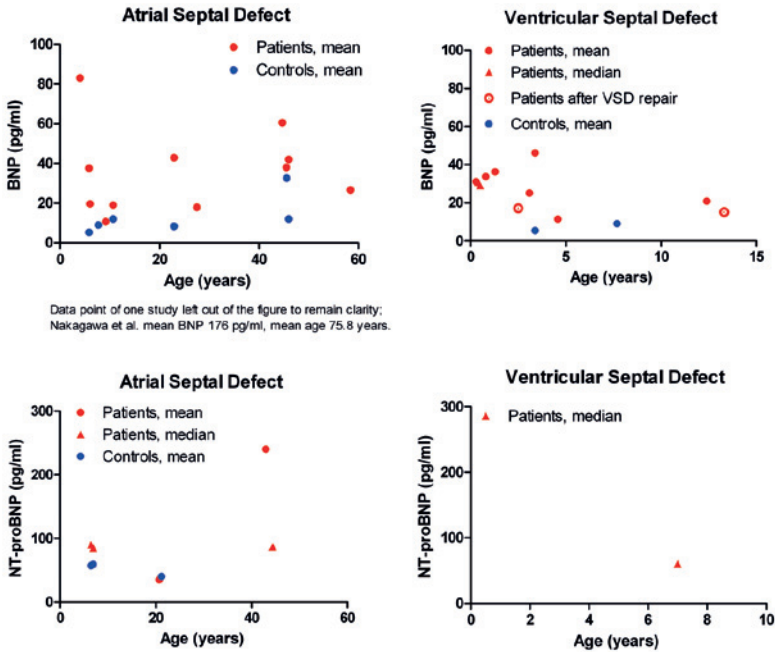
FIGURE 2. BNP and NT-proBNP measurements per cardiac diagnosis
Mean/median values of BNP, NT-proBNP and age for patients and controls per cardiac diagnosis. Each symbol reflects one study patient population or control population.

Correlations between brain natriuretic peptide and the ratio of pulmonary to systemic blood flow (Qp/Qs) were assessed in seven studies and ranged from non-significant up to highly significant (r=0.71, p<0.001).[4] However, atrial septal defect size was not or only weakly related to brain natriuretic peptide measures in four studies .[5,9,16,20] In one study, an exercise test was performed, which revealed a negative correlation between maximum oxygen uptake and brain natriuretic peptide values.[18]

In eight studies, longitudinal data were available, describing sequential brain natriuretic peptide measurement before and after percutaneous or surgical atrial septal defect closure.[6,8,10,13,15,16,19,20] Initially, brain natriuretic peptide levels increased notably within days after atrial septal defect closure (Figure 3). A few months post procedure, a decrease in brain natriuretic peptide levels was observed and they became comparable to pre-procedural levels or even lower (Figure 4).[8,10,13,15,16,19,20] When brain natriuretic peptide values were measured 1 year after closure, levels in percutaneous treated patients were comparable to those of control patients. However, surgically treated patients still revealed elevated brain natriuretic peptide levels one year after the procedure.[10] In one study, the decrease in right ventricular systolic pressure and right ventricular end-diastolic volume 12 months after atrial septal defect closure correlated with the changes in plasma brain natriuretic peptide (r= 0.6, p<0.01, r=0.63, p< 0.01, respectively).[16]

Ventricular septal defect

Short-term follow-up
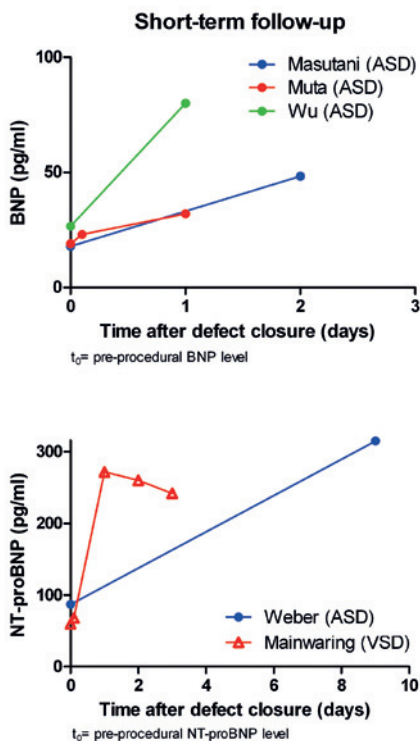
FIGURE 3. Short-term follow-up of BNP / NT-proBNP after defect closure
Data points within the same study are connected to maintain clarity.
However, no linear interpolation should be assumed.

A total of 11 articles concerning patients with ventricular septal defect were included, describing a total of 328 patients with unrepaired ventricular septal defect and 43 with repaired ventricular septal defect.[5,11,17,21–28] All studies comprised children with mean/median age ranging from 4 months to 13.3 years, whereas no studies in adult patients were found. None of the studies reported separate results for muscular or (peri) membranous ventricular septal defect. Compared with age-matched controls, brain natriuretic peptide values were higher in both unrepaired and repaired ventricular septal defect patients (mean/median plasma brain natriuretic peptide and N-terminal pro-brain natriuretic peptide values ranging from 11.4 to 46.1 pg/ml and 60 pg/ml, respectively; Figure 2). Correlations between age and brain natriuretic peptide levels differed widely from non-significant to highly significant negative correlations.[21,24,27] Patients with clinical signs of cardiac failure revealed higher brain natriuretic peptide values than those without clinical signs.[26,28]

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TABLE 2. Ventricular septal defect

Baseline characteristics				Natriuretic peptide		BNP and cardiac function parameters								
Author	No. of patients	age* (years)	NYHA	Function assessment	BNP* (pg/ml)	LV-EF (r)	Qp/Qs (r)	PAP (r)	RVEDD (r)	LVEDD/V (r)†‡	PVR (r)	VSD size (r)	RVEDP (r)	LVEDP (r)
Chen (21)	18	12.4±1.5 (4-28)	I,II	Echo	20.8±6.1	-0.69 p=0.002		0.71 p=0.001	0.59 p=0.01	0.56† p=0.02				
Jan (5)	25	4.6±5.6		Cardiac Catheterization Echo	11.4±13.5		0.6 p=0.002	NS				0.48 p=0.01		
Kunni (11)	91	3.4±0.4 (0.3-12)		Cardiac Catheterization Echo	46.1±7.3		0.75 p<0.0001			0.72‡ p<0.0001				
Mainwaring(22)	18	(0.2-15.6)		Cardiac catheterization	60(15-175)		0.85 p<0.001							
Oyamada(24)	48	0.8±0.6	CSHF+ CSHF-	Cardiac Catheterization Echo	33.7±16.5		0.41 p=0.004							NS
Paul (25)	21	0.5(0.1-1.1)		Echo	29(5-937)					NS†				
Suda (26)	59	3.1 (0.3-13)	CSHF+ CSHF-	Cardiac Catheterization	25±20		0.65 p<0.0001	0.72 p<0.0001			0.46 p<0.002		0.46 p<0.002	NS
Toyono (27)	24	0.3(0.2-17)		Cardiac Catheterization	31±18.9		0.59 p=0.003				-0.56 p=0.004			

(r): correlation coefficient. CSHF: clinical signs of heart failure. LVEDP: left ventricular end-diastolic pressure. NS: Not significant. PAP: pulmonary artery pressure. PVR: pulmonary vascular resistance. RVEDD: right ventricular end-diastolic diameter. RVEDP: right ventricular end-diastolic pressure. RVEDV: right ventricular end-diastolic volume. Qp/Qs: pulmonary-to-systemic flow ratio. BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics), IRMA (Shionoria). NT-proBNP was evaluated with ECLIA (Elecsys, Roche Diagnostics)

* Values are presented as mean±SD or median (range). † LVEDD: left ventricular end-diastolic diameter. ‡ LVEDV: left ventricular end-diastolic volume.

In total, eight articles described correlations between brain natriuretic peptide and cardiac function parameters (Table 2). Echocardiographic measured left ventricular end-diastolic dimensions correlated significantly with brain natriuretic peptide levels in two out of three studies.[11,21,25] The same observation was made for right ventricular end-diastolic dimensions.[21] In contrast, left ventricular end-diastolic pressure measured with cardiac catheterization was not related to brain natriuretic peptide.[24,26] In six studies, the amount of left-to-right shunt (Qp/Qs) was measured by echocardiography or cardiac catheterization. In all studies, a significant positive correlation between brain natriuretic peptide levels and Qp/Qs was observed.[5,11,22,24,26,27]

A significant correlation between brain natriuretic peptide and pulmonary artery pressure measured by echocardiography or cardiac catheterization was found in two out of three studies.[5,21,26] In patients with ventricular septal defect and severe pulmonary hypertension, a significant negative correlation between brain natriuretic peptide and pulmonary vascular resistance was observed.[27] In contrast, another study that included patients with both normal and elevated pulmonary pressures found a positive correlation between pulmonary vascular resistance and brain natriuretic peptide levels.[26]
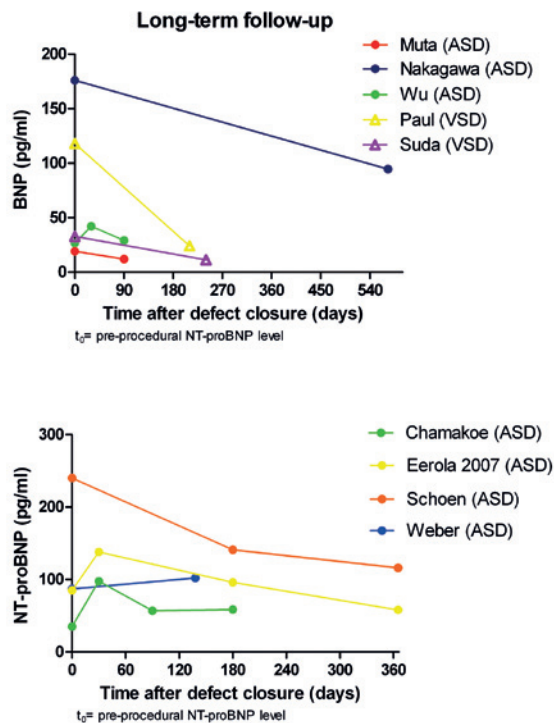

FIGURE 4. Long-term follow-up of BNP / NT-proBNP after defect closure
Data points within the same study are connected to maintain clarity.
However, no linear interpolation should be assumed

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Longitudinal data were provided in three studies, describing a total of 55 patients.[22,25,26] Brain natriuretic peptide values were measured before and after surgical closure of the defect. With sequential measurement, pre- and post-operatively, a fivefold increase in brain natriuretic peptide levels was observed 1 day after the procedure (Figure 3).[22] Brain natriuretic peptide values measured 8 months after ventricular septal defect repair were significantly lower than pre-procedural levels (Figure 4).[25,26] Brain natriuretic peptide was not related with blood pressure[21] or right atrial pressure.[26]

Eisenmenger syndrome

Results on patients with ventricular septal defect or, less frequently, atrial septal defect leading to Eisenmenger syndrome were reported in three articles, including a total of 56 patients with a mean/median age ranging from 40.8 to 45.3 years.[27,29–31] Mean brain natriuretic peptide ranged from 110.1 to 115.7 pg/ml.[29,31] Median N-terminal pro-brain natriuretic peptide was 709 pg/ml.[30] Correlations between brain natriuretic peptide and exercise capacity were evaluated by treadmill test or 6-minute walk distance. When the treadmill test was used, a negative correlation between brain natriuretic peptide and maximum oxygen uptake (r=0.39, p=0.006) was observed.[29] Brain natriuretic peptide levels were negatively correlated with 6-minute walking distance (r=-0.50, p<0.01).[30] Furthermore, a strong significant relationship between brain natriuretic peptide and oxygen saturation was seen (r=-0.45, p< 0.001).[29]

Discussion

This systematic review demonstrates that both brain natriuretic peptide and N-terminal pro-brain natriuretic peptide are potential markers for functional status, cardiac function, and haemodynamic status in patients with atrial or ventricular septal defect. Although patient numbers were small and most studies were originally not designed to assess the relationship between brain natriuretic peptide levels and cardiac function, some interesting results were gathered. Brain natriuretic peptide values in both patients with unrepaired atrial or ventricular septal defect were slightly increased when compared with age-matched controls. All studies that included both symptomatic and asymptomatic patients observed higher brain natriuretic peptide levels in patients with clinical symptoms than in asymptomatic patients.

In both congenital heart defects, a strong correlation between brain natriuretic peptide levels and the severity of left-to-right shunt and pulmonary artery pressure was found. These findings may have important clinical implications. They indicate that brain natriuretic peptide assessment may serve as an additional tool next to cardiac imaging to evaluate shunt severity and may help identify those patients in need of early intervention. However, these correlations were only investigated cross-sectionally, and therefore no firm conclusions on the prognostic value of brain natriuretic peptide and its contribution to timing of intervention can be drawn.

In six atrial septal defect studies, only children were included. Some of these patients were already in need of an intervention,[5] which indicates that these patients possibly had a large, haemodynamically

significant shunt with symptoms at earlier age. Nevertheless, no significant differences were observed between the mean/median brain natriuretic peptide levels of these studies describing children and those focusing on adults.

Several studies in this review concluded that no age-related differences were observed in the brain natriuretic peptide values[6,24] but patient numbers could have been too small to reveal a true relation, as we know from larger studies focusing on other patient groups which found brain natriuretic peptide levels to be age dependent.[32] This could explain the interestingly high mean brain natriuretic peptide values reported by Nakagawa et al,[15] as their study population comprised geriatric patients.

Brain natriuretic peptide is a well-established biomarker, which has proven its usefulness in acquired heart disease several years ago, and therefore it is surprising to see that not one study has reported on brain natriuretic peptide in adult patients with (corrected) ventricular septal defect. The only study with long-term follow-up is reported by Man et al, describing brain natriuretic peptide values for children with repaired ventricular septal defect 9.2 years after closure. They found brain natriuretic peptide values to be higher than those of healthy controls used in other studies. The fact that brain natriuretic peptide values do not normalize completely might be because of the residual scarring after surgery or the presence of the ventricular patch, which could influence ventricular function.

The findings on correlations between brain natriuretic peptide and pulmonary vascular resistance differed strongly between studies. This could be explained by the difference in study population as Suda et al[26] included mainly patients with normal pulmonary artery pressures and none of their patients revealed pulmonary vascular obstructive disease, whereas Toyono et al[27] only included patients with severe pulmonary hypertension.

Of the 24 patients that Toyono et al included in their study, four showed apparent Eisenmenger physiology. They found much lower brain natriuretic peptide levels (7.1 ± 1.1 pg/ml) in the Eisenmenger patients than brain natriuretic peptide levels reported for the three Eisenmenger syndrome studies.[27] Possibly, the difference could be explained by the fact that Toyono et al included only children, whereas the Eisenmenger syndrome studies included adult patients of similar age. All adult patients with Eisenmenger syndrome had higher brain natriuretic peptide levels than atrial and ventricular septal defect patients of similar age without Eisenmenger physiology.

Pre- and post-procedural brain natriuretic peptide measurement

Initially, in the first few hours and days after defect closure, a rise in brain natriuretic peptide is noticed followed by a significant decrease a few months later, resulting in natriuretic peptide levels almost comparable to those of healthy age-matched controls. This remarkable fluctuation in brain natriuretic peptide levels possibly mirrors the acute intracardiac haemodynamic changes for which the heart needs time to compensate or could be seen as a result of the direct influence of the surgical or percutaneous closure of the defect on the myocardium. Furthermore, Eerola et al[10] reported significantly higher brain natriuretic peptide levels in patients with atrial septal defect 1 year after surgical closure compared

with percutaneous closure. This could be explained either by faster haemodynamic improvement after percutaneous treatment or by differences in septal defect size, as larger defects will more frequently be closed with surgery.

Limitations

Most studies that reported data on the relationship between brain natriuretic peptide and cardiac function parameters were cross-sectional and used multiple measures for cardiac function. Several studies reported follow-up data of brain natriuretic peptide measurements without focusing on relationships with cardiac function parameters. Although atrial and ventricular septal defect are two of the most common types of congenital heart disease, the investigated patient numbers were very small. Furthermore, a great variety in brain natriuretic peptide levels was observed in all studies, which indicates that conclusions for individual patients should be drawn with caution.

Conclusion

Brain natriuretic peptide levels in asymptomatic patients with unrepaired atrial septal defect or ventricular septal defect are mildly increased compared with controls. After defect closure, brain natriuretic peptide levels initially rise significantly in the first few hours and days after the intervention, whereas after longer follow-up brain natriuretic peptide levels become comparable to pre-procedural values. Brain natriuretic peptide measurement might be a useful additional tool in the diagnostic work-up of patients with atrial or ventricular septal defect as brain natriuretic peptide levels are related to shunt severity and pulmonary artery pressure. Nevertheless, larger, prospective studies are clearly warranted to elucidate the true prognostic value of brain natriuretic peptide in patients with simple congenital heart disease.

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Chapter 4

The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review

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Abstract

Brain natriuretic peptide (BNP) and N-terminal pro–brain natriuretic peptide (NT-proBNP) are well-established markers for heart failure in the general population. However, the value of BNP as a diagnostic and prognostic marker for patients with structural congenital heart disease (ConHD) is still unclear. Therefore, the purpose of this study was to evaluate the clinical utility of BNP in patients with ConHD. We executed a PubMed literature search and included 49 articles that focused on complex congenital heart defects such as tetralogy of Fallot, systemic right ventricle, and univentricular hearts. Data on BNP measurements and cardiac function parameters were extracted. In all patients after correction for tetralogy of Fallot, BNP levels were elevated and correlated significantly with right ventricular end-diastolic dimensions and severity of pulmonary valve regurgitation. Patients with a systemic right ventricle had elevated BNP levels, and positive correlations between BNP and right ventricular function were seen. In patients with a univentricular heart, elevated BNP levels were observed before completion of the Fontan circulation or when patients were symptomatic; a clear association between BNP and New York Heart Association functional class was demonstrated. In conclusion, this review shows an overall increase in BNP values in complex ConHD, although differences between types of congenital heart anomaly are present. As BNP values differ widely, conclusions for individual patients should be drawn with caution. Further investigation with sequential BNP measurement in a large, prospective study is warranted to elucidate the prognostic value of BNP assessment in patients with ConHD.

Introduction

Congenital heart disease (ConHD) is the most prevalent form of congenital abnormality with an incidence of approximately 9 cases per 1,000 live births.[1] The number of adult patients with a congenital heart disease is steadily increasing due to the success of paediatric cardiology and open-heart surgery. However, few cardiac surgical repairs are curative. At adult age many patients will have complications such as valvular dysfunction and arrhythmias. The increasing number of adult ConHD patients also brings an increasing number of patients at risk of late ventricular dysfunction and heart failure. This is mainly seen in the more complex congenital heart diseases, such as tetralogy of Fallot (ToF), defects with a systemic right ventricle (RV) and univentricular hearts.

Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) have gained a lot of interest in the last 20 years.[2] These hormones are synthesized and released into the circulation by the ventricular myocytes in response to pressure overload, volume expansion, and increase in myocardial wall stress. Within the myocytes, the precursor pro-BNP is divided in the biologically active form BNP and the inactive NT-proBNP fragment. Once in the circulation, BNP has natriuretic, diuretic and vasodilatory effects on the internal climate.[2] Both markers show a comparable clinical utility for assessing cardiac impairment and are well-established markers of heart failure in the general population.[3]

Natriuretic peptides might be of clinical importance in the ConHD population because of their proven usefulness in acquired heart disease and the simplicity of assessment. Their role in the diagnostic approach and clinical decision making in patients with ConHD is not well defined. In this systematic review, we evaluate the recent literature on BNP and NT-proBNP activation and the relationship between these biomarkers and cardiac function in patients with complex congenital heart disease.

Methods

Search strategy, selection criteria and data extraction

On September 1, 2011, a PubMed literature search with focus on complex cardiac defects (including ToF, systemic RV and univentricular hearts) was conducted. Data from January 1990 to September 2011 were included. The following Medical Subject Headings and text keywords were used: 'natriuretic peptide, brain' or 'pro-brain natriuretic peptide' and 'heart defects, congenital' or 'tetralogy of Fallot' or 'transposition of great vessels' or 'Fontan procedure' or 'Norwood procedure' or 'congenitally corrected transposition of the great arteries'.

Each article title and abstract was screened to identify relevant studies. The search strategy was limited to articles concerning human subjects that were published in the English language. Articles concerning both children and adult patients were included. The BNP levels had to be reported per cardiac diagnosis. Consequently, articles that presented BNP levels for a group of ConHD diagnoses were excluded. We focused on complex cardiac defects because of the relative high incidence of adverse events as heart failure in these groups. Atrial septal defects and ventricular septal defects, aortic coarcta-

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tion, congenital aortic stenosis, and persistent ductus arteriosus (PDA), although also of interest, were excluded in the current study. References of selected papers were crosschecked with the same inclusion and exclusion criteria to identify articles missed by the search strategy.

Data were extracted on type of ConHD, age, sex, plasma BNP levels, and BNP immunoassay method. Furthermore, when reported in the article, BNP levels of controls, type of controls, and correlations between BNP and cardiac function parameters measured with echo, cardiac magnetic resonance (CMR) imaging, exercise test, New York Heart Association (NYHA) classification, reinterventions, and adverse events were collected. For all potentially relevant articles, eligibility was assessed by 2 authors (J.A.E. and J.W.R.H.). Disagreements were resolved by discussion. Because of the heterogeneity in functional tests and result presentation a formal meta-analysis linking BNP levels with functional parameters and outcome could not be conducted. In this article, both markers, BNP and NT-proBNP, will further be referred to as "BNP", unless a separate use is needed for clarification.

Results

The literature search yielded 200 potential eligible studies (Figure 1). We excluded 51 articles because BNP levels for >1 ConHD were reported without specification of BNP levels per diagnosis or age at time of assessment. In addition, 38 reports focusing on relative mild cardiac defects including atrial septal defect, ventricular septal defect, aortic coarctation, and persistent ductus arteriosus were excluded. Finally, 49 studies concerning ToF (n=20), systemic RV (n=13), or single ventricle morphology (n=16) were included in this systematic literature review. The main diagnostic tools used to quantify cardiac function were physical examination, echocardiography, and CMR imaging. Further, occasionally results of cardiopulmonary exercise tests, cardiac catheterization or cardiac computed tomography scan were reported. Longitudinal data were available in 6 of the 49 studies.

Tetralogy of Fallot

The value of BNP in patients with surgically repaired ToF has been studied in 20 articles describing a total of 770 patients with a median/mean age ranging from 4.2 to 30.9 years. [4-23] The BNP levels were significantly higher in Fallot patients (mean/median values of BNP and NT-proBNP ranging from 19 to 85 pg/ml and 85 to 231 pg/ml, respectively) when compared to age- and sex-matched controls (mean/median values of BNP and NT-proBNP ranging from 6 to 15.4 pg/ml and 38 to 111 pg/ml, respectively), although most patients were asymptomatic or only mildly symptomatic (Figure 2).[5-10, 12, 14, 16, 17] Patients with NYHA functional class II revealed significantly higher BNP values than patients with NYHA class I (p=0.01) (Table 1).[12, 15]

The severity of pulmonary valve regurgitation and RV end-diastolic volume showed a positive correlation with BNP in 7 of 9 studies (Table 1). [6, 9, 11, 12, 15-19] A great variety between correlations of BNP with RV function was seen, ranging from non-significant correlations up to highly significant correlations of
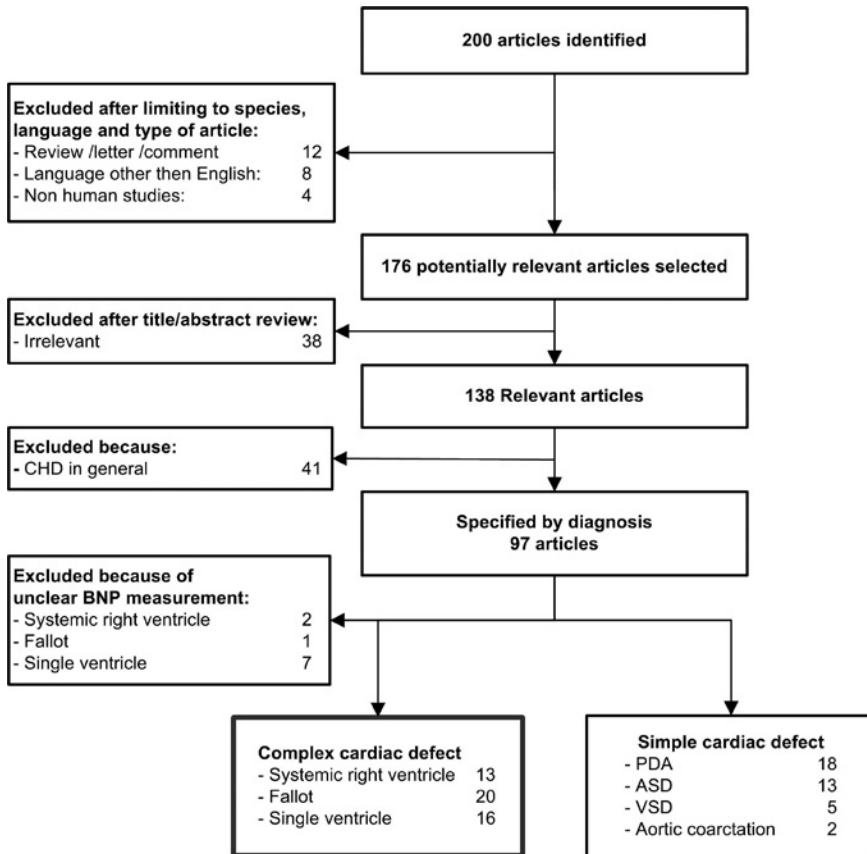
FIGURE 1. Literature search and selection
Numbers of articles for each step of the process are indicated. After reading titles and abstract, 103 articles were excluded on the basis of the exclusion criteria named in the Methods section. Another 48 articles were excluded after evaluation of full text. ASD=atrial septal defect; BNP=brain natriuretic peptide; CHD=congenital heart disease; PDA= persistent ductus arteriosus; VSD=ventricular septal defect

0.60 in comparable study populations using the same diagnostic tools. In none of the studies was a correlation observed between BNP and left ventricular (LV) function or LV end-diastolic volume.

In 7 studies, an exercise test was performed.[6, 7, 9, 15-18] Plasma BNP correlated negatively with exercise capacity and peak oxygen uptake.[8, 15-17] Furthermore, ToF patients had more pronounced increases in BNP levels post-exercise compared with healthy controls.[17]

Three studies with longitudinal data revealed a significant decrease of BNP levels 6 months or longer after pulmonary valve replacement compared with BNP levels before the intervention, mirroring the smaller RV end-diastolic volume and/or improved RV ejection fraction.[4, 15, 23]

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TABLE 1. Tetralogy of Fallot

Baseline characteristics						Natriuretic peptides		BNP / NT-proBNP and cardiac function parameters					
Article	No of patients	Age (years)	NYHA class	Function Assessment	Age at time of repair (years)	BNP (pg/ml)	NT-proBNP (pg/ml)	RV function (r)	RVEDV (r)	TR Vmax (r)	PR severity (r)	NYHA class	Peak VO2 (r)
Apitz(13)	16	14.2(9.8-24.9)	I	MRI	1.2(0.2-4.5)	19(7-42)		NS					
Brili(10)	25	28.4±8.3	I,II	Echo	18.8±6.7	85±87		NS					
Cheung(16)	32	14.7±3.1	I,II,III	Echo	4.6±2.5	21.9(7.8-470)		NS	0.72 p<0.001	NS			-0.43 p=0.03
Cheung(16)	32	14.7±3.1	I,II,III	MRI	4.6±2.5	21.9(7.8-470)			0.6 p=0.009		0.46 p=0.01		-0.43 p=0.03
Cetin(12)	25	14.1±4.4	I,II	Echo	4.9±5.1	28.3±24.1		-0.60 p=0.0001	0.7 p=0.0001		0.6 p=0.0001	+ p=0.0001	
Dodge-Khatami(23)	23	13.2(5.3-19.6)	I,II	MRI	1.6(0.3-4.6)		231±228	-0.47 p<0.05	NS				
Festa(9)	70	21±1	I,II	MRI/Echo	3.4±0.3		218±30	-0.32 p<0.01	0.40 p<0.001	0.27 p<0.05	NS		-0.57 p<0.001
Ishii(17)	26	9.6±3.3		Echo	2 to 3	44±34		-0.42 p=0.03		NS	+ p<0.05		
Khositseth(19)	21	12.1±2.5	I	Echo/MRI	4.48±1.68		195±303	NS	0.57 p=0.01				
Koch(15)	130	16.1±7.1	I,II	Echo	13±6.5	24(5-196)				NS	0.20 p=0.029	I vs.II p=0.012	
Norozi(6)	50	27.8±1.7	I,II	Echo	7.3±0.7		166±25		0.45 p<0.05	0.42 p<0.01	+ p=0.01		-0.63 p<0.001
Tatani(11)	49	14.7±10	I,II	Echo	5.4±5.3		211±219	NS	0.41 p=0.003		0.60 p<0.001		
Trojnarska(7)	60	27.6±8.2	I,II	Echo	7.5±5.3	34.8±27.1					NS		-0.29 p=0.03
v.d. Berg(18)	51	15(7-26)		MRI	0.8(0.2-2)		85(17-355)	NS	NS		0.005 p<0.05		NS
Wand(14)	21	11.6±5.2	I,II	Echo	mean 1.7 range(0.1-5)		median 202	-0.5 p=0.02	NS				NS

Values are presented as mean±SD or median(range). BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics), IRMA (Shionoria) or ADVIA Centaur (Siemens). NT-proBNP was evaluated with ECLIA (Roche Diagnostics). (r): correlation coefficient. +: positive correlation, not further specified. NS: Not significant. Peak VO2: peak oxygen uptake. PR severity: pulmonary regurgitation severity. RV function: right ventricular function. RVEDV: right ventricular end-diastolic volume. TR Vmax: tricuspid regurgitation maximum velocity.

Systemic RV

In 13 studies [24-36] levels of BNP were reported for patients with a systemic RV, including patients with transposition of the great arteries (TGA) after atrial switch operation (Mustard or Senning) and congenitally corrected TGA. A total number of 469 patients with a systemic RV were studied for BNP levels. All patients were included at adult age (mean/median age ranging from 19 to 35 years). The BNP levels were higher in systemic RV patients (mean/median BNP and NT-proBNP values ranging from 13.5 to 98 pg/ml and from 200 to 654 pg/ml, respectively), compared with controls (median BNP 17 pg/ml, range of mean NT-proBNP 48 to 57 pg/ml) in most studies, even when no signs or symptoms of heart failure were present (Figure 2). In addition, an association between BNP levels and NYHA functional class was reported in 3 studies (Table 2).[27, 29, 33]

A significant negative correlation between BNP levels and RV function measured by either CMR or echocardiography was found in 5 of 8 studies (correlation coefficients ranging from r =-0.42 to r =-0.54) (Table 2).[24, 25, 29, 33, 34] Secondly, a weaker but still significant positive correlation between BNP and end-diastolic RV volume was observed.[24, 25, 29, 33] Furthermore, a positive correlation was found between the severity of tricuspid valve regurgitation (TR) and BNP.[27, 35] In contrast, LV function did not correlate with BNP in any of the studies.
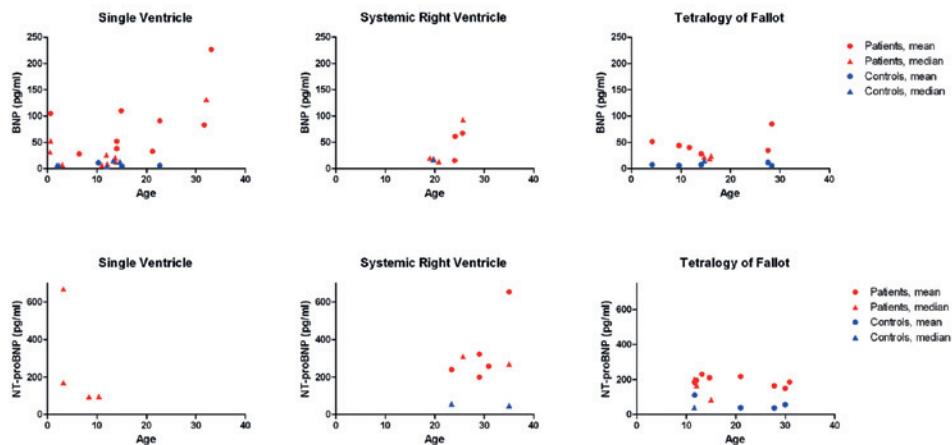
FIGURE 2. BNP and NT-proBNP measurements per cardiac diagnosis
Mean/median values of brain natriuretic peptide (BNP), N-terminal pro–B-type natriuretic peptide (NT-proBNP), and age for patients and controls per cardiac diagnosis. Each symbol reflects 1 study patient population or control population. Red circles indicate patients, mean; red triangles indicate patients, median; blue circles indicate controls, mean; blue triangles indicate controls, median. One result was left out of the figure to retain clarity (mean BNP 399 pg/ml by Law et al. [41] for single ventricle patients).

TABLE 2. Systemic right ventricle

| | Baseline characteristics | | | | | | Natriuretic peptides | | BNP / NT-proBNP and cardiac function parameters | | | | | |
Article	No of patients	Diagnosis/ surgery	Age (years)	NYHA class	Function assessment	BNP (pg/ml)	NT-proBNP (pg/ml)	RV function (r)	RVEDV (r)	RVESV (r)	TR severity (r)	NYHA class	Peak VO2 (r)
Chow(24)	44	Senning Mustard	19.7±4		Echo	19(6-522)		-0.43 p=0.001	0.37 p=0.009				
Dore(34)	29	Mustard ccTGA	30.9±10.9	I, II	Echo		258±243	-0.42 p=0.02					NS
Garg(28)	24	Mustard ccTGA	24(15-37)		MRI or ERNA	15.4±18.2		NS	NS	NS			NS
Koch(27)	48	Mustard ccTGA	19±5	I, II	Echo	20(5-198)		NS	NS		0.5 p<0.001	I vs II p=0.028	-0.35 p=0.02
Kozelj(33)	19	ccTGA	35±13.1	all	Echo MRI or CT		654±1535	-0.53 p=0.02	0.50 p=0.026	0.61 p=0.006	NS	0.49 p=0.032	
Norozi(32)	33	Mustard	23.4±7.4	I, II, III	Echo		240±230	NS	NS			NS	-0.46 p=0.03
Plymen(29)	35	Mustard Senning	29(18-40)	I, II	MRI		322±288	-0.54 p<0.001	0.43 p=0.01	0.53 p=0.001		I vs. II p=0.02	
Schaefer(25)	43	Mustard	29±4		Echo / MRI		200±148	-0.46 p=0.002	0.32 p=0.044				-0.32 p=0.04
Vogt(35)	16	Mustard Senning	25.6±3.7	I, II, III	Echo	67.3±47.5		NS			0.55 p<0.03	NS	

Values are presented as mean±SD or median(range). (r): correlation coefficient. NS: Not significant. ccTGA: congenitally corrected transposition of the great arteries. ERNA: equilibrium radionuclide angiography. Peak VO2: peak oxygen uptake. RVEDV: right ventricular end-diastolic volume. RVESV: right ventricular end-systolic volume. RV-function: right ventricular function. TR severity: tricuspid regurgitation severity. BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics) or IRMA (Shionoria). NT-proBNP was evaluated with ECLIA (Roche Diagnostics).

TABLE 3. Single ventricle

	Baseline characteristics						Natriuretic peptides		BNP / NT-proBNP and cardiac function parameters							
Article	No of patients	Surgery	Age (years)	NYHA class	Function Assessment		BNP (pg/ml)	NT-proBNP (pg/ml)	VEDV (r)	LV vs RV Morph.	AVR (r)	NYHA class	Peak VO2 (r)	SaO2	RA pressure (r)	Diastolic function (r)
Atz (48)	510	Fontan¶	mean 11.9 range(6-18)		Echo MRI		13(4-652)		+ p<0.01	NS	NS		NS			
Holmgren (39)	38	Shunt Glenn TCPC	0.5(0.5-0.9) 3(1.6-3.7) 12(5.2-17.9)		Echo		32(8-1220) 6.7(0-16) 9 (0-39)			p=0.02‡				NS		
Inai(46)	50	Fontan¶	22.7±3.6	I,II	Cardiac catheterization		91±14						NS			
Koch(38)	67	TCPC	13.8±5.8	I,II	Echo		13(5-290)			NS	0.38 p=0.002	I vs. II p=0.035	NS			
Law(41)	33	APC BDG Fontan¶	5.2(0.3-37.8)	all	Echo or Cardiac catheterization		median 84 median 38 median 38								0.54 p=0.04	
Lechner (50)	59	TCPC	8.4(2.1-25)	all†	Echo			96(11-376)		NS		r²=0.44† p<0.001				
Lechner (49)	78	BDG (CHF+) BDG (CHF-)	3.2(0.9-9.8)	all†	Echo and Cardiac catheterization			670(290-39763) 171(32-335)		p<0.05		0.90† p<0.001		NS	0.375 p=0.013	
Man (44)	35	Fontan¶	13.7±5.3		Echo		21(5-397)		NS							
Motoki(51)	68	Fontan¶ (young) Fontan¶ (adult) Cyanotic SVP	21.2±1.1 31.7±7.8 33.1±9.29	all	Echo		33±27 83±96 227±235		+ p<0.05					NS		
Ohuchi(40)	97	Fontan¶	14±5	all	Cardiac catheterization		46±76		β=0.24 p<0.0001	NS		II vs.III,IV p<0.01	-0.21 p<0.05	β=-0.34 p<0.0001		
Robbers-Visser(45)	28	TCPC	10(6.8-20.7)	all	MRI			98(25-483)	NS				NS			-0.31 p=0.009

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Values are presented as mean±SD or median(range). † functional class measured by NYUPHFI score (53). ‡ after second palliative step. BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics) or IRMA (Shionoria). NT-proBNP was evaluated with ECLIA (Roche Diagnostics). (r): correlation coefficient. ¶ Fontan: both TCPC and right atriopulmonary connection or right atrioventricular connection. NS: Not significant. +: positive correlation, not further specified. APC: aortopulmonary connection. AVR: atrioventricular valve regurgitation. BDG: bidirectional Glenn procedure. CHF+: with congestive heart failure. CHF-: without congestive heart failure. LV: left ventricle. Peak VO2: peak oxygen uptake. RA pressure: right atrial pressure. RV: right ventricle. SaO2: oxygen saturation. SVP: single ventricle patients. VEDV: ventricular end-diastolic volume.

In 5 studies, exercise tests were performed.[25, 27, 28, 32, 34] Plasma BNP correlated negatively with peak oxygen consumption in 3 of these studies. When comparing atrial switch patients with congenitally corrected TGA, no significant differences in BNP levels were found.[26, 27, 31] Furthermore, one study reported longitudinal data of 14 patients (median follow-up 1.4 years) and observed no differences in BNP levels (no changes in clinical findings were identified either).[27]

Single ventricle

Sixteen studies reported data on BNP in patients with univentricular hearts and Fontan physiology,[37-52] including a total of 1,185 patients. The studied Fontan patients mainly comprised children (mean/median age ranging from 0.6 to 33.1 years). Patients treated with a classic Fontan procedure had significantly higher levels of BNP compared with patients who had undergone the currently used Fontan approach (Figure 2, Table 3).[40, 42, 48] Young patients after the first palliative operation revealed higher BNP levels than patients after the bidirectional Glenn procedure or completion of the Fontan circulation with a total cavopulmonary connection (TCPC).[39, 41] After completion of the Fontan procedure by TCPC, the BNP values of asymptomatic patients were comparable to those of healthy age-matched controls.[39-41, 44, 47, 48] However, symptomatic patients defined as NYHA class ≥2 or New York University Pediatric Heart Failure Index ≥5 had significantly higher levels of BNP than did asymptomatic patients (Table 3).[38, 40, 49, 50] The New York University Pediatric Heart Failure Index score is an alternative instrument for measuring heart failure severity in children.[53]

Echocardiographic measured severity of atrioventricular valve regurgitation showed a positive correlation with BNP values.[38] There was one study reporting a correlation between variables of diastolic function and BNP.[44] No correlations were found between ventricular systolic function and BNP.[44, 45] When focusing on ventricular morphology, 2 studies found higher BNP levels in patients with an anatomical RV compared with patients with LV morphology,[39, 49] whereas 4 other studies, including a large study of 510 Fontan patients, did not find this anatomy-based difference.[38, 40, 48, 50]

In 7 of the 16 studies, an exercise test was performed. Only one study demonstrated a significant correlation between BNP and peak oxygen consumption in Fontan patients,[40] whereas 3 other studies found no significant correlation.[39, 49, 51] Mixed results were also found for pulse oxymetric saturation and plasma BNP.

Follow-up data revealed significantly higher levels of BNP in 5 patients who died from heart failure during the study period.[38] Another study, however found no prognostic value of BNP during 4 years of follow-up, including events in 11 patients.[46]

Discussion

This systematic review demonstrates that BNP is a potential robust clinical marker for functional status and cardiac function in ConHD. Although most studies were performed cross-sectional and originally

not designed to assess BNP, some conclusions can be drawn. Plasma BNP was increased in complex ConHD compared with controls or reference values, even when patients were asymptomatic. Exceptions to this finding are asymptomatic patients after TCPC; their BNP levels were comparable to healthy control patients. This review shows that, despite the overall increase in BNP, a wide range of BNP values is measured in most studies, and therefore, conclusions for individual patients should be drawn with caution. The studies with ToF and systemic RV patients mainly included asymptomatic and mildly symptomatic patients (NYHA I and II), and therefore, BNP values of more symptomatic patients (NYHA III to IV) are still uncertain. In contrast, in Fontan patients, strong positive correlations were found between BNP and NYHA class when all functional classes were studied.

Natriuretic peptides are known to be age and sex dependent,[54] and accordingly, reference values for BNP and NT-proBNP were mainly obtained from age- and sex-matched controls. In line with this assumption, the majority of the studies found higher BNP values in older patients, and female patients revealed higher levels of BNP than men.[48] However, age-adjusted reference values of BNP were not always used, which could explain discrepancies between study conclusions. Also, inappropriate controls subjects were used, including patients with (repaired) left-to-right shunts [8, 24, 44] or Kawasaki disease.[40]

Another potential direct cause of increased BNP production, hypoxia, could influence the results in single ventricle patients, as cyanosis is a common finding in uncorrected or partially corrected patients.[55] However, correlations between oxygen saturation and BNP were often not demonstrable in these patients.

Tetralogy of Fallot

Since Lillehei and colleagues [56] reported the first intracardiac surgical ToF repair in 1954, the outcome of patients after corrective surgery improved over the years. Despite an increasing post-operative survival, pulmonary valve regurgitation and RV dilatation and dysfunction often occur. Plasma BNP correlated with RV dilation and severity of pulmonary regurgitation in the majority of the studies. Together with the observed correlation between BNP and exercise capacity, these findings may have important clinical implications. The BNP measurement could contribute to the timing of pulmonary valve replacement in ToF patients with PR. However, the studies that have been conducted so far cannot be used to resolve this important issue, because most studies present cross-sectional data. Although 3 longitudinal studies found elevated BNP levels before pulmonary valve replacement, which decreased afterwards, results of individual BNP measurements differ widely. Large prospective studies are warranted to elucidate the true prognostic value of BNP in these patients.

Interestingly, Van den Berg et al.[18] failed to observe a correlation between NT-proBNP and RV size, presumably because their results on NT-proBNP, functional reserve and exercise performance were overall within normal ranges, reflecting the good clinical condition of their study population. Despite these findings the (modest) changes found in NT-proBNP were related to relevant RV loading condition

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abnormalities, worse functional capacity, and decreased functional reserve, confirming the diagnostic potential of BNP.[18]

Systemic RV

A ventricle with right ventricular morphology is not designed to pump as a systemic ventricle, which may lead to late RV dysfunction. The treatment of systemic ventricular dysfunction is challenging, and early detection is crucial. The BNP was positively correlated with RV dysfunction in most studies. One of the 3 study that failed to demonstrate a correlation between BNP and RV function did find a strong negative correlation between RV ejection fraction and atrial natriuretic peptide,[28] which is remarkable because of the very close correlation between atrial natriuretic peptide and BNP that is reported in adult ConHD patients.[57] Maybe the atria play a pivotal role, whereas Mustard and Senning patients have extensive atrial scars due to surgery. In addition, TR often coexists and tends to worsen progressively. Although Ebstein's anomaly may be present, in most cases, TR is secondary to annular dilation from RV failure, and tricuspid valve replacement is not convincingly helpful. Therefore, early detection of an increase in TR is needed. The BNP could contribute to this detection as a strong correlation was observed between plasma BNP and TR severity in several studies. One study by Kozelj et al.[33] could not confirm these findings, maybe due to their relative small study population, which might have been underpowered to demonstrate a correlation. In addition BNP was correlated with RV end-diastolic volume in most studies. Only Koch et al. could not demonstrate a relation between BNP and end-diastolic RV diameter.[27] Although, as they say, their retrospective study design has led to echocardiographic assessment of RV dimensions by variable investigators over several years, which might not have been accurate enough to detect a correlation.

Single ventricle

Patients with univentricular hearts and a Fontan circulation comprise a large scala of ConHD. Ventricular function is crucial in the long-term prognosis of Fontan patients. Because of the variable and enlarged ventricular anatomy reliable estimates of ventricular function with echocardiography are difficult to obtain and, preferably, CMR imaging should be used. Nevertheless, Robbers-Visser et al.[45] could not demonstrate a correlation between CMR-derived function parameters, primarily because the majority of patients presented with BNP levels within the normal range.

Interestingly, BNP levels in asymptomatic patients after TCPC were comparable to healthy controls, unlike BNP levels in asymptomatic Fallot or systemic RV patients. Completion of the Fontan circulation will cause unloading of the ventricle, which could explain lower BNP as BNP relates with ventricular volume load. However, a strong correlation between BNP and severity of heart failure was found in symptomatic patients. Therefore, BNP assessment in patients after TCPC may indeed contribute to early detection of heart failure.

Study limitations

Most studies were performed cross-sectional and originally not designed to assess BNP. Furthermore, overall investigated patient numbers were small, the used cardiac function parameters varied largely, and limited follow-up data are currently available. Therefore, future research should be done in a large, prospective study, preferably with sequential BNP and cardiac function assessment to determine the true prognostic value of BNP for patients with ConHD.

Conclusions

This systematic review has demonstrated BNP levels to be elevated in patients after correction for tetralogy of Fallot and in patients with a systemic RV, whereas BNP mainly correlated with end-diastolic RV dimensions and pulmonary regurgitation in Fallot patients and RV function in systemic RV patients. Patients with a univentricular heart had elevated BNP levels before completion of the Fontan circulation or when symptomatic, revealing a clear association between BNP and NYHA class. However, to elucidate the prognostic value of BNP assessment in ConHD, a large, well-designed, prospective study is warranted.

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Chapter 5

N-terminal pro-B-type natriuretic peptide and its relationship with cardiac function in adults with congenital heart disease

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Abstract

Objectives

The aim of this study was to determine the value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in adults with congenital heart disease (ConHD) and investigate its relationship with ventricular function and exercise capacity.

Background

NT-proBNP may detect early deterioration in cardiac function.

Methods

In this cross-sectional study, extensive echocardiography, exercise testing, and NT-proBNP measurements were performed on the same day in consecutive adult patients with ConHD.

Results

In total, 475 patients were included in this study (mean age of 34±12 years, 57% male, 90% New York Heart Association class I). The median NT-proBNP level was 15.1 pmol/l (interquartile range [IQR]: 7.1 to 31.3 pmol/l), and the NT-proBNP level was >14 pmol/l in 53% of patients. The highest NT-proBNP levels were observed in patients with Fontan circulation (36.1 pmol/l [IQR: 14.4 to 103.8 pmol/l]) and a systemic right ventricle (RV) (31.1 pmol/l [IQR: 21.8 to 56.0 pmol/l]), and the lowest values were seen in patients with aortic coarctation (7.3 pmol/l [IQR: 2.8 to 19.5 pmol/l]). NT-proBNP levels correlated with age (r=0.39, p<0.001) and were higher in women (median of 21.7 vs. 10.4 pmol/l; p<0.001). In patients with aortic stenosis or aortic coarctation, NT-proBNP levels correlated with diastolic function parameters of E/E' ratio (r=0.40, p<0.001) and left atrial dimension (r=0.36, p<0.001). In patients with a systemic RV, NT-proBNP levels correlated with RV annulus diameter (r=0.31, p=0.024). In patients with tetralogy of Fallot, the strongest correlations were observed with left atrial dimension (r=0.46, p<0.001) and left ventricular ejection fraction (r=0.37, p<0.001). NT-proBNP levels were associated with exercise capacity (n=198) (maximum workload: β=-0.08, p=0.021) and peak oxygen uptake (β=-0.012, p=0.011) in a multivariable regression model adjusted for age and sex.

Conclusions

NT-proBNP levels in adults with ConHD clearly differ by diagnosis and are related to echocardiographic parameters and exercise capacity. Disease-specific correlations contribute to the understanding of the main hemodynamic problems per diagnosis. Follow-up data are needed to elucidate the additional prognostic value.

Introduction

The remarkable improvement in survival due to the success of cardiac surgery, anesthesia, intensive care, and specialist (pediatric) cardiologic care has caused a rapid increase in the number of adults with congenital heart disease (ConHD).[1,2] As a result of this success, late complications are more often encountered, such as ventricular dysfunction, need for reintervention, arrhythmias, and sudden death. These adverse effects have important consequences for patients' prognosis and quality of life.[3] Therefore, early detection of deterioration in ventricular function and adequate timing of (re)interventions is crucial.

N-terminal pro-B-type natriuretic peptide (NT-proBNP), known as the inactive fragment of prohormone of brain natriuretic peptide, is primarily secreted by cardiac myocytes in response to abnormal ventricular wall stress and loading conditions.[4] NT-proBNP is a well-known marker of ventricular dysfunction and heart failure in patients with acquired heart disease.[5] The additional use of NT-proBNP as a marker for ventricular dysfunction in patients with ConHD has been suggested.[6] However, NT-proBNP has only been studied in a small number of patients with a specific type of congenital cardiac lesion, and the relationship between NT-proBNP level and cardiac function has not been assessed at all.[7] The wide spectrum of congenital heart lesions, each with their own degree of complexity and complications, suggests that disease-specific use of the marker might be required.[8] Furthermore, not all diagnostic and treatment options that are beneficial in patients with acquired heart disease can be extrapolated to patients with ConHD, as has been shown with medical treatment of heart failure.[9]

The aim of this study was to evaluate the value of NT-proBNP in adults with ConHD and investigate its relationship with cardiac function and exercise capacity.

Methods

Study sample

Patients were recruited consecutively at the adult ConHD outpatient clinic of the Erasmus Medical Center between May 2010 and October 2012. The following congenital cardiac diagnoses were included: aortic valvular stenosis (AoS), aortic coarctation (CoA), atrial septal defect, tetralogy of Fallot (ToF) (also including patients with pulmonary atresia and ventricular septal defect), transposition of the great arteries (TGA) corrected by arterial switch operation (ASO), systemic right ventricle (RV) (TGA corrected by Mustard procedure or congenitally corrected TGA), and Fontan circulation. Of all eligible patients, 95% agreed to participate. Exclusion criteria were defined as renal impairment (serum creatinine level >200 mmol/l) and age younger than 18 years.

Medical ethics and quality of data

The local medical ethics committee approved the study protocol. Written informed consent was obtained from all study participants. Several measures were taken to ensure optimal data quality. When

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patient enrollment was completed, one investigator compared the data entered in the electronic case report form with hospital records of 30 randomly selected study patients (6%), which were all in accordance. Before further analyses were conducted, manual edit checks were performed by the investigators to search for missing data, contradictory data entries, and values that were out of the specified normal range.

Clinical characteristics

On the day of inclusion in the study, all 475 patients underwent detailed 2-dimensional transthoracic echocardiography, 12-lead electrocardiography, and laboratory testing. A total of 198 patients also underwent bicycle ergometry on the same day. The following patient characteristics were recorded: age, sex, type of ConHD, history of prior interventions, body mass index, New York Heart Association (NYHA) functional class, blood pressure, heart rate, and oxygen saturation.

Echocardiography

Two-dimensional transthoracic echocardiography was performed by experienced sonographers using a commercially available system (iE33, Philips, Best, the Netherlands). Dimensions of the left ventricle (LV) (end-diastolic and end-systolic endocardial diameter), RV (annulus and apex-base distance), left atrium (4-chamber longitudinal and transversal diameter as well as parasternal long axis diameter), and right atrium (4-chamber longitudinal and transversal diameter) were measured. All ventricular measures were indexed for body surface area. Left ventricular systolic function was assessed by left ventricular ejection fraction using the biplane modified Simpson rule.[10] Right ventricular function was assessed by measurement of right ventricular fractional area change (FAC) and tricuspid annular plane systolic excursion. In patients with an RV supporting the systemic circulation, right ventricular FAC and tricuspid annular plane systolic excursion were used as systemic ventricle function measures. Furthermore, diastolic function was assessed using pulsed wave Doppler signals of the mitral or tricuspid valve inflow (E, A, E/A ratio, and deceleration time) and septal tissue Doppler imaging (E'). For the measured dimensions and function parameters, approximately 95% of the images were of sufficient quality.

Exercise test

Maximal exercise capacity (workload$_{max}$) and maximal oxygen uptake (VO$_{2max}$) were assessed by bicycle ergometry. Exercise test results were only obtained in patients undergoing bicycle ergometry for routine clinical follow-up (n=198). Workload was increased stepwise with 10 to 20 Watt/min. The results of exercise capacity were compared with the results of healthy subjects adjusted for age, sex, and body height and weight. Workload$_{max}$ and VO$_{2max}$ were considered decreased when <85% of the predicted value was achieved. Performance was considered maximal when a respiratory quotient of ≥1.1 was reached.

Laboratory testing

Peripheral venous blood samples were obtained from all participants after they had rested for at least 30 minutes. Plasma and serum were separated immediately after collection of blood samples, and NT-proBNP, creatinine, and hemoglobin levels were measured. NT- proBNP levels were determined using the Elecsys system (Roche Diagnostics, Basel, Switzerland). The cutoff value of normal in our hospital is ≤14 pmol/l.

Statistical analysis

Categorical variables are summarized as frequencies and percentages, and continuous variables with a normal distribution are reported as mean±standard deviation (SD). We report median values with inter-quartile range (IQR) in case of a non-normal distribution. Differences between cardiac diagnoses were compared using the Student unpaired *t* test or Wilcoxon rank sum test. Differences between more than 2 groups were investigated with 1-way analysis of variance or Kruskal-Wallis test. Because NT-proBNP values were not normally distributed, the variable was log transformed to create a normal distribution for further statistical analyses. When the test outcome comprised log-transformed NT- proBNP, these values were transformed backward to more informative NT-proBNP values. Correlation analyses between logNT-proBNP values and patient characteristics were performed using the Pearson correlation test or Spearman correlation test. A linear regression model was used to evaluate the relationship between NT-proBNP values and echocardiographic and bicycle ergometry parameters adjusted for age and sex.

All statistical tests were 2 sided, and a p-value of <0.05 was considered statistically significant. The Statistical Package for Social Sciences version 21.0 (SPSS, Chicago, Illinois) was used for all statistical analyses.

Results

A total of 475 patients (mean age of 34±12 years, 57% male) were included in the study. Baseline characteristics are listed in Table 1. All patients had a creatinine level <200 mmol/l (mean of 76.3±18.5 mmol/l). The median NT-proBNP level was 15.1 [IQR: 7.1 to 31.3] pmol/l, and was elevated in 53% of all patients. The distribution of NT-proBNP levels varied by diagnostic category (Fig. 1). Patients with a systemic RV (TGA corrected by Mustard procedure and congenitally corrected TGA) (median NT-proBNP level 31.1 [IQR: 21.8 to 56.0] pmol/l) or Fontan circulation had significantly higher NT-proBNP levels than patients with less complex ConHD lesions (mean of 34.9 [IQR: 21.4 to 59.9] pmol/l vs. 12.7 [IQR: 6.0 to 25.2] pmol/l, p<0.001).

NT-proBNP levels and patient characteristics

Levels of NT-proBNP were higher in women than in men (mean of 22.3 [IQR: 11.5 to 38.2] vs. 11.5 [IQR: 4.8 to 24.8] pmol/l, p<0.001). Furthermore, mean NT-proBNP levels increased with worsening NYHA

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TABLE 1. Baseline characteristics

	All patients	AoS	CoA	ASD	ToF	TGA ASO	TGA Mustard	ccTGA	Fontan
General									
Number of patients	475	88	59	48	168	27	50	11	24
Age (years)	34±12	34±12	32±13	43±5	35±13	22±2	35±5	42±15	28±9
Corrective surgery (%)	93	72	97	100	100	100	100	55	100
Age at corrective surgery (years)	7±10	23±12	7±11	7±3	5±7	0.4±2	1±2	26±14	4±3
Male (%)	57%	63%	56%	35%	59%	48%	68%	64%	54%
BMI (kg/m^2)	25±4	25±4	25±5	25±4	24±4	23±3	25±5	25±3	23±4
Systolic bloodpressure (mmHg)	125±16	124±15	129±17	130±19	125±16	122±12	124±15	126±15	122±16
Diastolic bloodpressure (mmHg)	79±11	78±10	80±11	80±12	78±12	76±9	80±12	82±10	76±12
Heart rate (beats/min)	73±14	75±13	70±14	71±12	76±13	65±13	72±14	75±9	74±13
Oxygen saturation (%)	99(76-100)	99(95-100)	99(95-100)	98(94-100)	98(76-100)	100(97-100)	97(88-100)	100(95-100)	95(80-100)
NYHA functional class:									
- I	426 (90)	83 (94)	59 (100)	46 (96)	149 (89)	27 (100)	37 (74)	10 (91)	15 (63)
- II	45 (9)	4 (5)	0	2(4)	18 (10)	0	12 (24)	1 (9)	8 (33)
- III	4 (1)	1 (1)	0	0	1 (1)	0	1 (2)	0	1 (4)
Electrocardiogram									
Rhythm:									
- Sinus rhythm	412(87)	81(92)	57 (96)	46 (96)	140 (84)	26 (96)	39 (78)	4 (36)	19 (80)
- Atrial fibrillation / flutter	13 (3)	2 (2)	1 (2)	0	4 (2)	0	1 (2)	2 (18)	1 (4)
- Paced rhythm	34 (7)	5 (6)	0	0	17(10)	0	6 (12)	4 (36)	2 (8)
- Atrial / nodal rhythm	16 (3)	0	1 (2)	2(4)	7 (4)	1 (4)	4 (8)	1 (10)	2 (8)
QRS duration (ms)	122±30	106±21	111±18	101±12	144±32	110±21	122±25	111±14	116±19
If QRS>120 ms: RBBB/LBBB/unspecified	167/16/41	9/3/9	11/6/12	1/0/2	110/2/10	6/0/4	26/1/1	0/1/0	

Values are n, mean±SD, or n(%). AoS: aortic stenosis, ASD: atrial septal defect, CoA: aortic coarctation, ASO: arterial switch operation; BMI: body mass index, bpm: beats per minute, CoA: aortic coarctation

ccTGA: congenitally corrected transposition of the great arteries, LBBB: left bundle branch block, NYHA: New York Heart Association,

RBBB: right bundle branch block, ToF: tetralogy of Fallot, TGA: Transposition of the Great Arteries

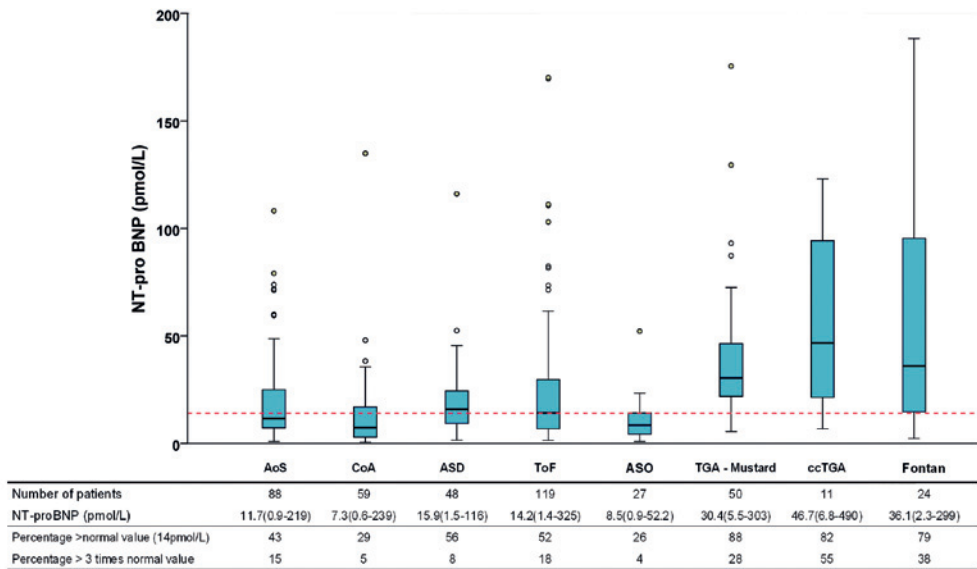|	AoS	CoA	ASD	ToF	ASO	TGA - Mustard	ccTGA	Fontan
Number of patients	88	59	48	119	27	50	11	24
NT-proBNP (pmol/L)	11.7(0.9-219)	7.3(0.6-239)	15.9(1.5-116)	14.2(1.4-325)	8.5(0.9-52.2)	30.4(5.5-303)	46.7(6.8-490)	36.1(2.3-299)
Percentage >normal value (14pmol/L)	43	29	56	52	26	88	82	79
Percentage > 3 times normal value	15	5	8	18	4	28	55	38

FIGURE 1. NT-proBNP levels by type of congenital heart disease
An overview of the median (range) of NT-proBNP levels for all included cardiac diagnoses. For each diagnosis, the percentage of patients with NT-proBNP levels above the reference value of 14 pmol/l is presented. Furthermore, the percentage of patients with levels of NT-proBNP 3 times the reference value or higher is shown.

functional class (NYHA class I: 13.3 [IQR: 6.6 to 26.7] pmol/l; NYHA class II: 42.7 [IQR: 19.7 to 120.0] pmol/l; NYHA class III: 172.5 [IQR: 95.4 to 279.1] pmol/l; p<0.001) (Fig. 2A). In patients with NYHA class I, 50% had NT-proBNP levels above the upper limit of normal (14 pmol/l). A significant correlation between NT-proBNP level and age was observed (r=0.39, p<0.001) (Fig. 2C). No relationship with blood pressure or body mass index was found.

NT-proBNP levels and electrocardiogram

Patients with atrial fibrillation or atrial flutter (3%) at the time of clinical assessment had significantly higher NT-proBNP levels than patients in sinus rhythm (87%) or with an artificial paced rhythm (7%) (p<0.001) (Fig. 2B). A significant relationship between NT-proBNP level and QRS duration was observed (p=0.005) (Fig. 2D), which was mainly driven by the correlations in patients with TGA after Mustard correction (r=0.41, p=0.005) and ToF (r=0.23, p=0.004).

Echocardiographic measurements

An overview of all echocardiographic measurements obtained for each diagnosis is presented in Table 2. In patients with a systemic LV, systolic ventricular function was normal (ejection fraction >50%) or only
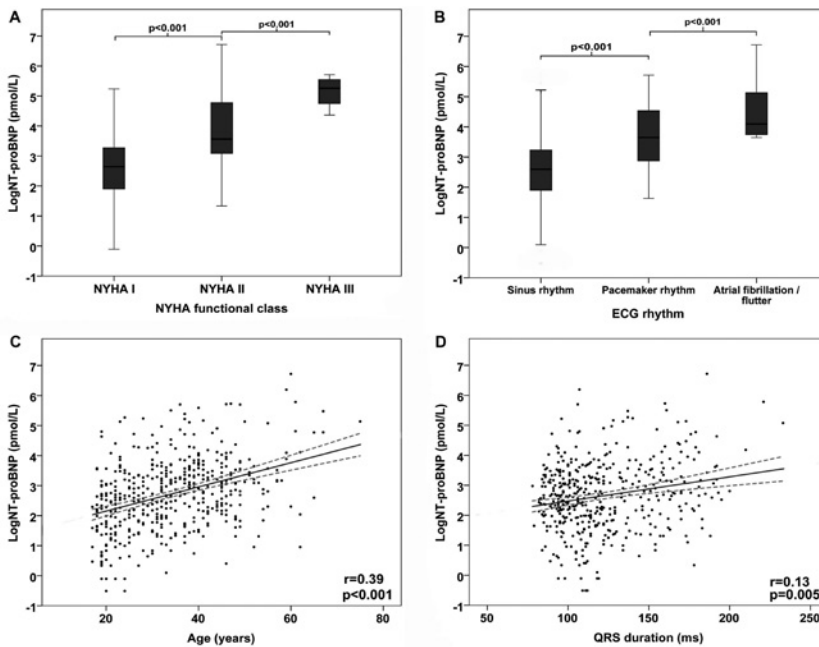
FIGURE 2. Relationship between NT-proBNP levels and baseline characteristics

(A) Mean logNT-proBNP level by NYHA class. (B) Mean logNT-proBNP level by ECG rhythm. (C) Correlation between logNT-proBNP level and age. The dashed lines show the 95% confidence interval for the mean. (D) Correlation between logNT-proBNP level and QRS duration. The dashed lines show the 95% confidence interval for the mean. ECG=electrocardiographic; NYHA=New York Heart Association.

mildly decreased. In 92% of the patients with a systemic RV, impaired right ventricular function, defined as a right ventricular FAC <35%, was found (median RV FAC of 24.2% [IQR: 19% to 29%]). Enlarged right ventricular annulus diameters were observed in patients with a systemic RV and ToF.

Echocardiographic parameters and NT-proBNP levels

All correlations between NT-proBNP levels and echocardiographic parameters are presented in Table 3.

Cardiac dimensions

A positive relationship between NT-proBNP levels and left ventricular dimensions indexed for body surface area was found, which remained significant after adjustment for age and sex. The strongest correlations between NT-proBNP level and left ventricular dimensions were seen in patients with AoS and patients with ToF. A positive correlation between NT-proBNP level and indexed right ventricular annulus dimension was observed in patients with a systemic RV and ToF. Furthermore, left atrial dimensions measured in 3 directions correlated significantly with NT-proBNP level (only the correlation with

TABLE 2. Echocardiographic findings

	AoS	CoA	ASD	ToF	TGA ASO	TGA Mustard	ccTGA	Fontan
LVEDD (mm / mm/m^2)	50±6/26±4*	50±5/27±3*	48±6/25±3*	48±6/26±3*	51±6/28±3*	n.m.	n.m.	53±12 / 30±8*
LVESD (mm / mm/m^2)	33±5/17±3*	31±6/16±3*	30±5/16±3*	32±6/18±4*	33±5/18±3*	n.m.	n.m.	36±13 / 21±8*
LA PLAX (mm)	36±7	35±7	38±7	38±7	34±8	n.m.	n.m.	54±19
LA 4 CH L (mm)	56±8	53±8	56±7	56±9	56±7	n.m.	66±11	73±2
LA 4 CH T (mm)	42±7	38±5	42±5	40±6	37±5	n.m.	49±13	n.m.
RVD annulus (mm/ mm/m2)	38±6 / 20±3*	39±6 / 21±3*	41±7/21±3*	46±8 / 24±4*	20±4*	51±6/27±3*	55±9 / 30±4*	n.m.
RVD apex-base (mm/ mm/m2)	83±7 / 44±5*	85±8 / 45±4*	65±7/34±5*	87±8 / 46±5*	45±5*	87±9/46±5*	80±6 / 42±5*	n.m.
RA no/mild/severe dilatation	18/9/5	42/8/3	21/16/1	44/59/48	20/4/1	1/13/32	3/7/0	n.m.
Systolic function								
LV ejection fraction (%)	57±9	59±8	54±8	51±8	57±8	n.m.	n.m.	51±5
good/mild vs moderate/severe impaired	84/4	59/0	48/0	153/15	22/0	47/2	11/0	18/2
RV fractional area change (%)	45±8	45±8	43±9	41±10	43±7	25±8	25±8	n.m.
RV TAPSE (mm)	20±2	25±6	19±4	17±5	18±4	12±3	14±3	n.m.
Diastolic function (mitral inflow)								
E/A ratio	1.62±0.67	1.69±0.5	1.33±0.4	1.69±0.7	2.39±0.9	1.75±0.9†	1.27±0.6†	1.46±0,5
E (m/s)	0.85±0.2	1.01±0.3	0.70±0.2	0.81±0.2	0.98±0.3	0.73±0.2†	0.98±0.3†	0,53±0.2
A (m/s)	0.58±0.2	0.63±0.21	0.55±0.2	0.52±0.2	0.42±0.1	0.51±0.3†	0.85±0.6†	0,41±0.5
Deceleration time (ms)	196±54	217±56	220±41	197±54	190±50	206±50†	219±109†	177±65
E/e' ratio	10.9±4.0	12.3±5.3	8.4±5.0	11.0±4.3	9.6±3.8	n.m.	n.m.	n.m.

Values are mean±SD or n. * indexed for body surface area. † tricuspid inflow.
LA 4CHL: left atrium four chamber longitudinal dimension, LA 4CH T: left atrium four chamber transversal dimension, LA PLAX: parasternal long axis, left atrium dimension, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, RA: right atrium, RV: right ventricle,
RVD: right ventricular dimension, n.m. : not measured

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left atrial longitudinal dimension measured in the 4-chamber view is shown). No relationship between NT-proBNP level and ventricular wall thickness was observed.

Systolic function

A significant negative correlation between left ventricular ejection fraction and NT-proBNP level was observed and was mainly driven by the significant correlations in patients with ToF (r=-0.37, p<0.001) and patients with AoS (r=-0.27, p=0.033). After adjustment for age and sex, the relationship remained significant. Right ventricular function, defined as right ventricular FAC, and NT-proBNP level were significantly related in the total group. This result was mainly driven by the findings in patients with ToF and the trend between NT-proBNP level and right ventricular FAC in patients with a systemic RV. Mixed results on tricuspid annular plane systolic excursion and NT-proBNP level were observed; patients with an atrial septal defect had a positive correlation and patients with a congenitally corrected TGA had a significant negative correlation. In patients with Fontan circulation who had moderate to severely

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TABLE 3. Correlations between logNT-proBNP levels and echocardiographic parameters

	Cardiac dimensions					Systolic function			Diastolic function			
	LVEDD*	LVESD*	RVD annulus *	RVD apex-base *	LA size	LV EF	RV FAC	TAPSE	E/A-ratio	E/E'-ratio	E'	A-wave
All diagnoses												
r	**0.169§**	**0.206§**	**0.398§**	0.091	**0.393§**	**-0.319§**	**-0.280§**	**-0.242‡**	-0.021	**0.326§**		
r²	0.028	0.043	0.151		0.154	0.102	0.078	0.058		0.106		
β	0.051	0.062	0.103		0.055	-0.043	-0.029	-0.055		0.083		
β adjusted for age and sex	**0.040‡**	**0.054§**	**0.092§**		**0.046§**	**-0.039§**	**-0.034§**	**-0.055§**		**0.052§**		
By diagnosis												
AoS	**0.337‡**	**0.324‡**	**0.283‡**	0.035	**0.455§**	**-0.265†**	-0.089	0.225	-0.021	**0.433§**	-0.313	0.165
CoA	0.102	-0.09	0.157	0.170	0.218	-0.052	**0.351†**	-0.479 (p=0.08)	-0.220	**0.480§**	**-0.438‡**	**0.444§**
ASD	0.163	0.087	0.202	-0.016	**0.313†**	0.042	0.118	**0.361†**	-0.042	-0.032	0.026	**0.330†**
Tetralogy of Fallot	**0.311‡**	**0.370§**	**0.270‡**	**0.211†**	**0.462§**	**-0.366‡**	**-0.248‡**	-0.134	0.066	**0.298§**	**-0.181†**	0.008
TGA - ASO	0.188	0.089	-0.007	-0.094	0.168	-0.364	0.340	0.101	0.145	0.239	0.320	0.031
Systemic RV	np	np	**0.305†**	0.207	n.p.	np	-0.263 (p=0.07)	-0.253	0.434 (p=0.08)	np	np	np
Fontan circulation	0.048	-0.117	np	np	np	-0.520	np	np	-0.216	np	np	np

* indexed for body surface area. Levels of significance: † p<0.05, ‡ p < 0.01, §p <0.001.
Log-NT-proBNP= log-transformed N-terminal prohormone of brain natriuretic peptide, np = not performed, RV FAC= right ventricular fractional area change

impaired ventricular function, NT-proBNP values were significantly higher than in patients with Fontan circulation who had normal or only mildly impaired ventricular function after adjustment for age and sex (p=0.023).

Diastolic function
Diastolic function parameters E/E' ratio, E', and A-wave showed a significant correlation with NT-proBNP values in patients with AoS, CoA, and ToF. Such relationships were not observed in patients with any of the other diagnoses. No relationship between NT-proBNP level and deceleration time or E/A ratio was observed.

Exercise test and NT-proBNP levels

Bicycle ergometry was performed in 198 patients (42%). Additionally, oxygen uptake was measured in 103 patients (22%) during the test. In 48% of the patients, a workload$_{max}$ of 85% of predicted was not reached. VO$_{2max}$ was decreased in 61% of the patients (Table 4). A higher logNT-proBNP level was associated with lower workload$_{max}$ (β=-0.08, p=0.021) and lower VO$_{2max}$ (β=-0.012, p=0.011) in a multivariable regression model adjusted for age and sex.

TABLE 4. Exercise test

Workload, maximum (%)	85±20
Less than 85% of predicted workload (%)	45
VO_2max (%)	82±22
Less than 85% of predicted VO_{2max}	61%
RQ at peak exercise	1.3±0.2
RQ less than 1	1%

Values are mean±SD or n.
RQ: respiratory quotient,
VO_{2max}= maximal oxygen uptake

Discussion

This cross-sectional study focused on NT-proBNP outcomes in adults with ConHD. Clear differences in NT-proBNP levels among patients with various congenital heart defects were shown. NT-proBNP levels ranged from mostly normal levels in patients with CoA to highly elevated levels in the majority of patients with complex ConHD, including patients with a systemic RV or Fontan circulation. Because this cross-sectional study shows results comparable to findings by Popelova et al.,[7] the presented values can possibly be used as reference values of NT-proBNP per cardiac diagnosis. As more patients with ConHD reach adulthood, many will encounter late complications. To determine the additional prognostic value of NT-proBNP, further fine-tuning and follow-up data are clearly needed.

Despite remarkable differences in NT-proBNP levels, the majority of patients were asymptomatic and in NYHA functional class I. Although NT-proBNP levels in asymptomatic patients were already raised and none of our patients were in NYHA class IV, our results suggest a positive correlation between NT-proBNP level and NYHA classification, similar to the well-known correlation in patients with congestive heart failure. NT-proBNP levels were higher in women than in men, which extends previous knowledge in acquired heart failure, and these higher levels remain present over time.[11] Consequently, sex-specific reference values are mandatory, but a larger multicenter study is needed.

We observed a clear relationship between NT-proBNP level and atrial arrhythmias. This has previously been found in patients with nonvalvular atrial fibrillation, in which higher NT-proBNP levels were associated with an increased risk of stroke and mortality.[12] In patients with ConHD, atrial arrhythmias are an important cause of morbidity as well.[13] Furthermore, a relationship between NT-proBNP level and QRS duration was observed in patients with a systemic RV and patients with ToF. A prolonged QRS duration is associated with an increased mortality rate in patients with ToF.[14] Hence, NT-proBNP may have a prognostic value.

In addition, the relationship between NT-proBNP level and exercise capacity strengthens the possible use of NT-proBNP as a prognostic marker, because exercise stress testing provides strong prognostic information in adults with ConHD.[15] Our observed distribution of NT-proBNP levels, with higher levels in those with more complex ConHD, is in line with findings of average exercise capacity as recently reported by Kempny et al.[16] When compared with healthy controls, both an increase in NT-proBNP level

and reduced peak VO$_2$ were most pronounced in patients with complex ConHD. Most importantly, significant correlations between echocardiographic parameters and NT-proBNP levels were observed, with notable differences between the various types of ConHD.

Left-sided heart lesions

Strongest relationship between left atrial size and NT-proBNP levels was observed in patients with AoS. NT-proBNP may contribute to detection of left atrial remodeling, which is directly associated with an increased mortality rate in asymptomatic patients with a severe acquired aortic stenosis,[17] and similar results were found in patients with heart failure with preserved ejection fraction.[18] In line with the fact that atrial size can indicate the presence of diastolic dysfunction,[19] several measures of diastolic function were related to NT-proBNP as well. These significant relationships were primarily seen in patients with left-sided cardiac pathology, such as AoS and CoA. Pressure overload caused by the aortic stenosis or previous hypertension in patients with CoA could be the origin of impaired cardiac relaxation. A recent observation suggests that after successful repair of CoA, pediatric patients more often have diastolic dysfunction than healthy subjects.[20] In patients with calcified aortic stenosis, NT-proBNP level was related to diastolic function parameters.[21] NT-proBNP could possibly be a useful supplementary tool to identify diastolic functional impairment in patients with left-sided lesions. Diastolic dysfunction may be the most important clinical problem in these patients.

Tetralogy of Fallot

In adults with corrected ToF, right ventricular dysfunction and right ventricular annulus dilation secondary to pulmonary regurgitation are major concerns and have both been linked to release of NT-proBNP.[22] Nonetheless, we observed stronger relationships between NT-proBNP and left heart side measures such as left ventricular ejection fraction and dimensions that strengthen the hypothesis that these left heart problems are of main concern in patients with repaired ToF. In contrast to 3 other (smaller) studies that reported no relationship between NT-proBNP level and left ventricular ejection fraction in patients with ToF,[23–25] our study did show a significant correlation. Furthermore, the relationship between NT-proBNP levels and diastolic function confirms the recent findings of Friedberg et al. that diastolic dysfunction is an important component in adults with ToF that occurs early in the clinical course when patients are still asymptomatic.[26] A recent study reported an incidence of left ventricular dysfunction of 21% in adults with corrected ToF, possibly the result of prior long-standing cyanosis at young age before repair, volume overload due to aortic regurgitation, or adverse ventricular-ventricular interaction.[27] An increasing body of evidence suggests that left ventricular dysfunction is encountered with increasing age in patients with corrected ToF.[27–29] NT-proBNP may contribute substantially to diagnosis and follow-up of left ventricular systolic and diastolic dysfunction.

Systemic RV

Highest NT-proBNP levels were found in patients with a systemic RV and were mainly related to right ventricular annulus dilation and decreased systemic right ventricular function. In these patients, the enlarged RV is primarily the result of right ventricular failure and may also lead to functional tricuspid regurgitation. The RV is less well suited to cope with high systemic pressure, possibly due to its triangular geometry and distinct myocardial fiber orientation. In our study, there were relationships between neurohormonal activation and right ventricular function and dimensions that are in line with previous studies, supporting the possible use of this marker as a supplementary test to monitor right ventricular function. Additionally, NT-proBNP may contribute to the timing of an intervention for tricuspid regurgitation.[30] Early detection of decline in right ventricular function is crucial because right ventricular failure might result in death or serious morbidity requiring cardiac transplantation.[31] Diastolic function parameters in patients with TGA after the Mustard procedure did not correlate with NT-proBNP levels. However, measurement of diastolic function using tricuspid valve inflow is disputable in patients who have undergone the Mustard procedure because of their stiff atria as a result of the intra-atrial baffles and extensive scar tissue.

Arterial switch operation

In contrast to patients with Mustard correction, patients with TGA corrected with ASO had notably low NT-proBNP values, mirroring their good clinical condition and good left ventricular and right ventricular function. As the ASO procedure, first described in 1976 by Jatene et al.,[32] has succeeded the Mustard procedure, patients who undergo ASO are typically younger than patients who undergo the Mustard procedure. Midterm follow-up shows that patients who undergo ASO do well in early adulthood,[33] although problems of the right ventricular outflow tract and aortic regurgitation may arise. This is the first study to report data on NT-proBNP after ASO and all patients were asymptomatic, so the use of natriuretic peptides in these patients has to be determined in a larger cohort and with longer duration of follow-up before firm conclusions can be drawn. Nevertheless, the low NT-proBNP levels in combination with the absence of symptoms are certainly promising for the long-term outcome of these patients.

Fontan circulation

In patients with Fontan circulation, elevated NT-proBNP levels were clearly related to decreased systolic ventricular function. Diastolic function parameters did not correlate with NT-proBNP levels. However, diastolic function is difficult to assess in patients with Fontan circulation. Individual anatomic differences due to various surgeries influenced the observed NT-proBNP values and the number of patients with Fontan circulation in our study was limited, so our results can probably not be extrapolated to all patients with a functional univentricular heart and should be interpreted with caution.

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Study limitations

Although we attempted to create homogeneous patient groups by dividing the patients into well-defined anatomy-based groups, individual differences caused by surgical history and disease severity withhold us from making firm conclusions.

Future perspectives

NT-proBNP levels can only be partly explained by echocardiographic parameters because the observed relationships were significant but not strong. Nonetheless, the relationship between NT-proBNP levels and echocardiographic function parameters in patients with congestive heart failure was similar.[34] To evaluate the exact impact of ventricular function on NT-proBNP levels, extensive investigation for each cardiac diagnosis is needed, including other possible influences such as arrhythmias, valvular disease, and surgical history. This study is a first attempt to create disease-specific NT-proBNP reference values for each congenital cardiac diagnosis. Finally, because this is a cross-sectional study, only correlations can be given. Longitudinal data will provide additional prognostic implications of these findings.

Conclusions

Levels of NT-proBNP clearly differ among various congenital heart lesions. Remarkable disease-specific correlations between NT-proBNP levels and echocardiographic parameters have been found. In patients with left-sided pathology, a higher level of NT-proBNP correlates with diastolic dysfunction parameters. In patients with a systemic RV, NT-proBNP levels are influenced by right ventricular dimension and right ventricular systolic function. In patients with ToF, elevated NT-proBNP levels are typically associated with deterioration in left ventricular function as well as left ventricular and left atrial dilation. Furthermore, NT- proBNP levels are related to exercise capacity. Hence, natriuretic peptides hold promise as a marker of cardiac dysfunction in adults with ConHD, but follow-up data are needed to determine the prognostic value.

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Chapter 6

Associations between N-terminal pro-B-type natriuretic peptide and cardiac function in adults with corrected tetralogy of Fallot

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Abstract

Background

Amino-terminal B-type natriuretic peptide (NT-proBNP) may detect early cardiac dysfunction in adults with tetralogy of Fallot (ToF) late after corrective surgery. We aimed to determine the value of NT-proBNP in adults with ToF, and establish its relationship with echocardiography and exercise capacity.

Methods and Results

NT-proBNP measurement, electrocardiography and detailed 2D-echocardiography were performed on the same day in 177 consecutive adults with ToF (mean age 34.6±11.8 years, 58% male, 89% NYHA I, 29.3±8.5 years after surgical correction). Thirty-eight percent of the patients also underwent a cardiopulmonary-exercise test. Median NT-proBNP was 16 [IQR 6.7-33.6] pmol/L, and was elevated in 55%. NT-proBNP correlated with right ventricular (RV) dilatation (r=0.271, p<0.001) and RV systolic dysfunction (r=-0.195,p=0.022), but more strongly with LV systolic dysfunction (r=-0.367, p<0.001), which was present in 69 patients (39%). Moderate or severe pulmonary regurgitation was not associated with higher NT-proBNP. Tricuspid and pulmonary regurgitation peak velocities correlated with NT-proBNP (r=0.305, p<0.001 and r=0.186, p=0.045, respectively). LV twist was measured with speckle-tracking echocardiography in 71 patients. An abnormal LV twist (20 patients, 28%) was associated with elevated NT-proBNP (p=0.030). No relationship between NT-proBNP and exercise capacity was found.

Conclusions

NT-proBNP levels are elevated in more than 50% of adults with corrected ToF, while they are in stable clinical condition. Higher NT-proBNP is most strongly associated with elevated pulmonary pressures, and with LV dysfunction rather than RV dysfunction. NT-proBNP has the potential to become routine examination in patients with ToF to monitor ventricular function and may be used for timely detection of clinical deterioration.

Introduction

Tetralogy of Fallot (ToF) is the most common form of cyanotic congenital heart disease (ConHD), with a birth prevalence of approximately 3-4 per 10,000 live births.[1] The survival of patients with ToF has improved considerably since Lillehei reported the first successful corrective surgery in 1954.[2] Despite satisfactory survival results of over 90%, 30 years after corrective surgery,[3,4] an increasing number of late complications are encountered such as pulmonary regurgitation with the need for reintervention, right and left ventricular dysfunction, aortic root dilatation and arrhythmias. Although no clear data on very long-term outcome are available yet, life expectancy is presumed to be diminished.[3]

Nearly all adults with ToF have some degree of residual pulmonary regurgitation (PR) due to repair of the right ventricular (RV) outflow tract during corrective surgery. Pulmonary regurgitation causes volume overload of the RV, which can lead to RV dilatation and dysfunction.[5] The progression of RV dysfunction may also affect the left ventricle (LV), whereas both ventricles are known to interact.[6,7] Up to 20% of all adults with ToF develop LV dysfunction.[8] Early detection of deterioration in ventricular function is crucial, as both RV and LV dysfunction can lead to heart failure and life-threatening ventricular arrhythmias, which are both associated with increased morbidity and mortality.[9]

Exercise capacity in adults with ToF is often diminished,[10] and a worse cardiopulmonary-exercise test is known to be predictive for adverse outcome in these patients.[11]

Another diagnostic tool that may be used to detect early changes in ventricular function and exercise capacity is the well-established heart failure biomarker N-terminal probrain natriuretic peptide (NT-proBNP). NT-proBNP is released from the cardiac myocytes in response to pressure and volume over-load, and is a marker of increased myocardial-wall stress. While natriuretic peptides have been proven to be of adjuvant diagnostic and prognostic value in patients with acquired heart failure,[12] less is known about the usefulness of NT-proBNP in ToF. A recent article demonstrated that even though the vast majority of adults with ToF are asymptomatic, they have elevated NT-proBNP levels.[13] The significance of this observation is unknown, and therefore the potential diagnostic and prognostic value of NT-proBNP remains to be determined. We established NT-proBNP levels in adult patients with ToF and assessed the echocardiographic and exercise-related determinants of elevated NT-proBNP.

Methods

Patient inclusion

Patients diagnosed with ToF were recruited consecutively at the adult ConHD outpatient clinic at Erasmus Medical Center between May 2010 and March 2013. All patients had to be 18 years of age or older.

Clinical assessment

All patients underwent an extensive 2D-transthoracic echocardiogram with speckle-tracking echocardiography, electrocardiogram, laboratory testing and were seen by a cardiologist on the same day. A subgroup of patients also underwent a cardiopulmonary-exercise test with maximum oxygen uptake (VO$_2$max). Exercise tests were not performed in all patients due to logistical reasons, and exercise results were only included in this study when the test was performed in the same week. The following patient characteristics were obtained: age, gender, surgical history, New York Heart Association (NYHA) functional class, body mass index (BMI), blood pressure, heart rate, and oxygen saturation.

Echocardiography

Two-dimensional echocardiography was performed by experienced sonographers with use of the commercially available system iE33 (Philips, Best, the Netherlands). Measured dimensions included the left ventricle (LV) end-diastolic and end-systolic endocardial diameter; right ventricle (RV) end-diastolic annulus and apex-base diameter; left atrium (LA) four chamber longitudinal diameter and area at the end of the ventricular systole. As quantitative measurement of the right atrium (RA) was not possible in all patients, we assessed RA size visually, which was then graded as no, mild or severe dilation.[14,15] Chamber dimensions were indexed for body surface area (BSA). Left ventricular systolic function was assessed on the basis of LV ejection fraction (LVEF) with use of the biplane modified Simpson's rule.[14] Right ventricular systolic function was assessed using tricuspid annulus plane systolic excursion (TAPSE), right ventricular fractional area change (RV FAC) and systolic excursion of the lateral tricuspid annulus (S') using tissue Doppler imaging (TDI). Diastolic LV function was assessed using pulsed wave Doppler of the mitral valve inflow (E, A, E/A-ratio and deceleration time) and septal TDI (E'). For the assessment of valvular regurgitation and stenosis, we used the recommendations of the European Association of Echocardiography.[16-18]

Speckle- tracking echocardiography

Speckle-tracking echocardiography (STE) was used to evaluate LV twist. For optimal STE, images of the apical and basal short-axis were obtained with a frame rate of ≥60 frames/second. Images were transferred to a QLAB workstation to perform offline analysis (Philips Medical Systems). The images were analysed with QLAB software version 9.0. LV twist was defined as the maximal value of simultaneous systolic apical rotation minus basal rotation. Twist patterns of ToF patients were compared with twist patterns of healthy individuals, who were defined as normal. A normal twist pattern is characterized by an end-systolic clockwise basal rotation and end-systolic counter-clockwise apical rotation.[19] Other twist patterns were defined as abnormal. Excellent intra-observer and inter-observer reproducibility for LV twist measurements using QLAB software has been described for our lab.[20]

Cardiopulmonary-exercise test

Maximal exercise capacity (workload$_{max}$) and maximal oxygen uptake during exercise (VO$_{2max}$) were assessed using bicycle ergometry. Workload was increased gradually by 10-20 watts per minute. Exercise capacity results were compared with reference values that were adjusted for age, gender, body height and weight. Performance was considered maximal when a respiratory exchange ratio (RER) of >1.0 was reached.

Laboratory testing

Peripheral venous blood samples were obtained from all patients after at least 15 minutes of rest. Creatinine levels were assessed since renal dysfunction is known to influence NT-proBNP levels. Renal dysfunction was defined as a creatinine level of ≥200μmol/l. Plasma NT-proBNP levels were measured using an enzyme immunoassay (Elecsys, Roche Diagnostics, Basel, Switzerland). The cut-off value of normal in our laboratory is ≤14 pmol/l.

Statistical analysis

Continuous variables were reported as mean ± standard deviation when normally distributed, or median and interquartile ranges (IQR) were reported when not normally distributed. Categorical variables were presented as frequencies and percentages. Differences in continuous variables between two groups were compared using the Student's unpaired *t*-test when normally distributed or Wilcoxon rank sum test when data distribution was skewed. Differences in continuous variables with normal distribution between more than two groups were investigated with one-way ANOVA, or when not normally distributed investigated with Kruskal Wallis test. Baseline characteristics were compared between patients with normal and elevated NT-proBNP levels. To compare categorical data, the Chi-square test or when applicable, the Fisher's exact test were used. Correlation analyses between NT-proBNP and patient characteristics were performed using the Pearson correlation test or the Spearman correlation test when data was skewed. Linear regression modelling was performed to evaluate the relationship between NT-proBNP and echocardiographic and bicycle ergometry parameters. We adjusted for baseline characteristics that were significantly associated with NT-proBNP, including age, gender and NYHA class which are known factors that influence NT-proBNP levels.[21] As NT-proBNP is non-parametric, the variable was log-transformed which created a normal distribution for further statistical analyses. All statistical tests were two-sided and a p-value of <0.05 was considered statistically significant. The Statistical Package for Social Sciences, version 21.0 (SPSS, Chicago, Illinois) was used for all statistical analyses.

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Medical ethics and data quality

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local medical ethics committee. Written informed consent was obtained from all patients. Several measures were taken to ensure optimal data quality. Before the statistical analyses, manual edit checks were performed by the investigators to search for missing data, contradictory data entries and for values that were out of the specified normal range. Data of a random sample of 15 participants (8%) was checked by an independent investigator; no discrepancies were observed between data in medical records and in the database used for statistical analyses.

Results

A total of 177 ToF patients were included in the study, 28 of whom had a diagnosis of ToF with pulmonary valve atresia (ToF/PA). Baseline characteristics of all study participants are summarized in Table 1. Median NT-proBNP level was 15.6 [IQR 6.7-33.6] pmol/L. In 55% of the patients the NT-proBNP level was above the reference value of normal (>14 pmol/L). None of the patients had renal dysfunction (median creatinine level 75 [IQR 65 – 83.5] μmol/L). In Table 1 the baseline characteristics are presented for all patients together, and specified for patients with normal or elevated NT-proBNP levels. NT-proBNP levels were significantly higher in women than in men (23.9 [IQR 13.8-41.3] pmol/L versus 9.6 [IQR 4.8-21.4] pmol/L, p<0.001). Median NT-proBNP levels increased with NYHA class (NYHA I 14.5 [IQR 6.3-29.4] pmol/L, NYHA II 29.7 [IQR 16.7-135.3] pmol/L, NYHA III (n=1) 169.6 pmol/L, p<0.001. Patients with elevated NT-proBNP had undergone corrective surgery at older age, and more often had a prior palliative shunt. In patients with normal NT-proBNP levels a transannular or RVOT patch was used more often during corrective surgery. NT-proBNP levels did not differ between patients with or without prior pulmonary valve replacement.

Electrocardiography

The majority of patients were in sinus rhythm (n=146, 83%), and had a right bundle branch block (n=118, 91%) (Table 2). In 22 patients (12%) QRS duration was ≥180 milliseconds. Mean QRS duration was longer in patients with an elevated NT-proBNP level. NT-proBNP levels were significantly higher in patients in atrial fibrillation (101.3 [IQR 40.5-661] pmol/L) than in patients in sinus rhythm (13.9 [IQR 6.3-26.9] pmol/L) or pacemaker rhythm (24.6 [IQR 14.3-43.8] pmol/L), p<0.001.

Echocardiography

Based on annulus and apex-base diameter, more than 50% of the patients had a dilated RV (Table 3). RV function (i.e. RV fractional area change<35%, TAPSE<16 and/or S'<10) was diminished in one-third of the patients. Right ventricular fractional area change was similar in patients with and without elevated

TABLE 1. Baseline patient characteristics

	All patients	NT-proBNP ≤14 pmol/l	NT-proBNP >14 pmol/l	*p*-value
Number of patients	177	80 (45%)	97 (55%)	
Age (years)	33 [26 - 43]	31 [24 - 35]	39 [29 - 47]	**<0.001**
Male patients	103 (58%)	62 (78%)	41 (42%)	**<0.001**
Body Mass Index (kg/m^2)	24.1±4.2	24.0±4.5	24.3±4.0	0.696
NYHA class (I / II) (%)	89 /11[a]	95 / 5	84 / 16[a]	**0.033**
Pulmonary valve atresia	27 (16%)	11 (14%)	16 (17%)	0.613
Associated lesions				
Atrial septal defect	10 (6%)	6 (6%)	4 (4%)	-
Muscular ventricular septal defect	1 (1%)	0	1 (1%)	-
Patent ductus arteriosus	7 (4%)	5 (6%)	2 (2%)	-
Aortic coarctation	1 (1%)	0	1 (1%)	-
Surgerical characteristics				
Age at time of corrective surgery (years)	2.8 [1.1 - 6.9]	1.7 [0.8 - 4.6]	4.8 [1.6 - 8.7]	**<0.001**
Time since corrective surgery (years)	29.7 [22.9-36.0]	27.0 [21.6-32.6]	33.5 [24.2-38.1]	**0.001**
Prior shunt	64 (37%)	21 (26%)	43 (44%)	**0.013**
- Blalock-Taussig shunt	46 (26%)	17 (21%)	29 (30%)	0.192
- Waterston shunt	18 (10%)	4 (5%)	14 (14%)	**0.039**
Patch used to broaden RVOT	111 (63%)	57 (71%)	54 (56%)	**0.011**
Pulmonary valve replacement	97 (55%)	46 (58%)	51 (53%)	0.513
Time corrective surgery - PVR (years)	20.3 [13.6-26.5]	19.1 [14.1 - 25.0]	20.3 [13.3 - 29.0]	0.520

Categorical variables are presented as number (percentage)
Continuous variables are presented as mean ± standard deviation or median [interquartile range]
P-values are given for the comparison of variables between patients with normal and elevated NT-proBNP
NYHA = New York Heart Association; RVOT = right ventricular outflow tract;
PVR = pulmonary valve replacement. [a] one patient was in NYHA functional class III

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NT-proBNP (39±10 versus 41±10%, p=0.255). Thirty-nine percent of the patients had a diminished LV function (LV ejection fraction <50%). Left ventricular EF was significantly lower in patients with elevated NT-proBNP than in patients with normal NT-proBNP (49±9% versus 54±6%, p=0.010). Correlations between NT-proBNP and echocardiographic parameters of cardiac function, dimensions, and valvular function are presented in Figure 1 and 2.

Sixty-five patients (31%) had moderate or severe pulmonary regurgitation. The severity of pulmonary regurgitation was not related to NT-proBNP in the total study population or in a subgroup of patients without prior pulmonary valve replacement (PVR). NT-proBNP was significantly higher in patients with more severe tricuspid regurgitation (Figure 2). The peak velocity of pulmonary regurgitation (PR$_{vmax}$) correlated with NT-proBNP levels (r=0.186, p=0.045). NT-proBNP levels also correlated with tricuspid regurgitation peak velocity (TR$_{vmax}$) (r=0.305, p<0.001). In 32 patients moderate or severe pulmonary stenosis was present which did not correlate with NT-proBNP levels. Aortic and mitral valve measurements were not correlated with NT-proBNP levels either.

TABLE 2. Electrocardiogram and bicycle ergometry

	All patients	NT-proBNP ≤14 pmol/l	NT-proBNP >14 pmol/l	*P*-value
Electrocardiogram				
Rhythm:				
- Sinus rhythm	146 (83%)	74 (92%)	72 (74%)	**0.001**
- Atrial fibrillation	4 (2%)	0	4 (4%)	-
- Pacemaker rhythm	18 (10%)	4 (5%)	14 (14%)	**0.039**
- Ectopic atrial / junctional rhythm	9 (5%)	2 (3%)	7 (7%)	-
Heart rate (beats per minute)	75±13	76±13	74±13	0.266
QRS duration (ms)	144±32	137±29	150±33	**0.010**
If QRS duration >120 ms:	127 (72%)	58 (76%)	69 (71%)	0.699
- Right bundle branch block	117 (91%)	53 (91%)	64 (93%)	0.970
- Left bundle branch block	2 (1%)	0	2 (3%)	-
- Non-specific IVCD	8 (5%)	5 (9%)	3 (4%)	-
QRS duration ≥ 180 ms	22 (12%)	7 (9%)	15 (16%)	0.099
Bicycle ergometry				
Number of patients	68 (38%)	31 (39%)	37 (38%)	
Maximal workload (% of predicted)	86 [74-98]	85 [80-92]	87 [67-103]	0.475
Maximal heart rate (% of predicted)	87 [78-95]	85 [77-96]	87 [79-94]	0.726
Peak oxygen uptake measurement (n=42)				
$VO_{2\,max}$ (% of predicted)	77 [70-88]	76 [71-81]	79 [66-96]	0.687
RER_{max}	1.37 [1.25-1.47]	1.45 [1.45-1.49]	1.26 [1.15-1.39]	**0.010**

Categorical variables are presented as number (percentage)
Continuous variables are presented as mean ± standard deviation or median [interquartile range]
P-values are given for the comparison of variables between patients with normal and elevated NT-proBNP
IVCD = intraventricular conduction delay, RER_{max} = maximal respiratory exchange ratio

The results of the multivariate analyses are summarized in Table 3. NT-proBNP was most strongly associated with TR_{vmax} and PR_{vmax}. The association between NT-proBNP and TR_{vmax} remained significant after adjustment for the presence of pulmonary stenosis (β=0.488, p=0.032). The correlation with diastolic function parameter E/E'-ratio was no longer significant.

Speckle-tracking echocardiography – left ventricular twist

Left ventricular twist was assessed in 73 patients (41%), who had sufficient-quality images of the basal and apical short-axis view. Twenty of these patients (27%) had an abnormal LV twist pattern. In the patients with an abnormal LV twist pattern, NT-proBNP levels were more often elevated than in patients with a normal LV twist pattern (70% versus 42%, p=0.030).
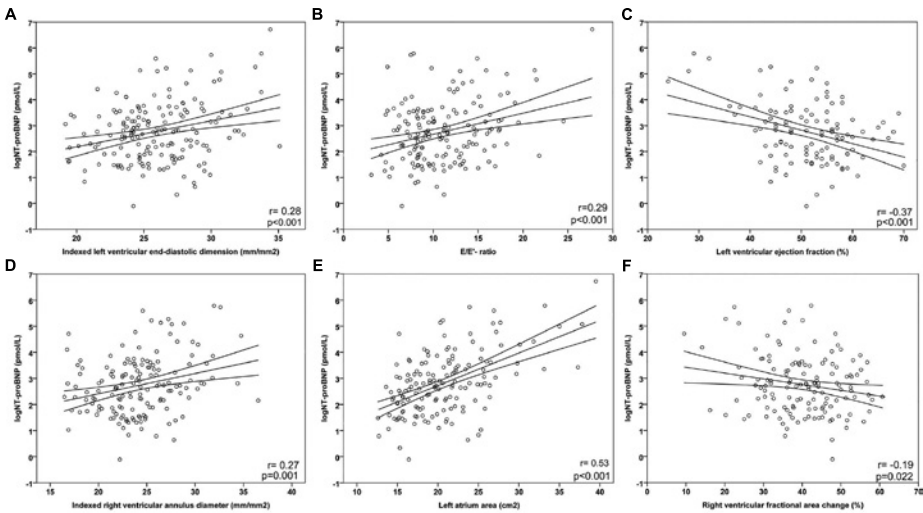
FIGURE 1. Correlations between NT-proBNP and cardiac function and dimensions
The correlations are presented for NT-proBNP and LV end-diastolic dimension indexed for BSA (A), E/E'-ratio (B), LV ejection fraction (C), RV annulus diameter indexed for BSA (D), LA area (E) and RV fractional area change (F). Correlation lines with 95% confidence interval are shown.
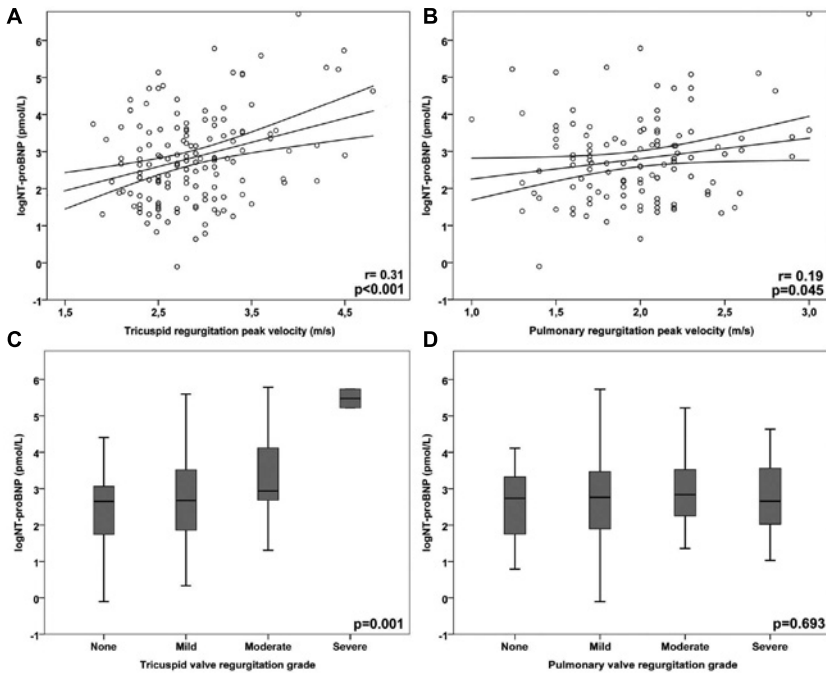

FIGURE 2. Correlations between NT-proBNP and parameters of valvular function
The correlations between NT-proBNP and TR peak velocity (A) and PR peak velocity (B) are presented. Associations between NT-proBNP and TR severity (C) and PR severity (D) are presented. Correlation lines with 95% confidence interval are shown.

TABLE 3. Echocardiographic findings and associations with logNT-proBNP

			Correlation analysis		Multivariable analysis[a]	
			(r)	p-value	(β)	p-value
LA longitudinal diameter	(mm)	56 ± 9	0.47	**<0.001**	0.048	**<0.001**
LA area	(cm^2)	21±5	0.53	**<0.001**	0.102	**<0.001**
LV end-diastolic diameter	(mm)	48±6	0.284	**<0.001**	0.059	**0.014**
LV end-systolic diameter	(mm)	33±6	0.342	**<0.001**	0.080	**<0.001**
RA size						
normal/mild/severe (n.a.)		48/61/51(17)		**<0.001**	0.462	**<0.001**
RV apex-base diameter	(mm)	87±8	0.177	**0.031**	0.035	**0.028**
RV annulus diameter	(mm)	45±8	0.271	**0.001**	0.063	**0.002**
LV ejection fraction	(%)	51.4±8.3	-0.367	**<0.001**	-0.049	**<0.001**
RV FAC	(%)	40.1±9.8	-0.195	**0.022**	-0.026	**0.001**
TAPSE	(mm)	18±5	-0.132	0.104	--	--
TDI RV free wall (S')	(cm/s)	9.5±2.4	-0.124	0.150	--	--
Mitral valve inflow						
E-wave	(m/s)	0.81±0.22	0.073	0.349	--	--
A-wave	(m/s)	0.52±0.16	0.069	0.379	--	--
E/A - ratio		1.7±0.74	0.017	0.824	--	--
Deceleration time	(ms)	196±54	-0.150	0.057	-0.003	0.053
E/E' - ratio		11.1±4.2	0.296	**<0.001**	0.030	0.125
Aortic stenosis vmax	(m/s)	1.11±0.32	0.080	0.340	--	--
Aortic regurgitation:				**0.002**	0.328	**0.024**
none/mild/moderate/severe (n.a.)		113/56/4/0 (4)		**0.002**	0.328	**0.024**
Pulmonary stenosis:						
mild/moderate/severe (n.a.)		142/31/2 (2)		0.252		
Pulmonary stenosis vmax	(m/s)	2.20±0.76	-0.198	0.220	--	--
Pulmonary regurgitation:						
none/mild/moderate/severe (n.a.)		42/65/28/37(5)		0.692	--	--
Pulmonary regurgitation vmax	(m/s)	1.97±0.39	0.186	**0.045**	0.512	**0.027**
Tricuspid regurgitation:						
none/mild/moderate/severe (n.a.)		50/107/16/2(2)		**0.001**	0.259	**0.034**
Tricuspid regurgitation vmax	(m/s)	2.86±0.57	0.305	**<0.001**	0.680	**<0.001**
Mitral regurgitation:						
none/mild/moderate/severe (n.a.)		134/40/1/0 (2)		0.350	--	--

Values are presented as mean ± standard deviation or frequencies
ms = milliseconds; m/s = meter per second; n.a. = not available; vmax = peak flow velocity
[a]adjusted for baseline characteristics age, gender, NYHA class, rhythm and age at corrective surgery

Cardiopulmonary-exercise test

An exercise-stress test was performed in 68 patients (38%). There was no difference in baseline character-istics of patients who underwent an exercise stress test and patients who did not. The median achieved percentage of predicted target workload was 86 [IQR 74 – 98]% (Table 2). Thirty-seven patients (54%) achieved <85% of the predicted target workload. Forty patients (58%) reached ≥85% of the target heart rate. Patients with normal exercise capacity had median NT-proBNP levels similar to those in patients with decreased exercise capacity. Additional peak oxygen uptake measurements were obtained in 42 patients. Median VO_{2max} was 76.5 [IQR 69.8 – 88.0] % of predicted. All patients reached an RER quotient of >1.0 (median 1.37 [IQR 1.25 – 1.47]). No significant association between NT-proBNP levels and VO_{2max} was observed. RER quotient was significantly lower in patients with elevated NT-proBNP (Table 2).

Discussion

In adults with tetralogy of Fallot late after corrective surgery NT-proBNP levels were elevated in over 50% of patients, although 89% of these patients were asymptomatic. Since higher NT-proBNP was associated with ventricular dysfunction, the biomarker could be of additive value for the detection of deteriorat-ing cardiac function. NT-proBNP correlated with systolic RV function, but more strongly with systolic LV function and dimensions. This may indicate the importance of LV dysfunction in patients with ToF, or possibly NT-proBNP release of the RV is in general less than the LV. Also a clear relationship with elevated pulmonary pressures was found, while no clear relation with severity of pulmonary regurgitation was observed. The higher NT-proBNP levels in women confirm the previously described sex-differences for NT-proBNP in the general population by Luchner et al.[22] The higher NT-proBNP levels in women and older patients underscore the need for sex and age-specific reference values for diagnostic purposes. The finding that half of the patients with ToF had elevated NT-proBNP possibly indicates the need for ToF-specific cut off-points to predict adverse outcome, or may indicate the presence of sub-clinical pathology, where NT-proBNP can be an early marker of further deterioration in ventricular function. This remains to be investigated with follow-up data.

NT-proBNP and echocardiographic parameters

The finding that higher NT-proBNP levels were associated with lower LV ejection fraction, is in line with similar findings in patients with acquired LV systolic dysfunction[23] and emphasizes the use of NT-proBNP as an additional tool for monitoring of LV dysfunction in ToF patients. Recent studies show that one out of five adult patients with corrected ToF develops LV dysfunction.[8] LV dysfunction could be caused by direct influences of longstanding cyanosis before corrective surgery, consistent with our finding of higher NT-proBNP levels in patients that underwent corrective surgery at older age. Also deterioration of RV function due to pressure and volume overload of the RV could be a cause of diminished LV function, because of adverse ventricular-ventricular interaction.[7] In children with corrected ToF, the relationship

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between NT-proBNP and LV function is not observed, presumably because LV function in these children is generally still normal.[24] Nevertheless, in adults with corrected ToF it seems that NT-proBNP is of additional value to detect deterioration in LV function. Perhaps NT-proBNP levels rise before echocardiographic signs of LV dysfunction become apparent, which provides the possibility for early detection and treatment, but this remains to be established in a prospective study.

NT-proBNP was also strongly related to peak velocities of tricuspid and pulmonary valve regurgitation, also after adjustment for the presence of pulmonary valve stenosis. These results are in line with the findings by Norozi et al[25] and confirm that higher natriuretic peptide levels are associated with higher pulmonary pressures in patients with corrected ToF. Elevated pulmonary pressures are associated with adverse outcome, and therefore the association between NT-proBNP and pulmonary pressures may indicate a possible prognostic role of NT-proBNP. Higher pulmonary pressures may have been a result of left-sided cardiac problems, or possibly an oversized prior palliative shunt at young age may have led to increased pulmonary arterial wall resistance. Since pulmonary wedge pressures were not available in our study, the exact mechanism behind these findings needs further investigation.

In our patients, the relationship between NT-proBNP and RV dilatation was stronger than the relationship between NT-proBNP and RV systolic function, which is confirmed by several other reports that describe NT-proBNP in patients with ToF.[26,27] The modest association between NT-proBNP and RV systolic function may be underestimated due to difficulties in RV function assessment. Although we have used all available new diagnostic methods, the currently used imaging techniques remain to have limitations regarding adequate quantification of systolic function due to the complex RV morphology. The relationship between NT-proBNP and RV dilatation is in line with the relationship between NT-proBNP and severity of TR, since a dilated RV annulus will be accompanied by more severe TR. RV dilatation is caused primarily by volume overload due to longstanding pulmonary regurgitation. Interestingly, NT-proBNP levels were elevated regardless of PR severity and independent of prior PVR. Although further enlargement of the RV can be prevented by PVR,[28] the optimal timing of surgical PVR remains challenging. Because NT-proBNP is positively correlated with RV dimension and function, NT-proBNP may be helpful as an additional tool in decision-making on PVR in individual patients. Possibly, the level of NT-proBNP and its changes over time are early signs of RV dysfunction and can differentiate between well-tolerated PR and PR needing reintervention. Whether higher NT-proBNP levels can mark the need for pulmonary valve intervention in ToF patients with a dilated RV needs to be determined.

NT-proBNP levels were higher in patients with more severe TR and larger atria. This supports the idea that NT-proBNP is secreted not only from the ventricles, but also from atrial cardiomyocytes and atrial granules in which NT-proBNP is stored.[29] Elevated intra-atrial pressure and stretching of the atrial wall due to volume overload will stimulate NT-proBNP release. This could also explain why AF is associated with higher NT-proBNP, since patients with enlarged atria are more prone to develop AF and AF itself can lead to further enlargement of the atria.[30] As only a few patients in our study were in AF it was not possible to evaluate the direct influence of AF on NT-proBNP adjusted for presence of atrial dilatation.

NT-proBNP and speckle-tracking echocardiography

NT-proBNP levels were highest in patients with an abnormal LV twist. This finding was also seen in a study by Mornos et al, which investigated patients with reduced LVEF.[31] The correlation between this new echocardiographic technique and NT-proBNP is promising because both techniques might be able to detect changes in cardiac function earlier than currently used tests, such as conventional echocardiography or cardiac magnetic resonance imaging (CMR). As knowledge of speckle-tracking echocardiography in adult congenital heart disease including tetralogy of Fallot is still limited,[32,33] further research in this field is clearly warranted. Also newer modalities in CMR imaging, using gadolinium or CMR-feature tracking could contribute to establishing early markers for deterioration.

NT-proBNP and exercise capacity

Among the 68 patients that underwent bicycle ergometry, we observed no correlation between NT-proBNP and exercise capacity and VO_{2max}. Although higher NT-proBNP is associated with decreased exercise capacity and VO_{2max} in adult ConHD in general,[13] results for Fallot patients in previous studies are contradicting. Possibly our patient population was too small to demonstrate a relationship, whereas Norozi et al did find a significant correlations between NT-proBNP and $VO2_{max}$[25] in adults with corrected ToF. However, since the results of Koch and colleagues are comparable to our results, the exact relationship between exercise capacity and NT-proBNP in these patients is still unclear. As decreased exercise capacity is a known determinant of less favourable prognosis in patients with ConHD,[34] the relationship with NT-proBNP has to be studied in a larger cohort of ToF patients.

Study limitations and future perspectives

Magnetic resonance imaging is the gold standard for precise determination of ejection fraction and ventricular volumes. Nevertheless, echocardiography is a well-established and the most widely used imaging tool, thus the observed significant correlations between echo measurements and NT-proBNP are of great value.

    This study was a single-centre study and its cross-sectional design did not make it possible to determine the prognostic value of NT-proBNP. The higher NT-proBNP levels in female patients and increase of NT-proBNP with age do indicate the need for gender and age-specific reference values.

Conclusion

NT-proBNP levels are elevated in more than 50% of the adults with corrected ToF, while they are in a stable clinical condition. Higher NT-proBNP levels are most strongly associated with elevated pulmonary pressures, and left ventricular dysfunction rather than with right ventricular dysfunction. NT-proBNP has the potential to become a routine investigation in patients with ToF to monitor ventricular function and

may be used for timely detection of clinical deterioration. The positive correlations between NT-proBNP and RV dilation and dysfunction indicate that there may be a possible future role for NT-proBNP in the difficult decision of reintervention in patients with corrected ToF.

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Chapter 7

Association between N-terminal pro-brain natriuretic peptide and quality of life in adult patients with congenital heart disease

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Abstract

Aims

Advances in medical treatment have resulted in increased life expectancy in congenital heart disease. Consequently, the focus of management has shifted from reducing mortality to reducing long-term morbidity with the goal of improving quality of life. A predictor of quality of life might be N-terminal pro-brain natriuretic peptide, a well-established marker for heart failure. We aimed to determine the association between N-terminal pro-brain natriuretic peptide and quality of life in patients with congenital heart disease.

Methods

We collected blood samples from consecutive patients who were initially operated between 1968 and 1980 (47.8% women; mean age 40.2±5.4 years). The 36-item Short-Form Health Survey was completed to assess subjective health status as measure of quality of life. Analysis was performed for the entire group and for subgroups defined as simple versus complex congenital heart diseases. Median N-terminal pro-brain natriuretic peptide level was 15.2 pmol/L (overall range 1.3–299.3 pmol/L). N-terminal pro-brain natriuretic peptide levels were associated with the subdomain physical functioning (β-0.074, p=0.031). This association remained significant after adjustment for age and sex (β-0.071, p=0.038) and after adjustment for age, sex, BMI, left ventricular function and renal function (β-0.069, p=0.048). In complex congenital heart disease, the association between N-terminal pro-brain natriuretic peptide and physical functioning remained significant in multivariable analysis (β-0.076, p=0.046). No associations were found in the simple congenital heart disease group or on the other health status subdomains.

Conclusion

In adults operated for congenital heart disease, N-terminal pro-brain natriuretic peptide is associated with the subdomain physical, primarily in the complex subgroup.

Introduction

The last decades, the many advances in the medical care of patients with congenital heart disease have resulted in an increased survival. Due to this, the prevalence of adults living with congenital heart disease is increasing. This population is estimated to increase by 5% per year and currently consists of more adults than children.[1] The focus of attention has shifted from pure survival to long-term morbidity, quality of life and their determinants.

Several studies have reported on the short- and long-term outcome of quality of life in congenital heart disease patients. Although some studies reported impairments of specific quality of life scales, other studies indicated that overall quality of life was comparable to that seen in the general population.[2, 3] A study by Moons et al.[4] showed even better scores in congenital heart disease than the general population. Diminished quality of life has also been reported, especially in the domain of physical functioning.[5-7]

The use of biomarkers in congenital heart disease is gaining more attention with brain natriuretic peptide and N-terminal pro–B type natriuretic peptide being the most prominent biomarkers. These objective markers have shown to be of diagnostic and prognostic value since they are related to severity and prognosis in patients with heart failure due to acquired heart disease. [8-11] In two recent systematic reviews by Eindhoven et al.[12, 13] an overall increase in brain natriuretic peptide levels was seen in more complex congenital heart disease. Unfortunately, the prognostic value of individual brain natriuretic peptide levels is still under debate, because differences exist between types of congenital heart disease and lack of prospective studies.

Until now, little is known about the relationship between objective measurement of brain natriuretic peptide levels and subjective measurement of quality of life in patients with congenital heart disease. Prior research on brain natriuretic peptide levels and quality of life in patients with congestive heart failure showed no correlation.[14] Hence, both markers seem to have independent value in evaluating present clinical status and in predicting long-term functioning.

In this study, our aim was to assess the cross-sectional association between N-terminal pro-brain natriuretic peptide levels and subjective quality of life as measured with the Short-Form Health Survey-36, a generic health status questionnaire, in a cohort of patients with congenital heart disease.

Materials and methods

Inclusion criteria

Patients who had undergone corrective open-heart surgery between 1968 and 1980 were enrolled in the study. This included all consecutive patients who underwent corrective open-heart surgery for atrial septal defect, ventricular septal defect, pulmonary stenosis, tetralogy of Fallot or transposition of the great arteries in the Erasmus Medical Center and were younger than 15 years at the time of surgery.

Previous follow-up investigations on this cohort were undertaken in 1990/1991 and in 2000/2001. Patients' baseline characteristics, medical and psychosocial results have been reported in detail previously.[15, 16]

The target population of our third follow-up, conducted in 2010 and 2011, consisted of the 412 patients who participated in the previous two follow-ups. We excluded 39 patients, of whom 10 had died - causes: six cardiovascular, three unknown, and one accident, one had undergone heart transplantation, and 28 patients were lost to follow-up. Of the 373 eligible patients, 102 refused to participate in this third follow-up due to practical reasons, such as work, distance to hospital, resulting in a response rate of 73%.

Patients were approached uniformly and invited to visit the hospital for extensive cardiac and psychological examination. A cardiologist performed cardiac and medical examination during their visit. The health status questionnaire was completed during the hospital visit. Owing to practical reasons - work, children - 20 patients completed the questionnaires at home. If patients had trouble reading or understanding, the questionnaire was administered verbally.

Laboratory testing

After at least 30 minutes of rest, peripheral venous blood samples were obtained from all participants. Plasma and serum were separated immediately after blood sample collection and N-terminal pro-brain natriuretic peptide and creatinine levels were measured. N-terminal pro-brain natriuretic peptide levels were determined using the Elecsys system (Roche Diagnostics, Basel, Switzerland). The Elecsys system cut-off value of normal N-terminal pro-brain natriuretic peptide level is ≤14 pmol/L.

Subjective health status

Health status was assessed using the 36-item Short Form Health Survey.[17] The 36-item survey consists of 36 items with standardised response choices that contribute to eight health status domains, that is, physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health. Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores, and then transforming the raw scores to a scale from 0 to 100.[17] A higher score on the 36-item survey sub domains represents better functioning. A high score on the bodily pain scale indicates freedom from pain. Previous use of the Dutch version of the 36-item survey has shown good reliability and validity.[18]

Informed consent

The research protocol was approved by the institutional ethics committee and complies with the 1975 Declaration of Helsinki. Before participating, all patients signed informed consent.

Statistical analysis

Baseline characteristics of the study population are presented as proportions for categorical variables and as means ± standard deviations for continuous variables. Patients were analysed as a total sample and as subgroups. Patients with corrected atrial septal defect, ventricular septal defect and pulmonary stenosis were classified as simple congenital heart disease - unless they had complications such as severe ventricular dysfunction - whereas patients with tetralogy of Fallot or transposition of the great arteries (Mustard repair) were classified as moderate to complex congenital heart disease.[19] Group differences were examined using the Chi-square test (Fisher's exact test if appropriate) for nominal variables, while one-way ANOVA was used for continuous variables. Univariable linear regression models were used to examine the association between continuous N-terminal pro-brain natriuretic peptide levels and continuous 36-item survey scores.

Multivariable models were used to correct for potential confounder effects of N-terminal pro-brain natriuretic peptide level, such as age, sex, body mass index, renal function, and left ventricular function. Owing to small numbers, multivariable models for subgroups were limited to adjust for age and sex. Two-dimensional echocardiography was used to assess left ventricular function - for patients with transposition of the great arteries, this was the systemic right ventricle - with "eyeballing", which was categorized into good, reasonable, moderate or poor functioning. All statistical analyses were performed using SPSS for Windows 20.0 (SPSS Inc., Chicago, Illinois, USA).

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Results

Patient population

Of the 271 eligible patients in this third quality of life cohort, 20 patients had no N-terminal pro-brain natriuretic peptide measurements due to practical reasons - filled in questionnaires at home - and were excluded from further analysis. There was one patient who visited the outpatient clinic who refused blood sampling. Of the remaining 250 patients, five questionnaires were excluded because of incomplete answers – three because of mental retardation and two refused. Therefore, the final analyses were performed on 245 patients (47.8% female; mean age 40.2± 5.4 years, range [30-56] years). In Table 1, the median N-terminal pro-brain natriuretic peptide and the mean 36-item survey scores are presented. Patients with complex disease were younger, had a worse left ventricular function, higher N-terminal pro-brain natriuretic peptide levels and lower 36-item survey scores on physical functioning and general health (Table 1).

N-terminal pro-brain natriuretic peptide and health status in all congenital heart disease

Univariable regression analyses with N-terminal pro-brain natriuretic peptide were executed for each of the eight health status subdomains. N-terminal pro-brain natriuretic peptide levels showed a significant inverse association with the subdomain physical functioning (β= -0.74, p=0.031), whereas no significant

TABLE 1. Baseline characteristics

	Total sample (n=245)	Simple (n=164)	Moderate/Complex (n= 81)	p-value
Age, years	40.2 ± 5.4	41.0 ± 5.3	38.4 ± 5	**<0.001**
Gender, female (%)	47.8	51.2	40.7	
Body mass index, kg/m^2	25.3 ± 4.5	25.4 ± 3.5	25.2 ± 4.4	0.718
ConHD (%)				
- ASD	27.8	41.5	--	
- VSD	27.8	41.5	--	
- PS	11.4	17.1	--	
- TOF	21.2	--	64.2	
- TGA	11.8	--	35.8	
Creatinin (µmol/L)	74.9 ± 14.7	75 ± 14.2	74.7 ± 16.0	0.902
LV function (%) *				<0.001
- good	73.2	85.4	52.3	
- mildly impaired	23.8	12.6	43.2	
- moderately impaired	0.4	0.7	0	
- severely impaired	2.5	1.3	4.5	
Residual lesions (n)**	20	0	20	
NT-proBNP (pmol/L)	15.2[1.3-299.3]	13.1[1.3-116.1]	23.4[2.8-299.3]	**<0.001**
SF-36 scores:				
- Physical functioning	89.3 ± 16.7	90.0 ± 16.4	86.0 ± 17.0	**0.028**
- Role physical functioning	89.5 ± 25.8	90.1 ± 25.8	88.4 ± 26.1	0.640
- Bodily pain	84.6 ± 20.9	83.7 ± 22.1	86.5 ± 26.1	0.334
- Social functioning	92.1 ± 16.4	91.3 ± 17.6	93.5 ± 13.9	0.330
- Mental health	82.8 ± 14.5	83.4 ± 13.4	81.7 ± 16.5	0.386
- Role emotional functioning	91.5 ± 24.3	91.1 ± 24.5	92.4 ± 23.8	0.686
- Vitality	72.6 ± 19.7	72.8 ± 19.6	72.3 ± 20.1	0.869
- General Health	73.0 ± 21.4	75.9 ± 22.1	67.2 ± 18.3	**0.002**

Values are presented as mean ± sd., median [range] or percentages.
* Echocardiography was performed in 255/245 (92%) patients
** Baffle leakage (n=1), baffle obstruction (n=8), moderate/severe tricuspid regurgitation (n=16), moderate/severe pulmonary stenosis (n=11).
ConHD=congenital heart disease; ASD=atrial septal defect; VSD=ventricular septal defect;
PS = pulmonary stenosis; TOF = tetralogy of fallot; TGA =transposition of the great arteries;
LVF = left ventricular function; NT-proBNP = N-terminal pro-brain natriuretic peptide;
SF-36 = 36-item short form health survey

association was found in the other seven subdomains (Table 2). This association with physical functioning remained significant after adjusting for age and sex (β= -0.070, p=0.038) and age, sex, body mass index, left ventricular function and renal function (β= -0.069, p=0.048).

TABLE 2. Association between NT-proBNP and SF-36 domains in all ConHD patients

	Univariable analysis		Multivariable analysis*		Multivariable analysis**	
	β	*p*-value	β	*p*-value	β	p-value
SF-36 subdomains						
Physical functioning	-0.074	**0.031**	-0.070	**0.038**	-0.069	**0.048**
Role physical functioning	0.280	0.665	0.052	0.412	0.049	0.428
Bodily pain	0.067	0.117	0.064	0.131	0.075	0.113
Social functioning	0.007	0.824	0.009	0.785	0.015	0.673
Mental health	0.018	0.536	0.019	0.644	0.010	0.774
Role emotional functioning	0.003	0.955	0.020	0.735	0.009	0.892
Vitality	0.029	0.471	0.038	0.344	0.052	0.241
General health	-0.067	0.122	-0.063	0.153	-0.049	0.311

* adjusted for age and sex; **adjusted for age, sex, BMI, LV function and renal function.

Simple versus complex congenital heart disease

In a second model, the eight health status subdomains were analysed separately for type of congenital heart disease - simple versus complex. In univariable analysis, no association was seen between N-terminal pro-brain natriuretic peptide levels and the eight subdomains in both the simple and the complex congenital heart disease groups. After adjusting for the socio-demographics age and sex, a significant inverse association with physical function was found (β -0.076, p=0.046; Table 3) in the complex group, whereas no significant relation was seen on the other seven subdomains. The subdomains in the simple group showed no relation with N-terminal pro-brain natriuretic peptide (Table 3*)*.

TABLE 3 Association between NT-proBNP and SF-36 subdomains in ConHD subgroups

	Simple				Complex			
	Univariable analysis		Multivariable analysis*		Univariable analysis		Multivariable analysis*	
	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
SF-36 subdomains								
Physical functioning	0.038	0.678	0.096	0.307	−0.072	0.064	−0.076	**0.046**
Role physical functioning	0.127	0.380	0.179	0.226	0.017	0.826	0.034	0.660
Bodily pain	0.038	0.762	0.095	0.452	0.064	0.133	0.060	0.158
Social functioning	0.016	0.875	0.069	0.497	−0.006	0.864	−0.004	0.901
Mental health	−0.02	0.984	0.046	0.549	0.034	0.381	0.032	0.415
Role physical emotional	0.090	0.511	0.159	0.261	−0.030	0.672	−0.017	0.813
Vitality	0.20	0.867	0.098	0.381	0.036	0.435	0.039	0.412
General health	0.033	0.791	0.073	0.569	−0.42	0.335	−0.041	0.358

* adjusted for age and sex

Discussion

The relationship between biomarkers and quality of life in congenital heart disease patients is not well known. This is the first study that focused on the relationship between N-terminal pro-brain natriuretic peptide levels and quality of life in the specific population. Previous studies have mainly been conducted in patients with congestive heart failure, where N-terminal pro-brain natriuretic peptide already is an established marker of prognosis and severity of disease. Our results show that higher levels of N-terminal pro-brain natriuretic peptide are associated with lower scores on the 36-item survey on the subdomain physical functioning, but not with the other seven subjective health domains. In addition, we showed that this relation was found only in complex congenital heart disease patients, but not in simple congenital heart disease.

The general assumption that congenital heart disease patients have lower quality of life is a misconception for patients who underwent repair of their congenital heart disease. However, this is not true for patients who could only be palliated. Several studies have found an equivalent or even better subjective health status in patients who have undergone repair, as compared with healthy counterparts.[2-4] However, in patients who had merely palliative surgery, a diminished psychosocial outcome has been found.[20] Objective measures most often relate to severity of disease, although results differ among the various types of congenital heart disease.[6,19]

However, the severity of disease does not necessarily reflect lower quality of life scores.[21] The contradictory results found on quality of life scores could be attributed to different outcomes used and methodological flaws.[22]

Some studies report that physical limitations will not be reflected on generic health status questionnaires. A study by Kamphuis et al.[6] showed a weak correlation between objective physical indices and related domains of subjective health status and health-related quality of life. Limited exercise capacity usually does not hamper patients with congenital heart disease in their daily activities, and rigorous activities are most often not undertaken.[23] It seems that most of the congenital heart disease patients learn to cope with their physical limitations and, if present, adapt their way of living and expectations.

It is evident that more complex congenital heart disease results in lower performance on exercise capacity.[24] Negative correlations between plasma brain natriuretic peptide levels and exercise testing have been reported. Trojnarska et al.[25] showed a negative correlation between brain natriuretic peptide and oxygen uptake during cardiopulmonary testing in a heterogeneous group of congenital heart disease patients. These results were consistent in other reports.[26, 27] In addition, when a 6-minute walk test was conducted, a negative correlation between N-terminal pro-brain natriuretic peptide levels and 6-minute walking distance was observed.[28] Not all studies support these results, as in Fontan patients no direct relation was observed between brain natriuretic peptide levels and exercise capacity by peak oxygen consumption.[29, 30] A possible direct association between increase in plasma brain natriuretic peptide levels and decrease in exercise capacity has never been supported by reports. Although in most congenital heart disease patients diminished physical functioning is not reflected on overall generic quality of life scores. It could be helpful to pay attention specifically to the physical functioning subscale

(subdomain). Both elevated levels of brain natriuretic peptide and diminished physical functioning should trigger clinical awareness on possible early deterioration of patients' cardiac function and further evaluation of exercise performance can be considered.

A previous study in patients with heart failure showed no relationship between N-terminal pro-brain natriuretic peptide changes over time and short-term changes in health status.[14] Furthermore, a report by Hogenhuis et al.[31] demonstrated that N-terminal pro-brain natriuretic peptide levels correlate more with cardiac function than parameters that reflect physical functioning on quality of life scales. Hence, previous results on the relation between quality of life and brain natriuretic peptide are scarce. No firm conclusions can be drawn when comparing these results to other cardiac diseases.

The use of biomarkers is still limited in congenital heart disease. Whereas elevated levels of N-terminal pro-brain natriuretic peptide correlate with long-term functioning and mortality in heart failure patients, not many long-term (prospective) studies have been conducted in congenital heart disease patients. The systematic reviews by Eindhoven et al.[12, 13] give a clear picture of the evidence until now. The use of the biomarkers is most often limited to short-term changes – that is, peri-operative - and most studies were not designed to evaluate natriuretic peptides. Therefore, our finding that N-terminal pro-brain natriuretic peptide is related to physical functioning is of interest and a first step in this field, which has yet to be explored. It is evident that larger, prospective studies are needed to evaluate the use and predictive value of biomarkers in congenital heart disease.

A first limitation of this study is the small number of patients per diagnosis in the current study sample. Recent studies have clearly shown that N-terminal pro-brain natriuretic peptide levels differ between types of congenital heart disease.[32,33] Therefore, conclusions in subgroup analyses should be drawn with caution. A second limitation is the cross-sectional design. Prospective results, especially long-term, could give a better understanding of changes in both N-terminal pro-brain natriuretic peptide levels and quality of life in congenital heart disease patients. Third, outcomes of this cohort of relatively older patients, all operated before 1980, may not be generalizable to the current population of congenital heart disease patients undergoing cardiac surgery. Medical treatment and support has drastically changed over the past decades with improved outcomes.

Conclusion

In conclusion, the current study shows an association between cross-sectionally assessed N-terminal pro-brain natriuretic peptide levels and Quality of Life (assessed with a generic health status questionnaire) on the subdomain physical functioning, predominantly in complex congenital heart disease patients. No association was found between N-terminal pro-brain natriuretic peptide and the 7 other subdomains.

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7

Chapter 8

High-sensitive troponin-T in adult congenital heart disease

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Abstract

Background

Adult congenital heart disease (ACHD) patients are at risk of late complications including arrhythmias, heart failure and sudden death. High-sensitive troponin-T (hs-TnT) is the standard for diagnosing acute coronary syndrome, but is also associated with cardiac function and prognosis in other cardiac diseases.

Objectives

To describe hs-TnT levels in ACHD patients, and determine their relationship with cardiac function and other biomarkers.

Methods

Consecutive ACHD patients, visiting the outpatient clinic, underwent echocardiography, exercise testing and venipuncture on the same day.

Results

In total 587 patients were included (median age 33[IQR 25-41] years, 58% male, 90% NYHA class I). Hs-TnT was above the detection limit of 5 ng/L in 241 patients (41%), of whom 47 (8%) had hs-TnT levels above the 99th percentile of normal. Hs-TnT levels were highest in patients with a systemic RV or pulmonary hypertension. Patients with non-elevated hs-TnT were younger   (32[IQR 24-40] versus 42[IQR 36-60] years, $p<0.001$). Hs-TnT was higher in men (<5[IQR <5-7.8] ng/L) than women (<5[IQR <5-6.0], $p<0.001$). The prevalence of hs-TnT ≥14 ng/L was higher in patients with NYHA≥II (36%, $p<0.001$), systemic systolic dysfunction (38%, $p<0.001$), non-sinus rhythm (43%, $p<0.001$) and elevated pulmonary pressures (39%, $p<0.001$). Hs-TnT correlated with NT-proBNP (r=0.400, $p<0.001$).

Conclusions

Hs-TnT above the 99th percentile of normal is observed in a non-trivial portion of stable ACHD patients, especially in those with a systemic RV or elevated pulmonary pressures. Since this biomarker of myocardial damage is related to NT-proBNP and ventricular function in ACHD patients, its potential predictive value seems promising and further investigation of underlying mechanisms is warranted.

Introduction

As a result of successes in cardiac surgical and clinical care the number of adults with congenital heart disease (ACHD) is increasing rapidly.[1,2] The growing ACHD population entails a large number of patients who will develop late complications including arrhythmias, cardiac dysfunction, heart failure or sudden death.[1]

Cardiac troponin-T is mostly known for its important diagnostic and prognostic value in acute coronary syndromes, as it is a specific marker for cardiomyocyte injury.[3] With the recent introduction of high-sensitive assays for cardiac troponin-T,[4] smaller amounts of cardiomyocyte damage became detectable in various other cardiac conditions, including hypertension,[5] hypertrophic cardiomyopathy,[6] acute and chronic heart failure.[7] High-sensitive troponin-T (hs-TnT) improves risk stratification and is associated with adverse outcome in various cardiac diseases.[8, 9] Troponin release is reported in one selected subgroup of children with congenital heart disease, but information on expression of hs-TnT in ACHD is lacking.[10]

Based on previous studies, N-terminal pro-B-type natriuretic peptide (NT-proBNP), a well-established heart failure biomarker, may carry incremental diagnostic and prognostic value in ACHD.[11, 12] High-sensitive C-reactive protein (hs-CRP) may also have a role. Likewise, the novel biomarker hs-TnT could provide more detailed information about pathophysiological aspects and early detection of cardiac dysfunction in ACHD patients, either alone or in combination with other biomarkers.

We sought to describe levels of hs-TnT in ACHD patients and assess their relationship with cardiac function parameters derived from echocardiography, exercise testing, as well as hs-CRP and NT-proBNP.

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Methods

Patient inclusion

Between May 2011 and April 2013 all consecutive patients that visited the ACHD outpatient clinic of Erasmus MC were approached to participate in this study. The following congenital cardiac diagnoses were included: valvular aortic stenosis (AoS), aortic coarctation (CoA), corrected tetralogy of Fallot (ToF) (including patients with pulmonary valve atresia and ventricular septal defect (VSD)), transposition of the great arteries (TGA) operated by arterial switch procedure (TGA-ASO) or by Mustard procedure (TGA-Mustard), congenitally corrected TGA (ccTGA), complex TGA with VSD or double-outlet right ventricle corrected by Rastelli or reparation à l'étage ventriculaire procedure (Rastelli/REV), univentricular hearts corrected by Fontan procedure (Fontan), or pulmonary hypertension after an (corrected) ASD or VSD (PH). Patients were excluded if they were aged <18 years, or had severe renal dysfunction defined as creatinine of >200μmol/L.

The study was carried out according to the principles of the Declaration of Helsinki. The study protocol was approved by the institutional medical ethics committee. Written informed consent was obtained from all participating patients.

Data collection

At day of inclusion, patients visited the cardiologist, underwent extensive two-dimensional-echocardiography, and venous blood samples were taken. A subset of patients underwent bicycle ergometry. Patient characteristics were collected: age, sex, congenital diagnosis, prior interventions, New York Heart Association (NYHA) class, blood pressure, heart rate, body mass index (BMI), body surface area (BSA), and oxygen saturation.

Echocardiography

Two-dimensional greyscale harmonic images were obtained using a commercially available iE33 ultrasound system (Philips Medical Systems, Best, the Netherlands), equipped with a transthoracic broadband S5-1 (1 – 5 MHz) or X5-1 matrix transducer (composed of 3040 elements, with 1-5 MHz extended operating frequency range). We measured dimensions of the left ventricle (LV)(parasternal long-axis end-diastolic and end-systolic diameter), right ventricle (RV) (apical 4-chamber annulus and apex-base diameter), and left atrium (LA)(apical 4-chamber longitudinal and transversal diameter) according to the current ASE/EAE guidelines.[13] Chamber dimensions were corrected for BSA. Left ventricular systolic function was assessed visually and graded as normal, mildly, moderately, or severely impaired. Left ventricular ejection fraction (EF) was measured using the modified Simpson's rule.[13] Right ventricular systolic function was assessed visually, and quantified with RV fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). In patients with a morphologic RV in the subaortic position, visual assessment, RV FAC and TAPSE were used to assess systemic (right) ventricular function. Diastolic function of the systemic ventricle was assessed with use of pulsed wave Doppler imaging of the mitral or tricuspid valve inflow, respectively, from which E, A, E/A ratio and deceleration time was retrieved. Pulmonary arterial pressures were defined 'elevated' when early diastolic pulmonary regurgitation flow velocity was >2.5 m/s or, in absence of right ventricular outflow tract obstruction, tricuspid regurgitation flow velocity of >3.0 m/s. In patients with TGA-Mustard, left ventricular outflow tract obstruction and mitral regurgitation flow velocity were used.

Laboratory testing

Peripheral venous blood samples were taken after at least 30 minutes of rest. Blood samples were stored at -80°C within 2 hours. We assessed creatinine and hemoglobin levels. Concentrations of serum hs-TnT, hs-CRP and NT-proBNP were determined by electrochemiluminesence immunoassays (Roche Diagnostics, Basel, Switzerland). Lower limits of detection were 5 ng/L for hs-TnT and 0.3 mg/L for hs-CRP. The cut-off values for normal, i.e. 99th percentile of reference distribution, of the assays were 14 ng/L for hs-TnT, 5 mg/L for hs-CRP and 14 pmol/L for NT-proBNP.

Exercise testing

As part of their routine follow-up, several patients underwent bicycle ergometry on the same day as the venipuncture and echocardiogram. According to the standard protocol, workload increased gradually with 20 watt/minute. We collected information on maximal exercise capacity in these patients, and compared their results with healthy controls of similar age, sex, body height and length.

Statistical analysis

Continuous variables are presented as mean±standard deviation (SD), or median and interquartile range (IQR). Categorical variables are presented as frequencies. Patients were classified according to their hs-TnT level: below the detection limit (<5 ng/L), detectable but normal (5-13.9 ng/L), or elevated (≥14 ng/L). Differences in continuous data between these categories were evaluated by ANOVA or Kruskal-Wallis tests, whereas differences in categorical data were evaluated by χ^2-tests or Fisher's exact tests. Analyses of covariance (ANCOVA) were applied to study differences in echocardiographic parameters between the three categories, while adjusting for potential confounders (age, sex and NYHA class). Correlations between hs-TnT and NT-proBNP and hs-CRP were assessed by Spearman's rank correlation. Values below the limit of detection of hs-TnT and hs-CRP were transformed to 50% of the lowest value: 2.5 ng/L for hs-TnT and 0.15 mg/L for hs-CRP.

Multivariate logistic regression analyses were performed to determine the relationship between hs-TnT (<14 vs. ≥14 ng/L), NT-proBNP (<14 vs. ≥14 pmol/L) and hs-CRP (<5 vs. ≥5 mg/L) as determinants of NYHA class, systemic ventricular function and rhythm, adjusted for age and sex.

All tests were two-sided and a *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

Baseline characteristics of the 587 included patients are summarized in Table 1. The largest diagnostic groups were ToF (n=174) and congenital AoS (n=140). PH patients (n=7) comprised patients with PH after atrial septal defect closure proven with cardiac catheterization (n=4) and patients with Eisenmenger syndrome (n=3). Median age was 33[IQR 25-41] years, 58% was male, and most patients were in NYHA class I (90%). Four patients (ToF (n=3), TGA-Mustard (n=1)) had undergone a percutaneous coronary intervention (PCI) in the past, and three patients (all AoS) had prior coronary bypass grafting (CABG). All patients had normal renal function (median creatinine level was 75[IQR 67-84] μmol/L) and none of the patients was anemic (median hemoglobin 9.3[IQR 8.6-9.8] mmol/L).

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TABLE 1. Baseline characteristics

	All patients	AoS	CoA	ToF	TGA-ASO	TGA-Mustard	ccTGA	Fontan	PH	Rastelli/REV
Number of patients	587	140	108	174	21	66	20	40	7	11
Age (years)	33[25-41]	33[25-43]	31[23-43]	34[26-44]	21[20-25]	34[31-38]	41[30-52]	26[21-34]	59[40-74]	25[21-30]
Male	341(58)	85(61)	58(54)	104(59)	10(48)	44(67)	13(65)	20(50)	0	8(73)
NYHA functional class:										
- I	527(90)	135(96)	107(99)	156(89)	21(100)	54(82)	17(85)	29(72)	1(13)	8(73)
- II	56(9)	4(3)	1(1)	18(10)	0	11(16)	3(15)	10(25)	6(75)	3(27)
- III	4(1)	1(1)	0	1(1)	0	1(2)	0	1(3)	0	0
Previous corrective surgery	514(87)	87(62)	105(95)	175(100)	21(100)	66(100)	7(35)	40(100)	3(43)	11(100)
Age at corrective surgery (years)	4[0.7-12]	23[15-33]	3[0-12]	3[1-7]	0.1[0-0.2]	0.7[0-2]	14[7-58]	5[3-8]	73[39-73]	2[2-5]
Body Mass Index (kg/m^2)	25±4	25±4	25±5	24±4	24±3	25±4	24±3	22±3	33±7	23±4
Systolic blood pressure (mmHg)	126±16	126±15	132±17	125±17	121±13	125±15	125±13	121±17	120±16	123±14
Diastolic blood pressure (mmHg)	79±12	80±11	80±11	78±12	73±11	79±12	78±10	76±12	69±13	74±13
Heart rate (beats per minute)	73±14	76±14	70±13	76±13	69±15	72±13	68±18	75±13	76±15	69±13
Oxygen saturation (%)	99[97-100]	99[98-100]	99[98-100]	99[97-100]	99[99-100]	97[95-99]	100[98-100]	94[90-97]	96[88-98]	99[96-100]
Electrocardiogram										
Rhythm:										
- Sinus rhythm	507(86)	133(95)	102(94)	146(84)	20(95)	51(77)	8(40)	33(82)	5(71)	10(9)
- Atrial fibrillation	15(3)	2(1)	2(2)	4(2)	0	2(3)	2(10)	1(3)	2(29)	0
- Paced rhythm	44(7)	5(4)	1(1)	16(9)	0	8(12)	9(45)	4(10)	0	1(9)
- Atrial/nodal rhythm	21(4)	0	3(3)	9(5)	1(5)	5(8)	1(5)	2(5)	0	0
QRS duration (milliseconds)	121±28	105±20	113±18	143±32	109±24	119±22	120±19	115±18	97±9	148±27
If QRS > 120 milliseconds:										
- RBBB	164(28)	6(4)	13(12)	108(62)	4(19)	21(32)	0	8(20)	0	5(46)
- LBBB	25(4)	4(3)	12(11)	2(1)	0	1(2)	2(10)	3(8)	0	1(9)
- NIVCD	38(6)	9(6)	8(7)	8(5)	3(14)	1(2)	2(10)	4(10)	0	3(27)

Values are presented as mean±sd, median[IQR] or n(%).
LBBB=left bundle branch block; NIVCD=non-specific intraventricular conduction delay; NYHA=New York Heart Association; RBBB=right bundle branch block;
Other abbreviations as mentioned previously.

Hs-TnT

Hs-TnT was above the detection limit of 5 ng/L in 241 patients (41%), of whom 47 (8%) had hs-TnT ≥14 ng/L, the 99th percentile of normal. In 8 patients (1%) hs-TnT was >50 ng/L. Elevated hs-TnT was observed mostly, though not exclusively, in patients with a systemic RV, i.e. TGA-Mustard and ccTGA, and in patients with PH (Figure 1). None of the patients with elevated hs-TnT had clinical signs or symptoms of angina, or ECG changes indicating acute cardiac ischemia. Of the 7 patients with known coronary artery disease (prior PCI or CABG) only one patient had elevated hs-TnT of 47.2 ng/L.
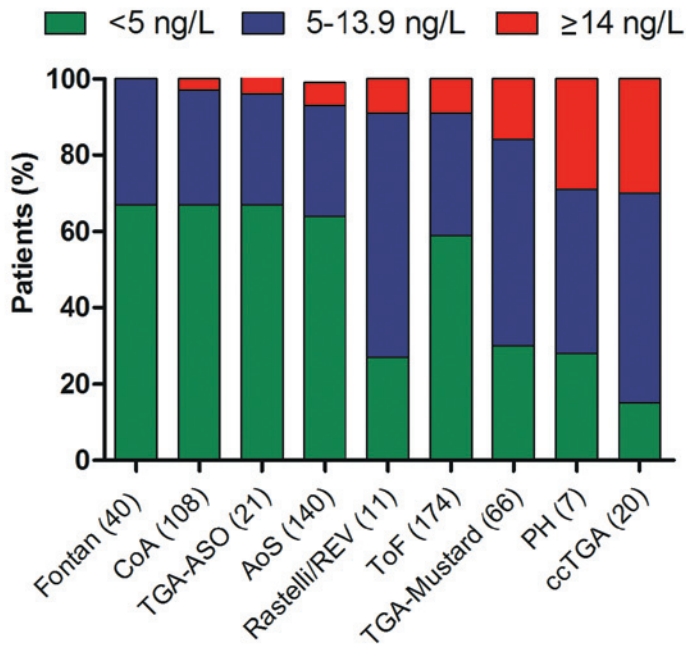
FIGURE 1. High-sensitive TnT levels for each type of congenital heart disease
Percentages of patients with non-detectable, detectable but normal, and elevated hs-TnT for each congenital diagnosis, sorted by percentages of elevated hs-TnT.

Hs-TnT and baseline characteristics

Patients with elevated hs-TnT were older, and more often in NYHA class ≥II (Table 2). Hs-TnT levels were significantly higher in men (median <5 [IQR <5-7.8] ng/L) than women (median <5 [IQR <5-6.0] ng/L, $p<0.001$). Oxygen saturation tended to be lower in patients with higher hs-TnT ($p=0.066$). Hs-TnT was not related to blood pressure or heart rate.

Hs-TnT levels were significantly lower in patients in sinus rhythm (<5 [IQR <5-6.7] ng/L) than in patients in atrial fibrillation (12.7[IQR 7.5-18.6] ng/L) or with a pacemaker rhythm (7.3 [IQR <5-13.9] ng/L,

p<0.001). Higher hs-TnT was associated with longer QRS duration, which remained significant after adjustment for age, sex and NYHA class (*p*<0.001).

TABLE 2. Hs-TnT and baseline characteristics

Number of patients	hs-TnT non-detectable (<5 ng/L) n=346	hs-TnT detectable, normal (5-13.9 ng/L) n=194	hs-TnT elevated (≥14 ng/L) n=47	*p*-value
Age (years)	30[23-38]	36[28-46]	42[36-60]	**<0.001**
Male	50%	71%	64%	**<0.001**
NYHA functional class ≥II	6%	11%	36%	**<0.001**
Systolic blood pressure (mmHg)	125±16	129±16	126±20	**0.017**
Oxygen saturation (%)	99[97-100]	98[97-100]	98[97-100]	0.296
Sinus rhythm	91%	85%	57%	**<0.001**
Heart rate (bpm)	74±13	72±14	74±15	0.104
QRS duration (milliseconds)	116±26	129±29	133±36	**<0.001**

Continuous variables as mean±sd or median[IQR].
Frequencies as percentage

Hs-TnT and echocardiography and exercise testing

After adjustment for age, sex and NYHA class, patients with elevated hs-TnT had significantly lower LV EF and RV FAC than patients with non-detectable or detectable normal hs-TnT (Table 3). Elevated hs-TnT levels were associated with larger LA dimension, RV annulus dimension and LV dimensions.

In patients with ToF, higher hs-TnT was associated with worse LV EF (*p*=0.017), but not with RV FAC (*p*=0.181), also after adjustment for age, sex and NYHA class. In patients with CoA higher hs-TnT was associated with larger LA dimension, larger LV end-diastolic dimension and increased posterior wall thickness. ACHD-specific associations between hs-TnT and echocardiographic parameters were observed (Online Supplementary Table A to E).

Thirty-three patients (6%) met the echocardiographic criteria for elevated pulmonary pressures. Estimated mean systolic pulmonary pressure in these patients was 67±20 mmHg. In total 40% of these patients had elevated hs-TnT. Median hs-TnT in these patients was higher than in patients with normal pulmonary pressures (11.2 [IQR 5.9-17.0] ng/L versus <5 [IQR <5-6.9] ng/L, *p*<0.001), which remained significant after adjustment for age, sex, and NYHA class.

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Bicycle ergometry was performed in 142 patients (24%). There was no significant relationship between hs-TnT and exercise capacity. Maximal workload and maximal heart rate were not associated with hs-TnT level.

TABLE 3. Hs-TnT and echocardiographic parameters adjusted for age, sex and NYHA functional class

	hs-TnT non-detectable (<5 ng/l)	hs-TnT detectable, normal (5-13.9 ng/l)	hs-TnT elevated (≥14 ng/l)	
Number of patients	n=346	n=194	n=47	*p*-value
Dimensions				
LA longitudinal dimension (mm)	54±8	57±9	64±12	**0.001**
LA transversal dimension (mm)	39±6	42±6	46±11	**0.009**
LV posterior wall (mm)	8.6±1.4	9.3±1.9	8.7±1.4	**0.031**
Interventricular septum (mm)	8.7±1.8	10.0±2.3	9.7±2.6	**0.003**
LV EDD/BSA (mm/m^2)	26±4	26±4	28±4	0.051
LV ESD/BSA (mm/m^2)	17±3	17±4	20±5	**0.015**
RV annulus/BSA (mm/m^2)	22±4	23±5	26±5	**0.001**
RV apex-base/BSA (mm/m^2)	45±5	45±5	47±6	**0.023**
Ventricular function				
LV ejection fraction (%)	55±8	56±8	47±11	**0.010**
RV fractional area change (%)	41±10	39±12	32±14	**0.004**
TAPSE (mm)	18±5	18±6	15±6	0.085
*Systemic diastolic function**				
E' (cm/sec)	8.7±2.5	7.5±2.6	6.9±2.6	**0.020**
E/A-ratio	1.7±0.7	1.6±0.6	1.5±0.7	0.387
E/E'	10.9±4.6	12.8±5.6	12.6±6.0	**0.005**

Continuous variables are presented as mean±sd
BSA=body surface area; EDD=end-diastolic diameter; ESD=end-systolic diameter; LA=left atrium;
LV=left ventricle; RV=right ventricle; TAPSE=tricuspid annular plane systolic excursion;
* Mitral valve inflow if systemic LV; tricuspid valve inflow if systemic RV

Hs-TnT and other cardiac biomarkers

Hs-TnT correlated with NT-proBNP, but not with hs-CRP (Figure 2). Both elevated hs-TnT and NT-proBNP were associated with the presence of systolic systemic ventricular dysfunction, worse NYHA class and loss of sinus rhythm (Table 4). The association of NT-proBNP with ventricular dysfunction appeared stronger than that of hs-TnT. Hs-CRP was not associated with NYHA class, ventricular function or ECG rhythm after adjustment for age, sex, hs-TnT and NT-proBNP.
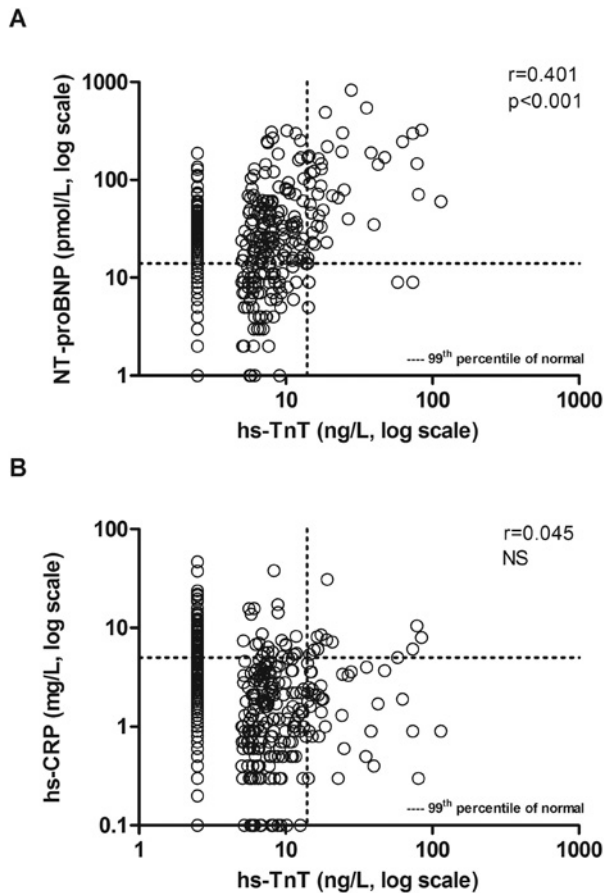
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FIGURE 2. High-sensitive TnT and the relationship with NT-proBNP and hs-CRP

TABLE 4. Associations of cardiac biomarkers with NYHA class, systolic dysfunction and loss of sinus rhythm

		total(n)	NYHA ≥II§		Systolic dysfunction§		Loss of sinus rhythm§	
			n(%)	OR [95%CI]	n(%)	OR [95%CI]	n(%)	OR [95%CI]
hs-TnT	<14 ng/L	540	43(8)	1	68(13)	1	60(11)	1
	≥14 ng/L	47	17(36)	3.46[1.62-7.37]†	18(38)	2.29[1.09-4.82]*	20(43)	3.04[1.48-6.24]
NT-proBNP	<14 pmol/L	273	9(3)	1	7(3)	1	13(5)	1
	≥14 pmol/L	309	51(17)	3.51[1.62-7.64]†	79(26)	16.92[7.40-38.69]‡	67(22)	3.56[1.84-6.88]‡
hs-CRP	<5 mg/L	491	43(9)	1	75(15)	1	64(13)	1
	≥5 mg/L	93	17(18)	1.82[0.94-3.55]	11(12)	0.57[0.28-1.20]	16(17)	1.03[0.54-1.97]

*$p<0.05$, † $p<0.01$, ‡ $p<0.001$
§ adjusted for age, sex, and the other two biomarkers

Discussion

This study demonstrates that hs-TnT is modestly elevated in almost 10% of stable ACHD patients in an outpatient-clinic setting during routine check-up. Elevated hs-TnT was most often observed in patients with a systemic RV or elevated pulmonary pressures. None of these patients was known with significant coronary artery disease or heart failure. Hs- TnT was associated with cardiac function and NYHA class, which indicates that it carries value to monitor cardiac function in ACHD patients, and also suggests that it may potentially predict clinical outcome in these patients.

Release of hs-TnT in patients with ACHD

With the introduction of the high-sensitive assays, levels of troponin T became detectable in an earlier stage of disease, and larger subset of patients. This study is the first to describe hs-TnT in a heterogeneous population of ACHD patients, and therefore the explanation of the mechanism behind the presence of detectable hs-TnT in these patients can only be speculative. Our ACHD population is probably best comparable to patients with acquired LV dysfunction, in whom causes of hs-TnT release are likely to be multifactorial, as is proposed for congestive heart failure.[14] In chronic heart failure detectable hs-TnT is found in nearly 100% of patients, with a significant majority above the 99th percentile.[15] A first attempt to unravel hs-TnT release in ACHD is proposed in Figure 3, summarizing potential etiologies, which are discussed hereafter.

The most important cause of troponin release is coronary ischemia, and type I myocardial infarction must always be considered.[14] Although type I myocardial infarction is less obvious in ACHD patients because of their relative young age, coronary artery disease will become increasingly important in this ageing population.[1] Nevertheless, only one of 7 patients in our study with known coronary artery disease treated previously with a PCI or CABG, had elevated hs-TnT, however, without complaints or ECG changes.

Another mechanism for troponin release could be oxygen supply-demand inequity causing subendocardial ischemia or even type II myocardial infarction. In patients with systemic RV, elevated hs-TnT could be the result of the single coronary artery supplying the systemic (right) ventricle with oxygen, which may be insufficient once this systemic RV becomes more hypertrophic or dilated. Both ventricular hypertrophy and increased LV mass have proven to be independent determinants of increased hs-TnT in the general population.[16] Reduced oxygen supply could also be caused by anemia or hypotension. However, at the time of their outpatient clinic visit, not one patient in our study was anemic or hypotensive.

Another cause of subendocardial ischemia, and necrosis or apoptosis, is chronic volume- and pressure-overload. This is seen with various severities in most congenital heart lesions, caused by varying hemodynamic mechanisms. The negative influences of prior cardiac surgery at young age, residual lesions and scarring may underlie chronic volume- and pressure-overload. The consequent increased myocardial-wall stress is known to be present, as is mirrored by increased natriuretic peptides in ACHD
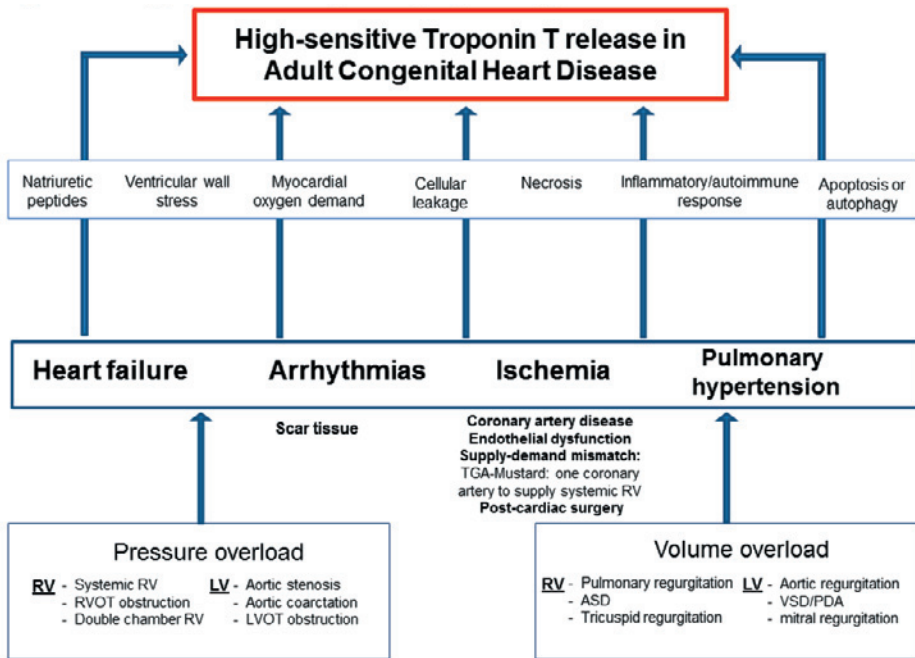
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FIGURE 3. Hypothesis on pathophysiology of hs-TnT release in ACHD

patients.[11, 17] It has even been suggested that possibly all ACHD patients have some degree of heart fail-ure.[18] For example, in patients with ToF, chronic volume-overload as a result of pulmonary regurgitation is often encountered. While in patients with AoS or CoA, the LV will suffer from chronic pressure-overload. Increased myocardial-wall stress may warrant more oxygen and this increased oxygen demand might cause myocardial ischemia and damage. Interestingly, patients with a Fontan circulation had remarkably low hs-TnT levels, which is more difficult to explain. They all underwent multiple cardiac operations, often have suboptimal oxygen saturation at adult age, and more often are in NYHA II or III. However, creation of a Fontan circulation leads to a relatively underloaded ventricle, which possibly results in less myocardial damage and consequently low hs-TnT levels, as has been recently proposed in children.[19] The elevated, though lower hs-TnT levels in patients with TGA-Mustard in comparison with ccTGA could be an expression of the preload limitation in TGA-Mustard patients, or be the result of more ccTGA patients being paced. These two diagnoses are often seen as one, which may be too simple.

Also hs-TnT could be released due to supraventricular arrhythmias. Patients with supraventricular arrhythmias often have elevated hs-TnT, as a result of increased myocardial wall stress or myocardial ischemia due to supply-demand mismatch or micro embolisms.[20, 21]

Other non-cardiac mechanisms that influence hs-TnT levels should also be considered: renal dis-ease,[22] as well as inflammatory and auto-immune reactions can cause reduced troponin clearance.[23] However, not one patient in our study had severe renal dysfunction or autoimmune disease.

Currently, there is no evidence that one can distinguish between cell death by necrosis[24] reflecting irreversible myocardial damage or apoptosis,[25] but an increased hs-TnT is associated with adverse prognosis in other cardiac conditions.[8, 9, 16]

Hs-TnT and cardiac function

Hs-TnT was associated with cardiac dimensions and systolic function, which indicates that this biomarker may be useful to monitor ventricular function and detect function deterioration. Similar correlations with EF have been demonstrated in patients with chronic heart failure.[26] Detectable or elevated hs-TnT could indicate the presence of on-going myocardial damage, and may reflect sub-clinical deterioration of ventricular function. Whether patients with elevated hs-TnT levels are indeed those patients that will develop cardiac dysfunction and have an increased mortality risk, and whether adequate medical treatment will lower hs-TnT levels remains to be elucidated in longitudinal studies.

Hs-TnT and elevated pulmonary pressures

A substantial number of ACHD patients develop pulmonary arterial hypertension, which is associated with adverse outcome.[27] As observed in a small study, hs-TnT is elevated in a substantial number of patients with PH due to congenital heart disease, and seems associated with an increased mortality risk.[28] Possibly, myocardial damage in these patients can be explained by chronic pressure overload of the RV due to elevated pulmonary pressures, or associated cyanosis, especially in patients with Eisenmenger syndrome. With the additional use of hs-TnT we may potentially be able to identify those ACHD patients at high risk for adverse outcome.

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Relation with other cardiac biomarkers

Physiologically distinct biomarkers, i.e. hsTnT (disruption of cell membrane), NT-proBNP (wall stress) and hs-CRP (i.a. inflammation), could have complementary roles as diagnostic or prognostic markers. Combined elevation of troponin and BNP contributes to increased risk for events compared to a single biomarker in patients with chronic heart failure.[29] Also, in patients with acute decompensated heart failure a multimarker approach provides superior risk stratification, as was demonstrated by Pascual-Figal et al.[30] While in our study hs-TnT and NT-proBNP were independently associated with systolic ventricular function, NYHA class and ECG rhythm, the independent value of hs-CRP could not be designated. Whether a multimarker approach can also be used in ACHD patients remains to be investigated in a follow-up study.

Clinical implications and future perspectives

The association between hs-TnT and cardiac function parameters indicates that hs-TnT holds promise as a marker for cardiac function and prognosis. Such a biomarker, that can identify patients at risk for adverse events, and meanwhile reassure patients at low risk who may require less care, would be of great value. Patients with elevated hs-TnT may be those in need for reintervention or those that should start with heart failure medication. However, a large, prospective study is needed to investigate this additional clinical role of hsTnT in ACHD. Doctors treating ACHD patients should realize that hs-TnT might be elevated in asymptomatic ACHD patients.

Limitations

This study was performed in a single, tertiary center where most congenital heart diagnoses were available for inclusion. Thereby our study cohort is heterogeneous, and some lesions are underrepresented due to referral bias, particularly the simpler lesions. None of the patients was in NYHA class IV, and therefore we cannot draw any conclusions on the use of hs-TnT in ACHD patients in this NYHA class. Furthermore, in this study hs-TnT was measured once. To investigate whether hs-TnT is continuously elevated requires further longitudinal investigation with multiple hs-TnT measurements over time.

Conclusions

High sensitive TnT above the 99th percentile of normal was found in nearly 10% of stable ACHD patients, especially in those with a systemic RV or elevated pulmonary pressures. Because hs-TnT was related to NYHA class, ECG rhythm, NT-proBNP and ventricular function, it seems a promising biomarker for assessment of heart failure and clinical outcome.

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Chapter 9

Release of growth-differentiation factor 15 and associations with cardiac function in adult patients with congenital heart disease

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Abstract

Background

Growth-differentiation factor-15 (GDF-15), a cytokine with broad cardiac and non-cardiac activity, has diagnostic and prognostic value in various disease, including heart failure. We aimed to investigate the release of GDF-15 in adults with congenital heart disease (ConHD), and assess the association with cardiac function and functional capacity.

Methods

Consecutive adults with ConHD underwent electrocardiography, echocardiography, and venepuncture, and were seen by a cardiologist at the outpatient clinic. A subset of 143 patients underwent bicycle ergometry on the same day.

Results

In total, 587 patients (median age 33[IQR 25-41] years, 59% men and 90% in NYHA I) were included. Median plasma GDF-15 was 618[IQR 487–867] ng/L. In 87 patients (15%), GDF-15 was above the upper limit of normal (<1109 ng/L). GDF-15 levels were higher in older patients (r=0.367, p<0.001). GDF-15 was higher in patients with elevated pulmonary pressure (median 1114 [IQR 796-2320 ng/L) than in patients with normal pulmonary pressure (median 606 [IQR 481-826] ng/L, *p*<0.001). GDF-15 correlated positively with NT-proBNP (r=0.445, *p*<0.001). After adjustment for age, sex, NT-proBNP, hs-CRP and hs-TnT, GDF-15 above the upper limit of normal was independently associated with NYHA class (odds ratio for NYHA≥II: 3.5[95% CI 1.8 -6.8], *p*<0.001), and decreased exercise capacity (odds ratio for workload>85%: 0.2[95% CI 0.06-0.8], *p*=0.018), but not with systolic ventricular function or ECG rhythm.

Conclusion

GDF-15 is elevated in a substantial number of stable adult ConHD patients, and high in those with elevated pulmonary pressures, regardless of underlying congenital diagnosis. GDF-15 is associated with NYHA, NT-proBNP and exercise capacity, suggesting the marker has diagnostic and potential prognostic value in adults with ConHD.

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Introduction

Growth-differentiation factor-15 (GDF-15) is a member of the transforming growth factor β (TGF-β) cytokine family.[1] As a stress-responsive cytokine with broad activity, GDF-15 plays a role in multiple diseases including cardiovascular disease, but also in various cancers, renal failure and diabetes.[2] Although most GDF-15 studies in cardiovascular disease focused on acute coronary syndromes, where this biomarker is strongly expressed in the infarcted human heart,[3] recently the role of GDF-15 in heart failure gained more interest. In mouse models of pressure overload, GDF-15 has been detected in myocardium, and the marker is expressed in hypertrophic and dilated cardiomyopathy.[4,5] Considering heart failure as a syndrome that affects multiple organ systems, this new biomarker, which reflects cardiac and extra-cardiac abnormalities, may provide additional diagnostic and prognostic information beyond well-known cardiac-specific biomarkers such as amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitive troponin (hs-TnT). Furthermore, levels of GDF-15 are associated with all-cause mortality in patients with heart failure caused by acquired heart disease, independent of known prognostic variables such as left ventricular (LV) function, New York Heart Association (NYHA) class, and incremental to NT-proBNP and hs-TnT.[6,7]

Heart failure is a prominent determinant of outcome in adults with congenital heart disease (ConHD).[8] Only 2 studies describe GDF-15 in patients with ConHD. In young adults operated for various ConHD, GDF-15 was found to be associated with maximal oxygen uptake and NT-proBNP, and suggested to be a surrogate marker for heart failure risk in asymptomatic individuals.[9] A relationship between GDF-15 and cardiac function is reported in children and adolescents with a Fontan circuit.[10] However, information on the expression of GDF-15 in older ConHD patients is non-existing.

In this study we aim to describe the release of GDF-15 in a diverse cohort of adults with ConHD, and investigate the diagnostic value of GDF-15 in relation to cardiac function and early determinants of heart failure.

Methods

All consecutive patients visiting the outpatient clinic of Erasmus MC between May 2011 and April 2013 were approached. The following congenital cardiac diagnoses were included: congenital valvular aortic stenosis (AoS), aortic coarctation (CoA), repaired tetralogy of Fallot (ToF) (also including patients with pulmonary atresia and ventricular septal defect), transposition of the great arteries after Mustard procedure (TGA-Mustard), after arterial switch operation (TGA-ASO), congenitally corrected TGA (ccTGA), complex TGA with VSD or double-outlet right ventricle corrected by Rastelli or reparation à l'étage ventriculaire procedure (Rastelli/REV), univentricular hearts repaired by Fontan procedure (Fontan) and pulmonary hypertension after a (corrected) atrial or ventricular septal defect (PH). Patients were excluded if they were younger than 18 years of age, had severe renal dysfunction (defined as creatinine >200μmol/L) or were pregnant at time of their visit to the outpatient clinic. The local medical ethics committee approved the study protocol, and written informed consent was obtained from all study participants.

On the day of inclusion patients were examined by a cardiologist, and a 12-lead electrocardiogram, detailed echocardiogram and (non-fasting) venous blood samples were obtained. In addition, in a subset of patients bicycle ergometry was performed.

Baseline characteristics

The following baseline patients characteristics were collected: age, sex, NYHA functional class, body length, weight, body mass index (BMI), body surface area (BSA), cardiac medical history, age at time of corrective surgery, number of (re)interventions, blood pressure, heart rate, cardiac medication use, oxygen saturation measured by digital pulse oximetry, and renal function measured by serum creatinine.

12-lead electrocardiogram

A 12-lead electrocardiogram was obtained and analysed by one investigator (JAE). Information was collected on heart rhythm, QRS duration, and corrected QT-time. When QRS duration was more than 120 milliseconds the presence and type of bundle-branch block was assessed.

Two-dimensional echocardiogram

Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system iE33 (Philips Medical Systems, Best, the Netherlands) equipped with a transthoracic broadband S5-1 (1-5 MHz) or X5-1 matrix transducer (composed of 3040 elements, with 1-5 MHz extended operating frequency range). Cardiac dimensions and function were assessed according to the current ASE/EAE guidelines[11]: LV end-systolic and end-diastolic endocardial diameter from parasternal long-axis, RV annulus and apex-base diameter from the apical 4-chamber view, and LA longitudinal and transversal diameter from the apical 4-chamber view. LV function was assessed subjectively by so-called eyeballing, and graded as normal, or mildly, moderately or severely impaired. LV function was also quantified by LV ejection fraction (EF) using the modified Simpson's method.[11] RV function was assessed subjectively with eyeballing, and quantified by tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC). Diastolic function of the systemic ventricle was assessed with use of pulsed wave Doppler imaging of the mitral or tricuspid valve inflow, respectively, from where E, A, E/A-ratio and deceleration time were retrieved. Pulmonary arterial pressures were defined 'elevated' when early diastolic pulmonary regurgitation flow velocity was >2.5 m/s or, in absence of right ventricular outflow tract obstruction, tricuspid regurgitation flow velocity of >3.0 m/s. In patients with TGA-Mustard, left ventricular outflow tract obstruction and mitral regurgitation flow velocity were used, respectively. Approximately 95% of the images were of sufficient quality to assess dimension and function parameters.

Bicycle ergometry

A subset of 143 patients (24%) underwent bicycle ergometry. Bicycle ergometry was not part of the study protocol, but only performed for routine check-up once every 3 years. Results were only included when the exercise test was performed in the same week as the other study investigations. Maximal workload and heart rate were assessed by bicycle ergometry with gradual workload increment of 20 watt per minute (Ramp protocol), and compared to values of healthy individuals of similar age, sex, height and weight. A value of ≥85% of predicted was considered normal. Additional peak oxygen uptake (VO_{2max}) during exercise was performed in 40 patients (7%). When a respiratory quotient (RER) of ≥1.1 was reached, performance was considered maximal.

Laboratory testing

Venous blood samples were taken after at least 30 minutes rest, and were processed and stored within 2 hours at minus 80 degrees Celsius until further analysis. Hemoglobin, creatinine and NT-proBNP were assessed in the clinical chemistry laboratory of the Erasmus MC, as part of the routine patient care. Hs-TnT, high-sensitive C-reactive protein (hs-CRP) and GDF-15 were determined for research purpose only by batch analysis in the same laboratory. Electrochemiluminescence immunoassays (Roche Diagnostics, Basel, Switzerland) were used for plasma NT-proBNP, hs-TNT, hs-CRP and GDF-15. Lower limits of detection were 5 ng/L for hs-TnT and 0.3 mg/L for hs-CRP. The 99th percentile as reference limit of normal was 14 pmol/L for NT-proBNP, 14 ng/L for hs-TnT, and 5 mg/L for hs-CRP. Plasma GDF-15 was analysed by a pre-commercial assay. The lower limit of detection for the GDF-15 assay was 400 ng/L, whereas the 97.5[th] percentile as upper limit of normal for the assay was 1.109 ng/L.[6] To assess reproducibility, GDF-15 measurements were performed twice in a random sample of 96 patients.

Statistical analysis

Continuous variables with a normal distribution were presented as mean ± standard deviation (SD), or when data was skewed, as median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Patients were classified according to tertiles of the observed GDF-15 distribution: <521.5 ng/L (T1), 521.5-745 ng/L (T2), >745 ng/L (T3).

Differences in continuous data between these groups were assessed by ANOVA or Kruskal-Wallis test. Differences in categorical data were evaluated by X^2-test or Fisher's exact test. Differences in GDF-15 levels between men and women, patients with normal versus impaired ventricular function and elevated versus non-elevated pulmonary pressures were assessed with use of Mann-Whitney U test. Correlations between GDF-15 and NT-proBNP, hs-TnT and hs-CRP were assessed by Spearman's rank correlation test.

Analyses of covariance (ANCOVA) were applied to study differences in echocardiographic and exercise parameters between the three GDF-15 categories, while adjusting for potential confounders (age,

sex, NYHA functional class and ECG rhythm). Multivariate logistic regression analyses were performed to determine the relationship between biomarkers levels, i.e. normal vs. above the upper limit of normal: GDF-15 (classified as <1109 ng/L versus ≥1109 ng/L), and NT-proBNP (<14 vs. ≥14 pmol/L), hs-TnT (classified as <14 vs. ≥14 ng/L) and hs-CRP (<5 vs. ≥5 mg/L) as potential determinants of NYHA functional class, systemic ventricular function and rhythm, adjusted for age, and sex.

Results of GDF-15 assay reproducibility were analysed using the method of agreement as described by Bland-Altman.(12) All tests were two-sided and a *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences, version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

In total, 588 patients were eligible for the study. One patient with strongly elevated GDF-15 turned out to be pregnant and was excluded from further analyses. Baseline characteristics of the final 587 participating patients are presented in Table 1. Median age was 33[IQR 25-41] years, 59% were men and 90% were in NYHA functional class I. None of the patients had severe renal dysfunction, i.e. creatinine >200 μmol/L.

Median GDF-15 level was 618 [IQR 487 – 867] ng/L. Figure 1 presents the distribution of GDF-15 levels among all patients. Results for reproducibility of GDF-15 assessment are presented in Figure 2. After log-transformation of GDF-15 the distribution remained skewed. In 39 patients (7%) GDF-15 was below the limit of detection, <400 ng/L, whereas in 87 patients (15%) GDF-15 was above the upper limit of normal, 1109 ng/L. Median levels of GDF-15 for each ConHD are shown in Figure 3. For all diagnosis except PH, median GDF-15 levels were below the upper reference value of normal. GDF-15 level was significantly higher in women (705 [IQR 522 – 1079] ng/L) than in men (574 [IQR 471 – 750] ng/L), *p*<0.001. GDF-15 correlated positively with age (r=0.367, p<0.001). GDF-15 was associated with NYHA functional class: median GDF-15 was in NYHA I 601 [IQR 479 – 810] ng/L, NYHA II 864 [IQR 614 – 1697] ng/L and in NYHA III 2533 [IQR 2161 – 3951] ng/L, *p*<0.001.

GDF-15 levels were higher in patients who used beta-blockers, ACE-inhibitors or diuretics, (1098 [IQR 574-1295] ng/L) than in patients without any of this cardiac medication (705 [IQR 464-760] ng/L), *p*<0.001.

12-lead-electrocardiogram

In total, 507 patients (86%) were in sinus rhythm, 15 patients (3%) were in atrial fibrillation, 44 patients (8%) had a pacemaker rhythm and 21 patients (4%) had an atrial or junctional rhythm. In total 229 patients (39%) had a QRS duration >120 milliseconds. In 165 patients (72%) a right bundle branch block was observed, 26 patients (11%) had a left bundle branch block and in 38 patients (17%) there was an unspecified intraventricular conduction delay. Mean corrected QT time was 409±31 milliseconds.

TABLE 1. Baseline characteristics

	Patients (n=587)
Age (years)	33 [25-41]
Men	344(59)
NYHA functional class:	
I	526(90)
II	56(9)
III	5(1)
Surgical repair	513(87)
Age at surgical repair (years)	3.7 [0.7-11.9]
Systolic bloodpressure (mmHg)	126±16
Diastolic bloodpressure (mmHg)	79±12
Heart rate (beats per minute)	73±14
BMI (kg/m^2)	25±4
Oxygen saturation (SaO$_2$%)	99 [97-100]
Cardiac medication use:	
Betablocker	89(15)
ACE inhibitor	86(15)
Diuretic	70(12)
Anti-arrhythmic drugs	53(9)
Laboratory results:	
NT-proBNP (pmol/L)	15 [7-33]
hs-TnT (ng/L)	4.3 [<3-7.3]
hs-CRP (mg/L)	1.4 [0.6-3.5]
Hemoglobin (mmol/L)	9.2±1.0
Creatinin (µg/L)	77±18
Included congenital heart disease:	
Congenital aortic stenosis	139(24)
Aortic coarctation	107(18)
Tetralogy of Fallot	175(30)
TGA-arterial switch operation	22(4)
TGA-Mustard	65(11)
ccTGA	20(3)
Fontan	40(7)
Rastelli/REV	11(2)
Pulmonary hypertension	8(1)

Values are mean±sd, median [IQR] or n (%).
ACE inhibitor =angiotensin converting enzyme inhibitor. Other abbreviations as described previously.
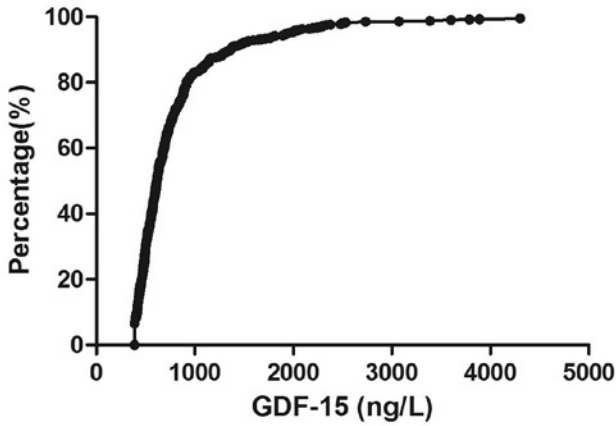
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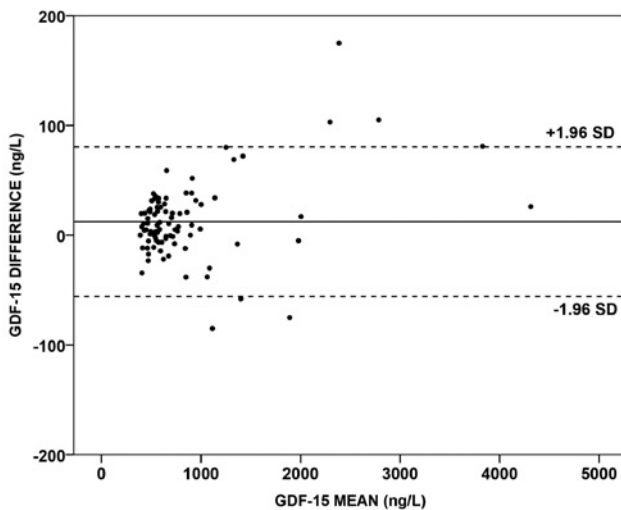FIGURE 1. Distribution of GDF-15 in the study population

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FIGURE 2. Bland-Altman plot for reproducibility of GDF-15 assay

Median levels of GDF-15 for each of the observed ECG rhythms were 603 [IQR 479 – 802] ng/L for patients in sinus rhythm, 785 [IQR 554 – 1272] ng/L for pacemaker rhythm, 828 [IQR 565 – 1072] ng/L for atrial/junctional rhythm and 1644 [IQR 736 – 2268] ng/L for patients with atrial fibrillation. GDF-15 was significantly lower in patients with sinus rhythm (603 [IQR 478–802] ng/L) than in patients with non-sinus rhythm (840 [IQR577-1340] ng/L, *p*<0.001)

There was no significant association between GDF-15 level and QRS duration. In patients with higher GDF-15 levels, QTc time was longer (*p*< 0.001).
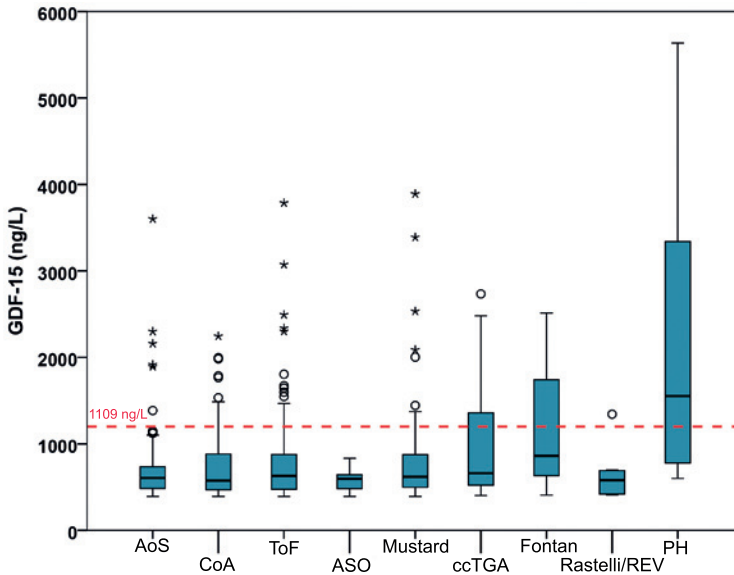
FIGURE 3. GDF-15 levels for each congenital heart disease
The red line indicates the GDF-15 upper limit of normal

Echocardiography

Left ventricular dilation was observed in 103 patients (18%). Mean LV EF was 55±9%, and LV EF was <50% in 55 patients (9%). Median RV FAC was 40 [IQR 32-48]%, and was decreased (<35%) in 103 patients (18%). TAPSE was less than 16 mm in 86 patients (15%).

In Table 2 the relationship between GDF-15 levels and echo parameters is presented. A higher level of GDF-15 was associated with a larger LV end-diastolic dimension and RV annulus dimension. GDF-15 was significantly higher in patients with moderately or severely impaired systolic function of the systemic ventricle (n=87, 15%) than in patients with normal or mildly impaired ventricular function (n=501, 85%) (604 [IQR 479-830] versus 732 [IQR 530-1033] ng/L, p=0.003). Also a higher level of GDF-15 was associated with lower LV EF and lower RV FAC. These associations remained significant after adjustment for age, sex, NYHA and ECG rhythm.

Pulmonary pressure, assessed with echocardiography, was elevated in 34 patients (6%). GDF-15 was elevated in 17 (50%) of these patients. GDF-15 was significantly higher in patients with elevated pulmonary pressure (median 1114 [IQR 796-2320 ng/L) than in patients with normal pulmonary pressure (median 606 [IQR 481-826] ng/L, p<0.001).

Bicycle ergometry

Bicycle ergometry was performed in 143 patients (24%). Mean peak workload was 83±21% of predicted, mean peak heart rate was 85±12% of predicted. In total 75 patients (52%) did not reach 85% of the expected workload, and 65 patients (46%) did not reach 85% of their target heart rate. After adjustment for age, sex, NYHA class and ECG rhythm, higher GDF-15 remained significantly associated with lower maximal workload and lower maximal heart rate, as is presented in Table 2.

TABLE 2. Echocardiography and exercise testing

GDF-15 tertiles	T1 <521.5 ng/L (n=196)	T2 521.5 – 745 ng/L (n=196)	T3 >745 ng/L (n=195)	ANCOVA *p*-value*
Echocardiography				
LA longitudinal dimension (A4CH)(mm)	55±8	55±8	57±10	0.897
LA transversal dimension (A4CH)(mm)	39±6	40±6	42±7	0.870
LV end-diastolic dimension (mm)	50±6	48±6	49±7	**0.030**
LV end-diastolic dimension/BSA (mm/m^2)	26.0±3.5	25.8±3.6	26.6±4.2	0.583
Interventricular septum (mm)	9±2	9±2	9±2	0.978
Posterior wall (mm)	9±2	9±2	9±1	
RV annulus dimension (mm)	42±8	42±8	44±9	**0.019**
RV apex-base dimension (mm)	86±8	83±8	84±8	**0.025**
LV ejection fraction (%)	57±9	56±8	51±8	**0.003**
RV fractional area change (%)	40±10	41±12	37±11	**0.019**
TAPSE (mm)	18±6	17±5	17±5	0.489
E/A ratio	1.7±0.6	1.7±0.7	1.5±0.6	0.446
E/E'	10.9±5.1	11.1±4.1	12.8±5.7	0.831
Bicycle ergometry (n=143)				
Maximum heart rate (% of predicted)	88±11	85±11	82±12	0.054
Maximum workload (% of predicted)	90±17	81±21	77±23	**0.001**

Values are mean±sd.
*adjusted for age, sex, NYHA class and ECG rhythm
A4CH= apical 4 chamber view, LA= left atrium, LV= left ventricle
TAPSE= Tricuspid annular plane systolic excursion, RV = right ventricle

GDF-15 combined with other biomarkers

Correlations between GDF-15 and other blood biomarkers are presented in Figure 4. GDF-15 correlated positively with NT-proBNP (r=0.445, *p*<0.001), with hs-TnT (r=0.233, *p*<0.001), hs-CRP (r=0.215, *p*<0.001). An inverse correlation was observed with haemoglobin (-0.120, *p*=0.006). Levels of GDF-15 and NT-proBNP in relation to NYHA class are depicted in Figure 5. After adjustment for age, sex, NT-proBNP, hs-TNT and hs-CRP, GDF-15 above the upper limit of normal remained associated with NYHA class (odds

ratio for NYHA II or III: 3.5 [95% confidence interval 1.8 to 6.8]; p <0.001), and decreased exercise capacity (odds ratio for workload>85% of predicted: 0.2 [95% confidence interval 0.06 to 0.8], p=0.018) but not with systolic ventricular function or ECG rhythm.
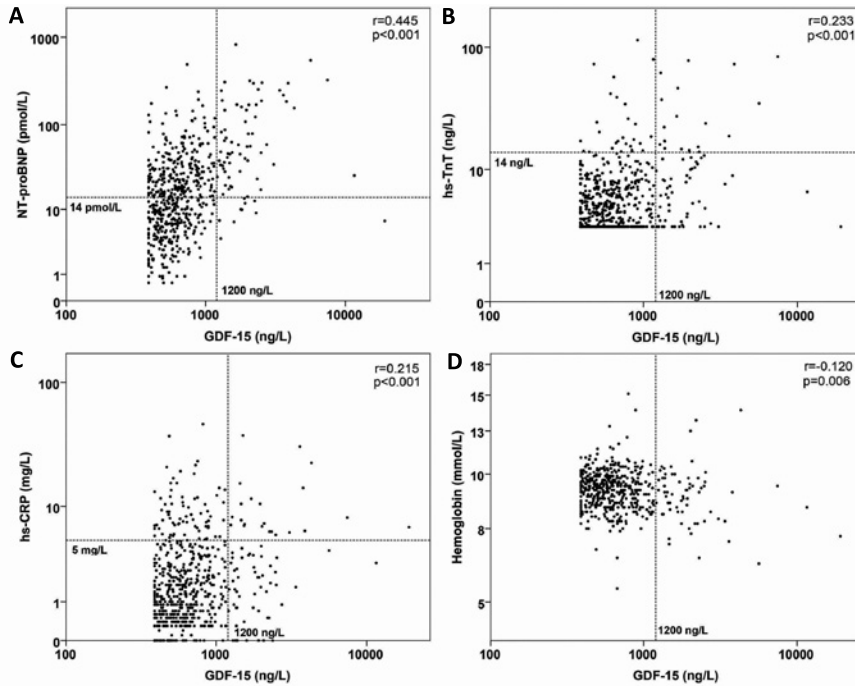

FIGURE 4. Correlation between GDF-15 and other biomarkers:
(A) GDF-15 and NT-proBNP, (B) GDF-15 and hs-TnT, (C) GDF-15 and hs-CRP, (D) GDF-15 and hemoglobin
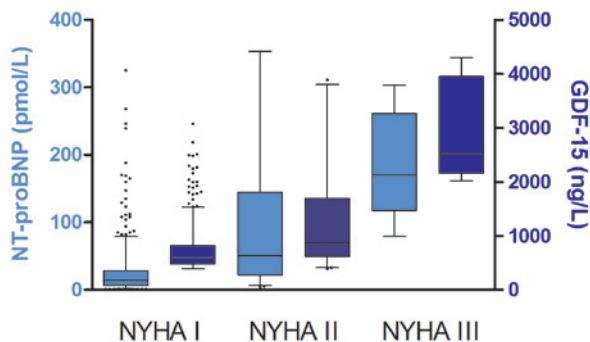

FIGURE 5. GDF-15 and NT-proBNP presented for each NYHA functional class

Discussion

This study describes the distribution of the novel biomarker GDF-15 in a large cohort of adults with stable ConHD. There is a broad range of GDF-15 levels in this population, but GDF-15 appeared highest in patients with ConHD complicated by elevated pulmonary pressures. GDF-15 was associated with NYHA functional class, exercise capacity, NT-proBNP and the presence of elevated pulmonary pressure, regardless of the underlying congenital diagnosis. These results suggest that GDF-15 has the potential to be an important diagnostic tool in adult ConHD patients.

GDF-15 and clinical parameters

We observed a clear association between GDF-15 and NYHA class, which is in agreement with the two previous reports in younger patients with ConHD.[9,10] The observed relationship is comparable with, and possibly even stronger than, the known correlation between NT-proBNP and NYHA functional class, which is present in adult ConHD.[13]

NYHA classification can be criticized as a subjective measure of heart failure, with substantial intra-observer variability. Importantly, however, we also found a relationship between GDF-15 and objective measures for functional capacity and heart failure, including NT-proBNP and exercise capacity. Exercise capacity is a known marker of mortality in adults with ConHD.[14] Since the vast majority of our patients were asymptomatic, the associations between GDF-15 and heart failure parameters suggest that GDF-15 may help identify those patients at risk for adverse outcome already in an asymptomatic phase. Earlier identification of high-risk patients could result in better, more intensive follow-up, earlier start of medical drug therapy or, if needed, better timing for reinterventions. Early signs to intervene could prevent from further clinical deterioration in this relative young population.

Although there were no clear differences in median GDF-15 levels for the various congenital diagnoses, GDF-15 was significantly higher in patients with elevated pulmonary pressures. In half of the patients with elevated pulmonary pressures GDF-15 was elevated, which corresponds with a previous study reporting GDF-15 levels above 1200 ng/L in 55% of the patients with idiopathic pulmonary arterial hypertension.[15] In those patients elevated GDF-15 was associated with an increased risk for lung or heart transplantation or death, and added prognostic value to NT-proBNP and other hemodynamic parameters that were all independently associated with a poor outcome. Repeated measurements of GDF-15 after initiation of medical therapy showed that changes over time in GDF-15 were positively associated with changes in NT-proBNP and venous oxygen saturation indicating that GDF-15 could contribute to identify those patients that respond well to treatment.[15] Whether GDF-15 can distinguish between patients that will or will not benefit of treatment remains to be investigated in a longitudinal study, which we are currently initiating.

GDF-15, other cardiac biomarkers and their potential prognostic value

In line with other cardiac diseases including chronic heart failure and myocardial infarction, GDF-15 showed a significant relationship with NT-proBNP blood concentrations,[16,17] as well as with hs-TnT and hs-CRP. It must be appreciated that, although these correlations were not very strong, it suggests the notion that all markers provide information, albeit from different pathophysiological pathways presumably. Together with biomarkers NT-proBNP (myocardial wall stress), hs-TnT (cardiomyocyte damage) and hs-CRP (inflammation), GDF-15 could contribute to the understanding of the multiple processes involved in the heart failure syndrome. Prior studies have shown that GDF-15 may have a cardioprotective function, where it has anti-apoptotic and anti-hypertrophic effects on the heart.[3,5] On the other hand, the effect on cardiac remodelling may be duel: a pro-hypertrophic effect of GDF-15 has also been reported.[18] The anti-apoptotic effect could explain the modest but significant correlation between GDF-15 and hs-TnT in adult ConHD patients observed in this study. In chronic heart failure GDF-15 has gained attention because of its independent prognostic value for long-term mortality, incremental to NT-proBNP.[6]

Possibly, combining these biomarkers could improve risk stratification for adverse events in adults with ConHD as well. Which biomarker has the strongest predictive value for adverse outcome including death and occurrence of heart failure, remains to be determined with a longitudinal study.

Limitations

Because this was a single centre study, external validation of our finding will be necessary. Although this study comprises a relatively large patient population in the field of adult ConHD, the various diagnostic groups might have been too small to draw firm conclusions on diagnosis-specific relationship with cardiac function. Obviously, this study that explored a single measurement fails short to generate evidence on the course of GDF-15 over time. Our findings warrant further analysis of this marker in a longitudinal study. The reference value of normal for GDF-15 is determined from studies focusing on older patients. Previous studies and our study have demonstrated that GDF-15 is age-dependent. Therefore, the true reference value for our patient population, though relatively young could be lower than the value used in this study. This would imply that even more patients have an elevated level of GDF-15. A healthy reference population should be investigated to determine age-specific reference values for GDF-15.

Conclusion

GDF-15 is elevated in a substantial number of adult patients with ConHD, regardless of underlying congenital heart defect, and seems associated with elevated pulmonary pressures and parameters of functional capacity. GDF-15 is, independent of NT-proBNP, associated with NYHA functional class and exercise capacity indicating that GDF-15 may have incremental diagnostic and prognostic value for clinical follow-up of adults with ConHD.

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9

Part IV

Speckle-tracking echocardiography in adult congenital heart disease

Chapter 10

Quantitative assessment of systolic right ventricular function using myocardial deformation in patients with a systemic right ventricle

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Abstract

Aims

Late systolic dysfunction of the systemic right ventricle (RV) in patients with transposition of the great arteries (TGA) is of major concern. Right ventricular global longitudinal strain (GLS) might be able to identify early dysfunction.

Methods and Results

Adults with TGA after Mustard operation (TGA-Mustard) or congenitally corrected-TGA (ccTGA) underwent echocardiography, electrocardiography, and NT-proBNP measurement. Using speckle-tracking echocardiography, we analyzed longitudinal strain and strain rate, and compared findings in both patients groups, to healthy controls and with clinical parameters. We included 42 patients (mean age 37±7 years, 69% male) with a systemic RV [32 TGA-Mustard (34±4 years after corrective surgery) and 10 ccTGA], and 32 healthy controls (mean age 36±11 years). Global longitudinal strain of the systemic RV was lower in patients than GLS of the systemic LV in controls (-14.2±3.5 vs. -20.0±3.0%, P<0.001). Average LS of the RV lateral wall was lower in patients with TGA-Mustard (-15.5±3.4%) than ccTGA (-18.3±3.6%, P=0.047). Right ventricular GLS tended to be lower in patients in NYHA class II than I, and correlated with NT-proBNP (r=0.49, P<0.001), RV fractional area change (r=-0.39, P=0.019), RV apex-base-diameter (r=0.37, P=0.021), and QRS duration (r=0.41, P= 0.014).

Conclusions

Global longitudinal strain of the systemic RV in patients is lower than GLS of the systemic LV in healthy controls, especially in the apical segment, and tended to be lower in TGA-Mustard than ccTGA patients. Since RV GLS correlates with RV function, myocardial deformation is useful as a more quantitative tool to measure systemic RV function. Decreased GLS was associated with elevated NT-proBNP and tended to correlate with worsening NYHA class, which strengthens the potential prognostic value of GLS in patients with a systemic RV.

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Introduction

In patients with transposition of the great arteries corrected by Mustard operation (TGA-Mustard) and congenitally corrected TGA (ccTGA) the morphologic right ventricle (RV) supports the systemic circulation.[1] Right ventricular geometry is not made to encounter this chronic pressure overload.[2] Therefore, the main concern regarding the long-term outcome of these patients is the function of the systemic RV. Although the RV can tolerate systemic pressures during childhood, after the third decade of life progressive deterioration of RV function is documented.[3, 4]

Right ventricular dysfunction and failure are important determinants of adverse outcome,[5] hence adequate monitoring and early detection of deterioration in RV function is crucial. Nonetheless, assessment of RV function is difficult, given its complex geometry. Increasing data suggest that measures of myocardial deformation during systole, e.g. systolic strain and strain rate are strong indices of ventricular function.[6] With myocardial deformation assessed by speckle-tracking echocardiography (STE), regional myocardial function is quantified,[7] and ventricular dysfunction may be detected in an earlier phase than with conventional echocardiography. Myocardial fibres of the RV are mostly longitudinally orientated[2] and therefore global RV function is thought to be best reflected by longitudinal myocardial deformation.[8] In patients with a systemic RV, strain imaging to evaluate RV function is feasible,[9-11] but information on additional diagnostic and prognostic value for clinical practice is still limited.[12] Furthermore, differences between patients with TGA-Mustard and ccTGA have not been assessed yet.

We hypothesized that myocardial deformation is reduced in adults with a systemic RV compared with healthy controls, and that it is related to clinical and echocardiographic parameters of cardiac function. In this study, we aimed to assess RV function with myocardial deformation in patients with TGA-Mustard and patients with ccTGA, and compare both patients groups. Furthermore, the relationship between RV myocardial deformation and clinical parameters including conventional echocardiography, electrocardiography, and NT-proBNP was assessed to determine the clinical value of RV myocardial deformation.

Methods

Patient inclusion

Consecutive patients with Mustard-TGA or ccTGA seen at the adult congenital cardiology outpatient clinic of Erasmus MC between April 2011 and December 2013 were approached to participate in this prospective study. Patients had to be ≥18 years of age. Exclusion criteria were insufficient image quality for adequate speckle tracking and irregular heart rhythm. To compare echocardiographic data, a control group of healthy volunteers of similar age was used. All healthy volunteers had no medical history or current symptoms of cardiovascular disease. The study was carried out according to the principles of the Declaration of Helsinki and the local medical ethics committee approved the study protocol. Written informed consent was gathered from all patients and healthy controls.

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Data collection

Baseline characteristics were collected, including age, sex, age at time of corrective surgery, time since corrective surgery, cardiac medical history, and New York Heart Association (NYHA) functional class. In all patients physical examination, a standard 12-lead electrocardiogram, a detailed echocardiogram, and venous blood samples were performed.

Echocardiography

Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using a commercially available iE33 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with a transthoracic broadband S5-1 (1-5 MHz) or X5-1 matrix transducer (composed of 3040 elements, with 1-5 MHz extended operating frequency range). The guidelines of the American Society of Echocardiography were used for chamber quantification.[13,14] Right ventricular dimensions (annulus and apex-base diameter) were measured from the apical four-chamber view. Left ventricular and RV function was assessed visually using the so-called 'eyeballing' and graded as normal, mildly, moderately, or severely impaired. Additionally, RV function was assessed using tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (FAC), RV dP/dT from the tricuspid regurgitation (TR) continuous wave signal, and systolic excursion of the lateral tricuspid annulus (S') using the tissue Doppler imaging (TDI). The recommendations of the European Association of Echocardiography were used for the assessment of valvular stenosis and regurgitation.[15] In addition to the standard echo protocol, greyscale images were obtained for STE at a frame rate of >60 Hz. All images were transferred to a dedicated workstation (QLAB, Philips Medical Systems) for further offline analysis.

Speckle-tracking analyses

All speckle-tracking analyses were performed using QLAB STE package, version 9.0 (Philips Medical Systems). In patients with a systemic RV, the apical four-chamber view was used to assess global longitudinal strain (GLS) of the systemic RV, average longitudinal strain (LS) of the RV lateral wall, average LS of the septal wall, and segmental strain and segmental strain rate of the six ventricular wall segments (Figure 1). Similar measurements were performed in healthy controls using the apical four-chamber view: GLS of the systemic LV, average LS of the RV lateral wall, average LS of the septal wall and average LS of the LV lateral wall. Average LS of the RV lateral wall in patients was compared with average LS of the subpulmonary RV lateral wall as well as average LS of the systemic LV lateral wall in healthy controls. Longitudinal strain was defined as the maximal negative value of the strain curve during systole. Strain rate was defined as the most negative value on the strain rate curve during systole. The QLAB LV algorithm was used for measurements of the LV and RV.
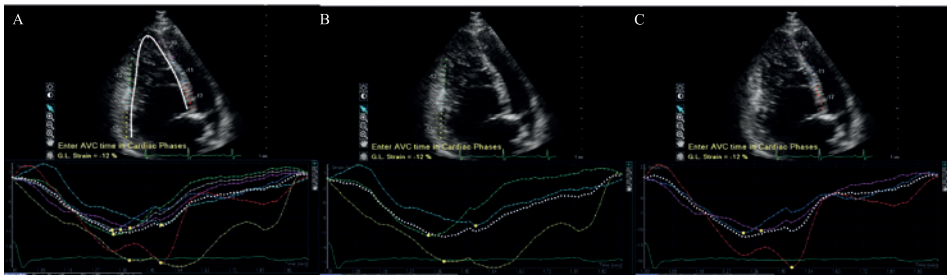
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FIGURE 1. Two-dimensional longitudinal strain analysis of the RV in a TGA-Mustard patient.
(A) GLS of the systemic ventricle composed of seven segments. (B) Average LS of the RV lateral wall composed of three segments. (C) Average LS of the septal wall composed of three segments.

Laboratory testing

Peripheral venous blood samples were obtained in all participants after they had rested for 30 minutes. Renal function was assessed by creatinin levels. Severe renal dysfunction was defined as a creatinin level of >200 µmol/L. Plasma NT-proBNP levels were determined with the use of a commercially available electrochemiluminesence immunoassay kit (Elecsys, Roche Diagnostics, Basel Switzerland). The reference value for normal in our laboratory is <14 pmol/L.

Statistical analysis

Continuous variables with a normal distribution are presented as mean ± standard deviation (SD) or, when data was skewed, as median and interquartile range (IQR). Categorical variables are presented as frequencies and percentages. The Student's *t*-test was used to compare normally distributed, continuous variables between patients and controls, or between ccTGA and TGA-Mustard patients; the Mann-Whitney-*U* test was performed in case of a skewed distribution. When GLS of the systemic RV was compared between more than two groups, i.e. for the various degrees of systemic ventricular dysfunction, one-way ANOVA was used. Frequencies between patients and controls were compared using the χ^2-test or Fisher's exact test. Correlations between echocardiographic parameters and NT-proBNP were tested with the use of the Pearson's correlation test or Spearman's Rho correlation test. Multivariable linear regression analyses were used to assess associations between GLS of the systemic RV and NT-proBNP, adjusted for age, sex and NYHA functional class. Since the distribution of NT-proBNP was skewed, NT-proBNP values were log-transformed which created a normal distribution that was used for further analysis.

Intraobserver variability of GLS was assessed by repeated analysis of the Qlab data sets at least one month after the initial analysis and blinded to the initial results by one investigator (J.A.E.). To assess interobserver variability, a second investigator (M.E.M) performed GLS analysis. The agreement between two measurements was expressed using the 95% confidence interval and determined as the mean of the differences ±1.96SD, as described by Bland-Altman.[16]

A p-value of <0.05 was considered statistically significant. All statistical tests were performed using SPSS Statistics, version 21.0 (SPSS Inc, Chicago, IL, USA).

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Results

Baseline patient characteristics

Fifty-seven patients with a systemic RV were eligible. Fifteen patients were excluded because of re-stricted visualization and/or inadequate image quality of the RV images needed for STE. In total, 42 patients were included in this study (mean age 36.9±7.4 years, 69% male); 32 patients with TGA-Mustard and 10 patients with ccTGA. The control group consisted of 32 healthy volunteers with a mean age of 36.3±11.5 years (60% male). Baseline characteristics of the patients are listed in Table 1. Time since operation of patients with TGA-Mustard was 33.9±4.3 years. In 12 patients (29%), TGA was associated with ventricular septal defect. In two patients, mild baffle obstruction was observed and one patient had mild baffle leakage, but these residual lesions were well tolerated and haemodynamically insignificant.

All patients were in NYHA functional class I or II. None of the patients had severe renal dysfunction. Eighty-one percent of the patients was in sinus rhythm. Of these patients, QRS duration was 121±20 ms, and 60% had QRS duration of ≥120 ms.

Echocardiography

The echocardiographic findings are presented in Table 2. Right ventricular function was at least mildly impaired in all, and moderately or severely impaired in 62% of the patients. Median RV FAC was 24 (IQR 5–39)%. Left ventricular function was normal or mildly impaired in all but one patient. Moderate to severe TR was observed in 40% of the patients. None of the patients had more than mild pulmonary regurgitation or aortic regurgitation. Right ventricular apex-base diameter was smaller in ccTGA patients than TGA-Mustard patients, and ccTGA patients more often had more than mild TR than TGA-Mustard patients; all other echocardiographic findings did not differ significantly.

GLS of the systemic ventricle

Global longitudinal strain of the systemic RV in patients was significantly lower than GSL of the systemic LV in healthy controls (-14.2±3.5% vs. -20.1±3.0%, p<0.001) (Figure 2). Global longitudinal strain of the systemic RV did not significantly differ between patients with TGA-Mustard and ccTGA (-13.9±3.2% versus -15.1±4.4%, p=0.334) (Figure 3).

Average LS of the ventricular walls

Average LS of the RV lateral wall was -16.1±3.6% for patients with a systemic RV, which was significantly reduced compared to average LS of the RV lateral wall (-26.6±4.4%, p<0.001) and average LS of the LV lateral wall (-20.5±3.9%, p<0.001) in healthy controls. Also, average LS of the septal wall was significantly lower in patients than in healthy controls (-12.5±4.0% versus -20.8±3.1%, p<0.001).

TABLE 1. Baseline patient characteristics

	All patients (n=42)	TGA-Mustard (n=32)	ccTGA (n=10)	p-value *
Age (years)	36.9 ± 7.4	35.6 ± 5.6	40.8 ± 10.8	0.141
Male	29 (69)	22 (69)	7 (70)	0.687
Age at operation (years)	-	1.3 ± 1.4	-	
Time since operation (year)	-	33.9 ± 4.3	-	
Concomitant cardiac lesions:				
Ventricular septal defect (corrected)	12 (29)	10 (32)	2 (20)	0.696
Pulmonary stenosis >mild	6 (14)	5 (16)	1 (10)	1.000
Baffle stenosis or leakage	-	3 (9)	-	
NYHA class (I / II)	34 / 8	26 / 6	8 / 2	1.000
Heart rate (beats per minute)	72 ± 19	73 ± 16	67 ± 27	0.443
Systolic blood pressure (mm Hg)	125 ± 14	125 ± 15	123 ± 13	0.676
Diastolic blood pressure (mm Hg)	80 ± 13	80 ± 14	82 ± 7	0.606
Height (meters)	1.75 ± 0.1	1.75 ± 0.1	1.72 ± 0.1	0.339
Weight (kilograms)	78 ± 16	79 ± 17	74 ± 13	0.398
Body Mass Index (kg/m2)	25.5 ± 4.6	25.7 ± 5.0	24.9 ± 3.0	0.624
Peripheral oxygen saturation (%)	98 [96 - 100]	97 [96 - 99]	99 [97 - 100]	0.069
Pacemaker implantation	8 (19)	4 (13)	4 (40)	**0.012**
ICD implantation	3 (7)	2 (6)	1 (10)	1.000
- combined PM / ICD implantation	2 (5)	1 (3)	1 (10)	0.424
Electrocardiography				
- Sinus rhythm	34 (81)	30 (94)	4 (40)	**0.001**
- Pacemaker rhythm	6 (14)	1 (3)	5 (50)	**0.002**
- Atrial rhythm	2 (5)	1 (3)	1(10)	0.424
QRS duration (milliseconds)	120 ± 19	121 ± 20	111 ± 15	0.297
QRS > 120 milliseconds	17 (40)	16 (50)	1 (10)	0.342
Cardiac medication				
Beta-blocker	9 (21)	4 (13)	5 (50)	**0.023**
ACE inhibitor	14 (33)	9 (28)	5 (50)	0.259
Diuretics	8 (19)	6 (19)	2 (20)	0.930
Anti-arrhythmic drug	5 (12)	3 (9)	2 (20)	0.577
Laboratory results				
Creatinine (μmol/L)	78 [68 - 83]	74 [68 - 83]	81 [74 - 88]	0.119
NT-proBNP (pmol/L)	27.4 [17.6-55.2]	29.9[21.7-53.9]	19.1[10.3-66.6]	0.259

Categorical variables are presented as frequencies (percentage).
Continuous variables are presents as mean ± SD or median [interquartile range].
* TGA-Mustard versus ccTGA. ACE = angiotensin converting enzyme; AV = atrioventricular;
ICD = implantable cardioverter defibrillator; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PM = pacemaker; SR = sinus rhythm; TGA = transposition of the great arteries
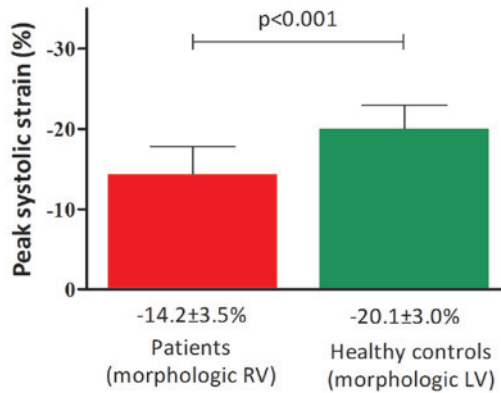
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FIGURE 2. GLS of the systemic ventricle in patients and healthy controls.
Strain values are presented as mean and standard deviation

Average LS of the RV lateral wall was significantly decreased in patients with TGA-Mustard compared with ccTGA (-15.5±3.4% vs. -18.3±3.6%, p=0.047), while no significant difference in average LS of the septal wall was seen (Figure 3, Table 2).

Segmental strain and strain rate

The results for segmental strain are shown in Table 3 and Figure 4. The significant reduction in strain of patients compared with controls was seen in all segments, but most prominent in the apical segments. Additionally, segmental strain rates of all three segments of the RV lateral wall were significantly lower in
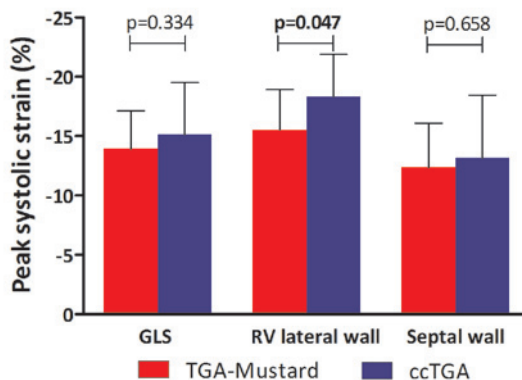
FIGURE 3. GLS of the systemic RV and average LS of the ventricular walls in both patient groups.
Strain values are presented as mean and standard deviation

TABLE 2. Echocardiographic findings

	All patients (n=42)	TGA-Mustard (n=32)	ccTGA (n=10)	p-value
RV dimensions				
RV annulus diameter (mm)	49±7	50±6	49±11	0.795
RV apex-base diameter (mm)	84±9	86±9	78±10	**0.038**
RV systolic function				
- good	0	0	0	0.607
- mildly impaired	16 (38)	12 (38)	4 (40)	
- moderately impaired	21 (50)	17 (53)	4 (40)	
- severely impaired	5 (12)	3 (9)	2 (20)	
fractional area change (%)	24 ± 7	24 ± 8	23 ± 7	0.538
RV TDI S' lateral wall	--	8.4 ± 1.4	NM	--
TAPSE (mm)	--	12 ± 3	NM	--
dP/dT RV (mmHg/s)	--	833 ±277	NM	--
Strain parameters				
GLS of the systemic RV (%)	-14.2 ± 3.5	-13.9±3.2	-15.1 ± 4.4	0.334
LS of the RV lateral wall (%)	-16.1 ± 3.6	-15.5 ± 3.4	-18.3 ± 3.6	**0.047**
LS of the septal wall (%)	-12.5 ± 4.0	-12.3 ± 3.7	-13.1 ± 5.3	0.658
LV systolic function				
- good	31 (74)	24 (75)	7 (70)	0.760
- mildly impaired	10 (24)	7 (22)	3 (30)	
- moderately impaired	1 (2)	1 (3)	0	
- severely impaired	0	0	0	
Valvular function				
Tricuspid regurgitation grade				
- none	5 (12)	2 (6)	3 (30)	**0.006**
- mild	20 (48)	19 (59)	1 (10)	
- moderate	13 (30)	7 (22)	6 (60)	
- severe	4 (10)	4 (13)	0	
Mitral regurgitation Vmax (m/s) (n=11)	2.8 ± 0.8	3.0 ± 0.8	2.3 ± 0.4	0.076
Pulmonary regurgitation, early diastolic, Vmax (m/s) (n=20)	2.0 ± 0.7	2.1 ± 0.7	1.4 ± 0.3	0.070
Pulmonary regurgitation, late diastolic, Vmax (m/s) (n=17)	0.9 ± 0.6	0.9 ± 0.7	0.6 ± 0.2	0.396
Tricuspid regurgitation Vmax (m/s) (n=25)	4.8 ± 0.4	4.8 ± 0.4	4.9 ± 0.4	0.627

Values are presented as frequencies (percentage) or mean ± SD.
LV = left ventricle; RV = right ventricle; NM = not measured; TDI = Tissue Doppler Imaging;
TAPSE = Tricuspid Annular Plane Systolic Excursion; DP/DT = ; Vmax = peak flow velocity

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patients compared with controls (Table 3). Segmental strain and strain rate between TGA-Mustard and ccTGA patients was not significantly different.

TABLE 3. Segmental strain and strain rate

	All patients	Healthy controls		TGA-Mustard	ccTGA	p-value
Number of patients	42	32		32	10	
Lateral wall						
Longitudinal strain (%)	Systemic RV	Subpulmonary RV	Systemic LV	Systemic RV	Systemic RV	
Lateral wall. basal	-19.5±7.7	-28.6 ± 7.9‡	-24.4 ± 7.0†	-20.8 ± 7.9	-15.6 ± 5.9	0.064
Lateral wall. midwall	-14.7±6.8	-26.5 ± 5.5‡	-19.4 ± 6.0†	-13.8 ± 6.7	-18.0 ± 6.6	0.108
Lateral wall. apical	-14.2±6.7	-28.7 ± 7.6‡	-17.3 ±5.3*	-13.3 ± 6.7	-16.7 ± 6.3	0.164
Strain rate (% / sec)	Systemic RV	Subpulmonary RV	Systemic LV	Systemic RV	Systemic RV	
Lateral wall. basal	-1.25±0.54	-1.69 ± 0.45‡	-1.45 ± 0.34	-1.32 ± 0.58	-1.01 ± 0.33	0.109
Lateral wall. midwall	-1.06±0.32	-1.73 ± 0.67‡	-1.17 ± 0.34	-1.04 ± 0.33	-1.10 ± 0.30	0.653
Lateral wall. apical	-0.98±0.48	-1.66 ± 0.57‡	-1.19 ± 0.35*	-0.93 ± 0.44	-1.16 ± 0.59	0.199
Septal wall						
Longitudinal strain (%)	Systemic RV		Systemic LV	Systemic RV	Systemic RV	
Septal wall. basal	-10.5 ± 5.2	--	-18.2 ± 4.5‡	-9.6 ± 4.7	-12.7 ± 6.0	0.117
Septal wall. midwall	-12.2 ± 5.5	--	-21.4 ± 4.5‡	-11.6 ± 5.1	-14.1 ± 6.8	0.245
Septal wall. apical	-13.8 ± 5.6	--	-22.9 ± 5.6‡	-14.1 ± 4.9	-12.8 ± 8.0	0.653

Values are presented as mean ± SD.
RV= right ventricle; LV=left ventricle.
Levels of significance for comparison with systemic RV parameters in patients: *p<0.05, †p<0.01 ‡p<0.001

GLS of the systemic RV and baseline patient characteristics

Global longitudinal strain of the systemic RV tended to be lower in men than in women (-13.5±3.3% vs. -15.7±3.6%, p=0.067). These sex differences were not seen among the healthy controls. Global longitudinal strain of the systemic RV tended to be lower in patients in NYHA functional class II than class I (-12.2±3.6% vs. -14.6±3.4%, p=0.083). Global longitudinal strain of the systemic RV correlated with QRS duration (r=0.412, p=0.014). There were no associations between GLS and age, blood pressure, heart rate or time since Mustard surgery. Global longitudinal strain of the systemic RV in the six patients with a pacemaker rhythm did not differ from patients without a pacemaker rhythm (-15.0±3.7% vs. -14.0±3.5%, p=0.503).

GLS of the systemic RV and echocardiographic parameters

Global longitudinal strain of the systemic RV correlated with RV apex-base diameter (r=0.374, p=0.021). Global longitudinal strain of the systemic RV was significantly lower in patients with RV function graded as moderately to severely impaired (-12.7±3.3%) compared with patients with normal or mildly impaired RV function (-16.8±2.1%, p<0.001). Global longitudinal strain of the systemic RV correlated with RV FAC

(r=-0.391, p=0.019). No correlation with TAPSE was observed. Global longitudinal strain of the systemic RV was measured for the various degrees of TR: no TR (-9.9±3.0%), mild TR (-14.2±3.1%), moderate TR (15.8±3.2%), and severe TR (-14.4±3.4%). There were no significant differences between GLS of the systemic RV in patients with no compared to mild pulmonary regurgitation.
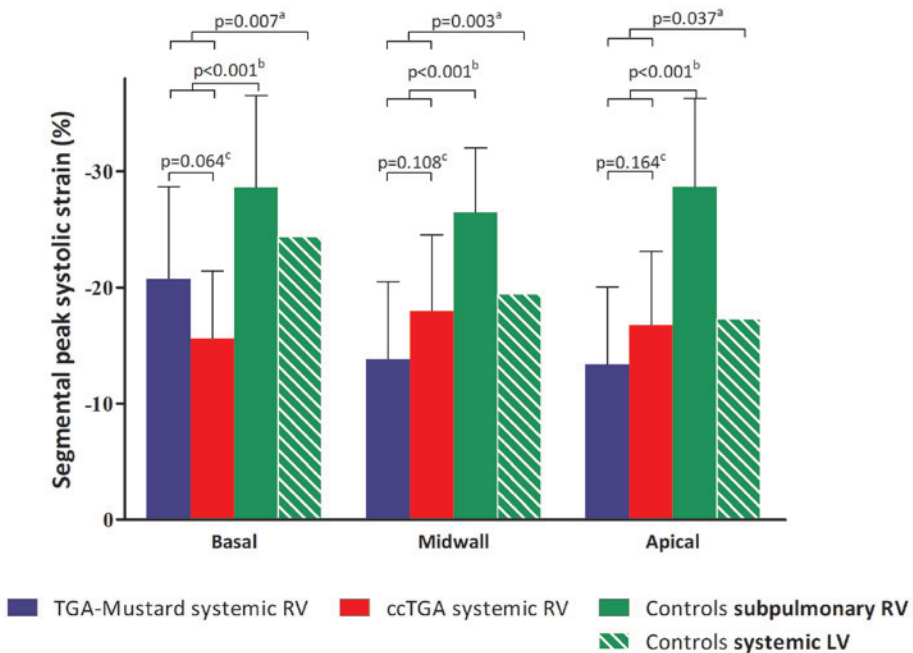

FIGURE 4. Segmental strain values of the lateral wall.
Levels of significance are presented for comparison of: (A) systemic LV lateral wall in patients vs. systemic LV lateral wall in healthy controls, (B) systemic RV lateral wall in patients vs. subpulmonary RV lateral wall in healthy controls, (C) systemic RV lateral wall in TGA-Mustard patients vs. ccTGA patients.

GLS of the systemic RV and NT-proBNP

The median NT-proBNP level was 27.4 (IQR 17.7 – 55.2) pmol/L. NT-proBNP was elevated in 88% of the patients, i.e. above 14 pmol/L, the cut-off point used in our hospital. Global longitudinal strain of the systemic RV correlated negatively with NT-proBNP (Figure 5). After adjustment for age, sex, and NYHA class in a multivariable regression model, GLS of the systemic RV remained significantly associated with NT-proBNP (β=0.117, p=0.006).
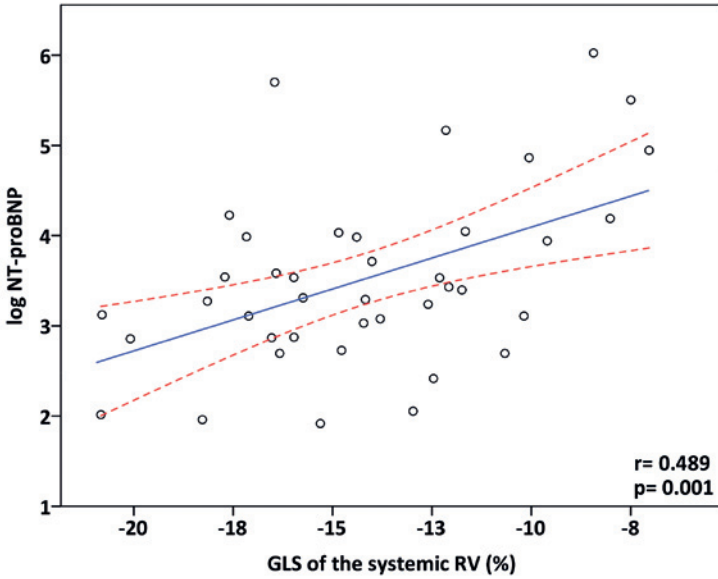
FIGURE 5. Correlation between GLS of the systemic RV and NT-proBNP

Interobserver and intraobserver variability

The interobserver variability was -0.26±1.71% for the GLS of the systemic RV at the apical four-chamber view, and intraobserver variability was -0.01±1.32% for GLS of the systemic RV (Figure 6).
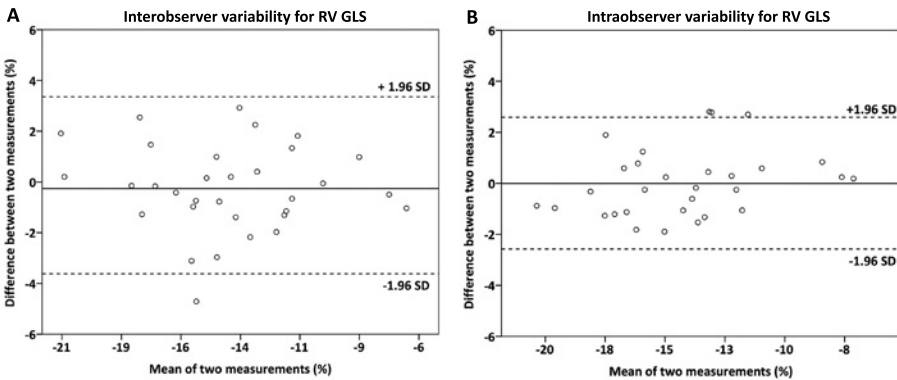
FIGURE 6. Bland-Altman plots for intra- and interobserver variability for measurement of GLS of the systemic RV. (A) Interobserver variability, (B) intraobserver variability.

Discussion

This prospective study demonstrates that patients with a systemic RV have decreased GLS of the systemic ventricle when compared with healthy controls, which is most pronounced in the apical segments, suggesting that apical function has suffered most from chronic pressure overload. Moreover, decreased GLS of the systemic RV is associated with increased NT-proBNP release and possibly with worsening NYHA functional class as well, indicating the potential prognostic value of GLS. Although GLS did not differ between patient groups, average LS of the lateral wall was lower in patients with TGA-Mustard than in patients with ccTGA.

Quantitative assessment of systemic RV function

Right ventricular function in patients with a systemic RV is known to deteriorate progressively at adult age.[3, 17] Although echocardiography is a well-established diagnostic tool to quantitatively assess LV function, its use to quantify RV function is questioned because an adequate geometry model for RV volumes is lacking, especially in the context of congenital heart disease.[18] Therefore, novel quantitative echocardiographic techniques to assess RV function that are less angle- and ventricular geometry dependent, including tissue Doppler and STE, recently gained more interest in patients with a systemic RV.[10, 19, 20]

When compared with healthy controls, the decrease in LS was significant in all RV segments, but most pronounced in the apical segments. Although RV basal function is diminished, it is presumably better preserved than RV apical function. A systemic RV has to encounter much higher (systemic) pressures than a subpulmonary RV. The different geometry of a systemic RV, a rounder-shaped ventricle, could cause a shift in myocardial wall stress. This could explain the observed differences in segmental strain. That chronic pressure overload seems to be the main cause of diminished GLS is underlined by similar results for decreased GLS in pressure-overloaded RVs due to pulmonary hypertension. [21, 22]

Decreased GLS of the systemic RV correlated with RV dysfunction assessed by RV FAC; however, no relationship was observed between GLS and TAPSE. A previous study by De Caro et al.[23] demonstrated that TAPSE is not a useful measure in patients with a systemic RV. Deteriorating RV function is also reflected by prolonged QRS duration and RV annulus dilation, which both have been described to be associated with worse prognosis.[24]

Right ventricular dysfunction often results in dilation of the RV annulus, which frequently leads to progressive TR in patients with a systemic RV. Prevention of TR progression is of great importance. Whether tricuspid valve surgery in these patients is helpful or not, needs to be confirmed in a large cohort study.[25] Significant TR is associated with unfavourable clinical outcome. Reduced GLS of the systemic RV was not only associated with worse RV function, but also with prolonged QRS duration. This demonstrates the potential value of STE for quantitative monitoring of cardiac function, which may also lead to more adequate treatment of RV dysfunction, which could eventually avoid TR progression in these patients. Since our GLS values were comparable with the findings of other studies,[8,12,26] the feasibility of STE for RV function assessment in patients with a systemic RV is strengthened. Nevertheless,

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more follow-up data are needed to determine whether GLS is indeed predictive for clinical endpoints, including TR progression, in patients with a systemic RV.

GLS of the systemic RV and NT-proBNP and NYHA classification

This is the first study that investigated the relationship between RV myocardial deformation and NT-proBNP release in patients with a systemic RV. NT-proBNP, a marker of increased myocardial wall stress,[27] is elevated in the majority of patients with a systemic RV.[28] NT-proBNP correlated with GLS of the systemic RV. The correlation between NT-proBNP and GLS is scattered, although stronger than previous reported modest correlations between NT-proBNP and other RV systolic function measurements such as RV FAC.[28] Hence, this correlation is not strong, both markers may provide complementary information. A recent study by Westhoff-Bleck et al.[29] demonstrated the potential prognostic value of NT-proBNP to predict the risk of heart failure, heart transplantation and mortality in patients with a systemic RV. Together with the possible association between RV GLS and clinical events demonstrated by Kalogeropoulos et al,[26] the relationship between RV GLS and NT-proBNP could indicate a possible future role for both diagnostic tools in the evaluation of the patients' prognosis. This will have to be confirmed in a longitudinal study.

Global longitudinal strain of the systemic RV tended to be lower in patients in NYHA class II than patients in NYHA class I. Similar to NT-proBNP, NYHA functional class has shown to be an independent predictor for worse clinical outcome, i.e. heart failure, heart transplantation, and death, in patients with a systemic RV.[29] Since GLS of the systemic RV was reduced in patients in NYHA II as well as in patients in NYHA I, one could criticize the additional value of reduced strain on outcome. On the other hand, GLS tended to be more reduced in patients in NYHA II, which could indicate subclinical deterioration and underline the potential prognostic value of GLS in these patients. Because our study population was small and included only patients in NYHA functional class I or II, we cannot draw firm conclusions on the relationship between GLS and NYHA classification.

Differences between Mustard surgery and congenitally corrected TGA

Average LS of the lateral wall was lower in patients with TGA-Mustard than in patients with ccTGA, while with conventional echocardiographic clear differences between the two groups have not been described previously. There were no significant differences in baseline characteristics besides the prior cardiac surgery in TGA-Mustard patients. Possibly, the lower LS was caused by the prior surgical intervention. Loss in RV longitudinal contractile function with compensatory gain in transversal contraction is seen in patients after other cardiac surgery, i.e. coronary artery bypass surgery.[30] Pettersen et al.[19] described a similar phenomenon in young adolescents after Senning surgery, where circumferential strain exceeded LS in the systemic RV lateral wall.

Another reason for better preserved LS in patients with ccTGA could be that their RV is more resistant to chronic pressure overload because the RV of ccTGA patients encounters systemic pressure from birth, whereas patients with TGA-Mustard go through a period without pressure overload of the RV. Further-

more, the difference could be explained by the absence of additional atrial function to contribute to RV function in patients with TGA-Mustard. Although we know that both patients with TGA-Mustard and ccTGA will develop RV dysfunction and heart failure,[3, 33] this difference in average LS of the lateral wall may indicate that deterioration in RV function is less progressive in patients with ccTGA than in patients with Mustard-TGA. However, the difference in RV GLS between the patients groups did not reach significance and therefore this difference warrants further investigation in a larger study.

Limitations

The assessment of RV function with echocardiography remains difficult, partly due to its complex ge-ometry. Technical difficulties in visualizing the RV lateral wall, which is situated behind the sternum must be taken into account. Our study described myocardial deformation in a longitudinal direction only, whereas circumferential strain may be important as well, as is stated by Pettersen et al.[19] However, our study population was older, and in our experience, the suboptimal acoustic window for short-axis images (i.e. imaged in the near field because of anterior displacement of the enlarged RV) made it impossible to have reliable circumferential and radial strain measurements in these older patients. Therefore, these measurements were not performed. The large RVs in our relatively old patient cohort may also explain why one-fourth of the patients in our study had to be excluded because of inadequate image quality for STE. This is substantially more than previous studies reporting exclusion rates of 10-15%.[8,12] However, since LS from speckle-tracking analysis has a good intra- and interobserver variability and is a predictor for all-cause mortality in patients with left-side heart failure, this strain parameter holds promise as a risk predictor for patients with a systemic RV. Furthermore, our study population was relatively small, and therefore our results will have to be confirmed by a larger study.

Comparing a systemic RV of patients with healthy controls is difficult. To make the comparison as complete as possible, we compared the patients' systemic RV to the lateral wall of the morphologic RV as well as the systemic LV in healthy controls. The QLAB LV algorithm was used to assess RV function, which is debatable because of the difference in ventricular contraction pattern.[19]

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Conclusion

Global longitudinal strain of the systemic RV is lower in patients than GLS of the systemic LV in healthy controls, which is most pronounced in the apical segments, suggesting that apical function has suffered most from the chronic pressure overload. Since RV GLS correlates with RV function and dimensions, future use of GLS as a more quantitative tool to measure RV function may be well possible. The associa-tions between reduced RV GLS and increased NT-proBNP levels as well as the tendency to worsening NYHA class indicate the potential prognostic value of strain measurement in patients with a systemic RV.

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Chapter 11

Assessment of ventricular function in adults with repaired tetralogy of Fallot using myocardial deformation imaging

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Abstract

Objectives

To study global and regional right ventricular (RV) and left ventricular (LV) deformation in adult patients with repaired tetralogy of Fallot (ToF), and their relationships with conventional diagnostic parameters.

Background

Many patients with repaired ToF have RV volume overload due to pulmonary regurgitation (PR) which could affect RV and LV function. The influence of volume overload on regional RV and LV deformation long after surgical ToF repair is not completely clear yet.

Methods

In this prospective study, ToF patients underwent echocardiography, electrocardiography, cardiac magnetic resonance imaging, bicycle ergometry, and NT-proBNP measurement on the same day. With speckle-tracking echocardiography, we analysed peak systolic global longitudinal strain (GLS), segmental longitudinal strain and strain rate of the RV lateral wall, LV lateral wall and septum. Echocardiographic findings were compared with those of healthy controls.

Results

We included 95 ToF patients (61% male, age 33.0±9.6 years, age at repair 3.7±4.4 years) and 85 healthy controls of similar age and sex. Patients had a lower RV lateral wall GLS than controls (-18.1±4.5% vs. -26.5±4.5%, P<0.001), especially at the apical segment (-15.9±7.4% vs. -28.2±7.7%, P<0.001), and a lower RV strain rate. LV GLS was lower in patients (-17.5±2.5% vs. -19.6±1.9%, P<0.001), mainly due to decreased strain of the interventricular septum. Patients with a PR fraction >25% had higher LV GLS and RV lateral wall GLS than patients with a fraction ≤25% (P=0.005, P=0.044, respectively). No relationships were found with NT-proBNP or exercise capacity.

Conclusions

Right ventricular lateral wall longitudinal strain and strain rate are decreased in adults late after ToF repair, especially of the apical segment suggesting that apical function is most affected in these volume overloaded RVs. Regarding the LV, the septal strain is decreased indicating that RV dysfunction adversely affects LV function, probably due to mechanical coupling of the ventricles.

Introduction

Tetralogy of Fallot (ToF) is the most prevalent form of cyanotic congenital heart disease.[1] Early surgical repair has dramatically improved the survival of ToF patients. However, sequelae such as pulmonary regurgitation (PR) leading to progressive right ventricular (RV) dilation and dysfunction, arrhythmias, and sudden cardiac death remain a great concern.[2, 3] The progression of RV dysfunction also seems to affect left ventricular (LV) function.[4-6]

Right and especially LV dysfunction are important indicators of clinical outcome.[4, 5, 7] Therefore, early detection of ventricular dysfunction is important. Echocardiographic evaluation of biventricular function in ToF patients has been challenging because of the complex shape of the ventricles. Speckle-tracking echocardiography (STE) provides objective measurements to quantify segmental and global ventricular function, independently of angle and ventricular geometry.[8] One of the measurements is strain imaging, also known as myocardial deformation imaging, which may detect ventricular dysfunction in a pre-clinical phase. Although strain imaging is mainly developed for LV mechanics, it can also be used to study RV myocardial deformation.[9]

In ToF patients with normal LV ejection fraction (EF), decreased LV longitudinal strain has been reported suggesting subclinical LV myocardial damage.[10] RV peak systolic longitudinal strain and strain rate are decreased in patients with repaired ToF according to a few studies.[10, 11] However, these studies have been performed mainly in children.

Our aim was to evaluate LV and RV deformation in adults with ToF late after their initial surgical repair, and to investigate relationships with ventricular dimensions and function, severity of valvular diseases, exercise capacity, and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP).

Methods

We prospectively recruited patients who had undergone surgical ToF repair between 1968 and 1995. The study protocol included echocardiography, 12-lead electrocardiography (ECG), bicycle ergometry, cardiac magnetic resonance (CMR) imaging, and NT-proBNP measurement, all performed on the same day. Exclusion criteria were the presence of a pacemaker, atrial fibrillation, and poor quality of echocardiographic images. Baseline characteristics were collected as current age, sex, and surgical data. Echocardiographic data of the patients were compared with data of healthy controls. The healthy controls were voluntarily recruited via an advertisement and had no medical history, medication or current symptoms suggesting cardiovascular disease.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local medical ethics committee. Written informed consent was obtained from all patients.

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Echocardiography

Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using an iE33 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with a transthoracic broadband S5-1 (1-5 MHz) or X5-1 matrix transducer (composed of 3040 elements, with 1-5 MHz extended operating frequency range). We used the guidelines of the American Society of Echocardiography for chamber measurements, including LV EF (Simpson's method), RV fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE).[12, 13] These measurements were used in combination with visual assessment to grade systolic LV and RV function. For valvular regurgitation and stenosis, we used recommendations of the European Association of Echocardiography.[14-16].

Speckle-tracking analysis

Offline analyses of the data sets were performed using STE by QLAB version 9.0 (Philips Medical Systems). The interventricular septum was considered an LV structure because QLAB has been developed for LV mechanics. To analyze LV peak systolic segmental longitudinal strain and segmental strain rate, we defined the endocardium of the LV lateral wall and septum at the standard apical four-chamber view (Figure 1A). LV global longitudinal strain (GLS) was based on strain values of 17 segments measured at the apical two-, three-, and four-chamber views (Figure 1). For the analysis of RV lateral wall GLS, segmental strain and segmental strain rate, we defined the endocardium of the lateral wall at the RV-centered apical four-chamber view (Figure 2). The LV algorithm was applied to both ventricles. After positioning the tracking points on an end-diastolic frame, the program tracked these points on a frame-by-frame basis. When tracking was suboptimal, we retraced the endocardial border. Peak systolic longitudinal strain and strain rate were defined as the peak negative values on the strain and strain rate curves during the ejection phase. Data were exported to a spreadsheet program (Excel; Microsoft Corporation, Redmond, WA, USA).

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a Signa 1.5-Tesla whole-body scanner (GE Medical Systems, Milwaukee, WI, USA) with dedicated phased-array cardiac surface coils. Details of the used MR sequence have been reported previously.[17] For CMR analyses, a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass version 5.2 (Medis Medical Imaging Systems, Leiden, the Netherlands). The ventricular volumetric data set was quantitatively analyzed by one investigator using manual outlining of endocardial borders in end-systole and end-diastole. Biventricular end-diastolic volume, end-systolic volume, stroke volume (SV), EF, and pulmonary regurgitation (PR) fractions were calculated and compared with reference values.[18]
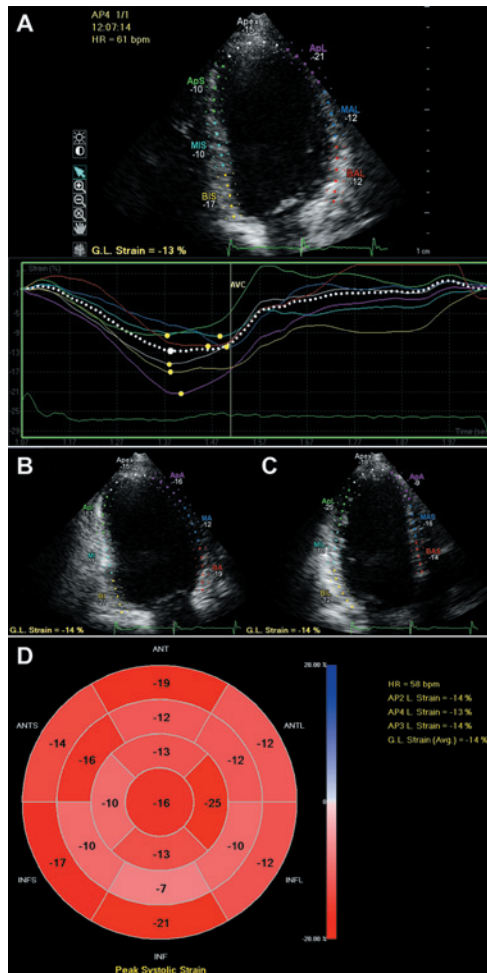
FIGURE 1. Left ventricular longitudinal strain measurements.
The left ventricle was traced at the apical four- (A), two- (B), and three-chamber view (C). The walls were automatically divided into seven segments at each view. Strain and strain rate curves were plotted for each segment. Left ventricular global longitudinal strain was based on the average of 17 segments (D).

Cardiopulmonary exercise testing

Maximal work load, heart rate and oxygen consumption (VO_2) were assessed on a bicycle ergometer with gradual workload increments of 20 Watts per minute (Ramp protocol), and compared with normative data.
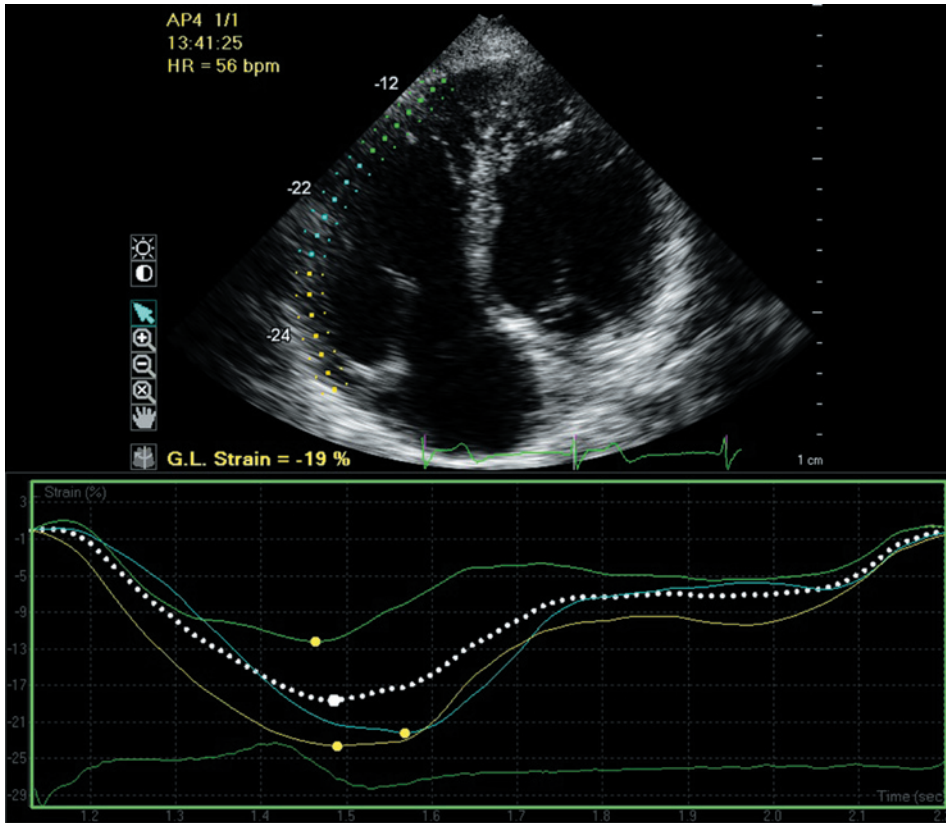
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FIGURE 2. Right ventricular longitudinal strain measurements.
The right ventricular lateral wall was traced from base to apex. Strain and strain rate curves were plotted for each segment. Global longitudinal strain of the lateral wall was based on the three regional values.

NT-proBNP measurement

Peripheral venous blood samples were collected after 30 minutes of rest. Plasma NT-proBNP levels were determined with use of the commercially available electrochemiluminescence immunoassay Elecsys (Roche Diagnostics, Basel, Switzerland). The normal value for NT-proBNP in our hospital is <14 pmol/L.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR). Categorical variables are presented as frequencies and percentages. For comparison of normally distributed continuous variables in one group we used the paired t-test, between two groups the Student's t-test, and between more than two groups the one-way ANOVA test. In case of skewed distribution of continuous variables, the Mann-Whitney-U test was applied. For comparison of frequencies the χ^2-test or Fisher's exact test was used. For quantifying correlations between two variables, the

Pearson correlation test was applied. Multivariable regression analyses were performed for associations between strain values and baseline characteristics.

Intraobserver variability was assessed by repeated analysis of the data sets at least half a year after the initial analysis (MEM). Assessment of interobserver variability was performed by a second observer (JM) in half of the data sets. The agreement between two measurements was determined as the mean of the differences ±1.96SD.[19] Additionally, the coefficient of variability (SD of the differences of two measurements divided by their mean) was provided.

All statistical analyses were performed using the Statistical Package for Social Sciences version 21 (SPSS Inc., Chicago, Illinois, USA). The statistical tests were two-sided and a $P<0.05$ was considered statistically significant.

Results

Study population

An overview of the patient participation is presented in Figure 3. Table 1 shows the baseline characteristics of the study population. The patients were studied 29.2±7.4 years after initial surgical repair. Thirty-seven (39%) underwent pulmonary valve replacement (PVR) 21.7±7.7 years after surgical repair. Table 2 presents conventional echocardiographic characteristics.
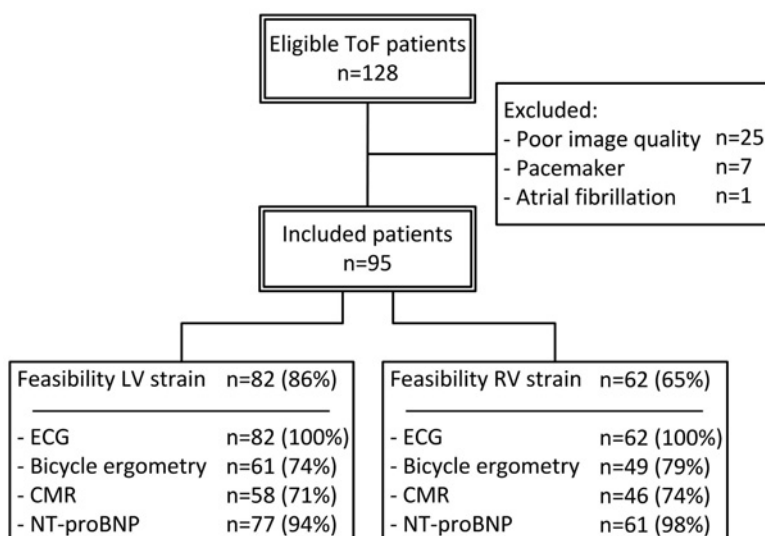

FIGURE 3. Flow chart of the study patients.
An overview of the patient inclusion, feasibility of strain measurements, and number of patients per additional diagnostic test. Bicycle ergometry was not performed in 29 patients mainly due to refusal or inability; CMR not in 25 due to refusal or claustrophobia. CMR=cardiac magnetic resonance imaging; ECG=electrocardiography; LV=left ventricular; RV=right ventricular.

TABLE 1. Baseline characteristics of ToF patients and healthy controls

	patients	controls	
Number of patients	(n=95)	(n=85)	*p*-value
Age at time of study (yrs)	33.0±9.6	34.4±11.6	0.362
Male	58(61%)	48(56%)	0.533
BMI (kg/m^2)	23.9±4.3	23.7±3.1	0.726
Systolic blood pressure (mmHg)	125±16	125±13	0.967
Diastolic blood pressure (mmHg)	76±12	76±9	0.817
NYHA functional classification			
Class I	93(98%)	85(100%)	0.499
Class II	2(2%)	-	
Rhythm			
Sinus rhythm	91(96%)	85(100%)	0.123
Atrial rhythm	4(4%)	-	
QRS duration (ms)	141±28	99±9	**<0.001**
RBBB	75(79%)	-	
QRS duration >180 ms	7(7%)	-	
Age at operation (yrs)	3.7±4.4	-	
Type of repair			
Transannular patch	63(66%)	-	
Infundibulectomy	29(31%)	-	
Unknown	3(3%)	-	
Prior palliative shunt	21(22%)	-	

Categorical data are presented as n(%), and continuous data as mean±standard deviation. Bold font style represents statistically significant differences. BMI=body mass index; NYHA=New York Heart Association; RBBB=right bundle branch block

TABLE 2 Conventional echocardiographic characteristics of ToF patients and healthy controls

Characteristic	patients	controls	*p*-value
LV end-diastolic dimension (mm)	48±6	48±4	0.693
LV end-systolic dimension (mm)	32±7	29±4	**0.001**
LV fractional shortening (%)	33±10	40±7	**<0.001**
LV EF Simpson's (%)	51±8	58±5	**<0.001**
RV longitudinal dimension (mm)	87±9	79±7	**<0.001**
RV basal dimension (mm)	44±8	37±6	**<0.001**
RV FAC (%)	40±9	45±8	**0.011**
TAPSE (mm)	19±4	28±4	**<0.001**
Valvular disease (patients)	mild	moderate	severe
Aortic regurgitation	23(26%)	1(1%)	-
Aortic stenosis	2(2%)	-	-
Mitral regurgitation	15(22%)	1(1%)	-
Pulmonary regurgitation	32(34%)	15(16%)	27(29%)
Pulmonary stenosis	41(43%)	15(16%)	2(2%)
Tricuspid regurgitation	56(60%)	7(7%)	-

Continuous data are presented as mean±standard deviation; categorical data as n(%). EF=ejection fraction; FAC=fractional area change; LV=left ventricular; RV=right ventricular; TAPSE=tricuspid annular plane systolic excursion

Left ventricular longitudinal strain and strain rate

The mean LV GLS in patients was significantly lower (less negative) than in controls, mainly due to decreased midventricular and apical septal strain (Figure 4). Table 3 presents LV strain rate values.

Right ventricular longitudinal strain and strain rate

The mean RV lateral wall GLS was significantly lower in patients than in controls, as well as the strain of the three segments separately (Figure 5). In patients, the RV apical strain was lower than the RV basal strain (P<0.001) and midventricular strain (P=0.010). In controls, strain values of the three segments were comparable. Table 3 presents RV strain rate values.

Relationships with baseline characteristics and clinical parameters

Table 4 presents the results of a subgroup analysis for age groups, sex, and operative characteristics. Age at repair correlated weakly with RV lateral wall GLS (r=-0.31, P=0.013) and LV GLS (r=-0.24, P=0.037). After multivariable regression analysis adjusting sex, current age and body surface area, associations were no longer significant between age at repair and RV lateral wall GLS (β=-0.27, P=0.130), or LV GLS

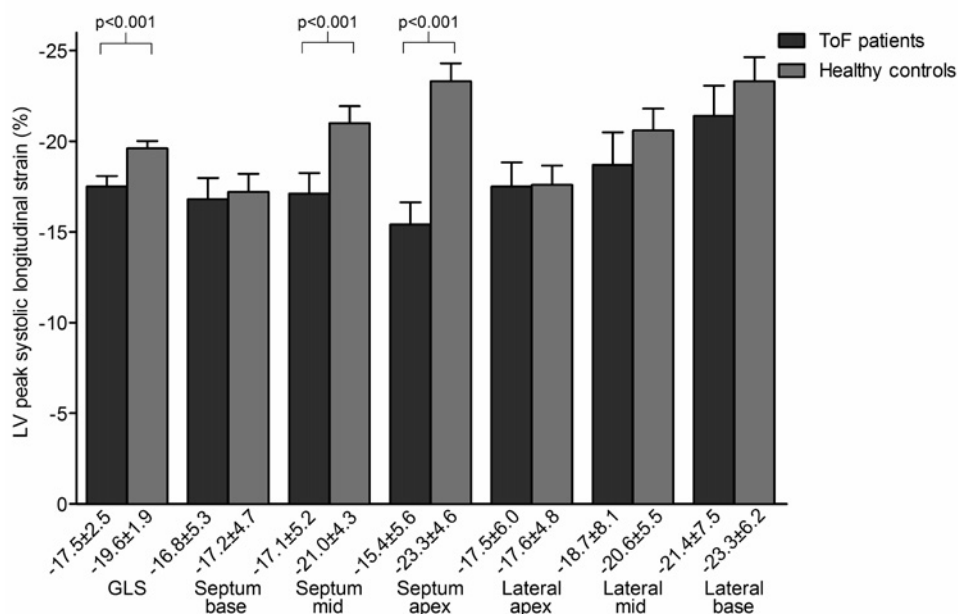
FIGURE 4. Mean LV global and segmental longitudinal strain of ToF patients (n=82) and healthy controls (n=85). Peak systolic LV GLS was based on measurements at the apical two-, three- and four-chamber view. Strain values of the six segments were measured at the apical four-chamber view. The error bars show 95% confidence interval. Only significant P-values are depicted. GLS=global longitudinal strain; LV=left ventricular.
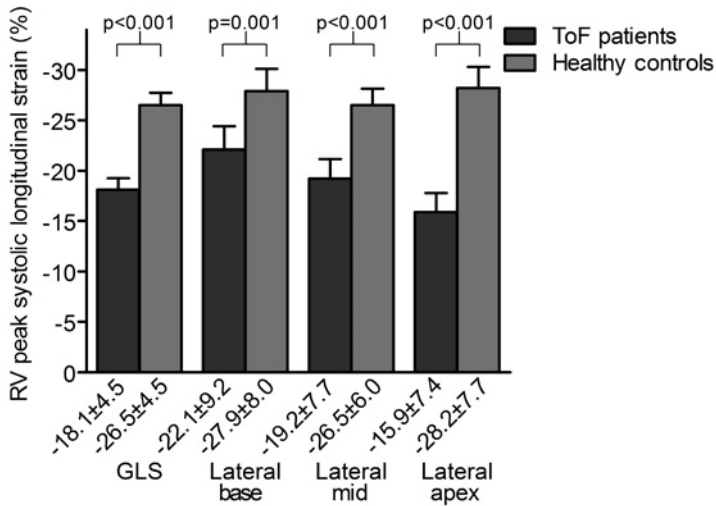
FIGURE 5. Mean RV lateral wall global and segmental longitudinal strain of ToF patients (n=62) and healthy controls (n=54).
Peak systolic RV lateral wall strain was measured at the apical four-chamber view. The error bars show 95% confidence interval. GLS=global longitudinal strain; RV=right ventricular.

TABLE 3. The peak systolic strain rate of the LV septal wall, LV lateral wall, and RV lateral wall of ToF patients and healthy controls

	patients	controls	p-value
LV strain rate (%/s)			
Septum, base	-1.10±0.34	-1.01±0.27	0.064
Septum, midventricular	-1.14±0.38	-1.18±0.27	0.460
Septum, apex	-1.10±0.32	-1.21±0.18	**0.008**
Lateral, apex	-1.19±0.39	-1.18±0.40	0.940
Lateral, midventricular	-1.47±0.60	-1.25±0.38	**0.006**
Lateral, base	-1.52±0.53	-1.47±0.48	0.517
RV strain rate (%/s)			
Lateral, base	-1.43±0.46	-1.67±0.57	**0.017**
Lateral, midventricular	-1.43±0.47	-1.68±0.61	**0.014**
Lateral, apex	-1.17±0.46	-1.66±0.55	**<0.001**

Strain rate values are presented as mean±standard deviation. LV=left ventricular; RV=right ventricular

(β=-0.27, P=0.070). The QRS duration correlated with RV lateral wall GLS (r=0.31, P=0.015) which means that patients with a longer QRS duration had lower RV strain. QRS duration did not correlate with LV GLS.

With cardiopulmonary exercise testing, the mean peak heart rate was 88±9% of normal; peak workload 88±17%; and peak VO_2 81±17%. No significant correlations were found between these variables and biventricular GLS.

The median NT-proBNP level was 13.1 [IQR 5.5-23.4] pmol/L. NT-proBNP was elevated in 42 (47%) patients. Log-transformed NT-proBNP tended to correlate with LV GLS (r=-0.22, P=0.067), but not with RV lateral wall GLS.

TABLE 4. Subanalysis for age groups, sex, operative characteristics and pulmonary valve disease in ToF patients

		N	LV GLS (%)	P-value	N	RV lateral wall GLS (%)	p-value
Age (years)	<30	34	-17.1±2.3	0.259	32	-17.6±4.0	0.381
	≥30	41	-17.8±2.7		30	-18.6±5.0	
Sex	Male	43	-16.9±2.4	0.014	40	-16.7±3.9	0.001
	Female	32	-18.3±2.4		22	-20.6±4.5	
RBBB	Yes	61	-17.6±2.6	0.567	50	-17.9±4.5	0.587
	No	14	-17.2±2.0		12	-18.7±4.7	
Age at repair (years)	<2	40	-16.8±2.1	0.011	33	-17.0±3.9	0.037
	≥2	35	-18.3±2.7		29	-19.3±4.9	
Surgical era	≤1980	30	-17.5±2.6	0.956	23	-18.0±5.2	0.924
	>1980	45	-17.5±2.4		39	-18.1±4.2	
Transannular patch	Yes	49	-17.4±2.5	0.794	45	-18.2±4.3	0.759
	No	24	-17.6±2.4		15	-17.8±5.3	
Preoperative palliative shunt	Yes	16	-17.7±3.2	0.605	17	-19.0±5.5	0.338
	No	58	-17.4±2.3		45	-17.7±4.1	
Right bundle branch block	Yes	61	-17.6±2.6	0.567	50	-17.9±4.5	0.587
	No	14	-17.2±2.0		12	-18.7±4.7	
PR grade, echocardiography	None	19	-17.1±2.8	0.576	12	-18.9±5.0	0.049
	Mild-moderate	35	-17.4±2.6		30	-16.7±3.9	
	Severe	21	-17.9±2.0		20	-19.7±4.6	
PS grade, echocardiography	None	28	-17.5±2.5	0.922	23	-19.1±4.8	0.190
	Mild-moderate	45	-17.4±2.5		37	-17.5±4.4	
	Severe*	2	-18.9±2.0		2	-16.9±2.1	
PR fraction, CMR (%)	≤25	27	-16.8±2.4	0.005	21	-17.2±3.8	0.044
	>25	20	-18.6±1.6		20	-19.9±4.5	
Pulmonary homograft	Yes	32	-17.0±2.7	0.167	24	-16.8±3.9	0.087
	No	43	-17.8±2.3		38	-18.9±4.7	

Strain rate values are presented as mean±SD. *Because of the small number of patients with severe pulmonary stenosis, they were excluded from statistical analysis. †Difference in statistical outcome between PR grade assessed with echocardiography and with CMR could be caused by the smaller number of patients with CMR. CMR=cardiac magnetic resonance; PR=pulmonary regurgitation; PS=pulmonary stenosis.

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Relationships with echocardiographic parameters

A positive correlation was found between RV lateral wall GLS and LV GLS (r=0.37, *P*<0.001), and in the patient group itself (r=0.36, *P*=0.013).

Figure 6 shows a strong correlation between RV lateral wall GLS and TAPSE, and moderate correlation with RV longitudinal dimension. The RV segments separately correlated also significantly with TAPSE
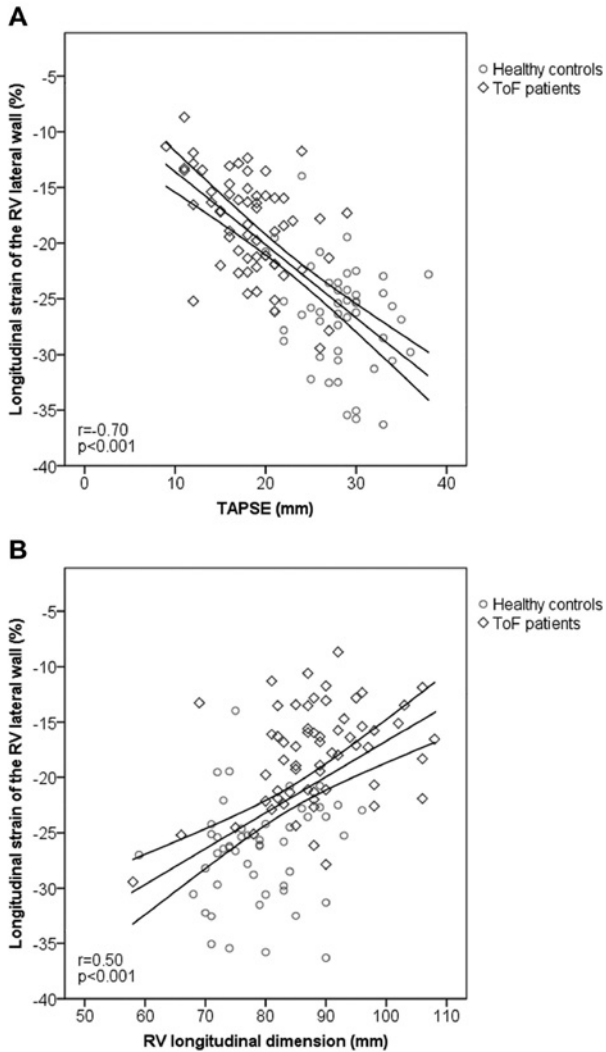

FIGURE 6. Correlations between RV lateral wall GLS with conventional parameters.
Significant correlations were observed between RV lateral wall GLS and TAPSE (A), and RV end-diastolic longitudinal dimension (B). RV=right ventricular; TAPSE=tricuspid annular plane systolic excursion.

and RV longitudinal dimension. Table 5 summarizes correlations between biventricular GLS and other echocardiographic parameters.

Patients with an LV EF<50%, had a lower LV GLS (-15.5±2.6%) than patients with a normal LV EF (-18.4±2.2%, *P*<0.001). Right ventricular lateral wall GLS in patients with a diminished RV FAC, i.e. <35%, tended to be lower (16.9±4.0%) than in patients with a normal RV FAC (-19.2±4.6%, *P*=0.094). Table 4 shows a subanalysis for the severity of pulmonary valve disease. No significant differences were found with regard to tricuspid regurgitation.

TABLE 5. Correlations and differences between global longitudinal strain and echocardiographic parameters of ToF patients

	LV GLS	
	Pearson's r	*p-value*
LV end-diastolic dimension	0.04	0.769
LV end-systolic dimension	0.34	0.003
LV fractional shortening	-0.43	<0.001
LV EF Simpson's	-0.45	<0.001
	RV lateral wall GLS	
	Pearson's r	*p-value*
RV longitudinal dimension	0.37	0.003
RV basal dimension	-0.16	0.221
RV FAC	-0.22	0.108
TAPSE	-0.48	<0.001

EF=ejection fraction; FAC=fractional area change; GLS=global longitudinal strain; LV=left ventricular; RV= right ventricular; TAPSE=tricuspid annular plane systolic excursion

Relationships with CMR parameters

Table 6 presents CMR-derived ventricular volumes and EFs, and their correlations with GLS. Three patients (5%) had LV dilation, and 30 (45%) RV dilation. When focused on the three RV segments separately, the midsegment is the only segment of the RV lateral wall that correlated with RV EF (r=-0.34, *P*=0.022), and indexed RV SV (r=-0.37, *P*=0.011).

Inter- and intraobserver variability

The mean difference of the interobserver measurements was -0.06±1.54% for the LV GLS at the apical four-chamber view, and 0.05±2.72% for the RV lateral wall GLS. The mean difference of the intraobserver measurements was -0.14±1.40% for the LV GLS, and -0.01±2.04% for the RV lateral wall GLS (Figure 7).

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TABLE 6. CMR parameters and correlations with global longitudinal strain in ToF patients

		LV GLS	
	Mean±SD	*Pearson's r*	*p-value*
LV SV/BSA	45±9	-0.217	0.114
LV ESV/BSA	32±11	0.478	<0.001
LV EDV/BSA	77±15	0.204	0.139
LV EF (%)	59±8	-0.509	<0.001
		RV lateral wall GLS	
	Mean±SD	*Pearson's r*	*p-value*
RV SV/BSA	58±16	-0.311	0.036
RV ESV/BSA	60±28	-0.068	0.654
RV EDV/BSA	118±40	-0.178	0.236
RV EF (%)	51±9	-0.097	0.520

BSA=body surface area (m^2); EDV=end-diastolic volume (mL); ESV=end-systolic volume (mL); GLS=global longitudinal strain; LV=left ventricular; RV=right ventricular; SD=standard deviation; SV=stroke volume (mL)
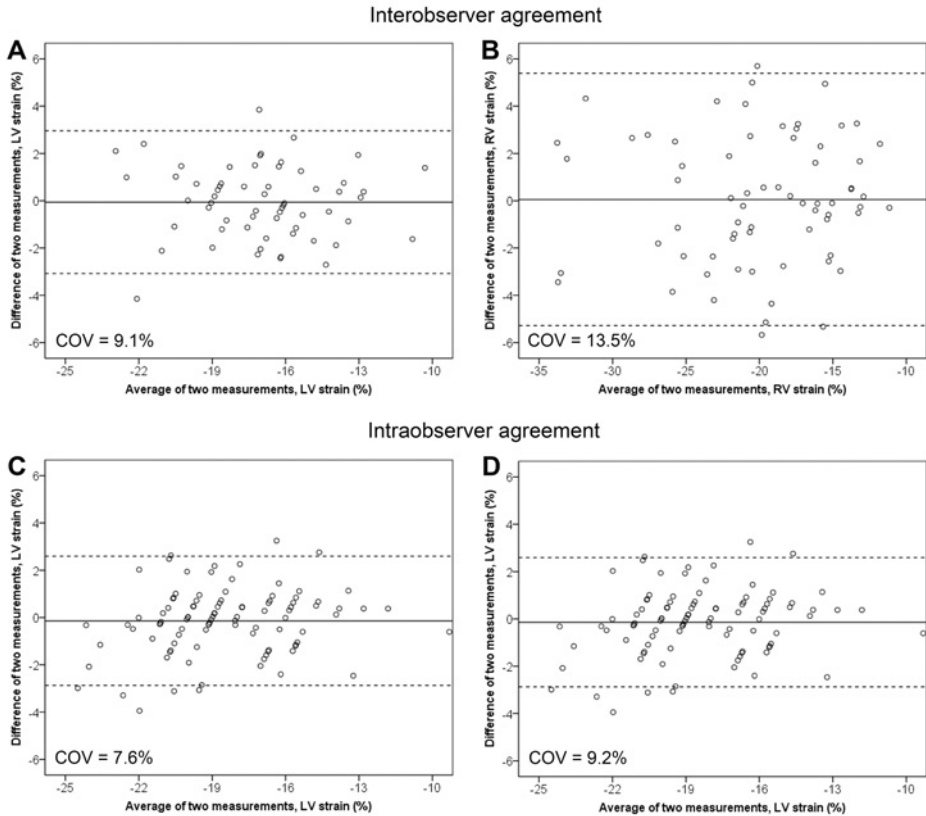

FIGURE 7. Bland-Altman plots demonstrating inter- and intraobserver agreement. Left ventricular strain and right ventricular lateral wall strain for inter- (A,B) and intraobserver agreement (C,D) were measured at the apical four-chamber view. The solid lines depict the mean difference of two measurements, and the dashed lines depict the limits of agreement (mean difference ±1.96SD). COV=coefficient of variability.

Discussion

In this prospective study, RV as well as LV peak systolic longitudinal strain are decreased in ToF patients. Of the RV lateral wall, especially the apical deformation is impaired, suggesting that apical function is affected most in these volume overloaded RVs. With regard to the LV, the septal strain is decreased, which indicates potential ventricular-ventricular interaction.

Right ventricular longitudinal strain

The RV lateral wall global and segmental longitudinal strain were decreased in the patients, presumably as a result of chronic volume overload. The apical strain was more decreased than the strain of the other RV segments, conforming that RV basal and midventricular function are better preserved than RV apical function. These findings are in line with other studies that report a decrease in RV lateral wall strain in ToF patients, however these studies have included only a small group of patients.[10, 11, 20] The reason why the apical lateral wall segment is most sensitive to volume overload is not exactly clear. It has been suggested that especially the RV apical function is an important component of RV adaptation to loading conditions,[21, 22] which could be explained by the RV geometric configuration. The inlet and outlet parts have a narrow configuration, wherefore the apical part is more affected by wall stress. The higher regional wall stress results in a dilated and more rounded apical shape. This remodeling could lead to greater reduction in apical contractile function, resulting in more decreased strain.[22, 23]

Decreased RV lateral wall strain has been reported in patients with pressure overload due to pulmonary hypertension, and has been shown as a predictor of clinical outcome.[24] Whether RV lateral wall strain is also a predictor of outcome in ToF patients is unknown, however it appears to have discriminative ability for decreased quality of life in these patients.[25]

Remarkably, patients with severe pulmonary regurgitation had less decreased RV lateral wall GLS than patients with none to moderate regurgitation. The exact underlying mechanism is unclear and follow-up is necessary to evaluate RV deformation over time. Timing of PVR in ToF patients is controversial and the optimal indications are not completely clear yet. After PVR, RV EF does often not improve,[26] suggesting that irreversible myocardial damage has already been occurred when using a more conservative approach. Decreased strain may be present before changes in EF become visible, and may help identifying patients in need of PVR before the onset of irreversible ventricular dysfunction. However, to conclude that decreased strain is an early and subclinical sign of ventricular dysfunction in these patients, and could be an additional criterion for reinterventions, a prospective study is required.

The age at initial repair correlated significantly with RV lateral wall GLS and also, but weaker, with LV GLS. It remains questionable that this finding of higher absolute strain really means that repair at older age is favorable for the systolic function of both ventricles.

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Ventricular-ventricular interaction

LV dysfunction is a strong independent determinant of clinical outcome [4, 7, 27] making early detection of LV dysfunction important. Right ventricular dysfunction may lead to LV dysfunction in ToF patients.[4-6] The RV lateral wall GLS of the patients in our study showed a relationship with LV GLS, which also suggests ventricular-ventricular interaction. Decreased LV GLS was mainly caused by decreased strain of the midventricular and apical septum, both interventricular segments. Moreover, decreased RV function in ToF patients results in a smaller or impaired LV twist.[28]

Right ventricular pressure and volume loading are likely to affect the LV through several potential interventricular mechanisms, e.g. changes in septal curvature, shared myocardial fibers[29, 30] and electro-mechanical dyssynchrony. Additionally, in ToF patients, mechanical interventricular interaction is also caused by the interventricular septal patch that leads to dysfunction of at least a part of the ventricular septum.[30] A prospective follow-up study is needed to conclude whether decreased septal strain is a pre-clinical sign of LV dysfunction.

Relationships with clinical parameters

Right ventricular lateral wall GLS correlated with TAPSE and modestly with CMR-derived indexed RV SV, but not with RV EF. In normal subjects, TAPSE has been shown to correlate strongly with RV EF,[31] but studies focusing on TAPSE in abnormal RV anatomy are scarce and not convincing. Mercer-Rosa et al. described in ToF patients an association of TAPSE with CMR-derived RV SV, but not with RV EF,[32] which is corresponding with our results. An explanation for the lack of correlation between RV lateral wall GLS and RV EF could be that in case of changed loading conditions, the RV compensates decreased longitudinal strain with an increase in radial or circumferential strain to preserve its EF. Scherptong et al. reported that during a four-year follow-up in adults with ToF, the RV EF remained unchanged, whereas RV GLS was significantly decreased.[20] Hayabuchi et al. described that children with repaired ToF had a decreased RV longitudinal septal strain, but a normal circumferential strain and increased radial strain.[33] These deformation characteristics may be the same or even more pronounced in adults.

Another explanation could be that we measured only the RV lateral wall GLS at the apical four-chamber view which does not reflect the entire RV. Wald et al. demonstrated with CMR data from ToF patients that regional RV outflow tract abnormalities adversely affect global RV EF.[34] Whether it is feasible and reliable to measure RV longitudinal strain at different views with echocardiography to get a better estimation of RV function, is unknown and has to be investigated.

Limitations

We measured peak systolic longitudinal deformation. Analysis of radial and circumferential deformation may have provided additional information, but shortening of the RV is larger longitudinally than radially, and therefore contributes more to RV contraction.[35] We assumed that the same applies to RVs in ToF

patients. In addition, RV radial and circumferential strain measurements are not available on our echo-cardiography system. Rotational movements play a significant role for the LV function, but we decided to measure strain in longitudinal direction making comparisons and correlations with RV strain clearer.

Conclusions

The RV lateral wall longitudinal strain and strain rate are decreased in ToF patients, most pronounced in the apical segment. This suggests that apical function is affected most in these volume overloaded RVs. With regard to the LV, the strain of the septum is decreased indicating that RV dysfunction negatively affects LV function, probably due to the mechanical ventricular coupling. Whether decreased strain is an early and subclinical sign of ventricular dysfunction in these patients, and whether decreased strain could be an objective criterion for reinterventions, is unclear and requires a prospective longitudinal study.

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Chapter 12

Abnormal left ventricular rotation and twist in adult patients with corrected tetralogy of Fallot

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Abstract

Aims

Left ventricular (LV) dysfunction is a major determinant of late adverse clinical outcome in adult patients with tetralogy of Fallot (ToF). Therefore, early detection is important. Speckle-tracking echocardiography (STE) has emerged as a quantitative technique to assess LV function. The aim of this study was to evaluate LV rotation and twist with STE in adult ToF patients and their association with right ventricular (RV) and LV dimensions and function, exercise capacity, and NT-proBNP level.

Methods

Eighty-two ToF patients and 56 healthy controls matched for age and gender underwent echocardiography, electrocardiography, cardiac magnetic resonance imaging (CMR), bicycle ergometry, and NT-proBNP measurement. For STE, short-axis parasternal views were obtained at the LV base and apex. We analysed LV apical and basal rotation curves and calculated LV twist.

Results

Of the 82 ToF patients (55% male, age 33±10 years, 98% NYHA I), 58 (71%) had normal twist, but lower than the controls [12.5 (IQR: 6.6) vs. 16.9 (IQR: 8.2) degrees, *p*= 0.002] mainly due to decreased apical rotation. Twenty-one (26%) patients had abnormal apical rotation which was associated with larger LV dimensions and decreased systolic biventricular function. Multivariable regression analyses showed positive relations of LV twist with biventricular systolic function measured with echocardiography as well as CMR.

Conclusion

The majority of adults with corrected ToF show a reduced LV twist. Strikingly, one-quarter of these patients have an abnormal apical rotation which is associated with decreased systolic LV and RV function. These findings suggest that abnormal apical rotation is a new objective diagnostic criterion for detection of ventricular dysfunction.

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Introduction

Nowadays, a growing number of adult patients require regular follow-up after surgical correction of te- tralogy of Fallot (ToF) in early childhood. These patients often present with pulmonary regurgitation (PR), right ventricular (RV) dysfunction, and arrhythmias. After the third post-operative decade their risk of death increases.[1–3] RV dysfunction has been studied extensively in ToF patients and its progression may also affect left ventricular (LV) function.[2,4,5] Therefore, the LV has recently gained more attention. Several studies found a close relationship between RV and LV function in patients with corrected ToF, indicating the potential pathophysiological role of ventricular interaction that may lead to clinical deterioration at long-term follow- up.[6–8] Although ventricular interactions and the influence of RV dilatation on LV shape and function have not been studied in detail, and although the mechanisms have not been completely elucidated,[9,10] LV dysfunction is a strong independent determinant of clinical outcome[2,11–13] making early detection of LV dysfunction important.

In the assessment of LV function, speckle-tracking echocardiography (STE) has extended the pos- sibilities from evaluating linear to rotational deformation and allows angle-independent quantification of complex LV motion patterns, e.g. rotation and twist.[4,10,12,14.] Many studies have demonstrated that LV rotation and twist are feasible in clinical settings, and that they may provide a useful clinical measure for early detection of a subclinical state that is likely to progress into heart failure. Whether this is also true for patients with ToF is unknown. Our hypothesis is that LV dysfunction develops in most adult patients a long time after initial correction of ToF. Therefore, we used STE in adult patients with corrected ToF to investigate LV rotation patterns and twist and its association with RV and LV dimensions and function, the severity of PR, and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) level, a commonly used biomarker for heart failure.

Methods

We approached consecutive patients who had undergone surgical repair for ToF between 1968 and 1995 and who were seen at our adult congenital cardiology outpatient clinic. The exclusion criteria were the presence of left bundle branch block, atrial fibrillation, pacemaker, or echocardiographic im- ages with insufficient quality for adequate speckle tracking. Baseline characteristics were collected as age, gender, type of reparative surgery, and duration of follow-up since operation. The study protocol included 12-lead electrocardiography (ECG), echocardiography, cardiac magnetic resonance imaging (CMR), bicycle ergometry, and NT-proBNP measurement. Echocardiographic data were compared with those of healthy controls. The healthy controls were employees of the university or the hospital who had no medical histories or current symptoms suggesting cardiovascular disease. We aimed to compose a control group with the same age and sex distribution as in the patient group. Because we could not find for every single patient a matched control, we decided to match the whole patient group to a control group. The medical ethics committee approved the study, and informed consent was obtained from all patients and healthy controls.

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Echocardiography

Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (iE33; Philips Medical Systems, Best, the Netherlands) equipped with a broadband (1 to 5-MHz) S5–1 or X5-1transducer (frequency transmitted 1.7 MHz; frequency received 3.4 MHz). We used the guidelines of the American Society of Echocardiography for our chamber measurements, including LV and RV dimensions, volumes, LV ejection fraction (EF), and RV fractional area change (FAC).[15,16] For the assessment of valvular regurgitation and stenosis, we used the recommendations of the European Association of Echocardiography.[17–19] To optimize STE, images were obtained at a frame rate of >60 frames/s. Parasternal short- axis images at the LV basal level (showing the tips of the mitral valve leaflets) with the cross-section as optimal as possible were obtained from the standard parasternal position. To obtain a short-axis image at the LV apical level, the transducer was positioned one or two intercostal spaces more caudally, as we have previously described.[20] All images were transferred to a QLAB workstation (Philips Medical Systems) for offline analysis.

Speckle-tracking analysis

Analysis of the data sets was performed using STE by QLAB version 9.0. To assess LV rotation, we defined the endocardium and epicardium at each of the two levels. Subsequently a speckle-tracking region of interest was automatically generated to include the myocardium on an end-diastolic frame. After positioning the tracking points, the program tracked these points on a frame-by-frame basis using a least squares global affine transformation. The rotational component of this affine transformation was then used to generate rotational profiles. Data were exported to a spreadsheet program (Excel; Microsoft Corporation, Redmond, WA, USA).

Counterclockwise rotation, as viewed from the apex, was expressed as a positive value, and clockwise rotation as a negative value. The peak apical rotation (AR) and peak basal rotation (BR) were analysed during the ejection phase. We defined peak AR .4 degrees as normal (mean AR of the healthy controls – two standard deviations). BR was defined abnormal when the rotation was absent, reversed, or prolonged. The twist was defined as the maximal value of simultaneous systolic AR—BR. In the present study, various LV rotation patterns were recognized. A normal twist pattern was characterized by end-systolic clockwise BR and end-systolic counterclockwise AR.[21] All other patterns were defined as abnormal. Because of the presence of abnormal twist patterns, we could not perform analysis on LV torsion (i.e. LV twist normalized for LV length).

The QLAB software showed good intra-observer and inter-observer reproducibility of LV twist measurements[22] and we found excellent agreement of the first 10 patients analysed by two independent observers. Therefore, we did not perform reproducibility analysis.

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CMR imaging

CMR results were only obtained in patients undergoing CMR for routine clinical follow-up. CMR imaging was performed using a Signa 1.5-Tesla whole-body scanner (General Electric Medical Systems, Milwaukee, WI, USA) with dedicated phased-array cardiac surface coils. Details of the used MR sequence have been reported previously.[23] For CMR analyses, a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass (version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands). The ventricular volumetric data set was quantitatively analysed using manual outlining of endocardial borders in end-systole and end-diastole. Biventricular end-diastolic volume (EDV), end-systolic volume (ESV), EF, and valvular regurgitation fractions were calculated.

Exercise capacity

Maximal exercise capacity and oxygen consumption ($VO_{2\,max}$) were assessed by bicycle ergometry. Exercise test results were only obtained in patients undergoing bicycle ergometry for routine clinical follow-up on the same day as the echocardiography. Workload was increased stepwise with 10 - 20 W/min. The results were compared with the results of healthy subjects adjusted for age, sex and body height.

NT-proBNP levels

Peripheral venous blood samples were collected after 30 minutes rest. Plasma NT-proBNP levels were determined with the use of a commercially available electrochemiluminescence immunoassay kit (Elecsys, Roche Diagnostics, Basel, Switzerland). NT-proBNP ≤14 pmol/L is defined as normal in our laboratory.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR). Categorical variables are presented as frequencies and percentages. For comparison of normally distributed continuous variables between patients and controls Student's t-tests were used; in case of skewed distribution Mann-Whitney-U tests. For comparison of frequencies the chi-square test or Fisher's exact test was used. For quantifying correlations between two variables, the Pearson or Spearman correlation test was applied. Multivariable regression analyses were performed for associations between rotational parameters and systolic function, adjusted for gender, BMI, age of repair, the use of a transannular patch, and pulmonary valve replacement (PVR). All statistical analyses were performed using PASW SPSS version 20 (SPSS Inc, Chicago, Illinois, USA). *P* values <0.05 were considered statistically significant.

Results

Characteristics of the study population

A total of 123 ToF patients underwent echocardiography with focus on the LV rotation and twist. Forty-one (33%) of these patients were excluded: in 15 the visualization of the apex was inadequate and in 10 the visualization of the base; 8 had poor quality in both views; 4 had a pacemaker; 2 were in atrial fibrillation, 1 had a left bundle branch block; and 1 was pregnant. In the remaining 82 patients, adequate tracking was possible in the apical shot-axes view and basal short-axis view, so they formed the study population. The control group consisted of 56 individuals matched for gender and age (50% male, age 31±7 years). Table 1 shows the clinical and echocardiographic characteristics of the study population. The patients were studied 29.2±7.4 years after initial corrective surgery; at the time of the study 98% of them were in NYHA class I. Thirty-seven (45%) patients received a pulmonary homograft because of

TABLE 1. Clinical and echocardiographic characteristics of the study population.

Clinical characteristics	Patients (n=82)
Age at time of study (yrs)	32.6 ± 9.7
Male, n (%)	45 (55)
Type of repair, n (%)	
Transannular patch	60 (73)
Infundibulectomy	22 (27)
Pulmonary homograft, n (%)	37 (45)
Echocardiography, n (%)	82 (100)
TAPSE (mm)	18 ± 5
Pulmonary regurgitation, n (%)	
Mild	30 (37)
Moderate	8 (10)
Severe	24 (29)
Pulmonary stenosis, n (%)	
Mild	33 (40)
Moderate (≥ 3.0 m/s)	12 (15)
Severe (≥ 4.0 m/s)	2 (2)
Tricuspid regurgitation, n (%)	
Mild	49 (60)
Moderate	7 (9)
Severe	-
Aortic regurgitation, n (%)	
Mild	21 (28)
Moderate	1 (1)
Severe	-
Aortic stenosis, n (%)	
Mild	1 (1)
Moderate - severe	-

TAPSE: tricuspid annular plane systolic excursion

severe PR 20.1±7.9 years after the initial operation. Five of whom, underwent recent PVR <1 year before echocardiography. Seventy-five (91%) patients were in sinus rhythm and 7 (9%) in atrial rhythm. All these patients had a regular rhythm. The mean QRS complex duration of the patients with ToF was 140±31 ms. A complete right bundle branch block was present in 57 (70%) of the patients, an incomplete right bundle branch block in 6 (7%), and unspecified delayed conduction in 5 (6%). RV systolic function assessed with eyeballing was graded in four groups: normal (n=23), mildly impaired (n=45), moderately impaired (n=13), and severely impaired (n=1). LV systolic function was also graded in normal (n=44), mildly impaired (n=37), and severely impaired (n=1).

Apical rotation and basal rotation

Figure 1 represents the LV rotational parameters of the healthy controls and the patients with corrected ToF. The AR was normal in all healthy controls (10.1 [IQR 4.4] degrees). The median AR in the patients with corrected ToF was 8.1 [IQR 7.7] degrees. Sixty-one (74%) of these ToF patients had a normal AR (9.4 [IQR 6.2], p=0.349 compared to the controls), and 21 (26%) ToF patients had an abnormal AR. This abnormal AR was due to reversed rotation in 11 patients, reduced rotation (<4 degrees) in 8, and absent rotation in 2.
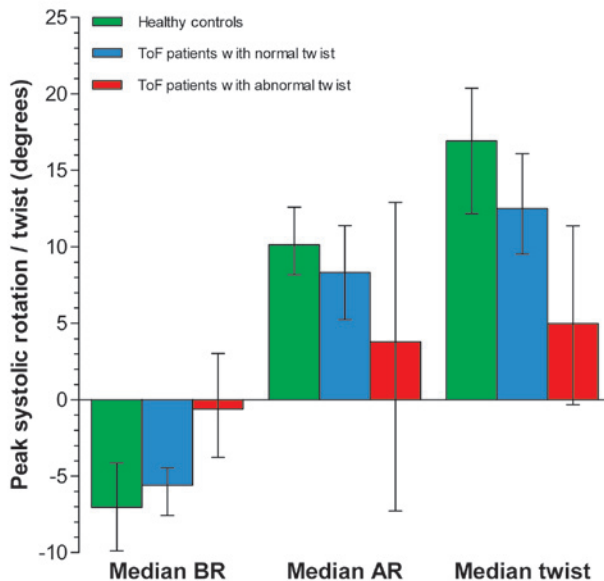

FIGURE 1. Rotational parameters of the left ventricle in patients with tetralogy of Fallot and in healthy controls. BR = basal rotation, AR = apical rotation. The error bars show interquartile ranges.

The median BR of the healthy controls was -7.0 [IQR 5.8] degrees; of the ToF patients it was -5.2 [IQR 3.6] degrees. Of these patients, 66 (80%) had a normal BR. Of the 16 (20%) patients with abnormal BR, 9 patients had reversed BR, 6 absent BR, and 1 prolonged BR.

Table 2 presents the comparison of demographic and echocardiographic variables between the groups of corrected ToF patients with normal AR and those with abnormal AR. The patients with abnormal AR had larger LV dimensions than the patients with normal AR, and more had a decreased systolic LV and RV function. There were no differences in the severity of pulmonary stenosis or regurgitation between the two groups.

Left ventricular twist

All healthy controls and 58 (71%) patients with corrected ToF showed a normal twist pattern. However, these patients had a significantly lower LV twist than controls (12.5 [IQR 6.6] vs. 16.9 [IQR 8.2] degrees, p=0.002) (Figure 1). Twenty-four (29%) patients had an abnormal twist pattern. Figure 2 shows the various rotation patterns we observed. In 11 patients, the abnormal twist pattern was due to abnormal BR, in 8 patients it was due to abnormal AR (Figure 2b) and in 5 to abnormal rotation at both levels (Figure 2c).

Pulmonary valve replacement, interventricular septum, rhythm, and NT-proBNP

The median BR, AR and twist were similar between the patients without PVR, recent PVR and PVR >1 year before echocardiography.

The interventricular septal motion differed significantly between the groups of ToF patients with normal LV twist pattern and those with abnormal twist pattern. In the patient group with normal twist pattern, 45% had septal flattening or paradoxal wall motion against 75% in the group with abnormal twist (p=0.013). Between the normal and abnormal BR groups was a trend toward significance in interventricular septal motion (48% vs. 75%, p=0.056), but no difference was found between the normal and abnormal AR groups.

No significant difference was observed with regard to the rhythm: 55 (95%) of the patients with normal twist pattern were in sinus rhythm, and 20 (83%) of the patients with abnormal twist pattern (p=0.186).

NT-proBNP levels were collected in 77 (94%) patients. The median NT-proBNP level was 13.1 [IQR 18.1] pmol/L. The NT-proBNP levels were similar in patients of the abnormal twist group and those of the normal twist group.

Analyses with systolic function measured with echocardiography

LV EF was assessed using biplane Simpson's method. In 54 (66%) patients, image quality of the 2- and 4-chamber views was sufficient for adequate tracing of the LV. The measurement of RV FAC was possible in 58 (71%) patients. Table 3 presents the comparison of rotational parameters between patients with

TABLE 2. Comparison of structural parameters in patients with normal and abnormal AR

		Normal AR (n=61)	Abnormal AR (n=21)	P value
Surgery	Age at repair (years)	3.5 ± 6.3	2.7 ± 2.8	0.557
	Type of repair, n (%)			
	Transannular patch	42 (69)	18 (86)	0.133
	Infundibulectomy	19 (31)	3 (14)	
	Pulmonary homograft	27 (44)	10 (48)	0.790
Physical examination	Body mass index (kg/m^2)	23 ± 4	26 ± 4	**0.037**
ECG	QRS duration (ms)	140 ± 30	140 ± 33	0.981
Echocardiography, n (%)	Right atrial dilatation			
	None	26 (43)	7 (33)	0.581
	Mild - moderate	24 (39)	11 (52)	
	Severe	11 (18)	3 (14)	
	Right ventricle			
	End-diastolic annulus (mm)	42 ± 8	43 ± 7	0.772
	End-diastolic apex-base (mm)	88 ± 10	86 ± 8	0.416
	TAPSE (mm)	18 ± 5	19 ± 5	0.780
	RV FAC (%)	41 ± 9	36 ± 8	0.126
	Left ventricle			
	End-systolic dim/BSA	17 ± 3	19 ± 4	**0.011**
	End-diastolic dim/BSA	25 ± 3	27 ± 3	**0.038**
	E/A ratio	1.69 ± 0.61	1.82 ± 1.12	0.612
	E/E' ratio	10.4 ± 4.2	9.4 ± 3.3	0.356
	Deceleration time (ms)	199 ± 58	186 ± 44	0.334
	LV ejection fraction (%)	53 ±6	48 ± 6	**0.008**
	Systolic LVF, n(%)			
	Normal	38 (62)	6 (29)	**0.008**
	Impaired	23 (38)	15 (71)	
	Systolic RVF, n(%)			
	Normal	21 (34)	2 (9)	**0.028**
	Impaired	40 (66)	19 (91)	
	IVS, n(%)			
	Normal	28 (46)	10 (48)	0.253
	Flattening	26 (43)	11 (52)	
	Paradoxal	7 (11)	0 (0)	
	Pulmonary stenosis, n (%)			
	None-mild	50 (82)	18 (86)	1.000
	Moderate-severe	11(18)	3 (14)	
	Pulmonary regurgitation, n (%)			
	None-mild	35 (57)	15 (71)	0.255
	Moderate-severe	26 (43)	6 (29)	
	Tricuspid regurgitation, n (%)			
	None-mild	58 (95)	17 (81)	0.067
	Moderate-severe	3 (5)	4 (19)	
Laboratory, n (%)	NT-proBNP > 14 pmol/L	25 (44)	11 (55)	0.390

TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; BSA, body surface area; E/A ratio, ratio of early filling to late filling velocity on transmitral Doppler; E/E'-ratio, ratio of early filling velocity on transmitral Doppler to early relaxation velocity on tissue Doppler; LVF, left ventricular function; RVF, right ventricular function; IVS, interventricular septum.
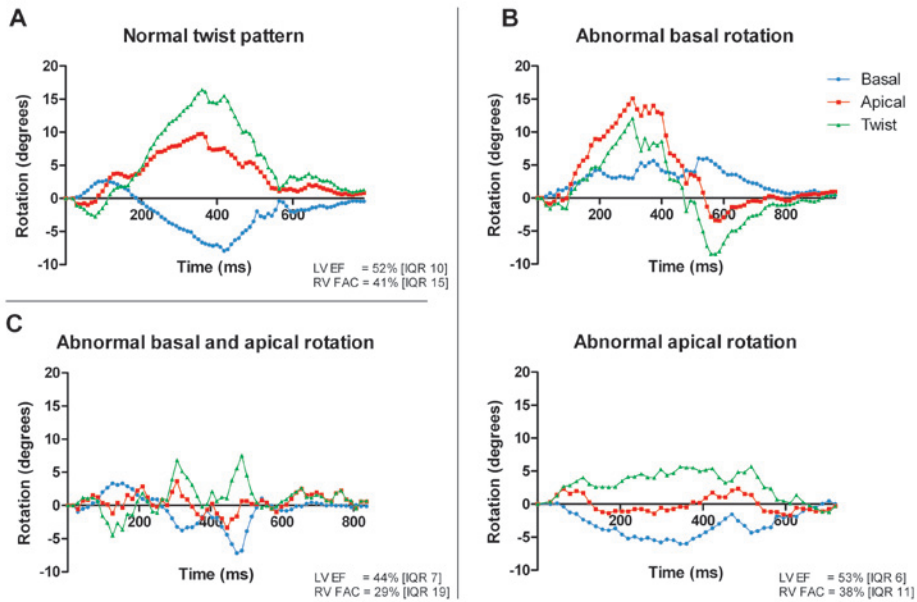
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FIGURE 2. Various rotation types in patients with corrected ToF.
Fifty-eight patients had a normal twist pattern (A); of the patients with abnormal twist pattern, 11 had an abnormal basal rotation and 8 an abnormal apical rotation (B); 5 had both abnormal basal and abnormal apical rotation (C). Note that 8 patients with normal twist pattern have reduced apical rotation (<4 degrees). LV EF = left ventricular ejection fraction, RV FAC = right ventricular fractional area change.

normal vs. abnormal RV FAC, and in patients with normal vs. abnormal LV EF. The median twist was significantly lower in patients with abnormal RV FAC and in patients with abnormal LV EF.

Multivariable regression analysis adjusted for gender, BMI, age of repair, the use of a transannular patch, and PVR showed a significant association between twist and LV EF (β=0.47, p=0.001) and between twist and RV FAC (β=0.35, p=0.010) measured with echocardiography. Figure 3 shows the correlations between LV EF and RV FAC with the LV rotational parameters. LV EF was stronger correlated with AR than BR, whereas RV FAC was stronger correlated with BR.

TABLE 3. Comparison of rotational parameters in patients with normal and abnormal systolic function

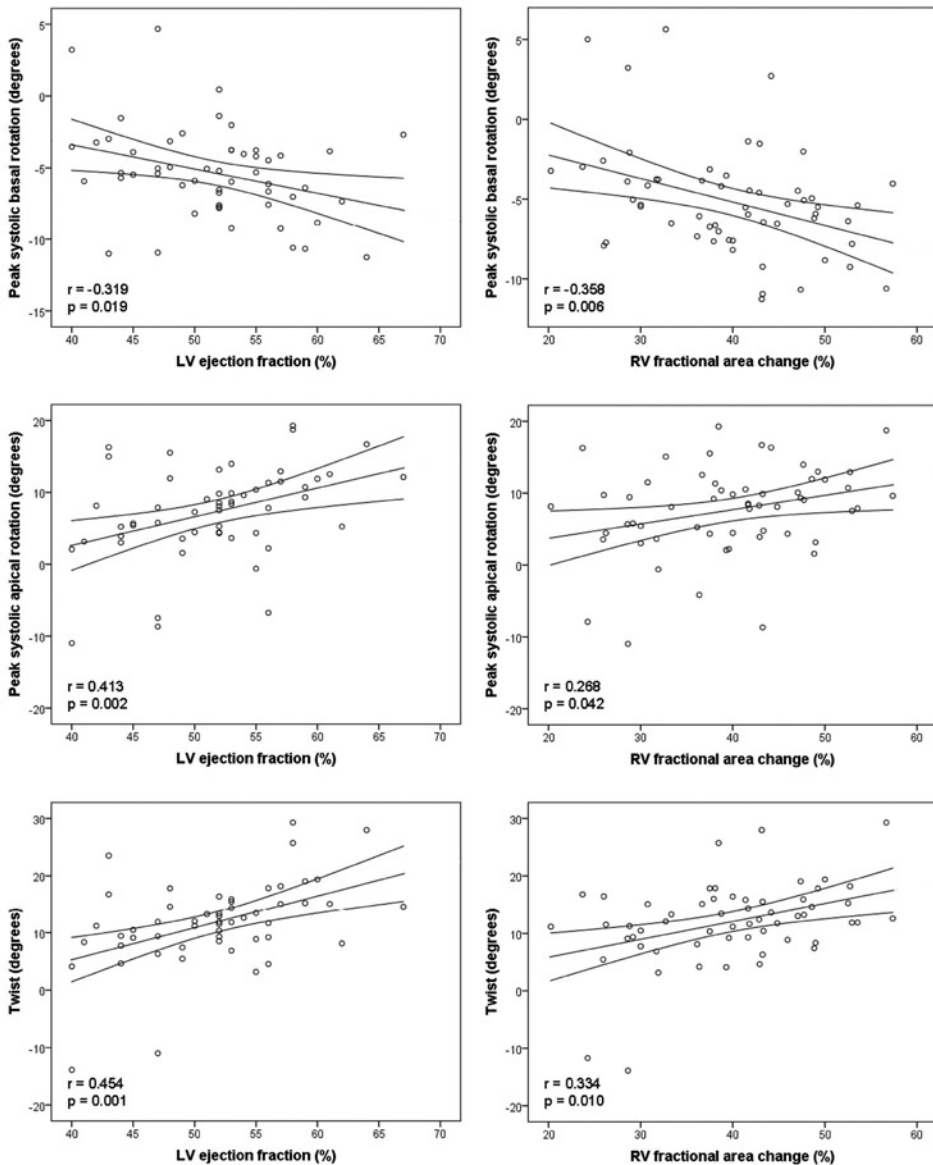|	RV FAC <35%	RV FAC ≥35%	p-value
Basal rotation (degrees)	-3.8 (3.1)	-6.1 (3.1)	0.003
Apical rotation (degrees)	5.7 (6.3)	9.2 (7.3)	0.074
Twist	10.5 (6.5)	13.2 (6.4)	0.016
	LV EF <50%	LV EF ≥50%	
Basal rotation (degrees)	-4.9 (2.7)	-6.1 (3.7	0.033
Apical rotation (degrees)	5.2 (6.1)	9.1 (6.6)	0.021
Twist	9.1 (6.4)	13.2 (5.5)	0.006

Results presented as median (IQR)

FIGURE 3. Correlations between LV rotational parameters and LV ejection fraction and RV fractional area change.

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CMR imaging

Fifty-three (65%) patients underwent CMR, in 50 of whom ventricular volumes and EF could be measured and in 47 PR fraction. The median time interval between echocardiography and CMR was 0.0 [IQR

0.52] years. None of the patients underwent reintervention during this time interval. After adjustment for gender, BMI, age of repair, the use of transannular patch, and PVR, significant associations were found between BR and RV EDV normalised to BSA (β=0.337, p=0.009), and RV ESV normalised to BSA (β=0.425, p=0.002), but not between AR and RV volumes.

Additionally, RV EF was significantly associated with BR (β=-0.43, p=0.003), and twist (β=0.30, p=0.034). LV EF was significantly associated with AR (β=0.61, p<0.001), and twist (β=0.60, p<0.001).

No correlations were found between rotational parameters and PR grades.

Exercise capacity

In 55 (67%) patients an exercise study was performed, 26 of whom underwent VO_{2max} measurement. The median workload capacity was 86% [IQR 22] and the median VO_{2max} was 83% [IQR 28]. We compared the median maximal work load, maximal heart rate, VO_{2max} and RER_{max} (all in % of expected) between the normal and abnormal twist group, between the normal and abnormal AR group, and between normal and abnormal BR group. Only maximal heart rate between the normal and abnormal twist group differed significantly (89 vs. 84%, p=0.044).

The maximal workload correlated significantly with BR and with twist (r=-0.276, p=0.041; r=0.306, p=0.023, respectively).

Discussion

This study demonstrates that LV twist is reduced in adults with corrected ToF, mainly as a result of decreased apical rotation. Over a quarter of patients had an abnormal apical rotation that was associated with larger LV dimensions and decreased biventricular systolic function.

Reduced left ventricular twist

In normal left ventricles, the dynamic interaction between subendocardial and subepicardial fibre helices leads to a twisting deformation. This twisting deformation has an important role in optimizing LV ejection. The understanding of LV twist in congenital heart disease is extremely limited. Reduced LV twist was reported in a few studies performed in children with corrected ToF.[24,25] In this study, 71% of the ToF patients had a normal twist pattern, but the twist was reduced in degrees. The study by Takayasu et al. described that the torsion in ToF patients was reduced due to decreased apical rotation and/or reversed BR. Forty-one per cent had a positive BR at the time of peak torsion.[24] We found a reversed basal pattern in 11% of the patients, 7% had no basal rotation, and 1% a prolonged rotation. These last two patterns were not described by Takayasu.

A relation between RV and LV systolic functions has been previously described in ToF patients. Broberg et al.[11] described that moderate-to-severe RV systolic dysfunction is more prevalent in patients with LV dysfunction. RV pressure and volume loading are likely to predispose the LV to the adverse

effects through several potential interventricular coupling mechanisms. In patients with ToF, mechanical interventricular interaction is observed by the obligatory interventricular septal defect patch that results in dysfunction of at least a portion of the ventricular septum[26, 27] and may contribute to the abnormal BR.

In the study of Puwanant et al.[28], the pulmonary artery pressure was inversely correlated with LV twist in patients with pulmonary hypertension due to septal flattening. In patients with ToF, it has been hypothesised that the ventricular septal shift due to RV pressure overload during the systolic phase and/or RV volume overload during the diastolic phase may be a mechanism that underlies suboptimal ventricular interactions. Our study also demonstrates a significant difference in septal motions between the groups with and without normal twist pattern. Between abnormal septal motions and abnormal BR a trend toward significance was found, but not between abnormal septal motions and abnormal AR. This finding suggests that abnormal septal motion influences BR, rather than AR, and therefore influences the twist.

Neurohormonal interventricular interaction probably also plays a role, because ventricular loading conditions activate the renin-angiotensin-aldosteron system, which in turn instigates myocardial fibrogenesis.[29] The suggestion that abnormal twist is a sign of cardiac dysfunction is supported by the finding of Mornos et al.[30] that log-transformed NT-proBNP levels correlated inversely with LV twist. In our study, we did not find a correlation.

In addition to these findings in literature, multivariable regression analyses showed significant associations between systolic function and rotational parameters, these were strongest between LV systolic function and AR, and between RV systolic function and BR. To assess if subclinical reduced twist really progresses to LV dysfunction represented as decreased LV EF, follow-up of patients is needed.

The value of apical rotation in ToF

In models of LV mechanics it has been shown that the LV myocardial fibre architecture is important for LV function. Van Dalen et al.[31] demonstrated that especially LV AR is influenced by LV configuration and highlights the vital influence of cardiac shape on LV systolic function.

In this study, abnormal AR was observed in more than one-quarter of all ToF patients. This group showed a significantly higher incidence of biventricular systolic dysfunction and larger LV dimensions.

Sheehan et al. reconstructed the RV of ToF patients and normal subjects in 3 dimensions. Patients with ToF had only at the apical level a significantly enlarged RV cross-sectional area. Second, the cross-sectional apical shape was rounder in patients with ToF. This RV apical dilatation may lead to distortion of LV apical geometry and altered fiber orientation of the apex of the heart, which can result in abnormal or decreased AR[32]. Our study demonstrates that impaired systolic RV function, assessed with eyeballing and with RV FAC, is related with reduced or abnormal LV apical rotation in adult patients with corrected ToF, likely by alteration of LV configuration. However, we did not observe a relation between the echocardiographic RV dimensions, i.e. annulus and apex-base, and AR. To investigate the predictive value of abnormal AR in patients with ToF, a prospective study is essential.

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Limitations

Adequate STE could not be performed in all patients because of the insufficient image quality. Also RV dilatation may hamper imaging because of the replacement of the LV apex as the acoustic window. Therefore, in this study all the images were obtained with great caution to reassure the acquisition of the true apex. If there was any doubt of image quality, the patient was excluded.

Imaging of the apical and basal levels was performed sequentially instead of simultaneously, thus introducing a potential error in the twist calculation. To minimize this error, we have matched the RR intervals of the 2 segments before generation of the twist.

We realised that the use of LV EF measured with biplane Simpson's method is questionable in patients with ToF, because of the altered LV shape due to RV volume overload. However, it is the most suitable echocardiographic method for LV EF at this moment. In one-third of the patients image quality was insufficient for this measurement, due mainly to the LV shift. With regard to the various rotation patterns we observed, LV EF was more often missing in the abnormal rotation groups. Therefore, the median LV EF could be overestimated in these groups.

Conclusion

The majority of adults with corrected ToF have a reduced LV twist as assessed with speckle-tracking echocardiography. Strikingly, in more than one-quarter of the ToF patients an abnormal AR is observed, which is associated with larger LV dimensions and decreased systolic biventricular function. These findings suggest that abnormal AR is a new and additional objective diagnostic criterion for detection of ventricular dysfunction.

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Part V

Summary and Discussion

Chapter 13

Summary

Summary

Congenital heart disease (ConHD) is the most prevalent form of congenital abnormality in new-borns. Due to successes in cardiac surgery and specialized congenital cardiac care the number of adult patients with ConHD is increasing rapidly. Surgical repair is hardly ever curative and many patients have residual lesions. This leads to an increased risk for complications including arrhythmias, ventricular dysfunction leading to heart failure and cardiac death. The goal of this thesis is to investigate long-term outcome, and novel, non-invasive diagnostic tools as biomarkers to assess cardiac function and functional capacity in adults with ConHD. **Chapter 1** is the general introduction of this thesis that provides the aims and outline of this thesis.

In **Chapter 2** we present results on outcome up to 40 years in patients with transposition of the great arteries, who underwent Mustard repair at young age, retrieved from a uniquely designed longitudinal study in which patients were investigated in-hospital every ten years. Two-third of the patients are still alive after 39 years, which is clearly diminished compared to the general Dutch population. The main causes of late mortality are sudden cardiac death and failure of the systemic RV. After nearly 40 years only 19% of the patients are free from events, i.e. arrhythmias, reintervention, heart failure or heart transplantation. Reinterventions have been required mainly for baffle-related complications. RV function is diminished in all but one patient, and a substantial number of patients developed heart failure in the last ten years. Predictors for heart failure are early post-operative arrhythmias and older age at operation. The diminished RV function and impaired exercise capacity prelude clinical deterioration and more cardiac failure can be expected in the near future.

An overview of previously published literature on natriuretic peptides is presented for patients with ConHD. **Chapter 3** describes natriuretic peptides BNP and NT-proBNP in patients with a simple congenital heart lesion: atrial and ventricular septal defect. Levels of BNP are increased in these patients in comparison to healthy controls. After percutaneous defect closure BNP levels decrease to levels comparable to controls, though after surgical defect closure BNP levels remain slightly elevated. Because BNP levels correlate strongly with shunt severity and pulmonary artery pressures, measurement of BNP might be a useful tool in the diagnostic work-up before atrial and ventricular septal defect closure.

Chapter 4 provides a systematic review of published literature on natriuretic peptides in patients with complex ConHD, focusing on patient with tetralogy of Fallot, systemic RV and Fontan circulation. In patients with tetralogy of Fallot and systemic RV BNP levels are increased compared to healthy age-matched controls, and correlate with various parameters of cardiac function. In patients with a univentricular heart, BNP levels are elevated before completion of the Fontan circulation with a total cavopulmonary connection, or when they are symptomatic, but seem no longer elevated in asymptomatic patients after completing the Fontan circulation. No data on prognostic value is available. Because of the small study populations conclusions should be drawn with caution on the use of BNP in these patients.

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In **Chapter 5** results are presented of a prospective study focusing on biomarker activity in adult patients with ConHD in an outpatient-clinic setting. NT-proBNP levels are described in 475 adult patients with ConHD and associations with echocardiography and exercise capacity are investigated. In 50% of these asymptomatic patients NT-proBNP levels are elevated. Higher NT-proBNP levels are associated with patient characteristics including older age, female gender, QRS duration, atrial fibrillation, and higher NYHA functional class. The levels of NT-proBNP differ with complexity of ConHD: highest levels are observed in patients with systemic RV or Fontan, while lowest levels of NT-proBNP are seen in patients with aortic coarctation and TGA after arterial switch operation. NT-proBNP levels correlate with systolic RV function in patients with a systemic RV. Higher NT-proBNP levels in patients with Fontan circulation are associated with impaired ventricular function. In patients with aortic stenosis and aortic coarctation NT-proBNP is mainly associated with diastolic LV function. Concerning exercise capacity, higher NT-proBNP is independently associated with lower maximal workload and lower peak oxygen uptake. In conclusion, NT-proBNP levels in ACHD patients differ with underlying diagnosis and its severity and are related to echocardiographic parameters and exercise capacity.

In **Chapter 6** the role of NT-proBNP for patients with repaired tetralogy of Fallot is discussed in more detail. NT-proBNP levels are elevated in more than 50% of the patients. NT-proBNP levels correlate with RV dilatation and dysfunction, but more strongly with LV systolic dysfunction, which is present in nearly 40% of the patients. The level of NT-proBNP is not associated with moderate or severe pulmonary regurgitation. NT-proBNP is associated with tricuspid and pulmonary regurgitation peak velocities. In these patients there is no relationship observed between exercise capacity and NT-proBNP.

Chapter 7 delineates the relationship between NT-proBNP and quality of life in 245 adult patients with ConHD. Besides reducing mortality, medical treatment is also focused on reducing morbidity and improving quality of life. Subjective health status as a measure of quality of life is assessed with the 36-item Short-Form health survey. In adult patients with complex ConHD, NT-proBNP is associated with quality of life, on the health status subdomain physical functioning, but not with the other 7 subdomains.

In **Chapter 8** high-sensitive troponin-T (hs-TnT) is assessed in 587 adult patients with ConHD in an outpatient setting. Hs-TnT above the 99th percentile of normal is found in a substantial number of asymptomatic patients, especially in those patients with a systemic RV or with associated elevated pulmonary pressures. Higher hs-TnT is associated with higher NYHA class, non-sinus rhythm, systolic ventricular dysfunction, and elevated pulmonary pressures. Hs-TnT correlates with NT-proBNP. Because this biomarker of myocardial damage is associated with ventricular function and NT-proBNP, it has diagnostic value and potential to serve as a predictor for heart failure and clinical outcome in adults with ConHD.

In **Chapter 9** we provide an overview of the release and diagnostic value of a novel biomarker, growth-differentiation factor 15, for the first time in adult patients with ConHD. Growth-differentiation factor 15 is elevated in a substantial number of adult patients with ConHD, and is associated mostly with elevated pulmonary pressures and exercise capacity. Independent of NT-proBNP, growth-differentiation factor 15

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is associated with exercise capacity and NYHA functional class, two important parameters for the clinical condition in adult patients with ConHD.

In **Chapter 10** we describe the use of speckle-tracking echocardiography to assess myocardial deformation in adult patients with a systemic RV, i.e. patients with congenitally corrected transposition of the great arteries and patients with transposition of the great arteries after Mustard repair. Global longitudinal strain of the systemic RV in patients is reduced compared to that of the systemic LV in healthy controls, most prominently in the apex. Reduced longitudinal strain is associated with cardiac function, higher NT-proBNP and tends to be associated with worsening NYHA class. Longitudinal strain is more reduced in patients with transposition of the great arteries after Mustard repair than congenitally corrected transposition of the great arteries, which was so far unknown and warrants further study.

Chapter 11 delineates the use of myocardial deformation as a measure for ventricular function in adult patients after repaired tetralogy of Fallot. Due to pulmonary regurgitation, patients with repaired tetralogy of Fallot often have RV volume overload and dilatation. The effect of RV volume overload on RV and LV myocardial deformation is assessed in 95 patients and 95 healthy controls of similar age and sex. RV longitudinal strain is reduced in patients compared to healthy controls, especially in the apical segment. Also longitudinal strain of the LV is reduced compared to controls, especially longitudinal strain of the septal wall. This indicates that not only RV dysfunction but also LV dysfunction occurs in these patients and that the two might be interrelated.

Chapter 12 focuses on the mechanism of LV contraction in 82 adult patients with repaired tetralogy of Fallot. Rotation and twist of the LV are assessed with use of speckle-tracking echocardiography and compared to 56 healthy controls. The majority of patients with repaired tetralogy of Fallot have a reduced twist of the LV. One-fourth of these patients with a reduced twist have an abnormal apical rotation. Abnormal apical rotation is associated with diminished LV as well as RV systolic function. Since both LV and RV systolic function are associated with LV rotation parameters, the hypothesis of ventricular-ventricular interaction is strengthened. Abnormal apical rotation could be a novel, objective diagnostic criterion to detect ventricular dysfunction in adult patients with repaired tetralogy of Fallot.

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Chapter 14

General discussion

General discussion

The aim of this thesis was to investigate adult patients with ConHD with focus on long-term outcome, and novel, non-invasive diagnostic tools that can contribute to accurate assessment of cardiac function and functional capacity. Cardiac laboratory biomarkers were investigated on their release and associations with cardiac function parameters, as well as the subsequent implications for clinical care. Furthermore, the feasibility, clinical value and future perspectives of speckle-tracking echocardiography were investigated. This technique has not been studied extensively in adults with ConHD. Within this general discussion we will address the proposed research questions, discuss our findings against the background of published literature and deliberate on clinical implications and future directions.

Late complications in adult congenital heart disease

The number of adult patients with ConHD is rapidly growing and patients get older as a result of successes in cardiac surgery and congenital cardiac care.[1] Although most of these adult patients live a normal life, they often have residual anatomical and/or functional abnormalities. This entails complications at adult age including arrhythmias, heart failure, need for re-intervention and sudden cardiac death.[2-4] To identify patients at risk for complications and adverse outcome, adequate monitoring of cardiac function and early detection of function deterioration are crucial. This could result in a more adequate medical treatment regime or more precise timing for re-intervention.

At adult age, heart failure is one of the most common complications and a main cause of death in ConHD patients.[3] Highest incidence of heart failure is seen in patients with more complex ConHD,[4] as was demonstrated in the first chapter of this thesis for patients with TGA after Mustard repair. The original heart failure syndrome in acquired heart disease comprises a triad of cardiac abnormality, exercise limitation and neurohormonal activation.[5] In the past some investigators stated that all patients with ConHD meet these criteria and therefore all would have heart failure by definition.[6] The presence of a cardiac abnormality is unmistakable, but whether the last two conditions are applicable to all ConHD patients is debatable. A recent large study by Kempny et al reporting on exercise capacity provided the first evidence to support this hypothesis.[7] They demonstrated that exercise capacity is diminished in almost all adult patients with ConHD compared to healthy controls, though there are substantial differences between the various congenital heart lesions. Diagnosis-specific reference values for cardio-pulmonary exercise testing were presented. These specific reference values should be taken into account by clinicians for clinical decision-making or when advising patients on choice of sports activities and choice of occupation.

The third pillar of the heart-failure triad, neurohormonal activation, is less well studied and hence one of the main topics of this thesis. Possibly, also for neurohormonal activation specific reference values are mandatory. Laboratory biomarkers could potentially serve as a tool to improve risk-stratification for identification of those patients that will develop late complications. Better risk-stratification, preferably in an early stage, will identify high-risk patients that require close observation or treatment. And in addi-

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tion, defining low-risk patients is important to reassure these patients and diminish regular checks with possible financial benefits as well.

However, information on the diagnostic and prognostic value of natriuretic peptides and other cardiac laboratory biomarkers in patients with ConHD is limited, as we demonstrated in the two systematic reviews in this thesis.[8, 9] Therefore, we initiated a prospective study, the BioCon study, in an outpatient clinic setting, focusing on biomarker activity and the relationship with echocardiographic parameters and exercise capacity in adult patients with ConHD. Blood samples were analysed for biomarkers, e.g. natriuretic peptides, hs-TnT, hs-CRP and GDF-15. In this thesis we present the first results and we looked at associations with clinical and echocardiographic data in a cross-sectional manner. This study is also the start of a prospective follow-up study with sequential biomarker measurement to assess the prognostic value of biomarkers in adults with ConHD.

Natriuretic peptides in adult congenital heart disease

Natriuretic peptides BNP and NT-proBNP are well-established biomarkers in acute and chronic heart failure due to acquired heart disease.[10-13] However, their role in the diagnostic approach and decision making in patients with ConHD is not well defined. Chronic, lifelong volume and pressure overload may be present as a result of residual lesions after surgery in childhood, which could influence natriuretic peptides release.[14] This could result in a different approach for the use of natriuretic peptides in ConHD patients from patients with acquired heart disease.

Results from the BioCon study, described in several chapters of this thesis, demonstrated that NT-proBNP levels are elevated in more than half of the adult patients with ConHD who were nearly all asymptomatic and in a stable condition.[15, 16] There are clear differences in NT-proBNP levels among the various congenital heart lesions. The level of NT-proBNP seems to be determined by the complexity of ConHD: highest values are observed in patients with a systemic RV or Fontan circulation, whereas lowest values are seen in patients with aortic coarctation and TGA after arterial switch operation. Furthermore, disease-specific correlations between NT-proBNP and echocardiographic cardiac function parameters are identified. NT-proBNP is most strongly related to LV ejection fraction in patients with tetralogy of Fallot, RV systolic function in patients with a systemic RV, and diastolic LV function in patients with CoA and congenital AoS. In short, the strongest relationships are seen with systemic ventricular function in all ConHD, independent of ventricular morphology and underlying ConHD. The findings in this thesis are in line with previous smaller reports,[17, 18] and indicate that BNP carries diagnostic value to monitor systemic ventricular function in adult ConHD patients. Those patients with elevated NT-proBNP have worse ventricular function and hence may be the ones that benefit most from heart failure medication, and are in need of frequent follow-up.

It is interesting to see that NT-proBNP also mirrors the patients' subjective perception of physical functioning.[19] Higher NT-proBNP showed an association with worse NYHA functional class comparable to the well-known association between NT-proBNP and NYHA in patients with heart failure due to acquired

heart disease, which in those patients is associated with increased risk for heart failure hospitalization and mortality.[20, 21] The potential prognostic value of NT-proBNP was also presented by the significant relationship between NT-proBNP and exercise capacity. Exercise capacity is known to be associated with adverse cardiac outcome in adult ConHD patients.[22] One small study of 49 patients with various ConHD demonstrated that natriuretic peptides predict mortality after a follow-up period of 8 years, and similar findings were observed in a study focusing only on adults with a systemic RV.[23, 24] Those findings will have to be confirmed in a larger study that can draw conclusions for all ConHD, with diagnoses-specific recommendations.

Because of the significant influence of age and sex on BNP levels in adults with ConHD,[15] that is also known in the general population,[21] age and sex-specific reference values are needed. Whether disease-specific reference values for each ConHD are needed is not clear yet. BNP could be an elevated but stable marker over time, and seen as 'normal' for some congenital heart lesions. Meanwhile elevated NT-proBNP could indicate the presence of subclinical on going deterioration and be a sign of adverse outcome in these patients. We support this last hypothesis, which is strengthened by findings in this thesis, but remains to be confirmed by follow-up.

A drawback of NT-proBNP is the large variety between individuals, which limits the conclusions based on one single NT-proBNP measurement in a specific patient. Possibly, the changes in NT-proBNP over time will provide more information, and reflects deteriorating or improving cardiac function. A recent meta-analysis of randomized controlled trials focusing on patients with heart failure due to acquired heart disease has shown that natriuretic peptide-guided treatment of heart failure was beneficial in patients aged <75 years. [25] In these patients natriuretic peptide-guided therapy reduced all-cause mortality, and heart failure as well as cardiovascular hospitalization. Possibly, sequential NT-proBNP measurement could provide information on cardiac function, guide medical treatment and provide insight in prognosis of adult patients with ConHD. This will be studied in the near future as part of the BioCon prospective study.

Furthermore, since natriuretic peptides comprise a single measure of the neurohormonal system, it would be interesting to combine the findings of our studies with data concerning the renin-angiotensin-aldosterone and sympathoadrenergic axes. So far these fields have hardly been studied[26] and might provide novel insight in why for example heart failure drugs seem to be less effective in ConHD patients, especially in patients with a systemic RV.[27]

High-sensitive cardiac troponin-T in adult congenital heart disease

Cardiac troponin-T is a protein unique to the cardiomyocyte.[28] Increases in troponin-T are highly specific for myocardial damage, and have been utilized for the past two decades as markers for defining myocardial infarction.[29] With the introduction of high-sensitive assays[30] small amounts of troponin-T reflecting cardiomyocyte damage or cell leakage became detectable in apparently healthy subjects, and other cardiovascular diseases including acute and chronic heart failure, hypertension and hypertro-

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phic cardiomyopathy.[31-33] The whole concept of troponin use had to be changed. Instead of elevated or non-elevated troponin, this novel high-sensitive biomarker should be interpreted as a continuous
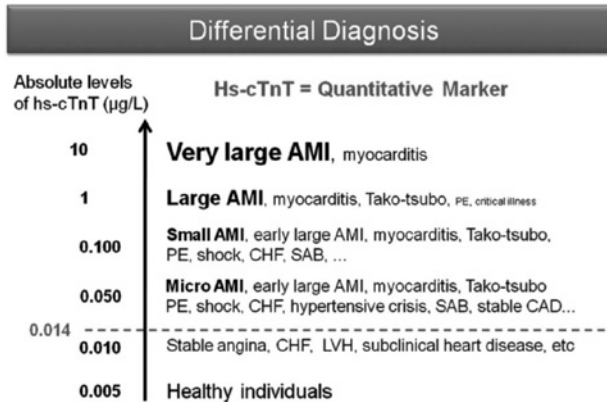

FIGURE 1. Hs-TnT differential diagnosis (published with permission from Twerenbold et al.[34])

variable with a differential diagnoses for each degree of absolute hs-TnT level (Figure 1).[34] Patients with ConHD could also be added to this figure, as is demonstrated in this thesis.

As part of the BioCon study, the release of hs-TnT was assessed for the first time in adult patients with ConHD in an outpatient setting. In this thesis we demonstrate that hs-TnT is elevated in nearly 10% of adults with ConHD, most often in patients with TGA operated on by Mustard repair, congenitally corrected TGA or patients with ConHD associated elevated pulmonary pressures. The level of hs-TnT is associated with cardiac function, NYHA functional class and NT-proBNP, which indicates that this marker carries diagnostic value in these patients. A recently published small study in patients with pulmonary arterial hypertension due to ConHD presented a similar percentage of patients with elevated hs-TnT. This study showed an inverse relationship between hs-TnT and survival.[35]

The pathophysiological mechanism behind release of hs-TnT in these mostly asymptomatic patients can only be speculative, and is likely to be multifactorial. Although coronary ischemia is less obvious in these relatively young patients, it should always be considered because of its major impact on cardiac function and outcome if untreated. However, in most patients an acute coronary syndrome is unlikely and other causes including oxygen supply/demand mismatch, chronic volume- and pressure overload, renal disease, arrhythmias, inflammatory- and auto-immune reactions could all be involved in the release of hs-TnT.[36-41]

Hs-TnT is associated with various parameters that have proven prognostic value in adult ConHD. In addition, elevated hs-TnT is a predictor for heart-failure hospitalization and cardiac mortality in various other cardiac disease.[33, 42] Therefore, although no follow-up data is available yet, we postulate that elevated hs-TnT is associated with myocardial damage and consequently will result in an increased risk for deteriorating cardiac function, heart failure and eventually death. So although evidence is still limited,

we believe that those patients with elevated hs-TnT should be followed closely at the outpatient clinic. Potential causes of hs-TnT release should be searched in one of the suggested aetiologies and treated accordingly. In those patients with elevated hs-TnT, the measurement should be repeated after a certain time period to see if hs-TnT is elevated chronically or decreased.

It is important for doctors in the emergency department to know that hs-TnT levels can be elevated in asymptomatic, stable adult patients with ConHD. They must be able to differentiate between acute cardiac ischemia and chronic subclinical on-going myocardial damage, using a thorough patient history, physical examination and rise and fall in troponin values.[43]

Other novel cardiac biomarkers in adult congenital heart disease

The interpretation of natriuretic peptides can be difficult because of the large biological variation. The ideal biomarker should reflect ventricular function but should show less variation in individual values than natriuretic peptides. Novel biomarkers GDF-15 and hs-CRP have incremental prognostic value over NT-proBNP in acquired heart failure.[33] In chapter 9 of this thesis we described GDF-15 in stable ConHD patients in an outpatient setting. Because of the good correlation with functional capacity, incremental to NT-proBNP, this marker also seems to be promising for heart failure in adult patients with ConHD.

Since natriuretic peptides, hs-TnT and GDF-15 all seem to have diagnostic and potentially prognostic value, we will have to focus on the incremental value for each of the biomarkers. With the BioCon prospective study we will assess which one of the biomarkers, or combination of biomarkers has the strongest predictive value for adverse outcome in adults with ConHD.

Speckle-tracking echocardiography in adult congenital heart disease

In addition to cardiac laboratory biomarkers, two-dimensional speckle-tracking strain imaging to measure myocardial deformation may be of use to evaluate LV and RV function, and to gain insight in the presence of ventricular-ventricular interaction. For patients with a systemic RV and patient with repaired tetralogy of Fallot adequate assessment of especially RV function is of great importance. Because of the complex geometry of the RV this is difficult with conventional echocardiography. The use of speckle-tracking echocardiography will now be delineated in the context of other diagnostics for the two diagnoses separately.

Transposition of the great arteries

Surgical management of patients with TGA has changed substantially. Nowadays the arterial switch operation is performed,[44] but until the mid-1980s most patients underwent the atrial switch operation (Senning[45] or Mustard procedure[46]). In 1968 the surgical program for ConHD started in the Erasmus MC, Rotterdam. All consecutive patients younger than 15 years of age, operated for ConHD between 1968 and 1980, were included in a longitudinal study to investigate physical and psychosocial aspects; "the Rotterdam Quality of Life study". This uniquely designed study evaluated patients in-hospital every 10

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years in 1990, 2001 and in 2012. In this thesis we report on the outcome after nearly 40 years for patients with TGA that underwent Mustard surgery as part of that longitudinal study. A survival rate of 68% after 40 years was observed. This is clearly diminished compared to the general Dutch population, and the fact that one-third of these patients died is worrisome. Late mortality appears to be caused by two main problems: sudden cardiac death and heart failure-related mortality.[47]

Ventricular arrhythmias were the sole cause of death in the last decade of this study. This raises the question whether more patients with a systemic RV should receive an ICD for primary prevention. Decisions on this topic are complicated for several reasons. First, patient selection for ICD implantation is difficult. According to the ESC acute and chronic heart failure guidelines patients should receive an ICD for primary prevention when they are symptomatic and have an LV ejection fraction below 35%.[5] However, one of the patients in our study who died from VF had only mild RV function impairment, with a low a priori risk for ventricular arrhythmias. On the other hand, a recent study showed that out of 23 patients with atrial switch operation that were identified as high-risk patients and given an ICD for primary prevention, only one patient received an appropriate ICD shock over a median follow-up of 3.5 years.[48] This emphasizes the current difficulty of risk-stratification in these ConHD patients. Probably we need disease-specific indications. In addition, we know that in young patients with an ICD inappropriate shocks occur more often mainly due to supraventricular tachycardias, and these inappropriate shocks lead to more psychological problems.[49, 50] Furthermore, the relatively narrow baffles make lead implantation difficult and leads may cause obstruction. Patients are also relatively young, so likely they will require at least one lead renewal, which entails associated risks for complications. At the moment ICD implantation should be limited to those patients with proven increased risk for ventricular arrhythmias being symptomatic, sudden cardiac death survivors or with sustained ventricular tachycardia confirmed on Holter-monitoring. Long-term rhythm evaluation with use of implantable loop recorders may contribute to detection of subclinical arrhythmias that may prelude life-threatening ventricular arrhythmias and sudden death. So far in adult ConHD implantable loop recorders have only been studied retrospectively,[51] but we propose a prospective study to see whether patients at high-risk are identifiable with use of these devices.

The second major concern in adult patients after Mustard repair is the RV, which is not build to sustain the systemic circulation over a lifetime. Systemic ventricular dysfunction is an increasing and major concern, whereas only one patient still had a normal RV function in our study. RV dysfunction will lead to cardiac failure in time.[52] We observed an on-going decline in RV systolic function over the last 30 years, and a substantial number of patients subsequently developed heart failure. Patients after Mustard repair beyond the third decade of life are likely to encounter a period of accelerated decline with heart failure symptoms and eventually premature death.

Early detection of those patients at high-risk could be improved by using natriuretic peptides and hs-TnT in TGA-Mustard patients. Both markers were considerably higher among these patients in comparison to other ConHD, and both were independently associated with cardiac function. As a predictor of hospitalization, heart failure and mortality, first evidence has appeared that NT-proBNP could be a

potential important risk predictor in these patients.[24] Although for hs-TnT no longitudinal data is there yet, the higher levels of hs-TnT reflect myocardial damage and will most likely be associated with adverse outcome as well.

To quantify RV function more accurately in patients with a systemic RV, a novel echocardiographic technique, speckle-tracking echocardiography was studied in this thesis. Although feasibility was limited to 75% due to difficult visualization of the dilated RVs in these relatively old TGA-Mustard patients, reproducibility was good with a low intra-observer and inter-observer variability comparable to other studies.[53, 54] Strain parameters in TGA-Mustard patients were significantly reduced in comparison to healthy controls, and correlated with conventional cardiac function parameters. Reduced longitudinal strain was associated with increased NT-proBNP as well as a tendency to worsening NYHA class. Global longitudinal strain has recently been shown to be a superior predictor for mortality to ejection fraction for patients with left-sided heart failure.[55] This thesis provides evidence that this novel semi-automatically calculating technique could be a useful tool to quantitatively monitor ventricular function over time and hence detect dysfunction in an early stage of the disease.

Early detection of cardiac dysfunction can prevent patients from developing cardiac failure by adequate treatment strategies. Heart failure therapy from acquired heart disease is extrapolated to patients with a systemic RV, however this seems to be less successful. Standard heart failure drugs can be prescribed to Mustard patients, but are probably less effective than in acquired heart disease, as is demonstrated by several negative drug trials.[27, 56] New treatment options should be examined in this patient population. Possibly there is a place for advanced pacing devices, such as cardiac resynchronization systems. Furthermore, given the growing number of patients with cardiac failure we expect that more patients will qualify for ventricular assist devices or heart transplantation in the near future, although currently experience is still limited and technical difficulties are present in ConHD patients.[57]

The incidence of supraventricular tachycardias increases substantially in older patients.[47] This is worrisome because these tachycardias are a predictor for sudden cardiac death in Mustard patients.[58] Although new baffle stenosis or leakage are less often encountered at older age, they were the main cause of reintervention and remain a point of attention and should be treated aggressively with surgical or catheter intervention with a low threshold.

TGA after Mustard repair versus congenitally corrected TGA

Patients with a systemic RV are often studied as one group. Interestingly, in several of our studies, differences between TGA-Mustard patients and ccTGA patients were visible. Longitudinal strain tended to be more reduced in Mustard patients than in ccTGA patients. Furthermore, in our studies on NT-proBNP and hs-TnT, both biomarkers were elevated in both group, but median NT-proBNP as well as hs-TnT levels was higher in patients with ccTGA. Lower strain parameters mirroring decreased RV function in Mustard patients could have several causes including a direct influence of prior cardiac surgery, loss of additional atrial function to support RV function, or the fact that the systemic RV in ccTGA patients had to encounter systemic pressure from birth and therefore may be better resistant to pressure overload.

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On the other hand, the biomarker values are remarkable and contradictory to the strain parameters. Higher NT-proBNP in ccTGA patients could be caused by the larger percentage of ccTGA patients with a pacemaker. Pacing is known to increase NT-proBNP levels.[59] Furthermore, higher NT-proBNP levels in ccTGA patients could be the result of NT-proBNP release from atrial tissue, which is lower in Mustard patients because of the baffles. The higher values of NT-proBNP and hs-TnT in patients with ccTGA may reflect worse outcome. Previous small studies report heart failure more often as well as worse survival in ccTGA patients[60, 61] compared to outcome of patients with TGA-Mustard described in this thesis. However, a study with direct comparison of these two patients groups should be performed to define the true differences, to determine if different treatment strategies for each diagnosis are needed.

Arterial switch operation
In contrast to patients with TGA after Mustard repair, NT-proBNP levels were notably low in patients with TGA corrected by arterial switch operation, mirroring their good clinical condition and normal cardiac function.[62] Late outcome in these patients is still unknown, because the surgical procedure is performed since the mid-1980s. However, the low NT-proBNP levels in combination with the absence of symptoms are certainly promising for the long-term outcomes of these patients.

Tetralogy of Fallot
Survival of patients with repaired tetralogy of Fallot is satisfactory, with rates of over 90% after 30 years.[63] Meanwhile, the need for reintervention after repair of tetralogy of Fallot is substantial. Nearly all patients have some degree of pulmonary regurgitation as a result of the trans-annular patch that was used during surgical repair. Pulmonary regurgitation can lead to RV dilatation and dysfunction and will eventually require pulmonary valve replacement.[64] Adequate timing of pulmonary valve replacement is still a subject of debate.

In patients with tetralogy of Fallot the ventricle of interest has been the RV for years, while less attention was drawn to the LV. However, recent studies demonstrate that LV dysfunction is often observed in these patients, and is associated with heart failure and sudden cardiac death.[65, 66] Especially in this population, LV dysfunction is thought to be related to RV dysfunction by ventricular-ventricular interaction.[67] In this thesis we demonstrate that higher NT-proBNP is associated with RV dysfunction, but more strongly with LV dysfunction and higher pulmonary pressures, especially in older patients.

Furthermore, Chapter 11 and 12 focussed on speckle-tracking echocardiography in patients with repaired tetralogy of Fallot. Longitudinal strain of the RV was diminished compared to healthy controls, mainly in the apical segment. Also, LV twist is reduced in the majority of these patients compared to controls, mainly as a result of decreased apical rotation. Those with abnormal apical rotation had larger left ventricles and decreased systolic function of both the LV and RV. RV dilatation, especially in the apex, could result in altered LV geometry and consequently leading to abnormal apical rotation and decreased LV efficiency. Adverse ventricular-ventricular interaction may also be influenced by abnormal

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interventricular septum motion, as in our study abnormal septum motion was more often seen in patients with abnormal twist.

These studies provide more insight in ventricular contraction patterns in patients with tetralogy of Fallot. The studies show that ventricular-ventricular interaction exists and abnormal LV torsion is present in patients after tetralogy of Fallot repair. The clinical impact of our findings is yet unknown, but may well prove to be important. LV and RV deformation as well as LV torsion may become valuable for early detection of biventricular dysfunction. A prospective study is needed to shed further light on the underlying mechanisms that can help us understand the influences that lead to biventricular dysfunction. Which one of the two ventricles starts to deteriorate first? What is the influence of pulmonary regurgitation, or residual RV outflow tract obstruction and pulmonary stenosis? What about aortic root dilatation? Do patients with an abnormal LV twist have a worse prognosis? As soon as these questions are answered, myocardial deformation measurements could be used to change treatment, including more precise timing for pulmonary valve replacement, medication or the need for cardiac resynchronization therapy.

Conclusions and future perspectives

This thesis provides a serious attempt to delineate the role of cardiac biomarkers in adult congenital heart disease. NT-proBNP, hs-TnT and GDF-15 are associated with NYHA class and correlate with each other as well as with cardiac function parameters in various degrees. All three laboratory markers carry diagnostic value by reflecting cardiac function, albeit with various impact and through different pathways. Therefore these markers could contribute to cardiac function monitoring, alone or together, in adult patients with ConHD.

However, the biomarkers studied in this thesis are not ideal. With a single measurement, individual values differ significantly. The suggestions for use of these biomarkers are hence more difficult to extrapolate to an individual patient. It is rather unlikely that all processes that are involved in the heart failure syndrome could be captured with one biomarker. Therefore, a multi-marker approach with blood sampling at multiple time points, in which the combination of biomarkers and course of biomarker levels is assessed, seems a plausible future direction.

And maybe we have to look further than these protein-based biomarkers. Recently, research emerged in the field of micro-RNA's (MiRNAs), that are presented as novel cardiac biomarkers. MiRNAs are short, noncoding RNA sequences that regulate gene expression at the posttranscriptional level by targeting the 3'-untranslated region of mRNA sequences. MiRNAs are involved in most all cellular processes, also in the heart. In heart disease, abnormal expression of MiRNAs is observed.[68] In 2008 circulating miRNAs were discovered in the blood. Compared to protein-based biomarkers, advantages of these miRNAs are their remarkable stability in the circulation; they are regulated in a tissue- and pathology-specific manner and can be detected with high sensitivity and specificity.[69] MiRNAs are very interesting research purposes, and possibly they could become of use as novel disease markers or treatment targets in the future.

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The growing number of adult patients with ConHD, especially those patients with moderate and highly complex ConHD, will entail an increasing demand for specialized care. The combination of cardiac laboratory biomarkers and novel echocardiographic biomarkers can help us to unravel mechanisms behind cardiac failure in patients with ConHD. This thesis is a step forward towards better risk-stratification in adult patients with ConHD.

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Part VI

Appendices

Nederlandse samenvatting

Aangeboren hartafwijkingen zijn de meest voorkomende aangeboren afwijking bij pasgeborenen. Door verbetering in hartchirurgie en gespecialiseerde cardiologische zorg worden deze patiënten steeds ouder en neemt het aantal volwassen patiënten met een aangeboren hartafwijking snel toe. Operaties op kinderleeftijd zorgen zelden voor compleet herstel en veel patiënten hebben dan ook restafwijkingen. Deze restafwijkingen zorgen voor een verhoogd risico op complicaties zoals ritmestoornissen, hartfalen en overlijden. Het doel van dit proefschrift is het in kaart brengen van de lange termijn uitkomsten en het onderzoeken van nieuwe "biomarkers" om de hartfunctie en inspanningscapaciteit van volwassen patiënten met een aangeboren hartafwijking te beoordelen. **Hoofdstuk 1** is de algemene inleiding van dit proefschrift, waarin het doel en de indeling van het proefschrift wordt beschreven.

In **Hoofdstuk 2** worden de lange termijn uitkomsten gepresenteerd van patiënten met een transpositie van de grote vaten (hartafwijking waarbij de lichaamsslagader en longslagader verkeerd zijn aangesloten) die hiervoor op jonge leeftijd, in de jaren 70 in Rotterdam, een Mustard operatie hebben ondergaan. In het kader van de unieke "Rotterdam, Quality of Life" studie zijn deze patiënten elke 10 jaar uitvoerig onderzocht in het ziekenhuis. Nu, na 39 jaar, is 2/3 van deze patiënten nog in leven, wat laat zien dat de overleving duidelijk verminderd is in vergelijking met de algemene Nederlandse bevolking. De belangrijkste oorzaken van overlijden op latere leeftijd zijn plotse hartdood en hartfalen. Slechts 1 op de 5 patiënten is na 39 jaar vrij gebleven van ingrepen of complicaties, zoals ritmestoornissen, nieuwe ingrepen, hartfalen en harttransplantatie. De rechter hartkamer, die in deze patiënten de systeemcirculatie ondersteunt, is in functie verminderd bij vrijwel alle patiënten. Tevens heeft een aanzienlijk deel van deze patiënten met een systeem rechter hartkamer hartfalen ontwikkeld in de laatste 10 jaar. Uit onze studie blijkt dat het hebben van ritmestoornissen vroeg na de Mustard operatie en een oudere leeftijd waarop de Mustard operatie werd uitgevoerd voorspellers zijn voor het krijgen van hartfalen. De duidelijk verminderde kamerfunctie van het hart in combinatie met een verminderde inspanningscapaciteit laten zien dat er een reële kans bestaat dat deze patiënten verder achteruit zullen gaan en er meer hartfalen op zal treden in de nabije toekomst. Aan de andere kant is de inspanningscapaciteit niet slechter dan 10 jaar geleden.

De volgende hoofdstukken gaan over de zogenaamde natriuretische peptiden; BNP en NT-proBNP. Dit zijn eiwitten die vrijkomen in het bloed zodra de wand van de hartkamers onder spanning komt te staan als gevolg van druk- en/of volume overbelasting. We kunnen deze eiwitten bepalen na afname van een buisje bloed. Uit eerder onderzoek is gebleken dat deze "biomarkers" belangrijke informatie geven over de hartfunctie en prognose bij patiënten die hartfalen ontwikkelen bij een verworven hartaandoening. Bij patiënten met een aangeboren hartafwijking is nog erg weinig bekend over deze biomarkers.

Er wordt een overzicht gegeven van alle literatuur over natiuretische peptiden bij patiënten met een aangeboren hartafwijking. In **Hoofdstuk 3** worden natriuretische peptiden bij patiënten met een

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atriumseptumdefect (gaatje in het tussenschot van de boezems van het hart) en patiënten met een ventrikelseptumdefect (gaatje in het tussenschot van de kamers van het hart) beschreven. BNP waarden in het bloed van patiënten zijn verhoogd in vergelijking tot gezonde individuen. Na sluiting van het septumdefect met een 'parapluutje' via de lies, verlagen de BNP waarden naar waarden die vergelijkbaar zijn met gezonde individuen. Echter bij patiënten waarbij het septumdefect met een hartoperatie gesloten wordt, blijven de BNP waarden licht verhoogd.

Hoofdstuk 4 geeft een systematisch overzicht van gepubliceerde artikelen over BNP en NT-proBNP bij patiënten met een complexe aangeboren hartafwijking. Hieronder vallen patiënten met een 'tetralogie van Fallot' (hartafwijking waarbij er sprake is van een gaatje in het tussenschot van de hartkamers, een verdikte klep naar de longslagader, een iets naar het midden verschoven grote lichaamsslagader en verdikte wand van de rechter hartkamer), patiënten met een rechter kamer die de systeem circulatie ondersteunt (zoals bij de eerder genoemde patiënten na Mustard operatie), en patiënten met een Fontan circulatie (hartafwijking waarbij het hart slechts één functionele hartkamer heeft in plaats van twee). Bij patiënten met een tetralogie van Fallot of systeem rechter kamer zijn BNP waarden verhoogd in vergelijking met gezonde individuen van dezelfde leeftijd en hetzelfde geslacht. Bij patiënten met een Fontan circulatie zijn BNP waarden verhoogd voorafgaande aan de laatste hartoperatie die de Fontan circulatie compleet maakt, of op het moment dat zij klachten hebben. Daarnaast is de hoogte van het BNP gerelateerd aan verschillende parameters van hartfunctie. Het is nog onduidelijk of het hebben van een verhoogd BNP ook aangeeft dat patiënten met een aangeboren hartafwijking een slechtere uitkomst op de lange termijn zal hebben, dat wil zeggen eerder hartfalen ontwikkelt of komt te overlijden. Gezien de kleine hoeveelheden patiënten in de studies moeten conclusies over het gebruik van BNP in volwassen patiënten met een aangeboren hartafwijking in dit systematisch review met enige terughoudendheid getrokken worden. Er is behoefte aan grote, goed uitgevoerde studies.

In **Hoofdstuk 5** worden de resultaten gepresenteerd van een studie die werd opgezet om specifiek te kijken naar activiteit van de biomarker NT-proBNP in volwassen patiënten met een aangeboren hartafwijking. NT-proBNP werd gemeten in 475 volwassenen met een aangeboren hartafwijking die werden gezien op de polikliniek. Hierbij werden relaties tussen de hoogte van het NT-proBNP en de hartfunctie en inspanningscapaciteit onderzocht. In meer dan 50% van deze patiënten zijn de NT-proBNP waarden verhoogd. Een hoger NT-proBNP wordt gezien bij patiënten met een oudere leeftijd, vrouwelijk geslacht, een onregelmatig hartritme genaamd boezemfibrilleren en patiënten met klachten die passen bij hartfalen. De hoogte van het NT-proBNP neemt toe met toenemende complexiteit van de aangeboren hartafwijking: hogere NT-proBNP waarden worden gezien in patiënten met een systeem rechter kamer en Fontan circulatie, terwijl patiënten met minder complexe afwijkingen, zoals een aorta coarctatie (aangeboren vernauwing in de lichaamsslagader), de laagste NT-proBNP waarden hebben. In patiënten met een systeem rechter kamer is de hoogte van het NT-proBNP gerelateerd aan de rechter kamerfunctie: hoe slechter de hartkamerfunctie, des te hoger het NT-proBNP. In patiënten met een aangeboren aortaklepstenose (een verdikking van de hartklep naar de lichaamsslagader) of aorta coarc-

tatie wordt hoger NT-proBNP gevonden bij patiënten met afwijkende relaxatie van de hartkamers. Wat betreft inspanningscapaciteit: hoger NT-proBNP is gerelateerd aan verminderde maximale inspanning en verminderde maximale zuurstofopname tijdens inspanning. Concluderend is de hoogte van het NT-proBNP afhankelijk van de onderliggende aangeboren hartafwijking en de ernst daarvan, en gerelateerd aan echocardiografische bevindingen en inspanningscapaciteit.

In **Hoofdstuk 6** wordt verder ingegaan op de rol van NT-proBNP in volwassen patiënten met gecorrigeerde tetralogie van Fallot. NT-proBNP waarden zijn verhoogd in meer dan 50% van deze patiënten. Hoger NT-proBNP is gerelateerd aan een verwijde rechter hartkamer en verminderde rechter kamerfunctie, maar nog sterker gerelateerd aan verminderde linker kamerfunctie. Verminderde linker kamerfunctie is aanwezig in 40% van de patiënten en lijkt van belang om te vervolgen bij volwassen patiënten met gecorrigeerde tetralogie van Fallot. In deze patiëntengroep blijkt NT-proBNP niet gerelateerd aan inspanningscapaciteit.

Hoofdstuk 7 beschrijft de relatie tussen NT-proBNP en kwaliteit van leven in 245 volwassen patiënten met een aangeboren hartafwijking. Naast het verminderen van sterfte is medische behandeling ook gericht op het verbeteren van kwaliteit van leven. Subjectieve gezondheidstoestand als een maat van kwaliteit van leven is gemeten met de 'SF-36' vragenlijst in patiënten met een aangeboren hartafwijking. In volwassen patiënten met een complexe aangeboren hartafwijking is NT-proBNP gerelateerd aan kwaliteit van leven op het subdomein lichamelijk functioneren, maar niet met de overige 7 subdomeinen van de SF-36.

In **Hoofdstuk 8** wordt hs-TnT beschreven, een biomarker die schade van de hartspier weerspiegelt en een van de belangrijkste metingen is bij een acute hartaanval. Hs-TnT wordt onderzocht in een poliklinische setting in 587 volwassenen met een aangeboren hartafwijking. Hs-TnT is verhoogd in een aanzienlijk aantal patiënten, met name in patiënten met een systeem rechterkamer of verhoogde longslagaderdrukken, zonder dat er bij hen sprake is van een hartaanval. Hoger hs-TnT wordt met name gezien bij patiënten met klachten passend bij hartfalen, verminderde hartkamerfunctie, verhoogde longslagaderdrukken of met een onregelmatig hartritme. De hoogte van het hs-TnT is gerelateerd aan de hoogte van het NT-proBNP. Aangezien hs-TnT gerelateerd is aan hartfunctie en de hartfalen biomarker NT-proBNP, blijkt dat hs-TnT diagnostische waarde heeft en mogelijk kan fungeren als voorspeller voor het ontstaan van hartfalen en klinische uitkomst in volwassenen met een aangeboren hartafwijking.

In **Hoofdstuk 9** wordt een overzicht gegeven van de diagnostische waarde van een nieuwe biomarker, GDF-15. Dit is de eerste keer dat deze biomarker wordt beschreven in volwassen patiënten met een aangeboren hartafwijking. GDF-15 is verhoogd in een aanzienlijk aantal patiënten, en verhoogde GDF-15 wordt met name gezien bij patiënten met verhoogde drukken in de longslagader en verminderde inspanningscapaciteit. Onafhankelijk van de hoogte van het NT-proBNP is GDF-15 geassocieerd met inspanningscapaciteit en NYHA klasse, welke twee belangrijke maten zijn voor de conditie van patiën-

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ten met een aangeboren hartafwijking. Dit betekent dat GDF-15 mogelijk in de toekomst als soortgelijke maat gebruikt zou kunnen worden voor deze patiënten.

In **Hoofdstuk 10** wordt het gebruik van speckle-tracking echocardiografie, een nieuwe echotechniek om het samentrekken van het hart beter te kunnen beoordelen, beschreven in volwassen patiënten met een systeem rechterkamer. Hieronder vallen patiënten met een transpositie van de grote vaten geopereerd met de Mustard operatie en patiënten met een 'congenitaal gecorrigeerde transpositie van de grote vaten'. Bij de congenitaal gecorrigeerde transpositie van de grote vaten zijn door een afwijking in de ontwikkeling van het hart de rechter en linkerhartkamer van positie verwisseld. De rechterkamer voorziet daardoor de systeemcirculatie van bloed. Verkorting van de hartspier in de lengte richting van de hartkamer, gemeten met speckle-tracking echocardiografie, heet 'longitudinale piek-strain'. Longitudinale piek-strain is verminderd in patiënten met een systeem rechter kamer ten opzichte van longitudinale piek-strain van de systeem linker kamer in gezonde vrijwilligers. Verminderde longitudinale piek-strain wordt geassocieerd met verminderde hartfunctie, hoger NT-proBNP en lijkt mogelijk gerelateerd aan het hebben van klachten passend bij hartfalen. Longitudinale piek-strain lijkt sterker verminderd in patiënten met transpositie van de grote vaten gecorrigeerd middels Mustard operatie dan in patiënten met een congenitaal gecorrigeerde transpositie van de grote vaten. Dit verschil tussen deze twee patiënten groepen was tot op heden niet bekend en zal verder onderzocht moeten worden.

Hoofdstuk 11 bevat informatie over het gebruik van longitudinale piek-strain als maat voor hartkamer-functie in volwassen patiënten na operatie voor tetralogie van Fallot. Na een operatie op jonge leeftijd houden patiënten met tetralogie van Fallot vaak lekkage van de klep naar de longslagader over, wat leidt tot volume overbelasting en verwijding van de rechter hartkamer. Het effect van volume overbelasting van de rechter hartkamer op de hart functie, gemeten met longitudinale piek-strain van de rechter en linker hartkamer, is onderzocht in 95 patiënten en 95 gezonde vrijwilligers (controles) van dezelfde leeftijd en geslacht. Rechter kamer longitudinale piek-strain is verminderd in patiënten, met name in de punt van het hart, vergeleken met controles. Tevens is longitudinale piek-strain van de linker hartkamer verminderd, met name in het septum van het hart. Wij vonden dat niet alleen verminderde rechter kamerfunctie maar ook verminderde linker kamerfunctie gezien wordt in patiënten met tetralogie van Fallot en dat deze twee mogelijk aan elkaar gerelateerd zijn.

Hoofdstuk 12 richt zich op het samentrekkingsmechanisme van de linker hartkamer in 82 patiënten met geopereerde tetralogie van Fallot. De linker hartkamer trekt op verschillende manieren samen: in de lengte richting, in de breedte, en met een ronddraaiende beweging. In dit hoofdstuk hebben we specifiek naar de ronddraaiende bewegingen gekeken. De punt van de linker hartkamer en de basis van het hart draaien in een gezond hart in een tegengestelde richting. Deze twee draaiingen samen worden 'twist' genoemd. Draaiing en twist van de linker hartkamer zijn onderzocht in patiënten met tetralogie van Fallot met behulp van speckle-tracking echocardiografie en vergeleken met 56 gezonde controles. Het merendeel van de patiënten met geopereerde tetralogie van Fallot heeft een verminderde twist van

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de linker hartkamer. Een kwart van deze patiënten met verminderde twist heeft daarbij een abnormale draaiing van de punt van de linker hartkamer. Abnormale draaiing van de punt van de linker hartkamer blijkt gerelateerd te zijn aan verminderde linker en rechter hartkamerfunctie. Aangezien zowel linker als rechter hartkamerfunctie gerelateerd zijn aan draaiing van de linker kamer, wordt met de bevindingen in deze studie het idee bevestigd dat beide hartkamers elkaar beïnvloeden. Abnormale draaiing van de punt van het hart is mogelijk een nieuw, objectief diagnostisch middel voor het detecteren van verminderde hartfunctie in volwassen patiënten met geopereerde tetralogie van Fallot.

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Abbreviation list

ACHD	=	adult congenital heart disease
AOS	=	aortic stenosis
AR	=	apical rotation
ASD	=	atrial septal defect
ASO	=	arterial switch operation
BMI	=	body mass index
BNP	=	brain natriuretic peptide
BR	=	basal rotation
BSA	=	body surface area
CABG	=	coronary artery bypass grafting
CAD	=	coronary artery disease
ccTGA	=	congenitally corrected transposition of the great arteries
CMR	=	cardiac magnetic resonance imaging
COA	=	aortic coarctation
ConHD	=	congenital heart disease
GDF-15	=	growth-differentiation factor 15
GLS	=	global longitudinal strain
Hs-CRP	=	high-sensitive C-reactive protein
Hs-TnT	=	high-sensitive troponin T
FAC	=	fractional area change
E/A ratio	=	ratio of early filling to late filling velocity on transmitral Doppler
ECG	=	electrocardiogram
EDV	=	end-diastolic volume
E/E'	=	ratio of early filling velocity on transmitral Doppler to early relaxation velocity on tissue Doppler
EF	=	ejection fraction
ESV	=	end-systolic volume
IQR	=	interquartile range
IVS	=	interventricular septum
LS	=	longitudinal strain
LV	=	left ventricle
LVEDD	=	left ventricular end-diastolic diameter
LVEDV	=	left ventricular end-diastolic volume
LVESD	=	left ventricular end-systolic diameter
LVESV	=	left ventricular end-systolic volume
LVF	=	left ventricular function

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NT-proBNP	=	amino-terminal pro-hormone of brain natriuretic peptide
NS	=	not significant
NYHA	=	New York Heart Association
PAH	=	pulmonary arterial hypertension
Peak VO$_2$	=	maximal oxygen uptake
PR	=	pulmonary regurgitation
PVR	=	pulmonary valve replacement
RER	=	respiratory exchange ratio
RV	=	right ventricle
RVD	=	right ventricular diameter
RVEDV	=	right ventricular end-diastolic volume
RVESV	=	right ventricular end-systolic volume
RVF	=	right ventricular function
RQ	=	respiratory quotient
SD	=	standard deviation
STE	=	speckle-tracking echocardiography
SV	=	stroke volume
TAPSE	=	tricuspid annular plane systolic excursion
TCPC	=	total cavopulmonary connection
TDI	=	tissue Doppler imaging
TGA	=	transposition of the great arteries
ToF	=	tetralogy of Fallot
TR	=	tricuspid regurgitation
VO$_2$max	=	maximal oxygen uptake
VSD	=	ventricular septal defect
Vmax	=	maximal velocity
Workload$_{max}$	=	maximal workload

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PhD portfolio

Summary of PhD training and teaching activities

Name:	Jannet Eindhoven	PhD period:	2011-2014
	Erasmus MC, Cardiology	Promotors:	Prof. J.W. Roos-Hesselink
	Department of Adult Congenital Heart Disease		Prof. H. Boersma
	Research school: COEUR	Co-promotor:	Dr. A.E. van den Bosch

PhD training

	Year	Workload (ECTS)
General PhD courses		
Biostatistical Methods I: Basic Principles, CC02	2011	5,7
BROK course	2011	1,5
English Biomedical Writing and Communication	2013	4,0
Courses		
COEUR - Arrhythmia Research Methodology	2012	1,5
COEUR - Intensive Care Research	2012	1,5
COEUR - Cardiovascular Clinical Epidemiology	2012	1,5
Masterclass Pulmonary Hypertension, London, UK	2012	1,5
Masterclass Functional & Applied Clinical Anatomy of the Heart	2013	0,3
COEUR research seminars	2011, 2012, 2013	2,4
Conferences& symposia		
ESC congress	2012, 2013, 2014	6,0
AEPC congress	2014	2,0
EUROECHO congress	2012,2013	4,0
AHA congress	2013	2,0
Davos wintermeeting	2012,2014	3,0
Karel V symposium	2011, 2012, 2013	1,0
NVVC congress	2012,2013	3,0
Teaching activities		
Supervising research of 2nd year medical students	2012, 2013	1,0
Presentation advanced echocourse on congenital heart disease	2013	0,6
Total		***42,5 ECTS***

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Oral presentations

JA Eindhoven, AE van den Bosch, JF Veenis, M Witsenburg, JS McGhie, JAAE Cuypers, JW Roos-Hesselink, H Boersma; *High Sensitive Troponine-T in Adult Congenital Heart Disease*
> **European Society of Cardiology congress 2014, Barcelona, Spain**

JA Eindhoven, ME Menting, AE van den Bosch, JS McGhie, M Witsenburg, H Boersma, JW Roos-Hesselink; *Quantitative Assessment of Systolic Right Ventricular Function and its Relationship with NT-proBNP in Patients with a Systemic Right Ventricle*
> **Association for European Paediatric and Congenital Cardiology 2014, Helsinki, Finland**

JA Eindhoven; *Heart Failure in Adult Congenital Heart Disease*
> **Wintermeeting 2014, Davos, Switzerland**

JA Eindhoven, AE van den Bosch, TPE Ruys, P Opic, JAAE Cuypers, M Witsenburg, JS McGhie, H Boersma, JW Roos-Hesselink; *Evaluation of NT-proBNP and Cardiac Dysfunction in Adult Patients with Congenital Heart Disease*
> **NVVC spring congress 2013, Noordwijkerhout, the Netherlands**

JA Eindhoven; *Echocardiography and the Treatment of Pulmonary Hypertension*
> **Wintermeeting 2013, Davos, Switzerland**

JA Eindhoven, AE van den Bosch, JAAE Cuypers, M Witsenburg, JS McGhie, H Boersma, JW Roos-Hesselink; *Determinants of Elevated NT-proBNP in Adult Congenital Heart Disease: an Echocardiographic Study*
> **NVVC autumn congress 2012, Papendal, the Netherlands**

JA Eindhoven, AE van den Bosch, H Boersma, JW Roos-Hesselink; *Brain Natriuretic Peptide in Complex Congenital Heart Disease*
> **NVVC spring congress 2012, Noordwijkerhout, the Netherlands**

Moderated poster presentations

JA Eindhoven, ME Menting, AE van den Bosch, JS McGhie, M Witsenburg, H Boersma, JW Roos-Hesselink; *Quantitative Assessment of Systolic Right Ventricular Function using Longitudinal Strain in Patients with a Systemic Right Ventricle*
> **European Society of Cardiology congress 2014, Barcelona, Spain**

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JA Eindhoven, AE van den Bosch, ME Menting, JAAE Cuypers, M Witsenburg, JS McGhie, TPE Ruys, H Boersma, JW Roos-Hesselink; *Impaired Ventricular Function and Pulmonary Pressures are related to NT-proBNP in Patients with Corrected Tetralogy of Fallot*

> **EUROECHO-Imaging congress 2013, Istanbul, Turkey**

JA Eindhoven, AE van den Bosch, TPE Ruys, P Opic, JAAE Cuypers, JS McGhie, M Witsenburg, H Boersma, JW Roos-Hesselink; *Cardiac Dysfunction and its Relationship with N-Terminal pro-Brain Natriuretic Peptide in Adult Patients with Congenital Heart Disease*

> **EUROECHO-Imaging congress 2013, Istanbul, Turkey**

Poster presentations

JA Eindhoven, AE van den Bosch, TPE Ruys, P Opic, JAAE Cuypers, JS McGhie, M Witsenburg, H Boersma, JW Roos-Hesselink; *N-Terminal ProBrain Natriuretic Peptide and its Relationship with Cardiac Dysfunction in Adult Patients with Congenital Heart Disease*

> **American Heart Association congress 2013, Dallas, USA**

JA Eindhoven, AE van den Bosch, JAAE Cuypers, M Witsenburg, H Boersma, JW Roos-Hesselink; *Determinants of Elevated NT-proBNP in Adult Congenital Aortic Stenosis: an Echocardiographic Study*

> **EUROECHO-Imaging congress 2012, Athens, Greece**

JA Eindhoven, AE van den Bosch, PR Jansen, H Boersma, JW Roos-Hesselink;
> *Brain Natriuretic Peptide in Patients with Fontan Physiology – a systematic review*
> **European Society of Cardiology congress 2012, Munich, Germany**

JA Eindhoven, AE van den Bosch, PR Jansen, H Boersma, JW Roos-Hesselink;
> *Brain Natriuretic Peptide in Patients with Tetralogy of Fallot – a systematic review*
> **European Society of Cardiology congress 2012, Munich, Germany**

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List of publications

1. **JA Eindhoven**, AE van den Bosch, RM Oemrawsingh, JA Cuypers, M Witsenburg, I Kardys, R van Schaik, JW Roos-Hesselink, E Boersma. Release of growth-differentiation factor 15 and associations with cardiac function in adult patients with congenital heart disease. *Submitted*

2. **JA Eindhoven**, AE van den Bosch, I Kardys, JF Veenis, JS McGhie, JA Cuypers, M Witsenburg, R van Schaik, E Boersma, JW Roos-Hesselink. High-sensitive troponin T in adult congenital heart disease. *Submitted*

3. ME Menting, AE van den Bosch, JS McGhie, **JA Eindhoven**, JA Cuypers, M Witsenburg, ML Geleijnse, WA Helbing, JW Roos-Hesselink. Assessment of ventricular function in adults with repaired tetralogy of Fallot using myocardial deformation imaging. *Submitted*

4. **JA Eindhoven**, ME Menting, AE van den Bosch, JS McGhie, M Witsenburg, JA Cuypers, E Boersma, JW Roos-Hesselink. Quantitative assessment of systolic right ventricular function using myocardial deformation in patients with a systemic right ventricle. *Eur Heart J Cardiovasc Imaging 2014 Oct 9*

5. **JA Eindhoven**, ME Menting, AE van den Bosch, TPE Ruys, M Witsenburg, JA Cuypers, JS McGhie, E Boersma, JW Roos-Hesselink. Associations between N-terminal pro-B-type natriuretic peptide and cardiac function in adults with corrected tetralogy of Fallot. *Int J Cardiol* 2014 Jul 1;174(3):550-6

6. JA Cuypers, **JA Eindhoven**, MA Slager, Opic P, EM Utens, WA Helbing, M Witsenburg, AE van den Bosch, M Ouhlous, RT van Domburg, D Rizopoulos, FJ Meijboom, AJ Bogers, JW Roos-Hesselink. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J.* 2014 Jul 1;35(25):1666-74.

7. ME Menting, **JA Eindhoven**, AE van den Bosch, JA Cuypers, TP Ruys, BM van Dalen, JS McGhie, WA Helbing, M Witsenburg, M Geleijnse, JW Roos-Hesselink. Abnormal left ventricular rotation and twist in adult patients with corrected tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging* 2014 May;15(5):566-74.

8. **JA Eindhoven**, AE van den Bosch, E Boersma, JW Roos-Hesselink. Reply: amino terminal fragment of pro-B-type natriuretic peptide for complex congenital heart diseases: one for all, all for one? *J Am Coll Cardiol* 2014 Apr 8;63(13):1343-4.

9. Y Onuma , T Muramatsu, C Girasis, N Kukreja, HM Garcia-Garcia, J Daemen, N Gonzalo, N Piazza, **JA Eindhoven**, RT van Domburg, PW Serruys; interventional cardiologists of the Thoraxcenter (2000-

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2005). Single-vessel or multivessel PCI in patients with multivessel disease presenting with non-ST-elevation acute coronary syndromes. *Eurointervention* 2013 Dec 8;9(8):916-22.

10. JO Younge, **JA Eindhoven**, EM Utens, P opic, JA Cuypers, AE van den Bosch, M Witsenburg, RT van Domburg, MG Hunnink, JW Roos-Hesselink. Association between N-terminal pro-brain natriuretic peptide and quality of life in adult patients with congenital heart disease. *Cardiol Young*. 2013 Nov 21:1-7

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About the author

Jannet Eindhoven was born on July 6th 1986 in Gouda, the Netherlands. In 2004 she graduated from secondary school at the Emmauscollege, Rotterdam, and started medical school at the Erasmus University Rotterdam. During her medical study she developed and supervised practical lessons in physical examination and medical skills on behalf of the medical curriculum at the Erasmus MC Rotterdam. From the third year of medical school onwards she participated in clinical research at the department of Cardiology at Erasmus MC, under supervision of dr. Ron van Domburg. She obtained her Medical Doctors' degree in 2011.

In March 2011 she started her PhD project entitled 'Cardiac Biomarkers in Adult Congenital Heart Disease' supervised by her two promotors prof.dr. Jolien W. Roos-Hesselink and prof.dr. Eric Boersma. During this period she studied the long-term outcome of patients with congenital heart disease and the use of novel biomarkers including laboratory markers and speckle-tracking echocardiography.

From September 2014 onwards she works as a resident at the department of Cardiology at the Erasmus MC, Rotterdam. Besides her work she enjoys travelling and sports including tennis and cycling.

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