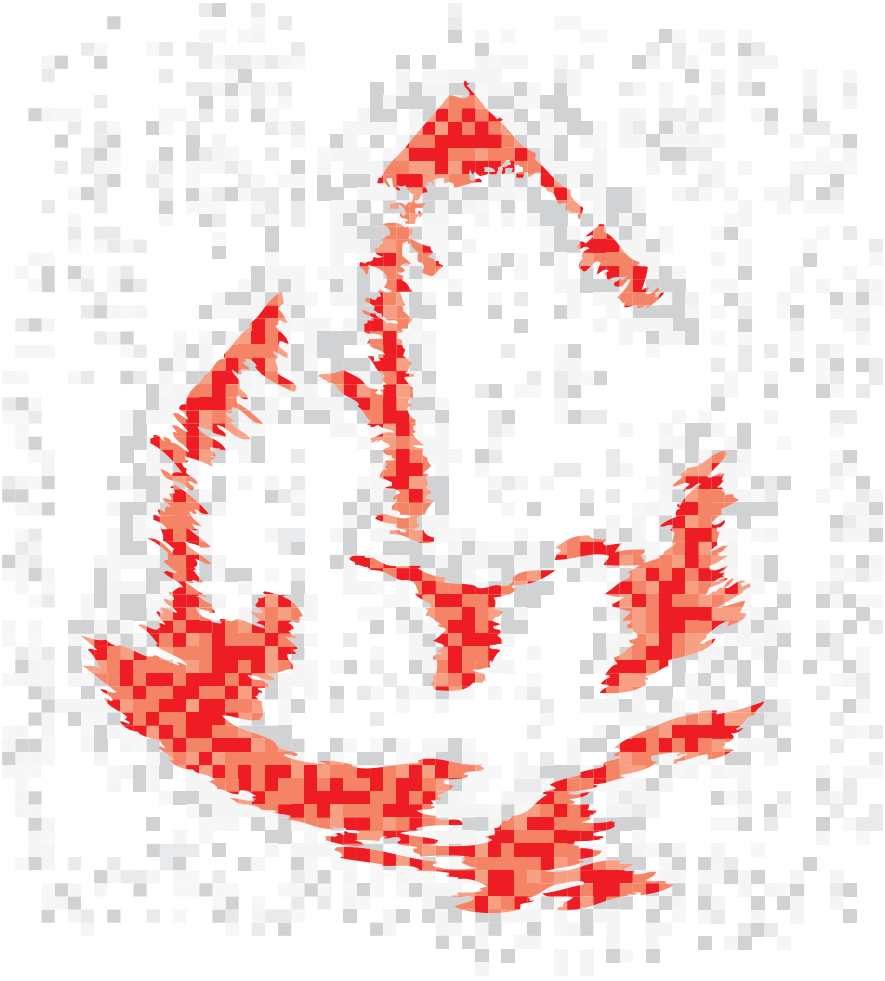
ADULT CONGENITAL HEART DISEASE

Clinical outcome and novel echocardiographic techniques



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Klinische uitkomsten en nieuwe echocardiografische technieken

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Voor mijn lieve mama

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CHAPTER 1

General introduction
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GENERAL INTRODUCTION

Adult congenital heart disease

Congenital heart disease (CHD) is the most common type of birth defect with a prevalence of 8.0 per 1000 births.[1] The eight most common heart defects at birth are ventricular septal defect (VSD, 34%), atrial septal defect (ASD, 13%), persistent ductus arteriosus (10%), pulmonary stenosis (8%), tetralogy of Fallot (ToF, 5%), coarctation of the aorta (CoA, 5%), transposition of the great arteries (TGA, 5%) and aortic stenosis (4%).[2] With the introduction of and improvements in diagnostic procedures, cardio-thoracic surgery, anaesthesia, intensive care and specialised pediatric and adult cardiology care, life expectancy has increased enormously. Nowadays, about 90% of patients with CHD, often after successful surgery at young age, reach adulthood. This results in a growing number of adults with CHD with an estimation of 35,000 in the Netherlands.[3]

Although survival has improved, morbidity is still substantial. The most common complications in adult CHD are arrhythmias and heart failure. In the Netherlands, the estimated incidence of heart failure in adults with CHD is 1.2 per 1,000 patient-years and differs amongst the various congenital lesions.[4] Heart failure is less often observed in patients with simple lesions, e.g. ASD and VSD, while higher incidences are reported in patients with more complex lesions, e.g. ToF and TGA. Chronic heart failure is often the result of ventricular dysfunction and is the main cause of mortality: 26% of all deaths.[4]

Early detection of ventricular dysfunction

Adequate assessment of ventricular function is essential to identify patients at risk for complications or adverse outcome. Echocardiography remains the first-line investigation and continues to evolve, with improved functional assessment. Echocardiography can provide information on the basic cardiac anatomy, venous return, connection of the atria and ventricles, and origin of the great arteries. It allows evaluation of the morphology of cardiac chambers, ventricular function, and evaluation of shunt lesions. Assessment of ventricular volume overload and pressure overload is of major importance. Although echocardiography is easy to perform, inexpensive and patient-friendly, and can provide comprehensive information, its limitations must also be taken into consideration. With conventional two-dimensional (2D) echocardiography, complex cardiac anatomy can be difficult to visualise and a reliable and reproducible method for ventricular function assessment is lacking. These issues apply especially to the right ventricle (RV) that is positioned closely behind the sternum and is important to evaluate in CHD.[5] Moreover, the currently used conventional echocardiographic technique fails to

detect early (subclinical) ventricular dysfunction. Early recognition of ventricular dysfunction could result in a more adequate medical treatment regimen and better timing of cardiac (re)intervention. These improvements in treatment may avoid further deterioration in cardiac function with subsequent development of heart failure, and will ultimately result in a better survival. Therefore, novel echocardiographic techniques for quantitative assessment of ventricular function, and techniques for better visualisation of the RV are warranted.

Cardiac anatomy

In the left ventricle (LV), fibres in the subepicardium run in a left-handed direction, fibres in the mid layer run circumferentially, and fibres in the subendocardium run in a right-handed direction (Figure 1A). These myocardial fibres are connected to each other, with a smooth transition from subendocardium to mid layer, and then to subepicardium, along the long-axis. Contraction of these three layers of myocardial fibres causes besides longitudinal, circumferential, and radial movements of the heart, also a rotational movement (Figure 1B).[6]

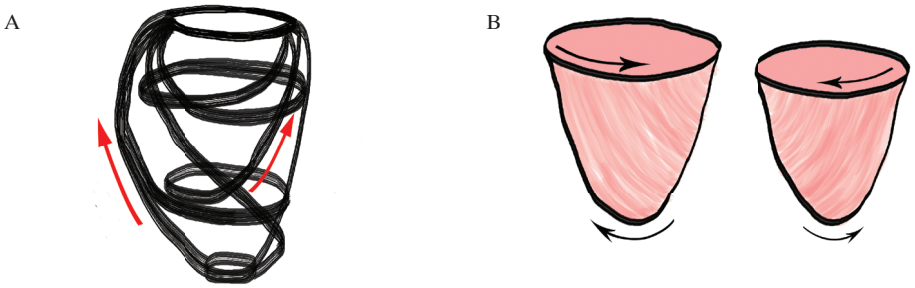

Figure 1 Fibre orientation of the left ventricle
Fibres in the subepicardium run in a left-handed direction, fibres in the mid layer run circumferentially, and fibres in the subendocardium run in a right-handed direction (A). Contraction of these fibres causes a rotational movement of the heart (B).

Leonardo da Vinci already described the rotational movement of the LV in the 16th century,[7] and in 1669 Richard Lower described this movement as "the wringing of a linen cloth to squeeze out the water".[8] Over the past three centuries, the twisting movement of the LV has continued to intrigue clinicians and researchers in their quest to understand the performance of the human heart.[9] The subepicardium and subendocardium rotate in opposite directions during contraction. When both layers contract simultaneously, the larger radius for the outer subepicardium results in a mechanical advantage of the epicardial fibres in dominating the overall direction of rotation.[10] Therefore, the base rotates in clockwise direction and the apex in counterclockwise direction. The twisting movement is necessary because

shortening of the myocardial fibres is about 15-20%, whereas the actual ejection fraction of the human heart is 60 to 70%.[6, 11] This ejection fraction could be reached with the involvement of twisting.

Although it has been customary to consider LV function and RV function as separate entities, this approach is flawed. The continuity between the myocardial fibres of the LV and RV functionally binds the ventricles together. This continuity, together with the common interventricular septum and pericardium, contributes to ventricular interaction.[12, 13]

Speckle-tracking echocardiography

Speckle-tracking echocardiography (STE) is a novel echocardiographic technique that enables to quantify regional and global myocardial function, relatively independently of angle and ventricular geometry.[14] Grey-scale 2D-echocardiographic images consist of a speckled pattern which is unique for each region of the myocardium. The geometric position of the speckles changes from frame-to-frame with the surrounding tissue motion. With the use of STE, these ultrasonic speckles can be tracked and subsequently myocardial-deformation parameters, such as strain and rotation, can be calculated (Figure 2). Strain describes the deformation of an object normalised to its original shape and size and can be measured in longitudinal, radial and circumferential directions. Rotational deformation enables the analysis of complex LV motion patterns.[15] Increasing data suggest that STE may provide useful clinical measurements for detection of subtle ventricular dysfunction that is likely to progress into heart failure.[16, 17] Information about the use of STE for LV and RV function in adults with CHD is limited, especially the LV twist in CHD is not completely elucidated. The relatively angle- and geometry independence of STE could be a useful advantage in adults with CHD, who often have complex ventricular geometry and varying intrathoracic positions and orientation of the heart.

The use of iRotate for visualising the right ventricle

There is an increased recognition of assessing RV function in the acute phase and during follow up as a prognostic factor in a variety of disease states such as CHD, left-sided heart failure and pulmonary hypertension.[13] However, unlike the LV that can be completely visualised from one apical window, a multi-view approach is needed for a comprehensive evaluation of RV size and function because of its complex geometry and retrosternal position.[18, 19] Serial follow-up of RV dimensions and function measures results in considerable inaccuracies from oblique plane acquisitions due to the lack of anatomic landmarks used as reference points.[19] A standardised multi-view echocardiographic approach for the assessment of RV,

based on anatomic landmarks and taken from one echocardiographic window, could increase the accuracy of RV dimensions and function measures in routine follow-up. The iRotate mode is a new visualisation tool developed by Philips[20], which consists of a transducer that rotates electronically to obtain the required view within the acoustical window, rather than manually rotating the transducer. Therefore, iRotate provides a multiplane echocardiographic approach from the

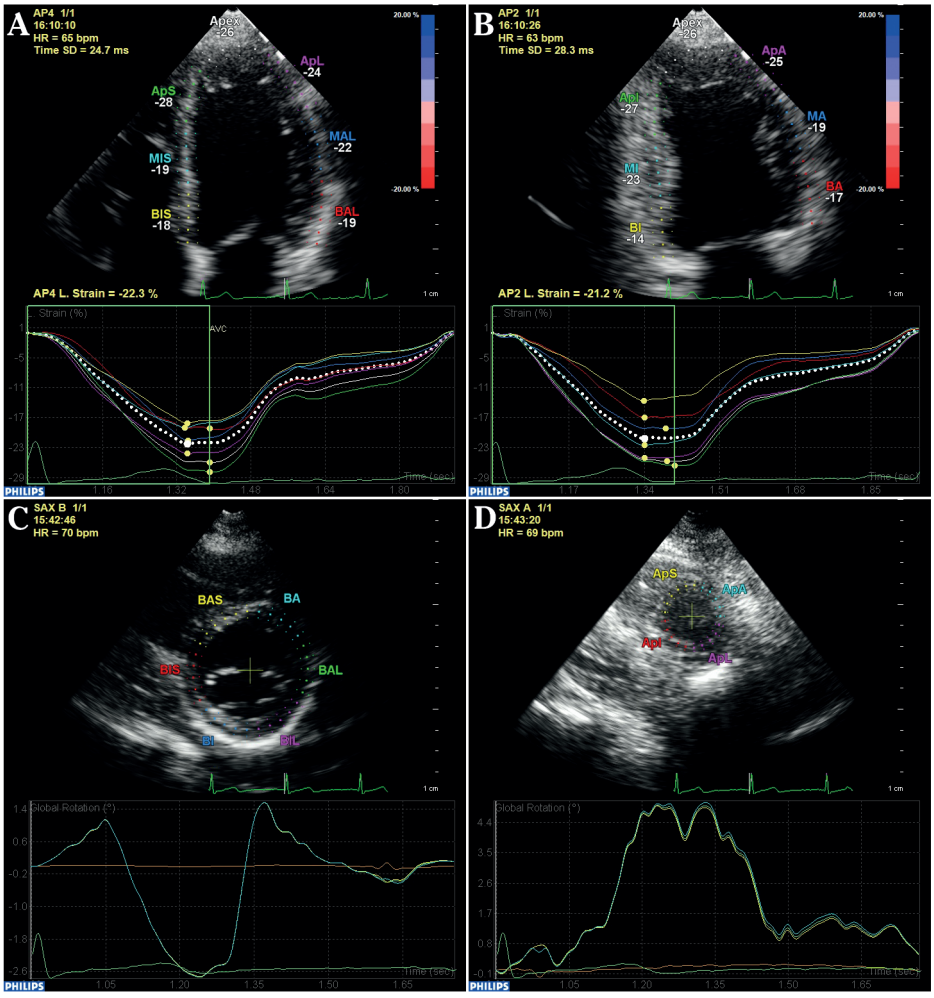

Figure 2 Speckle-tracking echocardiography

With this echocardiographic technique, the motion of the ventricular walls can be analysed by tracking the speckled pattern of the myocardium during the cardiac cycle. Various myocardial-deformation parameters can be measured in different directions, such as longitudinal strain of the left ventricle from the apical four-chamber view (A) and two-chamber view (B); and rotation of the base (C) and apex (D) from the short-axis view.

same window without moving the transducer. Whether this new echocardiographic modality is feasible and reproducible for the evaluation of the RV has to be investigated.

Types of congenital heart defects

Tetralogy of Fallot

Tetralogy of Fallot is the most prevalent form of cyanotic CHD. This disease comprises four cardiac anomalies: VSD, overriding of the aorta, variable forms of RV outflow obstruction and RV hypertrophy (Figure 3).[21] The technique of surgical repair has remained largely unchanged in its basic principles since the original description.[22] The repair consists of VSD closure and the relief of RV obstruction, usually with a transannular patch, and usually resulting in free pulmonary regurgitation.[23] However, progress in circulatory support, surgical techniques and preoperative and postoperative care have enabled an important reduction in the age at which this operation can be performed. This may influence long-term results, which should be considered a factor in interpretation of current data on long-term outcome. In general, the survival of these patients has remarkably improved: 90% of patients are currently alive 30 years after successful surgical repair in early childhood.[24-26] Despite these satisfactory results, survival is lower than in the normal population, and little is known about long-term functional outcome and life expectancy beyond 30 years.[26, 27] Although anatomic repair has been achieved, complications such as pulmonary regurgitation, RV dysfunction, arrhythmias,

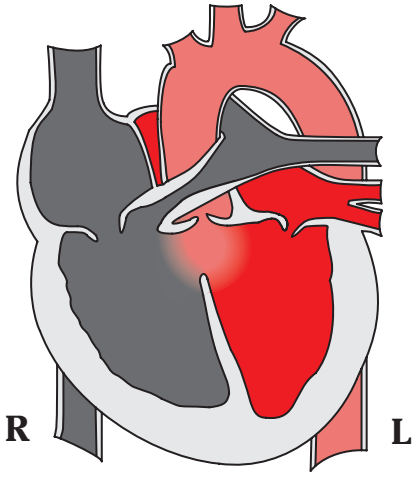

Figure 3 Tetralogy of Fallot
Tetralogy of Fallot consists of a ventricular septal defect with an overriding aorta, pulmonary narrowing and a hypertrophied right ventricle.

and sudden death are found in late survivors.[21, 28, 29] RV dysfunction may affect LV function resulting in more attention for the LV in this patient group.[30] Although the influence of RV dilatation on LV shape and function has not been studied in detail, LV dysfunction is a strong independent determinant of clinical outcome.[31, 32] This makes early detection of both RV and LV dysfunction important.

Ventricular septal defect

A VSD (Figure 4) is by far the most common type of CHD in children.[2] A VSD can be an isolated cardiac lesion but can also be associated with other congenital cardiac malformations.[33] Small VSDs may remain without hemodynamic consequences, but a significant left-to-right shunt will cause LV overload, pulmonary arterial hypertension, ventricular dysfunction and aortic regurgitation.[33, 34] Surgical closure at young age is the method of choice and often results in good long-term survival with low morbidity.[35] Therefore, most such patients have been discharged from routine cardiological follow-up. For both patients and their treating physicians, it is essential to know whether the pre-operative left-to-right shunt and the VSD patch affect biventricular function in the long term. However, information on mortality and morbidity beyond 30 years after surgical VSD closure is scarce.

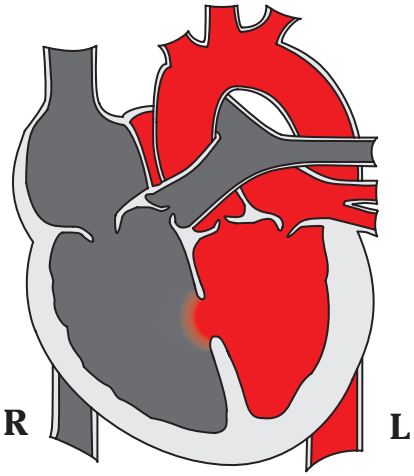

Figure 4 Ventricular septal defect
A ventricular septal defect is a defect in the wall between the left and the right ventricles.

Atrial septal defect

An ASD (Figure 5) is the most common CHD at adult age.[36] Most children with an isolated ASD are free of symptoms, but the rates of complaints increase with advancing age.[37] Before closure, patients with an ASD have right-sided volume

overload caused by left-to-right shunting. Some patients also have anomalous pulmonary venous return which will result in right-heart overload. The RV volume overload is well tolerated for many years,[38] but eventually diminished RV function and heart failure tend to occur resulting in an increased morbidity, e.g. arrhythmia and exercise intolerance, and higher mortality.[37, 39]After successful surgical repair at young age, the life expectancy up to 30 years is similar to that of the general population.[40, 41] Transcatheter closure offers a less invasive alternative for patients with a suitable ASD.[5, 37] Even when ASD repair is performed in childhood, RV dilatation or impaired RV function could be found in a substantial part of the patients.[42] The effect of preoperative chronic volume loading on RV function in later life is still not completely elucidated.

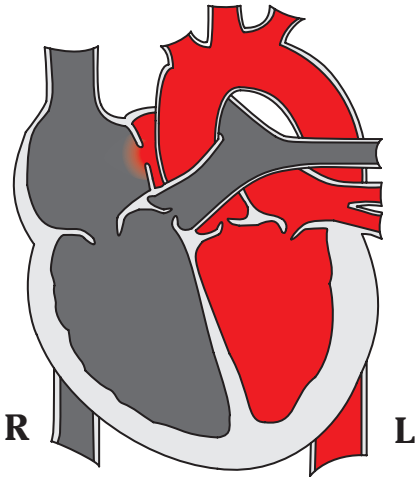

Figure 5 Atrial septal defect
An atrial septal defect is a defect in the wall between the left and the right atria.

Transposition of the great arteries

Transposition of the great arteries means that the aorta arises from the morphologic RV and the pulmonary artery from the morphologic LV (Figure 6). The first surgical option for patients born with TGA was the atrial switch procedure as described by Senning in 1959 and Mustard in 1964.[43] In patients with TGA repaired by Mustard operation and in patients with congenitally corrected TGA, the morphologic RV supports the systemic circulation. The RV geometry is not suitable to encounter this chronic pressure overload.[13] Therefore, the main concern regarding the long-term outcome of these patients is dysfunction of the systemic RV.

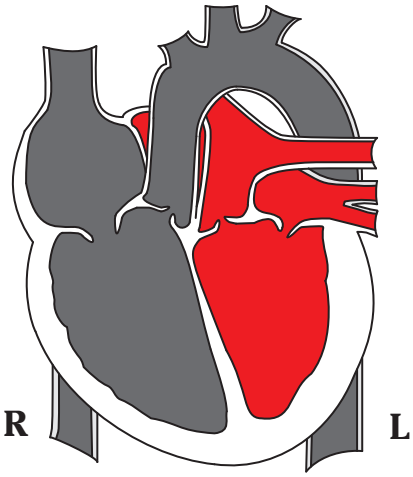

Figure 6 Transposition of the great arteries
Transposition of the great arteries is a heart defect in which the two main arteries, the aorta and the pulmonary artery, are reversed.

Coarctation of the aorta

Coarctation of the aorta is defined as a condition with a constricted aortic segment in the area where the ductus arteriosus inserts (Figure 7). There are known associated lesions, such as a bicuspid aortic valve and mitral valve stenosis.[5] CoA causes LV pressure overload which can lead to increased myocardial wall stress, LV dysfunction, and the development of arterial collaterals. Despite successful repair, late cardiovascular problems can occur including systemic hypertension in

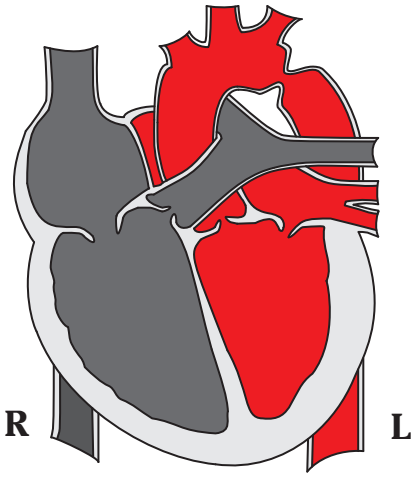

Figure 7 Coarctation of the aorta
Coarctation of the aorta is a narrowing of the aorta at about the level of the ductal structure.

up to 75% of patients and heart failure in 15%.[44-47] Early detection of LV dysfunction is important for risk stratification and early initiation of treatment.

Aims

The aim of this thesis is to investigate the long-term outcome in adult patients with CHD and to evaluate novel, non-invasive echocardiographic techniques in a healthy adult population and in adult patients, which can contribute to an accurate quantitative assessment of LV and RV function. With the more precise assessment of early ventricular dysfunction, we aim for a better outcome for patients with CHD.

OUTLINE OF THE THESIS

Novel echocardiographic techniques and measurements have been applied to a healthy population of 147 volunteers from 20 to 72 years old and equally distributed in sex. First, in **Chapter 2**, we establish normal adult longitudinal strain values for the LV using 2D-STE and identify associations with anthropometrics. In **Chapter 3**, we investigate whether there are unique anatomical landmarks in the RV that could be used as reference points to accurately depict the entire RV from one standard echocardiographic view. We evaluate the feasibility of this multi-plane imaging mode in the healthy volunteers. Additionally, we examine the feasibility of this imaging technique in a cohort of patients with RV volume overload or RV pressure overload.

The second part of this thesis focuses on the clinical outcome and early detection of ventricular dysfunction in patients with repaired ToF. Results on very long-term outcome of patients after ToF repair are scarce. In **Chapter 4**, we describe the survival and clinical outcome up to 40 years after surgical repair in a uniquely designed, prospective study, where the patients underwent a thorough in-hospital examination in 1990, 2001 and again in 2012. In patients with ToF, RV as well as LV dysfunction are of major concern at adult age. Other complications, such as arrhythmias and reinterventions, are also described. Additionally, the subjective health status is assessed. In **Chapter 5**, we investigate the feasibility of strain imaging with STE for the assessment of RV and LV function in this patient group. We evaluate the ventricular interaction and determine the relationship of these strain measurements with clinical parameters. In **Chapter 6**, we examine the use of STE to assess LV rotation and twist, and determine relationships with conventional echocardiography, cardiac magnetic resonance imaging, and exercise capacity in patients with ToF. The use of N-terminal pro-B-type natriuretic peptide

(NT-proBNP), a laboratory cardiac biomarker released from cardiomyocytes in response to ventricular stretch and volume overload, and its association with cardiac function in adults with ToF is described in **Chapter 7**.

The third part of this thesis provides information on the clinical outcome and early detection of ventricular dysfunction in adult patients with other types of CHD. We report the survival and clinical outcome in longitudinally followed patient cohorts 30 to 40 years after surgical VSD closure in **Chapter 8** and after ASD closure in **Chapter 9**. Additionally, we detect determinants of clinical outcome and we evaluate the present subjective health status of these patients. In **Chapter 10**, we delineate the feasibility and measurements of RV and LV strain imaging using STE in patients with a surgically repaired ASD at young age. We evaluate the mechanical interaction between the ventricles and we determine associations between strain measurements and clinical parameters. The feasibility to assess longitudinal strain for quantification of systolic RV function in patients with a systemic RV (Mustard patients and congenitally corrected TGA) will be discussed in **Chapter 11**. In **Chapter 12**, we focus on the feasibility of STE-derived strain in patients with repaired CoA, a left-sided outflow tract anomaly. We study relationships between LV strain measurements and patient characteristics such as smoking, interventions, hypertension, aortic valve morphology, and other associated congenital cardiac lesions, but also with conventional echocardiographic measurements and the biomarker NT-proBNP.

Finally, in **Chapter 13** we will reflect on and discuss the most important findings of this thesis. Concluding remarks and future perspectives are provided for clinical practice and research.

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PART I

Novel echocardiographic techniques in a healthy population

CHAPTER 2

Normal myocardial strain values using 2D speckle-tracking echocardiography in healthy adults aged 20 to 72 years

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ABSTRACT

Aims

Evaluation of left ventricular (LV) myocardial deformation by speckle-tracking echocardiography (STE) is useful for clinical and research purposes. However, strain measurements depend on the used software. Normative data for QLAB 10 (Philips) are scarce. Additionally, little is known about the influence of anthropometric factors. We aimed to establish normal adult STE-derived strain and strain rate values, and to evaluate associations with anthropometrics.

Methods

Hundred-and-fifty-five healthy subjects aged 20 to 72 years (≥28 subjects per decile) were prospectively gathered and examined with electrocardiography and two-dimensional echocardiography. With STE, we assessed peak systolic global longitudinal strain (GLS), segmental longitudinal strain and strain rate from the three standard apical views.

Results

We included 147 healthy subjects (age 44.6 ± 13.7 years, 50% female, LV GLS -20.8 ± 2.0%). Men had significantly lower LV GLS than women (-20.1 ± 1.8% vs. -21.5 ± 2.0%, $P<0.001$), but no association was found with age. LV GLS was significantly lower with higher blood pressure, body surface area (BSA), LV volumes and some indices of diastolic function. Indexing absolute LV GLS for BSA, strengthened the correlations with systolic blood pressure (r=-0.44, $P<0.001$), QRS duration (r=-0.38, $P<0.001$), LV end-diastolic volume (r=-0.62, $P<0.001$), LV end-systolic volume (r=-0.70, $P<0.001$), E-wave (r=0.39, $P<0.001$), and E-prime (r=0.30, $P<0.001$). The systolic strain rates of most segments correlated with BSA.

Conclusions

Our study resulted in normative LV GLS values assessed with QLAB 10. The values are independent of age, but male sex, higher BSA and higher blood pressure negatively influence GLS. Therefore, these factors should be taken into account for strain interpretation in clinical practice.

INTRODUCTION

The quantification of cardiac chamber dimensions and function is the cornerstone of cardiac imaging.[1] Conventional two-dimensional (2D) and Doppler echocardiography are the most commonly used noninvasive modalities and are valuable tools, especially for the assessment of global systolic and diastolic function. The most widely used measurement for left ventricular (LV) systolic function in a clinical setting is ejection fraction. However, this parameter is limited in abnormally shaped or dilated LVs due to the geometric assumptions used in the 2D-biplane method. In addition, regional systolic dysfunction could be missed with this method.[1]

During the last decade, 2D-speckle-tracking echocardiography (STE) has become available which provides quantitative assessment of global and segmental ventricular function by measuring myocardial deformation, largely independent of angle and ventricular geometry.[2,3] Strain in longitudinal direction, one of the measures of deformation, is the most widely used type of strain and is a robust index for clinical studies.[4] With the use of myocardial deformation imaging, ventricular dysfunction may be detected in a pre-clinical phase.[5]

Although STE is widely used for the assessment of LV function, myocardial deformation parameters are dependent on the equipment that is used and therefore results of machines and software packages from different vendors are not interchangeable.[4,6] However, there has been an improvement in between-vendor concordance in LV global longitudinal strain (GLS) since the work of the joint standardization task force.[7] Erasmus MC routinely uses the Philips iE33 and EPIQ7 ultrasound systems, and QLAB software for analyzing datasets (Philips Medical Systems, Best, the Netherlands). Normal reference values of STE-derived longitudinal strain are scarce using QLAB software [8], especially strain values established with the software versions after the standardization initiative.[7] Because of this lack of adequate normal data, the clinical value of STE data in patients is suboptimal. In addition, little is known about the influence of anthropometric factors on these strain values.

The aim of this prospective cohort study was to obtain normal LV longitudinal strain and strain rate values in healthy volunteers aged from 20 to 72 years. Secondly, we wanted to identify the influence of age, sex, body mass index (BMI), body surface area (BSA), blood pressure, ECG findings and ventricular size and volumes on strain.

METHODS

Study population

This prospective cohort study was conducted in 2014-2015 in 155 healthy volunteers aged 20 to 72 years, who were stratified into 5 age groups: 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 72 years (n≥28 in each group, equal distribution in sex). The subjects were recruited via an advertisement for healthy subjects. The inclusion criteria required that subjects had normal results on physical examination and electrocardiography (ECG). Subjects were excluded when they met any of the following criteria: (prior) cardiovascular disease; cardiovascular risk factors consisting of hypertension, diabetes mellitus or hypercholesterolemia; systemic disease or medication known to influence cardiac function; or the finding of cardiac abnormalities during examination. Professional athletes, morbidly obese subjects (BMI >40 kg/m^2), pregnant women and women with breast implants were also excluded.

All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all participants.

Clinical assessment

The subjects' visit consisted of physical examination, 12-lead ECG, venous blood sampling, and 2D-echocardiography. Physical examination included height, weight, blood pressure, saturation, and results of heart, lungs and abdominal findings. Blood samples were taken to determine serum creatinine as an indicator for renal function.

Echocardiographic image acquisition

All echocardiographic studies were performed by 2 experienced sonographers (JM, WV). Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using an iE33 or EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with a transthoracic broadband X5-1 matrix transducer (composed of 3040 elements with 1-5 MHz). Standard apical 4-chamber (A4C), 2-chamber (A2C) and 3-chamber (A3C) views were obtained for STE at frame rates of ≥50 frames/sec.[9]

Conventional echocardiographic measurements

For chamber measurements we used the current guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[1] From the A4C, pulsed-wave Doppler examination was performed to obtain peak mitral inflow velocities at early (E) and late (A) diastole and E deceleration

time. Tissue Doppler imaging was performed to obtain myocardial tissue velocity at the septal mitral annulus at early diastole (E'). LV end-diastolic, LV end-systolic and LV ejection fraction were derived with the biplane method of disks based on one cardiac cycle using QLAB software.

Speckle-tracking analysis

The data sets were blinded regarding the subject's ID. Offline analyses were performed by 2 independent observers (MM, JM) using QLAB 10 (Philips Medical Systems, Best, the Netherlands). Cardiac cycles were defined by the positioning of R-waves. Aortic valve closure time was used to define end-systole[3] by selecting the frame of closure on the A3C view.

To assess peak systolic LV longitudinal strain and strain rate, the endocardial and epicardial borders were traced in the A4C, A3C and A2C on an end-diastolic frame. The program automatically divided the walls in several segments (LV algorithm based on 17-segment model) and tracked these points on a frame-by-frame basis. When tracking was suboptimal, we readjusted the borders. Segments with persistently inadequate tracking were excluded from analysis. Peak systolic strain and strain rate values were defined as the peak values on the curves during the ejection phase of one cardiac cycle. Figure 1 shows examples of longitudinal strain analyses. Data were exported to a spreadsheet program (Excel; Microsoft Corporation, Redmond, WA, USA). All references to strain changes consider the absolute value of the number, so that higher or increase in longitudinal strain means a more negative number and lower or decrease means a less negative number.[10]

Statistical analysis

The data distribution was checked using histograms and the Shapiro-Wilk test. Depending on the distribution, continuous data are presented as mean±standard deviation (SD), or median with first and third quartile [Q1-Q3] or interquartile range [IQR]. Categorical data are presented as frequencies and percentages. For comparison of normally distributed continuous variables in one group we used the paired *t*-test and between two groups the Student's *t*-test. In case of skewed distribution, the Mann-Whitney-U test was applied. For comparison of frequencies the χ^2-test was used. Linear regression analysis was used to explore the relationship between strain and baseline characteristics. Variables that reached $P<0.001$ and did not show collinearity with other variables were included in a multivariable model. In case of collinear variables, the variable with the highest correlation coefficient was included. All statistical analyses were performed using SPSS statistics version 21 (IBM Corp., Armonk, NY, USA). The statistical tests were two-sided and a $P<0.05$ was considered statistically significant.

Intraobserver agreement (MM) was assessed by repeated analysis in a sample of 20 subjects (n=4 per decile, randomly selected) >1 month after the initial analysis, in randomly mixed order, and blinded to the initial results. Assessment of interobserver agreement was performed by a second observer (JM) in the same sample. The agreement between 2 measurements was determined as the mean of

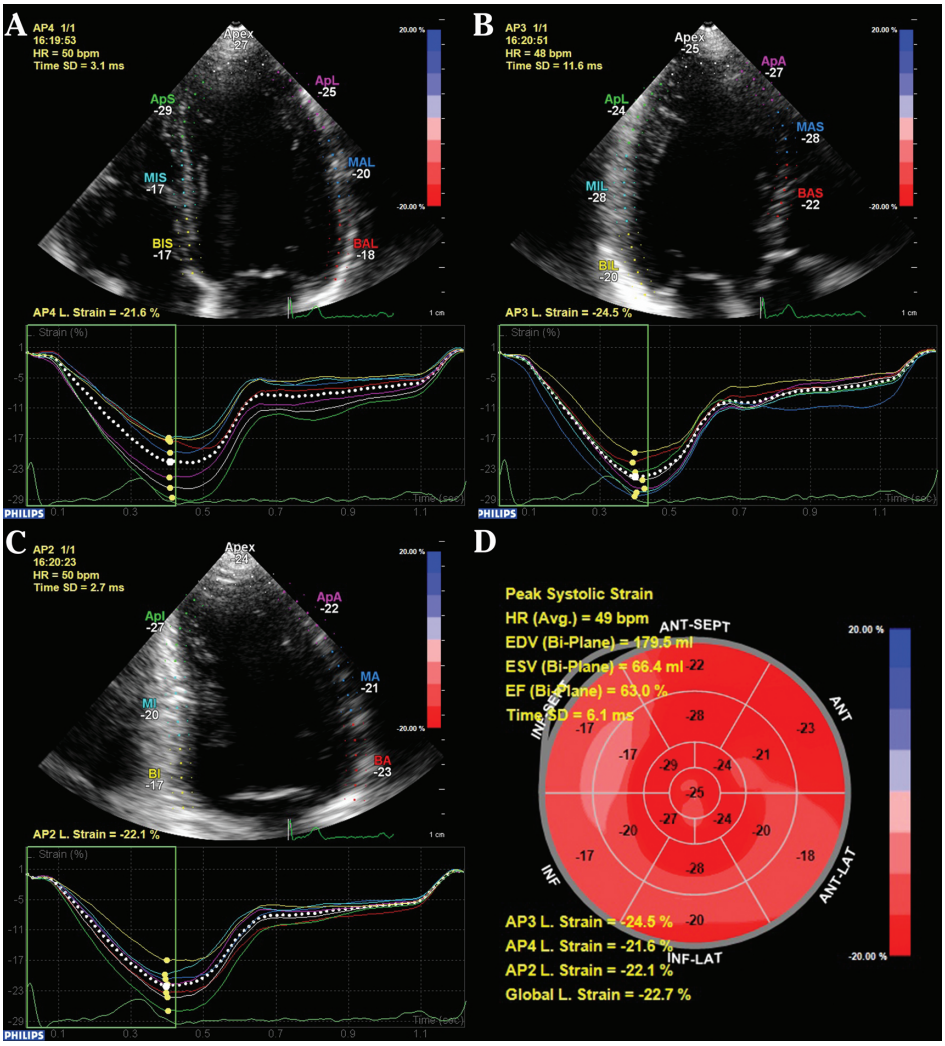


Figure 1 Example of left ventricular longitudinal strain measurements in a healthy individual
The left ventricle was traced in the apical four-, three-, and two-chamber views at end-diastole. The walls were automatically divided into seven segments at each view and the global longitudinal strain at each view was calculated (A-C). The segmental strains were plotted in a bull's eye and the left ventricular global longitudinal strain based on a 17-segment model was calculated (D).
AP2 = apical two-chamber; AP3 = apical three-chamber; AP4 = apical four-chamber; GL = global longitudinal.

the differences ±1.96SD.[11] Additionally, the coefficient of variation was provided (SD of the differences of 2 measurements divided by their mean).

RESULTS

Study population

Of the 155 subjects who came to our medical centre, 147 were included (age 44.6 ± 13.7 years, 50% female). Table 1 shows the characteristics of the study population per age group. Eight subjects were excluded for various reasons: breast implants (n=2), valvular pathology (n=2), surgically closed patent ductus arteriosus (n=1), hypertension (n=1), morbid obesity (n=1), and right bundle branch block on ECG (n=1). Due to technological reasons, the echocardiographic images of 2 subjects had not been exported to the QLAB working station.

Left ventricular longitudinal strain

Among the 145 remaining subjects, the feasibility of peak systolic LV GLS on A4C and A2C was 99%, on A3C 97%, and LV GLS based on all three apical views 97%. Figure 2 shows the feasibility per segment on each view. The mean LV GLS of the healthy subjects was -20.8 ± 2.0%. The mean global and segmental strains of the three apical views are summarized per age group in Table 2. LV GLS did not decrease significantly with advancing age (Figure 3). However, comparing GLS of subjects >55 years old (n=35) versus ≤55 years (n=106), resulted in a lower strain in the older subjects (-20.2 ± 2.0% vs. -21.0 ± 2.0%, *P*=0.029). In all age groups, the apical segments showed higher peak systolic strain than the basal segments.

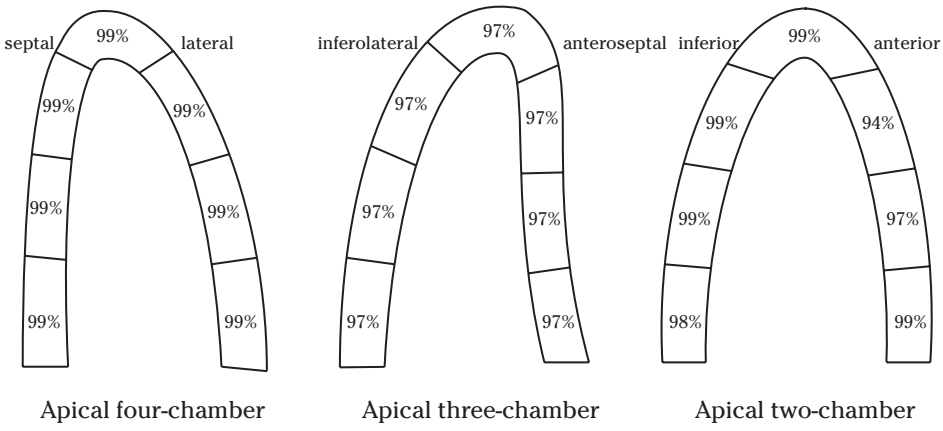


Figure 2 The feasibility of strain calculation per segment
Each number reflects the percentage of possible strain measurements of that segment in our cohort.

Table 1 Characteristics of the study population

	Age group (yrs)				
	20-29	**30-39**	**40-49**	**50-59**	**60-72**
Characteristic	**n=32**	**n=28**	**n=28**	**n=31**	**n=28**
Sex, female	16 (50%)	14 (50%)	14 (50%)	16 (52%)	14 (50%)
Age (years)	26 ± 3	35 ± 3	44 ± 3	55 ± 3	64 ± 3
Current smoker	2 (6%)	1 (4%)	4 (14%)	5 (16%)	1 (4%)
Physical examination					
Body mass index (kg/m^2)	22.3 ± 2.1	24.1 ± 3.4	24.6 ± 3.7	25.4 ± 2.8	25.8 ± 3.1
Body surface area (m^2)	1.84 ± 0.17	1.89 ± 0.18	1.92 ± 0.22	1.92 ± 0.18	1.90 ± 0.19
Systolic blood pressure (mmHg)	124 ± 13	121 ± 10	123 ± 12	130 ± 15	137 ± 17
Diastolic blood pressure (mmHg)	76 ± 8	78 ± 7	80 ± 10	83 ± 11	83 ± 8
ECG					
Sinus rhythm	32 (100%)	28 (100%)	28 (100%)	31 (100%)	28 (100%)
Heart rate (bpm)	61 ± 11	60 ± 8	61 ± 10	62 ± 9	65 ± 10
PR interval (ms)	156 ± 24	150 ± 21	156 ± 24	159 ± 16	173 ± 18
QRS duration (ms)	96 ± 8	97 ± 9	97 ± 9	95 ± 10	97 ± 10
Echocardiography, left ventricle					
End-diastolic dimension (mm)	46.4 ± 3.2	46.9 ± 3.2	45.3 ± 3.9	44.8 ± 4.5	44.0 ± 5.1
End-systolic dimension (mm)	28.6 ± 3.2	28.3 ± 3.3	28.4 ± 4.6	28.2 ± 4.2	28.0 ± 6.2
E wave (m/s)	0.80 ± 0.16	0.75 ± 0.16	0.66 ± 0.15	0.65 ± 0.11	0.59 ± 0.13
A wave (m/s)	0.39 ± 0.14	0.43 ± 0.08	0.47 ± 0.10	0.56 ± 0.12	0.62 ± 0.17
Deceleration time (ms)	177 ± 29	181 ± 32	185 ± 29	194 ± 31	216 ± 64
E' (cm/s)	12.5 ± 1.8	10.4 ± 1.6	9.2 ± 1.6	8.2 ± 1.8	6.8 ± 1.7
E/A-ratio	2.27 ± 0.77	1.80 ± 0.40	1.43 ± 0.38	1.21 ± 0.34	1.01 ± 0.32
E/E'-ratio	6.45 ± 1.35	7.27 ± 1.47	7.29 ± 1.71	8.11 ± 1.44	9.04 ± 2.42
End-systolic volume (mL)	47 ± 11	47 ± 13	51 ± 15	45 ± 12	48 ± 16
End-diastolic volume (mL)	117 ± 23	120 ± 23	125 ± 31	116 ± 21	116 ± 31
End-systolic volume / BSA (mL/m^2)	25.4 ± 5.1	24.7 ± 6.2	26.2 ± 5.5	23.2 ± 5.1	25.0 ± 6.9
End-diastolic volume / BSA (mL/m^2)	63.9 ± 9.5	63.1 ± 9.9	64.1 ± 10.9	60.5 ± 8.0	60.6 ± 12.2
Ejection fraction (biplane) (%)	60.4 ± 3.6	61.4 ± 5.0	59.2 ± 4.5	61.9 ± 5.3	59.2 ± 4.5

Values are presented as n (%) or mean ± SD. A = peak mitral inflow velocity at late diastole; E = peak mitral inflow velocity at early diastole; E' = early diastolic annular myocardial velocity.

Relationships with left ventricular global longitudinal strain

Males had significantly lower LV GLS than females (-20.1 ± 1.8% vs. -21.5 ± 2.0%, P<0.001). Figure 4 presents the median GLS for males and females stratified by age.

Table 3 shows the results of univariable and multivariable regression analyses with GLS as dependent variable. There was a linear decrease in GLS with increasing blood pressure and BSA, but no relationship was found with age as continuous

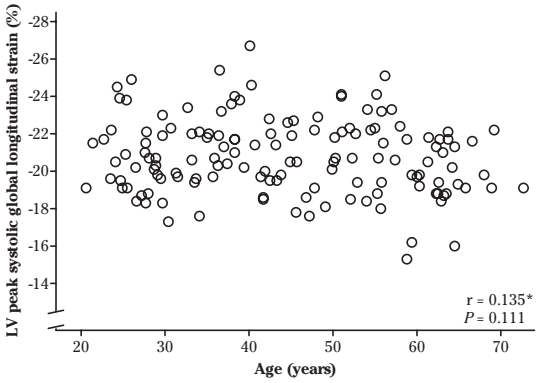
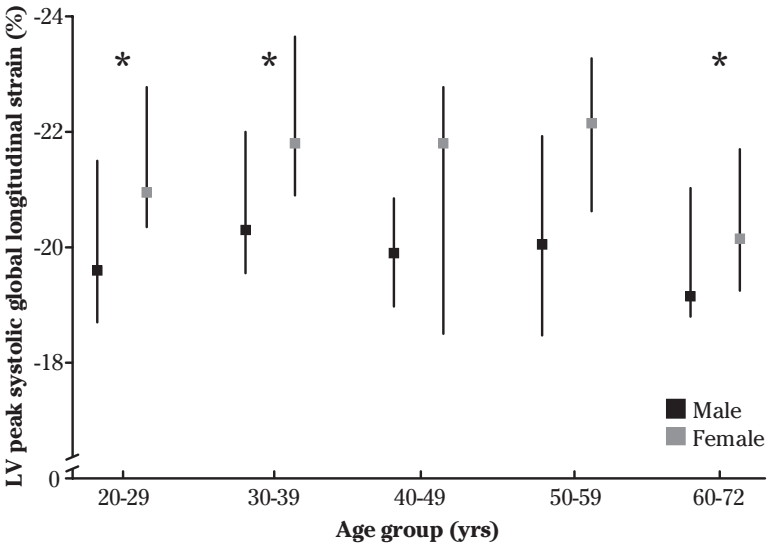


Figure 3 Correlation between left ventricular peak systolic global longitudinal strain and age
This scatter plot represents one person's left ventricular peak systolic global longitudinal strain value versus his/her age. No significant relationship could be observed between these two variables.
*To aid interpretation of the Pearson's correlation coefficient, global longitudinal strain has been analyzed as positive number. LV = left ventricular.



	20-29	30-39	40-49	50-59	60-72
Male	-19.6% [2.8]	-20.3% [2.5]	-19.9% [1.9]	-20.1% [3.5]	-19.2% [2.2]
Female	-21.0% [2.4]	-21.8% [2.8]	-21.8% [4.3]	-22.2% [2.7]	-20.2% [2.5]

Figure 4 Median left ventricular global longitudinal strain stratified by sex and age
*P<0.05 Strain values are presented as median [IQR] by sex and age group. LV = left ventricular.

variable. A higher GLS was associated with more favourable indices of diastolic function and with smaller LV end-diastolic and end-systolic volumes.

Because of the relationship between GLS and BSA, we additionally performed univariable regression analysis of GLS indexed for BSA. Indexing for BSA strengthened most of the significant correlations with the subjects' characteristics (Table

3). In multivariable analysis, sex, systolic blood pressure, E wave and LV end-systolic volume remained significant predictors for GLS indexed for BSA (Table 3).

Left ventricular longitudinal strain rate

LV peak systolic strain rates per age group are given in Table 4. Linear regression analysis showed lower strain rates on the A4C and A2C with increasing age. Strain rates were comparable between men and women. Correlation analysis between strain rate and BSA showed that on the A4C 6 out of 7 segments correlated significantly, on the A3C 1 out of 7, and on the A2C 5 out of 7.

Table 2 Left ventricular peak systolic global and segmental longitudinal strain

Age (years)	20-29	30-39	40-49	50-59	60-72	*P*-value*
	n=31	n=28	n=27	n=30	n=27	
GLS (%)	-20.8 ± 1.9	-21.3 ± 1.9	-20.7 ± 2.2	-21.1 ± 2.4	-20.0 ± 1.5	0.189
GLS apical 4-chamber	-21.1 ± 2.0	-21.4 ± 2.1	-20.9 ± 2.5	-21.0 ± 2.9	-19.9 ± 1.7	0.068
Basal septal	-16.4 ± 2.3	-16.9 ± 2.7	-16.5 ± 3.2	-15.8 ± 3.5	-14.1 ± 2.7	0.001
Mid septal	-18.6 ± 3.1	-18.6 ± 2.7	-16.8 ± 3.7	-17.0 ± 3.3	-16.0 ± 2.8	0.001
Apical septal	-27.0 ± 3.4	-27.3 ± 2.7	-27.4 ± 3.9	-28.4 ± 4.6	-27.1 ± 3.6	0.377
Apex	-25.2 ± 2.5	-25.1 ± 2.5	-24.5 ± 3.2	-25.2 ± 3.9	-23.9 ± 2.6	0.349
Apical lateral	-23.4 ± 2.5	-23.1 ± 3.1	-21.8 ± 3.7	-22.0 ± 3.8	-20.7 ± 2.4	0.003
Mid lateral	-18.9 ± 3.4	-20.2 ± 2.7	-20.5 ± 3.0	-20.1 ± 3.4	-18.5 ± 2.8	0.883
Basal lateral	-19.1 ± 2.5	-19.3 ± 3.0	-19.3 ± 3.3	-19.3 ± 3.6	-19.1 ± 2.1	0.961
GLS apical 3-chamber	-20.2 ± 2.5	-21.5 ± 2.4	-21.4 ± 2.5	-21.4 ± 3.3	-20.8 ± 2.7	0.264
Basal inferolateral	-17.3 ± 3.7	-18.5 ± 3.1	-19.8 ± 3.6	-18.9 ± 3.5	-19.9 ± 4.0	0.016
Mid inferolateral	-21.2 ± 3.6	-22.8 ± 4.1	-22.3 ± 3.2	-21.9 ± 4.4	-21.2 ± 4.2	0.748
Apical lateral	-21.4 ± 3.2	-22.2 ± 3.2	-21.5 ± 3.6	-22.3 ± 4.5	-20.6 ± 2.8	0.684
Apex	-22.4 ± 3.2	-23.4 ± 3.0	-23.4 ± 4.4	-23.4 ± 4.7	-22.2 ± 3.5	0.586
Apical anterior	-23.3 ± 4.1	-24.7 ± 4.1	-25.3 ± 5.7	-24.4 ± 6.2	-24.3 ± 4.4	0.273
Mid anteroseptal	-19.7 ± 3.1	-20.4 ± 3.7	-20.0 ± 4.3	-20.8 ± 4.6	-19.8 ± 2.9	0.449
Basal anteroseptal	-17.4 ± 3.2	-19.4 ± 3.2	-18.2 ± 2.8	-19.4 ± 3.7	-18.4 ± 3.8	0.131
GLS apical 2-chamber	-20.9 ± 2.1	-21.0 ± 2.1	-20.1 ± 2.6	-20.8 ± 2.5	-19.3 ± 1.9	0.015
Basal inferior	-16.8 ± 2.9	-16.9 ± 3.0	-17.1 ± 3.5	-16.5 ± 3.7	-15.2 ± 3.2	0.087
Mid inferior	-19.3 ± 2.9	-18.7 ± 3.0	-18.1 ± 3.3	-18.3 ± 3.2	-17.0 ± 2.6	0.006
Apical inferior	-25.5 ± 3.0	-25.9 ± 2.7	-24.5 ± 3.4	-26.2 ± 3.3	-24.4 ± 2.8	0.258
Apex	-23.4 ± 2.7	-24.0 ± 2.6	-22.3 ± 3.0	-24.0 ± 3.3	-21.9 ± 2.3	0.155
Apical anterior	-21.7 ± 3.0	-22.0 ± 3.2	-20.6 ± 3.3	-22.5 ± 3.9	-19.5 ± 2.7	0.084
Mid anterior	-21.1 ± 3.2	-20.9 ± 3.1	-19.2 ± 3.3	-19.8 ± 3.9	-19.4 ± 3.4	0.006
Basal anterior	-19.1 ± 2.9	-19.4 ± 4.3	-19.7 ± 3.8	-19.3 ± 3.1	-18.6 ± 3.2	0.359

Values are presented as mean ± SD. *Using linear regression analysis. GLS = global longitudinal strain.

Table 3 Univariable and multivariable regression analyses of left ventricular global longitudinal strain

	LV GLS					LV GLS / BSA				
	Univariable		Multivariable			Univariable		Multivariable		
	Pearson's r	*P*-value	Unstandardized β	Standardized β	*P*-value	Pearson's r	*P*-value	Unstandardized β	Standardized β	*P*-value
Age (years)	-0.14	0.111				-0.13	0.127			
Sex (female)	0.34	**<0.001**				0.64	**<0.001**	1.04	0.29	**<0.001**
Physical examination										
Body surface area (m^2)	-0.35	**<0.001**	0.92	0.09	0.337	-	-			
Body mass index (kg/m^2)	-0.26	**0.002**				-	-			
Systolic blood pressure (mmHg)	-0.40	**<0.001**	-0.04	-0.26	**0.001**	-0.44	**<0.001**	-0.03	-0.21	**<0.001**
Diastolic blood pressure (mmHg)	-0.36	**<0.001**				-0.44	**<0.001**			
ECG										
Heart rate (bpm)	-0.21	**0.012**				-0.05	0.523			
QRS duration (ms)	-0.14	0.089				-0.38	**<0.001**	-0.01	-0.04	0.512
Echocardiography, left ventricle										
End-diastolic dimension (mm)	0.08	0.324				-0.15	0.087			
End-systolic dimension (mm)	0.02	0.855				-0.15	0.072			
E wave (m/s)	0.34	**<0.001**	1.99	0.16	**0.031**	0.39	**<0.001**	1.53	0.14	**0.014**
A wave (m/s)	-0.01	0.870				0.03	0.771			
Deceleration time (ms)	-0.17	0.050				-0.22	**0.009**			
E' (cm/s)	0.26	**0.002**				0.30	**<0.001**			
E/A-ratio	0.19	**0.021**				0.21	**0.011**			
E/E'-ratio	0.01	0.907				0.02	0.809			
End-diastolic volume (mL)	-0.32	**<0.001**				-0.62	**<0.001**			
End-systolic volume (mL)	-0.53	**<0.001**	-0.07	-0.47	**<0.001**	-0.70	**<0.001**	-0.06	-0.43	**<0.001**
Ejection fraction, biplane (%)	0.69	**<0.001**				0.58	**<0.001**			

Global longitudinal strain has been analyzed as positive number to aid interpretation of correlations.
Variables that reached a $P<0.001$ and did not show collinearity with other variables were included in the multivariable model. In case of collinear variables, the variable with the highest correlation coefficient was included in the multivariable model. A = peak mitral inflow velocity at late diastole; E = peak mitral inflow velocity at early diastole; E' = early diastolic annular myocardial velocity.

Table 4 Left ventricular peak systolic strain rates per age group

Age (years)	20-29	30-39	40-49	50-59	60-72	*P*-value*
	n=31	n=28	n=27	n=30	n=27	
Apical 4-chamber						
Basal septal (s^{-1})	-0.79 ± 0.12	-0.84 ± 0.11	-0.81 ± 0.18	-0.77 ± 0.14	-0.69 ± 0.13	0.002
Mid septal	-0.92 ± 0.15	-0.92 ± 0.15	-0.85 ± 0.18	-0.87 ± 0.17	-0.78 ± 0.13	0.002
Apical septal	-1.26 ± 0.18	-1.26 ± 0.16	-1.25 ± 0.19	-1.25 ± 0.16	-1.16 ± 0.20	0.134
Apex	-1.22 ± 0.17	-1.16 ± 0.13	-1.12 ± 0.18	-1.12 ± 0.19	-1.02 ± 0.14	<0.001
Apical lateral	-1.22 ± 0.22	-1.11 ± 0.16	-1.01 ± 0.23	-1.04 ± 0.23	-0.90 ± 0.13	<0.001
Mid lateral	-1.00 ± 0.13	-1.03 ± 0.14	-0.98 ± 0.17	-0.99 ± 0.15	-0.91 ± 0.13	0.026
Basal lateral	-1.00 ± 0.16	-0.97 ± 0.17	-0.99 ± 0.16	-0.90 ± 0.16	-0.91 ± 0.12	0.008
Apical 3-chamber						
Basal inferolateral	-0.93 ± 0.15	-1.01 ± 0.17	-0.98 ± 0.18	-0.94 ± 0.14	-0.93 ± 0.23	0.733
Mid inferolateral	-1.03 ± 0.18	-1.09 ± 0.19	-1.06 ± 0.17	-1.05 ± 0.15	-1.02 ± 0.20	0.547
Apical lateral	-1.00 ± 0.17	-1.05 ± 0.13	-1.00 ± 0.14	-1.02 ± 0.21	-0.93 ± 0.15	0.097
Apex	-1.01 ± 0.13	-1.06 ± 0.11	-1.05 ± 0.17	-1.04 ± 0.21	-0.99 ± 0.19	0.948
Apical anterior	-1.05 ± 0.16	-1.11 ± 0.15	-1.12 ± 0.24	-1.09 ± 0.26	-1.09 ± 0.24	0.405
Mid anteroseptal	-0.97 ± 0.13	-0.99 ± 0.16	-0.99 ± 0.20	-0.97 ± 0.16	-0.94 ± 0.20	0.873
Basal anteroseptal	-0.84 ± 0.16	-0.95 ± 0.16	-0.92 ± 0.15	-0.92 ± 0.18	-0.87 ± 0.19	0.595
Apical 2-chamber						
Basal inferior	-0.80 ± 0.15	-0.79 ± 0.09	-0.80 ± 0.15	-0.77 ± 0.13	-0.71 ± 0.12	0.013
Mid inferior	-0.92 ± 0.15	-0.87 ± 0.11	-0.89 ± 0.16	-0.89 ± 0.13	-0.83 ± 0.13	0.053
Apical inferior	-1.17 ± 0.14	-1.17 ± 0.12	-1.12 ± 0.15	-1.13 ± 0.11	-1.06 ± 0.16	0.004
Apex	-1.08 ± 0.14	-1.07 ± 0.10	-1.01 ± 0.15	-1.03 ± 0.11	-0.96 ± 0.13	0.001
Apical anterior	-1.01 ± 0.17	-1.00 ± 0.12	-0.95 ± 0.16	-0.99 ± 0.16	-0.91 ± 0.15	0.028
Mid anterior	-0.98 ± 0.17	-0.98 ± 0.16	-0.92 ± 0.14	-0.91 ± 0.17	-0.91 ± 0.16	0.005
Basal anterior	-0.89 ± 0.17	-0.89 ± 0.15	-0.90 ± 0.17	-0.87 ± 0.13	-0.84 ± 0.14	0.088

Values are presented as mean ± SD. *Using linear regression analysis.

Intra-observer and inter-observer agreement

The intra-observer agreement for LV GLS was 0.01 ± 0.57%, and the inter-observer agreement -0.67 ± 0.91%. Figure 5 presents the linear correlation and Bland-Altman plots for the intra-observer and inter-observer measurements.

DISCUSSION

To our best knowledge, this prospective cohort study consisting of 147 healthy volunteers and who are stratified per age decade, is the first study reporting normal LV longitudinal strain values after the strain standardization initiative of the

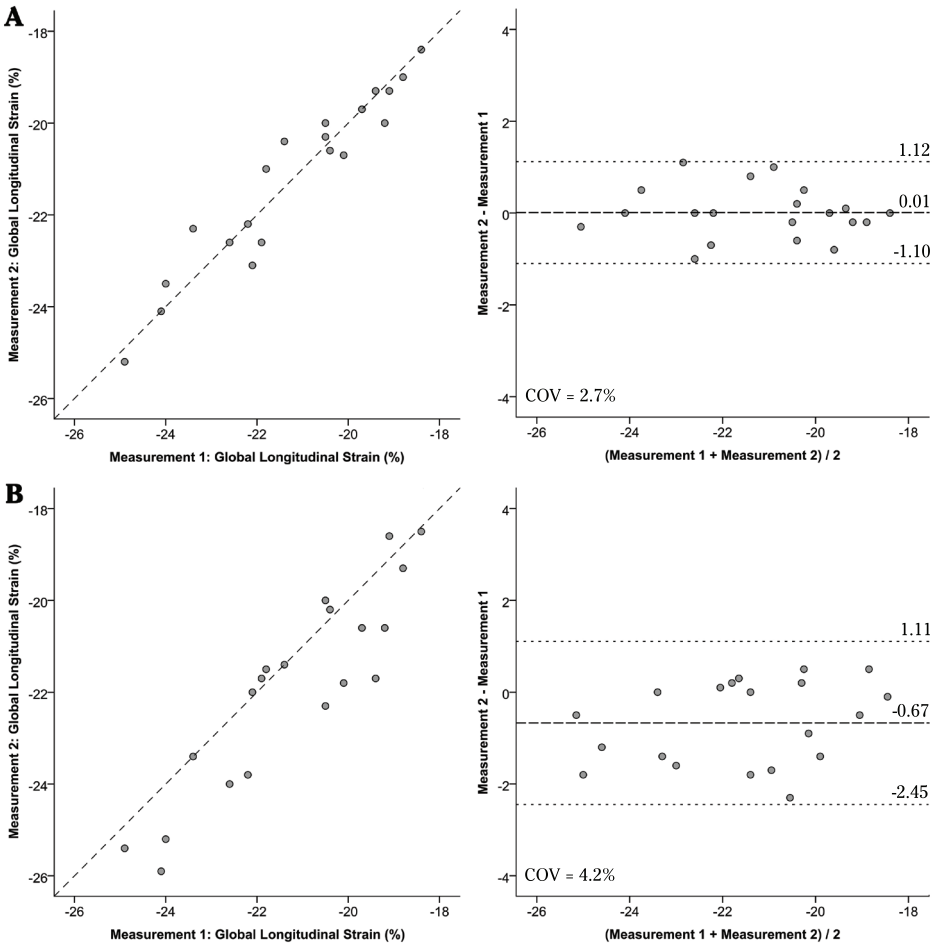


Figure 5 Linear correlation and Bland-Altman plots for intra-observer and inter-observer measurements of left ventricular global longitudinal strain

First row (A) refers to intra-observer agreement with one observer analyzing the same dataset twice. Second row (B) refers to inter-observer agreement with two observers analyzing the same dataset. In the Bland-Altman plots on the right side, the striped lines depict the mean difference of two measurements, and the dashed lines depict the limits of agreement (1.96SD). COV = coefficient of variation.

task force.[10] Sex, BSA and blood pressure were the most important anthropometric factors that influence LV GLS assessed with QLAB, whereas age did not. Strain rates were lower with increasing age and did not differ between men and women.

Left ventricular longitudinal strain

LV GLS was feasible in 97% of the subjects, and GLS on A4C and A2C even in 99%, which is an important amenity for the wider use of GLS on a daily basis in the clinical setting. The mean GLS of our study cohort was -20.8 ± 2.0%, which is

comparable with the reported -19.7% in a meta-analysis.[8] However, the majority of included studies in that meta-analysis used software of another vendor. Moreover, the included studies are dated and therefore newer versions of the software are already in use.

We observed LV segmental strain heterogeneity: longitudinal strain gradually increased from the basal to apical segments in all age groups, which is in line with the results reported by Sun et al.[12] Nowadays, analyzing regional ventricular function becomes more-and-more important. An increasing number of studies state that it is especially the function of some of the regions that are impaired in different types of heart diseases, for example decreased basal strain in hypertrophic cardiomyopathy and aortic stenosis.[13,14] Even in patients with primarily right-heart pathology, evaluating regional LV deformation could be of particular importance. Patients with repaired tetralogy of Fallot had a decreased LV septal strain indicating that right ventricular dysfunction negatively affects LV function, which is called ventricular-ventricular interaction.[15]

Relationships with sex, age and body surface area

The cut-off value for normal LV ejection fraction is higher in women than men.[1] The same should be applied for longitudinal strain, because we found significant greater values in women, which corroborates with previous STE studies[12,16] and a recent study with feature-tracking cardiovascular magnetic resonance (CMR).[17] In a relatively large sample of the general population, where longitudinal strain was measured with colour Doppler myocardial imaging,[18] no sex differences were found, neither in a meta-analysis by Yingchoncharoen et al.[8] The different vendors that have been included might have had an influence.

We did not observe a clear relationship between age and GLS, neither per age decade, nor as linear correlation. This might be explained by our relatively low sample size. On the other hand, the absence of a relationship was also reported on GLS assessed with feature-tracking CMR.[17] However, we did find a significant difference in strain between subjects ≤55 years old and subjects >55. Dividing subjects in groups younger and older than 55 years has also been performed by Sun et al. resulting in a slightly lower strain in the older patients.[12] In a study including over 1,200 healthy individuals with a maximum age of 89 years, systolic strain was also lower with increasing age.[19] Due to the fact that age often goes along with higher blood pressure and BSA, it seems plausible that at a certain age, decrease in strain could occur. After adjustment for various anthropometric variables, GLS did not associate with age as continuous variable in a meta-regression analysis.[8] Therefore, we postulate that age itself is not the most important and clinical relevant factor for interpreting strain results. However, we did not include subjects >72

years. Those subjects may have a lower GLS than the subjects of our cohort, but this assumption has to be investigated. It is however, not easy to include subjects above 72 years of age without history of or risk factors for cardiovascular disease.

We found a weak to moderate positive correlation between GLS and BSA. Such correlation had also been described with the use of feature-tracking CMR in healthy controls,[17] and, though weaker, with STE.[12] Because of this correlation and the possible interaction between BSA and other anthropometric and echocardiographic measurements, we decided to index GLS for BSA. This indexation resulted in stronger correlations regarding systolic and diastolic blood pressure, some diastolic function indices and LV end-diastolic and end-systolic volumes. Additionally, the sex-difference in strain became larger. That is why we advise to correct for BSA and sex.

Relationship with blood pressure

Even though all our subjects were healthy and did not have hypertension, we still observed a moderate correlation between higher blood pressure and lower GLS. A similar correlation was also found in a meta-analysis with a larger sample of healthy subjects.[8] In patients with hypertension, decreased GLS was reported in the presence of a normal or even supranormal LV ejection fraction.[20] As a compensatory mechanism for preserving the ejection fraction, these patients had an increased twist compared to normal controls.[20] It is generally known that, besides aging,[21] hypertension is associated with alterations in diastolic LV function.[22] In our healthy cohort, some of the diastolic function indices, such as E wave, deceleration time, E prime and E/A ratio showed significant relationships with GLS. Even after implementation the 'E wave' in a multivariable regression model, it remained a significant determinant for GLS. A recently published paper of the CARDIA study described that higher cumulative exposure to blood pressure over 25 years from young adulthood to middle age was associated with lower LV longitudinal strain and diastolic dysfunction, but not with LV ejection fraction.[23] These findings reflect that GLS is a load dependent parameter and that a relatively small increase in afterload will result in lower longitudinal strain. The fact that GLS correlates with blood-pressure values at the time of echocardiography in our cohort, makes no distinction whether GLS is just a pure reflection of the current degree of afterload or a reasonable and sensitive marker for incipient LV dysfunction caused by chronic hypertension. The definition of hypertension is traditionally based on office blood-pressure measurements.[24] However, blood pressure could be elevated in the office and normal out of the office which is termed white-coat hypertension, whereas masked hypertension refers to a normal blood pressure in the office and abnormally high out of the medical environment.[22] Hence, out-of-office blood-

pressure measurements play an important role in hypertension management,[22,24] but home and ambulatory blood-pressure monitoring both have their limitations. It would be helpful if STE-derived strain can serve, already in a preclinical state, as an objective diagnostic tool to determine the severity of hypertension without the interference of overestimation (white-coat hypertension) or underestimation (masked hypertension). Whether decreased strain really can serve as an early marker and reasonable predictor of hypertension and future heart failure in this patient population has to be investigated in a follow-up study.

Left ventricular longitudinal strain rate

In contrast to strain, longitudinal strain rates of most of the segments did significantly decrease over the age decades, but regarding sex no clear differences were found. Studies evaluating the effects of age on strain rate are scarce, and studies reporting strain rates measured with the newer STE software versions even more. Although not measured with STE but with Doppler imaging, strain rate showed significant dependence on age in some studies.[18,19,25] It has been supposed that slower calcium cycling with age leads to longer systolic contraction periods. This physiological mechanism may be an explanation for the fact that decrease in tissue displacement is less age-related than decrease in velocity.[25,26] Therefore, peak systolic strain could be preserved despite lower peak strain rate.

Intra-observer and inter-observer agreement

The intra-observer and inter-observer agreement were excellent and evidently better than previously reported by others.[12,16] The improvement is probably a result of the more automated software that now have been used and is an important finding making GLS more sound for clinical use.

Study limitations

Between-vendor variability is often mentioned as a limitation to the clinical application of strain imaging. In this study, we only used Philips ultrasound equipment and QLAB software. However, after the implementation of the standardization process, the variability of GLS in the later developed software versions between two leading ultrasound manufactures have been reduced [7] making the values reported by us more widely applicable nowadays. Due to the relatively small sample size, the conclusions should be interpreted with caution.

CONCLUSIONS

Our study resulted in normative LV GLS values assessed with QLAB 10 in a healthy population aged 20 to 72 years. Sex, BSA and blood pressure influence LV GLS, whereas age does not. Indexation of GLS for BSA results in stronger correlations regarding blood pressure and sex. For interpretation of strain results in clinical practice, it is crucial to take these factors into account. That is why we advise to correct strain measurements for BSA and sex.

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CHAPTER 3

A novel 13-segment standardized model for assessment of right ventricular function using two-dimensional iRotate echocardiography

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ABSTRACT

Aims

The aim of this study was to evaluate the feasibility of transthoracic two-dimensional (2D) iRotate, a new echo modality, to assess the whole right ventricle (RV) from a single transducer position based on anatomic landmarks.

Methods and Results

The anatomic landmarks were first defined based on three-dimensional echocardiographic datasets using multiplane reconstruction analyses. Thereafter, we included 120 healthy subjects (51% male, age range 21-67 years). Using 2D iRotate, four views of the RV could be acquired based on these landmarks. The anterior, lateral, inferior wall (divided into three segments: basal-mid-apical), and right ventricular outflow tract (RVOT) anterior wall of the RV were determined. The feasibility of visualization of RV segments and Tricuspid annular plane systolic excursion (TAPSE) and TDI measurements were assessed. To evaluate this model for diseased RVs, a small pilot study of 20 patients was performed. In 98% of healthy subjects and 100% of patients, iRotate mode was feasible to assess the RV from one single transducer position. In total, 86% and 95%, respectively, of the RV segments could be visualized. The visualization of the RVOT anterior wall was worse 23% and 75%, respectively. TAPSE and TDI measurements on all four views were feasible 93% and 92%, respectively, of the healthy subjects and in 100% of the patients.

Conclusion

With 2D iRotate, a comprehensive evaluation of the entire normal and diseased RV is feasible from a fixed transducer position based on anatomic landmarks. This is less time-consuming than the multiview approach and enhances accuracy of RV evaluation. Imaging of the RVOT segment remains challenging.

INTRODUCTION

Assessment of right ventricular (RV) function is increasingly recognized as a prognostic factor in a variety of diseases such as left-sided heart failure, pulmonary hypertension and congenital heart disease in the acute phase and during follow up.[1] In everyday clinical practice, two-dimensional (2D) transthoracic echocardiography (TTE) remains the technique that is most often used for the assessment of ventricular function. Unlike the left ventricle (LV) that can be completely visualized from one apical window, for a comprehensive evaluation of RV size and function, a multiview approach is necessary.[2-6] However, this multiview approach is impractical in a routine setting: it is time-consuming, operator dependent, and inaccurate due to the complex RV geometry. Current echocardiographic methodologies do not provide a robust assessment of RV function. Serial follow-up of RV measurements and function parameters result in significant inaccuracies from oblique plane acquisitions due to the lack of fixed landmarks.[2, 4] A standardized echocardiographic approach taken from one acoustic window where an anatomic landmark in the image plane can be used to identify a specific RV wall could increase the accuracy of assessment of RV function in routine follow-up. The aim of this study was: (1) to investigate whether there are unique anatomic landmarks that could be used as a reference point to depict a specific RV wall from one standard acoustic window, the apical window, (2) to evaluate the feasibility of 2D transthoracic iRotate mode, a new echo modality, to comprehensively assess the RV based on these anatomic landmarks, and (3) to demonstrate in a small pilot group of patients with a diseased RV the feasibility of this technique for further investigation.

METHODS

Definition of anatomic landmarks based on 3D echo

In order to identify anatomic landmarks, seen in views that demonstrate specific RV walls, and to determine how to steer a 2D imaging plane (iRotate, Philips Medical systems, Best, the Netherlands) using a matrix-array transducer in order to acquire these views, we first examined several three-dimensional (3D) echocardiographic data sets. A total of 15, 3D datasets, acquired from the apical window, from normal subjects, and from patients with acquired and congenital (dilated RVs) heart disease, were examined with the TomTec 4D cardio-View 3.0 (TomTec-Arena version 1.2, TomTec, Munich, Germany) using the multiplane reconstruction analysis (MPR). The TomTec software features a quad screen display with three 2D

cut planes (sagittal, transverse, and coronal) and a 3D volume cube, created from a 3D volume dataset. With MPR, three planes (sagittal, transverse, and coronal) can be positioned through a region of interest and moved simultaneously. The four-chamber (4C) view displayed in the sagittal plane was adjusted to center the interventricular septum (IVS)-RV apex along the midline and then transected at the base of the right and left ventricle (Figure 1A). The corresponding short-axis view, displayed in the transverse plane, shows anterior, lateral, and inferior wall of the RV (Figure 1B and 1C). With the MPR, it is possible to rotate around the IVS in this transverse plane, thereby anatomic landmarks could be defined in the corresponding sagittal plane.

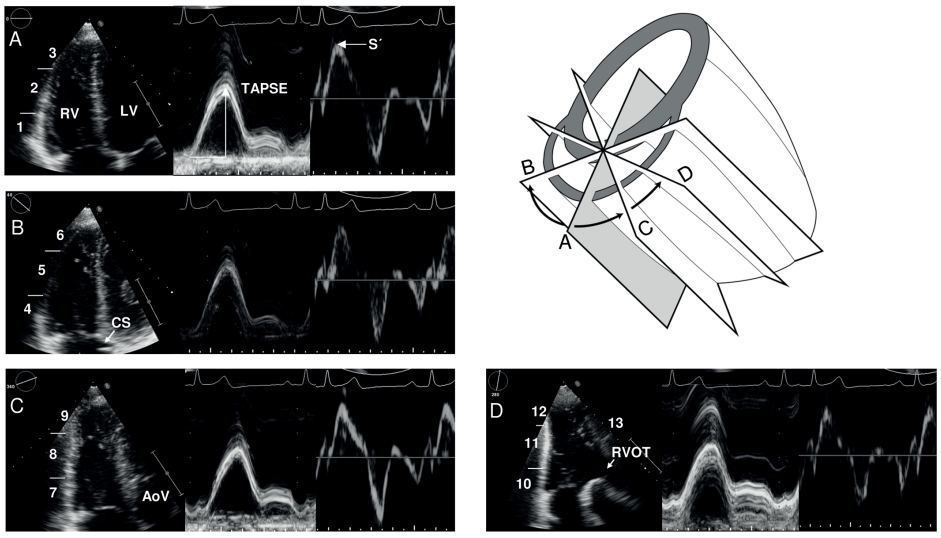

Figure 1
A. Display of the sagittal plane from the TomTec 4D Cardio-View multiplane reconstruction analysis program showing the right side of the interventricular septum (IVS) along the centerline. The white solid line depicts the position of the cut plane for the transverse image, B. **B.** Display of the transverse plane showing the basal short-axis view of the right ventricle (RV). The cut plane (white solid line) transverses the lateral wall of the RV, IVS and left ventricle (LV). **C.** Schematic drawing of the transverse plane of the RV as seen in B. The RV walls displayed are as follows: Ant = anterior; Lat = lateral; Inf = inferior.

Identified anatomic landmarks

In all examined 3D datasets, the four walls (anterior, lateral, inferior, and right ventricular outflow tract (RVOT) anterior wall) of the RV could be identified according to a unique anatomic landmark. The anatomic landmarks that we identified were as follows:

- Mitral valve (standard 4C view): showing the lateral wall of the RV
- Coronary sinus: showing the anterior wall of the RV

- Aortic valve: showing the inferior wall of the RV
- RVOT: showing the RVOT anterior and inferior wall of the RV.

The rotation around the IVS and the corresponding anatomic landmark identified in the sagittal plane are shown in Figure 2.

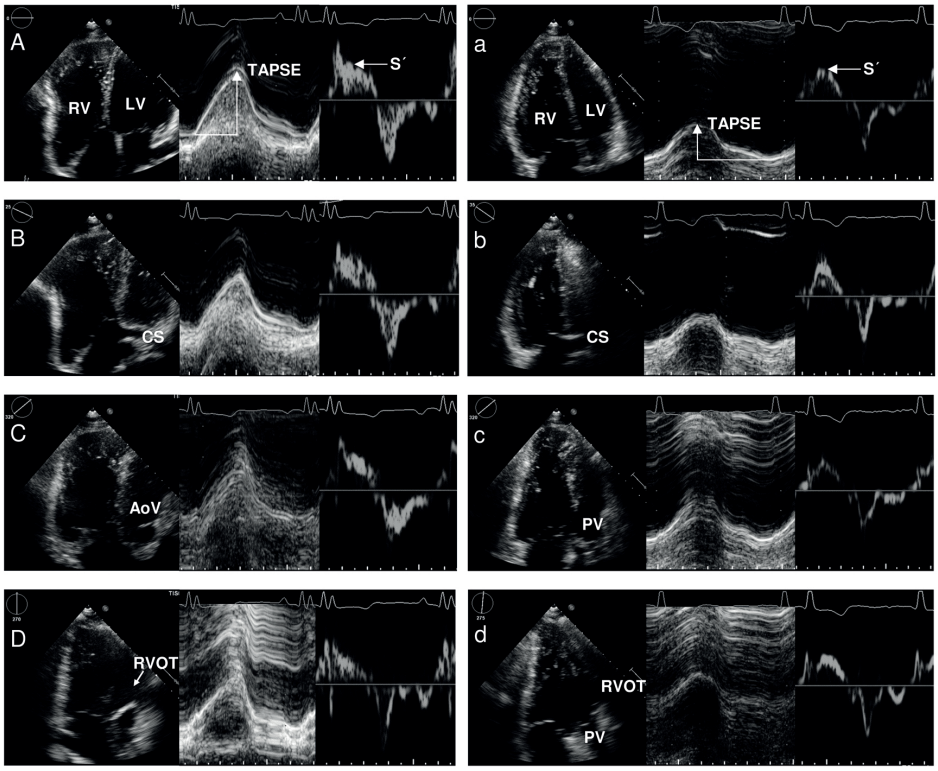

Figure 2

Schematic drawings and multiplane reconstruction of echocardiographic images displayed using the TomTec 4D Cardio-View analysis program. Left: schematic drawing and echocardiographic images of the cut planes A-D displaying the right ventricle (RV) in the transverse plane, viewed from the RV aspect. LV=left ventricle. Right: schematic drawing and echocardiographic images of the cut planes A-D from the RV and corresponding landmark in the sagittal plane. **A.** Four-chamber view (0°). Landmark mitral valve giving rise to the lateral wall. **B.** Coronary sinus view (+40°). Landmark coronary sinus (CS) giving rise to the anterior wall. **C.** Aortic view (-40°). Landmark aortic valve (AoV) giving rise to the inferior wall. **D.** Coronal view (-90°). Landmark right ventricular outflow tract (RVOT) giving rise to the RVOT anterior wall.

Assessment of RV function with iRotate mode

The study was conducted in two phases: First, our proposed model was examined in healthy subjects, and then, a pilot study on patients with a diseased RV was performed.

Healthy population

We prospectively recruited 120 healthy subjects (51% male, age range 21-67 years) with no medical history or current symptoms that suggested cardiovascular disease. All subjects underwent physical examination, a standard 12-lead electrocardiogram and a detailed echocardiogram with the addition of four apical views of the RV, according to the unique anatomic landmarks as described above. Exclusion criteria were any abnormal findings on the physical examination, electrocardiogram, or echocardiogram. 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 subjects.

Pilot study patients

An additional, pilot test population, which is comprised of 20 adult patients (55% male, age range 18-70 years) with RV pathology, consequent to congenital heart disease, was studied to observe whether this 13-segment model was feasible in a diseased state. We did not perform this pilot test to evaluate RV function in a quantitative manner. The patients prospectively included were referred to the echocardiography department for routine measurements of their cardiac function and had a sufficient acoustic window. Ten patients had a volume overloaded RV due to atrial septal defect (n=4), tetralogy of Fallot with severe residual pulmonary regurgitation (n=6). Ten patients had a pressure overloaded RV (Doppler tricuspid regurgitation velocity >3m/sec), pulmonary hypertension (n=3), pulmonary homograft stenosis (n=2), systemic RV consequent to an atrial switch operation in infancy for D-transposition of the great arteries (n=5). All patients were in New York Heart Association (NYHA) class I or II. A complete 2D echocardiogram including four additional apical RV views was acquired as for the healthy subjects.

Transthoracic 2D iRotate mode

Two experienced echocardiographers (JMcG, WV) performed the 2D echocardiograms including four additional apical views of the RV acquired with iRotate mode. In iRotate mode a full electronic rotation of 360° (adjustable by 5° steps) can be performed.[7] All studies were acquired in harmonic imaging using an iE33 or EPIQ7 ultrasound system (Philips Medical systems, Best, the Netherlands) equipped with a X5-1 matrix-array transthoracic probe. From the apical window, a standard apical 4C view was adjusted to acquire a focused nonforeshortened RV view with the IVS-RV apex centered along, or as near as possible, to the midline of the sector. With the iRotate mode an approximate 130° electronic rotation was performed. Using the anatomic landmarks, as defined above, four standard views of the RV were acquired during end-expiratory breath-hold (Figure 3).

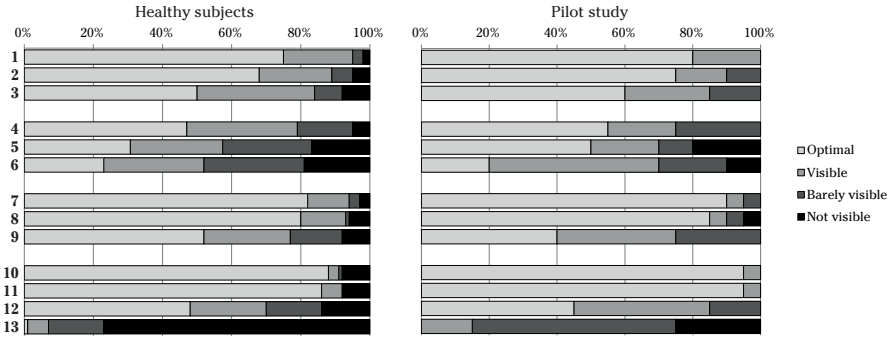

Figure 3
Schematic drawing of the cut planes (A-D) with their corresponding echocardiographic images:
Left: 2D right ventricle (RV) image. Center: Tricuspid annular plane systolic excursion (TAPSE). Right: Tricuspid annular peak systolic velocity (S') for each cut plane in a healthy subject. Mean value of TAPSE and S' calculated from all views is 33 mm and 13.9 cm/sec, respectively. (A) Four-chamber view with segments 1-3, (B) coronary sinus view with segments 4-6, (C) aortic view with segments 7-9, (D) coronal view with segments 10-13.

- Four chamber view at 0°
- Coronary sinus view at approximately +40°
  (slight posterior angulation of the transducer maybe necessary)
- Aortic view at approximately -40°
  (slight anterior angulation of the transducer maybe necessary)
- Coronal view (RVOT) at approximately -90°

Images of a pressure and volume overloaded RV acquired with 2D iRotate are shown in Figure 4.

Learning curve

The impact of a learning curve on the feasibility of endocardial borders delineation of RV segments in our proposed model was sought by comparing data from the first consecutive 20 subjects with the following consecutive 20 subjects.

Right ventricular wall segmentation according to the echocardiographic views

We analyzed the walls of the RV in the four views and divided each wall into three segments: basal, mid-, and apical segment (segments 1-12). In the coronal view, the RVOT anterior wall was defined as the 13th segment (Figure 3). The IVS was not included in this model, as it does not exclusively reflect RV function.[4, 8] In total, the visualization of the RV wall was evaluated for 13 segments. An experienced echocardiographer (JMcG) analyzed all the 13 segments in a dynamic format and graded each segment: 0 = not visible; 1 = partially visible (part of the segment or

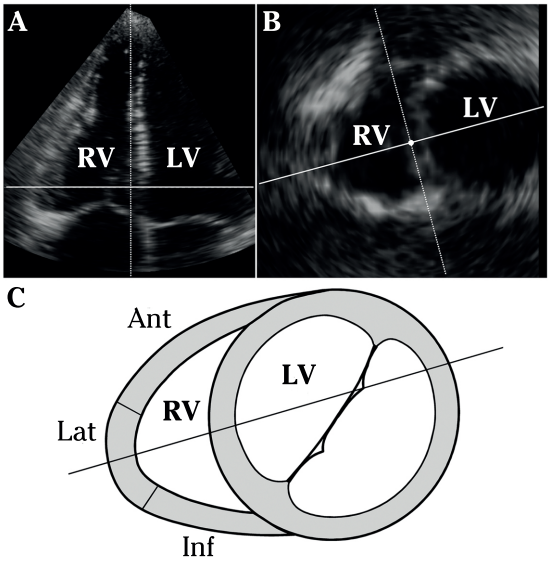

Figure 4
Left **(A-D).** 2D iRotate in a patient with severe residual pulmonary regurgitation and impaired right ventricle (RV) systolic function. Left**:** 2D RV image. Center**:** Tricuspid annular plane systolic excursion (TAPSE). Right**:** Tricuspid annular peak systolic velocity (S'). Mean values of TAPSE and S' calculated from all views are 17 mm and 6.1 cm/sec, respectively. Right (a-d). 2D iRotate in a patient with a systemic RV and impaired systolic function. Left**:** 2D RV image. Center**:** TAPSE. Right**:** TDI S'. Mean values of TAPSE and TDI S' calculated from all views are 17 mm and 8.2 cm/sec, respectively. Note: both mean values of TAPSE and S' are lower than in the healthy subjects. A(a) = four-chamber view, B(b) = coronary sinus view, C(c) = aortic view, D(d) = coronal view.

the whole segment is visible during only part of the cardiac cycle); 2 = visible (the whole segment is visible during the entire cardiac cycle) and 3 = optimal (excellent delineation of endocardium during the entire cardiac cycle).

TAPSE and TDI

Tricuspid annular plane systolic excursion (TAPSE) was measured with 2D echocardiography-guided M-mode, and tricuspid annular peak systolic velocity (S') was measured with the pulsed-wave tissue Doppler imaging technique (TDI) in all four RV images acquired with iRotate mode at the: (1) lateral tricuspid annulus in the four-chamber view, (2) anterior tricuspid annulus in the coronary sinus view, (3) inferior annulus in the aortic view, and (4) inferior annulus in the coronal view. All measurements, as stated in the guidelines, were obtained with the ultrasound beam as parallel as possible to the direction of the tricuspid annular motion of that segment.[4] With sporadic use, when the ultrasound beam was not parallel to the tricuspid annular motion, a TAPSE measurement was taken directly on the 2D image at the end-diastolic position of the tricuspid annulus taken at the beginning

of the QRS complex and its greatest apical long-axis displacement. All recordings were performed during end-expiratory breath-hold.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as frequencies and percentages. Intra-observer agreement (JMcG) and inter-observer agreement (JMcG and MM) of the TAPSE and TDI peak systolic velocity (S') were assessed by repeated analysis in 30 datasets at least two months after the initial analysis. The agreement between two measurements was determined as the mean of the differences ± 1.96SD.[9] Additionally, the coefficient of variation (SD of the differences of two measurements divided by their mean) was provided. All statistical analyses were performed using SPSS statistics version 21.0 (IBM Corp., Armonk, NY, USA). A *P*-value of <0.05 was considered significant.

RESULTS

Healthy population

The normal population comprised of 120 subjects with normal cardiac anatomy and function. Baseline characteristics of the normal population are listed in Table 1.

The additional acquisition time for our proposed model of four additional RV views is approximately 1-2 minutes. The iRotate mode, to assess the RV from the standard apical window, was feasible in 118 of the 120 (98%) healthy subjects. Two subjects were excluded from the study due to absence of apical window. One or more of the RV views could not be acquired with iRotate mode in an additional six subjects.

Table 1 Baseline characteristics of healthy subjects

Characteristic	n=120
Age, years	43 ± 13
Men, n (%)	61 (51%)
Height, cm	174 ± 9
Weight, kg	74 ± 12
BMI, kg/m^2	24 ± 3
Systolic blood pressure, mmHg	125 ± 14
Diastolic blood pressure, mmHg	79 ± 9
QRS duration, ms	96 ± 9

Baseline characteristics are expressed as mean ± SD or n.

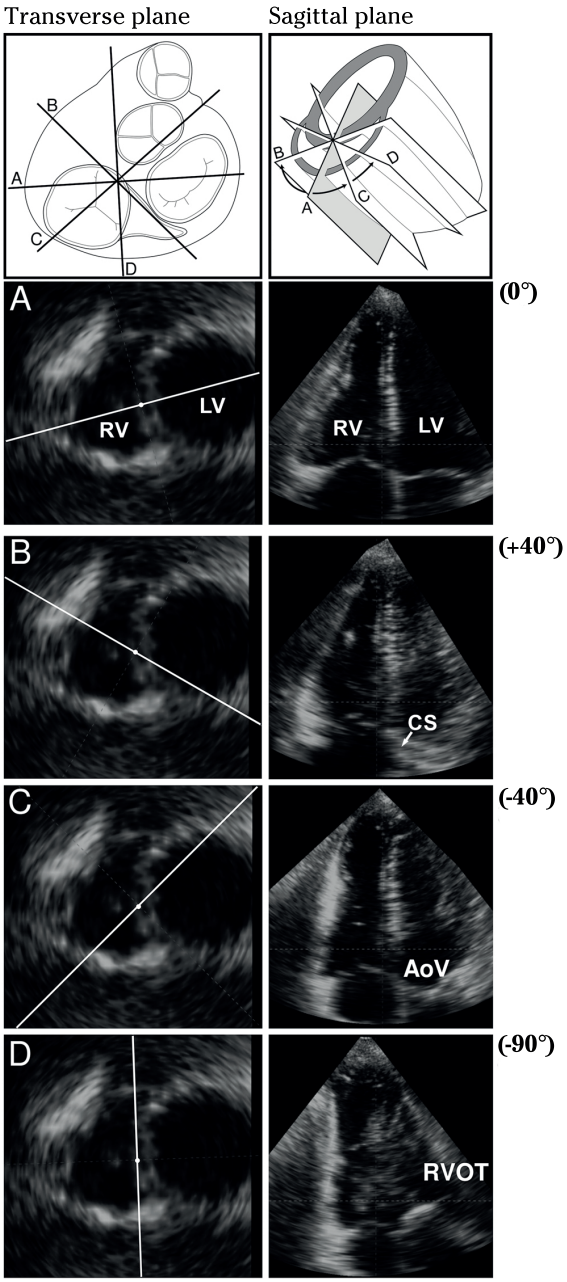

Figure 5 Feasibility of the right ventricular (RV) segments for each view. Left: Healthy subjects (n=120). 1344 (86%) of the total 1560 RV segments were visualized. Note: this low percentage is mainly due to the poor visibility of the 13th segment. Right: Pilot study (n=20). 248 (95%) of the total 260 RV segments were visualized. Basal-mid-apical segment: 1-3 (four-chamber view), 4-6 (coronary sinus view), 7-9 (aortic view), 10-12 (coronal view), 13 (right ventricular outflow tract anterior wall).

Visualization of 13 segments of the right ventricle

The feasibility of the RV segments is shown in Figure 5. In the first 20 subjects, 83% (215/260 segments) of the segments could be visualized; when excluding the RVOT segment, this was 88% (212/240 segments). In the following 20 subjects, 86% (224/260 segments) of the segments could be visualized; when excluding the RVOT segment, this was 91% (218/240 segments)

In total, 1344 (86%) of 1560 RV segments could be visualized. The RVOT segment was only visualized in 27 (23%) subjects. After exclusion of this segment, 1317 (91%) of the total 1440 RV segments were visualized.

TAPSE and TDI measurements

The feasibility per view and measurement of the TAPSE and the TDI velocity S' are shown in Table 2**.** The TAPSE and TDI velocity S' were lower in the coronal view than the mitral, aortic, and coronary sinus views.

Table 2 Mean values of TAPSE and TDI (S') for each RV view (n=120)

	TAPSE mm			TDI (S') cm/sec		
View	**N (%)**	**Mean ± SD**	**Range**	**N (%)**	**Mean ± SD**	**Range**
Four chamber	117 (98%)	26 ± 4	17 - 37	116 (97%)	12.0 ± 2.0	7.9 - 16.9
Coronary sinus	113 (94%)	27 ± 4	17 - 36	111 (93%)	12.0 ± 2.0	6.7 - 18.1
Aortic view	116 (97%)	25 ± 4	17 -3 3	113 (94%)	11.1 ± 2.1	6.3 - 15.6
Coronal view	111 (93%)	23 ± 3	14 - 33	110 (92%)	9.9 ± 1.9	6.1 - 14.0

Intra- and inter-observer variability

The mean differences and coefficients of variation for the intra- and inter-observer agreement of the TASPE and TDI velocity S' are displayed in Table 3.

Table 3 Intra- and inter-observer variability measurements for TAPSE and TDI (S') (n=30)

		Intra-observer		Inter-observer	
		Mean difference	**Coefficient of variation (%)**	**Mean difference**	**Coefficient of variation (%)**
TAPSE	Four chamber	0.0 ± 1.7	7	-0.4 ± 1.5	6
	Coronary sinus	-0.4 ± 2.5	10	0.0 ± 2.1	9
	Aortic view	-0.2 ± 2.5	10	0.0 ± 1.7	7
	Coronal view	-0.5 ± 1.8	8	0.3 ± 1.9	9
TDI (S')	Four chamber	0.3 ± 1.3	12	0.2 ± 0.6	8
	Coronary sinus	0.0 ± 1.4	13	0.3 ± 0.9	5
	Aortic view	0.3 ± 1.2	13	0.1 ± 0.7	7
	Coronal view	0.1 ± 0.8	9	0.0 ± 0.5	5

Pilot study patients

All patients in the pilot group had at least moderate RV dilatation. The RV systolic function varied between the diseased states. The iRotate mode was feasible in all study patients; the feasibility of the RV segments is shown in Figure 5. In total, 248 (95%) of 260 RV segments could be visualized. The RVOT segment was classed partially visible in 12 and visible in three patients. TAPSE and TDI velocity S' were feasible in all views in all patients.

DISCUSSION

The current study shows that among unselected healthy subjects, a 13-segment standardized model for RV assessment is feasible using 2D iRotate mode, based on unique anatomic landmarks and achieved from a single acoustic window. The visibility of the RVOT anterior wall remains challenging; however, the visibility was higher in the diseased RV.

It is recommended to record multiple 2D images for assessment of RV function.[4, 6, 10] This multiview approach, based on several acoustic windows, is susceptible to error (oblique views, operator dependency) and is a major limitation of RV assessment due to the lack of reproducibility on serial follow-up. Moreover, as this approach is not always feasible in the routine setting, often only the apical 4C view is acquired and an RV analyses consists of dimension, right ventricular fractional area change (RVFAC), and TAPSE and TDI (S') measurements. RV linear dimensions and regional function assessment are dependent on probe rotation and different views, and it is therefore recommended to state the window from which the measurement was performed in order to permit inter-study comparison.[4, 6] Our study provides a robust and standardized RV segmentation.

With the introduction of transthoracic 3D echocardiography, the assessment of RV size and function in adults and children was thought to improve and solve some of the problems of 2D echocardiography.[11] Theoretically, 3D echocardiography could provide all information that could be added using our proposed model. Several studies have extensively investigated RV function and found that 3D echocardiography improved the accuracy and reproducibility of RV assessment and identified RV dysfunction quite accurately.[12] However, most published data compose of small and rather selective patient populations based on moderate to good image quality.[13] In a real-world setting, Renella *et al.* evaluated 3D echocardiography of the RV in pediatric and congenital heart disease patients (age 1-20 years), and they found that RV volumes were measurable in only 58% of

the patients.[13] Moreover, current ASE/EACVI recommendations acknowledge the limitations of performing 3D RV assessment in every patient.[6]

In this study, a comprehensive evaluation of the RV can be achieved, from one acoustic window, with 2D iRotate mode based on anatomic landmarks. Compared to the standard multiview approach, 2D iRotate evaluation of the RV takes only a few minutes making it very attractive and robust for routine use in the echo-laboratory and at bedside. There is a short learning curve for data acquisition based on the fact that there was minimal increase in the feasibility score (83-86%) after the first 20 subjects. However, with less experienced echocardiographers, the learning curve could possibly be slightly longer. Of note, the 2D iRotate mode is limited to the matrix-array transducer. Furthermore, a true nonforeshortened RV view with the IVS-RV apex centered along, or as near as possible to, the midline of the sector is mandatory.

The feasibility of the RV segments, excluding the RVOT anterior wall, is good, with 81% of the segments adequately visible. The feasibility of the apical segments is less when compared to the mid- and basal segments, probably due to the sharp curvature of the RV apex and also, the known difficulty in obtaining high quality 2D images in the near field, which could contribute to this finding.[14]

The feasibility of RVOT anterior wall is poor, visible in only 23% of the subjects of which 16% were scored partially visible. Reduced feasibility was also observed in the anterior wall in the coronary sinus view when compared to the feasibility of the lateral wall (mitral view), inferior wall (aortic view), and inferior wall (coronal view). This suboptimal visualization of the most anterior segments of the RV could be explained by the retrosternal position of the heart in the thorax. Also the long axis of the normal sized heart is superior-inferior (vertical), which again would contribute to the difficulty in visualizing the most anterior segments, with echocardiography.[15]

RV wall deformation consists of three components: radial, longitudinal, and circumferential. Despite their limitations, TAPSE and TDI (S') are simple and reproducible measurements used to assess RV longitudinal systolic function.[4, 16, 17] As far as we know, our current study is the first study to assess multiple TAPSE and TDI (S¢) measurements from the tricuspid annulus. TAPSE was feasible in one view or more in 93% or more and TDI (S¢) 92% or more healthy subjects. Both measurements fell into consistent ranges for normal subjects as stated in the guidelines for the apical 4C view (reference values: TAPSE 16-30 mm, TDI 10-19 cm/s).[4] Inter- and intra- observer variability were acceptable as coefficients of variation were <10% and <14%, respectively. Recently Forsha *et al.* investigated RV strain in an 18-segment model of the RV in 40 healthy subjects. The RV strain analysis was feasible, and the global peak strain and peak dyssynchrony measures

fell into consistent range for normal subjects. The authors acknowledged that the lack of universal standardized RV views is an obvious limitation of the study. In our study, we provide standardized RV views and segmentation as the basis for future RV analysis.

The pilot study

These patients were included simply to demonstrate whether this model is feasible in the diseased RV. The results are encouraging; the feasibility of the segments is similar to the normal RV. The feasibility of the apical segment, as in the healthy subjects, remains less when compared to the mid- and basal segment. However, feasibility of the segments in the coronal and RVOT view appears to be slightly better than in the healthy subjects. This could be explained by the fact that in the diseased RV (dilated or hypertrophic), the long axis of the heart is often more horizontal, and therefore, the sternum will compromise the image quality to a lesser degree.[15] Also in the dilated RV, the apex is moved automatically more to the center of the 2D sector and the rotation around the RV with iRotate mode be noted to be easier than in the normal RV.

Clinical implementations

One of the critical limitations of 2D echo recordings is the potential for variability in the 2D planes during follow-up. Well-defined anatomic landmarks result in robust image orientation, precise echocardiographic follow-up, and less oblique plane acquisition, implying that this simple approach could minimize or avoid such variability. With this method of scanning, the RV walls are visualized in their long axis. This could allow strain and strain rate imaging to be performed on more segments of the RV and its complex contraction pattern to be evaluated in more detail. Further studies are warranted to investigate these issues.

Limitations

This study provides a novel model of RV assessment of a potential value. There are some study limitations. First, we did not perform test-retest repeatability in this study. Our study comprised of a relatively small sample of RV pathology. Our model might not be feasible in patients with extremely dilated LVs because we will be unable to align the IVS-RV apex in the center of the imaging sector. Therefore, the clinical utility and the incremental value of our proposed model need to be confirmed in a larger population. Moreover, a direct comparative study between our 2D iRotate model and 3D echocardiography in a large consecutive series is warranted.

CONCLUSION

2D transthoracic iRotate mode enables a comprehensive evaluation of the normal and diseased RV. Our proposed approach provides a standardized protocol for RV acquisition and assessment from a single acoustic window with a fixed transducer position, using simple anatomic landmarks. The anterior, lateral, inferior, and outflow tract anterior wall of the RV could be assessed; reducing acquisition time compared to the multiview approach and enhances the accuracy of RV evaluation. Further studies are warranted to discover the full potential of this new technique for evaluation of the RV in various diseased states.

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PART II

Clinical outcome and early detection of ventricular dysfunction in repaired tetralogy of Fallot

CHAPTER 4

Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction

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ABSTRACT

Background

Prospective data on long-term survival and clinical outcome beyond 30 years after surgical correction of tetralogy of Fallot are nonexistent.

Methods and Results

This longitudinal cohort study consists of the 144 patients with tetralogy of Fallot who underwent surgical repair at <15 years of age between 1968 and 1980 in our center. They are investigated every 10 years. Cumulative survival (data available for 136 patients) was 72% after 40 years. Late mortality was due to heart failure and ventricular fibrillation. Seventy-two of 80 eligible survivors (90%) participated in the third in-hospital investigation, consisting of ECG, Holter, echocardiography, cardiopulmonary exercise testing, N-terminal pro-brain natriuretic peptide measurement, cardiac magnetic resonance (including dobutamine stress testing), and the Short Form-36 questionnaire. Median follow-up was 36 years (range, 31–43 years). Cumulative event-free survival was 25% after 40 years. Subjective health status was comparable to that in the normal Dutch population. Although systolic right and left ventricular function declined, peak exercise capacity remained stable. There was no progression of aortic root dilation. A previous shunt operation, low temperature during surgery, and early postoperative arrhythmias were found to predict late mortality (hazard ratio, 2.9, 1.1, and 2.5, respectively). An increase in QRS duration and a deterioration of exercise tolerance and ventricular dysfunction did not predict mortality. Insertion of a transannular patch was a predictor for late arrhythmias (hazard ratio, 4.0; 95% confidence interval, 1.2–13.4).

Conclusions

Although many patients needed a reoperation or developed arrhythmias, late mortality was low, and the clinical condition and subjective health status of most patients remained good. Previous shunt, low temperature during surgery, and early postoperative arrhythmias were found to predict late mortality.

INTRODUCTION

Tetralogy of Fallot (ToF) is the most prevalent form of cyanotic congenital heart diseases.[1] Although mortality was substantial in the earliest era of surgical correction,[2] survival has improved dramatically over the years: 90% of patients are currently alive 30 years after successful surgical correction at a young age.[3–6] Despite these satisfactory results, survival up to 30 years is lower than in the normal population, and little is known about long-term functional outcome and life expectancy beyond 30 years.[5,7] Although anatomic correction and physiological correction have been achieved, complications such as pulmonary regurgitation leading to right ventricular (RV) dysfunction, recurrent obstruction of the RV outflow tract, arrhythmias, sudden death, and aortic dilation and regurgitation are found in late survivors.[1,8,9]

Information on outcome after correction beyond 30 years is limited and has mostly been collected retrospectively. Most previous studies focused on a selection of patients regularly seen at the outpatient clinic, which may lead to selection bias. Our study is part of a unique ongoing longitudinal follow-up that started in 1990. The patients are investigated in hospital every 10 years.[10,11] The aim of the present study is to provide data on survival and clinical course, including late sequelae, in survivors up to 40 years after initial correction and to detect predictors for outcome.

METHODS

Study patients

All consecutive patients who underwent surgical correction for ToF (excluding pulmonary atresia) in our institution between 1968 and 1980 at <15 years of age were included in this longitudinal study. The cohort was first studied in 1990, and the second follow-up was performed in 2001. For the current third follow-up, survival status of the patients was obtained from the Dutch National Population Registry. All patients who were alive and had participated in 1 or both of the earlier follow-up studies were invited for the third in-hospital investigation in 2011 to 2012. Detailed information describing the baseline characteristics, surgical procedure, and 10- and 20-year follow-up results has been reported previously.[10,11] The study protocol was approved by the institutional Medical Ethics Committee (2010-015). Written informed consent was obtained from all study participants.

Survival and adverse events

Survival was compared with the survival of the reference, age-matched Dutch population. Adverse events were defined as all-cause mortality, cardiac reinterventions (both percutaneous and surgical), symptomatic arrhythmias (needing medication or an intervention), stroke, heart failure (needing medication or hospital admission), and endocarditis.

Clinical assessment

Medical examination included history, physical examination, subjective health status assessment (Short Form-36), standard 12-lead ECG, 24-hour ambulatory Holter monitoring, 2-dimensional echocardiography, cardiopulmonary exercise testing, N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement, and cardiac magnetic resonance (CMR) imaging with dobutamine stress testing unless contraindicated. If a patient was unwilling or unable to visit the outpatient clinic, a questionnaire was sent to obtain information on morbidity and subjective health status and to receive permission for the use of information from medical records.

Subjective health status assessment

The scores on the 36-item short-form healthy survey (Short Form-36) of all study participants were compared with results of the normative Dutch population[12] and with their own results from 2001.

ECG and Holter monitoring

Standard 12-lead surface ECGs were analyzed for rhythm, PR interval, and QRS duration. ECGs with pacemaker rhythm were excluded from comparison of conduction times. A 24-hour Holter monitoring was performed with a Cardio Perfect Holter DR180+ 3-channel recorder (Welch Allyn Cardio Control, NorthEast Monitoring, Maynard, MA).

Echocardiography

A complete 2-dimensional transthoracic Doppler echocardiography was performed with the iE33 xMATRIX X5-1 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions and function were measured according to the current guidelines.[13,14] RV function was assessed visually to allow comparison with the 2 previous studies. Additionally, more objective measures, including fractional area change and tricuspid annular plane systolic excursion, were measured to quantify RV function.

Cardiopulmonary exercise testing

Maximal workload and peak oxygen consumption (peak V_{O_2}) were assessed by cardiopulmonary exercise testing using a bicycle ergometer with gradual workload increments of 20 W/min (ramp protocol) and compared with the values of normal individuals corrected for age, sex, height, and weight. The ratio of minute ventilation to carbon dioxide production (V_E/V_{CO_2}) was assessed at the anaerobic threshold and at maximum workload. Performance was considered maximal when a respiratory quotient of ≥ 1.1 was reached.

NT-proBNP measurement

Peripheral venous blood samples were collected after 30 minutes of rest. Plasma NT-proBNP levels were determined with the 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.

CMR imaging with dobutamine

CMR imaging was performed with a Signa 1.5-T whole-body scanner (GE Medical Systems, Milwaukee, WI) with dedicated phased-array cardiac surface coils. Details of the MR sequence used have been reported previously.[15] Images were collected at rest and after low-dose (7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and high-dose (20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) dobutamine administration. Contraindications for the use of dobutamine were previous sustained ventricular tachycardia (VT), frequently recurrent supraventricular tachycardia, and inflow or outflow obstruction of the ventricles. 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 a single investigator (J.A.A.E.C.) using manual outlining of endocardial borders in end systole and end diastole, excluding large trabeculae (visible on 3 subsequent slices) and the papillary muscles from the blood volume. Biventricular end-diastolic volume, end-systolic volume, ejection fraction (EF), and valvular regurgitation fractions were calculated and compared with reference values.[16]

Statistical analysis

For the descriptive data analyses, we used the Statistical Package for Social Sciences (version 20.0, SPSS, IBM Corp., Armonk, NY, USA). Continuous data are presented as mean with standard deviation or median with interquartile range. Categorical variables are presented as frequencies and percentages. For comparison of continuous variables between independent groups, the Student unpaired

t-test was used; for repeated measures, the paired *t*-test or Wilcoxon signed-rank test were performed. Frequencies of unpaired data were compared by use of the χ^2 test or Fisher exact test when applicable, and for paired data, the McNemar test was used. To quantify correlations between 2 variables, we used the Pearson correlation test or Spearman correlation test. For advanced statistical analyses of the longitudinal and survival data, the *R* software version 3.0.1 package was used (www.r-project.org). Univariable and multivariable Cox proportional hazard regression analyses were used to identify predictors for the predefined events: all-cause mortality, arrhythmias or pacemaker implantation, and pulmonary valve replacement (PVR). The following covariates were included in the models: early postoperative arrhythmias, temperature during surgery, palliative shunt before corrective surgery, insertion of a transannular patch, age at operation, and era of operation (before or after 1975). Because of the low frequencies for the aforementioned events, we used a penalized likelihood approach for estimating the Cox model.[17] To account for missing covariate data, we used a multiple imputation approach.[18] Wald tests were used to assess which covariates were most associated with the risk of each event. Time-dependent Cox regression analysis was used to assess the effects of the time-dependent covariates: QRS duration, VT on Holter, exercise capacity, and left ventricular (LV) fractional shortening on outcome. For description of survival of the total cohort and the Dutch reference population, the Kaplan–Meier method was used. Cumulative event incidences were computed with the use of a nonparametric estimator of cumulative incidence functions. All statistical tests were 2 sided, and the level of significance was at $P<0.05$.

RESULTS

Study patients

The original study cohort consisted of 144 consecutive patients who underwent surgical correction of ToF between 1968 and 1980. Baseline characteristics are presented in Table 1. Further baseline and surgical details have been reported previously.[10,11] For the present study 36 years (range, 31–43 years) after correction, 80 patients were eligible. Of them, 72 (90%) were included: 53 (66%) participated in-hospital and 19 (24%) gave permission to use the hospital records of their regular clinical follow-up. There were no differences in baseline characteristics between the participating and nonparticipating patients.

Table 1 Baseline characteristics

	Total	1990	2001	2012	No third study*	*P*-value†
	(n=144)	(n=79)	(n=79)	(n=72)	(n=72)	
Male, n (%)	87 (60)	46 (58)	44 (56)	42 (58)	45 (63)	0.609
Age at study, yrs (IQR)	-	18.5 [15.1-23.2]	30.4 [26.3-35.6]	39.8 [36.1-45.5]	-	-
Age at operation, yrs (IQR)	4.6 [1.7-6.6]	4.3 [1.4-6.5]	4.3 [1.4-6.6]	3.8 [1.4-6.6]	4.9 [1.8-7.2]	0.163
Prior palliation, n (%)	50 (35)	25 (32)	25 (32)	20 (28)	30 (42)	0.080
Transannular patch, n (%)	87 (60)	48 (55)	47 (54)	48 (67)	44 (51)	0.488
Hypothermia, n (%)						
Temperature <20°C	43 (30)	25 (32)	27 (34)	24 (33)	19 (26)	0.746
Temperature 20-35°C	89 (62)	52 (66)	50 (63)	47 (65)	42 (58)	
Temperature unknown	12 (8)	2 (2)	2 (3)	1 (1)	11 (15)	

IQR indicates interquartile range.
*Including deceased and emigrated patients. †2012 vs no third study.

Survival

Survival status was obtained in 136 patients (94%). Eight patients moved abroad and were untraceable. Cumulative survival after surgical correction was 83% after 10 years, 81% after 20 years, 78% after 30 years, and 72% after 40 years (Figure 1). In total, 35 of the 144 patients died, 23 within 30 days after surgery. Of the hospital survivors, cumulative survival was 98% after 10 years, 96% after 20 years, 92% after 30 years, and 86% after 40 years. In patients who survived 30 days postoperatively, incident mortality rate was 0.29 per 100 patient-years.

In the last 10 years, 6 patients died. Three patients died of end-stage heart failure 26, 28, and 38 years after surgery at 31, 32, and 51 years of age, respectively. Two of them had nonsustained VTs on Holter in 1990 or 2001. In 1 of these patients, death was triggered by an infection. Two other patients died of ventricular fibrillation 24 and 34 years after surgery at 28 and 41 years of age, respectively. One patient died after a shooting incident.

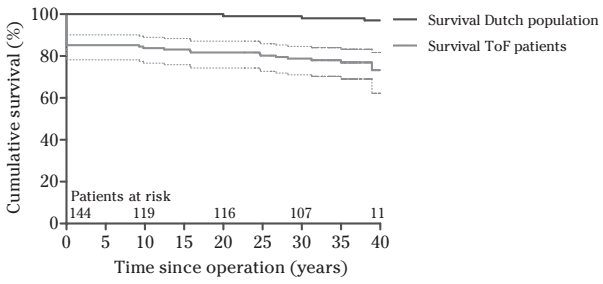

Figure 1 Kaplan–Meier plot describing survival in the studied cohort compared with the Dutch reference population. ToF indicates tetralogy of Fallot.

Adverse events

Cumulative event-free survival after 40 years was 25% (Figure 2). In the last 10 years, 35 patients (49% of the participants) were hospitalized at least once.

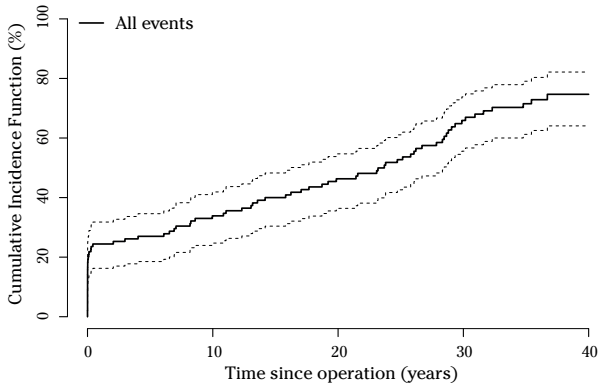

Figure 2 Cumulative incidence of all events.

Reinterventions

The cumulative incidence of reinterventions after 35 years of follow-up was 44% (Figure 3). In the last decade, 32 patients required ≥1 reinterventions: PVR (n=20); closure of a ventricular septal defect (n=8); balloon dilation of the pulmonary artery or branch (n=6); aorta-related reoperation (n=3), including 1 elective aortic arch replacement because of an aneurysm (aortic diameter, 57 mm); and infundibulectomy (n=1).

Pulmonary valve replacement

Despite a rather conservative approach to PVR in our center, 11 the cumulative incidence of PVR was 40% at 35 years (Figure 3). Of the participating patients, 35 underwent PVR at a median of 24 years (interquartile range, 16–29 years) after the initial correction. In the last decade, surgical PVR was performed in 19 patients for the first time, 2 of whom underwent transcatheter PVR later. One patient underwent transcatheter PVR after receiving a surgical homograft in 2000.

Arrhythmias

The cumulative incidence of symptomatic arrhythmias was 17% at 35 years (Figure 4). In the last decade, 5 patients had new symptomatic arrhythmias; 3 patients had atrial fibrillation and needed electric cardioversion. One of them underwent catheter ablation afterward. One patient had atrial flutter, and 1 patient was treated for arrhythmias of unknown origin in another hospital. In the last decade,

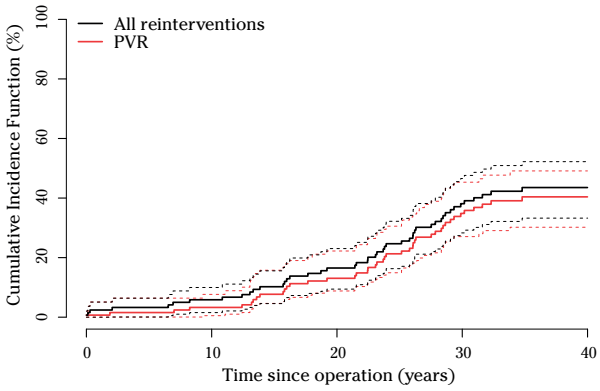

Figure 3 Cumulative incidences of pulmonary valve replacement (PVR) and all reinterventions.

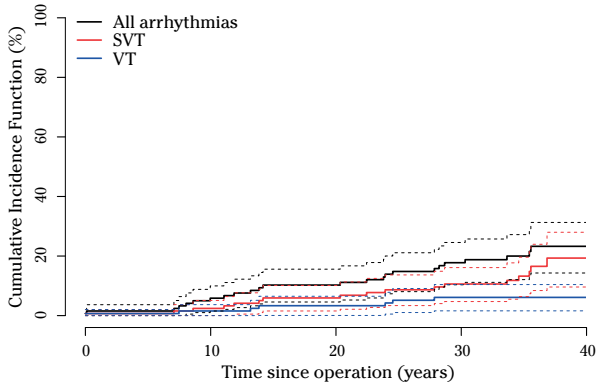

Figure 4 Cumulative incidences of supraventricular tachycardia (SVT), ventricular tachycardia (VT), and all arrhythmias, including implantation of pacemakers and cardioverter-defibrillators.

2 patients received a pacemaker and 2 received an implantable cardioverter-defibrillator (ICD). Both ICDs were implanted for secondary prevention after the patients experienced sustained VTs. One other patient had an ICD indication because of recurrent VTs but has refused implantation. Thirty-five years after surgical correction, the cumulative incidences of pacemaker and ICD implantation were 10% and 5% respectively.

Heart failure

The cumulative incidence of heart failure at 35 years of follow-up was 3%.

Stroke

In the last decade, 4 patients had a transient ischemic attack. Two of them had an open foramen ovale.

Endocarditis

Two patients were diagnosed with endocarditis: 1 had bacteremia with *Streptococcus oralis* 5 years after ICD implantation, which resolved on antibiotics only after the ICD had been removed. The other had bacteremia with *Streptococcus sanguis* 21 years after pulmonary homograft implantation. The patient was treated with antibiotics and remained free of recurrent bacteremia afterward.

Subjective health status assessment

Patients scored significantly better on the domains of role limitations resulting from physical or emotional problems, bodily pain, and social functioning compared with normative data (Figure 5). In direct comparison with their own previous results, patients showed a less favorable general health perception (P=0.042) than 10 years ago.

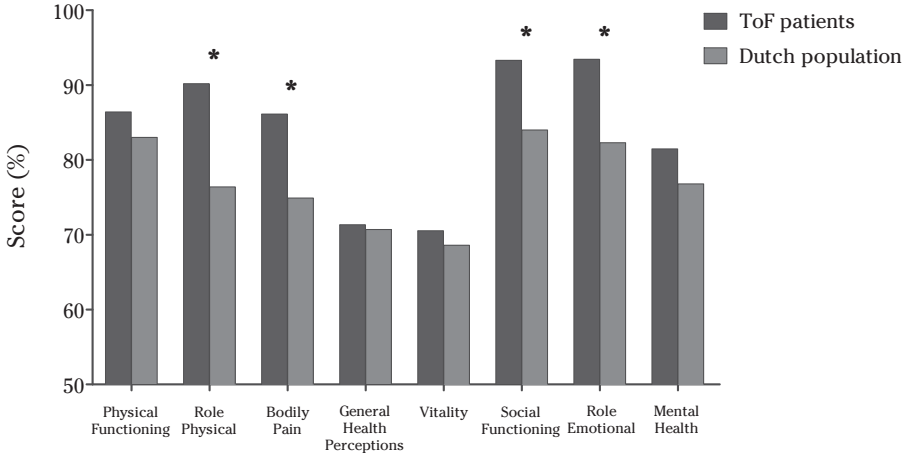

Figure 5 Results of Short Form-36 for patients with tetralogy of Fallot (ToF) and the normal Dutch population. Higher scores indicate more favorable subjective health status. *P<0.001.

ECG and Holter monitoring

The ECG and Holter findings are summarized in Table 2. None of the patients had ventricular pauses >3 seconds.

Echocardiography

Echocardiographic findings are summarized in Tables 2 through 4. The systolic function of both ventricles diminished in the last 10 years. In 21 patients (40%), the estimated RV pressure was >40 mm Hg, but in all but 3 patients, this was completely attributable to residual pulmonary stenosis. Normal diastolic LV function was observed in 35 patients (55%), impaired relaxation in 13 (20%), pseudonormal diastolic filling in 2 (3%), and restrictive relaxation pattern in 14 (22%). There was no progression of aortic root dilation in the last decade. No correlations were found between pulmonary regurgitation or tricuspid regurgitation and right atrial dilation, RV dilation, or RV function.

Cardiopulmonary exercise testing

Table 2 shows the results of bicycle ergometry. Forty percent of the patients had a reduced exercise capacity (<85% of expected workload). These patients did not significantly differ from those with a normal test result with regard to age at the time of operation, current age, or findings at echocardiography and CMR (dimensions and ventricular function).

NT-proBNP measurement

Median NT-proBNP level was 16.4 pmol/L (interquartile range, 6.7–32.0 pmol/L). An elevated NT-proBNP level (>14.0 pmol/L) was measured in 58% of the patients. NT-proBNP (logarithmic) correlated modestly with echocardiography-derived LV end-systolic dimension (r=0.31, P=0.03) and CMR-derived LV end-diastolic volume (r=0.36, P=0.01). No correlations were found with age at operation, current age, exercise capacity, or RV dimensions.

Table 2 Diagnostic measurements

				P*-value	
	1990	**2001**	**2012**	**2012 vs. 1990**	**2012 vs. 2001**
Electrocardiography	**n=79**	**n=79**	**n=70**		
Rhythm, n (%)					
Sinus	66 (84)	69 (87)	58 (83)	0.7	0.3
Atrial	6 (8)	5 (6)	4 (6)	0.7	1.0
Atrial flutter	1 (1)	3 (4)	0	-	-
Atrial fibrillation	0	0	1 (1)	-	-
Nodal	1 (1)	0	0	-	-
Pacemaker	5 (6)	2 (3)	7 (10)	1.0	0.1
PR interval (mean ± SD), ms	159 ± 32	162 ± 27	173 ± 41	**0.008**	**0.02**
PR >200 ms, n (%)	3 (4)	4 (6)	11 (18)	**0.02**	0.1
QRS duration (mean ± SD), ms	120 ± 29	135 ± 32	144 ± 32	**<0.001**	**<0.001**

Table 2 Diagnostic measurements (continued)

				P-value*	
	1990	**2001**	**2012**	**2012 vs. 1990**	**2012 vs. 2001**
QRS duration >120 ms, n (%)	27 (39)	46 (62)	46 (72)	**<0.001**	0.1
QRS duration >180 ms, n (%)	1 (1)	6 (8)	8 (13)	0.1	0.2
24-hour Holter	**n=70**	**n=76**	**n=56**		
Supraventricular arrhythmias, n (%)	15 (21)	44 (59)	29 (52)	**0.03**	1.0
Sinus node disease	12 (17)	20 (27)	14 (25)	0.5	1.0
SVT	7 (10)	27 (36)	19 (34)	0.3	0.8
Paroxysmal atrial fibrillation	1 (1)	1 (1)	1 (2)	1.0	1.0
Paroxysmal atrial flutter	0	1 (1)	0	-	-
VT 3-10 complexes, n (%)	7 (10)	9 (12)	10 (18)	1.0	0.4
VT >10 complexes, n (%)	0	1 (1)	1 (2)	-	1.0
Bicycle ergometry	**n=73**	**n=71**	**n=52**		
Maximal heart rate, (mean ± SD), %	86 ± 11	89 ± 10	86 ± 12	0.7	**0.04**
Maximal exercise capacity (mean ± SD), %	88 ± 17	83 ± 16	89 ± 18	0.6	**0.02**
Exercise capacity <85%, n (%)	26 (36)	39 (55)	21 (40)	1.0	0.3
Arrhythmia, n (%)	14 (19)	17 (24)	12 (23)	0.2	0.6
Vo_2 max (%)	-	-	81 ± 17	-	-
RERmax	-	-	1.4 ± 0.2	-	-
Ve/Vco_2, anaerobic threshold	-	-	27.0 ± 4.0	-	-
Ve/Vco_2, max workload	-	-	29.5 ± 4.1	-	-
Echocardiographic parameters	**n=79**	**n=79**	**n=70**		
RA dilation, n (%)	35 (44)	65 (82)	59 (86)	**<0.001**	0.7
RV dilation, n (%)	72 (91)	56 (71)	62 (89)	0.7	**0.01**
LA dilation, n (%)	3 (4)	12 (15)	23 (34)	**<0.001**	**0.01**
LV dilation, n (%)	1 (1)	7 (9)	7 (10)	0.4	1.0
RV systolic function normal, n (%)	-	54 (78)	19 (28)	-	**<0.001**
LV systolic function normal, n (%)	76 (96)	70 (90)	34 (50)	**<0.001**	**<0.001**
FS <20%, n (%)	3 (4)	7 (10)	6 (9)	0.6	0.7
Valve regurgitation (>trace) , n (%)					
AR	4 (5)	15 (19)	19 (28)	**<0.001**	0.1
MR	0	6 (8)	13 (19)	**0.004**	**0.004**
PR	65 (82)	62 (79)	43 (62)	**0.002**	**0.001**
TR	45 (57)	49 (62)	49 (71)	0.1	0.4
Vmax PR, m/s	1.8	1.8	2.0	**0.007**	0.1
Vmax TR, m/s	2.7	2.8	2.7	0.6	0.7
LA diameter, mm	32 ± 6	37 ± 7	39 ± 6	**<0.001**	**0.001**
LV diameter, mm	44 ± 6	49 ± 6	48 ± 7	**<0.001**	0.7
Aortic diameter, mm	32 ± 6	37 ± 6	36 ± 5	**0.002**	0.08

AR indicates aortic regurgitation; FS, fractional shortening; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; PR, pulmonary regurgitation; RA, right atrial; RERmax, maximum respiratory exchange ratio; RV, right ventricular; SVT, supraventricular tachycardia; TR, tricuspid regurgitation; Vmax, maximal velocity found with Doppler echocardiography; and VT, ventricular tachycardia.

**P*-values are displayed only for measures performed in two or all three studies.

Table 3 Diagnostic test results performed only in 2012: Echocardiography

	Median	IQR	Abnormal, n (%)*
PR Vmax, m/s	2.0	[1.7-2.3]	17 (46)
TAPSE, mm	18	[16-22]	10 (16)
RV FAC, %	38	[32-48]	15 (33)
LV EF, %	51	[45-57]	15 (42)
E/A ratio	1.4	[1.0-1.8]	6 (9)
E/E' ratio	9.4	[8.0-12.6]	6 (10)
DET, ms	190	[160-240]	27 (43)
IVC collapse >50%, n (%)	60 (94)		
HV ratio S>D, n (%)	7 (15)		

DET indicates deceleration time; FAC, fractional area change; HV S/D ratio, hepatic vein ratio of systolic to diastolic wave; IQR, interquartile range; IVC, inferior vena cava; LV EF, left ventricular ejection fraction; PR, pulmonary regurgitation; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and Vmax, maximal velocity found with Doppler echocardiography.
*According to the reference values in the guidelines for structural heart disease.[13,14]

Table 4 Diagnostic test results performed only in 2012: MRI

		7.5 µg/kg/min	20 µg/kg/min	*P*-value	
	At rest (n=49)	dobutamine (n=30)	dobutamine (n=26)	Rest vs 7.5 µg/kg/min	7.5 vs 20 µg/kg/min
LV EDV/BSA, mL/m^2	74 [64-86]	70 [62-84]	60 [55-71]	0.071	<0.001
LV ESV/BSA, mL/m^2	29 [22-37]	16 [13-22]	12 [10-17]	<0.001	<0.001
LV EF, %	61 [54-69]	77 [74-83]	80 [74-84]	<0.001	0.247
RV EDV/BSA, mL/m^2	96 [81-120]	92 [79-121]	89 [75-109]	0.417	<0.001
RV ESV/BSA, mL/m^2	49 [36-63]	36 [28-49]	35 [25-42]	<0.001	0.048
RV EF, %	49 [45-59]	63 [53-69]	64 [57-70]	<0.001	0.939

BSA indicates body surface area; EDV, end-diastolic volume; EF, ejection fraction ESV, end-systolic volume; FAC, fractional area change; LV, left ventricular; and RV, right ventricular.

CMR imaging

CMR was performed in 49 of the 72 patients (68%). Contraindications for CMR were either the presence of a pacemaker or ICD or claustrophobia. The results of CMR are summarized in Table 5. RV and LV end-diastolic dilation was observed in 15 patients (31%) and 2 patients (4%), respectively. In 23 patients (47%), RV EF was diminished, and in 14 (29%) patients, LV EF was diminished. RV EF correlated with LV EF (r=0.54, P<0.001). Thirty patients consented to dobutamine stress. In 5 of them, dobutamine administration was terminated before the dose was increased because of adverse effects: increase in ventricular extrasystoles, ventricular bigeminy, nonsustained VT, symptomatic blood pressure drop, and anxiety. All of these effects recovered spontaneously. LV EF and RV EF increased significantly after administration of 7.5 µg·kg^{-1}·min^{-1} dobutamine (P<0.001 for both), but after a dose of 20 µg·kg^{-1}·min^{-1}, there was no further increase (P=0.4 and P=0.9, respectively).

Predictor analyses

Results of the baseline parameters Cox regression analysis are presented in Table 5. Early postoperative arrhythmias, a palliative shunt before initial correction, and lower temperature during surgery were predictive of mortality. In the time-dependent Cox regression analyses, no predictors for mortality were found. Increase in QRS duration and decrease in maximally achieved workload during cardiopulmonary exercise testing over time were predictive for PVR (hazard ratio, 1.14 per 10-millisecond increase, P=0.023; and hazard ratio, 0.961, P=0.001, respectively) but not for mortality. Ventricular dysfunction on echocardiogram or arrhythmias on Holter in 1990 or 2001 did not predict adverse outcome. After adjustment for changes in QRS duration, exercise capacity, VTs on Holter, and LV fractional shortening, patients without a previous palliative shunt still showed

Table 5 Predictors of the clinical endpoints all-cause mortality, arrhythmias/pacemaker implantation, and PVR

	Univariable model			Multivariable model		
Endpoint	**HR**	**CI**	**P-value**	**HR**	**CI**	**P-value**
All-cause mortality						
Early postoperative arrhythmias	3.33	1.60-6.95	0.001*	2.52	1.18-5.36	0.017*
Temperature during surgery (per 1°C decrease)	1.18	1.05-1.30	0.003*	1.14	1.01-1.28	0.029*
Prior shunt	1.64	0.85-3.23	0.144	2.94	1.32-6.25	0.008*
Transannular patch	1.27	0.62-2.61	0.518	0.74	0.36-1.53	0.419
Age at operation	0.90	0.81-1.01	0.071	0.89	0.76-1.03	0.118
Operated after 1975	0.93	0.47-1.84	0.833	0.54	0.24-1.20	0.131
Arrhythmias/PM implantation						
Early postoperative arrhythmias	4.36	1.57-12.10	0.005*	3.68	1.29-10.52	0.015*
Temperature during surgery (per 1°C decrease)	1.00	0.90-1.12	0.923	1.01	0.89-1.14	0.906
Prior shunt	2.17	0.91-5.00	0.080	1.96	0.68-5.56	0.213
Transannular patch	5.91	1.37-25.47	0.017*	3.99	1.19-13.41	0.026*
Age at operation	1.00	0.86-1.15	0.947	0.95	0.79-1.15	0.621
Operated after 1975	0.58	0.25-1.38	0.219	0.41	0.16-1.03	0.059
Pulmonary valve replacement						
Early postoperative arrhythmias	1.90	0.79-4.57	0.149	1.33	0.55-3.25	0.525
Temperature during surgery (per 1°C decrease)	1.09	1.00-1.16	0.045*	1.02	0.93-1.11	0.650
Prior shunt	1.64	0.86-3.13	0.133	2.50	1.00-6.25	0.049*
Transannular patch	6.40	2.26-18.10	<0.001*	3.50	1.39-8.86	0.008*
Age at operation	0.91	0.82-1.01	0.087	0.92	0.79-1.05	0.215
Operated after 1975	2.72	1.29-5.76	0.009*	1.88	0.84-4.20	0.126

CI indicates confidence interval; HR, hazard ratio; PM, pacemaker; and PVR, pulmonary valve replacement.
*Significant.

a trend toward lower all-cause mortality (hazard ratio, 0.22; *P*=0.064). The presence of a supraventricular arrhythmia on ECG in 1990 or 2001 predicted mortality (hazard ratio, 13.9, *P*=0.016; and hazard ratio, 14.5, *P*=0.004, respectively).

DISCUSSION

In this unique prospective, longitudinal cohort study of an unselected cohort of ToF patients with detailed clinical evaluation and analysis of predictors for outcome, we found that late mortality up to 40 years was low. Early postoperative arrhythmias were found to be a new predictor for late mortality. Although morbidity was substantial, the subjective health status was excellent, and objective exercise capacity remained stable.

Mortality and major events

In the total cohort, cumulative survival 40 years after surgical correction was 72%, with one fifth of deaths occurring within 30 days after surgery. In the hospital survivors, cumulative survival was 86% after 40 years of follow-up. This is only slightly lower than survival in the general Dutch population. The causes of late death in our cohort were heart failure and arrhythmia, which is in accordance with the literature.[3,4,19,20] Morbidity was substantial in our population; only one quarter of the patients were free from events after 40 years. Reinterventions were required in nearly half of the patients, mostly PVR. This is considerably more than reported in other studies, probably reflecting the earlier era of initial operation and longer duration of follow-up in our study.[6,19,21]

Health status assessment

Exercise capacity was clearly impaired in our ToF patients but remained stable in the last 10 years. The lowest peak V_{O_2} in our study population was 51% of the predicted value. This is still considerably higher than the 36% described by Giardini *et al.*[22] as a cutoff value for greater risk of cardiac-related death. Remarkably, patients themselves reported favorable physical functioning and even less interference from physical problems in their work and daily activities than the reference Dutch population. This is in contrast to earlier reports by Knowles *et al.*,[23] who reported less favorable results in ToF patients compared with their healthy siblings. The better scores in our group may be due to different frames of reference, overcompensation, and social desirability.[24] Over time, our patients showed a decrease in general health perception scores, which can be related to age because this effect also is seen in the general population.[12]

Arrhythmias

Arrhythmias and sudden death are important late complications.[4,8,25] We found a lower prevalence of arrhythmias than described by Khairy *et al.*[25] In our study, supraventricular arrhythmias were common on Holter, but only 5 patients had symptomatic arrhythmias. The prevalence of SVT on Holter did not increase in the last decade and did not predict outcome. In addition, an increase in QRS duration did not predict arrhythmias or mortality. However, strikingly, 2 of the 3 patients with an atrial arrhythmia (atrial flutter) on ECG in 2001 died during the last 10 years. Their atrial arrhythmia could have been an indicator of worsening hemodynamics, but none of these patients had more than mild RV dysfunction, and only 1 had LV dysfunction in 2001. It seems that these supraventricular arrhythmias should not be considered insignificant.

Ventricular function

Late deterioration of RV and LV function has been an increasing concern.[26,27] Indeed, this was found in our study because systolic RV function was impaired in >75% and systolic LV function in 50% of the patients. Moreover, diastolic LV dysfunction was found often. The deterioration of LV function could be explained by adverse ventricular-ventricular interaction associated with RV dilation, which influences LV twist.[28] We found a significant association between RV and LV dysfunction. In addition, we found a modest but significant correlation between LV dimensions and NT-proBNP levels. In other studies, NT-proBNP levels correlated with both LV and RV dimensions and LV function.[29] Whether NT-pro-BNP predicts clinical outcome remains to be established. Administration of dobutamine during CMR led to an increase in RV EF and LV EF at a low dose, but no further increase was observed at a high dose. As described by Parish *et al.*,[30] who found a similar stress response, this is caused mainly by the lack in further decrease of RV end-systolic volume, indicating diminished contractile reserve. Because this is not apparent at rest, dobutamine stress CMR may contribute to the decision making in terms of intervention such as timing of PVR in these patients.[31]

Aortic dilation

Dilation of the ascending aorta is found in 15% to 87% of the ToF patients,[32] presumably inherent to volume overload resulting from the original overriding position of the aorta. Additionally, intrinsic vascular wall properties could play a role. We found aortic root dilation (≥40 mm) in 24% of our patients at the last follow-up. The long-term risk of aortic dilation in ToF patients has not been clarified yet. In our longitudinal follow-up, the aortic diameter did not increase over time, and

until now, no aortic dissection occurred. However, in 1 patient, the aortic arch was electively replaced because of an aortic diameter of 57 mm.

Predictors for late events

Patients with a palliative shunt before initial correction, that is, Waterston shunt, Blalock-Taussig shunt, or Potts anastomosis, were more at risk of dying or needing PVR than patients without them. Because in our cohort the use of a palliative shunt was related to the era of surgery rather than to anatomy, selection bias regarding more or less favorable anatomy is very unlikely. Therefore, our study supports early initial correction without previous shunt if the patient's condition tolerates.

Mortality was higher in patients who experienced early postoperative arrhythmias. In addition, these patients had a higher risk of late arrhythmias or pacemaker implantation. The occurrence of early arrhythmias and their relation to the increased risk of death and permanent pacing have previously been described in small series and, on the basis of our results, seem to have clinical relevance.[33,34] More attention for these early postoperative arrhythmias and their underlying mechanism is needed and may attribute to risk stratification for preventive interventions such as ICD implantation.

A QRS duration >180 milliseconds and an increase in QRS duration over time have been recognized as predictors for VT and late sudden death.[4,35] Our study showed a steady increase in QRS duration over time. However, all patients with a QRS duration >180 milliseconds in 1990 or 2001 are still alive, and QRS duration could not be identified as predictor for mortality in our study. Although the numbers in our study are small, supraventricular arrhythmias on ECG in 1990 or 2001 seem to be predictive of mortality. The importance of atrial arrhythmias as a predictor for outcome has been suggested before. However, the exact mechanism remains to be elucidated.[8]

The insertion of a transannular patch has received much attention as a possible cause of pulmonary regurgitation and long-term morbidity. Our results confirm the association of a transannular patch with PVR but not with mortality. These results are similar to the results of the study by Lindberg *et al*.[36] Furthermore, we found an association between the use of a transannular patch and the occurrence of late arrhythmias. Nowadays, surgeons tend to use smaller transannular patches to minimize pulmonary regurgitation and its long-term sequelae. Whether this will result in better outcome has to be established.

Study limitations

Although the number of patients in this study is relatively small, we report the results of a longitudinal follow-up of consecutive patients without selection bias related to disease severity. After a median follow-up of 36 years, we gathered medical information on 72 of the approached patients (90%). We found no significant differences in baseline characteristics between participating and nonparticipating patients; therefore, we believe that we have minimized selection bias.

From 1968 to 1980, the era in which our cohort was operated on, the standard surgical policy gradually changed from secondary correction after previous shunting, use of a large transannular patch, and surgery at very low temperature to primary correction at higher temperatures. These factors were accounted for in our analyses of predictors for outcome. We believe that there is no bias concerning temperature during surgery, but we cannot completely exclude that the use of a previous shunt was related to more complex anatomy.

Diagnostic methods have been changed during the last 36 years. For comparing echocardiography data of the present study with the previous studies, we had to use the same methods used in the past. Some of these techniques are not seen as being up-to-date. However, we also performed and reported innovative diagnostic methods available in 2012.

CONCLUSIONS

Long-term survival after successful surgical correction of ToF in childhood is good. Morbidity, however, is substantial, with almost half of the patients needing at least 1 reintervention. There is concern about the deterioration of both RV and LV function. Nevertheless, the clinical condition and subjective health status of most patients remain good, and aortic dimensions did not increase over time.

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CHAPTER 5

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

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ABSTRACT

Aims

Many patients with repaired Tetralogy of Fallot (ToF) have right ventricular (RV) volume overload due to pulmonary regurgitation (PR).We studied the effect of volume overload on global and regional RV and left ventricular (LV) deformation, and their relationships with conventional diagnostic parameters.

Methods and Results

In this cross-sectional study, 94 prospectively recruited ToF patients (61% male, age 32.8 ± 9.5 years, age at repair 1.9 [0.8–5.7] years, 39% pulmonary homograft) and 85 healthy controls of similar age and sex underwent echocardiography and electrocardiography. In a subset of patients, cardiac magnetic resonance imaging, bicycle ergometry, and NT-proBNP measurement were performed within the same day. With speckle-tracking echocardiography, we analysed peak systolic global longitudinal strain (GLS), segmental longitudinal strain and strain rate of the RV free wall, LV lateral wall, and septum. Patients had a lower RV free wall strain 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 lower RV strain rate. LV GLS was also lower (-17.4 ± 2.5 vs. -19.6 ± 1.9%, $P<0.001$), mainly due to the interventricular septum. Patients with PR >25% had higher LV GLS and RV free wall strain than patients with PR ≤25% ($P=0.004$, $P=0.039$, respectively). No relationships were found with NT-proBNP or exercise capacity.

Conclusion

RV free wall strain and strain rate are decreased in adults late after ToF repair, especially at the apical segment suggesting that apical function is most affected in these RVs. Regarding the LV, septal strain is decreased indicating that RV dysfunction adversely affects LV function, probably by 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 survival of ToF patients. However, residual lesions such as pulmonary regurgitation (PR) and right ventricular (RV) dysfunction are common after late repair.[2] RV dysfunction also seems to affect left ventricular (LV) systolic function.[3–6]

RV and especially LV dysfunction are important indicators of clinical outcome.[3,4,7] Therefore, early detection of ventricular dysfunction is essential. 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 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 deformation.[9]

In ToF patients with normal LV ejection fraction (EF), decreased LV longitudinal strain has been reported, suggesting subclinical LV myocardial damage.[10] Decreased RV longitudinal strain has also been described; however, these studies are mainly performed in small groups or in children.[10 – 12]

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

Study population

For this cross-sectional study, 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 a pacemaker, atrial fibrillation, and poor quality of echocardiographic images, resulting in inadequate speckle-tracking analysis of both ventricles. 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 subjects.

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 (1–5 MHz extended operating frequency range) at a frame rate of >60 frames/s. We used the guidelines of the American Society of Echocardiography for chamber measurements, including LVEF (Simpson's method), RV fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE).[8] For valvular regurgitation and stenosis, we used recommendations of the European Association of Echocardiography.[13–15]

Speckle-tracking analysis

Offline analyses of the data sets were performed using STE by QLAB version 9.0 (Philips Medical Systems). At the standard apical four-chamber view (A4C), we defined the endocardium of the LV lateral wall and septum to analyse LV peak systolic global longitudinal strain (GLS), segmental longitudinal strain, and strain rate (Figure 1A). The interventricular septal strain was measured along with the LV lateral wall, because QLAB has been developed for LV mechanics. LV GLS at A4C was considered feasible when at least six of the seven segments were measurable. For LV GLS based on the three apical views, at least 12 segments of the 17-segment model had to be measurable (Figure 1). For analysis of RV free wall strain, segmental strain, and strain rate, we defined the endocardium of the free wall at the RV-centred A4C (Figure 2). RV free wall strain was scored feasible when all three segments could be measured. The LV algorithm was applied for both ventricles. After positioning 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 value on the curve during the ejection phase. Data were exported to a spreadsheet program (Excel; Microsoft Corporation, Redmond, WA, USA). All references to strain changes consider the absolute value of the number, so that higher or increase in longitudinal strain means a more negative number and lower or decrease means a less negative number.[16]

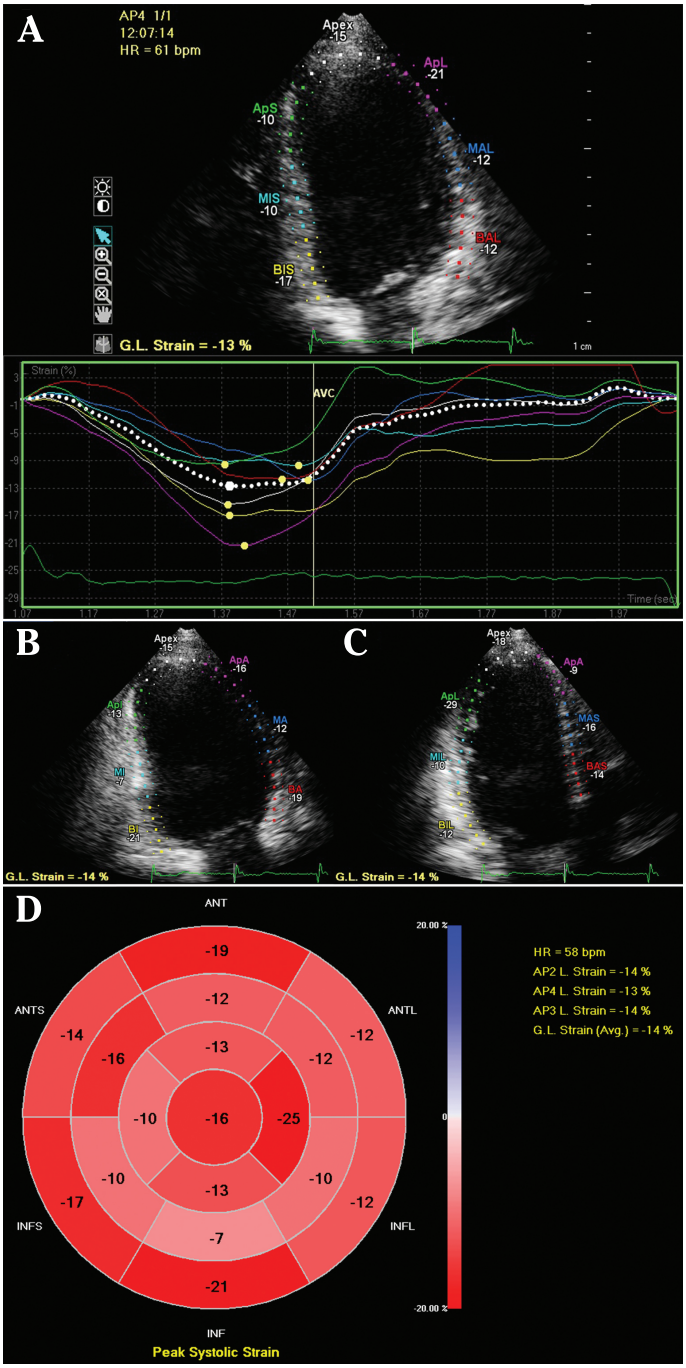

Figure 1 Left ventricular longitudinal strain measurements.
The left ventricle was traced at the apical four- (A), two- (B), and three-chamber view (C). The walls were automatically divided into seven segments at each view. Strain and strain rate curves were plotted for each segment. Left ventricular global longitudinal strain was based on the average of 17 segments (D).

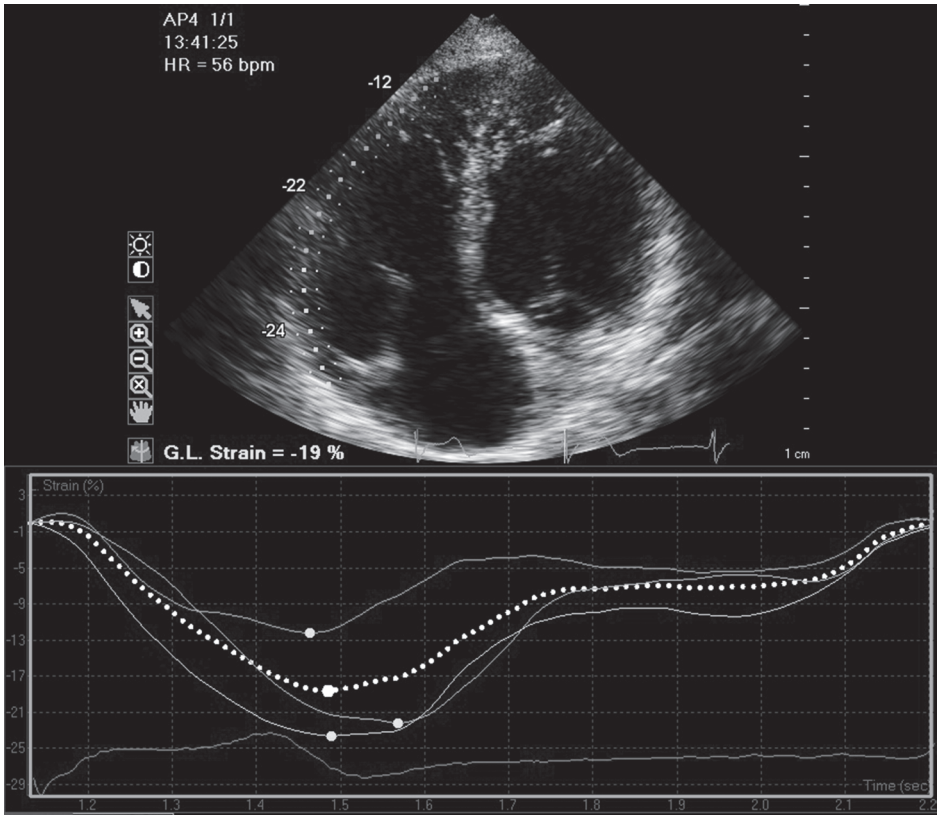

Figure 2 Right ventricular longitudinal strain measurements.
The right ventricular free wall was traced from base to apex. Strain and strain rate curves were plotted for each segment. Global longitudinal strain of the free wall was based on the three regional values.

CMR imaging

CMR imaging was performed using a Signa 1.5-T scanner (GE Medical Systems, Milwaukee, WI, USA) with dedicated phased-array cardiac surface coils. Details of the used CMR sequence have been reported previously.[17] For analyses, an Advanced Windows workstation (GE Medical Systems) was used, equipped with QMass and QFlow version 5.2 (Medis Medical Imaging Systems, Leiden, the Netherlands). The ventricular volumetric data set was quantitatively analysed by one investigator (J.C.) using manual outlining of endocardial borders in end-systole and end-diastole excluding large trabeculae (visible on three subsequent slices) and papillary muscles from the blood volume. Biventricular end-diastolic volume, end-systolic volume, stroke volume (SV), and EF were calculated using the disc summation method. To define the basal RV, images of the atria were acquired and the exact delineation was cross checked on other images. We included the portion of the RV outflow tract below the pulmonary valve in the RV volume measure-

ments. Pulmonary regurgitation fraction was determined from flow measurements in phase contrast sequences.

Cardiopulmonary exercise testing

Peak work load, heart rate, oxygen consumption (VO_2), respiratory exchange ratio (RER), and CO_2-equivalent ($EqCO_2$) were assessed on a bicycle ergometer with gradual workload increments of 20 W/min (Ramp protocol) and compared with normative data.

NT-proBNP measurement

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

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or as median with interquartile range (IQR). Categorical data are presented as frequencies and percentages. For comparison of normally distributed data 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. NT-proBNP values were log transformed to create a normal distribution. In case of skewed distribution, the Mann–Whitney U test was applied. For comparison of frequencies, the χ^2 test or Fisher's exact test was used and for quantifying correlations the Pearson or Spearman correlation test. Multivariable regression analysis was performed for associations between strain and baseline characteristics.

Intra-observer and inter-observer agreement of LV GLS at A4C and RV free wall strain were assessed by repeated analysis (M.M., J.M.) in more than half of the data sets and of RV segmental strain in a quarter of the data sets at least half a year after the initial analysis on the second cardiac cycle at the same images. The limits of agreement between two measurements were determined as the mean of the differences ± 1.96SD and presented in a Bland–Altman plot. Additionally, the coefficient of variation (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, IBM Corp., Armonk, NY, USA). The statistical tests were two sided, and $P<0.05$ was considered statistically significant.

RESULTS

Study population

Figure 3 presents an overview of the patient participation. Table 1 shows the baseline characteristics of the study population. Twenty patients have had a palliative shunt before initial repair with a median duration of 4 years [IQR: 3–6].The patients were studied 27 years [IQR: 23–35] after initial surgical repair. Thirty-seven (39%) patients underwent primary pulmonary valve replacement (PVR) due to severe PR 22 years [IQR: 18–26] after surgical repair and 6 years [IQR: 4–9] before the current study. None of the patients have had secondary PVR. In the subsets of patients with CMR, cardiopulmonary exercise testing, or NT-proBNP measurement, their baseline characteristics were also comparable with those of the healthy controls. Table 2 presents conventional echocardiographic characteristics. Table 3 shows the degree of PR in patients with PVR and patients without PVR.

LV longitudinal strain and strain rate

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

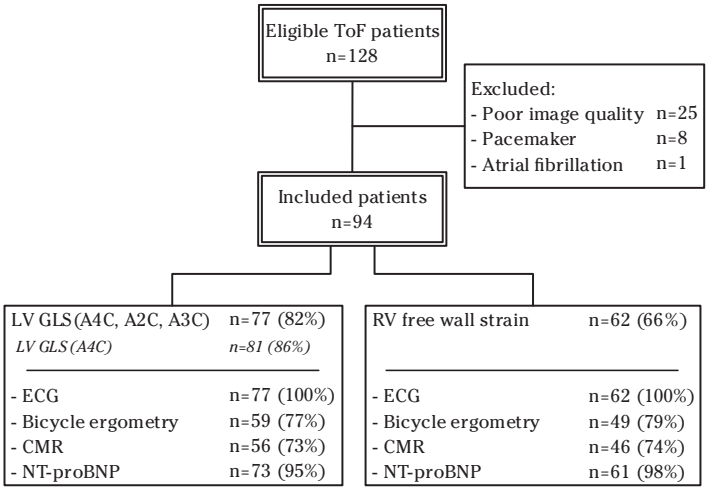

Figure 3 Flow chart of the study patients.
An overview of the patient inclusion, feasibility of strain measurements, and number of patients per additional diagnostic test. We defined image quality as poor when speckle-tracking analysis was infeasible for both ventricles. Bicycle ergometry was not performed in 24 patients mainly due to refusal or inability; CMR not in 28 due to refusal or claustrophobia.
A2C, apical two-chamber view; A3C, apical three-chamber view; A4C, apical four-chamber view; CMR, cardiac magnetic resonance imaging; ECG, electrocardiography; GLS, global longitudinal strain.

Table 1 Characteristics of the ToF patients and healthy controls

Clinical characteristics	Patients (n=94)	Controls (n=85)	*P*-value
Age at time of study (years)	32.8 ± 9.5	34.4 ± 11.6	0.308
Male	57 (61%)	48 (56%)	0.572
BMI (kg/m^2)	23.9 ± 4.3	23.7 ± 3.1	0.717
Systolic blood pressure (mmHg)	124 ± 16	125 ± 13	0.993
Diastolic blood pressure (mmHg)	76 ± 13	76 ± 9	0.770
NYHA functional classification			
Class I	92 (98%)	85 (100%)	0.498
Class II	2 (2%)	-	
Rhythm			
Sinus rhythm	90 (96%)	85 (100%)	0.123
Atrial rhythm	4 (4%)	-	
QRS duration (ms)	141 ± 28	99 ± 9	<0.001
RBBB	75 (80%)	-	
QRS duration >180 ms	7 (7%)	-	
Age at operation (years)	1.9 [0.8-5.7]	-	
Type of repair			
Transannular patch	63 (67%)	-	
Infundibulectomy	28 (30%)	-	
Unknown	3 (3%)	-	
Prior palliative shunt	20 (21%)	-	
Pulmonary valve replacement	37 (39%)	-	

Categorical data are presented as n (%), and continuous data as mean + SD or median [IQR]. Bold font style represents statistically significant differences. BMI, body mass index; NYHA, New York Heart Association; RBBB, right bundle branch block.

RV longitudinal strain and strain rate

The mean RV free wall strain was significantly decreased in patients, 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 4 presents RV strain rate values.

Relationships with baseline characteristics and clinical parameters

Table 5 presents the results of a sub-analysis for age groups, sex, and surgical characteristics.

Age at repair correlated weakly with RV free wall strain (r=-0.31, P=0.013) and LV GLS (r=-0.24, P=0.033). After multivariable regression analysis adjusting sex, current age, and body surface area, associations were no longer significant between age at repair and RV free wall strain (β=-0.27, P=0.130), or LV GLS (β=-0.28, P=0.053). No other correlations with surgical characteristics were found. The QRS duration

Table 2 Conventional echocardiographic characteristics of the ToF patients and healthy controls

Characteristic	Patients	Controls	*P*-value
LV end-diastolic dimension (mm)	48 ± 6	48 ± 4	0.694
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 ± 7	58 ± 5	**<0.001**
RV longitudinal dimension (mm)	88 ± 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 in patients	**Mild**	**Moderate**	**Severe**
Aortic regurgitation	23 (24%)	1 (1%)	-
Aortic stenosis	2 (2%)	-	-
Mitral regurgitation	15 (16%)	1 (1%)	-
Pulmonary regurgitation	32 (34%)	15 (16%)	27 (29%)
Pulmonary stenosis	40 (43%)	15 (16%)	2 (2%)
Tricuspid regurgitation	55 (59%)	7 (7%)	-

Continuous data are presented as mean + SD; categorical data as n (%). Bold font style represents statistically significant differences. EF, ejection fraction; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Degree of pulmonary regurgitation in patients with and without pulmonary valve replacement

Degree of PR	None, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)
PVR	11 (55)	19 (59)	6 (40)	1 (4)
No PVR	9 (45)	13 (41)	9 (60)	26 (96)

PR, pulmonary regurgitation; PVR, pulmonary valve replacement.

correlated with RV free wall strain (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 workload was 88 ± 17% of normal; peak heart rate 87 ± 9%; peak V_{O_2} 81 ± 17%; peak RER 1.36 ± 0.19 and peak Eq_{CO_2} 29.1 ± 4.7. No significant correlations were found between RV free wall strain and LV GLS with these parameters.

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=-0.23, *P*=0.052), but not with RV free wall strain.

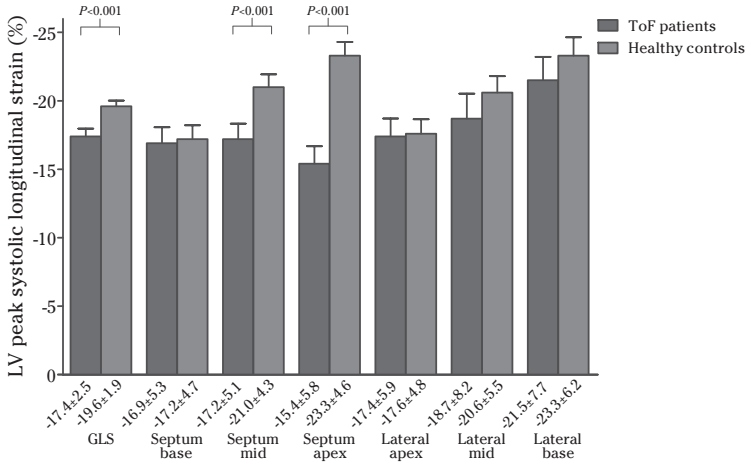

Figure 4 Mean LV global and segmental longitudinal strain of ToF patients (n=81) and healthy controls (n=85).

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.

Table 4 The peak systolic strain rate of the LV septal wall, LV lateral wall, and RV free wall of ToF patients and healthy controls

	Patients	**Controls**	***P*-value**
LV strain rate (s^{-1})			
Septum, base	-1.10 ± 0.34	-1.01 ± 0.27	0.047
Septum, mid	-1.14 ± 0.38	-1.18 ± 0.27	0.465
Septum, apex	-1.10 ± 0.32	-1.21 ± 0.18	0.007
Lateral, apex	-1.20 ± 0.39	-1.18 ± 0.40	0.721
Lateral, mid	-1.49 ± 0.60	-1.25 ± 0.38	0.003
Lateral, base	-1.51 ± 0.53	-1.47 ± 0.48	0.620
RV strain rate (s^{-1})			
Free wall, base	-1.43 ± 0.46	-1.67 ± 0.57	0.017
Free wall, mid	-1.43 ± 0.47	-1.68 ± 0.61	0.014
Free wall, apex	-1.17 ± 0.46	-1.66 ± 0.55	<0.001

Strain rate values are presented as mean ± SD.

Relationships with echocardiographic parameters

A positive correlation between RV free wall strain and LV GLS was found in all subjects (r=0.46, *P*<0.001) and in the patient group itself (r=0.37, *P*=0.010). Figure 6 shows a strong correlation between RV free wall strain with TAPSE and moderate correlation with RV longitudinal dimension. The RV segments separately

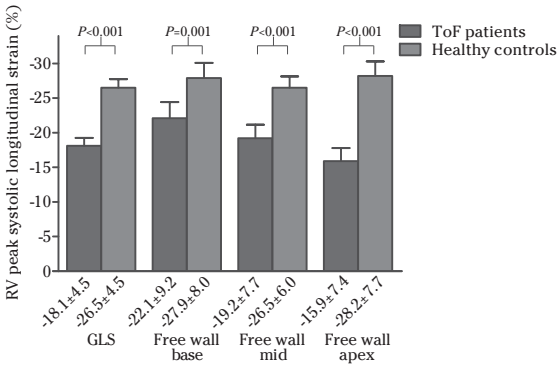

Figure 5 Mean RV free wall and segmental longitudinal strain of ToF patients (n=62) and healthy controls (n=54). Peak systolic RV free wall strain was measured at the apical four-chamber view. The error bars show 95% confidence interval. GLS, global longitudinal strain.

correlated also significantly with TAPSE and RV longitudinal dimension. Table 6 summarizes correlations between biventricular GLS and other echocardiographic parameters.

Patients with an LVEF <50% had a lower LV GLS (-16.3 ± 2.7%) than patients with an LVEF ≥50% (-18.4 ± 2.1%, *P*=0.001). RV free wall strain in patients with RV FAC <35% tended to be lower (-16.9 ± 4.0%) than in patients with normal RV FAC (-19.2 ± 4.6%, *P*=0.094). Table 5 shows a sub-analysis for the severity of pulmonary valve disease. No significant differences in LV GLS and RV free wall strain were found between patients with none, mild, or moderate tricuspid regurgitation.

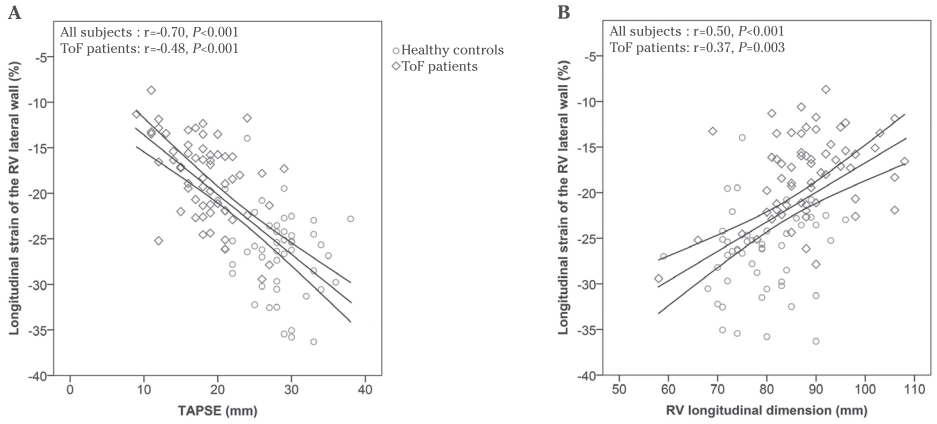

Figure 6 Correlations between RV free wall strain with conventional parameters.
Significant correlations were observed between RV free wall strain and TAPSE (A), and RV end-diastolic longitudinal dimension (B).TAPSE, tricuspid annular plane systolic excursion.

Relationships with CMR parameters

The median PR fraction was 20% [IQR: 0–43]. Patients with PR >25% had a significantly higher strain than patients with PR ≤25% (Table 5). In the group with PR >25%, none of the patients had a PVR vs. 16 (52%) PVR patients in the group with PR ≤25% (*P*<0.001). Table 7 presents CMR-derived ventricular volumes and EFs, and their correlations with GLS.

Table 5 Sub-analysis for age groups, sex, surgical characteristics, and pulmonary valve disease in ToF patients

		n	LV GLS (%)	*P*-value	n	RV free wall strain (%)	*P*-value
Age (years)	*<30*	35	-17.1±2.3	0.243	32	-17.6±4.0	0.381
	≥30	42	-17.7±2.6		30	-18.6±5.0	
Sex	*Male*	44	-16.8±2.4	**0.011**	40	-16.7±3.9	**0.001**
	Female	33	-18.3±2.4		22	-20.6±4.5	
Age at repair (years)	*<2*	41	-16.8±2.1	**0.011**	33	-17.0±3.9	**0.037**
	≥2	36	-18.2±2.6		29	-19.3±4.9	
Surgical era	*≤1980*	31	-17.5±2.6	0.894	23	-18.0±5.2	0.924
	>1980	46	-17.4±2.4		39	-18.1±4.2	
Transannular patch	*Yes*	49	-17.4±2.5	0.896	45	-18.2±4.3	0.759
	No	25	-17.5±2.4		15	-17.8±5.3	
Preoperative palliative shunt	*Yes*	17	-17.7±3.1	0.606	16	-19.5±5.3	0.144
	No	59	-17.3±2.3		46	-17.6±4.2	
RBBB	*Yes*	62	-17.6±2.6	0.389	50	-17.9±4.5	0.587
	No	15	-16.9±2.0		12	-18.7±4.7	
PS grade, echocardiography	*None (<2 m/s)*	30	-17.6±2.5	0.660[a]	24	-18.9±4.8	0.308[a]
	Mild-moderate (2-4 m/s)	45	-17.3±2.5		36	-17.6±4.4	
	Severe (≥4 m/s)	2	-18.9±2.0		2	-16.9±2.1	
PR grade, echocardiography	*None*	19	-17.1±2.8	0.516	12	-18.9±5.0	**0.049**
	Mild-moderate	37	-17.3±2.5		30	-16.7±3.9	
	Severe	21	-17.9±2.0		20	-19.7±4.6	
PR fraction, CMR (%)	*≤25*[18]	29	-16.7±2.3	**0.003**[b]	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	0.194	24	-16.8±3.9	0.087
	No	45	-17.8±2.3		38	-18.9±4.7	

Strain values are presented as mean+SD. Bold font style represents statistically significant differences.
CMR, cardiac magnetic resonance; PR, pulmonary regurgitation; PS, pulmonary stenosis; RBBB, right bundle branch block.
[a]Because of the small number of patients with severe pulmonary stenosis, they were excluded from statistical analysis. [b]Difference in statistical outcome between PR grade assessed with echocardiography and with CMR could be caused by the smaller number of patients with CMR.

Table 6 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	0.713
LV end-systolic dimension	**0.34**	**0.002**
LV fractional shortening	**-0.44**	**<0.001**
LV EF Simpson's	**-0.45**	**<0.001**
	RV free wall strain	
	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**

Bold font style represents statistically significant correlations.
EF, ejection fraction; FAC, fractional area change; GLS, global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

Table 7 CMR parameters and correlations with global longitudinal strain in ToF patients.

		LV GLS	
	Median [IQR]	*Spearman's* ρ	*P*-value
LV SV/BSA	44 [40-51]	-0.16	0.228
LV ESV/BSA	30 [25-37]	**0.41**	**0.002**
LV EDV/BSA	75 [68-87]	0.16	0.253
LV EF (%)	59 [52-65]	**-0.49**	**<0.001**
PR fraction (%)	20 [0-43]	**-0.42**	**0.003**
		RV free wall strain	
	Median [IQR]	*Spearman's* ρ	*P*-value
RV SV/BSA	55 [47-67]	**-0.32**	**0.030**
RV ESV/BSA	53 [40-70]	-0.12	0.436
RV EDV/BSA	106 [91-140]	-0.19	0.201
RV EF (%)	52 [45-56]	-0.11	0.485
PR fraction (%)	20 [0-43]	-0.28	0.075

Bold font style represents statistically significant correlations.
BSA, body surface area (m2); EDV, end-diastolic volume (mL); ESV, end-systolic volume (mL); GLS, global longitudinal strain; IQR, inter-quartile range; PR, pulmonary regurgitation; SV, stroke volume (mL).

Intra-observer and inter-observer agreement

The mean difference of the intra-observer measurements was -0.13 ± 1.40% for the LV GLS at A4C and -0.02 ± 2.00% for the RV free wall strain. The mean difference of the inter-observer measurements was -0.06 ± 1.49% for the LV GLS at A4C and 0.18 ± 2.68% for the RV free wall strain (Figure 7). The intra-observer agreement for RV segmental strain (3 segments) was -0.67 ± 4.53% and the inter-observer agreement was 0.33 ± 7.28%.

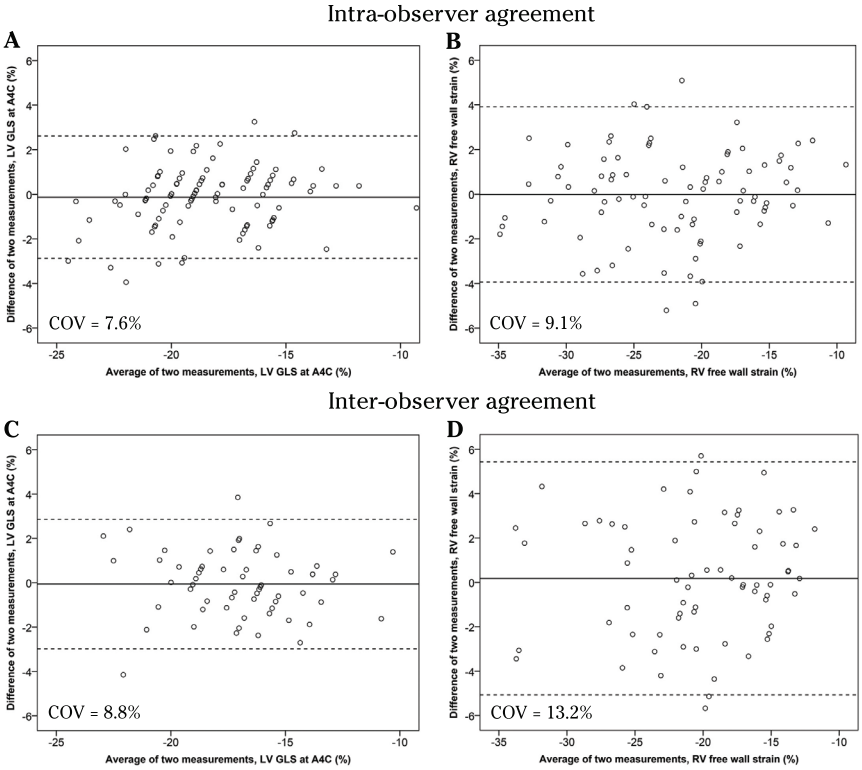

Figure 7 Bland–Altman plots demonstrating intra-observer and inter-observer agreement.
Left ventricular strain and right ventricular free wall strain for intra-observer (A and B) and inter-observer agreement (C and D) were measured at the apical four-chamber view. The solid lines depict the mean difference of two measurements, and the dashed lines depict the limits of agreement.
A4C, apical four-chamber view; COV, coefficient of variation.

DISCUSSION

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

RV longitudinal strain

In normal RV anatomy, longitudinal contraction is the major contributor to the overall RV performance.[19] The longitudinal strain of all three RV free wall segments was decreased in the patients, presumably as a result of chronic volume overload. Decreased free wall strain was also described by others; however, they

included only a small group of patients.[10,12] The apical strain was more decreased than the strain of the other RV segments, which was also observed in children,[11] confirming that RV basal and midventricular function are better preserved than apical function. The reason why the apical segment is most sensitive to volume overload is not exactly clear. It has been suggested that the RV apical part is more affected by wall stress, because it is thinner and more trabeculated than the inlet and outlet parts.[19,20] The higher regional wall stress results in a dilated and more rounded apical shape.[20] This remodelling could lead to greater reduction in apical contractile function resulting in more decreased strain. Another explanation could be that in some RVs a hypertrophied moderator band and trabeculations lead to a smaller regional volume and therefore might decrease the apical deformation.[21]

Remarkably, patients with severe PR had less decreased RV free wall strain than patients with none–moderate PR. Possibly, the higher strain values in patients with severe PR are a result of a compensatory mechanism. Moreover, the lower RV strain in patients with none–moderate PR could possibly be explained by the fact that some of them received a PVR after long-term suffering from severe PR. The exposure to severe PR and the reinterventions could lead to decreased RV strain. However, these hypotheses remain speculative. The exact underlying mechanism is unclear and follow-up is necessary to evaluate RV deformation over time.

Timing of PVR is controversial and the optimal indications are not completely clear yet. After PVR, RV EF does often not improve,[22] 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 might be of additional value in identifying patients in need of PVR. However, to conclude that decreased strain is an early sign of ventricular dysfunction in these patients and could be an additional criterion for reinterventions, a prospective longitudinal study is required.

Ventricular–ventricular interaction

LV dysfunction is a strong determinant of clinical outcome in ToF patients,[3,6,7] making early detection important. RV dysfunction may lead to LV dysfunction in ToF patients.[3 – 5,10,23] RV free wall strain of our adult patients was related with LV GLS, suggesting ventricular–ventricular interaction. Decreased LV GLS was mainly caused by decreased strain of the midventricular and apical septum, both interventricular segments. Also in children the assessment of ventricular–ventricular interaction revealed that RV free wall strain and LV GLS were closely related and that LV strain was significantly decreased at the mid and apical levels.[24] Moreover, decreased RV function in ToF patients results in smaller or impaired LV twist.[23,24]

RV pressure and volume loading are likely to affect the LV through several potential interventricular mechanisms, e.g. changes in septal curvature, shared myocardial fibres and electromechanical dyssynchrony. Additionally, in ToF patients, mechanical interventricular interaction is observed by the interventricular septal patch that leads to dysfunction of at least a part of the septum.[25] A prospective follow-up is needed to conclude whether decreased septal strain is a pre-clinical sign of LV dysfunction.

Relationships with clinical parameters

RV free wall strain correlated moderately with TAPSE and modestly with CMR-derived indexed RV SV, but not with RV EF. Mercer-Rosa *et al.*[26] described in ToF patients an association of TAPSE with RV SV, but not with RV EF which is corresponding with our results. An explanation for lack of correlation between RV free wall strain 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. During a 4-year follow-up in adults with ToF, the RV EF remained unchanged, whereas the RV GLS decreased significantly.[12] Hayabuchi *et al.*[27] described in children with repaired ToF a decreased RV longitudinal septal strain, but a normal circumferential and increased radial strain. These deformation characteristics may be the same or even more pronounced in adults. The lack of correlation could also be caused by the CMR-derived volumes that are observer dependent and sensitive to the used method.

Another explanation could be that RV free wall strain reflects deformation of the RV inflow and apical part, but not of the RV outflow tract. Many ToF patients have an outflow patch which could influence the regional function. Wald *et al.*[28] demonstrated with CMR that regional RV outflow tract abnormalities adversely affect global RV EF. 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.

RV free wall strain appears to have discriminative ability for quality of life in ToF patients;[29] however, whether decreased strain is a predictor of clinical outcome is unknown. Our study showed no correlation between RV free wall strain and exercise performance, which is in contrast with the observed correlation in children by Alghamdi *et al.*[30] Reasons for this discrepancy could be the differences in surgical era, patient age or, as described by Wald *et al.*,[28] that the RV outflow tract function is a more important determinant of exercise performance. We did not find significant relationships between NT-proBNP levels and strain values. However, single NT-proBNP measurements rarely allow meaningful correlations

with imaging parameters, and therefore, sequential measurements are needed to draw further conclusions.

RV strain values have not been adjusted to RV size to possibly reveal further correlations as was done in children,[11] because it is not recommended in the current guidelines.[8]

Intra-observer and inter-observer agreement

We found a higher variation in strain values of the RV than the LV. This could probably be explained by the fact that the RV free wall is more difficult to image than the LV, the RV consisted of fewer segments and that the algorithm has been developed for the LV shape. Although the variation is higher for RV free wall strain, the reproducibility is still good. The intra-observer and inter-observer variation of RV segmental strain was considerable, but the mean difference of the two measurements was small meaning that the observed decrease in strain was well reproducible.

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.[19] We assumed that the same applies to RVs of ToF patients. In addition, RV radial and circumferential strain measurements are not available on QLAB software. Rotational movements play a significant role for LV function, but we decided to measure strain in longitudinal direction making comparisons with RV strain clearer.

Cardiopulmonary exercise tests and CMR exams were not performed in about one quarter of the patients. Therefore, correlation analysis results should be interpreted with caution.

CONCLUSIONS

The RV free wall longitudinal strain and strain rate are decreased in ToF patients, most pronounced at the apical segment. This suggests that apical function is most affected 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 mechanical ventricular coupling. Whether decreased strain is an early and subclinical sign of ventricular dysfunction in ToF 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 6

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.

INTRODUCTION

Nowadays, a growing number of adult patients require regular follow-up after surgical correction of tetralogy 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 possibilities 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 images 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.

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 programme 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.

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, end-systolic volume (ESV), EF, and valvular regurgitation fractions were calculated.

Exercise capacity

Maximal exercise capacity and peak oxygen consumption (peak V_{O_2}) 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 min 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 means ± 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 χ^2 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 SPSS version 20 (IBM Corp., Armonk, NY, 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 short-axis 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 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).

Table 1 Clinical and echocardiographic characteristics of the study population

Clinical characteristics	Patients (n=82)
Age at time of study (years)	32.6 ± 9.7
Male, n (%)	45 (55)
Type of repair , n (%)	
Transannular patch	60 (73)
Infundibulectomy	22 (27)
Pulmonary homograft	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.

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 with 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.

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.

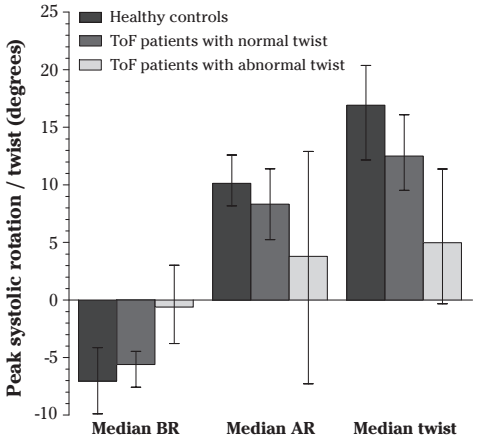

Figure 1 Rotational parameters of the left ventricle in patients with tetralogy of Fallot and in healthy controls.
BR, basal rotation; AR, apical rotation. The error bars show inter-quartile ranges.

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.

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	Right atrial dilatation, n (%)			
	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-syst dim/BSA	17 ± 3	19 ± 4	0.011
	End-dias 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	NT-proBNP >14, n (%)	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.

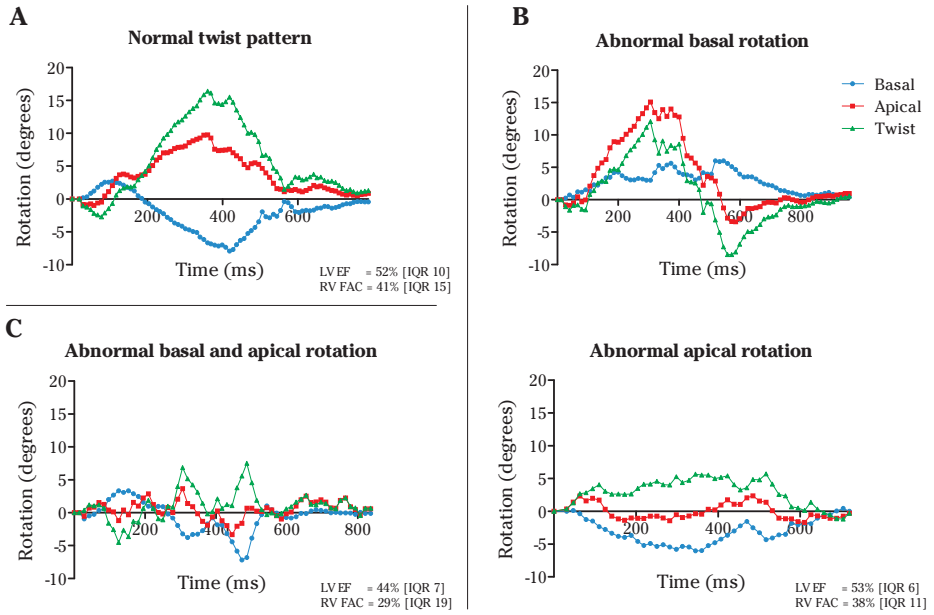

Figure 2 Various rotation types in patients with corrected ToF.
Fifty-eight patients had a normal twist pattern (A); of the patients with abnormal twist pattern, 11 had an abnormal BR and 8 an abnormal AR (B); 5 had both abnormal basal and abnormal AR (C). Note that 8 patients with normal twist pattern have reduced AR (,4 degrees). LV EF, left ventricular ejection fraction, RV FAC, right ventricular fractional area change.

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 towards 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 the biplane Simpson's method. In 54 (66%) patients, image quality of the two- and four-chamber views was sufficient for adequate tracing

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	5.7 [6.3]	9.2 [7.3]	0.074
Twist	10.5 [6.5]	13.2 [6.4]	0.016
	LVEF <50%	**LVEF ≥50%**	
Basal rotation	-4.9 [2.7]	-6.1 [3.7]	0.033
Apical rotation	5.2 [6.1]	9.1 [6.6]	0.021
Twist	9.1 [6.4]	13.2 [5.5]	0.006

The results are presented as median [IQR]. LV EF was measured with Simpson's method.

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 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.

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 reinterventions 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 end-diastolic volume normalized to BSA (β=0.337, *P*=0.009), and RV ESV normalized 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 peak V_{O_2} measurement. The median workload capacity was 86% (IQR: 22) and the

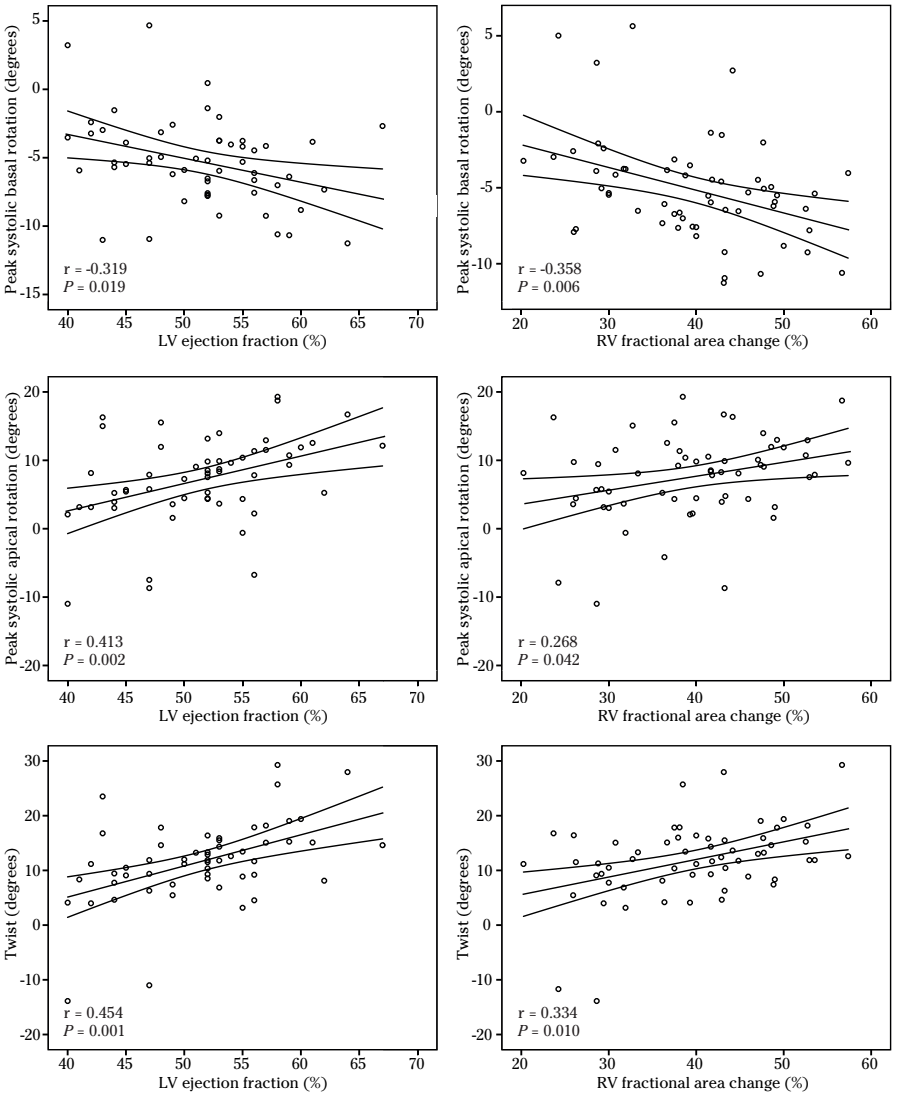

Figure 3 Correlations between LV rotational parameters and LV ejection fraction and RV fractional area change.

median peak V_{O_2} was 83% (IQR: 28).We compared the median maximal work load, maximal heart rate, peak V_{O_2} and peak RER (all in % of expected) between the normal and abnormal twist group, between the normal and abnormal AR group, and between the 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 work load 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 AR. Over a quarter of patients had an abnormal AR 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 AR 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 BR, and 1% a prolonged rotation. These last two patterns were not described by Takayasu *et al*.

A relationship 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 hypothesized 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 towards

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–aldosterone 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 the 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 three 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 fibre 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 AR in adult patients with corrected ToF, likely by alteration of LV configuration. However, we did not observe a relationship 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.

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 two segments before generation of the twist.

We realized that the use of LV EF measured with the 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 has 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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CHAPTER 7

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 overload, 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 peak oxygen uptake (peak V_{O_2}). 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 peak oxygen uptake during exercise (peak V_{O_2}) 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 ≥200 µmol/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 χ^2 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, IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

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.

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

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.

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)				
Peak $V_{O_2\,max}$ (% 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.

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 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

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

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,

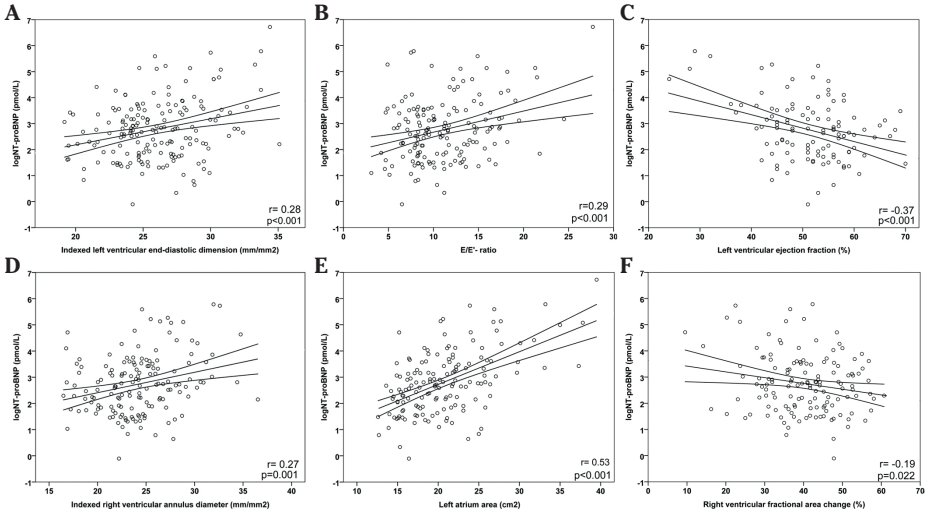

Figure 1 Correlations between NT-proBNP and cardiac function and dimensions.
The correlations are presented for NT-proBNP and LV end-diastolic dimension indexed for BSA (A), E/E'-ratio (B), LV ejection fraction (C), RV annulus diameter indexed for BSA (D), LA area (E) and RV fractional area change (F). Correlation lines with 95% confidence interval are shown.

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.

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).

Cardiopulmonary-exercise test

An exercise-stress test was performed in 68 patients (38%). There was no difference in baseline characteristics of patients who underwent an exercise stress test and

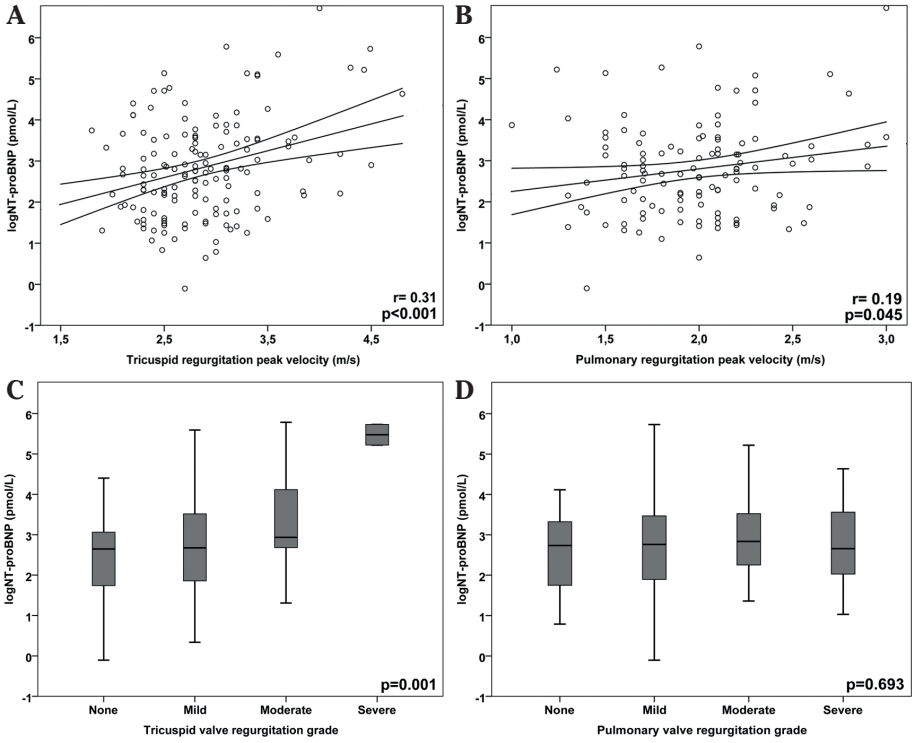

Figure 2 Correlations between NT-proBNP and parameters of valvular function.
The correlations between NT-proBNP and TR peak velocity (A) and PR peak velocity (B) are presented. Associations between NT-proBNP and TR severity (C) and PR severity (D) are presented. Correlation lines with 95% confidence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

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 peak VO_2 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 peak VO_2 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 deteriorating 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 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 peak VO_2. Although higher NT-proBNP is associated with decreased exercise capacity and peak VO_2 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 correlation between NT-proBNP and peak VO_2[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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PART III

Clinical outcome and early detection of ventricular dysfunction in other congenital heart anomalies

CHAPTER 8

The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure

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ABSTRACT

Background

Few prospective data are available regarding long-term outcomes after surgical ventricular septal defect (VSD) closure.

Objectives

Our objective was to investigate clinical outcomes > 30 years after surgical VSD closure.

Methods

Patients who underwent childhood surgical VSD closure between 1968-1980 were reexamined every 10 years. In 2012, we invited eligible patients to undergo another examination, including electrocardiography, Holter-monitoring, echocardiography, bicycle ergometry, NT-proBNP measurement and subjective health assessment.

Results

Cumulative survival was 86% at 40 years. Causes of mortality were arrhythmia, heart failure, endocarditis, post valvular surgery, pulmonary hypertension, non-cardiac, and unknown. Cumulative event-free survival after surgery was 72% at 40 years. Symptomatic arrhythmias occurred in 13% and surgical or catheter-based reinterventions in 12%. Prevalence of impaired right ventricular systolic function increased from 1% in 2001 to 17% in 2012 (P=0.001). Left ventricular systolic function was impaired but stable in 21%. Aortic regurgitation occurred more often in the last 20 years (P=0.039) and mean exercise capacity decreased (P=0.003). NT-proBNP (median 11.6 pmol/L [IQR:7.0-19.8]) was elevated (> 14 pmol/L) in 38%. A concomitant cardiac lesion, e.g. patent ductus arteriosus, and aortic cross-clamp time were determinants of late events (HR = 2.84 [95%CI:1.23-6.53]; HR = 1.47 per 10 minutes [95%CI:1.22-1.99], respectively). Patients rated their subjective health status significantly better than a reference population.

Conclusions

Survival up to 40 years after successful surgical VSD closure is slightly lower than in the general Dutch population. Morbidity is not negligible, especially in patients with a concomitant cardiac lesion.

INTRODUCTION

Ventricular septal defect (VSD) is by far the most common congenital heart defect, with a birth prevalence of 2.62 per 1,000 live births.[1,2] Small defects may not have hemodynamic consequences, but the presence of a significant left-to-right shunt can cause left ventricular (LV) overload, pulmonary arterial hypertension, ventricular dysfunction, arrhythmias, and aortic regurgitation.[3,4] Surgical closure at a young age is still the treatment of choice, and mid- to long-term results are good with regard to survival, morbidity, and quality of life.[5-7] Therefore, most such patients have been discharged from routine cardiological follow-up. For both patients and their treating physicians, it is essential to know whether the pre-operative left-to-right shunt and the VSD patch affect biventricular function or the conduction system in the long term. However, information on mortality and morbidity beyond 30 years after surgical VSD closure is scarce, and almost all such data were collected retrospectively, which introduces the possible bias of including only patients with residual morbidity who are still seen at outpatient clinics.

Our study is part of a unique, ongoing longitudinal follow-up of patients with congenital heart defects who underwent surgery at a young age at our institution between 1968 and 1980. The current study had 3 objectives: first, to evaluate survival 30 to 40 years after surgical VSD closure in an unselected cohort; second, to investigate the current clinical condition of survivors by extensive in-hospital examination and to detect determinants of outcome; and third, to evaluate the present subjective health status of survivors.

METHODS

Study patients

All consecutive patients who underwent surgical VSD closure at our institution between 1968 and 1980 at <15 years of age formed the original study cohort. This cohort was first studied in 1990, with a second follow-up performed in 2001.[5,6] In 2010 to 2012, survival status was obtained from the Dutch National Population Registry, and all surviving patients who had participated in 1 or both of the previous studies were actively invited to participate in a third study for clinical examination at the outpatient clinic of Erasmus Medical Center. The study protocol was approved by the institutional Medical Ethics Committee. Written informed consent was obtained from all participants.

Adverse events

Survival rates were compared with the expected survival rates of an age-matched Dutch population. Adverse events included all-cause mortality, surgical or catheter-based cardiac reinterventions, symptomatic arrhythmias (requiring medication, cardioversion, ablation, or insertion of a pacemaker/implantable cardioverter-defibrillator [ICD]), endocarditis, and heart failure (requiring medication or hospital admission). Mortality and events were defined as "early" when they occurred within 30 days post-operatively, and "late" when they occurred beyond 30 days. All events were assessed by 2 independent investigators (M.E.M., J.A.A.E.C.).

Clinical assessment

Examinations included history, physical examination, standard 12-lead electrocardiography (ECG), 24-h Holter monitoring, echocardiography, cardiopulmonary exercise testing, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement. If a patient was unwilling or unable to visit the outpatient clinic, questionnaires were sent to obtain information on morbidity and subjective health status, and to receive permission to use the patient's medical records.

Electrocardiography and 24-h Holter monitoring

Standard 12-lead surface ECGs were analyzed for rhythm, PR interval, and QRS duration. A 24-h Holter monitoring was performed with a CardioPerfect Holter DR180+ 3-channel recorder (Welch Allyn Cardio Control, NorthEast Monitoring, Maynard, Massachusetts). Sinus node disease (SND) was defined according to the Kugler criteria: nodal escape rhythm, sinus arrest >3 s, or severe sinus bradycardia (<30 beats/min at night or <40 beats/min during daytime).[8]

Cardiopulmonary exercise testing

Maximal workload, heart rate, and peak oxygen consumption (peak V_{O_2}) were assessed by bicycle ergometry with a gradual workload increment of 20 W/min (ramp protocol) and compared with normative values corrected for age, sex, height, and weight. Performance was considered maximal when a respiratory exchange ratio >1 was reached.

Echocardiography

A complete 2-dimensional transthoracic echocardiogram was performed with the commercially available IE33 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions, ventricular function, and valvular function were measured according to published guidelines.[9-12] LV and right ventricular (RV)

systolic function were assessed visually to enable comparison with the 2 previous studies. Systolic function was graded as normal or mildly, moderately, or severely impaired. Additionally, more objective measurements, including LV ejection fraction (Simpson's method), RV fractional area change, and tricuspid annulus plane systolic excursion, were used to quantify systolic ventricular function. Measurements were obtained by 2 independent observers (M.E.M.,J.A.A.E.C.).

NT-proBNP measurement

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

Subjective health assessment

The 36-item short-form health survey (SF-36) was completed to assess subjective health status. Results for the patients were compared with their results from 10 years earlier and with normative data from the general Dutch population.[13]

Statistical analysis

Continuous data are presented as mean ± SD or median with interquartile range (IQR) depending on the data distribution. Categorical data are presented as frequencies and percentages. Changes in patient characteristics since the follow-up study in 1990 and 2001 were evaluated by estimating a trend by use of mixed models, which take missing values into account. Changes in characteristics between 2001 and 2012 were analyzed by paired Student *t*-tests. Differences between independent subgroups were evaluated by unpaired Student t tests or Mann-Whitney U tests (continuous data) and by χ^2 test or Fisher exact test (categorical data). To quantify correlations between 2 variables, the Spearman correlation test was used.

Cumulative survival and event-free survival for all patients and for patients with successful VSD surgery (i.e., excluding early post-operative mortality) were determined by the Kaplan-Meier method. We compared the cumulative survival of isolated and nonisolated VSD patients by the log-rank test. Cumulative event incidences were computed with the use of a nonparametric estimator of cumulative incidence functions, with death as a competing risk. Univariable and multivariable Cox regression analyses were used to identify determinants of pre-defined adverse events: all-cause mortality, arrhythmias, reinterventions, heart failure, and endocarditis.

The mixed models were estimated by use of SAS software (version 9.3, SAS Institute, Inc., Cary, North Carolina). The cumulative incidence functions were estimated with R (version 3.1.1, R Foundation for Statistical Computing, Wien, Austria). All other statistical analyses were performed with the Statistical Package for Social Sciences (version 21, SPSS, IBM Corp., Armonk, NY, USA). The statistical tests were 2-sided, and $P<0.05$ was considered statistically significant. Further information on statistical analysis can be found in the Online Appendix.

RESULTS

Study patients

The original study cohort consisted of 174 consecutive patients who underwent surgical VSD closure between 1968 and 1980. Figure 1 presents an overview of patient participation for the current study. Baseline characteristics, including surgical details and follow-up duration, are presented in Table 1. Further baseline and surgical details have been reported previously.[5,6]

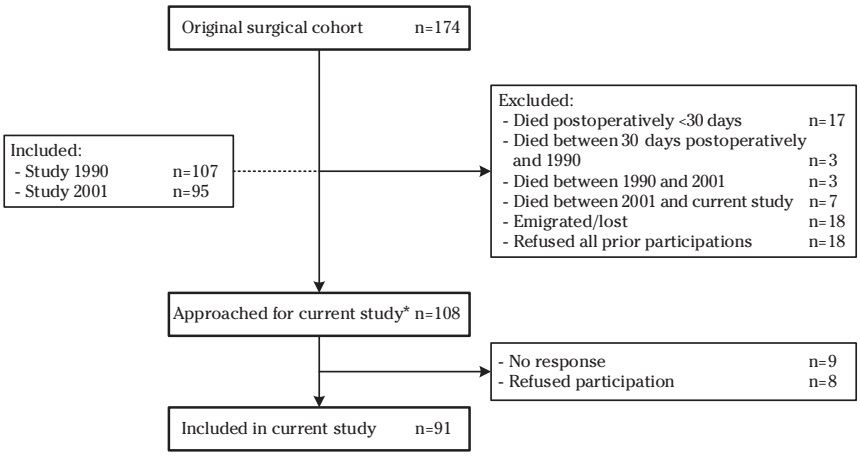


Figure 1 Flow chart of the study patients
One patient died shortly after participation in the study. We used the in-hospital examination results for this study and scored him as deceased in the survival analysis. *Patients who were alive, traceable, and participated in the studies of 1990, 2001, or both.

Median follow-up duration of the actively included patients was 35.8 years (IQR: 34.0 to 37.3 years; range 30.4 to 40.3 years). Of 91 patients, 70 participated in-hospital, and 21 completed the questionnaires and gave permission to use their hospital records. Twenty-seven of the 91 patients (30%) had 1 or more concomi-

Table 1 Baseline and follow-up characteristics of the study patients

	Total	1990	2001	2012	No third study*	*P*-value†
	(n=174)	(n=107)	(n=95)	(n=91)	(n=83)	
Male	96 (55)	64 (60)	57 (60)	56 (62)	40 (48)	0.077
Age at study (years)	-	19.2 [14.2-23.7]	29.2 [24.5-33.5]	39.6 [35.2-43.8]	-	-
Age at operation (years)	2.3 [0.5-6.9]	3.4 [0.6-7.1]	2.1 [0.6-6.5]	2.9 [0.5-6.5]	1.9 [0.5-7.1]	0.664
Age at operation <1 year	60 (34)	34 (32)	33 (35)	30 (33)	30 (36)	0.660
Pre-operative RV systolic pressure (mmHg)	70 [47-83]	69 [42-85]	68 [42-82]	68 [42-82]	70 [54-85]	0.371
Pre-operative Qp/Qs ratio	2.0 [1.7-2.8]	2.0 [1.7-2.8]	2.0 [1.7-2.9]	2.0 [1.7-2.8]	2.1 [1.6-2.8]	0.916
Type of VSD						
Perimembranous	134 (77)	91 (85)	78 (82)	74 (81)	60 (72)	0.157
Muscular	8 (5)	1 (1)	2 (2)	2 (2)	6 (7)	0.154
Nonisolated VSD	56 (32)	32 (30)	29 (31)	27 (30)	30 (36)	0.363
Previous PA banding	15 (9)	6 (6)	4 (4)	6 (7)	9 (11)	0.318
Hypothermia during surgery						
Temperature <20°C	70 (40)	38 (35)	37 (39)	33 (36)	37 (45)	0.285
Temperature 20-35°C	101 (58)	67 (63)	56 (59)	56 (62)	45 (54)	
Temperature unknown	3 (2)	2 (2)	2 (2)	2 (2)	1 (1)	
RV incision	82 (47)	56 (52)	46 (48)	46 (51)	36 (43)	0.344
VSD closure with patch	155 (89)	95 (89)	86 (91)	80 (88)	75 (90)	0.605
Postoperative arrhythmia < 30 days						
Tachyarrhythmia	10 (6)	5 (5)	4 (4)	4 (4)	6 (7)	0.522
Heart block	9 (5)	2 (2)	3 (3)	3 (3)	6 (7)	0.313
Cardiac arrest	3 (2)	-	-	-	3 (4)	-

Values are n (%) or median [interquartile range]. *Including deceased and emigrated patients. †2012 vs. no third study. PA = pulmonary artery; RV = right ventricular; VSD = ventricular septal defect.

tant cardiac lesions (nonisolated VSD), including patent foramen ovale (n=11), pulmonary stenosis (n=10), patent arterial duct (n=6), aortic coarctation (n=5), atrial septal defect (n= 4, of whom 2 had partial abnormal pulmonary venous return), mitral stenosis (n=2), and aortic stenosis (n=1). A patent foramen ovale was included as a concomitant lesion when an intervention was performed to close it. There were no discrepancies between assessments of the 2 evaluators regarding post-surgical events.

Survival

Information on survival was available for 156 patients (90%). Cumulative survival after surgical closure, including early post-operative mortality, was 89% at 10 years, 87% at 20 years, 85% at 30 years, and 78% at 40 years, which was significantly lower than in the general Dutch population of comparable age (Figure 2A). Thirty-one patients died, with 17 deaths occurring within 30 days of surgery. Cumulative survival after successful surgery, excluding early post-operative mortality, was 99% at 10 years, 96% at 20 years, 95% at 30 years, and 86% at 40 years, which was

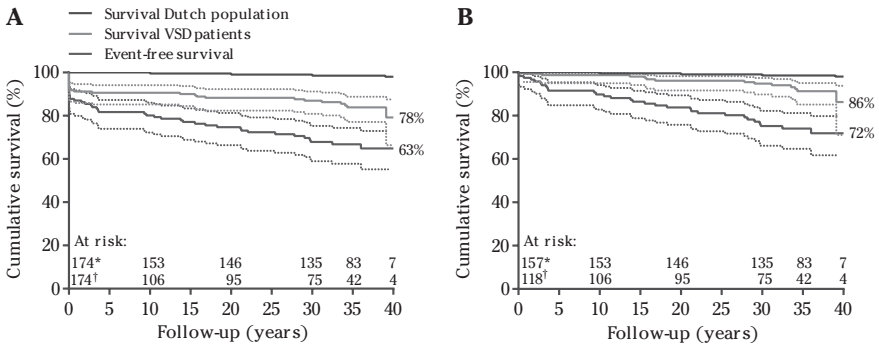


Figure 2 Cumulative survival and event-free survival of VSD patients with and without early post-operative mortality and events

Kaplan-Meier curves for survival and event-free survival of patients after surgical closure of ventricular septal defect (VSD), including early mortality and events within 30 days after surgery (A), and after exclusion of early mortality and events (B). Seventeen patients died within 30 days after surgery and 14 died during follow-up of the following causes: arrhythmia (n=4), heart failure (n=1), endocarditis (n=1), valvular surgery (n=1), pulmonary hypertension (n=1), noncardiac cause (n=4), and unknown (n=2). The dashed lines depict 95% confidence intervals. Survival curve of Dutch population represents survival from age 3 to 43 years. *Number of patients at risk for survival. †Number of patients at risk for event-free survival.

slightly lower than the general Dutch population (Figure 2B). Successful surgery was defined as the group without early post-operative mortality.

In the last 10 years, 8 patients died. One patient died of ventricular fibrillation 34 years after surgery at 34 years of age. He had received a pacemaker for SND 20 years earlier. One patient who had developed moderate aortic stenosis had sudden death, presumably due to an arrhythmia, 39 years after surgery at the age of 49 years. One patient died of heart failure as a result of severely dilated cardiomyopathy, 28 years after surgery, at the age of 28. There were 3 noncardiac deaths, attributable to breast cancer, lung cancer, and alcohol abuse 29, 33, and 31 years after surgery, respectively. The cause of death was unknown for 2 patients, who died 34 and 42 years after surgery, respectively.

Cumulative survival rates of isolated versus nonisolated VSD patients up to 39 years after surgery were comparable (93% vs. 88%) (Figure 3A).

Adverse events

Cumulative survival free of adverse events was 63% at 40 years (Figure 2A). When early post-operative mortality was excluded, event-free survival was 72% (Figure 2B). The event-free survival at 40 years was significantly better in isolated versus nonisolated VSD patients (79% vs. 57%, respectively) (Figure 3B).

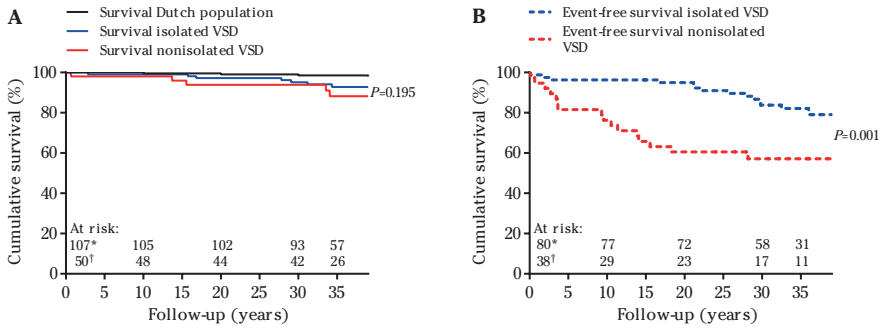


Figure 3 Cumulative survival and event-free survival of isolated and nonisolated VSD patients
Kaplan-Meier curves for survival (A) and event-free survival (B) of patients with isolated and nonisolated ventricular septal defect (VSD) (mortality, n=7/7; cardiac reintervention, n=2/12; arrhythmia, n=9/3; endocarditis, n=2/2; heart failure, n=3/1, respectively). Patients who died <30 days after surgery are excluded from this figure. *Number of isolated VSD patients at risk. †Number of nonisolated VSD patients at risk.

Reinterventions

Cumulative incidence of late reinterventions at 40 years of follow-up was 12% (Figure 4B). An overview of the reinterventions is summarized in Table 2.

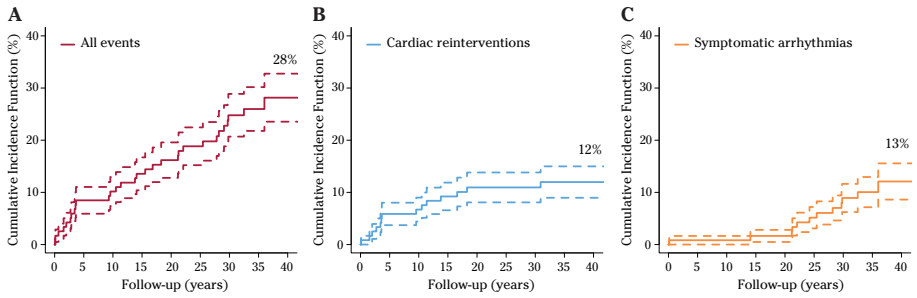


Figure 4 Cumulative incidence functions of events after exclusion of early post-operative mortality and events
Cumulative incidence function of all adverse events (A), surgical or catheter-based cardiac reinterventions (B), and symptomatic arrhythmias that required medication, cardioversion, ablation, or pacemaker/implantable cardioverter-defibrillator (C). Patients who died <30 days after surgery are excluded from this figure. The dashed lines depict 95% confidence intervals.

Arrhythmias

Cumulative incidence of late symptomatic arrhythmias including pacemaker implantation at 40 years was 13% (Figure 4C). In the last decade studied, 7 patients developed new symptomatic arrhythmias: 1 patient had recurrent atrial flutter and fibrillation, treated with electrical cardioversion and catheter ablation; 1

Table 2 Types of late cardiac reinterventions

First decade		**Second decade**	
Residual VSD	2	Resection aortic (re)coarctation	3
Resection pulmonary stenosis	2	Balloon dilation aortic (re)coarctation	2
Resection aortic coarctation	1	Residual VSD	1
Resection subvalvular aortic stenosis	1	Surgery for restenosis aortic valve	1
Closure patent ductus arteriosus	1	Aortic root replacement	1
False aneurysm ascending aorta	1	Aortic valve replacement	1
Closure sternal dehiscence	1	Pulmonary valve replacement	1
		Balloon dilation pulmonary stenosis	1
Third decade		**Fourth decade**	
Bentall procedure	1	Stenting aortic recoarctation	1
		Aortic valve replacement	1
		Mitral valve replacement	1

Information on late cardiac reinterventions (beyond 30 days after surgery) was available for 118 patients. Fourteen patients underwent one or more reinterventions. VSD = ventricular septal defect.

patient who had a pacemaker for 19 years had recurrent atrial fibrillation treated with electrical cardioversion; 1 patient had atrial fibrillation treated with verapamil; and 1 patient had paroxysmal atrioventricular reentrant tachycardia. The cumulative incidence of late pacemaker implantation, including ICD in 2 patients, was 7% at 40 years. In the last decade studied, 3 pacemakers were implanted: 1 for SND, 1 for severe bradycardia, and 1 for complete heart block. The last patient received a biventricular ICD because of ventricular tachycardias and diminished ejection fraction due to dilated cardiomyopathy. During total follow-up, 3 patients developed complete heart block.

Endocarditis

Cumulative incidence of late endocarditis at 40 years was 4%. During the last 10 years, 1 patient was diagnosed with pacemaker endocarditis caused by *Staphylococcus aureus*, which required treatment with antibiotic drugs and replacement of the pacemaker system.

Heart failure

Cumulative incidence of late heart failure at 40 years was 4%. During the last decade studied, 3 patients developed heart failure. One of them died during hospitalization, 1 was admitted to the hospital several times, and 1 was hospitalized for heart failure triggered by a pneumonia. One of these patients developed heart failure 9 years after epicardial pacemaker implantation, and 1 had diminished LV function before pacemaker implantation.

Electrocardiography and Holter monitoring

The ECG and Holter findings are summarized in Table 3. None of the patients had ventricular pauses longer than 3 s.

Cardiopulmonary exercise testing

Table 3 shows the results of bicycle ergometry. Of the 33 patients with a diminished exercise capacity (i.e., workload <85% of expected), 6 (18%) had 1 or more reinterventions compared with 1 (3%) in the group with normal exercise capacity (*P*=0.049). No differences were found with regard to current age, surgical characteristics, isolated versus nonisolated VSD, QRS duration, or ventricular function.

Table 3 Standard 12-lead and 24-h Holter electrocardiogram, bicycle ergometry and echocardiography

	1990	2001	2012	*P*-value
Electrocardiography	**n=107**	**n=95**	**n=79**	
Rhythm				
Sinus	104 (97)	86 (91)	72 (91)	<0.001
Atrial	1 (1)	2 (2)	2 (3)	0.430
Nodal	1 (1)	3 (3)	1 (1)	0.816
Pacemaker	1 (1)	4 (4)	4 (5)	0.102
Atrial flutter	0	0	0	-
PR interval (ms)*	148 ± 29	151 ± 28	159 ± 30	<0.001
PR ≥200 ms	5 (5)	7 (8)	6 (8)	0.287
QRS duration (ms)†	101 ± 21	113 ± 27	117 ± 27	<0.001
QRS duration ≥120 ms	26 (25)	29 (32)	25 (33)	0.306
QRS duration ≥180 ms	0	2 (2)	1 (1)	0.405
24-hour Holter	**n=103**	**n=92**	**n=68**	
Supraventricular arrhythmias	21 (20)	25 (27)	25 (37)	0.024
Sinus node disease	21 (20)	8 (9)	4 (6)	0.003
SVT	0	19 (21)	22 (32)	<0.001
Paroxysmal atrial fibrillation	0	0	1 (1)	-
Paroxysmal atrial flutter	0	0	0	-
VT 3-10 complexes	6 (6)	2 (2)	3 (4)	0.492
VT >10 complexes	0	0	0	-
Bicycle ergometry	**n=103**	**n=93**	**n=69**	
Maximal heart rate (%)	89 ± 9	88 ± 10	88 ± 12	0.013
Maximal workload (%)	94 ± 19	91 ± 24	87 ± 19	0.003
Workload <85%	30 (29)	37 (40)	33 (48)	0.009
Arrhythmias	5 (5)	10 (11)	5 (7)	0.464
Peak VO_2 (%)	-	-	87 ± 20	-

Table 3 Standard 12-lead and 24-h Holter electrocardiogram, bicycle ergometry and echocardiography (continued)

	1990	2001	2012	*P*-value
Echocardiographic parameters	**n=107**	**n=95**	**n=76**	
LA end-systolic dimension (mm)	32 ± 5	37 ± 6	38 ± 6	0.003
LV end-systolic dimension (mm)	32 ± 5	34 ± 5	33 ± 6	0.464
LV end-diastolic dimension (mm)	49 ± 6	52 ± 5	50 ± 6	0.255
LV fractional shortening (%)	34 ± 6	34 ± 7	35 ± 8	0.647
Fractional shortening <30%	19 (18)	24 (25)	19 (25)	0.256
LV posterior wall dimension (mm)	9 ± 2	10 ± 2	8 ± 2	0.594‡
Aorta end-diastolic dimension (mm)	30 ± 5	33 ± 5	33 ± 5	<0.001
Aortic valve regurgitation				
None-trace	95 (89)	79 (83)	59 (79)	0.039§
Mild-moderate	12 (11)	16 (17)	16 (21)	
Severe	0	0	0	
Mitral valve regurgitation				
None-trace	91 (87)	84 (88)	69 (92)	0.249§
Mild-moderate	14 (13)	11 (12)	6 (8)	
Severe	0	0	0	
Pulmonary valve regurgitation				
None-trace	81 (78)	68 (72)	66 (89)	0.108§
Mild-moderate	23 (22)	27 (28)	7 (10)	
Severe	0	0	1 (1)	
Tricuspid valve regurgitation				
None-trace	63 (62)	41 (43)	40 (53)	0.151§
Mild-moderate	38 (38)	54 (57)	34 (46)	
Severe	0	0	1 (1)	

Values are n (%), or mean ± SD. *Atrial, nodal, and pacemaker rhythm were excluded from analysis. †Pacemaker rhythm was excluded from analysis. ‡Significance test was based on log-transformed values. §Significance test was based on binary variables (none–trace vs. mild–severe).
LA = left atrium; LV = left ventricular; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Echocardiography

Echocardiographic findings are summarized in Tables 3 and 4. Systolic LV function was mildly impaired in 11 patients (14%), moderately impaired in 3 (4%), and severely impaired in 2 (3%). The percentage of patients with impaired systolic LV function was 14% in 2001 and 21% in 2012 (*P*=0.180). Normal diastolic LV function was observed in 63 patients (89%), pseudonormal diastolic function in 6 (8%), and restrictive relaxation pattern in 2 (3%). Systolic RV function was mildly impaired in 10 patients (13%) and moderately impaired in 3 (4%). The percentage of patients with impaired systolic RV function increased significantly over the last decade of study from 1% to 17% (*P*=0.001). Patients with impaired systolic RV function more often had an elevated estimated RV systolic pressure than patients with normal

Table 4 Results of additional diagnostic tests performed only in 2012

Parameter	n	Median	IQR	Abnormal, n (%)*
LVEF (%)	38	54	[49-61]	9 (24)
E/A ratio	72	1.3	[1.1-1.7]	2 (3)
E/E' ratio	71	8.5	[6.3-10.0]	5 (7)
Deceleration time (ms)	72	185	[158-218]	20 (28)
RV basal dimension (mm)	65	40	[34-46]	26 (40)
RV longitudinal dimension (mm)	64	77	[69-84]	12 (19)
TAPSE (mm)	61	19	[18-22]	3 (5)
RV fractional area change (%)	49	40	[37-43]	7 (14)
Estimated RV systolic pressure (mmHg)	53	28	[24-35]	10 (19)

*According to the reference values in the guidelines.[9,10] Right ventricular dimensions were measured during end-diastolic phase. IQR = interquartile range; LVEF = left ventricular ejection fraction; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

systolic RV function (42% vs. 12%, *P*=0.036), more often had a pacemaker (23% vs. 3%, *P*=0.033), and more often had impaired systolic LV function (69% vs. 11%, *P*<0.001). Diastolic LV function did not differ significantly between patients with impaired or normal systolic RV function. There were no significant differences in systolic biventricular function between patients with isolated and nonisolated VSD, with and without RV incision, or with and without VSD patch.

The percentage of patients with mild or moderate aortic regurgitation increased significantly over the last 20 years from 11% in 1990 to 21% in 2012 (*P*=0.039).

NT-proBNP measurement

NT-proBNP was measured in 68 patients. The median level was 11.6 pmol/l (IQR: 7.0 to 19.8 pmol/l), with an elevated level (>14.0 pmol/l) measured in 26 patients (38%). The highest value was 56.5 pmol/l, measured in a woman with an isolated VSD, in sinus rhythm, and without clinical signs of heart failure. Median NT-proBNP was comparable between patients with an isolated VSD (n=50) and those with a nonisolated VSD (n=18; 11.2 pmol/l [IQR: 6.9 to 18.4 pmol/l] vs. 14.3 pmol/l [IQR: 6.8 to 28.1 pmol/l], *P*=0.436). Patients with impaired systolic RV function (n=8) tended to have a higher NT-proBNP than patients with normal RV function (n=59; 16.2 pmol/l [IQR: 12.9 to 26.6 pmol/l] vs. 11.1 pmol/l [IQR: 6.4 to 19.5 pmol/l], *P*=0.063). No relationships were found with systolic LV function, ventricular dimensions, age at operation, current age, or exercise capacity.

Subjective health status assessment

Seventy-four patients completed the SF-36 health survey. The results are depicted in Figure 5. Patients obtained significantly better scores than the reference popula-

tion on all scales except for general health perceptions, which were comparable (P=0.089). The patients' results were comparable with their own results 10 years earlier, except for mental health, which they now rated better (85 ± 13% vs. 80 ± 11%, P=0.030).

Determinants of clinical outcome

Higher pre-operative systolic RV pressure tended to be a determinant of mortality (hazard ratio [HR]: 1.02; 95% confidence interval [CI]: 1.00 to 1.04). Univariable regression analyses identified nonisolated VSD, early post-operative arrhythmias, and aortic cross-clamp time as determinants of late events, including mortality. In multivariable regression analysis with these determinants, patients with non-isolated VSD or patients with longer aortic cross-clamp time had higher risk for events (HR: 2.84 [95% CI: 1.23 to 6.53]; HR: 1.47 per 10 min [95% CI: 1.22 to 1.99 per 10 min], respectively). Early postoperative arrhythmias showed a trend toward predicting later events (HR: 2.59 [95% CI: 0.92 to 7.29]). Patients with a complete heart block in the early post-operative period more often developed symptomatic arrhythmias during follow-up (HR: 9.7 [95% CI: 2.1 to 44.6]). No other baseline characteristics were significant determinants of outcome.

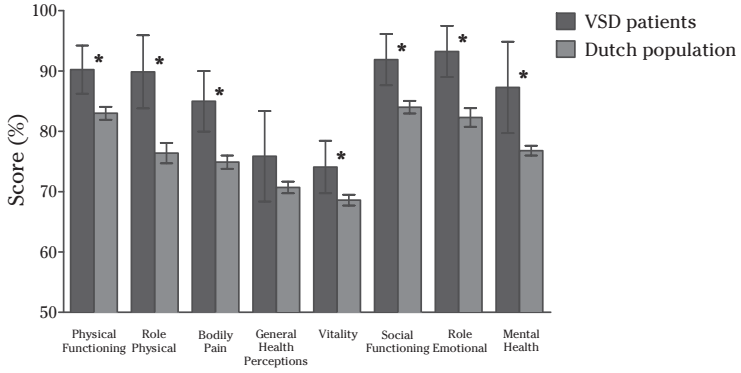


Figure 5 Results of SF-36 for VSD patients and the reference Dutch population
Higher scores represent more favorable subjective health status. A high score on the bodily pain scale indicates subject was free from pain. Error bars show 95% confidence interval. *P <0.01. SF-36 = 36-item short-form health survey; VSD = ventricular septal defect.

DISCUSSION

In this unique longitudinal cohort study of VSD patients who underwent surgical repair at a young age, survival up to 40 years was relatively good but lower than in the general Dutch population. Although morbidity was substantial, especially among patients with nonisolated VSD, the reported subjective health status was even better than normative data.

Mortality and adverse events

Cumulative survival 40 years after surgical VSD closure was 78% in our cohort. One-half of these deaths occurred within 30 days after surgery. Currently, pulmonary artery banding is performed only rarely, and advances in surgical and anesthesiology techniques and improvements in peri-operative care have greatly reduced peri-operative mortality.[14] In addition, the care during follow-up is better organized today. Therefore, these early results are not applicable to patients who have undergone surgery in more recent years. With the exclusion of in-hospital operative mortality, however, cumulative survival in our cohort was 86% at 40 years, which was still slightly lower than in the general population. In more than one-half of the cases, late mortality was cardiac related: cardiac arrest/sudden death, reoperation, and heart failure (Central Illustration).

Cumulative survival was similar between patients with isolated and nonisolated VSD. Morbidity was higher in patients with nonisolated VSD and was dominated by reinterventions for concomitant lesions, for example, aorta-related problems or pulmonary stenosis.

Health status and ventricular function

Most of our patients rated their physical functioning better than the reference population; however, their maximal workload at exercise testing was clearly lower than the reference population, with almost one-half of the patients having a diminished maximal workload. Furthermore, the maximal workload decreased over the last decades studied. The median peak V_{O_2} of 87% in our study population was a bit higher than the 73% in the study by Kempny *et al.*[15] This difference could probably be explained by the fact that they included patients who underwent exercise testing as part of their ongoing outpatient care, whereas our study included many patients who had been discharged from routine clinical follow-up.

The occurrence of aortic regurgitation appears to be an important issue after VSD surgery. In our cohort, 1 patient developed severe aortic regurgitation that necessitated aortic valve replacement, and in the other patients, the prevalence

of aortic regurgitation nearly doubled over the last 20 years of the study, from 11% in 1990 to 21% in 2012.

Systolic LV function remained stable over the last decade of study, but impaired systolic RV function increased. In our cohort, systolic RV dysfunction was not related to VSD patch or RV incision, but the vast majority of patients with systolic RV dysfunction had systolic LV dysfunction and more often had elevated RV systolic pressure. This relationship between RV and LV dysfunction could be explained in part by the presence of a pacemaker in a quarter of patients with RV dysfunction or by systolic ventricular interaction. In the case of systolic LV dysfunction, pulmonary pressure increases, which results in reduction of RV contractility. Moreover, ventricular interaction is mediated by forces at the interventricular septum and mechanical coupling through shared myocardial fibers: When the LV becomes more spherical, the fibers of the interventricular septum become less oblique, which reduces and impairs RV contractile function.[16,17] Systolic ventricular interaction is also observed in other congenital heart defects.[18,19] Another explanation for the higher prevalence of RV dysfunction over time may be the use of a more sophisticated echocardiographic assessment to facilitate the detection of dysfunction. Using tissue Doppler imaging, Klitsie *et al*.[20] found a systolic RV impairment up to 20 months after surgical VSD closure in children. Although subclinical RV impairment may not be of direct clinical relevance, it could be a first sign of systolic RV dysfunction and does stress the importance of detailed evaluation of RV function after VSD surgery.

NT-proBNP levels were elevated in more than one-third of the patients. This is striking, because the majority of patients were asymptomatic and had normal systolic biventricular function. No studies were found in the published data on BNP levels in adults after surgical VSD closure, and only a few in children,[21] which reported mildly increased levels. Prospective studies are necessary to elucidate the prognostic value of BNP in these patients.

Arrhythmias

In the last 10 years of the study, 4 patients developed supraventricular arrhythmias, and 3 required pacemaker implantation. Cumulative incidence of late symptomatic arrhythmias at 40 years was 13%. This was much lower than the incidence after surgical VSD closure at adult age[22] but higher than in patients who underwent surgery after 1980.[14,23] The incidence of arrhythmias after surgical closure of an atrial septal defect at young ages is higher.[24]

Recently, interest has been generated in development of percutaneous techniques to close VSDs; however, this technique is not implemented in routine clinical practice and has even ceased in most clinics because of the high rate of

post-procedural heart block (up to 8%).[4,25] This is higher than the incidence in our cohort after surgical closure at a young age (3%), as well as at an adult age.[22,23]

Subjective health status assessment

A remarkable finding of the SF-36 results was that patients reported a more favorable functioning than the reference Dutch population on 7 of the 8 scales and comparable functioning on 1 scale (general health perceptions). These propitious results for VSD patients may be attributable to different frames of reference than the normal population, more adequate coping with the disadvantageous consequences of the congenital heart defect at advanced age, overcompensation, or social desirability.[26]

Determinants of clinical outcome

Although numbers in our study were relatively small, patients with early post-operative arrhythmia tended to develop more late events. In another cohort of patients with surgically repaired VSD, transient and complete heart blocks were a risk factor for latemortality.[27] In that study, a substantial percentage of deceased patients had not received a pacemaker because either pacemakers had not been developed at that time or they were only newly available. The relation between early post-operative arrhythmias and arrhythmias during follow-up was also described after surgery at young age for other congenital heart defects.[24,28] The relation may be explained by surgical damage to the conduction system or by post-operative scar tissue and fibrosis. Early arrhythmias might therefore reveal patients at risk for late complications.

A simple concomitant cardiac lesion and longer aortic cross-clamp time during surgery were determinants of late events. The fact that patients with a concomitant cardiac lesion have a greater risk of events appears directly related to the relatively higher number of reinterventions in this group.

Study limitations

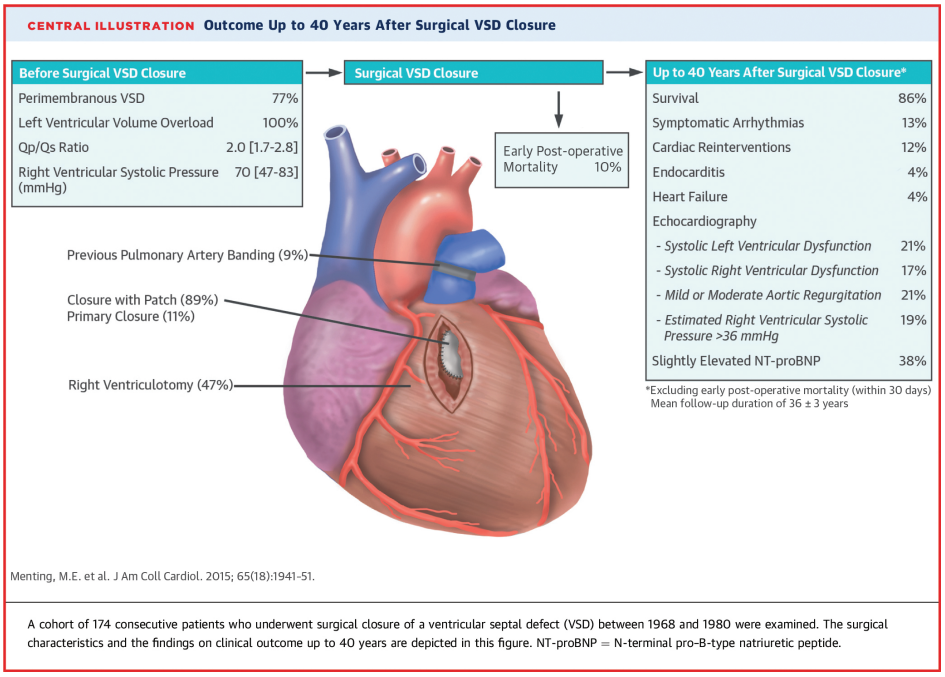
Although the number of patients was relatively small, we report results of a longitudinal follow-up of consecutive patients without selection bias related to disease severity. After a median follow-up of 36 years, we gathered medical information on 84% of the eligible patients. We found no significant differences in baseline characteristics between participating and nonparticipating patients. Therefore, we believe that we have minimized selection bias.

Diagnostic methods have changed over time. For comparisons of echocardiographic data with previous studies, we had to use the same methods as were used in the past, which may not be considered current state of the art. However, we also

performed and reported innovative diagnostic methods available in the current era.

CONCLUSIONS

Survival up to 40 years after successful surgical VSD closure is good but slightly lower than in the general Dutch population. Although many patients have been discharged from routine follow-up at outpatient clinics, morbidity is substantial, especially in patients with nonisolated VSD. There is concern about systolic LV and RV dysfunction, which were observed in 21% and 17% of patients, respectively, and about occurrence of aortic regurgitation, which almost doubled over the last 20 years of the study. Early postoperative arrhythmia is a borderline determinant and aortic cross-clamp time a significant determinant of late events. Therefore, clinical follow-up with long intervals seems advisable. Despite the reported morbidity, the subjective health status is excellent.



Central illustration. Outcome up to 40 years after surgical VSD closure

ONLINE SUPPLEMENT

Additional information on statistical analysis

Changes in patient characteristics since the follow-up study in 1990 and 2001 were evaluated by estimating a trend using mixed models which take missing values into account. For the continuous variables, a trend was estimated using linear mixed models. When the distribution of the variables deviated from normality, log-transformations were applied. For the binary variables, generalized linear mixed models were estimated with a logit-link function. The variables with three categories (aortic, mitral, pulmonary and tricuspid regurgitation) were recoded as binary variables (none-trace vs. mild-severe).

Univariable and multivariable Cox regression analyses were used to identify determinants of the predefined adverse events: all-cause mortality, arrhythmias, reinterventions, heart failure and endocarditis. The following baseline characteristics were included as determinants in the analyses: non-isolated VSD, age at repair, era of repair, preoperative systolic RV pressure, pulmonary-systemic flow ratio, preoperative palliation, temperature during surgery, RV incision, early postoperative arrhythmias, and aortic cross-clamp time. Baseline characteristics that turned out to be significant in the univariable Cox regression analysis, were implanted in the multivariable Cox regression model. For every ten events, one characteristic could be implemented in the multivariable Cox regression model.

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CHAPTER 9

The unnatural history of an atrial septal defect: Longitudinal 35 year follow up after surgical closure at young age

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ABSTRACT

Objective

To describe the very long-term outcome after surgical closure of an atrial septal defect (ASD).

Design

Longitudinal cohort study of 135 consecutive patients who underwent surgical ASD repair at age <15 years between 1968 and 1980. The study protocol included ECG, echocardiography, exercise testing, N-terminal prohormone of brain natriuretic hormone, Holter monitoring and cardiac MRI.

Main outcome measures

Survival, major events (cardiac reinterventions, stroke, symptomatic arrhythmia or heart failure) and ventricular function.

Results

After 35 years (range 30–41), survival status was obtained in 131 of 135 patients (97%): five died (4%), including two sudden deaths in the last decade. Fourteen patients (16%) had symptomatic supraventricular tachyarrhythmias and six (6%) had a pacemaker implanted which was predicted by early postoperative arrhythmias. Two reoperations were performed. One ischaemic stroke occurred. Left ventricular (LV) and right ventricular (RV) ejection fractions (EF) were 58 ± 7% and 51 ± 6%, respectively. RVEF was diminished in 17 patients (31%) and in 11 (20%) the RV was dilated. Exercise capacity and quality of life were comparable to the normal population. No clear differences were found between ASD-II or sinus venosus type ASD.

Conclusions

Very long-term outcome after surgical ASD closure in childhood shows good survival and low morbidity. Early surgical closure prevents pulmonary hypertension and reduces the occurrence of supraventricular arrhythmias. Early postoperative arrhythmias are predictive for the need for pacemaker implantation during early follow-up, but the rate of late pacemaker implantation remains low. Although RVEF was unexpectedly found to be decreased in one-third of patients, the functional status remains excellent.

INTRODUCTION

While transcatheter closure with a device is the current method of choice for correction in patients with a suitable atrial septal defect (ASD), surgical closure was first choice treatment until the 1990s and is still the only treatment for large and non-centrally located defects. After successful operation at a young age, the natural history of patients with ASD improved dramatically with life expectancy similar to that of the general population.[1-3]

The retrospective study of Murphy *et al.*[1] was the first to demonstrate the benefits of early surgical closure. The incidence of postoperative atrial arrhythmias appeared to be related to the age of the patient at the time of repair. Benefits of closure in childhood have been confirmed by others,[3-7] although persistent ventricular dilation has been reported in some but not all studies.

Early and mid-term follow-up of transcatheter ASD closure shows excellent results.[8] For a comparison of both closure techniques, information on outcome beyond 30 years is crucial.

The aim of the present study was to provide data on mortality, morbidity and ventricular function up to 40 years after surgery. The investigation is based on a unique longitudinal cohort of consecutively operated patients who we examine in hospital every 10 years using the same protocol.

METHODS

Study population

All patients who underwent surgical closure of secundum (ASD-II) or sinus venosus type ASD in our institution between 1968 and 1980 at an age <15 years were included in this study. The first follow-up study was performed in 1990, the second in 2000–2001 and the current third study in 2010–2011. Detailed information on the surgical procedure and earlier results have been published previously.[3,5] Current patient survival status was obtained from the Dutch National Population Registry. All living patients who participated in one or both of the earlier studies were approached for participation in the current study. The in-hospital cardiac examination included medical history, physical examination, standard 12-lead ECG, 24-h ambulatory ECG (Holter), echocardiography, bicycle ergometry with oxygen consumption measurement, N-terminal prohormone of brain natriuretic hormone (NT-proBNP), cardiac MRI (CMR) and the 36-item Short Form Health Survey (SF-36) questionnaire. If the patient was unwilling or unable to visit the

clinic, a written questionnaire was sent to obtain information on morbidity and permission to use available information from their medical records.

Major events

Survival was compared with that of the normal age-matched Dutch population. Major events were defined as cardiac reinterventions, stroke, symptomatic arrhythmia, heart failure or endocarditis. Arrhythmias were defined as symptomatic if antiarrhythmic medication was prescribed, cardioversion or catheter-based or surgical ablation had been applied, or pacemaker implantation was performed.

ECG and Holter monitoring

Standard 12-lead surface ECGs and Holter recordings were analysed as described previously.[3] ECGs with pacemaker rhythm were excluded for comparison of conduction times. Heart rate variability (HRV) was compared with that of 10 years earlier using the SD of all normal RR intervals (SDNN).

Echocardiography

Complete two-dimensional (2D) and colour flow Doppler imaging as well as pulsed-wave and continuous-wave Doppler echocardiography was performed using an iE33 xMATRIX X5-1 echocardiograph (Philips Medical Systems, Best, The Netherlands). All up-to-date techniques and definitions were used following the current guidelines.[9-15] For right ventricular (RV) function the following parameters were used: fractional area change (FAC) (normal if ≥35%), S′ of the tricuspid annulus (normal if ≥10 cm/s) and tricuspid annular plane systolic excursion (TAPSE) (normal if ≥16 mm). For left ventricular (LV) function, 2D ejection fraction (EF) according to the Simpson rule was obtained. For comparison with the two previous studies, ventricular function was also assessed visually. Dilation was defined as left atrial (LA) dimension >45 mm and LV end-diastolic dimension >58 mm.[3,5]

Bicycle ergometry

Maximal exercise capacity and peak oxygen consumption (peak V_{O_2}) were assessed by bicycle ergometry with gradual increments of workload of 20 Watts/min. Exercise capacity and peak V_{O_2} were compared with that of normal individuals corrected for age, gender, body height and weight. Exercise capacity and peak V_{O_2} <85% of the predicted value were considered to be decreased. Performance was considered maximal when a respiratory quotient (RER) of ≥1.1 was reached.

NT-proBNP

After a 30 min rest, venous blood samples were collected for determination of NT-proBNP. Standard kits to determine NT-proBNP levels were used (Roche Diagnostics, Basel, Switzerland) with a cut-off value for elevation of 14 pmol/L.[16]

CMR imaging

CMR imaging was performed using a Signa 1.5 Tesla whole body scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) using dedicated phased-array cardiac surface coils. Details of the MR sequence used have been reported previously.[17] For CMR analysis, a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass (V.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), SV, EF and the regurgitation fractions of the valves were calculated. The results were compared with reported normal values: RVEF ≤49% and LVEF ≤54% were considered decreased and RV EDV >107.5 mL/m^2, RV ESV >47.2 mL/m^2, LV EDV >102.5 mL/m^2 and LV ESV >38.7 mL/m^2 were considered enlarged.[18]

Health status assessment and family history

The results of the SF-36 questionnaire were compared with those in the normal Dutch population.[19] Patients were also asked for the presence of a congenital heart defect in one of their first- or second-degree relatives.

Statistical analysis

Continuous data are presented as mean ± SD unless indicated otherwise. Categorical variables are represented by frequencies and percentages. Comparison of continuous variables between independent groups was made by Student *t*-tests. In the case of a skewed distribution in paired groups, the Wilcoxon signed rank test was performed. When comparing frequencies, the χ^2 test or Fisher exact test was used where applicable, and for paired categorical data the McNemar test. For quantifying associations between two variables the Pearson correlation test was applied. Univariate and multivariate analysis of predictors of survival and major events was performed with the Cox proportional hazards model. A priori the following variables were selected: age at operation, ASD subtype, preoperative shunt size, cardiopulmonary bypass time and postoperative arrhythmia. HRV in 2001 was tested as a predictor for arrhythmias thereafter. The probability of survival and event-free survival over time was displayed as a Kaplan–Meier plot. The level of significance was chosen at $P<0.05$ (two-sided).

RESULTS

Survival

Information on survival status was obtained in 131 of the 135 patients. Four patients were lost to follow-up before 2001. During the total follow-up period, five patients died (4%). Two patients (both ASD-II) were found dead in bed 28 and 36 years after surgery. In neither of the patients was an autopsy performed. One of them had complained of palpitations 2 weeks before he died but he had not consulted a physician. The other was known to have diminished LV function attributed to longstanding RV pacing. Both patients had no risk factors for coronary disease. The other three patients died from non-cardiac causes (cancer in two, suicide in one). Cumulative survival after ASD surgery was 100% after 10 and 20 years, 98% after 30 years and 91% after 40 years (Figure 1). This is comparable to the normal Dutch population.20 Survival in the ASD-II and sinus venosus subgroups was not significantly different.

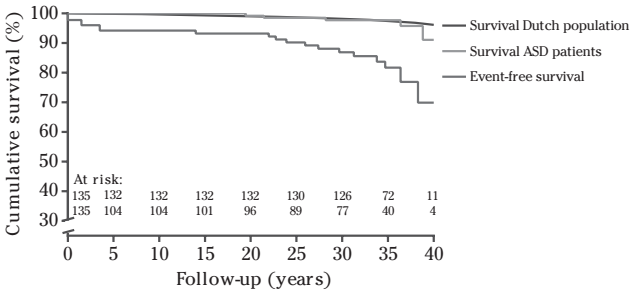

Figure 1 Survival and survival free of major events (defined as reoperation, arrhythmia, heart failure, endocarditis, pacemaker implantation, hospitalisation and death).
All-cause mortality, n=5; cardiac surgery, n=2; stroke, n=1; symptomatic arrhythmia, n=16. Survival of the normal population is shown from the age of 7.5 years, the mean age at operation of the cohort. ASD, atrial septal defect.

Study population

The original study cohort consisted of 135 patients (105 ASD-II and 30 sinus venosus type). Table 1 demonstrates their characteristics. Age at operation was 7.5±3.5 years (range 0–14). There was no in-hospital or early mortality. Of the 105 eligible patients (alive and participating in the earlier studies), 85 (81%) agreed to participate in the third follow-up study after a mean follow-up of 35 years (range 30–41). Of the 21 patients with sinus venosus defect, 19 had an anomalous pulmonary venous drainage; one patient had a persistent left superior caval vein.

Table 1 Patient characteristics

	Total	1990	2001	2011
Number of patients	135	104	94	85
Men, n (%)	59 (44)	44 (42)	39 (41)	33 (39)
Cardiac catheterization at diagnosis				
QP-QS ratio	2.3:1	2.3:1	2.3:1	2.3 ± 0.7
Peak systolic PA pressure, mmHg	26	26	26	26 ± 7
Surgical data				
Age at operation, years	7.5 ± 3.5	7.3	7.5	7.4 ± 3.5
Mode of closure				
Direct closure	76%	75%	75%	72%
Closure with patch	24%	25%	25%	28%
Sinus venosus type	22%	22%	23%	25%
Follow-up since surgery, years		15 (10-22)	26 (21-33)	35 ± 2.7(range 30-41)
Age at the time of study, years		22	33	43 ± 4.8 (range 32-54)

Major events

Event-free survival is plotted in Figure 1.

Reinterventions

Before 2001 one additional operation was performed for closure of a patent arterial duct. Between 2001 and 2011, one cardiac reoperation was necessary for symptomatic mitral valve regurgitation. Both operations were in patients with ASD-II.

Arrhythmia

Until 2001, 10 patients had symptomatic arrhythmias and, in the last 10 years, six additional patients developed symptomatic arrhythmias. One showed frequent symptomatic sinus arrests necessitating permanent pacemaker implantation. Three were treated medically for atrial flutter (n=1) or atrial fibrillation (n=2), one needed electrical cardioversion for atrial flutter and afterwards underwent catheter ablation and one patient was treated medically for supraventricular tachycardia (SVT). During the total follow-up period 16% of the patients developed symptomatic arrhythmias.

Heart failure

None of the patients developed heart failure.

Stroke

An ischaemic stroke occurred in one patient with sinus venosus type ASD. No evidence of residual shunt or arrhythmia was found.

ECG and Holter monitoring

Twelve-lead ECG data are presented in Table 2. Atrial flutter was found in two patients, of whom one was new. The QRS duration increased significantly during the last 10 years, but only one new case of right bundle branch block was found.

On the 24-h Holter no sustained ventricular tachycardia (VT) was found in 1990, 2001 or 2011 (Table 2). There was a trend towards more supraventricular arrhythmias over time. Atrioventricular (AV) conduction disturbances were observed in nine patients.

Heart rate variability

The mean SD of all normal RR intervals (SDNN) was 166.7 ± 57.9 ms in 2001 and 143.4 ± 42.0 ms in 2011 (P=0.2). There was no difference in HRV between patients with ASD-II and sinus venosus types.

Echocardiography

Echocardiographic findings are summarised in Tables 2 and 3. No residual shunts were found. A normal diastolic LV function was observed in 88% of patients, mild abnormal relaxation in 9% and pseudonormal diastolic filling in 3%. TAPSE was decreased in 22% of the patients, FAC was reduced in 10% and S′ was diminished in 43%. Comparing patients with ASD-II and sinus venosus defects, there were no significant differences except that S′ and TAPSE were significantly lower in patients with sinus venosus type whereas RV FAC was higher.

Table 2 Standard 12-lead electrocardiogram, 24-h Holter, bicycle ergometry and echocardiographic parameters in 1990, 2001 and 2011

				P-value*	
	1990	**2001**	**2011**	**2011 vs 1990**	**2011 vs 2001**
ECG					
Rhythm					
Sinus	93 (89%)	82 (89%)	63 (89%)	0.6	1.0
Atrial	6 (6%)	5 (5%)	3 (4%)	-	1.0
Nodal	1 (1%)	1 (1%)	0	-	-
Atrial flutter	0	1 (1%)	2 (3%)	-	1.0
Pacemaker	4 (4%)	3 (3%)	3 (4%)	0.5	1.0
PR interval	154	153	161	**0.002**	**<0.001**
PR >200 ms	3%	5%	9%	-	0.06

Table 2 Standard 12-lead electrocardiogram, 24-h Holter, bicycle ergometry and echocardiographic parameters in 1990, 2001 and 2011 (continued)

				P-value*	
	1990	**2001**	**2011**	**2011 vs 1990**	**2011 vs 2001**
QRS duration, ms	88.3	96.1	100.4	**<0.001**	**0.001**
QTc segment, ms	388	388	400	**<0.001**	**<0.001**
LVH or RVH	4.1%	4.6%	1.4%	1.0	1.0
24-hour Holter					
Supraventricular arrhythmias	44 (45%)	36 (41%)	39 (57%)	0.2	0.6
Sinus node disease	38 (39%)	27 (31%)	16 (24%)	0.3	0.5
SVT	6 (6%)	18 (21%)	30 (44%)	**<0.001**	0.06
Paroxysmal A fibrillation	0	0	0	-	-
Paroxysmal A flutter	0	1 (1%)	0	-	-
Continuous A flutter	0	1 (1%)	1 (2%)	-	1.0
VT 3-10 complex	3 (3%)	4 (5%)	4 (6%)	1.0	1.0
VT >10 complex	0	0	0	-	-
Conduction disturbances	17 (17%)	8 (9%)	10 (15%)	1.0	0.2
First degree AV block	14 (14%)	8 (9%)	7 (10%)	0.8	0.7
Second AV block	2 (2%)	0	2 (3%)	1.0	-
Third AV block	0	0	0	-	-
Bicycle ergometry					
Maximum heart rate (% of expected)	92%	92%	90%	0.6	0.5
Maximum exercise capacity (% of expected)	104%	95%	96%		-
Significant arrhythmia	0	0	0		-
Peak V_{O_2} (% of expected)	-	-	96%		-
RER max	-	-	1.3		-
Echocardiography					
RA dilation	5.8%	18.7%	23.5%	0.007	0.8
RV dilation	26.0%	23.5%	34.3%	0.2	0.5
LA dilation	1.0%	12.2%	15.7%	0.008	0.7
LV dilation	4.0%	8.8%	2.9%	1.0	0.1
LV systolic function normal	97.1%	95.5%	95.5%	0.6	1.0
RV systolic function normal	100%	100%	67.2%	-	**<0.001**
Valve insufficiency (>trace)					
AoI	0%	1.1%	2.9%	-	-
MI	11.5%	13.5%	20.0%	0.8	0.1
PI	44.2%	45.0%	55.7%	**<0.02**	**<0.02**
TI	42.3%	48.3%	57.1%	1.0	0.7
Vmax PI, m/s	1.6	1.5	1.7	0.7	0.8
Vmax TI, m/s	2.1	2.2	2.3	**0.03**	**0.03**

*Because of incomplete follow-up (paired) data, not all *P*-values are displayed.
AoI, aortic insufficiency; AV, atrioventricular; LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; MI, mitral insufficiency; PI, pulmonary insufficiency; RA, right atrium; RER, respiratory exchange ratio; RV, right ventricle; RVH, right ventricular hypertrophy; SVT, supraventricular tachycardia; TI, tricuspid insufficiency; Vmax, maximal velocity found with Doppler echocardiography; peak V_{O_2}, peak consumption (not performed in 1990/2001); VT, ventricular tachycardia.

Table 3 Echocardiographic parameters 2011

	ASD-II	Sinus venosus defect	*P*-value
Left ventricle			
E/A ratio	1.3 ± 0.4	1.3 ± 0.4	0.99
E/E' ratio	8.4 ± 5.0	8.5 ± 3.4	0.95
DET (ms)	226 ± 46	224 ± 49	0.94
LVEF Simpson (%)	56 ± 5	57 ± 9	0.56
Right ventricle			
TAPSE (mm)	19 ± 4	16 ± 2	<0.01
RV pressure (mmHg)	27 ± 5	26 ± 4	0.60
FAC (%)	43 ± 9	53 ± 7	<0.01
S' (mm)	11 ± 2	9 ± 2	<0.01

ASD, atrial septal defect; DET, deceleration time; E/A ratio, ratio early filling velocity on transmitral Doppler/late filling; E/E0 ratio, ratio early filling velocity on transmitral Doppler/early relaxation velocity on tissue Doppler; FAC, fractional area change of right ventricle; LVEF Simpson, left ventricular ejection fraction according to modified Simpson rule; RV, right ventricle; S′, tricuspid annulus maximal systolic tissue Doppler velocity; TAPSE, tricuspid annular plane systolic excursion.

Bicycle ergometry

The results of exercise testing in 1990, 2001 and 2011 are listed in Table 2. Eighteen patients (27%) had a diminished exercise capacity at last follow-up. Mean peak VO_2 was 96 ± 25% (range 60–194%). One-third had a mean peak VO_2 of <85%, one-third 85–100% and one-third performed >100%. The threshold RER of 1.1 was reached in 97%. Patients with reduced exercise capacity or peak VO_2 did not differ significantly from those with a normal test result with regard to preoperative shunt size, age at the time of operation or findings by echocardiography or CMR (dimensions and ventricular function). There were no significant differences between patients with ASD-II and sinus venosus defects but there was a trend towards a better workload in the patients with sinus venosus type ASD (P=0.07).

NT-proBNP

An increased NT-proBNP level (>14.0 pmol/L) was present in 53% of the patients. Values varied from 1.5 to 116 pmol/L with a mean of 15.0 pmol/L. No correlation between NT-proBNP and age, age at surgery, ASD type or LV and RV dimensions or function was found.

CMR imaging

CMR was performed in 57 patients. Reasons for not having a CMR investigation were patients' refusal, prematurely ended because of claustrophobia and two patients had a pacemaker. One study could not be analysed due to technical problems. The results of CMR are summarised in Table 4. There were no differences in

mean ventricular volumes or EFs between patients with ASD-II and sinus venosus type defects. However, there was a trend towards more dilated RV volumes in the sinus venosus group (dilated ESV in 57% vs 27%, *P*=0.054).

Health status assessment and family history

The mean scores on the SF-36 survey for the patients and the normal population are shown in Figure 2. Having had an event did not adversely affect SF-36 scores.

A self-reported family history of congenital heart disease was found in 23% of patients (n=16); of these, 56% were in first-degree relatives. The majority of family members also had an ASD (n=8). Other defects were a ventricular septal defect (n=3), patent ductus arteriosus (n=2), univentricular heart (n=1) and valvular heart disease (n=2). Some had more than one defect. Information on genetic testing was not recorded.

Table 4 Cardiac MRI

	ASD-II	Sinus venosus defect	*P*-value
LV EDV/BSA, mean ± SD (mL/m^2)	80 ± 15	83 ± 16	0.6
LV EDV dilation	5%	14%	0.3
LV ESV/BSA	33 ± 10	36 ± 11	0.4
LV ESV dilation	24%	43%	0.2
LV EF (%)	59 ± 7	57 ± 8	0.4
LV EF decreased	17%	29%	0.4
RV EDV/BSA	92 ± 15	96 ± 16	0.4
RV EDV dilation	17%	29%	0.4
RV ESV/BSA	44 ± 10	48 ± 11	0.2
RV ESV dilation	27%	57%	0.05
RV EF (%)	52 ± 6	50 ± 7	0.2
RV EF decreased	24%	50%	0.1

RV EF ≤49% and LV EF ≤54% were considered decreased and RV EDV >107.5 mL/m^2, RV ESV >47.2 mL/m^2, LV EDV >102.5 mL/m^2 and LV ESV >38.7 mL/m^2 were considered enlarged. BSA, body surface area; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricle; RV, right ventricle.

Predictors for late events

Univariate analysis identified only the occurrence of arrhythmias in the early postoperative period as a predictor for the need for permanent pacing during follow-up (HR=16 (95% CI 3 to 70); *P*<0.001). Multivariate analysis was not performed because the number of events was too low.

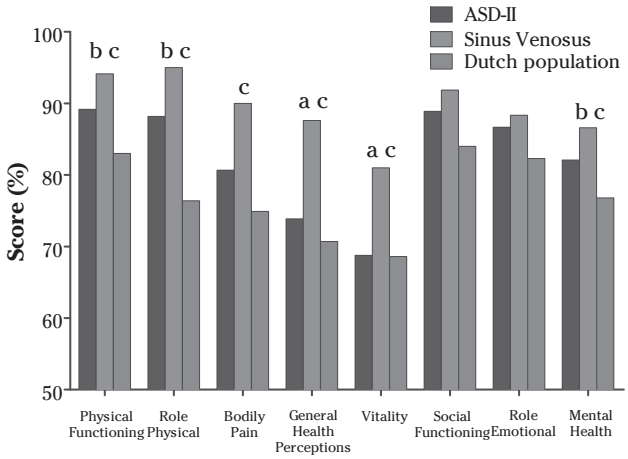

Figure 2 Results of the Short Form Health Survey questionnaire for patients with both types of atrial septal defect (ASD) and the normal Dutch population.
a=significant difference between patients with ASD-II and sinus venosus type ASD; b=significant difference between patients with ASD-II and the normal Dutch population; c=significant difference between patients with sinus venosus type ASD and the normal Dutch population. Higher scores reflect higher levels of functioning or well-being.

DISCUSSION

In this cohort of patients who underwent surgical closure of a haemodynamically significant ASD 30–41 years ago we found very good survival, no pulmonary hypertension, good exercise performance and a low incidence of supraventricular arrhythmias.

Total survival was comparable to the normal Dutch population. However, two patients in the ASD-II group suffered from sudden death in the last decade at the age of 36 and 40 years. In these patients arrhythmia as the cause of death cannot be excluded and is even very likely in one.

Signs of pulmonary hypertension, a major problem that may occur in patients without closure of the ASD,[1,21] were not found. In addition, the clinical condition of the patients appeared excellent with normal exercise capacity in most patients. Neither heart failure nor residual shunts were observed. One patient developed an ischaemic stroke but a clear relation to the heart defect could not be found. However, 6% of patients required pacemaker implantation during total follow-up.

Arrhythmias

Of the 41% (n=36) of patients with some form of asymptomatic atrial arrhythmia on Holter recording 10 years ago,[3] 8% had developed new symptomatic arrhythmias in the past 10 years. This was comparable to the incidence in patients with a negative Holter recording in 2001. Thus, the predictive value of the asymptomatic arrhythmias seen on Holter monitoring seems limited. The prevalence of atrial fibrillation in our patients (12%) is higher than in the general population (<0.5%)[22] but substantially lower than that reported in natural history studies of patients with ASD (up to 50%) and after surgical closure at adult age.[1,4,6,7,21,23] This indicates that early closure is beneficial in the very long term. Surgical scars do not seem to induce atrial flutters on a large scale. The lower incidence of atrial fibrillation appears to be related to earlier termination of the left-to-right shunt, thereby preventing right-sided pressure overload and further right atrium dilation which would have increased the vulnerability to atrial arrhythmias.[7,24] Whether device ASD closure will also prevent the occurrence of SVTs in the long term or will make patients prone to arrhythmias by direct stretching of the atrial septum or circular scar formation around the device remains to be established.

Ventricular dimensions, function and pressure

On echocardiography we found a mildly impaired RV function in one-third of our patients. This is somewhat unexpected as RV function was normal in all patients 10 years ago. This finding may be due to advances in the assessment of RV function as nowadays we use more sophisticated parameters than the mere visual assessment which was the only available method used in our earlier studies. We found no association between RV function and changes in QRS duration. The findings of FAC and S′ wave as well as the CMR results confirm abnormal RV function in a quarter of our patients. CMR was not performed in our earlier studies but RV dilation has also been described by others after shorter follow-up. De Koning *et al.*[25] described this in younger patients who had their surgical correction in a more recent era. In contrast to others and our results, no RV dilation on CMR was reported by Bolz *et al.* even though the same normal values were applied and the mean age at operation is comparable (6.5 vs 7.6 years).[26-28] However, their follow-up period was shorter.

Mild LV function impairment was found in one-fifth of our patients on CMR. This might be a result of the preoperative volume overload due to ventricular interaction. Literature on LV function after surgical ASD repair is lacking, but there are some reports of improvements of LV systolic function after transcatheter ASD closure.[29,30]

ASD-II versus sinus venosus type ASD

We did not find any significant difference in survival, occurrence of events, incidence of arrhythmias, ECG (QRS duration) and Holter-ECG or exercise capacity between patients undergoing surgery for ASD-II and sinus venosus defects. However, TAPSE and S′ were slightly reduced on echocardiography in patients with sinus venosus defects. On the other hand, RV FAC was higher in this group. Integrating all these results, patients with a sinus venosus defect may have a worse longitudinal RV function with probably a compensatory preserved circumferential function. New studies with larger patient groups are needed to confirm these findings.

Predictors for late events

The occurrence of arrhythmias in the early postoperative period showed a strong relation with the need for permanent pacing during early follow-up. Most pacemakers had been implanted in the early years after surgery, most are probably related to surgical damage to the conduction system for two of the three patients (66%) requiring pacemaker implantation within 4 years after surgery had a bradycardia as their postoperative arrhythmia. However, two patients needed a pacemaker for AV block very late after surgery. This is an unexpected finding for which we do not have a clear explanation.

We were not able to identify any other predictors for mortality, late events or ventricular dysfunction.

Study limitations

As in most studies in this field, the numbers are relatively low and therefore all results should be interpreted with caution. The number of patients lost to follow-up was limited with regard to information on survival status, but is larger considering study participation: only 65% of the survivors of the total cohort participated in the last follow-up. The patients considered ineligible for participation were either lost to follow-up, had moved far abroad or did not participate in the previous studies. We believe, however, that after a follow-up of almost 40 years, participation of 80% of eligible patients is very acceptable and can be regarded as a representative sample.

CONCLUSIONS

Very long-term (30–41 years) outcome after surgical ASD closure in childhood shows excellent survival and low morbidity, although two sudden unexplained deaths occurred at 28 and 36 years after surgery. No pulmonary hypertension and

a low incidence of supraventricular arrhythmias were found. The general health and exercise capacity of the patients are excellent and comparable with the normal Dutch population. Persistent RV dilation, which was observed in our earlier follow-up studies in this cohort of patients, was confirmed by CMR. Although EFs of both RV and LV are unexpectedly decreased and RV volumes remain enlarged in some of the patients, their clinical condition remains sound.

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CHAPTER 10

Ventricular myocardial deformation in adults after early surgical repair of atrial septal defect

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ABSTRACT

Aims

It is unknown whether right-ventricular (RV) volume overload caused by an atrial septal defect (ASD) still has its effect on RV deformation long after repair. We evaluated RV and left-ventricular (LV) deformation beyond 30 years after surgical ASD repair in childhood, and studied relationships with conventional diagnostic parameters.

Methods and results

In this prospective study, we included 102 subjects: 51 patients with repaired ASD(39% male, age 43.3 ± 4.9 years, age at repair 7.9 ± 3.6 years) and 51 healthy controls of similar age and sex. All subjects underwent echocardiography and electrocardiography. Additionally, ASD patients underwent cardiac magnetic resonance imaging (CMR), bicycle ergometry, and NT-proBNP measurement. With speckle-tracking echocardiography, we analysed peak systolic longitudinal strain of the RV lateral wall, LV lateral wall, and septum. RV lateral wall global longitudinal strain (GLS) was lower in patients (-20.4 ± 2.7%) than controls (-26.8 ± 4.2%, $P<0.001$), due mainly to decreased apical strain (-19.3 ± 6.2 vs. -28.8 ± 8.3%, $P<0.001$). RV lateral wall GLS correlated with CMR-derived RV and LV end-diastolic volumes ($\rho=0.49$, $P=0.014$; $\rho=0.53$, $P=0.005$), and with RV and LV end-systolic volumes ($\rho=0.43$, $P=0.034$; $\rho=0.46$, $P=0.019$). LV GLS was similar between patients and controls ($P=0.144$). No significant correlations were found with NT-proBNP or exercise capacity.

Conclusion

Although ASD repair was already performed in childhood, RV longitudinal strain, especially of the apical segment, is decreased in patients 35 years after surgery. This suggests that RV function has still been affected in the long run, probably due to the early RV volume overload, but possibly also as sequel of surgery.

INTRODUCTION

Atrial septal defect (ASD) is one of the most common congenital heart defects with an estimated birth prevalence of 1.6 per 1000 live births.[1] When repaired at young age, ASD patients have a life expectancy similar to the general population.[2-4] Before closure, patients with an ASD have right heart volume overload caused by left-to-right shunting. Some patients also have anomalous pulmonary venous return which will result in right heart overload. The right ventricular (RV) volume overload and increased end-diastolic dimensions are well tolerated for many years,[5] but eventually diminished RV function, hypokinesia, and heart failure tend to occur, resulting in an increased morbidity, e.g. arrhythmia, and also higher mortality.[6,7] Even when ASD repair is performed in childhood, some studies report RV dilation or impaired RV function in a substantial part of the patients.[4,8,9] The effect of the preoperative chronic volume loading on RV function in later life is still not completely elucidated.

The recent introduction of speckle-tracking echocardiography (STE) provides objective measurements to quantify segmental and global ventricular function, independently of angle and ventricular geometry.[10] One of the measurements is strain imaging, also known as myocardial deformation imaging, and may detect subtle ventricular dysfunction. Although strain imaging is mainly developed for left-ventricular (LV) mechanics, it can also be used to study the RV myocardial deformation.[11] Earlier studies, mainly performed in small patient samples with transcatheter ASD closure, have shown that RV peak systolic longitudinal strain values are increased before closure, and decreased after closure.[12-14] However, no data are available about strain in adult patients late after surgical ASD closure in childhood.

The aim of this study was to evaluate LV and RV myocardial deformation in adult patients at least 30 years after successful surgical ASD closure, and to investigate relationships with ventricular dimensions and function, exercise capacity, N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), and surgical characteristics.

METHODS

Study population

We approached all patients who had undergone surgical repair for ASD between 1968 and 1980 in our institution. The protocol of this prospective study included echocardiography, 12-lead electrocardiogram (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 or flutter, and poor quality of echocardiographic images. Baseline characteristics were collected as age, sex, and surgical data. Echocardiographic data of the patients were compared with data of healthy controls. The healthy controls were voluntarily recruited by an advertisement. They had no medical history or current symptoms suggesting cardiovascular disease and did not take chronic medication.

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.

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 ejection fraction (EF), RV fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE).[15,16] These measurements were used in combination with visual assessment to grade systolic LV and RV function. For the assessment of valvular regurgitation, we used recommendations of the European Association of Echocardiography.[17,18] For estimating the presence of pulmonary hypertension by echocardiography, we used the guidelines of the European Society of Cardiology.[19] To optimize STE, images were obtained at a frame rate of >60 frames/s.

Speckle-tracking analysis

Offline analyses of the data sets were performed using STE by QLAB version 9.0 (Philips Medical Systems, Best, the Netherlands). Peak systolic longitudinal strain and strain rate of six LV segments were measured at the standard apical four-chamber view. LV global longitudinal strain (GLS) was based on strain measurements of 17 segments at the apical four-, two-, and three-chamber views (Figure 1A). For the analysis of RV lateral wall GLS, RV segmental strain and RV segmental strain rate, we defined the endocardium at the RV-centred apical four-chamber view (Figure 1B). The LV algorithm was applied for both the LV and RV. After positioning the tracking points on an end-diastolic frame, the program tracked these points on a frame-by-frame basis. If tracking was suboptimal, we retraced the endocardial border. LV and RV longitudinal strain and strain rate were defined as the peak

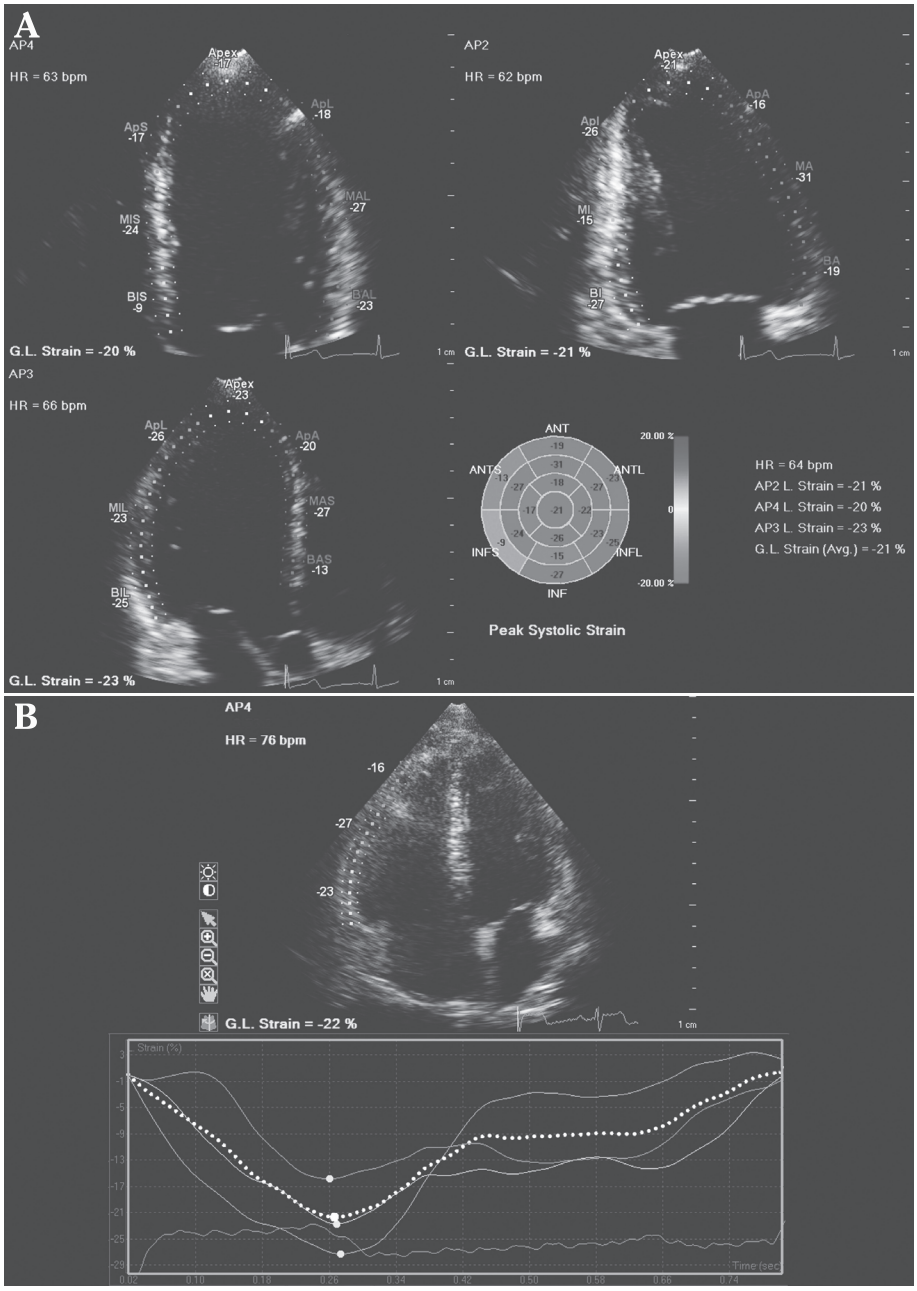

Figure 1 Left-ventricular (A) and right-ventricular (B) longitudinal strain measurements.
The left ventricle was traced at the apical four-, two-, and three-chamber views at end diastole. The walls were automatically divided into seven segments at each view. The segmental strain measurements were plotted in a bull's eye and the left-ventricular global longitudinal strain was calculated. The right-ventricular lateral wallwas traced from base to apex at end diastole. The lateral wall was automatically divided into three segments. The global longitudinal strain of the lateral wall was calculated from these three segments. AP4, apical four-chamber view; AP2, apical two-chamber view; AP3, apical three-chamber view; GL, global longitudinal.

negative value on the curve during the ejection phase. Data were exported to a spreadsheet program (Excel; Microsoft Corporation, Redmond, WA, USA).

Cardiac magnetic resonance imaging

CMR 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 CMR sequence have been reported previously.[20] 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), stroke volume (SV), and EF were calculated and compared with reference values.[21]

Cardiopulmonary exercise testing

Maximal work load, maximal heart rate and peak oxygen consumption (peak V_{O_2}) were assessed by a bicycle ergometer with gradual workload increments of 20 Watts per minute (Ramp protocol), and compared with the values of normal individuals corrected for age, sex, height, and weight.

NT-proBNP measurement

Peripheral venous blood samples were collected after 30 min of rest. Plasma NT-proBNP levels were determined with use of a 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 between two groups the Student's *t*-tests was used. 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 or Spearman correlation test was applied. Because NT-proBNP values were not normally distributed, the values were log-transformed to create a normal distribution for further statistical analyses. Adjustment for multiple comparisons was performed by the Bonferroni correction. All statistical analyses were performed using the Statistical Package

for Social Sciences version 21 (SPSS, IBM Corp., Armonk, NY, USA). The statistical tests were two-sided and a $P<0.05$ was considered statistically significant.

Intraobserver variability was assessed by repeated analysis of the data sets at least half a year after the initial analysis and blinded to the initial results. Assessment of interobserver variability was performed by a second observer in half of the data sets. The agreement between two measurements was expressed with Bland–Altman's limits of agreement (mean of the differences ± 1.96 SD).[22]

RESULTS

Study population

An overview of the patient participation and feasibility of the strain measurements is presented in Figure 2. Bicycle ergometry was not performed in two patients due to inability and CMR was not performed in five due to refusal or claustrophobia. In all healthy controls, LV strain measurements were feasible. RV lateral wall strain could be measured in 18 of the first (60%) 30 controls and, due to the steep learning curve, in 20 of the last (95%) 21 controls. Table 1 shows the baseline charac-

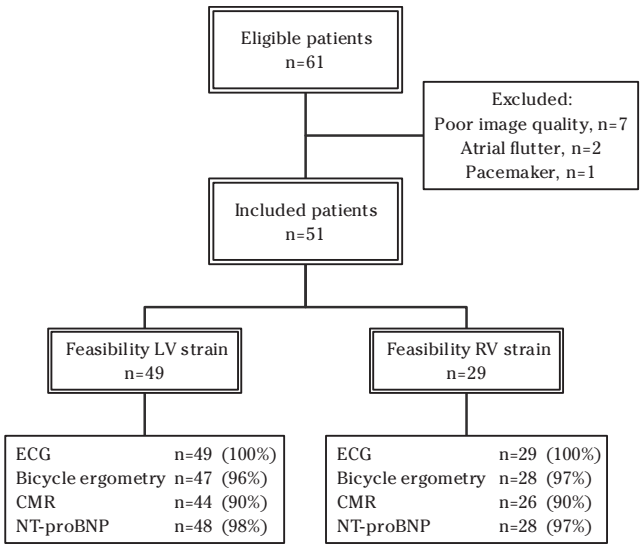

Figure 2 Flow chart of the study patients.
An overview of the patient inclusion, feasibility of left- and right-ventricular strain measurements, and the number of patients per additional diagnostic test. Left-ventricular strain was feasible in 38 patients with secundum type ASD and 11 with sinus venosus type; right-ventricular strain was feasible in 24 with secundum type ASD and five with sinus venosus type. CMR, cardiac magnetic resonance imaging; ECG, electrocardiography; LV, left ventricular; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide; RV, right ventricular.

Table 1 Characteristics of the study population

Clinical characteristics	ASD patients (n=51)	Controls (n=51)	*P*-value
Age at time of study (years)	43.3 ± 4.9	41.4 ± 10.8	0.249
Male	20 (39)	20 (39)	1.000
BMI (kg/m^2)	24.8 ± 3.9	23.9 ± 3.4	0.211
Systolic blood pressure (mmHg)	129 ± 19	122 ± 11	0.039
Diastolic blood pressure (mmHg)	81 ± 11	76 ± 10	0.061
NYHA functional classification			
Class I	48 (94)	51 (100)	0.243
Class II	3 (6)	-	
QRS duration (ms)	100 ± 11	98 ± 10	0.316
Incomplete RBBB	12 (24)	-	-
QRS duration >120 ms	2 (4)	-	-
Age at operation (years)	7.9 ± 3.6	-	-
Type of ASD			
Secundum type	39 (76)	-	-
Sinus venosus	12 (24)	-	-
Qp/Qs ratio	2.3 ± 0.7	-	-
Type of repair			
Direct closure	37 (73)	-	-
Patch	14 (27)	-	-

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

teristics of all patients and controls. In a subanalysis of patients with feasible RV strain, the characteristics were comparable with those of the controls.

The included patients were studied 35.4 ± 2.9 years after surgical closure. Five patients used cardiac medication: metoprolol (n=2), sotalol (n=1), flecainide (n=1), and ACE-inhibitor (n=1). Three of these also used statins and oral anticoagulants.

In all patients with a sinus venosus type defect, a patch was used for closure; of the patients with a secundum type defect, a patch was used in only two (5%) patients. All patients with sinus venosus type defect had a partial abnormal pulmonary venous return before repair. Patients with secundum type ASD and patients with sinus venosus type had a comparable preoperative Qp/Qs ratio [2.2 (IQR 1.7–2.7) vs. 2.1 (IQR 1.8–2.9), *P*=0.707] and preoperative mean pulmonary artery pressure [14 mmHg (IQR 12–16 mmHg) vs. 15 mmHg (IQR 11–17 mmHg), *P*=0.931, respectively].

Conventional echocardiographic characteristics of the patients and controls are presented in Table 2. Of these characteristics, only TAPSE differed significantly between patients with secundum type defect [20 mm (IQR 16–22 mm)] and sinus venosus defect [17 mm (IQR 13–18 mm), *P*=0.006]. In a subanalysis of patients with

feasible RV strain, no significant differences were found in LV and RV dimensions compared with those of controls.

One patient possibly had a minimal residual shunt. Pulmonary regurgitation was absent in 48 (94%) patients, mild in 2 (4%), and moderate in 1 (2%). Tricuspid regurgitation was absent in 20 (39%) patients, mild in 29 (57%) and moderate in 2 (4%). None of the patients had severe pulmonary or tricuspid regurgitation. Echocardiographic signs suggestive of pulmonary hypertension were not found.

Table 2 Conventional echocardiographic characteristics of the patients and healthy controls and CMR imaging characteristics of the patients

	Patients	**Controls**	***P*-value**
Echocardiography	*n=51*	*n=51*	
LV end-diastolic dimension (mm)	48 ± 5	48 ± 4	0.619
LV end-systolic dimension (mm)	30 ± 5	29 ± 4	0.233
LV fractional shortening (%)	38 ± 7	40 ± 7	0.071
LV ejection fraction Simpson's (%)	56 ± 5	58 ± 5	0.131
Systolic LV function, n (%)			
Normal	49 (96)	51 (100)	0.495
Mildly impaired	2 (4)	-	
Moderately impaired	-	-	
RV longitudinal dimension (mm)	75 ± 7	76 ± 6	0.682
RV basal dimension (mm)	40 ± 7	37 ± 6	0.035
RV FAC (%)	43 ± 8	46 ± 6	0.053
TAPSE (mm)	19 ± 4	29 ± 4	<0.001
Systolic RV function, n (%)			
Normal	34 (67)	51 (100)	<0.001
Mildly impaired	16 (31)	-	
Moderately impaired	1 (2)	-	
Cardiac magnetic resonance imaging	*n=46*		
LV end-diastolic volume (mL)	156 ± 32	-	
LV end-systolic volume (mL)	67 ± 22	-	
LV stroke volume (mL)	89 ± 17	-	
LV ejection fraction (%)	58 ± 7	-	
RV end-diastolic volume (mL)	179 ± 36	-	
RV end-systolic volume (mL)	88 ± 23	-	
RV stroke volume (mL)	91 ± 21	-	
RV ejection fraction (%)	51 ± 6	-	

FAC, fractional area change; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

Left-ventricular longitudinal strain

Figure 3 shows the peak systolic LV GLS and the peak systolic longitudinal strain of six different segments. The mean LV GLS was similar between patients and controls. When focused on the different segments of the LV, only the apical septal strain was significantly lower (less negative) in patients than in controls. The mid-septal strain tended to be lower in patients (*P*=0.059).

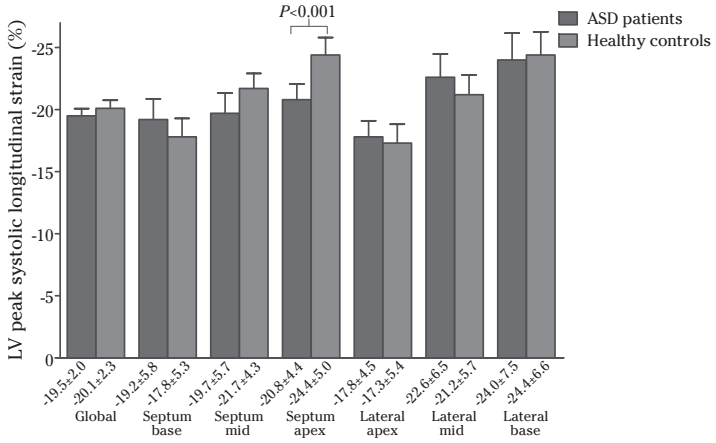

Figure 3 Left-ventricular global and segmental longitudinal strain in ASD patients (n=49) and healthy controls (n=51).
The peak systolic segmental longitudinal strain at the apical four-chamber view was feasible in 49 patients. Left-ventricular global longitudinal strain was based on the measurements at the apical two-, three-, and four-chamber views which was feasible in 39 of these 49 patients. In the healthy controls, all measurements were feasible. The error bars show 95% confidence interval. GLS, global longitudinal strain; LV, left ventricular.

Right-ventricular longitudinal strain and strain rate

Figure 4 shows the peak systolic RV lateral wall GLS and segmental longitudinal strain. The mean RV lateral wall GLS was significantly lower in patients than in controls. In 15 (52%) patients, the RV lateral wall GLS was lower than the strain value of the 95th percentile (-20.7%) of the controls. Of the three RV lateral wall segments, particularly the apical longitudinal strain was significantly lower in patients. In 13 (45%) patients, the RV apical strain was lower than the strain value of the 95th percentile (-18.5%) of the controls. A positive correlation was found between RV lateral wall GLS and LV GLS in the patient group (r=0.47, *P*=0.023).

With regard to the strain rate of the RV lateral wall, only the apical strain rate was significantly lower in patients (-1.35 ± 0.43s^{-1}) than controls (-1.69 ± 0.63s^{-1}, *P*=0.010).

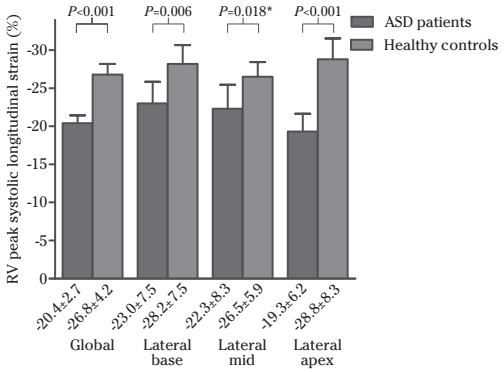

Figure 4 Right-ventricular lateral wall global and segmental longitudinal strain in ASD patients (n=29) and in healthy controls (n=38).

This figure presents the mean peak systolic right-ventricular lateral wall global longitudinal strain measured at the apical four-chamber view, and the mean peak systolic strain of the three segments of the right-ventricular lateral wall. The error bars show 95% confidence interval. *After adjustment for multiple comparisons by the Bonferroni correction, $P<0.017$ was considered statistically significant. GLS, global longitudinal strain; RV, right ventricular.

Surgical characteristics, ECG, NT-proBNP levels, and exercise testing

Patients with a secundum type defect had higher LV GLS and RV lateral wall GLS than patients with a sinus venosus defect [LV GLS: -19.5% (IQR -18.5; -21.6%) vs. -18.2% (IQR -17.2; -19.6%), $P=0.024$ and RV GLS: -21.2% (IQR -19.1; -23.1%) vs. -17.7% (IQR -16.8; -18.5%), $P=0.009$]. Qp/Qs-ratio before repair did not correlate with LV GLS nor with RV lateral wall GLS, but when focused on the segmental strain a significant correlation was found between Qp/Qs-ratio and the RV mid-segment (r=-0.46, $P=0.016$). Two patients had a preoperative mean pulmonary artery pressure ≥25 mmHg, namely 26 and 29 mmHg. One of these patients had a RV lateral wall GLS of -23.7% which is significantly higher than the mean RV lateral wall GLS in the patient group ($P<0.001$); in the other patient RV strain was not feasible. No correlations were found between strain and preoperative mean pulmonary artery pressure, age at repair, aortic cross-clamp time, or current age.

None of the patients had a complete right bundle branch block and 12 (24%) had an incomplete right bundle branch block. RV lateral wall GLS and LV GLS were comparable between patients with an incomplete right bundle branch block and patients without ($P=0.407$, $P=0.210$, respectively).

The median NT-proBNP level was 13.7 pmol/L [IQR 8.7– 23.4 pmol/L]. NT-proBNP was elevated in 25 (50%) patients. Log-transformed NT-proBNP did not correlate with LV GLS or RV lateral wall GLS.

With bicycle ergometry, all patients reached a respiratory exchange ratio >1.0 considering a maximal exercise performance. The mean peak heart rate was 91 ±

12% of the expected value; peak workload 97 ± 19%; and peak V_{O_2} 96 ± 27%. The peak workload tended to correlate with RV lateral wall GLS (r=0.34, *P*=0.076). No further evident relationships were found between these variables and LV GLS or RV lateral wall GLS.

Echocardiographic and CMR-derived parameters

CMR-derived characteristics are presented in Table 2. LV dilation was measured in 3 (7%) patients and RV dilation in 7 (16%). Twelve (26%) patients had a diminished LV EF and 16 (34%) a diminished RV EF. Of the CMR-derived dimensions and function, only the RV EF differed significantly between patients with ASD secundum type defect [51% (IQR 47–56%)] and with sinus venosus defect [48% (IQR 44–51%), *P*=0.044]. Correlations of strain measurements with echocardiographic-derived dimensions and with CMR-derived volumes are summarized in Table 3. After exclusion of the patients with a dilated RV, the mean RV lateral wall GLS remained significantly lower in patients (-20.6±2.9%, *P*<0.001) than controls.

Table 3 Correlations between left-ventricular global longitudinal strain and right-ventricular lateral wall global longitudinal strain with echocardiographic and CMR-derived parameters in ASD patients

	LV GLS		**RV lateral wall GLS**	
	Spearman's ρ	***P*-value**	**Spearman's ρ**	***P*-value**
Echocardiography	*n=39*		*n=29*	
LV end-diastolic dimension	-0.06	0.736	**0.38**	**0.041**
LV end-systolic dimension	-0.04	0.788	0.04	0.835
LV fractional shortening	0.07	0.682	**0.40**	**0.041**
LA parasternal long-axis dimension	-0.07	0.684	**0.41**	**0.027**
RV longitudinal dimension	0.04	0.823	**0.38**	**0.043**
RV basal dimension	0.26	0.115	0.13	0.512
CMR imaging	*n=37*		*n=26*	
LV end-diastolic volume	0.05	0.788	**0.53**	**0.005**
LV end-systolic volume	0.10	0.548	**0.46**	**0.019**
LV stroke volume	-0.10	0.539	**0.41**	**0.036**
LV ejection fraction	-0.11	0.513	-0.25	0.223
RV end-diastolic volume	0.19	0.267	**0.49**	**0.014**
RV end-systolic volume	**0.42**	**0.012**	**0.43**	**0.034**
RV stroke volume	-0.10	0.583	0.32	0.125
RV ejection fraction	**-0.37**	**0.028**	-0.19	0.358

Bold-face values represent statistically significant correlations. CMR, cardiac magnetic resonance; GLS, global longitudinal strain; LA, left atrium; LV, left ventricular; RV, right ventricular.

Inter- and intraobserver variability

The interobserver variability was -0.29 ± 1.64% for the LV GLS at the apical four-chamber view, and 0.39 ± 2.89% for the RV lateral wall GLS. The intraobserver variability was -0.21 ± 1.40% for the LV GLS at the apical four-chamber view, and 0.04 ± 1.99% for the RV lateral wall GLS (Figure 5).

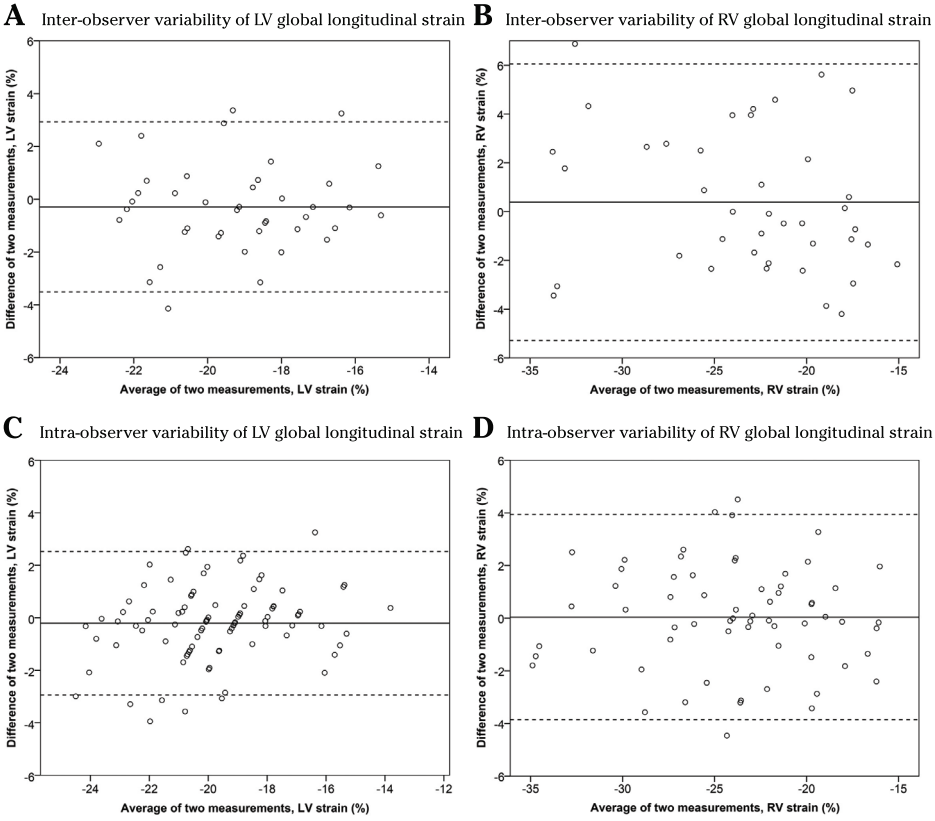

Figure 5 Bland–Altman plots of inter- and intraobserver variability for left-ventricular global longitudinal strain (A, C) and right-ventricular lateral wall global longitudinal strain (B, D).
The longitudinal strain measurements were assessed at the apical four-chamber view. The solid lines depict the mean difference of two measurements, and the dashed lines depict the limits of agreement (mean difference of the two measurements ± 1.96 SD).

DISCUSSION

A remarkable observation in this prospective study is the decreased RV global and segmental longitudinal strain in ASD patients more than 30 years after surgical repair at young age. To the best of our knowledge, this is the first study to assess

myocardial deformation with STE in adult ASD patients long after their initial repair.

Left-ventricular longitudinal strain

The mean LV GLS of our patients was comparable with that of controls. A study performed in adult ASD patients who underwent percutaneous closure also described a normal LV GLS before, as well as after the closure.[12] When focused on the different segments, the strain of the apical septum was decreased, possibly due to the diminished RV function which interacts with the septum. We did not see relationships of LV strain with LV echocardiographic and CMR-derived parameters, probably because of the small ranges and normal values in almost all patients in our group.

Right-ventricular longitudinal strain

Even though the patients were already operated in childhood, we still observed a decreased peak systolic RV lateral wall GLS. This reduction is presumably a result of preoperative chronic volume overload or is related to the closure technique. In children and adults with an open ASD, RV GLS is increased in comparison with healthy controls. This increase is caused by volume overload,[12-14,23] and induces RV remodelling which possibly also took place in our patient group before closure. In patients undergoing closure at adult age, RV dilation is a relatively common finding,[13,24] but even when closure is performed at young age, some studies report impaired RV function or dilation in a substantial part of the patients.[4,8,9] These findings in combination with our results suggest that even when ASD patients are operated at young age, RV remodelling already took place leading to decreased strain of the RV lateral wall.

In addition, the surgery itself, including factors such as closure technique, use of cardiopulmonary bypass or hypothermia, might also contribute to decreased RV deformation. To confirm that surgery is a possible cause, a longitudinal study is required comparing strain values of patients with a surgically closed ASD with values of patients with a percutaneously closed ASD after the same follow-up period.

The strain was most decreased in the apical segment, which is in line with studies by Van de Bruaene and Jategaonkar,[13,14] though almost all of these ASDs were closed percutaneously and at adult age. The more profound impairment of the apical deformation, could be explained by several possible causes.[25-27] The first explanation could be the RV geometry and anatomy: the apical portion of the RV is thinner and more trabeculated than the basal portion. When the wall is thinner, the passive wall stress is higher, which is inversely related with strain and therefore results in smaller longitudinal deformation. A second possible explanation is that

in remodelled RVs of ASD patients, the apical segment seems to be more straight than in healthy subjects. The wall stress is higher in structures with straight walls. Thirdly, it could be possible that in some RVs a hypertrophied moderator band and trabeculations lead to a smaller regional volume and therefore might decrease the apical deformation.[28] Lastly, it could be explained by alterations of β-adrenergic receptor signalling. RV volume overload leads to β-adrenergic signalling abnormalities, e.g. increased levels of β-adrenergic receptor kinase 1, and redistribution which result in a significant reduction in chamber contractility.

It is important to mention that myocardial deformation does not directly reflect contractility, but is influenced by preload, afterload, and ventricular volume.[29,30] However, these studies involved only the LV. In our study, lower RV lateral wall GLS was moderately associated with greater RV volumes. In a subanalysis of patients with RV volumes in the normal range, the RV lateral wall GLS remained significantly lower in patients than in controls. Thus, even when the possible confounding influence of ventricular volume is excluded, the mean RV lateral wall GLS of the patients remains decreased.

Surgical characteristics, ECG, NT-proBNP levels, and exercise testing

Patients with sinus venosus defect had lower RV and LV GLS than patients with secundum type defect. The TAPSE and CMR-derived RV EF were also lower in this group. These differences may be explained by the partial abnormal pulmonary venous return in patients with sinus venosus defect or by the surgical technique that has been used: all patients with sinus venosus type defect received a septal patch, whereas only a few of the patients with secundum type. The preoperative mean pulmonary artery pressure and Qp/Qs ratio were comparable between the two groups. These findings suggest that the type of defect itself or type of surgical repair play a more important role on RV GLS than the degree of RV volume overload. This is in accordance with the finding by Kowalik *et al*.[31] who concluded that RV deformation of the base and apex did not differ significantly in patients with various degrees of left-to-right shunts. However, a relationship was observed between RV deformation of the mid-segment and Qp/Qs ratio. Patients with moderate left-to-right shunts had the highest strain values.[31]We found that higher preoperative Qp/Qs ratio was associated with higher strain of the RV mid-segment.

The presence of an incomplete right bundle branch block does not seem to affect the RV lateral wall GLS in our cohort. We did not find a relationship between NT-proBNP levels and RV or LV GLS. The clinical relevance of NT-proBNP in this group of patients remains unknown.

Regarding the cardiopulmonary exercise testing in our study, RV lateral wall GLS tended to correlate with peak workload, which points out the potential clini-

cal significance of decreased RV lateral wall GLS. However, no relationship was found with peak V_{O_2}, which is in contrast with the relationship of RV apical strain with peak V_{O_2} found by Van De Bruaene *et al.*[14] This disagreement may be due to the smaller number of patients in our study with feasible RV strain as well as performed peak V_{O_2}. We could not draw conclusions with regard to arrhythmias, because patients with arrhythmias were excluded. Therefore, clinical relevance of decreased RV lateral wall GLS seems limited. To find out whether decreased strain is an early marker for detecting right heart failure in a preclinical phase which could lead to manifest and clinical relevant heart failure in later life, a longer follow-up of these patients needs to be established. Routine clinical follow-up with long intervals might be advisable for these patients.

Echocardiographic and CMR-derived parameters

A positive relationship was observed between RV lateral wall GLS and LV GLS. Furthermore, RV lateral wall GLS correlated not only significantly with RV parameters, such as longitudinal dimension and end-diastolic and end-systolic volumes, but also with LV parameters, such as fractional shortening and end-diastolic and end-systolic volumes. These findings are possibly a result of the mechanical interaction between the ventricles due to the continuity of the muscle fibres which binds the ventricles together.[27]

Limitations

We only 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.[27] We assumed that the same applies to the RVs in ASD patients. In addition, the RV radial and circumferential strain measurements are not available on our QLAB software. Rotational movements play a significant role for LV function, but we decided to measure strain in longitudinal direction making comparisons with RV strain clearer.

In case of RV disease, the interventricular septum could be affected. We considered the interventricular septum as an LV structure because the QLAB software has been developed for the LV shape.

Although we approached all eligible patients who were operated between 1968 and 1980 in our clinic, we must state that there could be a selection bias in participation of patients regarding disease severity. RV strain was feasible in 29 (57%) patients which could induce selection bias. However, baseline characteristics of patients with feasible RV strain, as well as without feasible RV strain, were comparable with the baseline characteristics of controls, apart from the higher BMI in

patients without feasible RV strain. The small number of patients with feasible RV strain (n=29) limits the statistical analyses and power of the study.

CONCLUSIONS

Even though surgical ASD repair was already performed in childhood, RV lateral wall GLS is significantly decreased 35 years after closure. This reduction in strain is presumably a result of chronic volume overload before repair, but also the surgery itself could have affected the RV. LV GLS is comparable between the patients and controls. A prospective longitudinal study is required to determine whether decreased strain is an early marker for detecting heart failure in a preclinical phase which could lead to manifest right heart failure. A routine clinical follow-up with long intervals might be advisable for these patients.

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CHAPTER 11

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 analysed 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.

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.

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.

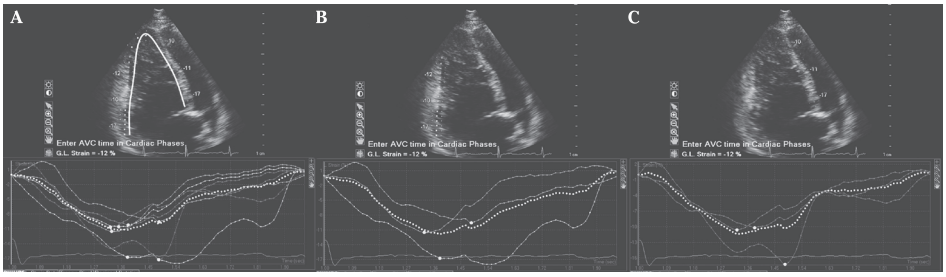

Figure 1 Two-dimensional longitudinal strain analysis of the RV in a TGA-Mustard patient.
(A) GLS of the systemic ventricle composed of seven segments. (B) Average LS of the RV lateral wall composed of three segments. (C) Average LS of the septal wall composed of three segments.

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, IBM Corp., Armonk, NY, USA).

RESULTS

Baseline patient characteristics

Fifty-seven patients with a systemic RV were eligible. Fifteen patients were excluded because of restricted 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.

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 (years)	-	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 (bpm)	72 ± 19	73 ± 16	67 ± 27	0.443
Systolic blood pressure (mmHg)	125 ± 14	125 ± 15	123 ± 13	0.676
Diastolic blood pressure (mmHg)	80 ± 13	80 ± 14	82 ± 7	0.606
Height (m)	1.75 ± 0.1	1.75 ± 0.1	1.72 ± 0.1	0.339
Weight (kg)	78 ± 16	79 ± 17	74 ± 13	0.398
Body Mass Index (kg/m^2)	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 (ms)	120 ± 19	121 ± 20	111 ± 15	0.297
QRS >120 ms	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].
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. *TGA-Mustard vs. ccTGA. Significant *P*-values <0.05 are indicated in bold.

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

Table 2

	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 V_{max} (m/s) (n=11)	2.8 ± 0.8	3.0 ± 0.8	2.3 ± 0.4	0.076
ulmonary regurgitation, early diastolic, V_{max} (m/s) (n=20)	2.0 ± 0.7	2.1 ± 0.7	1.4 ± 0.3	0.070
Pulmonary regurgitation, late diastolic, V_{max} (m/s) (n=17)	0.9 ± 0.6	0.9 ± 0.7	0.6 ± 0.2	0.396
Tricuspid regurgitation V_{max} (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; V_{max}, peak flow velocity.
Significant *P*-values <0.05 are indicated in bold.

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).

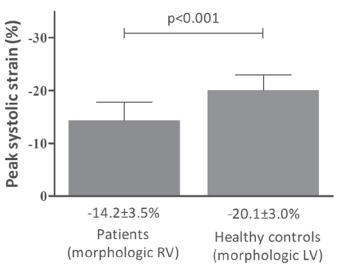

Figure 2 GLS of the systemic ventricle in patients and healthy controls.
Strain values are presented as mean and standard deviation.

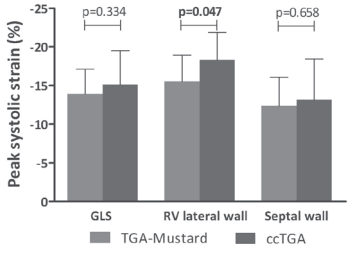

Figure 3 GLS of the systemic RV and average LS of the ventricular walls in both patient groups.
Strain values are presented as mean and standard deviation.

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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).

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 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 (s^{-1})	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).

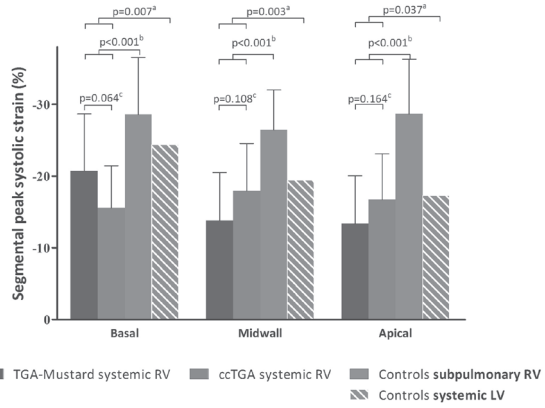

Figure 4 Segmental strain of the lateral wall.
Levels of significance are presented for comparison of: (A) systemic RV lateral wall in patients vs. systemic LV lateral wall in healthy controls, (B) systemic RV lateral wall in patients vs. subpulmonary RV lateral wall in healthy controls, (C) systemic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

GLS of the systemic RV and 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.

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).

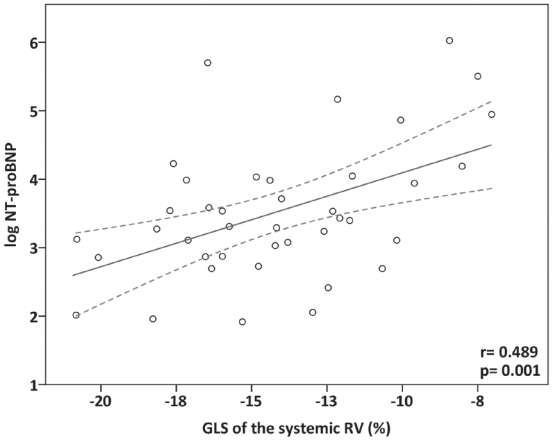

Figure 5 Correlation between GLS of the systemic RV and NT-proBNP.

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).

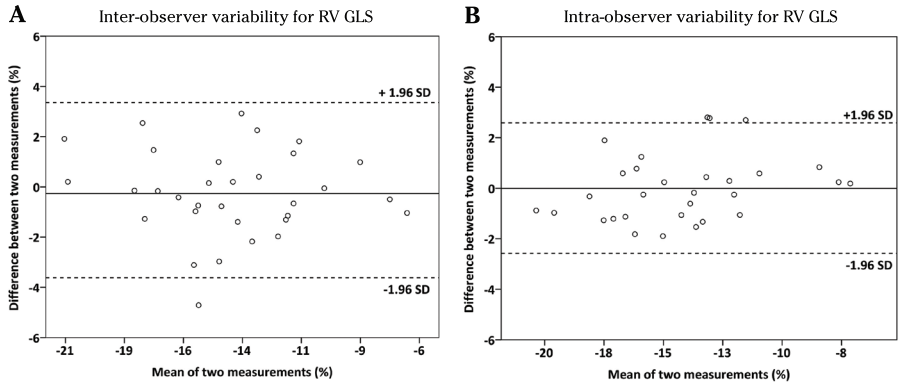

Figure 6 Bland–Altman plots for intra- and interobserver variability for measurement of GLS of the systemic RV.
(A) Interobserver variability; (B) intraobserver variability.

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, 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. Furthermore, 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 geometry. 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]

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 associations 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 12

Quantitative assessment of systolic left ventricular function with speckle-tracking echocardiography in adult patients with repaired aortic coarctation

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ABSTRACT

Purpose

Despite successful aortic coarctation (CoA) repair, systemic hypertension often recurs which may influence left ventricular (LV) function. We aimed to detect early LV dysfunction using LV global longitudinal strain (GLS) in adults with repaired CoA, and to identify associations with patient and echocardiographic characteristics.

Methods

In this cross-sectional study, patients with repaired CoA and healthy controls were recruited prospectively. All subjects underwent echocardiography, ECG and blood sampling within one day. With speckle-tracking echocardiography, we assessed LV GLS on the apical four-, three- and two-chamber views.

Results

We included 150 subjects: 75 patients (57% male, age 33.4±12.8 years, age at repair 2.5 [IQR:0.1-11.1] years) and 75 healthy controls of similar sex and age. LV GLS was lower in patients than in controls (-17.1±2.3% vs. -20.2±1.6%, $P<0.001$). Eighty percent of the patients had a normal LV ejection fraction, but GLS was still lower than in controls ($P<0.001$). In patients, GLS correlated with systolic and diastolic blood pressure (r=0.32, $P=0.009$; r=0.31, $P=0.009$), QRS duration (r=0.34, $P=0.005$), left atrial dimension (r=0.27, $P=0.029$), LV mass (r=0.30, $P=0.014$) and LV ejection fraction (r=-0.48, $P<0.001$). Patients with either associated cardiac lesions, multiple cardiac interventions or aortic valve replacement had lower GLS than patients without.

Conclusion

Although the majority of adults with repaired CoA seem to have a normal systolic LV function, LV GLS was decreased. Higher blood pressure, associated cardiac lesions, and larger left atrial dimension are related with lower GLS. Therefore, LV GLS may be used as objective criterion for early detection of ventricular dysfunction.

INTRODUCTION

Coarctation of the aorta (CoA) is common (5–8 % of all congenital heart defects) and is considered to be part of a generalized arteriopathy with a reduced compliance of arterial vascular walls, instead of only a circumscript narrowing of the aorta.[1-3] Patients can have associated lesions, such as a bicuspid aortic valve, subvalvular, valvular, or supravalvular aortic stenosis, and mitral valve stenosis.[3] CoA causes left ventricular (LV) pressure overload, which can lead to increased myocardial wall stress, LV systolic and diastolic dysfunction, and the development of arterial collaterals.[3] In order to relieve the obstruction, a surgical or transcatheter intervention is needed. Despite successful repair, late cardiovascular problems occur including systemic hypertension in 30–75 % of the cases,[4-6] compensatory LV hypertrophy, heart failure, coronary heart disease, stroke and sudden cardiac death.[6, 7] Early detection of LV dysfunction could be important for risk stratification or early initiation of treatment. Speckle-tracking echocardiography (STE) is a sophisticated technique that provides a quantitative assessment of the motion of myocardial tissue, independently of angle and ventricular geometry, which could detect subclinical myocardial dysfunction.[8,9] One of the measurements is strain imaging which is defined as deformation of the myocardial wall normalized to its original size. Because strain in longitudinal direction is the most widely used type of strain and is a robust index for clinical studies,[10] we have chosen to focus on longitudinal strain. One study recently described a significant lower LV global longitudinal strain (GLS) after CoA repair in a small cohort of heterogeneous patients including children and adults.[11] Our group of CoA subjects, age- and sex-matched, is the largest and oldest in which LV GLS has been studied to date.

The aim was to evaluate LV GLS in adults after CoA repair and healthy controls of similar age and sex, and to study relationships between GLS and patient characteristics such as smoking, interventions, hypertension, aortic valve morphology, other associated congenital cardiac lesions, and prior cardiovascular events, but also with conventional echocardiographic measurements and cholesterol and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) levels.

METHODS

Study population

Consecutive patients who were ≥18 years of age and had undergone CoA repair were recruited at the adult outpatient cardiology clinic at Erasmus MC between September 2011 and June 2014. Exclusion criteria were a pacemaker, irregular

heart rhythm, and poor quality of the echocardiographic images at all apical views for adequate STE. This prospective study's protocol included medical history, physical examination, echocardiography, 12-lead electrocardiography, and cholesterol and NT-proBNP measurements all on the same day. Patient characteristics included age, sex, medication, clinical parameters, type of initial repair, number of interventions (surgical or transcatheter), aortic valve replacement, aortic valve morphology, other associated congenital cardiac lesions and prior cardiovascular events (coronary artery disease, heart failure, stroke). Hypertension was defined as the requirement of antihypertensive drugs or when ≥3 times an elevated blood pressure was measured (systolic >140 mmHg or diastolic >90 mmHg). Healthy controls of similar age and sex were voluntarily recruited via an advertisement. They had no medical history or current symptoms suggesting cardiovascular disease and did not take any chronic medication.

All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all participants.

Echocardiographic image acquisition

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 X5-1 matrix transducer (composed of 3040 elements, with 1-5 MHz extended operating frequency range). Images were acquired at frame rates of >55 frames/sec. The echocardiographic studies were stored in Digital Imaging and Communications in Medicine (DICOM) format.

Conventional echocardiographic measurements

For chamber measurements and LV mass calculation, we used the current recommendations for cardiac chamber quantification.[12] For normal systolic LV ejection fraction (EF) assessed with the Simpson's method, we used the reference values of ≥52 % for males and ≥54 % for females.[12] In addition, LV systolic function was visually graded as normal or mildly, moderately or severely impaired. From the apical four-chamber view (A4C), pulsed-wave Doppler examination was performed to obtain peak mitral inflow velocities at early (E) and late (A) diastole and E deceleration time. Tissue Doppler imaging was performed to obtain myocardial tissue velocity at the mitral annulus at early diastole (E'). For left atrial (LA) size, we measured the anteroposterior diameter in the parasternal long-axis view and the LA area in the A4C at end-systole.[12] For the assessment and grading of valvular stenosis and regurgitation, we used the recommendations of the European Association of Echocardiography.[13–15]

Speckle-tracking analysis

Offline analysis of the data sets was performed using STE by QLAB version 9.0 (Philips Medical Systems, Best, the Netherlands). Analysis was performed according to the vendor's instructions. Cardiac cycles were defined by the positioning of R-waves.

To assess peak systolic LV GLS, the endocardial and epicardial borders were traced in the apical four-, three- and two-chamber views (A3C, A2C) on an end-diastolic frame (Figure 1a-c). The software automatically divided the walls in several segments (LV algorithm based on 17-segment model) and tracked these points on a frame-by-frame basis. When tracking was suboptimal, we readjusted

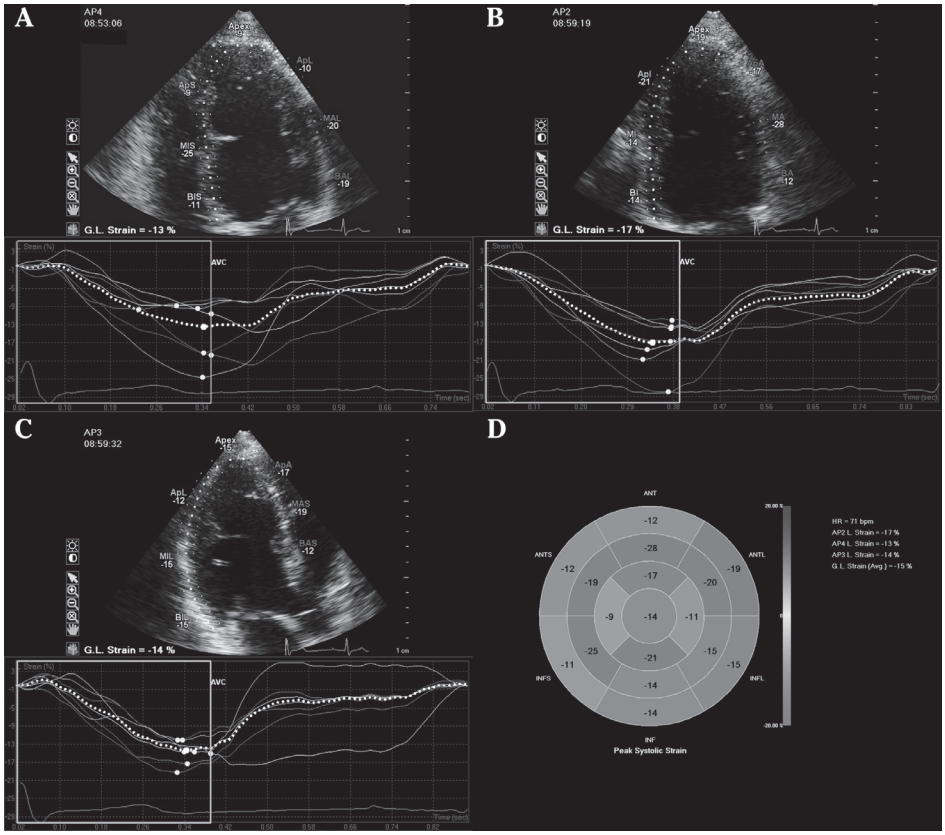

Figure 1 Example of left ventricular longitudinal strain measurements in a patient with repaired aortic coarctation.

The LV was traced in the apical four-, two-, and three-chamber views at end-diastole. The walls were automatically divided into seven segments at each view and the global longitudinal strain at each view was calculated (A-C). The segmental strain measurements were plotted in a bull's eye and the left ventricular global longitudinal strain based on all three apical views was calculated (D).

AP2 = apical two-chamber view; AP3 = apical three-chamber view; AP4 = apical four-chamber view; GL = global longitudinal.

the borders. Segments with persistently inadequate tracking were excluded from further analysis. Peak systolic strain values were defined as the peak values on the curves during the ejection phase. We reported the peak systolic LV GLS based on measurements of all three apical views (Figure 1d). Data were exported to a spreadsheet program (Excel; Microsoft Corporation, Redmond, WA, USA). All references to strain changes consider the absolute value of the number, so that higher or increase in longitudinal strain means a more negative number and lower or decrease means a less negative number.[8]

NT-proBNP measurement

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

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or as median with interquartile range [Q1-Q3]. Categorical variables are presented as frequencies and percentages. For comparison of normally distributed continuous variables between two groups the Student's *t*-test was used and in case of skewed distribution, the Mann-Whitney-U test. For comparison between three groups the Kruskal-Wallis sum 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 or Spearman correlation test was applied. Multivariable regression analysis was performed for patient characteristics which were significant associated with LV GLS. In case of collinearity of these variables, we implemented the variable with the strongest correlation into multivariable analysis. Because NT-proBNP values were not normally distributed, the values were log transformed for further statistical analyses.

Intra-observer and inter-observer agreement between two investigators (MM, RvG) were assessed by repeated analysis in two third of the data sets at least two months after the initial analysis on the second cardiac cycle at the same images and blinded to the initial results. The limits of agreement between two measurements were determined as the mean of the differences ±1.96 SD and presented in a Bland-Altman plot.[16] Additionally, the coefficient of variation (COV; SD of the differences of two measurements divided by their mean) was provided.

All statistical analyses were performed using SPSS statistics version 21 (IBM Corp., Armonk, NY, USA). The statistical tests were two-sided and a $P<0.05$ was considered statistically significant.

RESULTS

Study population

We included 75 adult patients (57% male, age 33.4±12.8 years) and 75 healthy controls of similar sex and age. Figure 2 presents an overview of the patient participation and feasibility of the measurements. Table 1 shows the characteristics of the study population. The median age at the initial CoA repair, surgical or transcatheter, was 2.5 years [0.1-11.0; range: 0-51] and the median follow-up after repair was 24.7 years [20.4-31.7]. Sixteen patients underwent aortic valve replacement 11.6 years [5.4-18.0] prior to this study. Six patients (8%) had a history of at least one cardiovascular event: transient ischemic attack (n=3), postoperative cerebrovascular accident after aortic valve replacement (n=1), subarachnoidal bleeding (n=1), and percutaneous coronary intervention because of progressive angina (n=1). Of the 20 patients with QRS duration >120 ms, 8 had a right bundle branch block, 6 a left, and 6 unspecified. Only one patient (1%) had an elevated cholesterol level of 7.7 mmol/L.

Conventional echocardiographic measurements of all subjects are presented in Table 2. All diastolic measurements in the CoA patients, except for deceleration time, were significantly different from normal controls. Visually assessed systolic

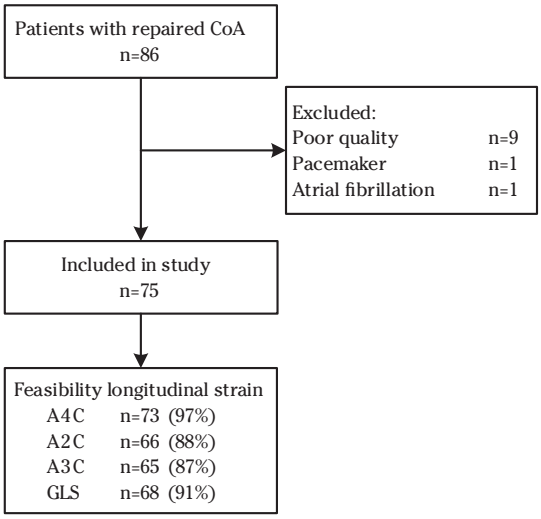

Figure 2 Flow chart of the study patients.
An overview of the patient inclusion and feasibility of the left ventricular longitudinal strain measurements at the different apical views.
A2C = apical two-chamber view; A3C = apical three-chamber view; A4C = apical four-chamber view; GLS = global longitudinal strain.

Table 1 Characteristics of the study population

Clinical characteristics	CoA patients n=75	Healthy controls n=75	*P*-value
Age at time of study (yrs)	33.4 ± 12.8	33.9 ± 10.6	0.793
Female	32 (43%)	32 (43%)	1.000
BMI (kg/m^2)	25.0 ± 4.1	23.4 ± 3.2	0.015
BSA (m^2)	1.90 ± 0.22	1.88 ± 0.16	0.675
Systolic blood pressure (mmHg)	132 ± 17	125 ± 13	0.007
Diastolic blood pressure (mmHg)	79 ± 12	76 ± 9	0.194
Smoker (current or former)	6 (8%)	2 (3%)	1.0
Hypertension*	38 (51%)	0 (0%)	<0.001
Any antihypertensive drugs	33 (44%)	0 (0%)	<0.001
Betablocker	15 (20%)	-	-
ACE inhibitor	13 (17%)	-	-
Angiotensin II antagonist	10 (13%)	-	-
Diuretics	7 (9%)	-	-
Aldosteron antagonist	2 (3%)	-	-
NYHA functional Class I / Class II	74 (99%) / 1 (1%)	75 (100%) / 0	-
Heart rate (bpm)	63 ± 11	64 ± 11	0.701
QRS duration (ms)	113 ± 19	97 ± 10	<0.001
QRS duration >120 ms	20 (27%)	0	-
Age at initial repair (yrs)	2.5 [0.1-11.0]	-	-
Type of initial repair			
End-to-end anastomosis	53 (70%)	-	-
Teflon patch aortoplasty	9 (12%)	-	-
Subclavian flap aortoplasty	8 (11%)	-	-
Bypass	3 (4%)	-	-
Stent	2 (3%)	-	-
Total number of cardiac interventions			
One	35 (47%)	-	-
Two	21 (28%)	-	-
Three or more	19 (25%)	-	-
Repeated coarctation repair	25 (33%)	-	-
Aortic valve replacement	16 (21%)	-	-
Native aortic valve morphology			
Bicuspid	52 (70%)	-	-
Tricuspid	21 (28%)	-	-
Unknown	2 (2%)	-	-
Other congenital cardiac lesions†	33 (44%)	-	-
Ventricular septal defect	20 (27%)	-	-
Patent ductus arteriosus	11 (15%)	-	-
PAPVR	3 (4%)	-	-
Other	9 (12%)	-	-
Cholesterol level (mmol/L)	4.9 [4.0-5.5]	-	-
NT-proBNP (mmol/L)	7.2 [3.6-16.7]		

*Requiring antihypertensive drugs or ≥3 times measured elevated blood pressure (systolic >140 mmHg or diastolic >90 mmHg). †Apart from bicuspid aortic valve.

Categorical data are presented as n (%) and continuous data as mean ± standard deviation or median [interquartile range]. ACE = angiotensin converting enzyme; BMI = body mass index; BSA = body surface area; NYHA = New York Heart Association; PAPVR = partial anomalous pulmonary venous return.

Table 2 Conventional echocardiographic measurements of the study patients.

Echocardiographic measurements	Patients (n=75)	Controls (n=75)	*P*-value
LA dimension (mm)	35 ± 6	33 ± 4	0.124
LV end-diastolic dimension (mm)	50 ± 5	48 ± 4	0.034
LV end-systolic dimension (mm)	31 ± 5	29 ± 3	0.010
LV interventricular septum (mm)	9.7 ± 2.7	8.3 ± 1.5	<0.001
LV posterior wall (mm)	9.0 ± 1.5	8.6 ± 1.2	0.052
LV mass (g)	169 ± 56	136 ± 30	<0.001
LV EF Simpson's (%)	57 ± 7	64 ± 4	<0.001
LV E wave (m/sec)	1.02 ± 0.25	0.76 ± 0.14	<0.001
LV A wave (m/sec)	0.69 ± 0.23	0.43 ± 0.11	<0.001
LV E/A ratio	1.58 ± 0.54	1.90 ± 0.57	0.001
LV deceleration time (ms)	207 ± 62	193 ± 32	0.098
LV E' (cm/sec)	9.0 ± 2.5	11.2 ± 2.8	<0.001
LV E/E' ratio	12.4 ± 5.9	7.1 ± 1.8	<0.001

Data are presented as mean ± standard deviation.
A = peak mitral inflow velocity at late diastole; E = peak mitral inflow velocity at early diastole; E' = early diastolic annular myocardial velocity; EF = ejection fraction; LA = left atrium; LV = left ventricle.

LV function was graded normal in 63 (84%) patients, mildly impaired in 11 (15%), and severely impaired in 1 (1%). The diastolic function was graded as a normal pattern in 54 (72%) patients, abnormal relaxation pattern in 3 (4%), pseudonormal filling pattern in 9 (12%), restrictive pattern in 5 (7%), and in 4 (5%) patients the diastolic function was not analyzable. Aortic stenosis (>2.5 m/s) was observed in 13 (17%) patients. Aortic regurgitation was graded mild in 32 (43%), moderate in 3 (4%) and severe in none of the patients. Mitral regurgitation was graded mild in 20 (27%), moderate in 3 (4%) and severe in none. Tricuspid regurgitation could be measured in 51 patients, of whom 3 (6%) had a peak velocity of >2.8 m/s.

Left ventricular global longitudinal strain

Patients had a significantly lower mean GLS based on all three apical views (-17.1±2.3%), GLS on A4C (-16.9±2.7%), GLS on A2C (-17.9±3.0%), and GLS on A3C (-16.9±2.4%) than the healthy controls (all P<0.001). A sub analysis in the 63 patients (84%) with a visually graded normal systolic LV function revealed that GLS was still significantly lower than in controls (Figure 3). LV EF was measurable in 49 patients of whom 39 (80%) had a normal EF. A sub analysis in these 39 patients, also showed that GLS in all three apical views separately was significantly lower than in controls (all P<0.001).

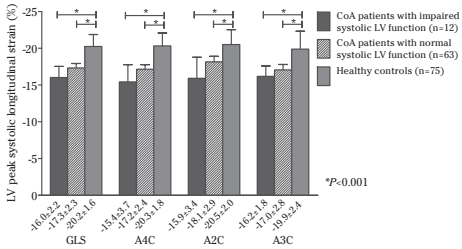

Figure 3 Left ventricular global longitudinal strain in CoA patients with visually graded impaired and normal left ventricular systolic function and in healthy controls.
This figure presents the mean peak systolic LV GLS based on the measurements in the apical four-, two- and three-chamber view, and the mean peak systolic longitudinal strain at these three views separately. Strain values of the patients with visually graded normal left ventricular systolic function and of patients with impaired left ventricular systolic function are both compared with those of healthy controls.
A2C = apical two-chamber view; A3C = apical three-chamber view; A4C= apical four-chamber view; GLS = global longitudinal strain; LV = left ventricular.

Relationships with patient characteristics

Table 3 present the relationships between LV GLS and patient characteristics. Patients with higher BMI, higher blood pressure or longer QRS duration had a lower GLS in all three apical views (Figure 4a and 4b). Patients who had one or more associated congenital cardiac lesions, who had undergone multiple cardiac interventions or who had undergone aortic valve replacement had a significantly lower GLS than patients without these interventions (Figure 5). No significant associations were found between GLS and current age, age at repair or repeated CoA repair.

Multivariable regression analysis with the variables 'systolic blood pressure', 'associated cardiac lesions' and 'aortic valve replacement' revealed that the systolic blood pressure and the presence of associated cardiac lesions were independently associated with LV GLS (β=0.290, *P*=0.009; β=0.353, *P*=0.002, respectively), and that a trend was seen regarding an aortic valve replacement (β=0.188, *P*=0.087). Other significant variables were not implemented in the multivariable analysis because of collinearity between the variables. Patients without comorbidity such as associated cardiac lesions, aortic valve replacement, cardiac reinterventions or hypertension (n=13) still had a lower GLS than the healthy controls (*P*=0.001).

In patients with elevated NT-proBNP, GLS on A4C was significantly lower (*P*=0.010) and GLS based on all three apical views tended to be significantly lower (*P*=0.057).

Relationships with conventional echocardiographic measurements

Table 3 summarises the relationships between LV GLS and echocardiographic measurements. Patients with a higher LV mass, lower LV EF or larger LA dimen-

Table 3 Correlations with left ventricular global longitudinal strain.

	Correlation coefficient	*P*-value
Patient characteristics		
Age*	0.18	0.132
Age at repair*	0.04	0.759
BMI*	**0.29**	**0.018**
Systolic blood pressure	**0.32**	**0.009**
Diastolic blood pressure	**0.31**	**0.009**
QRS duration	**0.34**	**0.005**
Cholesterol level	0.11	0.396
Ln NT-proBNP	0.11	0.393
Echocardiographic measurements		
LA dimension	**0.27**	**0.029**
LV end-diastolic dimension	0.08	0.509
LV end-systolic dimension	-0.02	0.889
LV interventricular septum*	**0.33**	**0.008**
LV posterior wall*	**0.38**	**0.002**
LV mass*	**0.30**	**0.014**
LV EF Simpson's	**-0.48**	**<0.001**
LV E wave	-0.23	0.058
LV A wave*	-0.03	0.815
LV E/A ratio*	-0.20	0.117
LV deceleration time*	-0.05	0.673
LV E'	-0.19	0.149
LV E/E' ratio*	-0.13	0.341

*Spearman's correlation coefficient

A = peak mitral inflow velocity at late diastole; BMI = body mass index; E = peak mitral inflow velocity at early diastole; E' = early diastolic annular myocardial velocity; EF = ejection fraction; LA = left atrium; Ln = natural logarithm; LV = left ventricle; NT-proBNP = N-terminal pro-Brain Natriuretic Peptide.

sion had a lower GLS based on all three apical views (Figure 4c and 4d). LA area did not correlate with GLS. A higher E wave was associated with a higher GLS on A4C (r=-0.25, *P*=0.035) and a trend was found towards higher GLS based on all three apical views. Online Resource 1 presents the clinical and echocardiographic characteristics stratified by tertiles of GLS values.

Intra-observer and inter-observer agreement

The intra-observer agreement for the GLS on A4C was 0.71±1.42% with a COV of 7.2%. The inter-observer agreement was -0.48±1.53% with a COV of 8.0%. Figure 6 depicts the Bland-Altman plots.

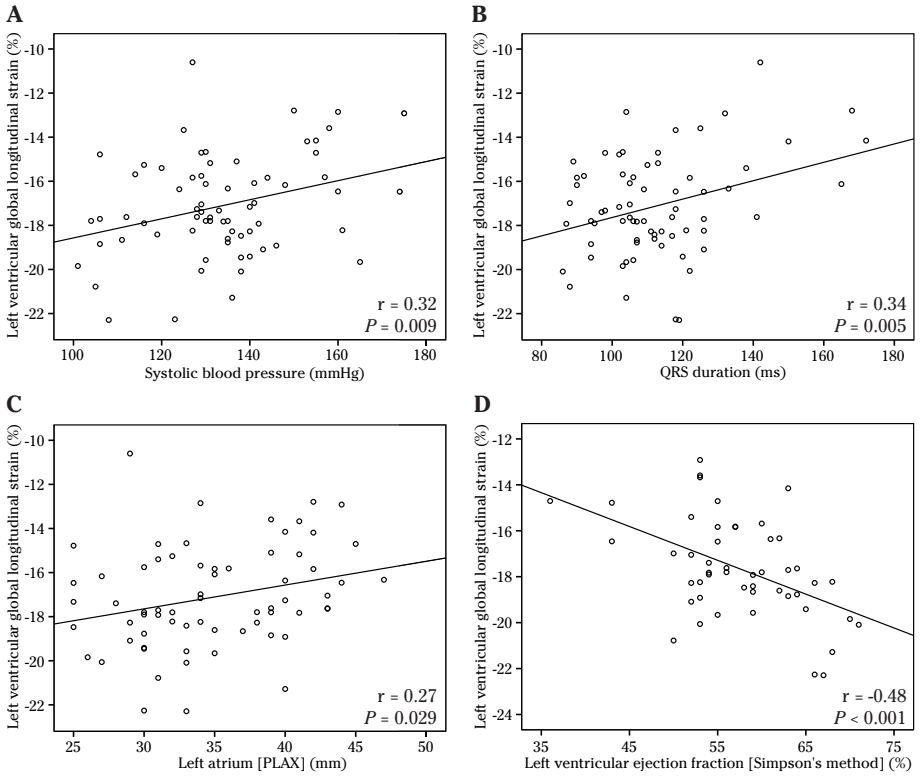

Figure 4 Scatter plots showing correlations with left ventricular global longitudinal strain.
Significant correlations were observed between LV GLS and systolic blood pressure (A), QRS-duration (B), left atrial dimension at parasternal long axis view (C), and left ventricular ejection fraction measured with Simpson's biplane method (D).

DISCUSSION

This prospective study shows that LV GLS is reduced in patients late after CoA repair, providing evidence of subclinical LV dysfunction, which is not detectable with conventional 2D-echocardiography. Although survival of CoA patients have been improved since the introduction of cardiac surgery and percutaneous interventions, morbidity after repair is still substantial. More than one third of these patients encounter late cardiovascular complications after CoA repair. However, these results are from the early years of cardiac surgery.[7] In order to reduce morbidity, detection of early ventricular dysfunction may identify patients at risk of developing ventricular failure or adverse cardiac events. LV GLS could probably be a useful prognostic follow-up tool in these patients.

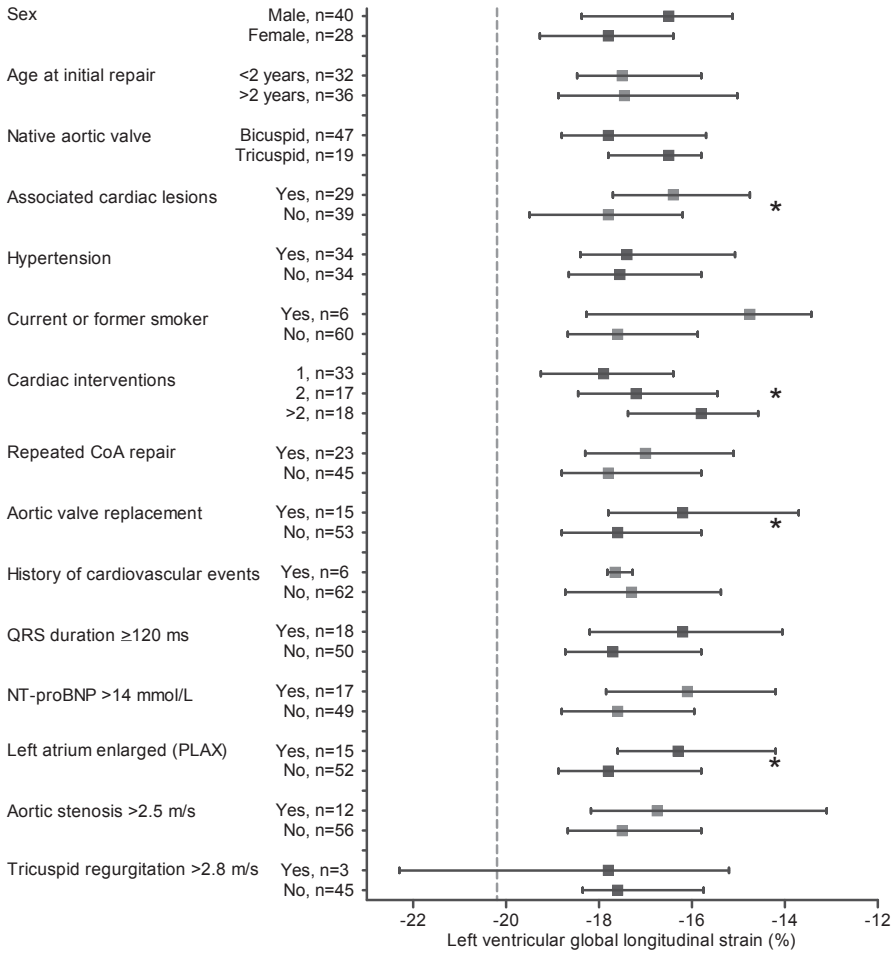

Figure 5 Comparisons of left ventricular global longitudinal strain in CoA patients sorted in various groups

Symbols present median and whiskers present interquartile range. The dashed grey line depicts the mean LV global longitudinal strain of the healthy controls. *P<0.05 PLAX = parasternal long axis view.

Decreased left ventricular global longitudinal strain

The feasibility of GLS was higher than the feasibility of EF by Simpson's method. This could be explained by the fact that with STE speckles are followed instead of tracing the endocardial border by Simpson's. The last method requires higher quality images. Another important finding is that adult patients after CoA repair have decreased LV GLS while their EF is measured as normal. This was also observed in a recent study with CMR feature tracking.[17] Older age at repair has been shown as a predictor for LV long-axis dysfunction [18], however, even in children with

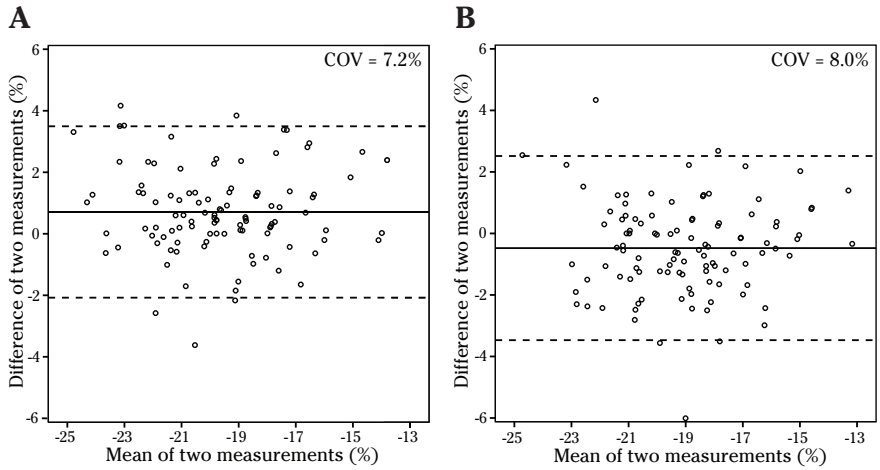

Figure 6 Bland-Altman plots demonstrating intra-observer and inter-observer agreement.
Left ventricular global longitudinal strain measurements on apical four-chamber view for intra-observer (A) and inter-observer agreement (B). The solid lines depict the mean difference of two measurements, and the dashed lines depict the limits of agreement. COV = coefficient of variation.

CoA repair, a decreased GLS was already observed whereas the EF was normal.[19] In our cohort, patients more often had impaired LV diastolic function than controls, which is in line with the observed abnormal LV diastolic function in children with CoA.[20] Lombardi *et al*. found a strong correlation between proximal ascending aortic elasticity and diastolic function in all children and suggested that, although CoA repair was successfully performed, persistently elevated aortic stiffness may lead to diastolic impairment. Arterial stiffness is a risk factor for cardiovascular events and mortality, and is associated with aging, hypertension and systemic disorders.[21] The relationship between arterial stiffness and intima media thickness with LV systolic and diastolic deformation has also been described in adults after CoA repair [11] and corresponds with our finding that blood pressure correlates with LV deformation. A meta-analysis of possible demographic and hemodynamic variables that contribute to LV GLS in healthy subjects showed that only blood pressure was independently associated with strain values.[22] However, even in the patient group without hypertension, we still observed a decreased GLS compared with controls suggesting that other factors apart from blood pressure have impact on LV GLS. Besides the arterial stiffness, GLS could also be affected by myocardial fibrosis or by inflammation.[23,24] The observed chronic inflammatory and possibly apoptotic reaction in adults with repaired CoA reflects a functional problem in all vessels, regardless of the initial lesion. This could be implied by the increased levels of circulated cytokines specifically related to vascular endothelial dysfunc-

tion.[24] All these factors may explain why CoA patients have an increased risk of developing late cardiovascular complications despite early repair and improved surgical procedures. To state whether decreased strain really enables the detection of preclinical LV dysfunction, follow-up studies are warranted in both children and adults. In addition, studies are needed to determine whether it is possible with the use of strain to distinguish between patients who will and who will not benefit from early treatment to reduce morbidity.

Relationships with patient characteristics

Univariable regression analysis showed that patients who had associated congenital cardiac lesions, who underwent multiple cardiac interventions or who underwent aortic valve replacement had a more decreased GLS. This adverse interaction could partly be explained by the interventions themselves and probably by the long-time exposure to volume or pressure overload. In contrast, we did not find a significant difference in strain between patients with one CoA repair versus repeated CoA repair. Higher current blood pressure is related to lower GLS in our patient group. However, there is no significant difference in GLS between patients who met the criteria for hypertension and those who did not. This could possibly be explained by the antihypertensive drugs used by these patients resulting in a normal blood pressure nowadays. These findings stress the importance of tight blood pressure regulation in this patient population even after successful CoA repair. The effect of tight blood-pressure control on GLS in these patients may be of interest and deserves further study.

Patients with CoA more often have hypertension and hypercholesterolemia which predispose to coronary artery disease.[6] However, only 6 (former) smokers were included in our study and only one patient had an elevated cholesterol level. Therefore, no conclusions can be drawn regarding these risk factors and GLS.

Relationships with conventional echocardiographic measurements

Although the anteroposterior LA diameter did not differ significantly from that of healthy controls, we observed that the LA diameter correlated with the GLS. This suggests LV-LA interaction which is in line with the arterial-LV-LA interaction observed in CoA patients [11], as well as in preclinical patients with cardiovascular risk factors.[25] An enlarged LA, even when measured only in anteroposterior direction, is associated with adverse cardiovascular outcomes.[26] In contrast, LA area did not correlate with GLS, possibly due to the poor image quality of the LA at the A4C. Furthermore, LV mass is an important risk factor for cardiovascular events.[27] In our study, a higher LV mass, but also thicker LV posterior wall and interventricular septum, both important parameters for LV mass, were associated with lower GLS.

The patients of our study cohort were relatively young with a mean age of 33 years, and therefore surveillance of GLS might be regarded as an important treatment target in reducing the risk for events.

Intra-observer and inter-observer agreement

The coefficients of variation for the intra-observer and inter-observer measurements were acceptable and comparable to other STE studies.[28,29]

Limitations

A limitation is the relatively heterogeneous group of patients restricting the ability to perform some subgroup analyses. Significant differences we found between subgroups should be interpreted with caution.

CONCLUSIONS

Despite a well-repaired CoA, the majority of adult patients have decreased LV GLS at late follow-up, while conventional 2D-echocardiography showed normal systolic LV function. Patients with higher blood pressure, associated congenital cardiac anomalies, higher LV mass or larger LA dimension have more decreased LV GLS. Whether decreased LV GLS will eventually lead to clinical heart failure and can identify patients in subclinical heart failure, and whether early detection can reduce morbidity, needs to be investigated in follow-up studies.

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ONLINE SUPPLEMENT

Online Resource 1. Clinical and echocardiographic characteristics stratified by global longitudinal strain values in tertiles

Tertiles (GLS, %):	**10.6-16.1%**	**16.2-17.9%**	**18.0-22.3%**	***P*-value**
	n=23	**n=22**	**n=23**	**Kruskal wallis**
Age (years)	37.1 [21.6-48.4]	27.8 [22.6-35.4]	30.2 [20.7-37.7]	0.394
Body mass index (kg/m^2)	26.3 [23.5-28.7]	24.4 [21.9-28.4]	22.8 [21.3-26.3]	0.097
Systolic blood pressure (mmHg)	131 [127-155]	131 [127-140]	135 [119-140]	0.583
Diastolic blood pressure (mmHg)	81 [75-90]	80 [74-85]	74 [67-79]	0.047
QRS duration (ms)	113 [103-138]	106 [97-118]	112 [104-119]	0.32
LA dimension (PLAX) (mm)	36 [32-41]	36 [30-42]	33 [30-35]	0.052
LV end-diastolic dimension (mm)	51 [46-55]	49 [47-53]	49 [45-53]	0.702
LV end-systolic dimension (mm)	31 [28-33]	31 [28-35]	31 [27-33]	0.812
Interventricular septum (mm)	10 [9-11]	9 [8-11]	9 [8-10]	0.018
LV posterior wall (mm)	10 [9-10]	9 [8-10]	8 [7-9]	0.023
LV mass calculated (g)	181.1 [146.9-214.2]	160.0 [138.3-210.7]	149.45 [120.2-175.0]	0.127
LV EF Simpson's (%)	54 [52-57]	56 [54-61]	61 [53-66]	0.032
LV deceleration time (ms)	185 [160-218]	191 [159-251]	201 [175-241]	0.784
LV E-top (m/sec)	0.87 [0.73-1.17]	1.00 [0.86-1.20]	1.10 [0.90-1.16]	0.092
LV E/A-ratio	1.33 [1.09-1.66]	1.49 [1.27-1.99]	1.58 [1.26-2.25]	0.161
LV E' (cm/sec)	8.11 [6.68-9.49]	9.80 [8.34-12.60]	8.89 [7.68-11.43]	0.035
NT-proBNP	9.4 [2.7-21.1]	7.2 [5.2-13.9]	5.5 [2.6-10.3]	0.475

Data are presented as median [1st quartile-3rd quartile].
E = peak mitral inflow velocity at early diastole; E' = early diastolic annular myocardial velocity; EF = ejection fraction; GLS = global longitudinal strain; LA = left atrium; LV = left ventricle; NT-proBNP = N-terminal pro-Brain Natriuretic Peptide; PLAX = parasternal long-axis view

Epilogue

CHAPTER 13

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

This thesis investigated the long-term outcome in adult patients with congenital heart disease (CHD) and evaluated novel, non-invasive echocardiographic techniques in both a healthy population and in adult patients with CHD. These novel echocardiographic techniques could contribute to a more accurate quantitative assessment of left ventricular (LV) and right ventricular (RV) function. Especially in the field of CHD, focus on the right heart is of eminent importance. Due to the fact that most acquired cardiovascular diseases affect primarily the LV, the emphasis in cardiology has predominantly been on imaging of the left heart. This has resulted in less clinical experience in how to study the RV. As a result of the retrosternal position and the complex shape of the RV, imaging and functional assessment with ultrasound can be difficult. With novel echocardiographic techniques as speckle-tracking echocardiography (STE) subtle changes in myocardial deformation can be detected, which may be a sign of early ventricular dysfunction.[1, 2] With the early detection of ventricular dysfunction, we aim for a better outcome for CHD patients. In this general discussion, we will address our research questions and discuss the outcomes against the background of published literature. We will end this chapter with a brief discussion on future perspectives.

Novel echocardiographic techniques in a healthy population

During the last decade, two-dimensional (2D) STE has become available which offers objective measurements to quantify regional and global ventricular function, independent of angle and ventricular geometry.[3] With the use of STE, ventricular dysfunction may be detected in a pre-clinical phase. However, information on normal ranges of STE-derived measures and the prognostic value of deviant measures is limited, especially in patients with repaired or unrepaired CHD.[1, 2, 4, 5]

The first part of this thesis focuses on novel echocardiographic techniques in the healthy population. We initiated an echocardiographic study with 155 healthy individuals, the Navigator study, to obtain normal values for STE-derived parameters. These subjects were recruited in a stratified fashion to provide at least fourteen participants of each sex, representing each age decade from 20 to 72 years. In addition, we evaluated possible associations between longitudinal strain and anthropometric factors, such as age, sex, body mass index, body surface area and blood pressure. **Chapter 2** demonstrated that LV peak systolic global longitudinal strain (GLS) was higher in female than male subjects. The higher LV GLS in women described by us corresponds to the study of Taylor *et al.*[6] who measured GLS with feature-tracking cardiovascular magnetic resonance (CMR). We could not provide a clear explanation for these higher values. This however is not an incidental find-

ing, as indicated by the decision of the European Society of Cardiology writing group on the current guidelines that the clinical cut-off values for normal LV ejection fraction are higher for women than men.[3] In recent years, increasing attention has been paid to sex differences regarding cardiovascular diseases. Differences in LV and RV structure and function have been described, including larger volumes and greater mass in healthy men than in healthy women.[7-9] In contrast, in a meta-analysis including 2,597 healthy normal subjects, no difference in LV GLS was found related to sex.[10] The different vendors that have been included in this study might have had an influence. Nevertheless, our findings of sex-dependent variations in longitudinal strain, and the earlier reported variations in cardiac mass and volume, advocate the use of sex-specific normal values for myocardial deformation in clinical practice.

Besides the finding that sex affects LV GLS, body surface area and blood pressure were also associated with LV GLS. Indexation of LV GLS for body surface area resulted in even stronger correlations regarding blood pressure and sex. Therefore, we advise to correct strain not only for sex, but also for body surface area, as only appropriate reference values can be used in the determination of normality or abnormality of ventricular function. In the light of this popular topic regarding more tailored reference values, it would be interesting to examine the possible differences in myocardial deformation with regard to races and ethnicities in large studies. These factors could also be crucial to take into account when interpreting strain results.

In clinical situations, the majority of ultrasound laboratories use several ultrasound machines from different vendors for routine echocardiographic examinations. One of the main disadvantages of STE is the intervendor variability. Published studies aiming to clarify differences in strain values between specific disease states and normal conditions often used different ultrasound vendors with different analytical software and cutoff values.[11] Intervendor peak strain values measured by vendor-specific software in the same subjects are frequently different and seem incomparable.[12] This limitation has raised concerns whether STE can become an acceptable mainstream methodology in daily clinical application, especially in laboratories with echocardiographic machines from multiple vendors.[13] In response to these intervendor discrepancies, a task force has been established consisting of members of the European Association of Cardiovascular Imaging, members of the American Society of Echocardiography and technical representatives from interested vendors to reduce the intervendor variability of strain measurement.[14, 15] They developed a consensus statement to communicate standard physical and mathematical definitions of various parameters commonly reported in myocardial-deformation imaging. Subsequent to the standardisation

created by this task force, the concordance in LV GLS between two leading ultrasound manufactures (Philips and GE Medical Systems) has been improved.[13] Our LV longitudinal strain measurements in healthy controls were assessed with QLAB 10 (Philips Medical Systems, Best, the Netherlands), a software package released after the work of the joint standardisation task force. To our best knowledge, our study was the first study reporting normal LV longitudinal strain values for QLAB software after the strain standardisation. Even though the task force worked toward harmonising GLS measurements resulting in acceptable intervendor variability, a certain variability still exists.[11] Until now, not all vendor systems and versions have been evaluated for improved intervendor concordance making it unjustified to extrapolate the results to all systems used in clinical work and research. Therefore, it remains of paramount importance to continue this task force and to bring vendors, cardiologists and scientists together to openly discuss the technical as well as the clinical issues they encounter. Exchange of their expertise and experiences will give vendors opportunities to tune their software, to provide more uniformity in results, and to make it more user friendly and less time-consuming. Only then can STE become a diagnostic tool in routine clinical care and patient follow-up. Although we strive for improvement and wider use of strain for diagnostic purposes, we may have to accept that complete concordance between strain measurements remains elusory as variability issues also occur in other cardiovascular-imaging modalities and measurements.

Assessment of RV function is of utmost importance in patients with CHD. Echocardiographic evaluation of RV is challenging because of the complex shape and its retrosternal position. Unlike the LV that can be completely visualised from one apical window, a multi-view approach is necessary for a comprehensive evaluation of RV size and function.[3, 16] Current echocardiographic methodologies do not provide a robust assessment of RV function. Due to the lack of fixed anatomic landmarks, serial follow-up of RV measurements results in significant inaccuracies.[16] In **Chapter 3**, our study showed that among the healthy subjects of the Navigator study, a 13-segment standardised model for RV assessment is feasible using 2D-iRotate mode. The iRotate mode is a new visualisation tool developed by Philips,[17] which consists of a matrix transducer that can electronically steer the ultrasound beam through 360° to obtain different views within the acoustical window, rather than manually rotating the transducer. The 13-segment model created by us was based on unique anatomic landmarks and achieved from a single acoustic window. As far as we know our study is the first to assess tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler imaging (S′) measurements from the tricuspid annulus on the multiple views. Although many segments of the RV walls could be visualised, the visibility of the RV outflow tract anterior wall remained

challenging. On the other hand, in the pilot study with the diseased RVs (dilatated or hypertrophic), the long axis of the heart was more horizontal and therefore the sternum distorted the image quality to a lesser degree. We would therefore expect that the rotation with iRotate mode around diseased RVs to be easier than around normal-sized RVs resulting in better image quality. Whether these multiple RV views are suitable for adequate STE and applicable for daily clinical use has to be investigated.

Clinical outcome and early detection of ventricular dysfunction in repaired tetralogy of Fallot

The second part of this thesis encompasses the evaluation of long-term outcome and complications in adult patients after tetralogy of Fallot (ToF) repair and the usefulness of STE in these patients to detect ventricular dysfunction at an early stage.

In **Chapter 4**, we described the clinical outcome of a unique prospectively followed cohort of unselected ToF patients.[18] After excluding postoperative mortality within 30 days, the 40-year survival after surgery was 86%. This is slightly lower than the survival of the general Dutch population. The causes of late mortality in our cohort were heart failure and arrhythmia which are in line with the literature.[19-22] However, those studies had a retrospective design and most of them had a shorter follow-up duration. In the fourth decade after surgery, the morbidity continued to worsen with an incidence up to 75%. The most frequent events were reoperations and arrhythmias. The systolic RV function was impaired in more than 75% of the patients and systolic LV function in half of the patients. Nonetheless, the self-perceived health status was excellent and objective exercise capacity remained stable over the last ten years. This generally good self-perceived health status among ToF patients, despite declining cardiac function, was also reported by others.[23] Self-assessment may be a misleading portrait of the disease state and may delay the presentation for treatment.[24] Heart failure is one of the main causes of death in adult ToF patients. To identify the patients who are at risk for heart failure, it is essential that their ventricular function could be adequately monitored and declining function to be detected earlier. Better risk stratification at an early stage would probably result in a more suitable medical treatment regimen or more precise timing for reinterventions. However, it must be stated that adequate medical therapy is not easy to achieve. Most of the commonly used and effective drugs which are prescribed in left-sided heart disease, have not been proven beneficial in patients with right-sided lesions such as ToF patients.

Amongst ToF patients, the RV has been the ventricle of interest for years. Progressive RV dilatation and dysfunction, as a result of pulmonary regurgitation, are

common and are well-established risk factors for adverse clinical outcomes.[25, 26] Nowadays, some studies report that LV dysfunction is also a strong independent determinant of clinical outcome. Therefore, late deterioration of both RV and LV function has been an increasing concern.[27-30] In our cohort, as described in Chapter 5, we indeed found a significant relationship between the dysfunction of RV and LV measured with conventional echocardiography and cardiac magnetic resonance imaging (CMR). Nonetheless, only limited data exist relating the early detection of LV dysfunction and the utility and prognostic importance of STE-derived values among patients with repaired ToF. In patients with acquired heart disease or chronic kidney disease, LV GLS assessed by STE is a predictor of cardiovascular events such as heart failure.[31] LV GLS is even a predictor superior to LV ejection fraction of all-cause and cardiovascular mortality.[32, 33] STE can not only be used for quantitative assessment of ventricular function by strain measurement, but also for better understanding of ventricular-ventricular interaction.

In **Chapter 5** and **Chapter 6**, we gained more insight into ventricular-ventricular interaction by evaluating STE-derived strain and rotational parameters in a cohort of adult patients with repaired ToF. In **Chapter 5** we described the results of peak systolic longitudinal strain of the LV and the RV free wall measured with STE in a cohort of 94 ToF patients and 85 healthy controls.[34] In this cross-sectional study, RV as well as LV peak systolic longitudinal strain were lower in the patients than in the healthy controls. Of the RV free wall, especially the apical deformation was impaired suggesting that apical function is most affected in volume overloaded RVs. The RV free wall strain of our adult patients was related with their LV GLS. Of the LV, the septal strain was mainly decreased. Both findings indicate potential ventricular-ventricular interaction. The assessment of ventricular-ventricular interaction in children also revealed that RV free wall strain and LV GLS were closely related and that LV strain was significantly decreased at the mid and apical levels.[35] Ventricular-ventricular interaction could probably be explained by the shared myocardial fibers, changes in septal curvature and electromechanical dyssynchrony. Additionally, in this chapter we reported a trend towards a significant relationship between LV GLS and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a well-established biomarker in acute and chronic heart failure due to acquired heart disease. Besides alterations in longitudinal strain, we also investigated rotational movements of the LV in 82 adult patients after ToF repair, as described in **Chapter 6**. The majority of ToF patients had a reduced LV twist compared with controls, mainly as a result of decreased apical rotation. Patients with a decreased or abnormal apical rotation had larger LV dimensions and worse systolic biventricular function.[36] These findings strengthen the hypothesis that RV dysfunction adversely affects LV function. Already in childhood, a reduced

LV twist could be observed.[35, 37] This reduced LV twist could be caused by RV dilatation. RV dilatation, which is most pronounced in the apical part, may lead to distortion of LV apical geometry and altered fiber orientation of the apex of the heart.[38] Subsequently, these alterations could result in abnormal or decreased LV apical rotation and eventually LV dysfunction. Adverse ventricular-ventricular interaction may also be affected by abnormal motion of the interventricular septum, because abnormal septal motion was more often seen in patients with abnormal twist. Another explanation for the ventricular-ventricular interaction could be the obligatory interventricular septal defect patch which had been used during repair. This patch results in dysfunction of at least a portion of the ventricular septum[39, 40] and may contribute to abnormal basal rotation. In **Chapter 7** we focused more in depth on the association between NT-proBNP and cardiac function in 177 adults with repaired ToF.[41] NT-proBNP levels were (slightly) elevated in more than 50% of the patients, while they were in stable clinical condition. Higher NT-proBNP levels were associated with LV dysfunction rather than RV dysfunction, and with larger LV and RV dimensions. Furthermore, patients with an abnormal LV twist pattern more often had elevated NT-proBNP levels than patients with a normal LV twist pattern. In children with repaired ToF, NT-proBNP was not related to systolic LV function, presumably because LV function in these children is generally still normal.[42]

These associations discussed above of STE-derived parameters and NT-proBNP in adults with repaired ToF are promising. Because STE may enable the detection of changes in cardiac function earlier than currently used tests, such as conventional echocardiography or CMR, this technique could actually play an important role in clinical decision making. Therefore, abnormal apical rotation, decreased longitudinal strain and elevated NT-proBNP levels are new and important objective diagnostic criterions for detection of early and subclinical ventricular dysfunction in ToF patients. Whether these measures really have the potential to be included in patients' routine examination to monitor ventricular function and to detect clinical deterioration before ventricular dysfunction becomes apparent, is unclear and remains to be established in a prospective study. Moreover, further research in this field is clearly warranted to determine whether the use of these measures as objective diagnostic tools really provide the possibility for more accurate timing of medical treatment or reinterventions. An important requirement for reliable follow-up measurements and cut-off values for treatment is that the intra-observer and inter-observer agreements of RV strain have to be improved. The variability of current RV measurements is too large to determine accurate and applicable reference values. The software packages we used had an algorithm developed for the LV. Hence, dedicated software packages should be developed

for the RV. Furthermore, the image quality of the RV walls has to be improved to result in greater feasibility and more adequate tracking. Advances in technology are promising and will probably result in better image quality in the future. On the other hand the Dutch population, including those with CHD, are becoming more adipose which makes the acquirement of good-quality images more troublesome. Therefore, we postulate that satisfying image quality of the RV will remain an issue in the forthcoming years.

Clinical outcome and early detection of ventricular dysfunction in other congenital heart anomalies

The third part of this thesis delineates the long-term outcome and ventricular function in patients with a repaired ventricular septal defect (VSD), repaired atrial septal defect (ASD), repaired coarctation of the aorta (CoA) or a systemic RV.

A VSD is by far the most common CHD in children.[43] The presence of a significant left-to-right shunt can cause LV overload, pulmonary arterial hypertension, ventricular dysfunction, arrhythmias, and aortic regurgitation.[44, 45] Surgical closure at young age is the treatment of choice. With a greater number of adults surviving decades after successful surgery, the urgency is growing for better characterisation of CHD-related morbidities and mortality that occur late after surgical intervention.[46] Because most such patients have been discharged from routine cardiological follow-up, limited data regarding outcomes in late survivors of VSD closure were available.[47-50] In addition, most studies that have been published included only patients who are still seen at the adult outpatient clinic, creating a publication bias. In **Chapter 8**, we provided additional information by describing the long-term outcome in a unique longitudinally followed cohort of VSD patients who underwent surgical repair at a young age.[51] After exclusion of early postoperative mortality, 40-year survival after surgical closure was 86%. This is slightly lower than of the general Dutch population, and comparable with the survival of our cohort with ToF patients.[18] In more than one-half of the cases, late mortality was cardiac related. An important issue after VSD surgery is the occurrence of aortic regurgitation. In our cohort, the prevalence of aortic regurgitation nearly doubled over the last twenty years of the study, from 11% in 1990 to 21% in 2012. Systolic LV function was impaired in 21% of the patients but remained stable over the last decade. Meanwhile, systolic RV dysfunction increased over the last ten years to 17%. The vast majority of patients with systolic RV dysfunction had systolic LV dysfunction and more often had elevated RV systolic pressure. This biventricular dysfunction could be explained either by the presence of a pacemaker in a quarter of patients with RV dysfunction or by ventricular-ventricular interaction. In the case of LV dysfunction, pulmonary pressure increases, which results in reduction

of RV contractility. Moreover, ventricular-ventricular interaction is mediated by forces at the interventricular septum and mechanical coupling through shared myocardial fibers: when the LV becomes more spherical, the fibers of the interventricular septum become less oblique, which reduces and impairs RV contractile function.[52, 53] Among children up to 20 months after surgical VSD closure, a systolic RV impairment was already found with tissue Doppler imaging.[54] Although this subclinical RV impairment may not be of direct clinical relevance, it could be a first sign of systolic RV dysfunction and stresses the importance of detailed evaluation of RV function after VSD surgery. The progressive decline in ventricular function at adult age raises concerns that a significant proportion of these patients are at risk for developing heart failure in the future.

The next two chapters shed further light on long-term outcome and ventricular function in patients after surgical ASD repair. In **Chapter 9** we described the results of a longitudinal follow-up of a cohort of patients who underwent surgical closure of a hemodynamically significant ASD at young age.[55] The 40-year survival was comparable with the normal Dutch population. Despite the morbidity of 30%, no heart failure was observed and the exercise performance was normal. On both conventional echocardiography and CMR, the RV function was abnormal in one-third of the patients. This was somewhat unexpected as RV function was normal in all patients ten years ago. Signs of pulmonary hypertension, a major problem that may occur in patients without closure of the ASD,[56] were not found. One-fifth of the ASD patients had mild LV dysfunction on CMR, which could be driven by ventricular-ventricular interaction. Literature on LV and RV deformation in adult patients late after surgical ASD repair was lacking. Therefore we used STE to assess longitudinal strain among 51 ASD patients at least 30 years after surgical repair as described in **Chapter 10**.[57] Even though these patients were already operated in childhood, peak systolic RV free wall GLS was lower than in healthy controls. Presumably, this reduction is either a result of the preoperative chronic volume overload or related to the closure technique. Both children and adults without ASD closure have higher RV GLS than healthy controls due to volume overload.[58-60] The RV volume overload induces ventricular remodelling which possibly also took place in our patient group before closure. Besides preoperative volume overload, the surgery itself, including factors such as closure technique and the use of cardiopulmonary bypass or hypothermia, might also contribute to decreased RV deformation. To confirm that surgery is a possible cause, a longitudinal study is recommended comparing strain of patients with a surgically closed ASD with strain of patients with a percutaneously closed ASD after the same follow-up length.

A remarkable finding is that the RV strain was most decreased in the apical segment, like we also observed in ToF patients. The more profound impairment of the apical deformation in both patient groups is a debatable subject. A first possible explanation may be the thinner and more trabeculated apical portion compared to the basal portion. When the wall is thinner, the passive wall stress is higher, which is inversely related with strain and therefore results in smaller longitudinal deformation. Secondly, remodelled volume overloaded RVs seem to have a more straight apical segment. Structures with straight walls have to deal with higher wall stress. Thirdly, it could be possible that in some RVs a hypertrophied moderator band and trabeculations lead to a smaller regional volume and therefore might decrease the apical deformation. Lastly, it could be explained by alterations of β-adrenergic receptor signaling. RV volume overload leads to β-adrenergic signaling abnormalities, e.g. increased levels of β-adrenergic receptor kinase 1, and redistribution which result in a significant reduction in chamber contractility.[61-64]

The mean LV GLS of the ASD patients was comparable with that of controls which is in line with adults who underwent percutaneous closure.[58] When focused on regional LV deformation, the strain of the apical septum was decreased. A similar but more pronounced finding was observed in our ToF cohort. Furthermore, LV GLS was positively correlated with RV free wall GLS in both patient groups. Thus, also findings in ASD patients support the principle of ventricular-ventricular interaction, i.a. due to the diminished RV function that interacts with the septum. However, the exact impact of the preoperative chronic volume loading on RV and LV function in later life is still not completely elucidated. We recommend following these patients to determine whether they will develop heart failure in the coming decades.

In **Chapter 11**, we examined a more challenging group of patients with STE: patients with a systemic RV.[65] A morphologic RV supports the systemic circulation in patients with transposition of the great arteries repaired by an atrial switch procedure (TGA-Mustard) and in patients with congenitally corrected TGA (ccTGA). RV geometry is not made to encounter this chronic pressure overload.[62] Therefore, patients with TGA-Mustard and ccTGA are afflicted by RV dysfunction leading to heart failure. This complication adds to morbidity and induces excess mortality in this population.[66-68] Hence adequate monitoring and early detection of deterioration in RV function is a key point in the follow-up of these patients. Our study demonstrated that patients with a systemic RV have lower GLS of the systemic ventricle than healthy controls. The lower strain is most pronounced in the apical segments, suggesting that apical function has suffered most from chronic pressure overload. Thus, besides volume overload as in ToF and ASD patients, also pressure overload affects the apical part particularly. GLS of the

systemic RV among patients in NYHA class II tended to be lower than among patients in NYHA class I. NYHA functional class has shown to be an independent predictor of worse clinical outcome, i.e. heart failure, heart transplantation, and death, in patients with a systemic RV.[69] The tendency of worsening NYHA class indicates the potential prognostic value of strain measurement in patients with a systemic RV. Average GLS of the RV free wall was lower in patients with TGA-Mustard than in patients with ccTGA. This is an interesting finding, while with conventional echocardiography clear differences between the two groups have not previously been described. Possibly, the lower free wall GLS was caused by the 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,[70] or gain in circumferential strain in young adolescents after Senning surgery.[71] Another reason for better preserved GLS in patients with ccTGA could be that their RV is more resistant to chronic pressure overload. The RV of ccTGA patients encounters systemic pressure from birth, whereas the RV of patients with TGA-Mustard did not. Furthermore, the difference could be explained by the absence of additional atrial function in patients with TGA-Mustard. Although we know that both patients with TGA-Mustard and ccTGA will develop RV dysfunction and heart failure,[66, 72] this difference may indicate that decline in RV function is less progressive in patients with ccTGA than in those with Mustard-TGA.

In **Chapter 12** we evaluated LV GLS in 75 adult patients after CoA repair and in 75 healthy controls. This patient group had been exposed to chronic LV pressure overload. Although survival among these patients has improved since the introduction of repair, the morbidity is still considerable.[73, 74] To improve cardiovascular outcome, early detection of LV dysfunction could be helpful. In a cross-sectional manner, we showed that LV GLS was reduced in many patients, which was not detectable with conventional 2D-echocardiography providing evidence of subclinical LV dysfunction. A comparable finding was also observed with feature-tracking CMR.[75] In addition, we found lower LV GLS when patients had higher blood pressure, associated cardiac lesions, aortic valve replacement or a larger left atrium. The association of LV GLS with blood pressure in CoA patients deserves additional attention because it corresponds with the association found in the healthy subjects described in Chapter 2. A recently published paper reported that higher cumulative exposure to blood pressure over 25 years from young adulthood to middle age was associated with lower LV longitudinal strain, but not with LV ejection fraction.[76] These findings reflect that a relatively small increase in afterload will result in lower LV GLS rather than lower LV ejection fraction. This may make strain a sensitive marker for incipient LV dysfunction caused

by higher blood pressure. To improve patients' cardiovascular outcome after CoA repair, earlier and/or stricter blood-pressure control might be essential. LV GLS may carry diagnostic and prognostic value in such strategy and may be more optimal than LV ejection fraction. The clinical utility of LV GLS in these patients and the precise effect of strict blood-pressure control on LV GLS deserve further study.

CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis sheds further light on the long-term outcome and ventricular function in adult patients with various types of CHDs. We also studied newly introduced echocardiographic techniques in both healthy controls and CHD patients. STE is a relatively inexpensive and safe imaging modality that provides a more accurate method in quantitative analysis of ventricular function than the currently used standard 2D-echocardiography. STE also enables detection of subtle changes in myocardial wall deformation. We hope that these advances will reduce morbidity in the future.

Nowadays, the survival of patients after surgical repair of various CHD types is good. Notwithstanding, the morbidity and the occurrence of ventricular dysfunction are substantial. The most frequent events are reinterventions and arrhythmias. Improvement of risk stratification to identify patients who are at high risk for developing complications is important. These high-risk patients would probably benefit from more frequent and intensified checks, adjustments in medical treatment or undergoing interventions, whereas in low-risk patients fewer checks are required. Such risk stratification may also improve the cost effectiveness in health care. Newer echocardiographic techniques described in this thesis seems to provide a robust tool for detection of subclinical functional and structural cardiac changes, and also for evaluating the natural history and the efficacy of therapeutic interventions over time. Based on the current results, however, we can only speculate that the early detection of abnormal RV and LV deformation may ultimately lead to a successful attempt to slow disease progression. For example, the benefit of earlier surgical or percutaneous reinterventions or neurohormonal blockade to reverse the ventricular remodelling and prevent clinical heart failure is unknown in this population. Our studies concerning the assessment of STE in patients, were conducted in a cross-sectional design. Prospective follow-up studies providing information about adverse events are warranted to determine the clinical and predictive value of STE and the effectiveness of a treatment.

Better understanding of the pathophysiology of CHD will probably enable us to modify the disease process resulting in regression of subclinical ventricular

changes. However, we must acknowledge that the precise nature of LV dysfunction after surgical ToF repair and the underlying mechanisms driving adverse ventricular-ventricular interactions in this condition remain incompletely understood. The role of surgical modifications at time of repair, pulmonary or aortic regurgitation, residual RV outflow obstruction, pulmonary stenosis, aortic recoarctation, aortic root dilatation, septal mechanics, electro-mechanical dyssynchrony, residual shunts and timing of interventions are all factors that could affect biventricular function in patients with CHD. Therefore, large prospective studies are required to define cause and effect.

The reproducibility of STE-derived LV longitudinal strain in healthy controls is good. We recommend the use of sex-specific and body-surface-area-dependent reference values. The reproducibility of LV longitudinal strain in CHD patients was acceptable. However, it should be emphasised that this imaging technique has its limitations. Although the complex-shaped RV could be visualised with conventional 2D-echocardiography and iRotate mode, the reproducibility of STE-derived strain from the RV was considerably lower than from the LV and thus worrying. The variability of RV strain was acceptable for research purposes, e.g. the assessment of regional dysfunction or analysing ventricular interaction. However, the variability was too large to establish accurate and applicable reference values for diagnostic purposes and for individual patient follow-up. The lower reproducibility of RV measurements may be caused by the lack of software packages specifically for the RV. At the moment we have to use an LV-based algorithm, hence, it is necessary for dedicated software packages to be developed for the RV. Reproducibility could be further increased by improving image quality of the RV walls. Advances in technology are promising and will probably result in better image quality in the future. On the other hand, patients are becoming more adipose which makes the acquirement of good-quality images more challenging. Therefore, we postulate that satisfying image quality of the RV will remain an issue the forthcoming years. Another limitation of STE we encountered, was the time-consuming offline-analysis. It would be a step forward to the widespread clinical use and routine day-to-day imaging when the analysis can be performed at bedside whereby the results of the measurements could immediately be seen on the screen. These observations underline the importance for innovations regarding a reliable, inexpensive and minimal time-consuming quantitative assessment of the RV. Subsequently, studies are required which critically validate newly introduced techniques in healthy volunteers and in patients afterwards.

Overall, this thesis provides an overview of long-term clinical outcome and cardiac function in adult patients with CHD. As a result of the observed morbidity, we advise a lifelong clinical follow-up for all CHD patients. The clinical use of STE

is promising in this field, although some limitations have to be overcome. We hope our results motivate new study fields that may eventually lead to an improvement in the prognosis of this patient group.

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NEDERLANDSE SAMENVATTING

Een aangeboren hartafwijking (AHA) is de meest voorkomende aangeboren afwijking bij pasgeborenen. De acht meest voorkomende hartafwijkingen bij geboorte zijn een ventrikelseptumdefect (gaatje in het tussenschot van de hartkamers [34%]), atriumseptumdefect (gaatje in het tussenschot van de boezems [13%]), open ductus Botalli (open verbinding tussen de aorta en de longslagader [10%]), pulmonalisstenose (een vernauwing van de longslagaderklep [8%]), tetralogie van Fallot (een combinatie van vier hartafwijkingen [5%]), coarctatio aortae (een vernauwing van de aorta [5%]), transpositie van de grote vaten (een verkeerde aansluiting van de slagaders uit het hart [5%]) en een aortastenose (vernauwing van de aortaklep [4%]). Door zowel de verbeteringen in diagnostiek, hartchirurgie, anesthesie en intensive care als de huidige gespecialiseerde cardiologische zorg, is de levensverwachting van patiënten met een AHA enorm toegenomen. Tegenwoordig bereikt ongeveer 90% van de kinderen met een AHA de volwassen leeftijd waardoor het aantal groeiende is. Hoewel de operaties op kinderleeftijd hebben gezorgd voor een betere levensverwachting, hebben veel patiënten nog wel te maken met restafwijkingen. Deze restafwijkingen zorgen voor een verhoogd risico op complicaties zoals ritmestoornissen en hartfalen, die kunnen leiden tot overlijden. Recent is een nieuwe echotechniek geïntroduceerd die in het bijzonder in staat is om vroege tekenen van een verminderde hartfunctie weer te geven: speckle-tracking echocardiografie (STE). Het Engelse woord 'speckle' betekent spikkel en deze techniek is in staat een microstukje van de hartspier in zijn beweging te volgen. Hierdoor is veel nauwkeuriger dan bij voorgaande technieken te zien hoe het hart werkt. Met de mogelijkheid om subtiele veranderingen in de functie van zowel de linker als de rechter hartkamer te meten, hopen wij hartfalen in een vroeger stadium te kunnen detecteren en daardoor mogelijkheden te creëren voor vroegere behandeling. Het is namelijk belangrijk om vroegtijdig in te grijpen om te proberen te voorkomen dat het hart onherstelbaar beschadigd raakt. Het vroeg opsporen van kamerdisfunctie bij volwassen patiënten met een AHA zou dus kunnen leiden tot een betere timing van een behandeling, medicamenteus dan wel een interventie, wat kan leiden tot een betere overleving en kwaliteit van leven bij deze patiënten.

Het doel van dit proefschrift is het in kaart brengen van de langetermijnuitkomsten bij volwassen patiënten met een AHA en het bestuderen van nieuwe, non-invasieve echocardiografische technieken in zowel een gezonde volwassen populatie als in volwassen AHA patiënten om de hartfunctie nauwkeurig te kunnen

beoordelen. **Hoofdstuk 1** is de algemene inleiding van dit proefschrift waarin het doel en de indeling van het proefschrift worden beschreven.

Nieuwe echocardiografische technieken in een gezonde populatie

Om normaalwaarden op te stellen voor verschillende parameters gemeten met STE, hebben wij een echocardiografische studie opgezet bestaande uit 155 gezonde vrijwilligers: de Navigator studie. De deelnemers zijn tussen de 20 en 72 jaar, met in iedere leeftijdscategorie van tien jaar minstens veertien deelnemers per geslacht. Een voorbeeld van een meting met STE is de "piek systolische longitudinale strain": de procentuele verkorting van de hartspier in lengterichting tijdens de contractiefase. Dit is een kwantitatieve en accurate maat voor hartkamerfunctie. In **Hoofdstuk 2** presenteren we de normaalwaarden voor linkerkamer piek systolische longitudinale strain per leeftijdscategorie en per geslacht. De strainwaarden van vrouwen zijn hoger dan die van mannen. Verder resulteert het hebben van een hogere bloeddruk of een groter lichaamsoppervlak in lagere strainwaarden. Daarentegen beïnvloedt leeftijd niet de hoogte van de strain. Naar aanleiding van deze bevindingen adviseren wij voor interpretatie van strainwaarden in de klinische praktijk normaalwaarden te hanteren die rekening houden met het geslacht en lichaamsoppervlak van de patiënt.

Patiënten met een AHA hebben vooral problemen met de rechter hartkamer. Vanwege het feit dat de meeste verworven hartziekten met name de linker hartkamer beïnvloeden, is tot nu toe vrijwel alle ervaring met echocardiografie links opgedaan. Daarnaast is er minder ervaring in het bestuderen van de rechter hartkamer, omdat deze kamer een complexere vorm heeft en achter het borstbeen ligt. Met de bestaande echotechnieken kan deze complexe vorm nauwelijks in kaart worden gebracht. Philips heeft een nieuwe visualisatiefunctie ontwikkeld, "iRotate", waarbij de matrixtransducer de geluidsgolven 360° elektronisch kan draaien met als voordeel dat de transducer met de hand stil kan worden gehouden op de borstkas. In **Hoofdstuk 3** wordt beschreven hoe met behulp van de iRotate functie de volledige rechter hartkamer in beeld kan worden gebracht vanuit één standaard echocardiografische view. Verschillende unieke anatomische kenmerken van de rechter hartkamer worden gebruikt als referentiepunten, zodat deze opnames makkelijk reproduceerbaar zijn. Alhoewel één wand lastig in beeld te krijgen is, de voorwand van de rechterkamer uitstroombaan, kunnen we stellen dat deze techniek bruikbaar is in een gezonde populatie, aangezien de overige rechterkamer wanden goed te visualiseren zijn in de gezonde vrijwilligers. We hebben deze techniek ook toegepast in een cohort van twintig patiënten met een vergrote rechter hartkamer door volume- of drukoverbelasting. Een opvallende bevinding is dat bij de patiënten de voorwand van de uitstroombaan beter te visualiseren is

dan in de gezonde populatie. De visualisatie van de overige rechterkamerwanden is vergelijkbaar met die van de gezonde vrijwilligers. Deze positieve bevindingen maken de techniek hoopgevend om toegepast te kunnen worden in de klinische praktijk. Om te bepalen of het ook mogelijk en betrouwbaar is om met STE strain te meten bij deze verschillende rechterkamerwanden verkregen met behulp van de iRotate functie, is vervolgonderzoek nodig.

Klinische uitkomsten en vroege opsporing van verminderde kamerfunctie bij gerepareerde tetralogie van Fallot

Het tweede deel van dit proefschrift richt zich op de klinische uitkomsten en de vroege opsporing van een verminderde hartfunctie bij patiënten met een gerepareerde tetralogie van Fallot. Tetralogie van Fallot is een aangeboren hartaandoening waarbij vier verschillende afwijkingen voorkomen: een gaatje in het kamertussenschot, een vernauwing bij of rondom de longslagaderklep, een overrijdende aorta en een dikkere rechterkamerspier. De langetermijnuitkomsten bij patiënten na chirurgische reparatie van een tetralogie van Fallot in de huidige literatuur zijn beperkt. In **Hoofstuk 4** presenteren we de overleving en klinische uitkomsten van patiënten met tetralogie van Fallot die op kinderleeftijd tussen 1968 en 1980 in Rotterdam een operatie hebben ondergaan. In het kader van de unieke “Rotterdam Quality of Life” studie worden deze patiënten elke tien jaar uitvoerig onderzocht in het ziekenhuis. Na een geslaagde operatie is nu, na 40 jaar, nog 86% van de mensen in leven, hetgeen net iets lager is dan in de algemene Nederlandse bevolking. De oorzaken van overlijden op de lange termijn zijn hartfalen en ritmestoornissen. Gedurende een follow-up van 35 jaar heeft ongeveer 75% van de patiënten te maken gehad met één of meer complicaties, waarvan het grootste deel bestaat uit re-interventies en ritmestoornissen. Hoewel het aantal complicaties lijkt te blijven toenemen met de leeftijd in deze groep patiënten, scoren ze hun kwaliteit van leven vergelijkbaar en op sommige schalen zelfs gunstiger dan de algemene Nederlandse bevolking van dezelfde leeftijd. Echter, meer dan de helft van de patiënten heeft een verminderde pompfunctie van het hart en daarom blijven zowel rechter- als linkerkamerdisfunctie een grote zorg bij deze patiënten.

In **Hoofdstuk 5** wordt verder ingegaan op de rechter- en linkerkamerfunctie van volwassen patiënten met tetralogie van Fallot waarvoor ze op kinderleeftijd zijn geopereerd. Aan deze operatie houden patiënten vaak lekkage van de longslagaderklep over wat leidt tot volumeoverbelasting en rechterkamervergroting. Het effect van deze volumeoverbelasting op de hartfunctie hebben we gemeten met behulp van linkerkamer en rechterkamer piek systolische longitudinale strain in 94 patiënten en in 85 gezonde controlepersonen van dezelfde leeftijd en hetzelfde geslacht. De longitudinale strain van de rechterkamer is lager in de patiënten dan

in de gezonde controlepersonen. Vervolgens hebben we in detail gekeken naar drie verschillende segmenten van de rechterkamerwand: het deel bij de punt (apex), het midden (mid) en het deel bij de klep (basis). Vooral het apicale deel toont een verminderde functie wat suggereert dat de apex het meest is aangedaan in volumeoverbelaste rechter hartkamers. Een afgenomen pompfunctie van de rechterkamer lijkt de linkerkamer te beïnvloeden. De verminderde longitudinale strain van de linker hartkamer wordt vooral veroorzaakt door een afgenomen functie van het kamertussenschot. Het mechanisme dat de ene hartkamer de andere hartkamer beïnvloedt, wordt ventriculaire interactie genoemd. Omdat een slechte linkerkamerfunctie gepaard gaat met meer klachten en een slechtere overleving, is het noodzakelijk op tijd in te grijpen bij achteruitgang van de rechter hartkamer om achteruitgang van de linker hartkamer te voorkomen.

Hoofdstuk 6 beschrijft de draaiende beweging van de linker hartkamer in 82 patiënten met geopereerde tetralogie van Fallot en 56 gezonde controlepersonen om meer inzicht te krijgen in de ventriculaire interactie. In een gezonde situatie draait tijdens de contractie het basale deel van de linkerkamer met de klok mee, terwijl de punt van het hart tegen de klok in draait. Het hart maakt daardoor een wringende beweging, ook wel twist genoemd. Deze twist kan met STE gemeten worden en wordt uitgedrukt in graden. De meerderheid van de patiënten heeft een verminderde of afwezige linkerkamer twist in vergelijking met de gezonde controles, voornamelijk vanwege een verminderde of abnormale draaiing van de punt van het hart. Patiënten met deze abnormale draaiing hebben een grotere linker hartkamer en slechtere linker- én rechterkamerfunctie. Aangezien beide kamers beïnvloed worden, sterkt deze bevinding het idee van ventriculaire interactie. Abnormale twist is mogelijk een nieuw, objectief diagnostisch criterium voor het opsporen van een verminderde hartfunctie in patiënten met gerepareerde tetralogie van Fallot.

Hoofdstuk 7 richt zich op de toepassing van N-terminal pro-B-type natriuretic peptide (NT-proBNP), een laboratoriummarker die gemeten kan worden in het bloed en wordt afgegeven door hartcellen als reactie op volumeoverbelasting en rek op de hartwand. Wij hebben de NT-proBNP gemeten in 177 patiënten met tetralogie van Fallot. De NT-proBNP waarden zijn verhoogd in meer dan 50% van de patiënten terwijl bij de meesten de klinische conditie goed en stabiel is. Hogere NT-proBNP waarden hebben een relatie met een verminderde rechterkamerfunctie, maar nog sterker met een verminderde linkerkamerfunctie. NT-proBNP zou daarom gebruikt kunnen worden bij de routinematige klinische controles van patiënten om de hartfunctie in de tijd te vervolgen en mogelijk ook voor het vroegtijdig opsporen van verslechtering van deze hartfunctie.

Klinische uitkomsten en vroege opsporing van verminderde kamerfunctie bij andere aangeboren hartafwijkingen

Het derde deel van dit proefschrift bevat informatie over de klinische uitkomsten en vroege opsporing van een verminderde kamerfunctie bij patiënten met andere typen AHA. In **Hoofdstuk 8** worden de langetermijnuitkomsten beschreven van een longitudinaal gevolgd patiënten cohort 40 jaar na chirurgische sluiting van een gaatje in het kamertussenschot (ventrikelseptumdefect, VSD). Dit onderzoek is een onderdeel van de "Rotterdam Quality of Life" studie. In het geval van een geslaagde operatie op kinderleeftijd, is na 40 jaar nog 86% van de patiënten in leven. Dit percentage is iets lager dan die van de algemene Nederlandse bevolking en is vergelijkbaar met die van de geopereerde tetralogie van Fallot patiënten. Een belangrijk probleem bij VSD patiënten is het ontstaan van lekkage van de aortaklep. De laatste twintig jaar is het aantal patiënten met deze kleplekkage bijna verdubbeld: van 11% in 1990 naar 21% in 2012. Een andere opvallende bevinding is dat een substantieel deel van de patiënten naast een verminderde linkerkamerfunctie, ook een verminderde rechterkamerfunctie heeft zonder dat ze klachten lijken te hebben. Deze kamerfunctie zou in de toekomst meer kunnen verslechteren wat uiteindelijk kan leiden tot klinisch hartfalen met klachten en een kortere levensverwachting. De VSD patiënten hebben naast een verminderde kamerfunctie in de laatste twintig jaar ook een toenemend aantal ritmestoornissen, terwijl het aantal chirurgische of percutane re-interventies redelijk stabiel blijft. De patiënten scoorden hun eigen kwaliteit van leven beduidend beter dan de algemene Nederlandse bevolking. Een aanzienlijk deel van deze patiënten is tegenwoordig niet meer onder controle bij een cardioloog. Aan de hand van ons onderzoek raden wij echter aan om patiënten na chirurgische sluiting van een VSD, ook al is dit een relatief eenvoudige AHA, levenslang poliklinisch te blijven vervolgen.

Hoofdstuk 9 bevat informatie over de langetermijnuitkomsten bij volwassen patiënten na het sluiten van een gaatje in het boezemtussenschot (atriumseptumdefect, ASD) op kinderleeftijd, ook een studie die onder de "Rotterdam Quality of Life" valt. Na 40 jaar is 91% van deze patiënten in leven, wat vergelijkbaar is met de algemene Nederlandse bevolking. Ondanks een redelijke morbiditeit van 30%, met name vanwege ritmestoornissen, hebben deze patiënten een goede inspanningscapaciteit. Net als de andere patiënten die aan een AHA zijn geopereerd, scoren ook de patiënten met een chirurgisch gesloten ASD hun kwaliteit van leven beter dan de algemene Nederlandse bevolking. Op zowel de standaard echocardiografie als op MRI is in een derde van de patiënten een verminderde rechterkamerfunctie te zien. Dit is een opmerkelijke bevinding, omdat tien jaar geleden de rechterkamer nog normaal was. Eén vijfde van de ASD patiënten heeft een milde verslechtering van de linkerhartkamerfunctie op MRI. Ondanks deze

verminderde hartkamerfunctie, hebben de patiënten (nog) geen klachten passend bij hartfalen. Het is dus belangrijk deze patiënten goed te vervolgen zodat we kunnen bepalen of deze verminderde pompfunctie verder achteruitgaat en of er een behandeling gestart moet worden.

Hoofdstuk 10 gaat verder in op de kamerfunctie van patiënten met een chirurgisch gesloten ASD. De piek systolische longitudinale strain van de linker- en de rechterkamer is gemeten in 51 patiënten en 51 gezonde controlepersonen gematcht in leeftijd en geslacht. Ook al zijn de patiënten reeds op kinderleeftijd geopereerd, de rechterkamer strain is lager dan bij de gezonde controles. Vooral het apicale deel van de rechterkamer is aangedaan, net zoals bij de patiënten geopereerd aan een tetralogie van Fallot. Deze verminderde kamerfunctie is mogelijk het gevolg van de volumeoverbelasting op de rechterkamer voor de sluiting van het ASD. Tevens kan ook de operatie zelf, inclusief het gebruik van de hartlongmachine of de hypothermie, bijdragen aan de verminderde rechterkamerfunctie. De linkerkamer strain is in de ASD patiënten 35 jaar na operatie vergelijkbaar met die van de gezonde controles. Ook al hebben we een licht verminderde pompfunctie van de rechterkamer gevonden bij patiënten met een op kinderleeftijd gesloten ASD, ze hebben er momenteel geen klachten van. Om te bepalen of deze verminderde kamerfunctie zich in de toekomst zal ontwikkelen tot hartfalen met klachten, zijn grote en langdurige onderzoeken nodig.

In **Hoofdstuk 11** wordt de longitudinale strain gemeten bij patiënten die een systeem rechter hartkamer hebben. Een systeem rechter hartkamer is een hartkamer die de morfologie heeft van een rechterkamer maar de functie heeft van een linkerkamer. Deze rechterkamer ondersteunt dus de systeemcirculatie in plaats van de longcirculatie. Het patiënten cohort bestaat uit 32 patiënten met een transpositie van de grote vaten geopereerd volgens de Mustard methode en tien 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 linkerkamer van positie verwisseld. Patiënten hebben een verminderde longitudinale strain van de systeem rechterkamer vergeleken met de systeem linkerkamer van gezonde controlepersonen. De afname in functie komt het meest tot uiting in het apicale deel van de rechterkamer. Dit suggereert dat de punt van het hart het meest beinvloed wordt door de drukoverbelasting. Deze bevinding komt overeen met de hierboven beschreven verminderde apicale functie bij patiënten met (voormalige) volumeoverbelasting. De verminderde longitudinale piek strain is gerelateerd aan verminderde hartfunctie, hogere NT-proBNP waarden en lijkt gerelateerd te zijn aan het hebben van klachten passend bij hartfalen. De longitudinale piek strain van de rechterkamer is lager in de patiënten die een Mustard operatie hebben

ondergaan dan in patiënten met een congenitaal gecorrigeerde transpositie van de grote vaten. Dit is een interessante bevinding, aangezien dit verschil niet eerder beschreven is met behulp van de standaard echocardiografie. Mogelijk wordt dit verschil veroorzaakt door de operatie die de patiënten hebben ondergaan, maar meer onderzoek is nodig om dit aan te kunnen tonen dan wel uit te kunnen sluiten.

In **Hoofdstuk 12** ligt de focus op de linkerkamerfunctie van patiënten met een gerepareerde coarctatio aortae, een vernauwing van de aorta, waardoor deze patiënten gedurende lange tijd een drukoverbelasting hebben gehad van de linker hartkamer. In dit prospectief cross-sectionele onderzoek is de linkerkamer piek systolische longitudinale strain gemeten in 75 patiënten en 75 gezonde controlepersonen gematcht in leeftijd en geslacht. Bij de meerderheid van de patiënten lijkt op het standaard echocardiogram dat ze een normale linkerkamerfunctie hebben, terwijl gemeten met STE toch een groot deel een verminderde longitudinale strain heeft. Deze verminderde strain is geassocieerd met hogere bloeddruk, het hebben van nog een andere AHA, een aortaklepvervanging en een grotere linkerboezem. Het verband tussen een hogere bloeddruk en een lagere strain is ook gezien bij de gezonde controles in Hoofdstuk 2 en geeft aan dat een minimale bloeddrukverhoging al snel subtiele veranderingen geeft aan de strain van de linkerkamer. Dit maakt piek systolische linkerkamer strain een sensitieve marker voor beginnende kamerdisfunctie veroorzaakt door hoge bloeddruk. Of de linkerkamer strain in de kliniek echt bruikbaar zal zijn, verdient verder onderzoek.

Concluderend blijkt dat het belangrijk is om alle mensen met een AHA levenslang te vervolgen, waarbij de nieuwste echotechnieken betere informatie lijken te verschaffen dan de standaard echocardiografie voor het vroegtijdig opsporen van problemen, zoals hartfalen.

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1. **Menting ME**, van Grootel RW, van den Bosch AE, Eindhoven JA, McGhie JS, Cuypers JA, Witsenburg M, Helbing WA, Roos-Hesselink JW. Assessment of systolic left ventricular function with speckle-tracking echocardiography in adult patients with repaired aortic coarctation.
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2. **Menting ME**, van den Bosch AE, McGhie JS, Eindhoven JA, Cuypers JA, Witsenburg M, Geleijnse ML, Helbing WA, Roos-Hesselink JW. Assessment of ventricular function in adults with repaired tetralogy of Fallot using myocardial deformation imaging.
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3. **Menting ME**, Cuypers JA, Roos-Hesselink JW. Reply: the unnatural history of the ventricular septal defect.
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4. **Menting ME**, Cuypers JA, Opic P, Utens EM, Witsenburg M, van den Bosch AE, van Domburg RT, Meijboom FJ, Boersma E, Bogers AJ, Roos-Hesselink JW. The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure.
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5. **Menting ME**, van den Bosch AE, McGhie JS, Cuypers JA, Witsenburg M, Geleijnse ML, Helbing WA, Roos-Hesselink JW. Ventricular myocardial deformation in adults after early surgical repair of atrial septal defect.
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7. **Menting ME**, van Mechelen R. Sinus rhythm with an isolated ST-segment elevation in V2.
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8. McGhie JS, **Menting ME**, Vletter WB, Frowijn R, Roos-Hesselink JW, van der Zwaan HB, Geleijnse ML, van den Bosch AE. A novel 13 segments standardized model for right ventricle function assessment using two-dimensional iRotate echocardiography.
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10. Cuypers JA, **Menting ME,** Konings EE, Opic P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Boersma E, Bogers AJ, Roos-Hesselink JW. Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction.
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12. Cuypers JA, Opic P, **Menting ME**, Utens EM, Witsenburg M, Helbing WA, van den Bosch AE, Ouhlous M, van Domburg RT, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at younge age.
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13. **Menting ME**, McGhie JS, Koopman LP, Vletter WB, Boersma E, Helbing WA, van den Bosch AE, Roos-Hesselink JW. Normal left ventricular strain values using 2D speckle-tracking echocardiography in healthy adults aged 20 to 72 years old.
Submitted

14. Cuypers JA, **Menting ME**, Opić P, Utens EM, Helbing WA,Witsenburg M, van den Bosch AE, van Domburg RT, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The

unnatural history of valvular pulmonary stenosis: outcome up to 40 years after surgical repair.
Submitted

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student:	Myrthe Eline Menting
Erasmus MC Department:	Cardiology, Adult Congenital Heart Disease
Research School:	Cardiovascular Research School (COEUR), Erasmus MC
PhD period:	November 2012 – November 2015
Promotors:	Prof.dr. J.W. Roos – Hesselink
	Prof.dr. W.A. Helbing
Copromotor:	Dr. A.E. van den Bosch

	Year	Workload (ECTS)
1. PhD training		
General academic and research skills		
Workshop Systematic Literature Retrieval in PubMed	2012	0.3
Biostatistical Methods I: Basic Principles, CC02	2013	5.7
Biomedical English Writing and Communication	2013	4.0
Workshop on Photoshop and Illustrator CS5	2013	0.3
BROK Course	2014	1.5
Open Clinica Training	2014	0.3
In-depth courses		
Masterclass Functional and Applied Clinical Anatomy of the Heart	2013	0.3
Myocardial Velocity and Deformation Imaging Course, Leuven	2013	0.6
Interactive Echo Course on Congenital Heart Disease	2013, 2014	0.6
COEUR - Cardiovascular Imaging and Diagnostics	2013	1.5
COEUR - Vascular Clinical Epidemiology	2014	1.5
COEUR - Congenital Heart Disease	2013, 2015	3.0
COEUR - Arrhythmia Research Methodology	2014	1.5
COEUR - Atherosclerotic and Aneurysmal Disease	2015	1.5
COEUR PhD Days	2012 - 2014	0.9
COEUR Research Seminars	2013 - 2015	2.0
Conferences and Symposia		
ESC Congress	2012 - 2015	4.8
AHA Scientific Sessions	2013, 2014	3.6
EuroEcho-Imaging Congress	2013, 2014	3.0
AEPC Annual Meeting	2014, 2015	3.3
Davos Wintermeeting	2013, 2014	3.0
NVVC Congress	2013 - 2015	2.7

Karel V Symposium	2012 - 2015	1.2
Aortic Pathology Symposium	2013, 2015	0.6
2. Teaching activities		
Lecturing		
Presentations COEUR - Congenital Heart Disease	2015	1.0
Supervising practicals and Master's theses		
Supervising research of 2nd year medical students	2013, 2014	0.6
Supervising research of 3rd year medical students	2014	0.3
Supervising research of 5th year medical student	2014	0.4
Supervising research of 6th year medical student	2015	0.4
Total		***50.4***

Oral presentations	
2015	The Netherlands Society of Cardiology (NVVC) Spring Congress, Noordwijkerhout, the Netherlands
2014	The Netherlands Society of Cardiology (NVVC) Autumn Congress, Papendal, the Netherlands
2014	Association for European Paediatric and Congenital Cardiology (AEPC) Annual Meeting, Helsinki, Finland
2014	Wintermeeting, Davos, Switzerland
2013	Wintermeeting, Davos, Switzerland
Moderated poster presentations	
2015	Association for European Paediatric and Congenital Cardiology (AEPC) Annual Meeting, Prague, Czech Republic
2014	Association for European Paediatric and Congenital Cardiology (AEPC) Annual Meeting, Helsinki, Finland
Poster presentations	
2015	European Society of Cardiology (ESC) Congress, London, United Kingdom
2014	EuroEcho-Imaging Congress, Vienna, Austria
2014	American Heart Association (AHA) Scientific Sessions, Chicago, USA
2014	European Society of Cardiology (ESC) Congress, Barcelona, Spain
2013	EuroEcho-Imaging Congress, Istanbul, Turkey
2013	American Heart Association (AHA) Scientific Sessions, Dallas, USA
2013	European Society of Cardiology (ESC) Congress, Amsterdam, the Netherlands
2013	The Netherlands Society of Cardiology (NVVC) Spring Congress, Noordwijkerhout, the Netherlands

ABOUT THE AUTHOR

Myrthe Eline Menting was born on January 25th 1988 in Spijkenisse, the Netherlands. After obtaining her Gymnasium diploma (Blaise Pascal, PENTA college CSG, Spijkenisse), she started medical school at the Erasmus University Rotterdam in 2006. During her medical study, she spent time in various committees of the study and student swimming association and worked as an Erasmus ambassador. She also worked as a medical assistant at the Cardiothoracic Intensive Care Unit, which aroused her enthusiasm for cardiology. In 2012, she obtained the degree of Medical Doctor cum laude. Subsequently, she started her PhD project entitled 'Adult Congenital Heart Disease: Clinical Outcome and Novel Echocardiographic Techniques' under the supervision of prof.dr. Jolien W. Roos-Hesselink and prof.dr. Willem A. Helbing. This project focused on long-term outcome of adult patients with congenital heart disease and the use of new non-invasive imaging techniques in this group of patients and resulted in this thesis. Meanwhile she is a committee member of the Juniorkamerdag, an annual symposium for investigators and residents in the field of cardiology.

From November 2015 onwards she is working as a resident (ANIOS) at the department of Cardiology at the Erasmus MC, Rotterdam. Besides her work she enjoys running, cycling, travelling and playing the guitar.

DANKWOORD

Drie jaar geleden begon ik met dit promotieonderzoek en de tijd is voorbij gevlogen. Wie had gedacht dat het zo'n mooie en onvergetelijke tijd zou worden? Hoewel er op dit proefschrift maar één naam staat, zou dit niet tot stand zijn gekomen zonder de hulp en steun van vele anderen. Een aantal van hen wil ik graag in het bijzonder noemen.

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