Functional cardiovascular assessment in congenital heart disease

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Functional cardiovascular assessment in congenital heart disease

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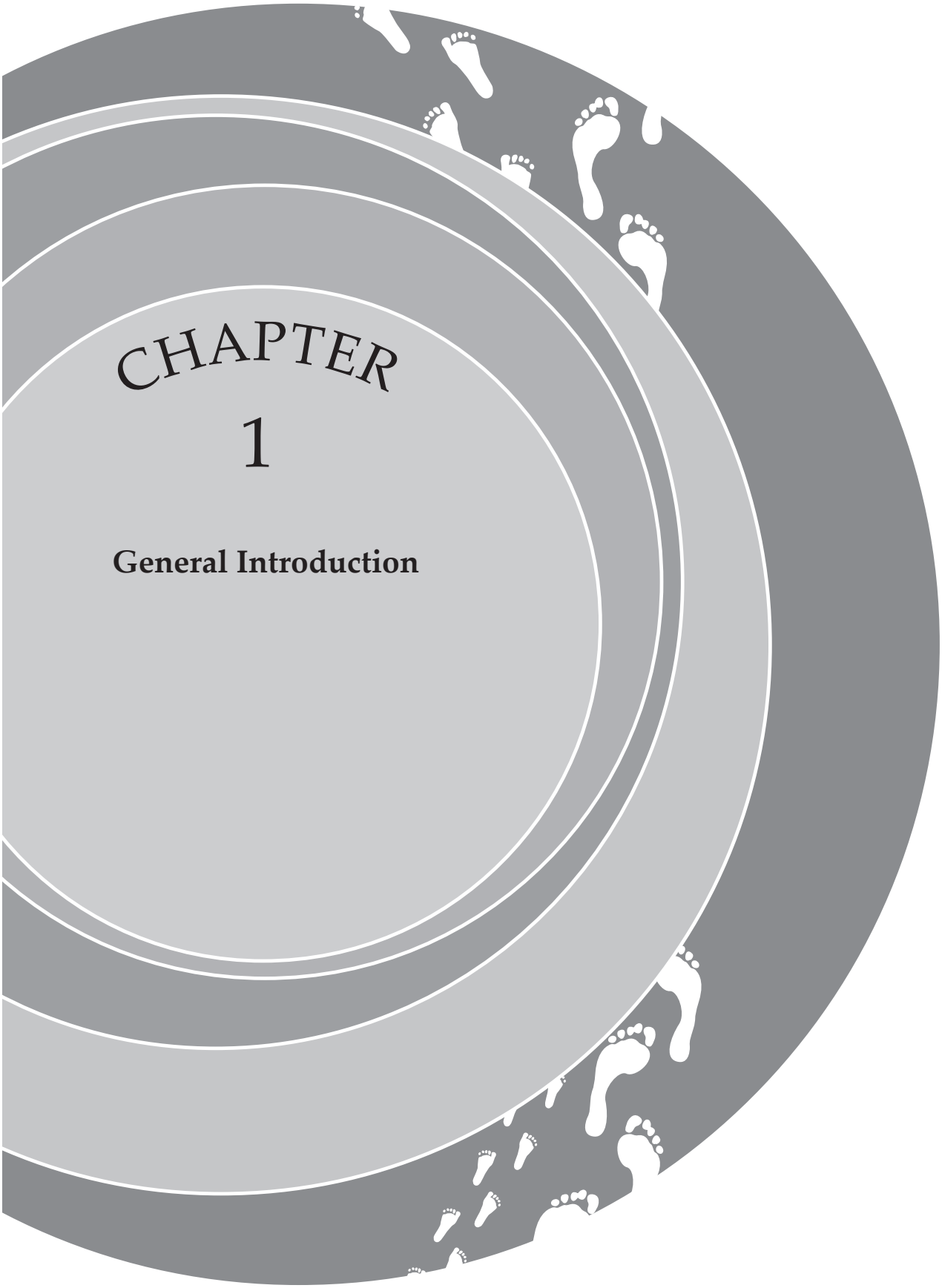


CHAPTER 1

General Introduction

General Introduction

Congenital heart disease (CHD) has an estimated incidence of about 5–6 per 1000 live births.[1] Variation in reported incidence of CHD mainly depends on the ability to diagnose trivial lesions. Incidence is not subjected to differences between countries or time periods.[1] In the Netherlands an estimated number of 1.500 children is born with CHD each year. The total estimated number of patients with CHD in the Netherlands is 50.000. About half of the patients with CHD is in the paediatric age group.[2]

The aetiology of CHD may be; 1) chromosomal (8 − 10%), 2) monogenetic (3 − 5%), and 3) multi-factorial (85%).[3] Numeric chromosomal abnormalities, such as trisomy 13, 18, 21, and Turner's syndrome are frequently associated with CHD.[4-9] Most life-born patients with trisomy 13 or 18 die within the first year of life, the majority with trisomy 21 or Turner's syndrome on the other hand survive to adulthood.[10-12] Monogenic genetic disorders occur as a direct consequence of a single gene being defective. Monogenic disorders may result in a combination of congenital abnormalities among which cardiovascular abnormalities (eg. Marfan syndrome, Ehlers-Danlos syndrome), but also in isolated cardiovascular disease (eg. long QT syndrome).[13] Monogenic disorders are inherited in a simple pattern according to Mendel's Laws (Mendelian disorders). In multi-factorial models the cause of the CHD is more complex and assumed to be a combination of genetic factors (polygenic) and non-genetic factors such as environmental factors (eg. maternal diabetes, maternal rubella infection) and teratogenic substances (eg. alcohol, anticonvulsive drugs, lithium).[13]

Many types of CHD require surgical or catheter-based interventions. In the 1960's before the widespread availability of cardiac surgery with cardiopulmonary bypass, about 50% of children in need of therapy died within the first year of life and less than 15% reached adulthood.[2] Major developments in the fields of diagnostics, anaesthesia, intensive care and cardiac surgery radically changed prognosis of patients with CHD. Peri-operative mortality declined and currently 85 − 95% of infants are expected to reach adulthood.[2,14] As such the number of adult patients with CHD in the Netherlands is growing with approximately 5% per year.[15]

Data on long-term outcome still are lacking in some areas of CHD. Nevertheless it has become clear that complete cure is only seldomly achieved.

The perception of "cure" after surgery for CHD is fostered by surgical descriptions of "total correction", but in most cases is incorrect.[16] The long-term outcome of corrected or palliated congenital heart disease is determined by residua (pre-interventional abnormalities, intentionally left unaffected by intervention), sequelae (unintended but foreseen results of intervention), and complications after intervention.[17] Following interventions for CHD almost all patients have residual abnormalities of some sort. This stresses the importance for professionals in the field to emphasise upon patients and parents that "corrective surgery" for CHD often is not curative.

In contrast to patients with acquired heart disease who at onset of disease may notice a distinct change in clinical condition or symptoms, patients with CHD may not detect the subtle continuous changes in their clinical condition.[18-21] By the time symptoms or exercise limitations become distinct with chronic cardiac overload, substantial or even irreversible ventricular remodelling and dysfunction may have occurred.[14,22-24] Therefore close serial follow-up of functional cardiovascular condition should be effectuated from early childhood on to monitor the effects of the hemodynamic load from either the original CHD or post-interventional residua, sequelae and complications. This requires development of adequate diagnostic tools and criteria to monitor patient's cardiac condition and guide the process of decision making regarding (re)interventions to preserve cardiac condition.[25] The requirement for follow-up of CHD during adolescence and adult life is likely to grow with increasing complexity of CHD treated and the need for reinvestigation and reintervention with time.[16]

One of the most frequent congenital heart lesions is tetralogy of Fallot. As with other CHD pace of deterioration of functional cardiovascular condition in surgically corrected tetralogy of Fallot with residual pulmonary regurgitation is unknown and as such can not be predicted. Especially data on patients corrected at young age, using transatrial transpulmonary techniques often is limited to a relatively short period following surgical correction. The studies described in this thesis specifically focussed on patients corrected according to contemporary surgical techniques at relatively young age.

Up to 76% of patients with Turner's syndrome have structural cardiovascular malformations.[6,8] With the majority of patients reaching adulthood, Turner's syndrome is one of the most important numeric chromosomal abnormalities within the field of cardiology. Aortic dilation makes up for a quarter to half of

the structural cardiovascular malformations in Turner's syndrome.[6-8] Aetiology of aortic disease in Turner's syndrome still is unknown. Furthermore during childhood virtually all patients with Turner's syndrome in the Western world are given high dosed growth hormone treatment for short stature.[26] However the potential long-term cardiovascular side-effects associated with this type of treatment remain unclear.

1 Tetralogy of Fallot

1.1 Background

Tetralogy of Fallot (TOF) is the most common cyanotic CHD. TOF constitutes 3.5% to 4.5% of all CHD.[1] The first complete description of TOF is credited to the French physician Etiennne Fallot who published his findings in 1888.[27] Males and females are almost equally affected. Most cases are spontaneous, although familial occurrences have been described.[28] With no other affected first-degree relatives, the recurrence risk in siblings is about 3%. TOF patients have a chance of approximately 10% to have a child with TOF, regardless of whether the father or mother is affected. If the affected parent has an affected sibling this risk increases to above 40% [28]. The precise aetiology still is unknown. In up to about 20% of TOF patients a microdeletion of the q11 region of the chromosome 22 (22q11 deletion) is found.[29] The 22q11 deletion is well known to be associated with Di George syndrome and velocardiofacial syndrome. The association of TOF with 22q11 deletion may point to the relationship between abnormal migration of cells from the neural crest and the anatomical features found.[30]

1.2 Anatomic characteristics of tetralogy of Fallot

TOF is characterised by a specific combination of four anatomical abnormalities. The central feature in TOF is an anterior-cephalad deviation of the septal insertion of the outlet (infundibular) septum relative to the septomarginal trabeculation.[31] The deviation of the muscular outlet septum combined with hypertrophy of septoparietal trabeculations results in a narrowed muscular orifice of the subpulmonary infundibulum which is found in approximately

75% of patients. This subpulmonary stenosis often is associated with a stenosis at the level of the pulmonary valve. In the remaining patients an isolated obstruction is found at the pulmonary valve level (10%), or patients have pulmonary valve atresia (15%). The deviation of the muscular outlet septum also accounts for both the ventricular septal defect (misalignment VSD) and the more rightward position of the aortic root.[31] Right ventricular hypertrophy, the fourth anatomical anomaly in TOF, is to be considered a hemodynamic consequence of the other anatomical lesions. As a consequence of the RV outflow tract obstruction, hypoplasia of the trunk of the pulmonary, the 2 mean branches and the more distal arterial braches may be seen.

This specific anatomical description of the malformations may suggest a clearly defined group of patients, but precise anatomy and hence hemodynamic consequences vary considerably. A more correct vision would be to regard Fallot's tetralogy as part of a spectrum of cardiac anomalies.

1.3 Clinical features and diagnosis of tetralogy of Fallot

The clinical features in patients with TOF reflect the amount of pulmonary blood flow, which in turn depends on severity of the right ventricular (RV) outflow tract obstruction or pulmonary stenosis, and the relative resistance of the systemic and pulmonary circulation. Only those infants with severe pulmonary stenosis at birth will immediately present with cyanosis due to predominant right to left shunting through the VSD. Pulmonary blood flow in this subgroup may be dependent on the ductus arteriosus. Closure of the ductus arteriosis within the first days of life may result in a circulatory collaps. However, most patients are acyanotic at birth. With increasing infundibular hypertrophy the transition from acyanotic to cyanotic disease often occurs with in the first year of life. A last group of infants with only mild pulmonary stenosis may be asymptomatic and acyanotic. They may even present with signs of congestive heart failure from a large left to right shunt.

Prolonged cyanosis will result in clubbing of the fingers and toes, extreme cyanosis (blue skin surface) and gray sclerae with engorged blood vessels. Furthermore complications from right to left shunting (abscesses and thromboembolic strokes of the brain) and from polycythemia (high thrombosis risk) may occur. Without surgical intervention most patients with TOF die during childhood: the survival rate is 66% at 1 year of age, 40% at 3 years, 11%

at 20 years, 6% at 30 years and 3% at 40 years.[32] Therefore intra-cardiac surgical repair is not only recommended to relieve symptoms but also to improve survival.

1.4 Surgery in tetralogy of Fallot

1.4.1 Surgical correction

Nowadays the natural history of TOF is virtually only seen in less developed countries where paediatric cardiac surgery along with general medical care is less developed. The first successful intra-cardiac repair using human cross-circulation was described by Lillehei in 1955.[33] The first successful repair using a pump oxygenator was performed one year later by Kirklin *et al.*[34] Corrective surgery includes closure of the VSD and relieve of the RVOT stenosis. Before the availability of intra-cardiac repair for TOF palliative shunting procedures were performed. Palliative shunt procedures aimed to increase pulmonary blood-flow, thereby reducing severity of cyanosis and improving exercise capacity. Different types of shunting procedures were developed including subclavian artery-pulmonary shunts ((modified) Blalock-Taussig shunt) and aorto-pulmonary shunts (Potts shunt, Waterston shunt and Central shunt).[35] However, palliative shunts have some well known long-term complications such as distortion of the pulmonary arterial branches and disproportional large shunt volumes causing pulmonary hypertension and LV volume overload.[32]

Currently many centres prefer a one-stage complete surgical correction performed at young age, a procedure that can be performed with low peri-operative mortality rates.[36-38] Palliative surgery or balloon pulmonary valvuloplasty is reserved for severely ill infants and patients for who complete repair is unsuitable, such as patients with underdeveloped pulmonary arteries. Correction at young age has the advantage of: 1) shortening of the period of possible neurological damage due to hypoxemia, 2) reduction of the risk for cerebral abscesses and emboli, 3) avoidance of longstanding RV pressure overload with the resultant myocardial hypertrophy and fibrosis, and 4) optimization of pulmonary artery growth. There is general agreement that there is no advantage of a delay of correction beyond the age of 1 year.[36,39] Nevertheless, controversy on optimal age for total repair of TOF still exists as several authors found post-operative outcome was worse in patients operated before the age of 3 months.[36,39,40] Among patients from the earliest era of

surgical correction of tetralogy of Fallot 5 years survival was 95%, 10 years survival was 92% and 25 years survival was 87%.[41] Older age at surgery was found to be a powerful predictor of poorer late survival.[41,42]

In recent years a trend towards the use of transatrial transpulmonary approaches at the cost of transventricular approaches is seen. The transatrial transpulmonary approach, first described in 1963 by Hudspeth *et al.*, has the theoretical advantage of elimination or reduction of right ventriculotomies.[43] Late complications like RV dilation and dysfunction, as well as ventricular arrhythmia are thought to in part derive from the site of the ventriculotomy. Multiple studies report superiority of the transatrial approach over the transventricular approach with regard to RV function, RV dimensions and ventricular arrhythmia risk during follow-up.[36,44,45] However, so far the comparison of both techniques in literature often is hampered by several data limitations. In many centres the transatrial transpulmonary technique was the successor of the transventricular technique and therefore data may reflect a different surgical era.[36,38] Simultaneous changes in other surgical preferences, such as age at repair, may have occurred.[36,46] In direct relation to the previous limitations follow-up duration in many studies is shorter with the transatrial transpulmonary technique. Furthermore institutions may choose one technique over the other based on patients characteristics, which though legitimate in itself, results in two less comparable patient populations.[37]

The optimal result after surgical correction would include absence of a gradient between the RV and the pulmonary trunk to normalise RV pressures, and a competent pulmonary valve. As with other CHD the term "corrective" is somewhat misleading as residual lesions are almost obligatory.[35] Nevertheless survival of surgically corrected TOF is good, though it remains somewhat below that in the general population.[41,42]

1.4.2 Residual defects

Residual lesions are frequent following correction of TOF. A residual VSD, most often caused by partial patch release or presence of multiple VSD's, is found in 10 − 20% of patients and requires re-operating in case of a large shunt volume (by definition a Qp/Qs-ratio > 1.5).[32,35] Residual gradients of the RV outflow tract are also found in approximately 20% of patients. Residual RVOT obstruction is a known important risk factor for early and late RV failure and therefore should carefully be avoided during surgery. In case of a post-

operative RV pressure > 50% of LV pressure reoperation is indicated.[35] The trade off for total desobstruction of the RV outflow tract at repair, mostly achieved by more extensive surgery, is disturbance of normal RVOT and pulmonary valve function. Therefore the most frequently encountered residual defect in repaired TOF is pulmonary regurgitation (PR).

Isolated pulmonary regurgitation has been shown to clinically be well-tolerated for decades by most patients.[47] However, during early adulthood - middle age, patients start to manifest symptoms of right sided heart failure and may present with sudden cardiac death.[47,48] Since symptoms from RV failure may appear only when advanced myocardial damage has occurred, the more subtle effects of PR may easily be missed.[25,49] The long-term negative effects of PR on RV dimensions, RV and LV function, exercise performance and arrhythmia have been well documented.[25,50,51] With the growing number of long-term survivors of initial corrective surgery the clinical management of TOF patient with residual PR is of growing importance. Though long-term deleterious effects of PR on right sided dimensions and global systolic function have extensively been addressed in literature, little is known on rate of progression of both processes over time and on the factors involved.

1.4.3 Treatment of PR

The most widely accepted treatment for PR is pulmonary valve replacement. The first reports on pulmonary valve replacement date from the early 1980's.[25] A first pulmonary valve replacement can be performed with a peri-operative mortality rate of 0 – 4%[52-57] and excellent mid-term survival.[52,54-57] Clinical status and RV volumes almost unanimously are shown to recover in response to pulmonary valve replacement,[23,55,56,58,59] but results on recovery of RV function are conflicting.[25,53,58] Optimal timing of pulmonary valve replacement appears crucial to prevent irreversible right ventricular (RV) damage.[23,55]

Prostheses used for pulmonary valve replacement have a limited lifespan and therefore the procedure should not be timed to soon. Freedom of repeated valve replacement has been reported in 58% to 86% of Fallot patients after 10 years of follow-up.[52,57] However lifespan of prostheses relates to age of the patient, with longer durability in adults than in children.[48]

2 Turner's syndrome

2.1 Background

Turner's syndrome is characterized by the absence of all or part of the normal second sex chromosome, which leads to a constellation of visible (dysmorphic) and non-visible physical findings in affected women.[60] Turner's syndrome was first described in 1768 by the anatomist Giovanni Morgagni who reported post-mortem findings of a woman with short stature, renal malformations and gonadal dysgenesis. In 1902 Funke described a girl with gonadal dysgenesis, short stature, absent puberty, congenital lympedema and a webbed neck.[61] The definitive description of the clinical features characteristic of Turner's syndrome was given by Ullrich in 1930. However the syndrome is named after Henry Turner, an American endocrinologist who in 1938 described 7 women with the characteristic phenotypic features of the syndrome.[62] Turner's syndrome occurs in 1 out of 2.000 to 3.000 live born girls.[60,63] Approximately half of the patients have X-chromosomal monosomy (45, X), 5 to 10% have a duplication of the long arm of one X-chromosome (duplication, 46, X, i(Xq)), the remaining have mosaicism for 45,X, with one or more additional cell lineages.[60] Turner's syndrome is associated with a 3-fold increase in overall mortality. Life expectancy of women with Turner's syndrome is reduced by up to 13 years.[61] Cardiovascular disease is the most common cause of death in adult women with Turner's syndrome.[61] Complications from other disease like diabetes also contribute importantly to mortality.[60]

2.2 Clinical features and diagnosis

There is a wide variation of clinical features seen in girls and women affected by Turner's syndrome. The phenotype in Turner's syndrome correlates with the exact cytogenetic appearance, with the most severe phenotype seen with 45,X.[61] Approximately ⅕ to ⅓ of affected girls are diagnosed as newborns because of puffy hands and feet or redundant nuchal skin. Approximately ⅓ is diagnosed in mid-childhood due to short stature while others show failure to enter puberty during adolescence. Diagnosis may be delayed until adulthood in approximately 10% of patients, almost exclusively those who enter puberty spontaneously and subsequently present with amenorrhea, infertility or

recurrent pregnancy loss. The clinical factors with the greatest impact on the lives of girls with Turner's syndrome are: 1) short stature, 2) ovarian failure and 3) congenital cardiovascular abnormalities.[26] These will be discussed in the following paragraphs.

2.2.1 Short stature

Short stature is the most common readily recognizable sign of Turner's syndrome found in at least 95% of all patients.[64] In north-western Europe mean adult height in women with the Turner's syndrome is about 147 cm, which is approximately 20 cm below the normal mean in women.[26] The cause of growth failure in Turner's syndrome is currently unknown, but is thought to be a primary bone defect. Candidate genes for short stature have been localized on the distal part of the short arm of the X and Y chromosomes, the so-called pseudoautosomal regions. A strong candidate gene for short stature found within these regions is the short stature homeobox-containing gene (SHOX gene) or pseudoautosomal homeobox containing osteogenic gene (PHOG). Point mutations of the SHOX/PHOG have been shown to be associated with short stature as well as some of the skeletal abnormalities found in Turner's syndrome.[61]

Supra-physiologically dosed growth hormone treatment has been shown to accelerate height velocity in Turner's syndrome[65,66] and result in normalization of final height in most girls with Turner syndrome.[65] However, studies that included a randomized control group are scarce and efficacy of growth hormone treatment could not be established in all studies.[60] Nevertheless in many countries growth hormone therapy currently is well accepted for treatment of short stature in Turner's syndrome.[26]

As important as efficacy of growth hormone (GH) treatment to increase adult height, is the safety of this treatment. Short-term safety of recombinant human growth hormone treatment in Turner's syndrome appears to be acceptable.[26,60] Increased blood pressure and insulin resistance have been reported during treatment, but resolved after discontinuation of therapy. Long-term effects of recombinant human growth hormone on for example the lifetime risk of type 2 diabetes, but also on cardiovascular status so far are unknown.[60]

2.2.3 Gonadal dysgenesis

Gonadal dysgenesis is a cardinal feature in Turner's syndrome as already emphasized by Henry Turner. Gonadal failure occurs in over 90% of patients.[64] A comparable percentage will require hormone replacement therapy to initiate puberty and complete growth.[60] Dependent on karyotype up to 40% of patients may undergo spontaneous pubertal development, and 2 − 5% may have spontaneous menses and the potential to achieve pregnancy.[61,64] Spontaneous fertility is most likely with mosaicism for a normal 46,XX cell lineage or a 47,XXX cell lineage of very distal Xp deletions.[60] Both the short (distal to Xp11) and long arm (Xq13-25 and Xq26-28) of the X chromosome contain "critical regions" vital for normal ovarian development.[60,61] Other genes, like the ZFX (zink finger) gene and the DFFRX (Drosophila fat facets related X), have also been identified as possible candidate genes for normal ovarian development .[61] Mechanism like aneuploidy and sex chromosome imbalance with impaired meiosis may contribute to a reduced number of germ cells and reduced survival of these cells.[60,61]

When induction of pubertal development is needed it is recommended to try and mimic normal pubertal development taking in account individual factors such as physiological issues and family history of age at onset of puberty.[26,60,64] Oestrogen substitution therapy during childhood includes a risk of premature epiphyseal closure. Therefore oestrogen therapy should be carefully timed as to minimize any negative effect on growth while inducing puberty at an approximately normal age.[60,64] Long-term oestrogen replacement therapy is important to prevent osteoporosis and reduce the risk for atherosclerosis.[61] Progestagen should be added after the first 12 − 24 months of oestrogen treatment to prevent endometrial hyperplasia and carcinoma.[60,61,64]

Most Turner patients are infertile, but various assisted reproductive techniques are now available. All pregnancies in patients with Turner's syndrome should be monitored by a multidisciplinary team, both in the preparation phase and during follow-up of the pregnancy.[64] The interest from cardiologic point of view in part results from the increasing number of reports on aortic dissection (also see paragraph 2.2.4.2) in the Turner syndrome during pregnancy.[8,67] All women are advised to undergo a full cardiologic assessment before pregnancy, including echocardiography or magnetic resonance imaging of the aortic root, the cardiac valves and left ventricular function.

2.2.4 Cardiovascular disease in Turner's syndrome

2.2.4.1 Structural cardiovascular malformations

Structural cardiovascular malformations, or congenital heart disease occur in up to ¾ of patients with Turner's syndrome.[6,8] Coarctation of the aorta and bicuspid aortic valve are common and represent respectively 25 − 30% and 25 – 35% of cardiovascular malformations in the Turner syndrome.[6-8] Besides structural cardiovascular malformations hypertension is frequently found in Turner's syndrome.[61,68] Already during childhood patients show higher pressure compared to a reference population, with hypertension found in up to 25% of girls.[69,70] Furthermore an abnormal circadian blood pressure rhythm with blunted nocturnal reduction in blood pressure was found in over 50% of girls with Turner syndrome which increases the risk of end-organ hypertensive damage.[69] The majority of Turner patients with hypertension have no obvious secondary cause of hypertension, despite the young age of onset.[61]

Bicuspid aortic valve usually is found as an isolated abnormality but may occur in association with other anomalies, particularly coarctation of the aorta. The cause of the abnormal aortic valve in Turner's syndrome is unknown. A bicuspid aortic valve may develop progressive valvular dysfunction both in terms of stenosis and insufficiency. Coarctation is especially common in Turner patients with webbing of the neck. This association together with the high incidence of coarctations found in aborted foetuses with 45,X and severe lymfedema, led to the theory that aortic coarctation in Turner's syndrome may be caused by abnormal lymphatic flow and compression of the descending aorta.[61,71]

2.2.4.2 Aortic dilation and dissection

For years aortic dilation was regarded a less common cardiovascular malformation in Turner's syndrome, with a reported prevalence up to 6.5%.[8] However, in recent studies using magnetic resonance imaging (MRI), aortic dilation was found in 25 − 50% of patients with Turner's syndrome and cardiovascular malformations.[6,7,72] Dilation and dissection most frequently (50 – 70% of cases), but not exclusively, occur in the ascending aorta.[6,8] Dilation of the ascending aorta was found in 20 − 40% of patients.[6,73,74]

Aetiology of aortic dilation in Turner's syndrome is unknown. Aortic dilation and dissection may occur at any age.[8,73] As in the normal population it has been well established in Turner's syndrome that coarctation of the aorta,

bicuspid aortic valve and hypertension are associated with a increased risk for aortic dilation and dissection.[8,75] However in 5 to 10% of women with Turner's syndrome and aortic root dilatation no associated risk factor for dilation is found.[73] Post-mortal findings in 71% of 25 Turner cases with histological data available, showed arterial cystic media degeneration similar to that seen in Marfan syndrome.[61] Increased incidence of complications after surgery for coarctation has been reported in Turner's syndrome as a result of apparent friability of the aortic wall.[8] A recent study in Turner's syndrome showed increased carotid-femoral pulse wave velocity, increased carotid intima-media thickness, and a larger carotid augmentation index.[74] All these reports support the hypothesis that connective tissue abnormalities might play a role in aortic disease in Turner's syndrome.

2.3 Cardiovascular effects of growth hormone

In Turner's syndrome growth hormone is given for the restricted (but still fairly long) period of time during which a gain in patient's final height can be accomplished. Especially when started at young age and given at supra-physiological dosages results on final height are good.[26,65] However, concerns have risen on the possible long-term cardiovascular side effects of supra-physiological GH-therapy in Turner's syndrome based on knowledge of cardiovascular side effects in other situations of growth hormone excess.

2.3.1 Effects on the heart

Growth hormone stimulates growth of the cardiomyocyte.[76,77] The effects of growth hormone on cardiac size and function appear to occur in stages. Administration of growth hormone to healthy controls rapidly induces changes in LV geometry and function.[76,78] Short term growth hormone induced myocardial hypertrophy has been shown to be reversible.[76] In response to GH the cardiomyocyte initially increases its size and cross-sectional area, reflecting parallel apposition of sarcomeres.[77] As such short term growth hormone excess results in concentric ventricular remodelling, which according to the law of Laplace results in decreased wall stress. During initial acromegaly and with short term growth hormone excess diastolic function remains unchanged, while heart rate and left ventricular contractility increase.[76-80]

In animal models of myocardial ischemia short-term GH/IGF-I excess reduced the extent of cell necrosis and apoptosis.[77] Initial GH/IGF-I induced myocardial hypertrophy in heart failure occurred proportional for the cardiomyocytes and the non-myocyte portion, thus without disproportional fibrosis.[77] Moreover short-term GH has been shown be able to restore reduced myocardial capillary density to normal levels. Finally short-term GH/IGF-I excess is thought to activate a myocardial energy-saving program, including reduced oxygen demand and improved calcium handling, which results in improved LV mechanical performance.[77,81] As such, short-term GH excess induces a physiological type of myocardial hypertrophy.

Pathological myocardial hypertrophy is characterized by cardiomyocyte lengthening or serial deposition of sarcomeres, which results in eccentric remodelling. With pathological hypertrophy decreased myocyte density is found due to necrosis and apoptosis of myocytes combined with increased myocardial fibrosis. Pathological myocardial hypertrophy, typically found with chronic heart failure, is also found with long-term untreated acromegaly. Over time patients with active acromegaly develop signs of LV diastolic dysfunction even in the absence of myocardial hypertrophy.[82,83] Diastolic dysfunction in acromegaly relates to disease activity and can be detected before evident systolic dysfunction.[81,83,84] Progressive pathological myocardial hypertrophy in acromegaly results in impaired LV performance, low cardiac output failure, impaired LV stress response and reduced exercise tolerance.[80] As such end-stage acromegaly may be regarded a congestive heart failure syndrome in which disease duration and activity independently predict mortality.[81]

The pathological type of hypertrophy seen with long-term acromegalic cardiomyopathy is a cause of concern in all (high dosed) GH treated patients populations, including patients with Turner's syndrome. During growth hormone treatment results have been reassuring with no signs of hypertrophy found in Turner's syndrome,[70,85] Noonan syndrome,[86,87] growth hormone deficiency,[88] or children with idiopathic short stature,[89,90] However data on possible long-term side-effects of growth hormone treatment are scarce, with almost no data available on cardiac status following discontinuation of treatment.[91]

2.3.2 Effects on the large arteries

The biophysical properties of the arterial wall depend on the presence and proportion of smooth muscle cells and major components of the extra-cellular matrix (collage and elastin).[92,93] The arterial media contains a mixture of collagen and elastin fibres typical for the respective vessel. The aorta contains about 60% elastin fibres and 40% collagen fibres.[92] Elastin fibres are highly extensible, have a remarkable longevity, but fracture at low stress and show no appreciable synthesis in the adult aorta. Collagen fibres on the other hand act as a stiff reinforcing component, are only relatively inextensible, but can resist much higher levels of stress. The mixture of components with different elastic properties results in a non-linear pressure-diameter (volume) relation of the aortic wall.[94,95] This non-linear provides elastic stability and prevents the aorta of dilating or rupturing.[92] Changes in content and composition of the extra-cellular matrix will influence the mechanical properties of the arteries.

A variety of factors and diseases influence aortic stiffness. Aortic distensibility in normal subjects negatively correlates with age, progression of atherosclerosis, abnormal lipid profile, and with post-menopausal state in women.[96-98] The degenerative changes of the aortic wall in Marfan syndrome, a heritable connective tissue disorder, result in increased aortic stiffness, as indicated by findings of decreased aortic distensibility and increased pulse wave velocity compared to healthy controls.[99] In Marfan syndrome both aortic diameter and distensibility are independent predictors of progressive aortic dilation.[100]

With aging plasma levels of anabolic hormones, among which GH and insulin-like growth factor-1, decrease. Growth hormone therapy has been shown to be able to reverse age-related catabolic changes.[96] Patients with growth hormone deficiency show wall thickening of large arteries and a tendency toward decreased compliance. In response to growth hormone substitution therapy patients with growth hormone deficiency showed a decrease in arterial wall thickness and an increase in arterial wall compliance.[101,102] In rats growth hormone was found to influence collagen metabolism and change the mixture of fibrous elements in the aortic wall which led to increased aortic wall distensibility in young animals.[103]

3 Imaging in congenital heart disease

3.1 Cardiac magnetic resonance imaging; general considerations

Imaging plays an increasingly important role in the diagnostic and the therapeutic management of CHD.[104] With various forms of CHD, among which TOF, the RV is subject to abnormal pressure and/or volume load and has been shown to be a major determinant of clinical outcome.[105] Accurate assessment of RV anatomy, volume and ejection fraction in CHD, both before and after reparative surgery requires one or more of the following imaging modalities: echocardiography, contrast X-ray angiography, radionuclide studies, computed tomography, and magnetic resonance imaging (MRI).[106]

Transthoracic echocardiography still is the workhorse of non-invasive imaging in CHD as it is non-invasive, low-cost, without ionising radiation and can be performed virtually anywhere.[51,104,107] However, echocardiography may be hampered by its limited imaging window, particularly in (adult) patients after previous surgery. For a long time conventional X-ray angiography has been used in addition to echocardiography if necessary for the evaluation of extra-cardiac vascular structures, both arterial and venous. Transoesophageal echocardiography shows better sensitivity and specificity for the evaluation of CHD compared to transthoracic echocardiography, but is semi-invasive and not well suited for evaluation of the anterior positioned RV.[108] Currently MRI is considered an extremely useful tool to study CHD as it combines the main advantages of echocardiography and conventional X-ray angiography. Like (transthoracic) echocardiography MRI provides accurate non-invasive information on morphology and function of the heart, while allowing for the evaluation of extra-cardiac vascular structures at the same time.

Many of the advantages of MRI over echocardiography and X-ray angiography also hold for computed tomography. However, MRI does not use ionising radiation and iodine-based contrast agents, which have a three times higher risk for contrast mediated reactions compared to gadolinium based MRI contrast agents.[107] Exposure to ionising radiation increases the risk of later malignancy in children, which is especially important in patients in need of repeated or serial examinations such as patients with CHD.[109]

Like other imaging techniques MRI has limitations and contra-indications. The most important practical limitations of MRI are the limited availability

and high cost. Cardiac MRI requires dedicated hardware and software, and specifically trained technologists and physicians. Acquisition of a full cardiac MRI examination requires relatively much time (30 − 60 minutes) but is tolerated well by most patients.[51,107] Children should be old enough to follow breath-hold instructions (approximately 7 − 10 years) to be scanned without (general) anaesthesia [51,107]. Most contraindications besides severe claustrophobia, arise from the effects of the magnetic field on magnetic or metallic prosthesis and implants (Table 1). Up to date listings of prosthesis and implants to verify possible contra-indications for MRI are published periodically and can be found on the internet (www.MRIsafety.com). Metal clips, suture wire in the sternum and vascular-coronary endoprosthesis (stents) do not represent a contra-indication for MRI. MRI is not contra-indicated with most valvular mechanical prosthesis, except with the oldest types. Pacing or defibrillator wires are a contra-indication for MRI as electromagnetic currents may induce internal heating of the wires.[110,111] Furthermore the magnetic field may interfere with the electronic components of pacemakers and internal cardiac defibrillators and cause malfunction, although with newer devices and wires there only appears to be a relative contra-indication.[110,112,113] Multi-slice computed tomography has emerged as an alternative modality for the population with an implantable metallic device, but requires slow heart rates which is a relative limitation in paediatric patients.[107]

Table 1. Contra-indications for magnetic resonance imaging

Pacemaker, implanted defibrillator or neurostimulator
Intracranial iron clips
Metallic intraocular foreign body
Metallic projectile fragment near a vital structure
Cochlear implant or hearing aid
Starr-Edwards mitral valve prosthesis
Claustrophobia
Critical patient with a Swan-Ganz catheter
Pregnancy (teratogenic effect not demonstrated)

3.2 Assessment of ventricular size

In CHD accurate (serial) assessment of biventricular size is important to evaluate the impact of cardiac loading on cardiac condition. For the assessment of ventricular size many imaging modalities such as 2D-chocardiography and biplane contrast ventriculography use mathematical assumptions for chamber shape. Such assumptions may be applicable to the conical shaped LV, but not to the geometrically more complex RV. Especially with RV dilation predefined geometrical models may no longer apply and errors may occur or increase. Biplane contrast ventriculography, which used to be the gold standard for RV evaluation, now has largely been replaced by newer "non-geometric" imaging techniques like cardiac magnetic resonance imaging, three-dimensional echocardiography and multi-slice CT.[104]

The problem of geometric assumptions with echocardiography is being overcome with recently developed 3D-techniques. Validation studies using 3D-echocardiography have shown promising results for RV volumetric measurements, with good correlations found with MRI measures.[114-116] Independent of the imaging technique used for volumetric ventricular assessments appropriate detection of the endocardial border is required. Using echocardiography this has been shown difficult for the heavy trabeculized RV. As a resultant a systematic underestimation of RV volume with both 2D- and 3D-echocardiography was found.[116,117] Further difficulties with 2D- (and 3D) transthoracic echocardiography may occur when the RV is positioned substernal, which is especially seen with hemodynamic overloading and congenital malformations.[118]

Compared to 2D-echocardiography nuclear imaging techniques offer RV volume assessment not dependent on RV geometric assumptions. However the technique does require views that exclude counts form other chambers, which can usually be obtained for the left ventricle but not always for the right ventricle.[119] Furthermore radionuclide angiography requires bolus-injections, a regular cardiac rhythm, has limited resolution compared to other imaging modalities, and uses ionising radiation (though at relative low doses).[104] Radionuclide angiography does provide a reliable quantitative measurement of RV ejection fraction and wall motion.[106,120]

Common to all tomographic imaging techniques is that they generate a contiguous set of image sections encompassing the ventricular cavity

to provide a three dimensional data-set from which ventricular volumes can be calculated without the need for geometric assumptions. Volumetric measurements obtained with computed tomography provide accurate stroke volumes and ejection fractions for the right ventricle, and highly reproducible RV volumes.[121-123] However computed tomography requires the use of intravenous contrast to provide sufficient differentiation between the ventricular lumen and the myocardium. Currently gradient-echo tomographic MRI has been established as the standard of reference for quantitative assessment of RV volume, mass, and function.[124,125] In contrast to computed tomography and echocardiography high contrast is obtained between the blood and the myocardium without the use of contrast agents. Tomographic cine MRI can be performed reliably and reproducibly for repeated ventricular measurements.[126,127]

3.3 Assessment of ventricular function

3.3.1 Ventricular function in general

Functional performance of the heart depends on both intrinsic and extrinsic factors. The most important intrinsic factor is the contractile state of the myocardium. Contractile state at the level of the myocyte depends on the interaction between actin and myosin, which in turn depends on cross-bridge formation regulated by cellular calcium homeostasis and calcium sensitivity of the myofilaments.[128-130] At the level of the ventricle contractile state is defined by the amount of pressure generated by the ventricle at a fixed volume (also see paragraph 3.3.2).

Extrinsic determinants of ventricular function include heart rate, preload, afterload and ventricular interaction. According to the formula of cardiac output (CO = heart rate * stroke volume) changes in heart rate may influence cardiac performance. During exercise ventricular end-diastolic volume remains approximately constant while end-systolic volume decreases, which results in a larger ventricular stroke volume.[131,132] Therefore the increase in heart rate with exercise together with the increase in stroke volume results in increased cardiac output.

Preload refers to the load imposed on the myocardium prior to contraction. Higher load is reflected by longer myocyte length or at the ventricular level by a larger end-diastolic volume. To a certain extent stroke volume as a measure

of cardiac pump performance is linearly related to end-diastolic volume, which is known as the Frank-Starling mechanism.[133] The Frank-Starling mechanism was partly explained by improved overlap and interaction of the myofilaments (force-length relationship) and partly by stretch-induced increase in calcium-sensitivity (length dependent activation).[134,135]

Afterload refers to the load that has to be overcome by the ventricle to be able to eject and is reflected by the build up of ventricular pressure until the semilunar valve opens. Afterload depends on several factors including total peripheral resistance, ventricular wall thickness and ventricular size. In Laplace's law for wall stress (Wall stress = Pressure*radius /2*wall thickness) ventricular size is reflected by radius (r). According the Laplace's law, ventricular dilation increases afterload while ventricular hypertrophy decreases afterload. Afterload is best reflected by arterial imput impedance, which, however, is hard to determine and therefore has limited clinical use.[136] For practical purposes afterload is frequently approximated by diastolic pressure in the great arteries and/or by end-systolic ventricular pressure.

Ventricular function is generally used to refer to function of the heart during the cardiac cycle. However during this cycle we can distinguish between a phase of ventricular contraction and ejection, and a phase of ventricular relaxation and filling. During both phases abnormalities in normal function may occur, but not necessarily at the same time. It is, therefore more appropriate to address both entities separately during discussions on ventricular (dys)function.

3.3.2 Systolic function

For the assessment of systolic function several groups of parameters can be distinguished; 1) isovolumic indices, 2) pressure-volume relation derived indices, and 3) ejection phase indices. The most commonly used isovolumetric index of systolic performance is the maximal rise in ventricular pressure (dP/dt_{max}). The dP/dt_{max} is highly sensitive to acute inotropic changes, but has marked inter-individual variation and strong preload dependency.[137,138] To deal with the preload dependency Little *et al*. introduced the dP/dtmax – end-diastolic volume relation.[137] According to the pressure volume relation, ventricular contractile state has been defined as the amount of pressure generated by the ventricle at a fixed volume. The linear relationship between end-systolic pressure and ventricular volume is better known as the end-systolic pressure-volume relationship (ESPVR).[139] The slope of the ESPVR is sensitive to changes

in inotropic state while relatively insensitivity to changes in preload and afterload and is used to measure ventricular contractility.[139-141] The ESPVR is derived from pressure-volume loops (PV-loops). A second parameter derived from PV-loops is stroke work, which refers to the total amount of external work performed by the ventricle and reflects the amount of energy used to propel blood during ventricular contraction. Glower *et al.* found stroke work and end-diastolic volume (a representative of preload) are linearly related which lead to the term preload recruitable stroke work relation (PRSW).[142] The PRSW is preload-independent and insensitive to changes in afterload within the physiological range.[137,143]

The common disadvantage of the so far discussed indices of systolic ventricular function is that they require an invasive procedure to be assessed. Therefore the clinical applicability in research projects and for repeated measurements is limited, especially in children. The parameters categorized as ejection phase indices on the contrary can be derived non-invasively. Stroke volume and ejection fraction can be derived using gradient-echo tomographic MRI, the standard of reference for quantitative assessment of (right) ventricular volume, mass, and function.[124] Compared to 2D-echocardiography the required sample size with MRI is substantially (80 to 90%) smaller to detect changes in ventricular ejection fraction or size.[144,145] Reproducibility values for the RV are generally lower compared to the LV and as such the sample sizes for RV studies should in general be somewhat larger than those for LV studies.[127] Breathhold cardiac MRI has been proven accurate and highly reproducible for ventricular function and size.[124,127,144,146] The major draw-back of stroke volume is its load-dependency. The preload-dependency of stroke volume can be reduced by using ejection fraction (EF). Ejection fraction can defined as the amount of flow ejected during systole (or stroke volume) relative to the total amount of blood present at the start of the ejection phase (or end-diastolic volume, considered a good representative of preload). Ejection fraction in turn is hampered by it's afterload-dependency with an inverse linear relationship between ejection fraction and afterload. Nevertheless ejection fraction has been shown to sensitively detect depression of myocardial contractility. Worse ejection fraction has been associated with poorer clinical status.[49] Like ejection fraction velocity of circumferential fiber shortening (V_{CF}), another ejection phase index of systolic function, is hampered by afterload-dependency.

3.3.2 Diastolic function

Cardiovascular disease may lead to the clinical heart failure syndrome. For the clinical management of patients at risk for development of heart failure early diagnosis of ventricular dysfunction is essential. Many patients present with symptoms of heart failure including exertional dyspnoea, fluid retention, and pulmonary oedema. Previous epidemiologic studies indicated nearly half of patients with heart failure have normal systolic function.[147] It has been shown that diastolic ventricular dysfunction in various cardiovascular diseases may precede systolic ventricular dysfunction.[148] As such adequate recognition of diastolic dysfunction may contribute to early detection of ventricular dysfunction.

Diastole is the period available for ventricular filling defined as the period following closure of the semilunar valve extending to the point of atrioventricular valve closure. Diastole can be divided into four phases: 1) isovolumic relaxation, 2) rapid early filling, 3) diastasis and 4) (late) atrial contribution to ventricular filling. Isovolumic relaxation stretches from closure of the semilunar valve to opening of the atrioventricular valve. Isovolumic relaxation depends on active excitation-contraction decoupling by the active release of actin-myosin crossbridges that were formed during systole. The process depends on the number of crossbridges formed during systole (increases with increased ventricular load) and the time available for uncoupling of crossbridges (depends on heart rate). Indices used for this purpose are peak pressure decline rate (dP/dtMin) and the time constant of pressure decay (tau = time needed for pressure to drop to about 37% of starting pressure), which require invasive pressure recordings.[149] Isolumic relaxation time can be assessed non-invasively using Doppler echocardiography by measuring the interval between pulmonary (or aortic) valve closure and the start of tricuspid (or mitral) flow.

Ventricular filling is composed of the remaining three phases: the rapid early filling phase, the diastasis and the late atrial contribution to ventricular filling. Rapid filling occurs directly after AV-valve opening. The driving force behind early inflow is a pressure gradient over the AV-valve present due to relaxation of the ventricle causing ventricular pressure to decline, which in turn causes an atrioventricular pressure gradient to arise. The velocity of this inflow (peak early filling rate) will be proportional to the driving force (atrioventricular pressure gradient). This pressure gradient in turn is

dependent on the ventricle's abilities for relaxation and is inversely related to the time constant of pressure decay (tau). Like the phase of isovolumic relaxation the phase of early filling depends on the active process of actin-myosin cross-bridge decoupling. As the ventricle enlarges during filling passive properties of the ventricle ultimately will prevent a further increase in ventricular volume. During this early filling phase ventricular pressure gradually increases which will cause the atrioventricular pressure gradient to decrease leading to a point of equalisation of pressures. This point in time, known as diastasis is characterised by zero ventricular inflow. In late diastole a second atrioventricular pressure gradient is created by atrial contraction. As such atrial contraction (atrial systole) acts as the driving force for late (atrial) diastole filling. Counteraction to the driving force in late diastolic is given by the passive mechanical properties of the ventricular myocardium (like compliance, distensibility, stress and elasticity), the overlaying pericardium, and ventricular interaction. The RV and LV interact especially during diastole when pressures are low. The position of the interventricular septum depends on the transseptal pressure difference. As such an increase of RV volume and/or pressure decreases LV filling.

Ventricular filling can be characterized non-invasively by Doppler echocardiography, radionuclide techniques, or MRI techniques. Irrespective of the technique used, all assess diastolic function by measuring indices of volume transient during ventricular filling.[149] Figure 1 shows a typical example of an AV-valve inflow pattern as assessed by velocity encoded cine MRI. Comparable curves can be obtained with radionuclide techniques and Doppler echocardiography (however with flow velocity on the Y-axis). As illustrated by Figure 1 indices that characterize the pattern of ventricular filling can be derived from such curves. The typical diastolic filling parameters measured from VEC MRI determined time-volume change curves are depicted in Table 2.

In the normal heart two thirds of stroke volume enter the ventricle during early diastole and about a fifth to a quarter of stroke volume enters during late diastole (A-peak). Therefore in healthy subjects the E/A-ratio will be expected to be larger than 1.0 (Figure 2). Abnormalities in the ventricular filling pattern may occur with cardiovascular disease and relate to degree of impairment of ventricular diastolic function. Relaxation related ventricular dysfunction interferes with the normal build up of the driving pressure gradient responsible

for early ventricular filling. The filling pattern of relaxation related diastolic dysfunction therefore is characterised by a smaller relative contribution of early ventricular filling (E-peak), prolongation of E-peak deceleration time, a larger relative contribution of atrial filling to total ventricular filling and a declined E/A-ratio (Table 2 and Figure 2). In patients with restrictive ventricular diastolic dysfunction the pattern is characterised by restriction of RV filling to the early phase with a relatively small contribution of atrial contraction to ventricular filling (Table 2 and Figure 2).

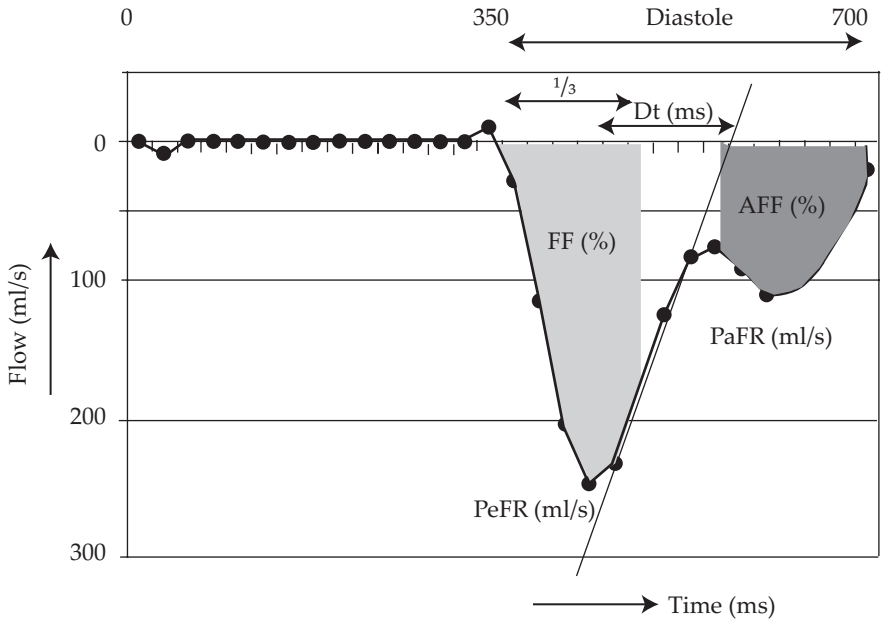
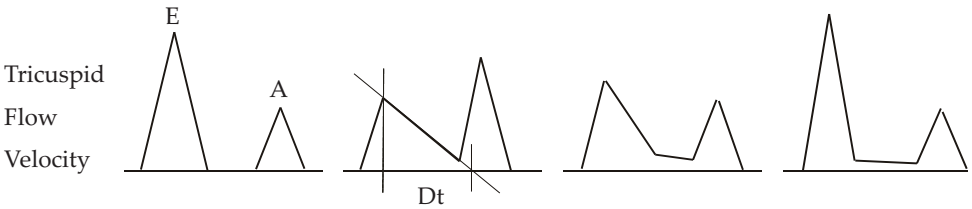


Figure 1: Phase velocity encoded mitral valve filling pattern
AFF = atrial filling fraction, Dt = deceleration time, FF = early filling fraction, PaFR = peak atrial filling rate, PeFR = peak early filling rate

Patients with repaired tetralogy of Fallot in the majority of cases have some degree of pulmonary regurgitation. At least part of these patients show free communication between the right ventricle and the pulmonary artery with instant filling of the RV from the pulmonary artery when ventricular relaxation starts. An isovolumic diastolic time period can not be detected in these patients and therefore not be studied. RV diastolic filling in most cases can be studied using Doppler echocardiographic inflow-pattern across the tricuspid valve.

However, in patients with PR filling of the RV occurs through both the tricuspid and pulmonary valve. In this setting Doppler echocardiography cannot adequately quantify total RV diastolic filling. In contrast to echocardiography phase velocity encoded (VEC) or flow-sensitised MRI offers volumetric flow quantification. Volumetric quantification allows for inclusion of both tricuspid and pulmonary flow into the analysis of RV filling by accumulation of curves (Figure 3). At rest VEC MRI has successfully been validated for the assessment of RV diastolic function in patients with PR.[150]

Right ventricular diastolic filling pattern:



Filling characteristics:				
1. Relaxation	Normal	Impaired	Impaired	Impaired
2. Compliance	Normal	Normal	Midly Decreased	Severly Decrease
Descriptives:				
1. Functional Type	Normal (Young)	Impaired Relaxation	Pseudo Normal	Restrictive Physiology
2. Severity of dysfunction	None	Mild	Moderate	Severe

Figure 2. Diastolic ventricular filling in the normal heart and with cardiovascular disease.

A = peak atrial filling, DT = deceleration time, E = peak early filling

Table 2. Indices of ventricular diastolic filling derived from VEC-MRI time-volume curves: changes from normal in relation to type of diastolic dysfunction

Index	Description	Relaxation	Restriction
PeFR (ml/s)	Peak early filling rate; first peak deflection from baseline during ventricular filling	–	+
TtPeFR (ms)	Time from end-systole to PeFR	+	0
FF (%)	Early filling fraction; ventricular volume increase during first ⅓ of diastole/stroke volume *100%	–	+
Dt (ms)	Deceleration time; time from PeFR to the exploration point of deceleration of flow to the baseline	+	0/+
PaFR (ml/s)	Peak atrial filling rate; peak deflection from baseline during atrial systole	+	–
AFF (%)	Atrial filling fraction; ventricular volume increase after atrial contraction / stroke volume *100%	+	–
E/A-ratio	Ratio of PeFR over PaFR	–	+

– = decrease, + = increase, 0 = constant

3A RV time – volume change curve: rest and stress

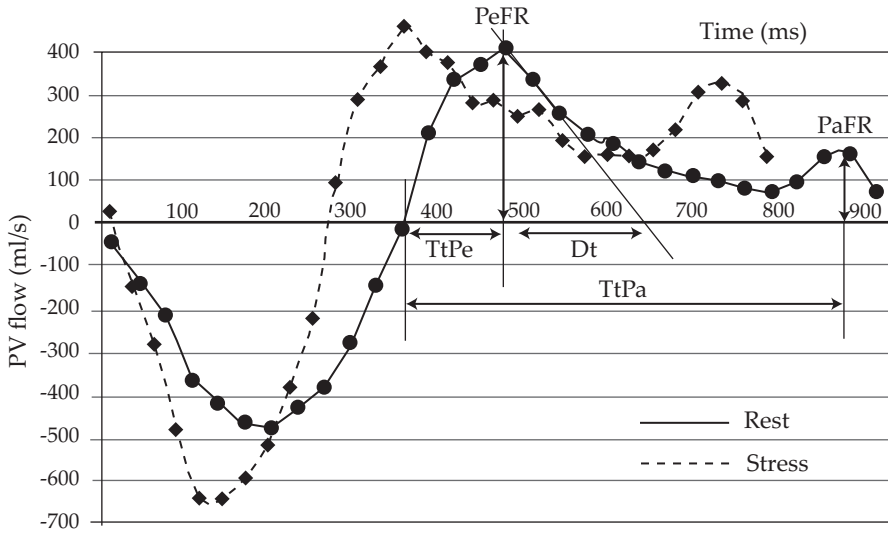
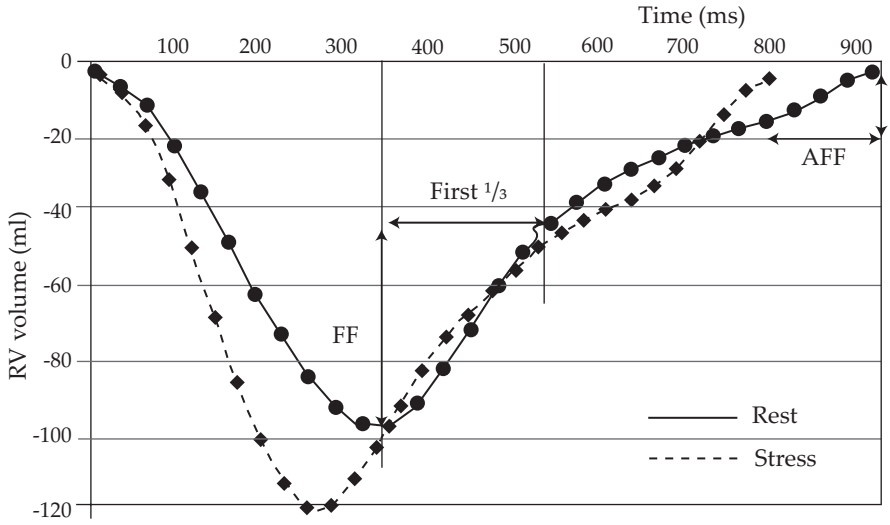


Figure 3. Diastolic filling in tetralogy of Fallot with pulmonary regurgitation
3A. Dt = deceleration time, PaFR = peak atrial filling rate, TtPa = time to PaFR, PeFR = peak early filling rate, TtPe = time to PeFR

3B RV time – volume curve: rest and stress



3B. AFF = atrial filling fraction, FF = early filling fraction

3.4 Arterial wall stiffness

One of the main functions of the aorta is maintenance of steady blood flow through the capillary bed by the transformation of pulsatile flow into continuous flow. For this purpose the central aorta and major arteries distend during systole and store up to 60% of the LV stroke volume. By recoil of the central arteries during cardiac diastole, blood is pushed towards the periphery. Efficacy of this function is determined by the biophysical wall properties, or stiffness, of the central arteries. Biophysical wall properties largely dependent on presence and proportion of smooth muscle cells and major components of the extra-cellular matrix (collage and elastin), or in short on arterial wall composition.[92,93]

The aortic biophysical wall properties seem to play a significant role in the pathogenesis of a variety of cardiovascular diseases such as atherosclerosis, hypertension, aneurysm formation, stroke, myocardial infarction, renal failure and Marfan's syndrome.[92] In these disease states arterial wall stiffness is increased.[93,151] Early detection of abnormal arterial wall function could provide a tool for early detection of cardiovascular disease. Methods for detection than

should be routinely available, non-invasive and safe, and allow for accurate and reproducible measurements.

Various imaging techniques proved to be suitable for this purpose, the most important ones being ultrasound and MRI. As with other applications ultrasound benefits from its readily availability and low cost. Its use however is limited to the larger and more accessible arteries. Hence, the technique is used mainly on the brachial, femoral and carotid arteries and the abdominal aorta. The main site of application for MRI, a technique with an unlimited acoustic window, is the (thoracic) aorta. To quantify arterial stiffness a host of indices have been introduced of which none has been proven superior and all have their problems during measurement and interpretation.[93] Direct measurement of arterial stiffness by imaging relates to measurement of change in arterial diameter and pressure at the same site.[92] As a resultant non-invasive techniques applied on the aorta (and other central arteries) are limited by the fact that blood pressures are determined indirectly at the site of a peripheral artery.[92] In measurements of pressure and diameter, stiffness can be expresses as: Distensibility, Compliance, Elastic modulus (Peterson) and Elastic modulus (Young) and Stiffness index (Table 3).

Table 3. Indices of arterial wall stiffness; definitions and formulas

Index	Definition	Formula
Arterial distensibility	Relative diameter or area change for a pressure increment	$\Delta D/\Delta P * D$ ($mmHg^{-1}$)
Arterial compliance	Absolute diameter or area change for a given pressure step at a fixed vessel length	$\Delta D/\Delta P$ ($cm^2/mmHg$)
Elastic modulus	The pressure step required for (theoretical)100% stretch from resting diameter at fixed vessel length	$\Delta P*D/ \Delta D$ (mmHg)
Young's modulus	Elastic modulus per unit area; the pressure step per square centimetre required for 100% stretch from resting length	$\Delta P*D/ (\Delta D*h)$ (mmHg/cm)
Stiffness index	Ratio of logarithm (systolic/ diastolic pressure) to (relative change in diameter)	Ln (Ps/Pd)/ [(Ds-Dd)/Dd] (nondimensional)

P = pressure, D = diameter, h = wall thickness, s = systolic, d = diastolic

Both ECG-gated spin echo and ECG-triggered cine-gradient-echo sequences have been validated to determine regional aortic distensibility and compliance with magnetic resonance imaging.[92] The main draw back of an ECG gated spin echo sequence is the difficulty of proper selection of the end-diastolic and end-systolic time-frames. Using ECG-triggered cine-gradient-echo sequences images are acquired throughout the cardiac cycle, which allows for accurate selection of the diastolic and systolic time-frames when scanned at an appropriate temporal resolution (approximately 25 ms).[92] The main disadvantage of gradient-echo sequences compared to spin echo sequences is the limited contrast between vessel wall and lumen. The limited contrast with gradient echo sequences can be overcome by using an appropriate spatial resolution (< 1mm) and a small flip angle (20 − 30 degrees).[92]

The velocity at which the pulse wave travels along the arteries largely depends on the biophysical wall properties of the vessel. Therefore, another measure of arterial wall stiffness is pulse wave velocity defined as the distance between two points divided by the time needed for the pulse wave to propagate between these points. Pulse wave velocity is related to arterial compliance according to the equation $C = 1/PWV^2*p$ [151] and to arterial distensibility according to the equation $PWV = \sqrt{(1/p*D)}$ (C = compliance, D = distensibility, PWV = pulse wave velocity, and p= blood mass density).[92]

Transthoracic Doppler ultrasound is limited by technical factors such as transducer placement and beam angle, but most important for the assessment of PWV in the aorta is the limited access to the central arteries.[93] Therefore, conveniently accessible (carotid and femoral artery) points of measurement have to be chosen and compromises have to be made for determination of arterial distance over which the pulse wave travels.[92,151] MRI is an alternative method for measuring PWV that allows accurate path length determination (along the centreline of the aorta) between two points of measurement.[92] To allow for good accuracy scanning should be performed at high temporal (approximately 25 ms) and spatial (1 – 2 mm) resolution.[92]

In summary phase velocity encoded MRI (cine-gradient-echo sequences) has been validated as an accurate tool for determination of both regional aortic distensibility and PWV.[92] The use of MRI-determined measurements related to the biophysical arterial wall properties has been put forward for (early) detection of aortic wall dysfunction and quantification of (small) intervention related effects on wall function, such as drug related effects.

4 Heart failure and the neuro-endocrine system

4.1 Heart failure; general considerations

Normal homeostasis is maintained by a complex system with the heart as the central component, the muscular pump necessary for propulsion of blood. Other contributors to normal homeostasis are the nervous tissue, endocrine organs, the endothelium, the kidneys, blood constituents, and skeletal muscles. Disruption of normal myocardial geometric integrity results in changed intracardiac pressures, wall stress and wall tension. This ultimately leads to loss of the normal flow pattern through the heart and a relative reduction in cardiac output.[152] To be diagnosed with heart failure according to the diagnostic criteria of the European society of cardiology (ESC) patients should have a clinical syndrome characterized by symptoms (breathlessness and fatigue), signs of salt and water retention, and cardiac dysfunction on cardiac imaging.[153] Both diagnostic guidelines of the ESC and the ACC/AHA state heart failure is a clinical diagnosis mainly based on carefully taken history and physical examination.[153,154]

In response to a reduction in cardiac output homeostatic mechanisms, focussed on restoring circulating volume by salt and water retention, vasoconstriction and increasing heart rate, are activated. In LV disease states it is commonly accepted that chronic insult to the myocardium and the resultant changes in geometry and structure, also known as remodelling, are accompanied by neurohormonal activation.[155,156] The resultant is a vicious cycle characterized by excessive neurohormonal stimulation that is responsible not only for the chronic expression of adverse hemodynamic abnormalities but also contributes to further myocardial and vascular remodelling, the hallmark of progressive HF.[155-157] This "neurohormonal concept" has been used during the design of recent treatment guidelines for heart failure.[153,154] Pharmacological manipulation of neurohormonal pathways is now the cornerstone of heart failure therapy with improved morbidity and mortality found with various drugs.[158-164]

The shared hallmarks of cardiac injury and heart failure seen with both congenital heart disease and conventional heart failure cohorts, calls to classify congenital heart disease as a heart failure state.[165] It is becoming increasingly clear that activation of neurohormonal pathways may also occur in congenital

heart disease.[165] Surprisingly few data is available on the relation between RV remodelling as a result of chronic PR and the level of neurohormonal activation. Therefore the prognostic significance of neurohormonal activation and the efficacy of interventions in neurohormonal pathways should be further elucidated.

4.2 Catecholamines

Catecholamines (norepinephrine and epinephrine) are secreted by the adrenal glands in response to sympathetic nervous system activation. The sympathetic nervous system is activated by decreased vascular perfusion pressure registered by the baroreceptors. The so-called "baroreceptor reflex" consists of; 1) an increase in heart rate (positive chronotropy) and ventricular contractility (positive inotropy), 2) vasoconstriction in the skin, splanchnic viscera and kidneys with shunting of blood away towards the heart and brain, 3) vasodilation of the afferent vasculature of the skeletal muscles. With chronic stimulation the sympathetic nervous input is taken over by peripheral and central chemo-reflexes and metabo-ergoreceptor reflexes.[166]

This response is only suitable for the acute compensation of insufficient circulating volume. Chronic sympathetic stimulation results in increased cardiac work with increased myocardial oxygen requirements, while a higher baseline vascular resistance (afterload) adds to the myocardial work requirements.[167] Circulating plasma level of norepinephrine closely correlates with degree of ventricular dysfunction and with prognosis of heart failure.[168,169] Long term catecholamine stimulation may lead to down-regulation of the β1-receptor, which ultimately reduces the myocardial ability to improve contractility to stimulation.[170-172]

Clinical trials suggest that long-term carefully dose-adjusted β-blocker therapy improve symptoms, ventricular ejection fraction, exercise time, quality of life, and possibly even long-term survival.[173-175] The negative inotropic and chronotropic effects of β-blockers initially worsen heart failure symptoms and some patients can not even tolerate the lowest dose.[176] For Carvedilol (a combined β-blocker, α-blocker, and antioxidant) comparable or even better beneficial results were found with heart failure.[161,177,178]

4.3 Renin-angiotensin-aldosterone system (RAAS)

The renin-angiotensin-aldosterone system (RAAS) is composed of a cascade of hormones initially triggered by the release of renin from the kidney (juxtaglomerular apparatus). RAAS contributes to maintaining vascular tone, optimal salt and water homeostasis, and forward cardiac output in human beings. The RAAS is stimulated by diminished renal flow. Renin cleaves angiotensinogen (a protein precursor produced in the liver) to form biologically inactive angiotensin I (AI). Angiotensin-I is converted to angiotensin II (AII) by angiotensin-converting enzyme (ACE). Finally, aldosterone is synthesized in the zona glomerulosa of the adrenal gland. Two subtypes of receptors, angiotensin type 1 (AT1) and angiotensin type 2 (AT2) receptors, mediate the major physiologic actions of angiotensin II. Amongst others AT1-receptors mediate; vasoconstriction, aldosterone stimulation, increased renal sodium reabsorption, vascular smooth muscle growth, endothelial dysfunction and activation of inflammatory cytokines. AT2-receptors mediate; vasodilation, antiproliferation (cardiomyocyte and vascular smooth muscle cells) , decreased renal sodium reabsorption, decreased myocyte hypertrophy, decreased cardiac fibrosis. Plasma renin and aldosterone are increased with heart failure.

Inhibition of the renin-angiotensin-aldosterone system can take place at multiple sites in the cascade by: angiotensin-converting enzyme (ACE) inhibitors, by angiotensin receptor blockers (ARBs), or by aldosterone antagonists. Angiotensin-converting enzyme (ACE) inhibitors given in addition to conventional therapy in patients with severe congestive heart failure improved symptoms and reduced mortality particularly due to reduced progression of heart failure among treated patients.[162,164] ARB's improved morbidity and survival in symptomatic heart failure when used as an alternative for ACE-inhibitors in case of intolerance, or in addition to ACE-inhibitors in patients that remained symptomatic.[179-181]

According to recent European heart failure guidelines ACE-inhibitors and/or ARB's are indicated in all patients with LV systolic dysfunction in NYHA class II-IV.[153] For patients in NYHA class I ARB's are only indicated if ACE-inhibitors are not tolerated. Aldosterone antagonists should be added in NYHA class I-II patients with LV dysfunction after a recent myocardial infarction, and in all NYHA class III-IV patients to improve survival and morbidity.[153]

4.4 Natriuretic peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) play an important role in the regulation of extracellular fluid volume and blood pressure homeostasis. ANP and its N-terminal prohormone (NT-proANP) are primarily produced by the right atrium. Brain natriuretic peptide (BNP) and N-terminal prohormone (NT-proBNP) are primarily secreted by the ventricular myocardium. Levels increase in response to increased wall stress with volume or pressure overload and to neuro-endocrine stimuli such as angiotensin II and endothelin.[182,183] NT-proANP and NT-proBNP, the physiological inactive fragments of the natriuretic prohormones have a longer plasma half-life and better in vitro stability compared to the biological active parts.[183,184] In patients with LV dysfunction NT-proBNP has at least identical and possibly better diagnostic value compared to BNP.[182,183] ANP and BNP have natriuretic, diuretic, vasodilative, and renin-inhibiting effects.[182,183] Natriuretic peptides may be regarded the natural antagonists of the renin-angiotensin system.

Markedly elevated levels of ANP and BNP, have emerged as a useful diagnostic marker in heart failure.[153] In congestive heart failure higher levels of NT-proBNP have been associated with future risk of CHF decompensation, CHF hospitalization and mortality, independent of other factors such as LV ejection fraction, peak oxygen consumption and NHYA class. The European Society of Cardiology considers normal values for natriuretic peptides to be specifically helpful for the exclusion of the diagnosis in patients clinically suspected of heart failure.[153]

4.5 Inflammatory mediators

Sufficiently high concentrations of inflammatory mediators can mimic certain aspects of heart failure, including progressive LV dysfunction, LV remodelling and cardiomyopathy.[185-187] The cardiomyocyte produces TNF-alpha in response to stress or injury.[187] Known effects of TNF in heart failure are negative myocardial inotropy, decreased β-adrenergic responsiveness, hypertrophy of the myocyte, ventricular dilation and dysfunction, increased apoptosis, extracullular matrix alterations, endothelial dysfunction and activation of fetal gene expression.[187] Elevated levels of TNF-alpha were found in patients with (advanced) heart failure.[185] In heart failure progressive increases of TNF-alpha

related to deteriorating NYHA class status.[185] Preliminary reports suggested TNF-alpha inhibition had beneficial effects, but several clinical trials were discontinued because of lack of efficacy or even higher rates of mortality in treated groups.[186]

Interleukin-6 is produced by many cell types among which endothelial cells. Typical stimuli for IL-6 secretion are IL-1, TNF, hypoxia and bacterial LPS.[186,188] IL-6 levels are elevated in the setting of heart failure and negatively relate to functional status.[188-190] IL-6 and related cytokines play a role in both myocyte hypertrophy and apoptosis, which suggest an important role in maintaining an equilibrium and in prevention of progression of compensated hypertrophy towards heart failure.[188]

The increase in pro-inflammatory cytokines is independent of the etiology of congestive heart failure.[186] Increased levels of pro-inflammatory cytokines are not accompanied by increased levels of anti-inflammatory cytokines, resulting in an imbalance of the cytokine network.[186] Failure of one target therapeutic approaches underlines the complexity of the cytokine network in relation to cardiac function. Future research probably should be directed against several factors involved in immuno-pathogenesis of heart failure to try and restore the imbalance between pro-inflammatory and anti-inflammatory markers.

4.6 Endothelin

Endothelin-1 (ET-1), the predominant isoform of the endothelin peptides, is produced by the endothelium and a variety of other cells including cardiomyocytes.[191] Synthesis is regulated by physicochemical factors such as pulsatile stretch, shear stress, and pH. A more complex regulation by vaso-constrictors, growth factors, cytokines, adhesion molecules, NO, prostacyclin, ANP and estrogens also exists.

In the clinical setting only plasma ET-1 concentrations can be measured. ET-1 acts through Gi-protein coupled receptors. ET_A receptors mediate vaso-constriction and cell proliferation, ET_B receptors are important for clearance of ET-1, endothelial cell survival, the release of nitric oxide and prostacyclin, and the inhibition of endothelin-converting enzyme. Levels of ET-1 are increased in patients with heart failure, correlated with the severity of heart failure, and were predictive of survival.[192,193] Because of the opposing actions of ET_A and ET_B receptors therapeutic implications must be carefully assessed.

Nevertheless various studies have shown (a)specific ET-receptor antagonists improve cardiovascular function and structure.[191,194]

4.6 High sensitive CRP

C-Reactive Protein (CRP) is produced in the liver during episodes of acute inflammation or infection. Serum levels of C-reactive protein are elevated in patients with heart failure.[195,196] Data on the prognostic value of CRP in chronic heart failure are inconsistent.[195] CRP levels often remain within the normal range (≤ 10 mg/L). Standard clinical assays lack sensitivity within this low range (3 − 8 mg/L), which prohibits effective risk prediction. High sensitive CPR (hsCRP) potentially enhances the prognostic and therapeutic capabilities and has now become available in inexpensive commercial kits.

CRP is a marker of inflammation in coronary artery disease.[197] Plasma levels of hsCRP were one of the strongest independent predictors of future cardiovascular events in apparently healthy men and women.[197] In chronic heart failure increased levels of CRP have been found and levels positively correlated with severity of disease (NYHA class, quality of life, worse hemodynamics).[195,196] Higher levels of serum CRP in dilated cardiomyopathy related to an increased mortality risk.[198] CRP predicted adverse clinical outcome in heart failure, independent of etiology and independent of the value of BNP.[196] Clinical data on hsCPR in relation to heart failure are limited. Its relation to interventions and prognosis have to be further determined.

5 Aims and outline of this thesis

5.1 Study aims in corrected tetralogy of Fallot

There is broad evidence that chronic residual PR in corrected TOF results in RV dilation, biventricular dysfunction, clinical deterioration and exercise intolerance, with an increased risk for ventricular arrhythmia and sudden cardiac death.[48,50,199-201] Over the last decades several trends were seen in the field of corrective surgery for TOF aimed at reducing late morbidity and mortality. These trends include surgery performed at young age and by transatrial transpulmonary approaches.

In patients corrected according to these current strategies there is a lack of long-term follow-up studies that applied appropriate diagnostic tools. Many studies included a mixture of patients from different surgical era, with optimal and suboptimal surgical results, such as a residual VSD or important pulmonary stenosis. This hampers interpretation of results and precludes assessment of long-term clinical condition after contemporary repair of TOF with (inevitable) PR, and of factors associated with decline in clinical condition in patients. In patients with TOF, surgically corrected at young age by a transatrial-transpulmonary approach, without residual VSD or important pulmonary stenosis, chapter 2 therefore aimed to:

- assess clinical condition at mid- to long-term follow-up, including assessment of biventricular volumes and function at rest by cardiac MRI
- identify factors associated with RV dilation, RV dysfunction and with decreased exercise tolerance

As with other cardiac disease states the assessment of diastolic function may play a role in (early) detection of ventricular dysfunction.[148,149] Different types of RV diastolic dysfunction have been reported in repaired TOF among which restriction to RV filling.[150,202-205] Reports have been equivocal on how restriction to RV filling affects late functional condition in repaired TOF.[150,203,204] Data on RV filling pattern changes with stress may provide additional information but so far has not been acquired. Therefore, in chapter 3 we aimed to:

- assess RV diastolic function in terms of RV filling pattern, at rest and during pharmacological stress;
- evaluate the effect of restrictive RV physiology, indicated by end-diastolic forward flow in the main pulmonary artery, on clinical condition.

Pulmonary valve replacement currently is the only widely accepted treatment option for PR. Criteria to guide timing of pulmonary valve replacement in TOF are mainly based on progression of RV dilation and presence of symptoms.[23,25,206,207] In heart failure literature it is commonly accepted that a chronic insult to the LV myocardium results in changes of ventricular geometry and structure accompanied by neurohormonal activation [155-157]. This neurohormonal concept has guided recent treatment guidelines for heart

failure.[153,154] Functional decline and especially loss of contractile reserve have also been shown of great prognostic value in LV disease states.[208-212] Surprisingly few data is available on RV remodelling as a result of chronic PR and its relation to neurohormonal activation or ventricular functional reserve. Considering LV heart failure guidelines this information is required. Therefore, in chapter 4 we aimed to:

- assess the level of neurohormonal activity, biventricular contractile reserve and maximal exercise capacity, in relation to the amount of residual PR and biventricular function at rest

Sudden cardiac death is a major cause of late mortality in repaired TOF which often is attributed to ventricular arrhythmia. Risk stratification for sudden cardiac death in corrected TOF successfully focused on indicators of electrical inhomogeneity in the surface ECG to predict ventricular arrhythmia.[50,213,214] Exercise is considered a predisposing factor for ventricular arrhythmia in congenital heart disease and guidelines for exercise restrictions have been published.[215] ECG markers for arrhythmia risk in TOF were all established at rest, while ECG changes with exercise were suggested to be relevant indicators of cardiac disease. In chapter 5 we therefore aimed to:

- assess pro-arrhythmogenic electrocardiographic changes in the surface ECG during maximal physical exercise
- evaluate the relation of electrocardiographic changes during exercise to severity of residual PR, degree of RV dilation and hypertrophy, severity of systolic dysfunction, and maximal exercise capacity

5.2 Study aims in Turner's syndrome

Structural cardiovascular malformations were demonstrated in ½ to ¾ of patients with Turner's syndrome.[6,7,60,73] Up to 50% of these patients show aortic dilation.[6,7,72] Aortic dilation may be complicated by aortic dissection, rupture and death. Risk factors for aortic dilation and dissection include aortic dilation, the bicuspid aortic valve and arterial hypertension, which all are relatively common findings in Turner's syndrome.[8,73,216-218] Pregnancy has been suggested to carry an increased risk for aortic dissection, and an increasing

number of Turner patients is included in oocyte donation fertility programs.[8,67] The so far unknown aetiology behind aortic disease in Turner's syndrome should be unravelled. Abnormalities in aortic wall composition may be behind aortic dilation and dissection, especially with disease in young subjects.[8,217] Phase velocity contrast MRI is an accurate, reproducible, non-invasive tool to determine aortic biophysical wall properties that indirectly reflect aortic wall composition.[92,93] Applying these MRI techniques in chapter 6 we aimed to assess:

- aortic dimensions and distensibility in young adults with Turner's syndrome treated with growth hormone during childhood in comparison to findings in healthy age, gender and body surface area matched controls
- the effect of growth hormone dose on aortic dimensions and distensibility

Supra-physiological dosed growth hormone therapy nowadays is well-established in Turner's syndrome.[26,65] If left untreated the growth hormone excess in acromegaly has been shown to results in dynamic changes of cardiac structure and function, that eventually result in "acromegalic cardiomyopathy" considered to be a heart failure syndrome.[77,81] This knowledge has raised concerns on possible cardiovascular side effects in all diseases that require growth hormone treatment during childhood, including Turner's syndrome. These concerns have been addressed during childhood with active growth hormone treatment and results were reassuring.[70,85-90] However data on cardiovascular status following discontinuation of treatment in Turner's syndrome (and other diseases) are lacking. Midterm after discontinuation of growth hormone treatment, we therefore:

- assessed biventricular size and function in young adults with Turner's syndrome and compared results to findings in healthy age, gender and body surface area matched controls
- evaluated the effect of growth hormone dose on biventricular size and function

5.3 Outline of this thesis:

In the first chapter an overview of literature is given on the topics discussed in this thesis, followed by the main study aims and the outline of this thesis.

Chapters 2 to 5 describe findings from an observational cross-sectional study of a cohort of patients with surgically corrected tetralogy of Fallot. Patients underwent surgical correction between 1980 and 1997 in either the Erasmus MC – Sophia Children's Hospital or the UMC Utrecht – Wilhelmina Children's Hospital. Selection criteria aimed to select patients with optimal post-operative results acquired with currently generally accepted surgical techniques performed at a relative young age.

In chapter 2 the clinical condition of patients with repaired TOF subjected to chronic residual PR was assessed at mid- to long-term follow-up. Tomographic cine MRI was used to quantify the degree of biventricular dilation and systolic dysfunction. Maximal bicycle exercise tests applying breath-by-breath measurement were used to quantify patient's functional capacity. Multiple linear regression analysis was employed on pre-operative, peri-operative and post-operative findings to identify predicators of decline in clinical condition.

In chapters 3 and 4 low dose (7.5 μg/kg/min) dobutamine stress MRI was used to evaluate cardiac response to stress in patients with corrected TOF and chronic residual PR. Chapter 3 describes right ventricular diastolic function by means of RV filling pattern. Phase velocity encoded magnetic resonance imaging was applied to derive combined RV time-volume-change curves that represent the total RV filling information (combined tricuspid and pulmonary valve flow information). From these curves indices of RV filling were obtained. Changes in RV filling pattern between rest and stress were evaluated. Special attention was given to differences between patients with and without end-diastolic forward flow in the main pulmonary artery.

Applying the same tomographic MRI techniques used in chapter 2, chapter 4 quantified the systolic biventricular response to stress. Furthermore plasma levels of neurohormonal markers previously proven to be associated with cardiac function were assessed. As such exercise capacity, cardiac functional stress reserve and level of neurohormonal activation could be related to determinants of clinical condition.

In chapter 5 changes in the surface ECG of Fallot patients are assessed and compared to findings in healthy controls. The changes that occurred with maximal physical exercise were related to determinants of clinical condition.

Chapters 6 and 7 of this thesis describe the findings on functional cardiovascular status from an observational MRI study among a cohort of young adult women with Turner's syndrome. All patients were treated with growth hormone during childhood and were former participants of a Dutch, randomized growth hormone dose response study. Patient data was compared to findings in healthy gender, age and body surface area matched controls.

Chapter 6 focused on aortic distensibility and dimensions in Turner's syndrome and their relation to the received growth hormone dose during childhood. Distensibility is a non-invasive measure of arterial wall stiffness known to be abnormal in patients with connective tissue disease and therefore abnormal aortic wall composition. Aortic dimensions and distensibility were assessed at four predefined levels along the thoracic aorta and the upper part of the abdominal aorta.

Chapter 7 assessed biventricular size and function in patients with Turner's syndrome to evaluate the possible long-term cardiac side-effects of supra-physiologically dosed growth hormone treatment during childhood.

In chapter 8 of this thesis the results from the studies described in chapters 2 to 7 are summarized and future research perspectives are discussed. This is followed by a short summary in Dutch.

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Clinical condition at mid- to long-term follow-up after transatrial-transpulmonary repair of tetralogy of Fallot

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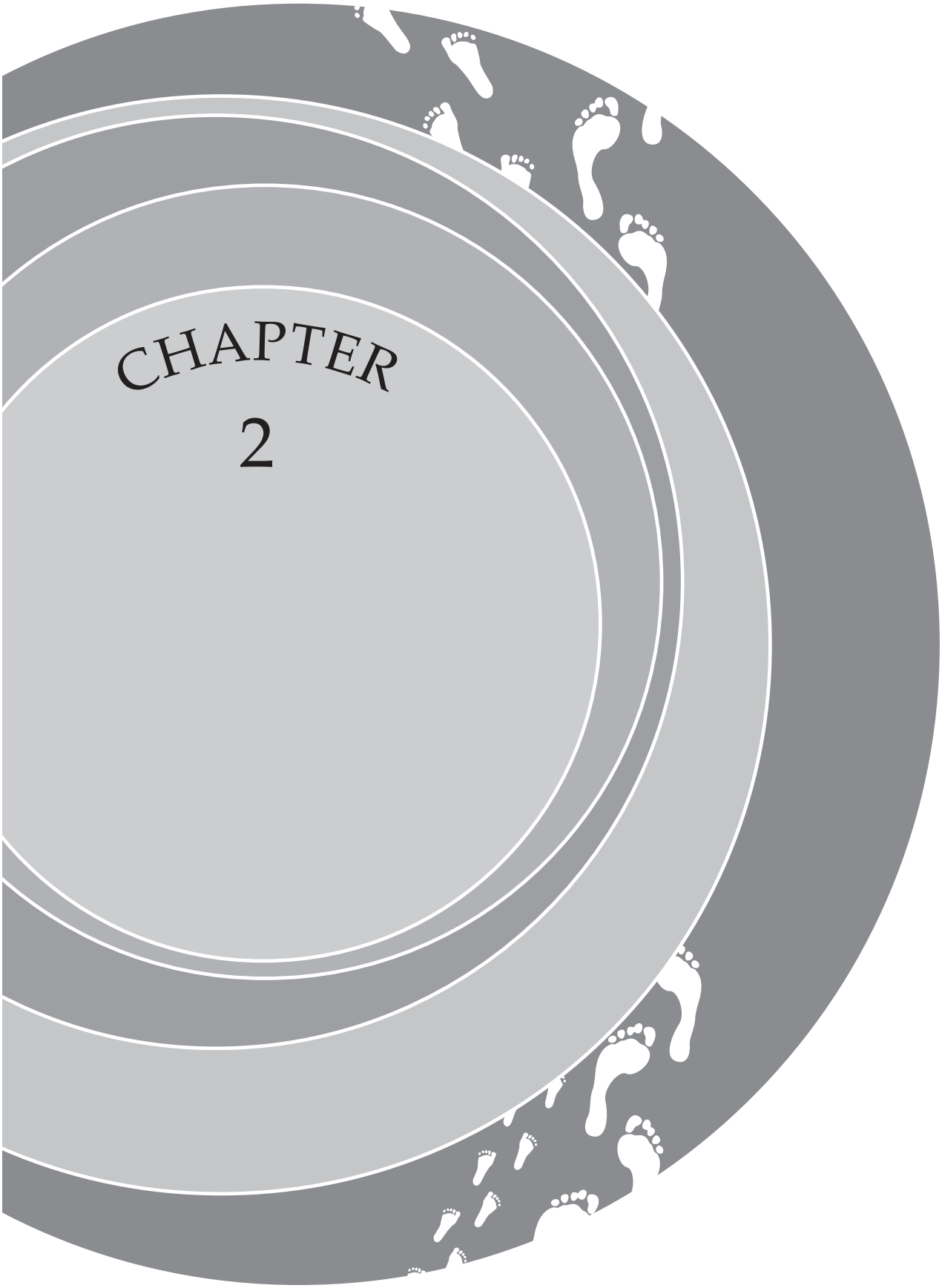
CHAPTER
2

Abstract

Objectives: To assess the clinical condition at mid-to-late follow-up in tetralogy of Fallot corrected by a transatrial-transpulmonary approach at young age, and to identify risk factors associated with RV dilation/dysfunction and with decreased exercise tolerance.
Methods: Fallot patients underwent cardiac MRI, maximal bicycle ergometry, ECG, Holter-monitoring and spirometry. Multivariate linear regression analyses was employed to determine independent predictors for selected clinical parameters.
Results: Fifty-nine patients (mean ± SD age) at repair 0.9 ± 0.5 years, interval since repair 14 ± 5 years) were included. The median pulmonary regurgitant (PR) fraction was 32% (0 − 57%). Compared to published data on healthy controls, Fallot patients had significantly larger RVEDV and RVESV, smaller RVEF, and smaller LVEF. $VO2_{max}$ was 97 ± 17 % and workload $_{max}$ 89 ± 13 % of predicted. Median QRS-duration was 110 ms (82 − 161 ms). No important ventricular arrhythmias were found. Compared to patients without a transannular patch, patients with a patch had more PR, a larger RV, worse RVEF and LVEF but comparable exercise capacity.

Multivariate regression analysis identified the following independent determinants for larger RV-volumes: longer interval since repair, longer QRS-duration, higher PR-percentage. For smaller RVEF: abnormal RVOT wall motion, longer interval since repair, longer QRS-duration. For smaller $VO2_{max}$: smaller RVEF and longer QRS-duration.
Conclusions: At mid- to-late follow-up clinical condition in tetralogy of Fallot corrected according to contemporary surgical approaches appears well preserved. However, even these patients show RV dilation and dysfunction associated with impaired functional capacity. Abnormalities relate to RVOT motion abnormalities, longer interval since repair, longer QRS-duration and more severe PR.

Introduction

Over the last decades peri-operative mortality of correction for tetralogy of Fallot (TOF) decreased for all ages, including infants.[1,2] Repair at a young age shortens the period the patient is subjected to systemic hypoxemia and to right ventricular (RV) pressure overload. These considerations have lead to a trend of primary correction performed at young age, aimed at optimal relief of RV outflow obstruction and closure of the VSD.[1,2] In addition, the concept of transatrial-transpulmonary repair for TOF gained popularity.[3] This concept aims at reducing the side effects associated with a ventriculotomy, such as RV myocardial and coronary artery damage. Outcome of TOF repair has extensively been described. Pulmonary regurgitation (PR) is a crucial factor in long-term outcome.[4] There is a lack of studies reporting on long-term follow-up, acquired with appropriate tools, in TOF patients repaired according to recent surgical strategies. Furthermore, most studies have included a mixture of patients with optimal and suboptimal surgical results, such as residual VSD or important pulmonary stenosis. This precludes assessment of optimal long-term effects of repair of TOF, and of factors associated with decline in clinical state after optimal repair, that is, clinical condition in patients with (inevitable) PR, but without additional problems. Therefore, the present study aimed 1) to assess clinical condition at mid- to long-term follow-up, including assessment of biventricular volumes and function by cardiac magnetic resonance imaging (CMR), 2) to identify factors associated with RV dilation, RV dysfunction and with decreased exercise tolerance, in TOF patients, operated at young age by the transatrial-transpulmonary approach and without residual VSD or important pulmonary stenosis.

Patients and Methods

A cross-sectional study of patients after surgical repair of TOF was performed. The local medical ethics committee approved our study protocol. Informed consent was obtained from patients or parents if patients were not of the legal age to provide consent. Patients were included for data collection between September 2002 and November 2004. The following inclusion criteria were used: 1) complete repair of tetralogy of Fallot without associated cardiac lesions,

including double outlet right ventricle (except patent ductus arteriosus), 2) age at repair ≤ 2 years, 3) transatrial-transpulmonary approach to repair, 4) duration of follow-up since repair ≥ 5 years. Patients with one or more of the following criteria were excluded: residual VSD, residual pulmonary stenosis (echo Doppler mean gradient > 30 mm Hg), repair with a homograft, mental retardation, known extracardiac pathology. Criteria were reviewed using patient's medical records. Pre-operative hemodynamic data was obtained from diagnostic heart catheterization reports.

Magnetic resonance imaging protocol

A 1.5 Tesla Signa CVi scanner was used with software releases V8 and V9.1 (General Electric, Milwaukee, USA). A cine volumetric data-set was acquired in short axis direction using a 2D fast imaging employing steady-state acquisition sequence (SSFP). Imaging parameters were: flip angle = 45°, TE set at min full, TR= 3.4 – 3.6 ms, 8 − 9 mm slice thickness, 0 − 1 mm inter-slice gap, 12 views/segment, readout bandwidth = 111Khz, a square FOV (30 − 34 cm), and a scanning matrix of 160 * 128. Twenty-four phases per cardiac cycle were reconstructed retrospectively.

Pulmonary valve flow measurements were performed perpendicular to flow using a standard 2D retrospectively gated flow-sensitised sequence. Thirty cardiac phases were reconstructed retrospectively. Imaging parameters were: 2D FSPGR, TR = 6 − 7 ms, TE = 3 ms, flip angle = 20^{o}, readout bandwidth = 90 Khz, 6 mm slice thickness, 6 views/segment, a rectangular FOV (75% in phase encoding direction) and a scanning matrix of 256 *128.

Magnetic resonance image analysis

CMR studies were analysed on an Advanced Windows workstation (General Electric, Milwaukee, USA). Flow images were quantitatively analysed using the Flow analysis software package V2.0 (Medis Medical Imaging Systems, Leiden, The Netherlands). Residual pulmonary stenosis was calculated using the simplified Bernoulli equation ($\Delta P = 4*Vmax^2$). Volumetric data was quantitatively analysed using the Mass analysis software package V3.1 (Medis Medical Imaging Systems, Leiden, The Netherlands), with parameters assessed according to analysis techniques widely reported in literature.[5] Volumetric CMR

parameters were indexed for BSA unless specified otherwise. Values outside the mean ± 2SD range in healthy controls were defined to be abnormal. On the cines an experienced observer assessed wall motion in the RVOT. Abnormal wall motion was defined as absent or outward movement of part of the RVOT wall during systole. To calculate the pulmonary regurgitant fraction, amount of PR was normalised for the systolic stroke volume across the pulmonary valve (PR-percentage = Backward flow/Systolic forward flow *100%). Critical upper limits for RV end-diastolic volume, 200 ml/m² in children and 170 ml/m² in adults, associated with absent return of RV-volume to normal size following pulmonary valve replacement have been reported and were applied on our population.[6,7]

Bicycle ergometry

Patients performed a symptom limited bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany), allowing breath-by-breath-ergometry. Workload was increased with 10 − 20 Watts per minute. Patients were encouraged to perform to exhaustion. Tests were regarded maximal with a respiratory quotient (RQ) ≥ 1.05 in children and ≥ 1.10 in adults at peak exercise. Exercise capacity was compared to that of normal individuals, corrected for age, sex, and weight.[8] Values > 85% of predicted were considered normal.

Spirometry

Preceding the exercise test patients performed a standard maximal forced vital capacity manoeuvre using a dry rolling seal spirometer (Jaëger, Würzburg, Germany). From the obtained loops the following parameters were derived: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), ratio FEV1/FVC, and maximum expiratory flow at 25% of FVC (MEF25). Results were compared to those from normal individuals corrected for age, gender and body composition and expressed as percentages of predicted values.

ECG

A standardised 12-lead ECG was obtained to assess QRS (ms), QTc (ms), and JTc (ms) duration. A 24-hours Holter monitoring was performed on a day with usual activities.

Statistical analysis

CMR results of patients were compared to a reference population from literature using the two-sample t-test.[9] Data were $\log_{10}$-transformed when appropriate to obtain approximately normal distribution. Results are expressed as mean ± SD for normally distributed data, otherwise as the median and range. Bivariate correlation coefficients were calculated using Spearman's method. Multivariate linear regression analyses (backward stepwise regression method) was employed to determine major independent predictors for outcome variables. Only variables significant in univariate analysis were included in these multivariate analyses. Percentages were compared using the χ^2-test. Analysis was performed using the SPSS-PC statistical software package version 11.5 (SPSS, Chicago, Il, USA). A p-value ≤ 0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Records of 169 eligible patients alive in 2002 and operated between 1980 to 1997 before the age of 2 years by a transatrial-transpulmonary approach at the Erasmus MC Rotterdam or the University MC Utrecht were checked. Reasons for exclusion were; residual VSD (n = 3), residual RVOT stenosis (> 30 mm Hg) (n = 11), repair with a homograft (n = 15), mental retardation (n = 16), extracardiac pathology (n = 7), lost to follow-up (n = 32). Eighty-five patients fulfilled all inclusion criteria and received an invitation for this study. Sixty-three (74%) patients agreed to participate. Four of our youngest participants (aged 5.9 – 6.5 years) did not complete the entire protocol and were excluded from all results. The characteristics of the remaining 59 patient are shown in Table 1.

Patients that refused to participate, and those lost to follow-up, did not differ from participants in mean age at repair, interval since repair, incidence of staged repairs or gender distribution. Patients did not use cardiac medication, 51(86%) were in NYHA class I (86%) and 8(14%) in class II.

In 42 (71%) patients a transannular patch (TAP) repair was performed. In the remaining 17 (29%) patients desobstruction of the RVOT was achieved using a combination of the following techniques: infundibulectomy, valvulotomy, commissurotomy or partial valvectomy. Pre-repair, patients with a TAP had a lower arterial oxygen saturation (86 ± 9 versus 92 ± 9 %, $p < 0.05$) and a higher RV/aortic peak pressure ratio (1.0 ± 0.1 versus 0.9 ± 0.1, $p < 0.05$) compared to patients without a TAP. TAP repairs were performed at younger age (median age at repair 0.6 (0.2 − 2.0) years versus 1.1 (range 0.3 − 2.0), $p < 0.05$). Interval since repair was comparable between patients with a TAP and those without (15 ± 5 years versus 13 ± 4 years, $p = 0.14$).

Table 1. Patient characteristics

	Patient Total n = 59 (100%)
Gender (M/F)	41/18
Age at repair (years)	0.8 (0.2 − 2.0)
Age at study (years)	15 (6 − 23)
Interval since repair (years)	14 (6 − 23)
BSA (m^2)	1.5 ± 0.4
Previous Blalock-Taussing shunt	3 (5%)
Preoperative measures RV/Aorta peak pressure ratio	1.0 ± 0.1
RV peak pressure (mmHg)	88 ± 9
Oxygen saturation (%)	87 (62 − 100)
Residual pulmonary stenosis (mmHg)	9 (3 − 29)

Data given are mean ± SD and median (range)

Cardiac magnetic resonance imaging

The median value for PR-percentage was 35% (range 0 − 57%). Patient CMR data was compared to data from literature assessed in healthy controls (Table 2).[9] Differences in CMR findings between patients with and without a TAP are shown in Table 3. Abnormal wall motion in the RVOT region was diagnosed

in 41(69%) patients. Cumulative incidence of abnormal wall motion was larger in patient with a TAP compared to those without (37 out of 42 patients versus 4 out of 17, $\chi^2 < 0.001$). Similar differences as for patient with or without a TAP were found with regard to PR, biventricular size and EF when comparisons were made for patients with abnormal RVOT wall-motion versus those with normal wall-motion (data not shown).

Table 2. Biventricular CMR results in patients and controls.

	TOF patients		Controls		Abnormal‡
Number patients	59		16		
Age (years)	15 ± 5		18 ± 2		
	Mean ± SD	Range	Mean ± SD	Limit#	Number (%)
RVEDV (ml/m²)	139 ± 37*	85 – 237	79 ± 9	97 (UL)	50 (85%)
RVESV (ml/m²)	72 ± 26*	35 – 145	32 ± 7	56 (UL)	50 (85%)
RVSV (ml/m²)	66 ± 14*	36 – 100	49 ± 6	61 (UL)	38 (64%)
RVEF (%)	49 ± 6*	32 – 60	61 ± 6	49 (LL)	29 (49%)
LVEDV (ml/m²)	81 ± 12	61 – 109	79 ± 9	97 (UL)	7 (12%)
LVESV (ml/m²)	36 ± 8*	16 – 53	29 ± 7	43 (UL)	10 (17%)
LVSV (ml/m²)	46 ± 7	31 – 67	49 ± 6	37 (LL)	4 (7%)
LVEF (%)	56 ± 6*	42 – 74	63 ± 6	51 (LL)	7 (12%)

* Significant difference ($p < 0.05$) compared to controls, # Limit of normal, UL (upper limit) = mean+2SD, LL (lower limit) = mean-2SD, ‡ Number of patients with abnormal CMR results (above UL or below LL of relevance), EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, SV = stroke volume

The RVEDV was > 170 ml/m² in 14(24%) patients and > 200 in 4(7%). Compared to patients with a RVEDV ≤ 170 ml/m², patients with a RVEDV > 170 had: smaller RVEF (50 ± 6 versus 44 ± 5 %, $p < 0.05$), comparable LVEF (57 ± 6 versus 55 ± 6 %, n.s.), and worse exercise capacity (percentage of predicted $VO2_{max}$ 99 ± 18 versus 90 ± 11 %, $p < 0.05$). All patients with RVEDV > 170 ml/m² had ≥ 12 years of follow-up (median 18 years, range 12 − 23) and a PR-percentage > 30% (median 46%, range 31 − 54%).

Table 3. Comparison of patients according to presence of a TAP in the RVOT[#]

	No patch n = 17 (29%)	**TAP repair n = 42 (71%)**
PR-percentage	14 ± 12	40 ± 11*
Residual pulmonary stenosis	13 ± 7	9 ± 6*
RV EDV (ml/m²)	106 ± 19	152 ± 35*
ESV (ml/m²)	51 ± 12	81 ± 25*
SV (ml/m²)	55 ± 10	71 ± 13*
EF (%)	52 ± 6	47 ± 6*
RVFWM (g/m²)	20 ± 4	26 ± 6*
LV EDV (ml/m²)	82 ± 12	81 ± 12
ESV (ml/m²)	34 ± 8	37 ± 8
SV (ml/m²)	48 ± 8	45 ± 7
EF (%)	59 ± 6	55 ± 5*
LVM (g/m²)	52 ± 9	53 ± 10

Data given are mean ± SD, * Significant difference compared to patients without a patch in the RVOT (T-test, $p < 0.05$), [#] Similar differences with regard to PR, biventricular size, wall mass and EF were found when comparisons were made for patients with normal and abnormal RVOT wall-motion (data not shown). EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, LVM = LV mass, RVFWM = RV free-wall mass, SV = stroke volume (All CMR parameters were indexed for BSA)

ECG and Holter monitoring

All patients were in sinus rhythm. Right bundle branch block was diagnosed in 80% of patients. Median QRS-duration was 110 ms (range 82–161 ms), mean QTc-duration was 408 ± 32 ms, and mean JTc-duration was 270 ± 23 ms. No differences were found for QRS-duration ($p = 0.47$), QTc-duration ($p = 0.39$) and JTc-duration ($p = 0.26$) between patient with or without a TAP.

During 24-hours Holter monitoring 5 patients showed ≥ 1 cardiac pauses > 1.9 sec. The longest observed pause lasted 2.3 sec. Two patients, both with a TAP, showed a non-sustained VT run of respectively 3 and 4 complexes at heart rates of 174 and 108 beats/min with a QRS duration in sinus rhythm of 105 and 130 ms respectively.

Spirometry

Mean FEV1 was 99 ± 12 % of predicted. Mean FVC was 94 ± 12 % of predicted. The median FEV1/FVC ratio was 89% (range 75 − 100%). Mean MEF25 was 89 ± 31 % of predicted. Mean FVC of predicted tended to be higher in patients without a TAP (97 ± 14 % versus 90 ± 12 %, p = 0.05). The other parameters were not different between patients with and without a TAP.

One patient showed severe obstructive abnormalities and exercise results of this patient were excluded from analysis. The parameters derived from the maximal flow-volume loops showed no significant correlations with percentage of predicted VO2max.

Bicycle ergometry

The patient with obstructive airway disease was excluded, 1 patient declined the test and 1 patient could not complete the test due to technical problems. Exercise data reflect results of the remaining 56 patients. Mean RQ at peak exercise was 1.2 ± 0.1. All patients reached our RQ criteria at peak exercise. Age at study correlated positively with RQ at peak exercise ($r = 0.44$, $p < 0.001$) and RQ during initial recovery ($r = 0.69$, $p < 0.001$). Peak oxygen consumption ($VO2_{max}$) was 40 ± 8 ml/kg/min, or 97 ± 17 % of predicted $VO2_{max}$ ($p = 0.20$), with a value < 85% found in 14(25%) patients. Mean peak workload was 149 ± 62 Watts, or 89 ± 13 % of predicted ($p < 0.05$), with value < 85% found in 18(32%) patients.

Percentage of predicted workload and percentage of predicted $VO2_{max}$ were not different between patients with a TAP and those without a TAP (respectively 88 ± 11 % versus 92 ± 17, p = 0.37) and 96 ± 15 % versus 99 ± 22, p = 0.59). Percentage of predicted workload and percentage of predicted $VO2_{max}$ were smaller in patients with abnormal RVOT wall-motion compared to patients with normal motion (respectively 86 ± 12 % versus 95 ± 13, $p < 0.05$) and 94 ± 16 % versus 103 ± 19, p = 0.07).

Determinants of exercise capacity

Factors significantly related to VO2max and percentage of predicted VO2max by univariate analysis were determined. Predictor variables originated from

the following 3 sets of parameters: A) Parameters determined at pre-repair diagnostic heart catheterization (RV peak pressure, arterial oxygen saturation, RV/Aorta – pressure ratio), B) Peri-operative parameters (age at repair, TAP (1 = present, 0 = absent)), C) Post-operative parameters (PR-percentage, interval since repair, RVOT wall-motion (1 = abnormal, 0 = normal), QRS-duration, QTc, JTc and all biventricular CMR determined measures).

Table 4. Predictors of peak oxygen consumption

	Univariate Analysis		Multivariate Analysis	
Predictor	**Regression Coefficient ± SE**	**P-value**	**Regression Coefficient ± SE**	**P-value**
Dependent: VO2 ml/kg/min				
LVSV (ml/m²)	0.5 ± 0.2	0.002	0.4 ± 0.1	0.001
Gender (male/female)	− 7.0 ± 2.2	0.002	5.9 ± 1.8	0.002
Interval since repair (years)	− 0.6 ± 0.2	0.004	− 0.5 ± 0.2	0.004
QRS duration (ms)	− 0.15 ± 0.06	0.008	− 0.10 ± 0.05	0.04
Constant			34.9 ± 7.5	––––––
RVEF (%)	0.53 ± 0.16	0.002		n.s.
PR−percentage	− 0.17 ± 0.06	0.009		n.s.
TAP (yes/no)	− 4.8 ± 2.2	0.04		n.s
RVOT motion (abnormal/normal)	− 5.3 ± 2.2	0.02		n.s.
RV peak pressure (mmHg)	− 0.18 ± 0.08	0.03		n.s.
Dependent: VO2 percentage of predicted				
RVEF (%)	1.6 ± 0.3	< 0.001	1.3 ± 0.3	< 0.001
QRS duration (ms)	− 0.4 ± 0.1	0.001	− 0.2 ± 0.1	0.05
Constant			59.4 ± 24.1	––––––––
RVESV (ml/m²)	− 0.23 ± 0.09	0.009		n.s.
LVSV (ml/m²)	0.8 ± 0.3	0.02		n.s.
LVEF (%)	1.2 ± 0.4	0.002		n.s.
Interval since repair (years)	− 1.5 ± 0.4	0.001		n.s.
RV peak pressure (mmHg)	− 0.39 ± 0.16	0.02		n.s.

Data given are regression coefficients ± standard errors, R^2 for the multiple regression model of VO_2 (ml/kg/min) and VO_2 (percentage of predicted) were respectively 0.49 and 0.36, EF = ejection fraction, ESV = end-systolic volume, LV = left ventricle, PR = pulmonary regurgitation, RV = right ventricle, RVOT = RV outflow tract, SV = stroke volume, TAP = transannular patch

Variables with significant relations (at the 0.05 level) identified by univariate analysis were used in multiple regression analysis to identify independent determinants. Results for both the univariate and multivariate linear regression analyses are shown in Table 4.

Determinants of RV CMR measures and PR-percentage

RV CMR parameters and PR-percentage were analysed using the same procedures described in the previous paragraph. During analyses on RVEDV, RVESV and RVEF the corresponding LV parameter was introduced in the model. Mathematically related RV CMR measures were not used in one model. Results for both the univariate and multivariate linear regression analyses are shown in Table 5.

Table 5. Predictors of RV CMR measures.

	Univariate Analysis		Multivariate Analysis	
Predictor	**Regression coefficient ± SE**	**P-value**	**Regression Coefficient ± SE**	**P-value**
Dependent: RVEDV (ml/m²)				
Interval since repair (years)	3.7 ± 0.9	< 0.001	1.4 ± 0.6	< 0.05
PR-percentage (%)	1.5 ± 0.2	< 0.001	1.3 ± 0.2	< 0.001
LVEDV (ml/m²)	1.3 ± 0.4	0.001	1.5 ± 0.2	< 0.001
Constant			− 54.8 ± 18.4	-----
TAP (yes/no)	42 ± 9	< 0.001		n.s.
RVOT-motion (abnormal/normal)	7 ± 9	< 0.001		n.s.
RV peak pressure (mmHg)	1.0 ± 0.3	0.005		n.s.
Dependent: Log_{10} RVESV (ml/m²)				
Interval (years)	0.016 ± 0.003	< 0.001	0.007 ± 0.003	< 0.01
PR-percentage	0.006 ± 0.001	< 0.001	0.005 ± 0.001	< 0.001
LVESV (ml/m²)	0.009 ± 0.002	< 0.001	0.007 ± 0.002	< 0.001
QRS-duration (ms)	0.003 ± 0.001	0.02	0.001 ± 0.001	< 0.05
Constant			1.15 ± 0.09	-----
RV peak pressure (mmHg)	0.004 ± 0.001	0.003		n.s.
TAP (yes/no)	0.17 ± 0.04	< 0.001		n.s.

(Continued)	Univariate Analysis		Multivariate Analysis	
Predictor	**Regression coefficient ± SE**	**P-value**	**Regression Coefficient ± SE**	**P-value**
Dependent: RVEF (%)				
Interval (years)	− 0.59 ± 0.14	< 0.001	− 0.3 ± 0.1	< 0.05
QRS-duration (ms)	− 0.12 ± 0.04	0.007	− 0.07 ± 0.03	< 0.05
LVEF (%)	0.49 ± 0.13	0.03	0.5 ± 0.1	< 0.001
RVOT-motion (abnormal/normal)	− 5.9 ± 1.6	< 0.001	− 3.1 ± 1.4	< 0.05
Constant			39.1 ± 7.0	-----
RV peak pressure (mmHg)	− 0.13 ± 0.06	0.03		n.s.
PR-percentage	− 0.12 ± 0.05	0.03		n.s.
TAP (yes/no)	-4.7 ± 1.7	0.007		n.s.
Dependent: PR-percentage				
TAP (yes/no)	22.5 ± 3.4	< 0.001	22.2 ± 3.3	< 0.001
RV peak press (mmHg)	0.39 ± 0.14	0.008	0.3 ± 0.1	0.02
Constant			− 5.7 ± 9.0	-----
RVOT-motion (abnormal/normal)	17.9 ± 4.0	< 0.001		n.s.
Arterial oxygen saturation	− 0.57 ± 0.21	0.01		n.s.
Interval since repair (years)	0.83 ± 0.41	0.05		n.s
RV free wall mass (g/m²)	1.1 ± 0.3	0.001		n.s

Data given are regression coefficients ± standard errors, R^2 for the multiple regression models of RVEDV, RVESV, RVEF and PR-percentage were respectively 0.76, 0.72, 0.53 and 0.53, EF = ejection fraction, ESV = end-systolic volume, LV = left ventricle, PR = pulmonary regurgitation, RV = right ventricle, RVOT = RV outflow tract, TAP = transannular patch

Discussion

This study provides quantitative data on clinical status at mid-to-late follow-up in TOF patients, corrected at a relatively young age by a transatrial-transpulmonary approach, and without other residual lesions but PR. TOF repair almost inevitably results in some degree of PR. Here the median PR-percentage was 35% (range 0 − 57). As expected with considerable volume overload, RV volumes were markedly elevated in our patients, with mean

values being approximately twice that in controls, and values above the upper limit of normal found in 85% of our patients (Table 2). Furthermore, RVEF and LVEF were decreased compared to controls, in respectively 49% and 12% of our patients. Despite these striking abnormalities, chronic RV volume overload seems to be well tolerated by these patients. All were in NYHA class I (86%) or II (14%), all were in sinus rhythm and none used cardiac medication. Mean percentage of predicted $VO2_{max}$ was not different from controls. Patients had normal lung function and no important ventricular arrhythmias were encountered.

This study identified independent predictors of several undesirable, but common problems during the follow-up of TOF. The most important predictor of poorer exercise capacity was a lower RVEF, which in turn was best predicted by abnormal RVOT wall motion. Larger RV dilation and poorer RVEF were associated with a longer interval since repair. This suggests that, even in Fallot patients corrected according to current surgical strategies and with optimal surgical result, gradual but slow deterioration of RV function with volume overload seems inevitable. Patients with already marked RV dilation subjected to chronic PR may develop symptoms over time, which stresses the need for serial follow-up.

RVOT function in repaired TOF

Previous studies have demonstrated the negative impact of TAP repair on PR and RV size.[10] In our study multivariate regression analysis showed that TAP repair was the most important independent predictor of PR-percentage, with a 22 ± 3 % point higher PR-percentage in patients with a TAP compared to those without a TAP (Table 5). A higher PR-percentage independently predicted larger RV-volumes, but not poorer RVEF. Poorer RVEF was independently predicted by abnormal RVOT wall motion. A previous study among adult Fallot patients, operated at older age than our patients, also found abnormal motion in the RVOT region to predispose for RV dysfunction.[10] Both that study and ours showed that abnormal wall motion is not restricted to patients with a TAP. This suggests wall motion abnormalities can be induced by other factors. Remarkably, Davlouros *et al*. found no difference in incidence of wall motion abnormalities between patients with and without TAP, while this difference was clearly present in our patients.[10] This may be explained by the different

primary surgical approach used, with a primary ventriculotomy used in most patients reported by Davlouros et al. However, other factors such as prolonged hypoxemia, present in the patients reported by Davlouros *et al.*, cannot be ruled out to play a role in RV wall motion abnormalities. The influence of surgery in the RVOT region on long-term outcome has also been studied by comparing transventricularly repaired TOF patients to patients with isolated pulmonary valve stenosis treated by pulmonary commissurotomy.[11] Freedom of adverse events related to RV dilation (defined as cardiac death, reoperation and NYHA class ≥ II) was better in patients after isolated commissurotomy despite similar degrees of moderate and severe PR found in both patient groups. These findings suggest that limited RVOT surgery contributes to better long-term outcome, which is supported by our study. Whether or not the recently described reconstructive technique of the pulmonary valve by Sung *et al.* further contributes to improved outcome remains a matter of ongoing observation.[12]

QRS-duration

In TOF a QRS-duration > 180 ms in adults and > 170 ms in children is known to predispose to malignant ventricular arrhythmia and sudden death.[13,14] QRS-duration did not exceed 170 ms in our patients. Residual PR and subsequent RV dilation have been associated with QRS prolongation.[14-16] Pulmonary valve replacement has been shown to reduce QRS-duration proportionally to the degree of RV volume reduction.[17,18] In our population QRS-duration was an independent predictor of RV-volume, but also of RVEF and exercise tolerance (Table 5). These predictive effects were present in the range below the reported critical values that predispose for arrhythmia and sudden death.

Prolongation of QRS duration has been related to electrical inhomogeneity.[19] In this regard ventricular dyssynchrony has been observed in TOF. Cardiac resynchronisation therapy in heart failure with prolonged QRS-duration has been proven beneficial for ventricular contractile function, symptomatic status, and mortality.[20,21] Thus far, results in congenital heart disease including TOF have been promising.[19] The relations found for QRS-duration with RVEF and exercise capacity in the present study suggest that functional gain may be achieved by cardiac resynchronisation therapy in selected TOF patients.

Long-term outcome of TOF

Pulmonary valve replacement currently is the only widely accepted treatment for residual PR in TOF. Optimal timing of this procedure seems crucial, but criteria so far have not been established.[4] Newer imaging techniques, such as CMR, are expected to supply the data required to design such criteria. Several groups studied outcome of pulmonary valve replacement using serial CMR data.[6,7,22] A RVEDV ≤ 170 ml/m² in adults and ≤ 200 ml/m² in children was found to relate to adequate recovery of RV volume.[6,7] Our patients with an RVEDV > 170 ml/m² had worse exercise capacity. Remarkably, all these patients had an interval since repair ≥ 12 years and a PR-percentage > 30%. Patients with a PR-percentage ≤ 30% PR did not demonstrate an RVEDV > 170 ml/m², irrespective of follow-up duration. Most large CMR based studies report on Fallot patients operated according to different surgical strategies than our patients (older age at repair, staged repairs, primary RV ventriculotomy, repair with RV to pulmonary artery conduits).[10,23] We demonstrate that previously obtained CMR criteria also identify worse clinical status in patients operated according to a currently widely accepted surgical approach. However, the long-term prognostic value of these criteria regarding mortality and morbidity still has to be determined in patients from any surgical era.[7]

Study limitations

Because of the potential negative effect of a ventriculotomy on long-term clinical state a transatrial-transpulmonary approach was chosen in all patients. The frequent use of a TAP illustrates total avoidance of a ventriculotomy in TOF is not feasible in clinical practice. Furthermore it created the opportunity to evaluate the effect of a TAP on clinical condition. Inclusion criteria limit this study to patients with "isolated" PR. As such our patients represent that part of daily clinical practice with optimally repaired initial pathology (VSD and RVOT obstruction). Because of the design difficulties in data interpretation introduced with various forms of ventricular overload are avoided.

We used CMR reference values from healthy controls of the same age range, obtained and analysed in similar ways as in the current study.[9] During the assessment of functional capacity we did not account for level of physical training. The RQ at peak exercise indicates all patients performed maximally.

As expected results show higher RQ values in older patients. Therefore peak results may better reflect maximal exercise capacity in older patients. This may have resulted in a slight underestimation of the magnitude of regression in exercise capacity over time.

The debate on optimal age at repair is still ongoing. As all our patients were corrected after the age of 2 months we can only speculate on further improvement of clinical state if patients were to be corrected in the neonatal period. We did not find important effects of age at repair on the outcome measures shown in Tables 4 and 5.

Clinical implications

The current study demonstrates that at mid-to-late follow-up symptomatic status, exercise performance and rhythm status remain relatively normal in Fallot patients after repair according to a transatrial transpulmonary approach. Deterioration of RV function and exercise capacity correlate with a longer interval since repair, but these moderate associations cannot be used to predict the pace of decline in the individual patient. Our results suggest that further improvement of clinical condition may be obtained by improving preservation of RVOT function and by reducing the effect of electrical inhomogeneity**.** The evolution of CMR, ECG and exercise data in this series as well as the need for, and effects of interventions should be re-evaluated in future studies.

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Diastolic function assessed with magnetic resonance imaging in repaired tetralogy of Fallot at rest and during stress: restrictive RV physiology is associated with worse clinical state at mid to long-term follow-up

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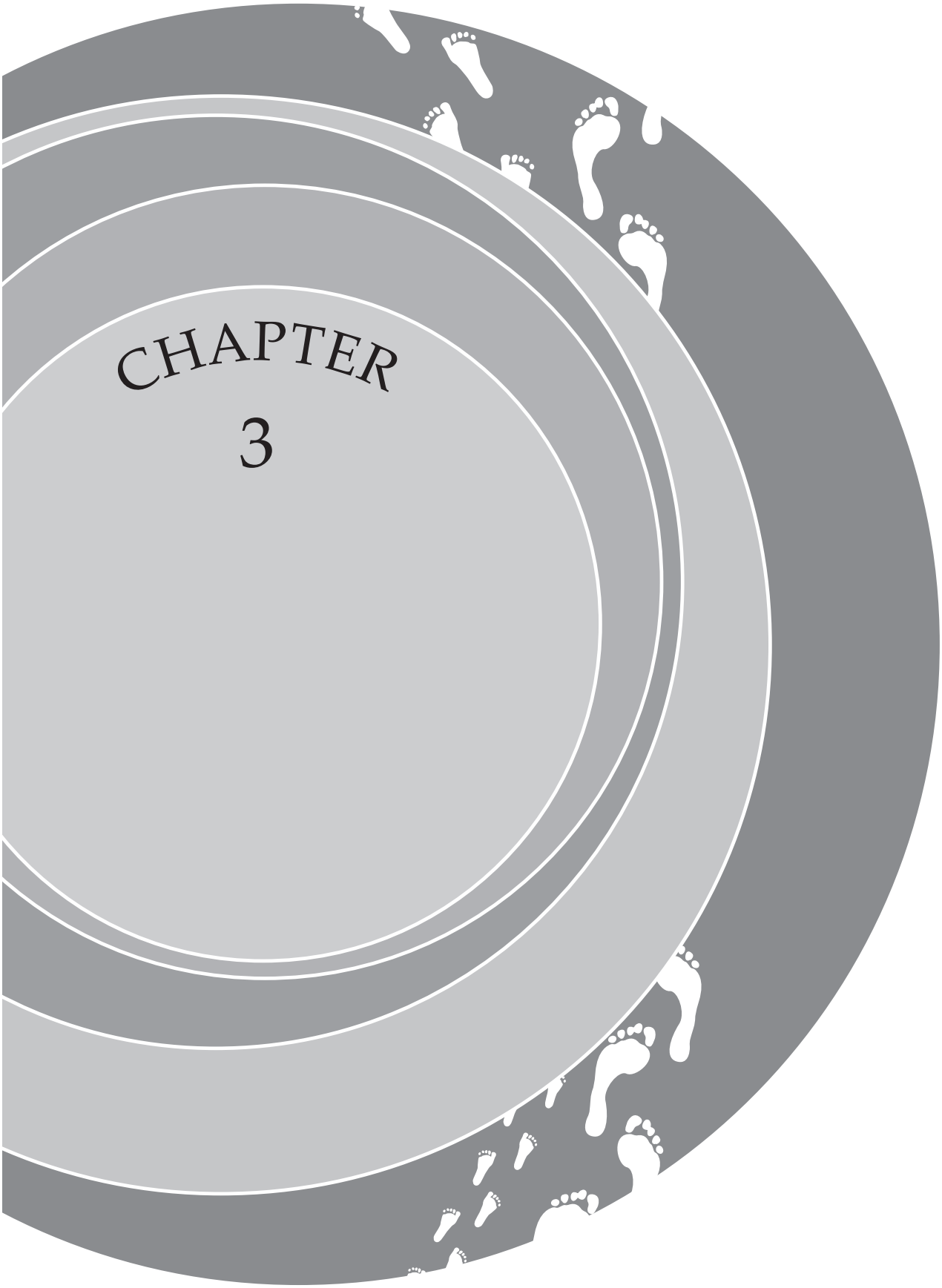
CHAPTER
3

Abstract

Purpose: To prospectively assess right ventricular (RV) diastolic function after repair of tetralogy of Fallot (TOF) at rest and during pharmacological stress and to study the relationship between end-diastolic forward flow in the main pulmonary artery (EDFF, indicative of restrictive RV physiology) and clinical state.

Materials and Methods: Approval of our institutional medical ethics committee was obtained. Informed consent was obtained from patients or parents. Patients with corrected TOF through the transatrial-transpulmonary approach underwent rest and stress (dobutamine 7.5 μg/kg/min) MRI, and maximal exercise testing. A 2D cine volumetric data set was acquired. Flow measurements were performed using a standard 2D flow-sensitized sequence. MRI flow curves of the tricuspid and pulmonary valve were combined into RV time-volume change curves, from which indices of RV filling were derived. Patients were compared with published control data. Student T-tests, Mann-Whitney U tests and ANCOVA were used for group comparisons. Paired T-tests were used to analyze paired data. One sample T-tests were used to compare patients to a reference population. P-value < 0.05 indicates significance.

Results: Thirty-six patients (mean (± SD) age at repair 0.9 ± 0.5 years, median age at inclusion 17 (range 7 − 23) years, 26 males and 10 females) were included. Abnormalities in RV filling included impaired relaxation (prolonged deceleration time, $p = 0.002$; smaller early filling fraction, $p = 0.02$) for the entire group compared to published data on healthy controls, and signs of restriction to RV filling (smaller atrial filling fraction, $p = 0.002$; higher E/A-ratio, $p < 0.001$) in patients with EDFF (n = 24) compared to those without EDFF (n = 12). Stress response was abnormal in patients with EDFF, who developed impaired RV relaxation, not appreciated at rest. Patients with EDFF had more severe pulmonary regurgitation ($p = 0.03$) and poorer exercise performance ($p < 0.001$).

Conclusion: In Fallot patients corrected according to currently widely accepted surgical strategies, EDFF in the pulmonary artery relates to worse clinical state at mid to long-term follow-up, as indicted by worse exercise capacity and more severe PR. Dobutamine stress imaging may "unmask" abnormalities in RV diastolic filling not appreciated by rest imaging alone.

Introduction

Outcome after surgical correction of tetralogy of Fallot (TOF) is good, despite the presence of pulmonary regurgitation (PR) in the majority of patients.[1,2] PR initially is well tolerated, but long-term negative effects of PR on RV dimensions, RV systolic function and exercise performance have been well documented.[3,4] Diastolic dysfunction may precede systolic dysfunction and therefore may play a role in early detection of ventricular dysfunction. Different types of RV diastolic dysfunction have been reported in repaired TOF.[5-8] Restriction to diastolic RV filling, indicated by end-diastolic forward flow (EDFF) in the main pulmonary artery, has been documented throughout follow-up.[5-8] Reports have been equivocal on how restriction to RV filling affects functional outcome in TOF.[5-8]

In most patients RV diastolic filling can be studied using the Doppler echocardiographic flow-pattern across the tricuspid valve. However, in patients with PR, RV filling occurs through both the tricuspid and pulmonary valve. In this setting Doppler echocardiography cannot adequately quantify total RV diastolic filling. Magnetic resonance flow-sensitive imaging techniques have successfully been validated at rest for the assessment of RV diastolic function in patients with PR.[6] Stress imaging may provide additional information, but to our knowledge has not been used to assess RV diastolic function in corrected TOF. Thus, the purpose of our study was to prospectively assess right ventricular (RV) diastolic function after repair of tetralogy of Fallot (TOF) at rest and during pharmacological stress and to study the relationship between EDFF in the main pulmonary artery (indicative of restrictive RV physiology) and clinical state.

Materials and Methods

Approval of our institutional medical ethics committee was obtained. Informed consent was obtained from patients or parents (if patients were not of the legal age to provide consent). Forty patients were included between October 2002 and February 2004. Patients were selected based on the following criteria: total repair before the age of two years, repair through the transatrial-transpulmonary approach, no residual intra-cardiac shunt, and a residual right

ventricular outflow tract (RVOT) Doppler gradient ≤ 40 mmHg. One author (JB) using patient's medical records reviewed these criteria as well as the presence of a transannular patch in the RV outflow tract and the use of medication. Patients with pulmonary atresia, absent pulmonary valve syndrome or other associated heart defects were excluded. The pre-operative parameters (arterial oxygen saturation, RV/Aortic systolic pressure ratio and hemoglobin) shown in Table 1 were obtained from diagnostic heart catheterization reports. Patient height and weight were measured and body surface area (BSA) was calculated. The total population was subdivided in groups: group I containing all patients with EDFF and group II containing those without EDFF. EDFF was defined present when detected at rest in more than 1 time frame at end-expiration. Independent of its volumetric amount, EDFF was considered pathologic and indicative of restriction to RV filling. Patient data obtained at rest was compared with published data on healthy controls by one author (JB).[6] Clinical state was assessed by cardiac MRI, assessing the amount of PR, RV volume and RV ejection fraction, and by maximal exercise testing.

Magnetic resonance imaging protocol

Imaging was performed on a 1.5-Tesla Signa CVi scanner using software releases V8 and V9.1 (General Electric Medical Systems, Milwaukee, WI, USA) and a 4-channel phased array cardiac coil. Standardized localizer imaging planes were acquired for flow-measurements of the tricuspid valve, pulmonary valve, and inferior vena cava, and a volumetric ventricular data set in short axis direction. Flow measurements were performed perpendicular to flow at end-expiration during breath-hold using a standard 2D flow-sensitized retrospectively gated sequence, starting at the R-wave. Special attention was given to adequate ECG registration and triggering. Thirty cardiac phases were reconstructed retrospectively. Imaging parameters were: 2D fast spoiled gradient echo, TR = 6 − 7 ms, TE=3 ms, flip angle = 20°, readout bandwidth = 90 Khz, 6 mm slice thickness, 6 views/segment, a rectangular FOV and a scanning matrix of 256 * 128.

The volumetric data set was acquired using the 2D fast imaging employing steady-state acquisition sequence (SSFP). Imaging parameters were: flip angle = 45°, TE set at min full, TR = 3.4 – 3.6 ms, 8 – 9 mm slice thickness, 0 − 1 mm inter-slice gap, 12 views/segment, readout bandwith = 111Khz, a square FOV

(30 − 34 cm), and a scanning matrix of 160 * 128. Twenty-four cardiac phases were reconstructed retrospectively.

Scans were performed at rest and repeated during dobutamine stress with a maximal dosage of 7.5 μg/kg/min. Heart rate (beats/min), heart rhythm and blood pressures (mmHg) were continuously monitored. Administration of dobutamine was decreased when heart rate increased > 50%, when systolic and/or diastolic blood pressure increased > 50% or decreased > 20%, when serious rhythm disturbances were seen and with complaints of the patient. No severe adverse effects of dobutamine, necessitating discontinuation of MRI examination, were seen.

Table 1. Patient characteristics

	Total group (n = 36)	**Group I (n = 24)**	**Group II (n = 12)**
Age at repair (years)	0.9 ± 0.5	1.0 ± 0.5	0.9 ± 0.5
Pre-operative oxygen saturation	87 ± 9	86 ± 9	89 ± 7
Pre-operative RV/Aorta systolic blood pressure ratio	0.98 ± 0.12	1.00 ± 0.13	0.95 ± 0.07
Pre-operative hemoglobin (mmol/L)	8.8 ± 1.3	9.0 ± 1.4	8.4 ± 0.9
Age at inclusion (years)	17 (7 − 23)	18 (10 − 23)	13 (7 − 23)
Interval since repair (years)	16 (7 − 22)	16 (10 − 22)	12 (7 − 22)
TAP repair	n = 23 (64%)	n = 17 (71%)	n = 6 (50%)*
BSA (m^2)	1.6 ± 0.4	1.7 ± 0.3	1.6 ± 0.5
RV EDV (ml/m^2)	138 ± 40	145 ± 41	124 ± 37
RV ESV (ml/m^2)	64 (36 − 145)	140 (84 − 237)	56 (36 − 137)
RV EF (%)	49 ± 7	49 ± 6	49 ± 9
RVFWM (gr/m^2)	24 ± 6	25 ± 7	23 ± 6
Residual PR (%)	36 (0 − 55)	39 (0 − 55)	17 (1 − 51)*
Residual PS (mmHg)	9 (4 − 29)	9 (4 − 29)	11 (6 − 29)

Data given are: number of patients (%), median (range) or mean ± SD,

* Significant difference ($p < 0.05$) between groups I and II, BSA = body surface area, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, RV = right ventricle, PR = pulmonary regurgitation, PS = pulmonary stenosis, RVFWM = RV free wall mass, TAP = transannular patch.

Magnetic resonance image analysis

MRI data analyses were performed by 1 author (JB) with 1 − 3 years of MRI experience supervised by a second author (WH) with 10 years of MRI experience. Flow images were quantitatively analyzed using the Flow analysis software package version 2.0 (Medis Medical Imaging Systems, Leiden, The Netherlands). Flow velocity curves were calculated by multiplying the manually drawn vessel/valve area on each time frame with the spatial average flow velocities. EDFF (ml) and PR (ml) were normalized for respectively net forward flow volume and systolic forward stroke volume measured in the pulmonary artery. Presence of retrograde flow coincident with atrial systole was assessed in the inferior vena cava. The volume of tricuspid insufficiency was normalized for total forward flow across the tricuspid orifice. Volumetric data were analyzed using the Mass analysis software package version 3.1 (Medis Medical Imaging Systems, Leiden, The Netherlands). End-diastolic and end-systolic time frames were used according to analysis techniques widely reported in literature to assess right ventricular end-diastolic volume, end-systolic volume, stroke volume, ejection fraction and wall mass.[9,10]

Calculations

RV time-volume change curves were reconstructed by summation of flow data from the main pulmonary artery and the tricuspid valve as previously described.[6] Time-volume curves were obtained by integration of the time-volume change curves (Figure 1). If heart rates (trigger delays) during both measurements were not identical the averaged heart rate (trigger delay) was calculated and used for the summated curves. From the RV curves the following indices of diastolic function were derived; 1) peak early filling rate (PeFR) (ml/s), 2) time to peak early filling rate (ttPeFR) (ms) measured from end-systole, 3) early filling fraction (FF) defined as volume increase (ml) during the first one-third of diastole normalized for ventricular stroke volume, 4) deceleration time (Dt) (ms), measuring the time from PeFR to the extrapolation point of deceleration of flow to the baseline, 5) peak atrial filling rate (PaFR) (ml/s), 6) time to peak atrial filling rate (ttPaFR) (ms) defined as time from end-systole to maximal increase in ventricular volume after atrial contraction, 7) atrial filling fraction (AFF) defined as the increase in ventricular volume after atrial

contraction normalized for ventricular stroke volume, and 8) the ratio of peak early filling rate over peak atrial filling rate (PeFR/PaFR ratio) (Figure 1). RV stroke volume (ml) was defined as the maximal ventricular volume measured on the ventricular time-volume change curve.

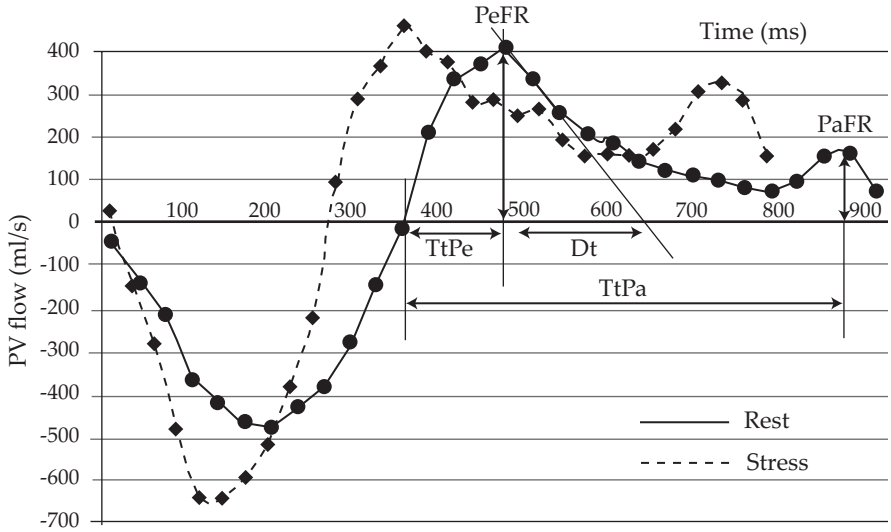

Figure 1A. RV Time-Volume Change Curve Abbreviations used:
Dt = deceleration time, PaFR = peak atrial filling rate, PeFR = peak early filling rate, TtPa = time to PaFR, TtPe = time to PeFR

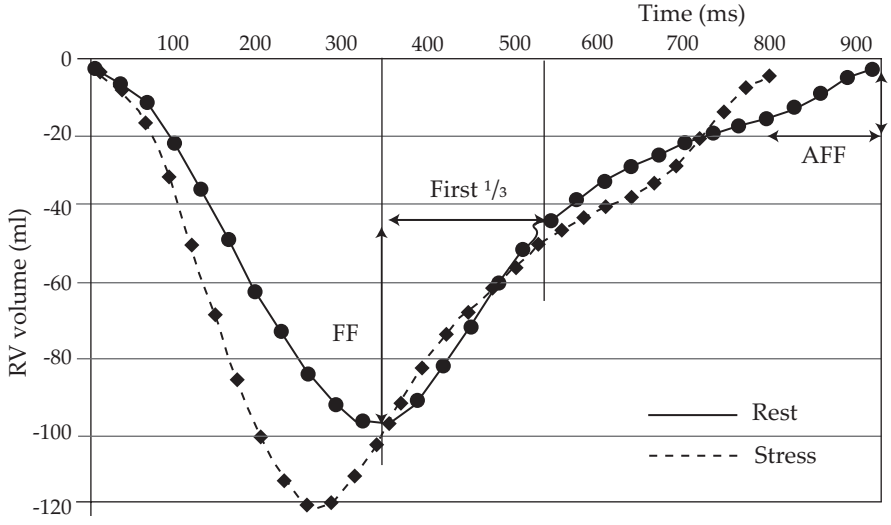

Figure 1B. RV Time-Volume Curve Abbreviations used:
AFF = atrial filling fraction, FF = early filling fraction (first ⅓ of diastole)

Exercise testing

To assess peak workload (Watts) and peak oxygen consumption (VO2max) all patients performed a maximal exercise test, using a stepwise incremental protocol on a Jaëger (Viasys Healthcare, Hoechberg, Germany) Oxycom Champion System allowing breath-by-breath-ergometry. Patients were encouraged to perform until exhaustion. The respiratory quotient was used to objectify maximal performance (respiratory quotient > 1.1 at peak exercise). Peak workload was compared to that of a reference population by one author (JB).[11]

Statistical methods

Results are expressed as mean ± 1SD for normally distributed data, otherwise the median and range are shown. Patient characteristics were compared between groups using the student T-test or the Mann-Whitney U test. Diastolic MRI parameters were compared using analysis of covariance with correction for heart rate and BSA to deal with possible confounding introduced by age differences in this partly pediatric population. To meet the data considerations of analysis of covariance all diastolic parameters except ttPeFR and FF had to be $\log_{10}$-transformed. Paired measurements were analyzed using the paired T-test during which diastolic time-related parameters were normalized for RR-interval duration and PeFR and PaFR for RV stroke volume. Mean percentage of predicted workload (Watts) was compared with the reference population using the one-sample T-test. In our patients the agreement between RV stroke volume as determined with tomographic cine MRI and as determined with velocity encoded MRI was evaluated using intra-class correlation coefficients (ICC). Analysis was performed using the SPSS-PC statistical software package version 11.5 (SPSS, Chicago, Illinois, USA). A p-value < 0.05 was considered to indicate statistical significance. No adjustments were made regarding the multiple tests performed.

Results

Patient characteristics

Four patients with incomplete MRI data were excluded from the final analysis (see below). Characteristics of the remaining 36 patients (26 (72%) males and 10 (28%) females) and of the subgroups (Table 1) showed that patients did not take medication related to their cardiac condition. Insufficiency of the tricuspid valve indexed for forward flow across the valve (median 4% (range 1 − 14%)) was found in 13(36%) patients: 8 in group I (4% (1 − 14%) and 5 in group II (3% (1 − 7%). Group I showed a tendency towards larger RV volumes (the respective p-values for RVEDV and RVESV were 0.07 and 0.09).

Magnetic Resonance Imaging

MRI data was incomplete due to bigeminy during stress in 1 patient and ≥ 1 missing/failed flow-measurement in 3 patients. In our patients the mean difference of RVSV determined using velocity encoded MRI minus RVSV determined using tomographic cine MRI at rest was –1 ml, and the SD of the difference was 8. The resulting ICC was 0.98, demonstrating excellent agreement between both methods. Similarly, for RVSV measured with stress the mean difference was 4 ml with a SD of the difference of 12. The associated ICC was 0.96, again demonstrating excellent agreement between both methods. Right ventricular free wall mass (g/m^2) in patients was larger compared with published control data (24 ± 6 versus 17 ± 2, $p < 0.05$).

RV diastolic function

Patients had a longer mean deceleration time and smaller FF compared with published control data (Table 2). This indicates impairment of RV relaxation. With stress (Table 3) increases of PaFR, AFF and deceleration time and decreases of ttPeFR, PeFR and PeFR/PaFR-ratio were seen. The change in filling-pattern with stress is compatible with further impairment of RV relaxation.

Table 2. Right ventricular indices of diastolic function at rest.

	All patients: (n = 36)	**Group I (n = 24)**	**Group II (n = 12)**	**Controls (n = 12)‡**
RVSV (ml/m²)	66 ± 15*	69 ± 14*	60 ± 14	46 ± 6
HR (/min)	75.2 ± 12.4	71.7 ± 11.1	82.1 ± 12.4	74.6 ± 10.9
CO (l/min/m²)	4.9 ± 1.3*	4.9 ± 1.1*	5.0 ± 1.7*	3.4 ± 0.7
FF (%)	47.6 ± 11.4*	52.2 ± 10.6†	38.6 ± 6.5*	55.1 ± 15.7
AFF (%)	23.3 ± 12.0	17.7 ± 7.8†	34.5 ± 11.0*	19.2 ± 8.0
PeFR/SV (/sec)	4.2 ± 0.8	4.2 ± 0.7	4.3 ± 1.1	4.5 ± 0.9
PaFR/SV (/sec)	2.4 ± 1.1	1.9 ± 0.7†	3.5 ± 1.1*	2.1 ± 1.1
Ratio PeFR/PaFR	2.1 ± 1.2	2.6 ± 1.2†	1.2 ± 0.3*	2.5 ± 1.3
Dt/RR (10^{-1})	2.7 ± 0.9*	2.5 ± 0.7*	3.0 ± 1.2*	1.9 ± 0.5
TtPeFR/RR (10^{-1})	1.4 ± 0.4	1.3 ± 0.3	1.6 ± 0.4	1.4 ± 0.3
TtPaFR/RR (10^{-1})	4.3 ± 1.0*	4.7 ± 0.8†	3.5 ± 0.9*	5.2 ± 1.5

Data given are: mean ± SD, * Significant difference compared to controls ($p < 0.05$) by analysis of covariance with correction for BSA and HR, † Significant difference compared to group II patients ($p < 0.05$) by analysis of covariance with correction for BSA and HR. Analysis with age as an additional covariate did not appreciably change results.

‡ Resting data on healthy controls from Helbing *et al*.[6]

AFF = atrial filling fraction, CO = cardiac output, Dt = deceleration time, EDFF = end-diastolic forward flow, FF = filling fraction, HR = heart rate, PaFR = peak atrial filling rate, PeFR = peak early FR, RR = duration RR-interval, SV = stroke volume, TtPa = time to PaFR, TtPe= time to PeFR.

Table 3. Right ventricular indices of diastolic function during dobutamine stress.

	All patients (n = 36)	Group I (n = 24)	Group II (n = 12)
SV (ml/m²)	76 ± 23* ▲	84 ± 18* ▲	61 ± 26* ▲
HR (/min)	85.7 ± 15.3* ▲	83.5 ± 13.9* ▲	90.3 ± 17.7
CO (l/min/m²)	6.6 ± 1.5* ▲	6.9 ± 1.5* ▲	5.9 ± 1.4* ▲
FF (%)	45.5 ± 9.8	47. 2± 10.0* ▼	41.6 ± 9.2
AFF (%)	27.7 ± 12.5* ▲	25.0 ± 12.7*† ▲	33.7 ± 9.2
PeFR/SV	3.9 ± 0.8* ▼	4.0 ± 0.8* ▼	3.9 ± 0.9
PaFR/SV	2.8 ± 1.1* ▲	2.5 ± 0.9* ▲	3.4 ± 1.2
Ratio PeFR/PaFR	1.7 ± 1.0* ▼	1.9 ± 1.1*† ▲	1.3 ± 0.5
Dt/RR (10^{-1})	3.3 ± 1.0* ▲	3.4 ± 1.0* ▲	3.1 ± 0.9
TtPeFR/RR (10^{-1})	1.2 ± 0.2* ▼	1.2 ± 0.2	1.3 ± 0.2* ▼
TtPaFR/RR (10^{-1})	4.1 ± 0.9	3.9 ± 1.0* ▼	4.2 ± 0.9

Data given are: mean ± SD, * Significant change compared to rest ($p< 0.05$); ▲ = increase, ▼ = decrease. † Significant difference compared to group II patients ($p< 0.05$) during stress by analysis of covariance with correction for BSA and HR. Analysis with age as an additional covariate did not appreciably change results.

AFF = atrial filling fraction, CO = cardiac output, Dt = deceleration time, EDFF = end-diastolic forward flow, FF = filling fraction, HR = heart rate, PaFR = peak atrial filling rate, PeF = peak early FR, RR = duration RR-interval, SV = stroke volume, TtPa = time to PaFR, TtPe = time to PeFR.

Patients with and without EDFF

At rest 24(67%) patients showed EDFF (group I). In 20(83%) group I patients flow was measured in the inferior vena cava which showed retrograde flow coinciding with atrial contraction in 16(80%) subjects. Twelve (33%) patients did not have EDFF (group II). In 7(58%) of them inferior vena cava flow-measurements were performed and retrograde flow was absent in all. Median contribution of EDFF to net forward flow in subgroup I was 6% (range 1 – 24%) and did not change significantly during stress (median 4%, range 0 – 18%). In 3 patients with EDFF present at rest, EDFF was absent during stress, while 3 patients without EDFF at rest showed EDFF during stress.

At rest, group II showed a larger mean AFF, smaller FF, smaller PeFR/PaFR-ratio, higher PaFR and shorter ttPaFR compared to group I (Table 2). Compared

to published data on healthy controls group II patients had a larger mean AFF, higher PaFR, longer deceleration time, smaller FF, and smaller PeFR/PaFR-ratio (Table 2). Group I only showed a longer deceleration time compared to published data on healthy controls.

With stress (Table 3) group I showed increases of AFF, PaFR, and deceleration time, while decreases were noted for FF, PeFR, PeFRc/PaFRc ratio, and ttPaFR. Group II had a shorter ttPeFR with stress without changes in any of the other RV diastolic parameters.

Exercise capacity

All patients successfully performed a maximal exercise test. Percentage of predicted workload for the total population was 92 ± 13%, which is significantly ($p < 0.01$) smaller than the predicted 100%. In group I this percentage was 89 ± 11% ($p < 0.001$ compared to 100%) and in group II it was 97 ± 17% ($p = 0.67$). Percentage of predicted workload was not significantly different ($p = 0.08$) between both subgroups. Mean VO2max was 39 ± 9 ml/kg/min in group I and 45 ± 8 in group II ($p = 0.09$).

Discussion

Our study demonstrates that RV diastolic filling abnormalities are present in TOF at mid- to long-term follow-up, even in patients operated according to currently widely accepted surgical strategies. Diastolic filling results from (in part) active relaxation in early diastole, and passive filling in the later parts of diastole. Compared with published control data, RV diastolic filling at rest in our total population demonstrated signs of impaired relaxation (prolonged deceleration time, smaller early filling fraction). EDFF, a generally recognized marker of restriction to RV filling,[5,7,12] was found in ⅔ of our patients (group I). Compared to group II (no EDFF), group I showed signs of restriction to RV filling, had more severe PR and tended to have a more dilated RV. Furthermore patients with EDFF had the poorest exercise performance compared to a reference population, which was not explained by a difference in global systolic RV function. Moreover, in direct comparison with published control data RV diastolic filling at rest was most abnormal in group II. Somewhat to our

surprise, considering the abnormal finding of EDFF, RV filling in group I was fairly normal compared with published control data. However dobutamine stress imaging revealed important RV diastolic filling abnormalities in this subgroup, which fit an increase in relaxation related abnormalities. In the group without EDFF, RV diastolic filling did not change, although EDFF occurred during stress in three patients without EDFF at rest.

End-diastolic forward flow and outcome in repaired TOF

The presence of EDFF, a marker of restriction to RV filling, immediately after TOF repair has been associated with longer ICU and hospital stays.[5] EDFF tends to disappear in the first weeks following repair,[5] but has been shown to predict presence of EDFF at midterm follow-up.[13] Reports have been equivocal on how restriction to RV filling, as evidenced by EDFF, effects long-term clinical state in repaired TOF. Gatzoulis *et al*. found patients with EDFF had shorter PR duration, less cardiomegaly and better exercise capacity, suggesting a protective effect of restriction to RV filling.[7] Other studies only partly confirmed these results.[8,13,14] At long-term follow-up our patients with EDFF had more severe PR compared to patients without EDFF, and had worse exercise capacity compared to a reference population. In a small and somewhat younger TOF population to ours, but using similar MRI techniques, exercise capacity was also found to be worse in patients with EDFF.[6] This observation could not be explained by differences in severity of PR, RV dilation or RV global systolic function.[6] In agreement with our study, and somewhat unexpected, RV diastolic filling abnormalities at rest were clearest in patient without EDFF. Considering the abnormal finding of EDFF we would expect most abnormal findings in patients with EDFF. In our study the use of stress imaging "unmasked" highly abnormal RV filling in the EDFF positive patients, which may serve to explain the observed exercise limitation.

The differences in results between studies on RV diastolic filling in repaired TOF may be due to differences in studied populations (age at repair, surgical techniques used, duration of follow-up since repair) and diagnostic tools used. We measured EDFF during breath-holds at end-expiration, as EDFF at inspiration is also seen in healthy subjects. In 16 (80%) out of 20 patients with EDFF in whom IVC flow was assessed, EDFF coincided with reverse IVC flow, a combination previously associated with restriction to RV filling.[5,7]

Detection of EDFF by MRI velocity mapping and Doppler echocardiography has been shown to be in good agreement.[6] In contrast to echocardiography flow-sensitized MRI offers volumetric flow quantification, which enables the inclusion of both tricuspid and pulmonary flow into the analysis of RV filling. Furthermore our study selectively studied patients operated according to current surgical strategies. Therefore ventricular dysfunction cannot be ascribed to myocardial damage after extensive ventriculotomies, or to longstanding pre-repair hypoxemia, or high RV pressures. Our results apply to TOF patients with residual PR and mild to moderate pulmonary stenosis only. We thus avoid difficulties in interpretation of results due to mixed pressure and volume overload effects.

Mechanisms of RV diastolic dysfunction

The substrate of restriction to RV filling in Fallot patients remains unknown. Potential relationships have been reported with age at repair, staging and timing of repair, degree of preoperative pulmonary stenosis and amount of post-operative PR.[5,8,13,14] In our study severity of PR was the only significantly different factor between patients with and without EDFF. Mechanisms underlying abnormalities of diastolic filling are complex. Combined hypoxemia and pressure overload, as present preoperatively in TOF, result in increased fibrosis of the RV.[15] However, it is unknown how these pre-operative factors contribute to postoperative diastolic abnormalities. Data on the effects of chronic volume overload on RV diastolic function are limited. Experimentally induced sub-acute PR resulted in increased RV myocardial compliance,[16] while RV diastolic function was well preserved after three months of RV volume overload in growing swine.[17] Chronic LV volume overload in rats resulted in diastolic filling abnormalities, with dynamic shifting of inflow patterns.[18] These models however only partly mimic the chronic and progressive RV volume-overload seen in TOF patients. For the LV hypertrophy is a common cause of diastolic filling abnormalities and heart failure.[19] The RV hypertrophy present in our TOF patients could not be associated to a particular type of diastolic filling abnormalities.

Changes in diastolic function with stress and aging

Changes observed with dobutamine stress in our patients are compatible with impaired relaxation. This is a highly abnormal finding since dobutamine is considered to improve diastolic relaxation.[20,21] In response to dobutamine stress healthy subjects show an increase of PeFR and/or PaFR, while the PeFR/PaFR-ratio remains unchanged or increased.[21,22]

In adults relaxation related impairment is observed with aging.[23] In children changes in diastolic function mainly appear during the first 3 years of life.[24,25] Therefore age is not a likely explanation for the differences found in diastolic filling between our subgroups.

Study limitations

The evaluation of diastolic function should include indices of isovolumic relaxation. However in the absence of normal pulmonary valve closure, as is the case in most operated TOF patients, isovolumic relaxation cannot be assessed.

Physical stress in the MR environment has been reported feasible.[26] We used pharmacological stress because of the limited bore diameter of the available MR-scanner. Ethical limitations of administrating dobutamine to healthy children prevented their inclusion. Therefore we compared our patient data at rest with published control data from a previous study performed in another center on another type of MRI-system but using similar techniques.[6]

A limitation of all non-invasive studies is the lack of pressure measurements. Increased RV filling pressures augments the effect of restriction to filling and may mask signs of impaired RV relaxation. However RV end-diastolic pressure usually is normal in post-operative TOF, as is the pulmonary vascular resistance in the absence of pulmonary valve stenosis.

To quantify blood flow we used phase velocity encoded (VEC) MRI which is regarded a valuable tool in congenital heart disease.[27,28] VEC MRI has many possible sources of errors including; technical issues (mismatched encoded velocity, inadequate temporal resolution, inadequate spatial resolution, phase offset errors, low signal-to-noise ratio), local flow/anatomy related issues (accelerated flow, vessel motion) and issues of proper imaging plane delineation (valve motion, deviation of the imaging plane).[27,29,30] Proper sequence set up

combined with careful planning can keep the overall error in the great vessels below 10%.[27,30] We have shown our RVSV results determined with VEC MRI are in excellent agreement with those determined using the current reference standard, multi-slice tomographic cine MRI.

Conclusion

In Fallot patients corrected according to currently widely accepted surgical strategies, EDFF in the pulmonary artery relates to worse clinical state at mid to long-term follow-up, as indicted by worse exercise capacity and more severe PR. Dobutamine stress imaging may "unmask" abnormalities in RV diastolic filling not appreciated by rest imaging alone.

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In patients operated for tetralogy of Fallot at young age, impaired exercise capacity, biventricular stress response and neurohormonal levels are not related to RV volume and pulmonary regurgitant fraction

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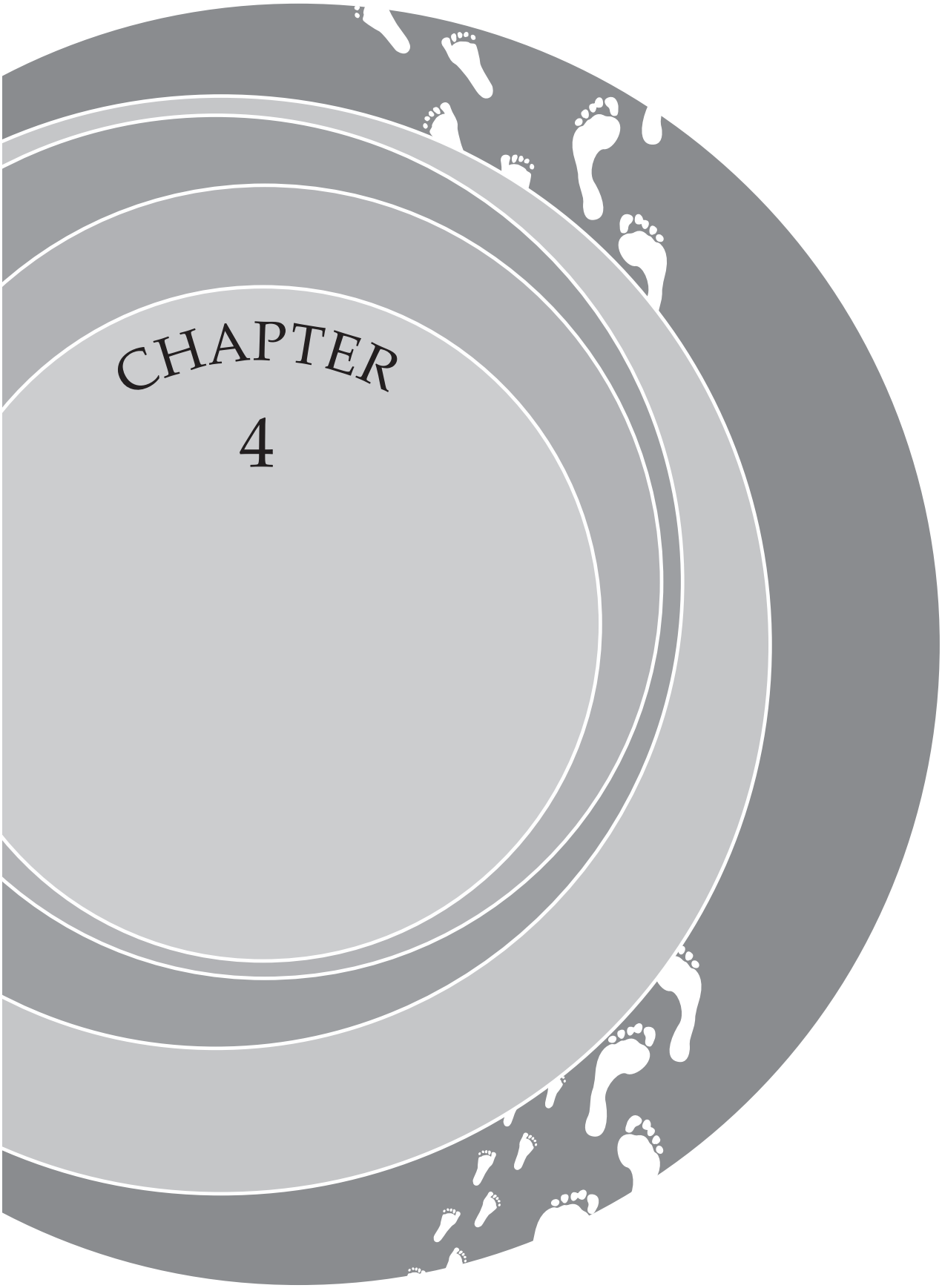
Submitted


CHAPTER
4

Abstract

Aims: To assess a.) neurohormonal activation, b.) biventricular contractile reserve (CR) and c.) exercise performance, in relation to PR-percentage and right ventricular volume in patients with tetralogy of Fallot (TOF) after repair at young age.

Methods and Results: In 53 TOF patients (maximal age at repair 2.0 years, interval since repair 15 (5) years) without residual lesions except PR, MR-imaging at rest and during dobutamine stress was performed. Ventricular CR,maximal workload, peak oxygen uptake and circulating levels of natriuretic peptides, catecholamines and inflammatory markers were assessed.

Median PR-percentage was 37% (range 0 − 57%). Levels of neurohormonal and inflammatory markers were normal in most patients, and did not correlate with PR-percentage or right ventricular size. High-risk levels of NT-proBNP indicated a smaller RV-CR and a smaller decrease of biventricular ESV. Biventricular systolic stress response was normal: mean (SD) ESV decreased (ΔRVESV –17 (8) ml/m², ΔLVESV –11 (5)), SV increased (ΔRVSV +12 (9) ml/m², ΔLVSV +9 (6)), CR was positive in all (RVCR +11 (5) %, LVCR +13 (6) %). Mean (SEM) $VO2_{max}$ was 96 (3) %, mean $workload_{max}$ 89 (2) % of predicted.

Conclusion: In TOF repaired at young age overall neurohormonal markers are normal and cardiac functional reserve and exercise tolerance are well preserved, irrespective of PR-percentage and RV volume.

Introduction

Chronic pulmonary regurgitation (PR) in tetralogy of Fallot (TOF) has been associated with deleterious changes in right, and also left, ventricular size and function.[1] In LV disease states, it is commonly accepted that a chronic insult to the myocardium will result in changes in geometry and structure of the ventricle that is accompanied by neurohormonal activation.[2] The neurohormonal concept has guided treatment guidelines for heart failure.[3,4] This concept has also been applied to the RV in congenital heart disease.[5] The level of neurohormonal activation has prognostic value in acquired and adult congenital heart disease, and has been suggested an early sign of impending heart failure.[5,6] Currently, pulmonary valve replacement is the only accepted treatment for chronic PR in TOF patients. Clinical indications for pulmonary valve replacement included clinical signs and symptoms, exercise performance, tricuspid regurgitation and biventricular function.[1,7] Surprisingly, few data is available on the relation between RV remodelling as a result of chronic PR and the level of neurohormonal activation and functional ventricular impairment. It is unclear whether the amount of PR and /or biventricular size in patients operated for TOF relate to neurohormonal activation and functional decline. Considering treatment guidelines in other cardiac disease states, this information is required.[3,4]

We hypothesize that increases of PR-percentage and/or RV volume result in increased neurohormonal levels and decreased functional reserve, as assessed by exercise testing and cardiac stress imaging. Aim of the study was to assess the level of a) neurohormonal activation, b) biventricular contractile reserve and c) exercise performance, in relation PR-percentage and RV volume in patients with TOF after repair at young age.

Methods

Patients

In a cohort study of patients after surgical correction of TOF, patients were invited to undergo CMR, maximal exercise testing and assessment of circulating neurohormonal levels. Inclusion criteria used were: 1) complete repair of TOF

without associated cardiac lesions, including double outlet right ventricle, 2) total surgical correction ≤ 2 years, 3) transatrial-transpulmonary approach to repair, and 4) post-operative time interval ≥ 5 years. Patients with one or more of the following criteria were excluded: 1) residual VSD, 2) residual pulmonary stenosis (echo Doppler mean gradient > 30 mm Hg), 3) repair with a homograft, 4) mental retardation, and 5) known extra-cardiac pathology. The local medical ethics committee approved our study protocol. Patients were included between September 2002 and November 2004 after written informed consent.

Exercise test

A Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany), allowing breath-by-breath-ergometry, was used for maximal exercise testing. Workload was increased stepwise with 10 − 20 watts/minute. Patients performed until exhaustion, as assessed using a cut-off ≥ 1.05 for the respiratory quotient (RQ) at peak exercise. Exercise capacity was compared to results from normal individuals.[8] Peak workload (Watts) and peak oxygen consumption (ml/kg/min) were obtained and expressed as percentages of predicted values, respectively referred to as $Workload_{max}$ and $VO2_{max}$. A 12-lead ECG was continuously monitored and QRS-duration was measured at rest.

Cardiac Magnetic Resonance Imaging

A 1.5-Tesla Signa CVi scanner was used, with software releases V8.4 and V9.1 (General Electric Medical Systems, Milwaukee, WI, USA) and a 4-channel phased array cardiac coil. Standardized localizer imaging planes were acquired to plan pulmonary and tricuspid valve flow-measurements, and a volumetric ventricular data set in short axis direction. Data was gathered during breath-holds at end-expiration.

Multi-phase, multi-slice volumetric data was acquired using a fast 2D cine scan employing steady-state free precession (SSFP). Imaging parameters: flip angle = 45°, TE set at min full, TR = 3.4 – 3.6 ms, 8 − 9 mm slice thickness, 0 − 1 mm inter-slice gap, 12 views/segment, readout bandwidth = 111Khz, square FOV (30 − 34 cm), scanning matrix of 160 * 128. Twenty-four phases per cardiac cycle were reconstructed retrospectively.

Flow measurements were performed perpendicular to flow using a standard 2D flow-sensitized scan. Scans were retrospectively gated starting the acquisitions on the R-wave. Temporal resolution was approximately 40 ms per cardiac phase and 30 phases were reconstructed retrospectively. Imaging parameters were: 2D FSPGR, TR = 6 – 7 ms, TE = 3 ms, flip angle = 20°, readout bandwidth = 90 Khz, 6 mm slice thickness, 6 views/segment, rectangular FOV (75% in phase encoding direction), scanning matrix of 256 *128.

All scans were performed at rest and repeated during dobutamine stress (maximal dose 7.5 μg/kg/min. Dobutamine infusion was decreased when heart rate increased > 50%, when systolic and/or diastolic blood pressure increased > 50% or decreased > 20%, when serious rhythm disturbances were seen, or with complaints of the patient.

CMR data-analysis

CMR studies were analyzed on a commercially available workstation (Advanced Windows, General Electric Medical Systems, Milwaukee, WI, USA). Flow images were quantitatively analyzed using the Flow analysis software package V2.0 (Medis Medical Imaging Systems, Leiden, The Netherlands). The amount of pulmonary regurgitation was normalized for forward systolic stroke volume in the main pulmonary artery (= PR-percentage). The amount of tricuspid regurgitation was normalized for the amount of forward flow over the tricuspid valve (= TR-percentage). The ventricular volumetric data set was quantitatively analyzed using the Mass analysis software package V3.1 (Medis Medical Imaging Systems, Leiden, the Netherlands).[9] Volumetric data was indexed for body surface area (m^2) unless stated otherwise. Changes in CMR parameters were calculated: Parameter Change (Δ) = $Parameter_{stress} - Parameter_{rest}$, Contractile Reserve (CR) = $EF_{stress} - EF_{rest}$. As in other studies CR was defined to be preserved with values > 0.[10,11] Previously Therrien *et al*. described patients with a RVEDV > 170 ml/m^2 did not show recovery of RV volume to normal (RVEDV < 108 ml/m^2) following pulmonary valve replacement for PR.[12] Based on RVEDV patients were divided into 3 groups: RVEDV < 108 ml/m^2, RVEDV 108–170 ml/m2, and RVEDV > 170 ml/m2.

Neurohormonal markers

Blood samples were drawn from a peripheral vein after 30 minutes rest in supine position. Plasma or serum were separated immediately after sample collection and stored at −70°C. Determination of catecholamines ((nor) epinephrine) was done by high-performance liquid chromatography (HPLC) with fluorometric detection.[13] Renin was determined by measuring the Angiotensin I generated during incubation in the presence of excess substrate with an in-house radioimmunoassay as described previously.[14] Natriuretic peptides (N-ANP and NT-proBNP), TNF-alpha, endothelin and high sensitive CRP (hsCRP) were measured using the following commercially available kits: Endothelin: quantiGlo immunoassay kit (R&D Systems, Abingdon, UK), BNP and ANP, immunoradiometric methods (Shionoria, Osaka, Japan), N-ANP, radioimmunoassay kit (Biotop, Oulu, Finland), NT-proBNP, electrochemiluminescence immunoessay (Elecsys, Roch Diagnostics, Mannheim, Germany), hsCRP, immunophelometric essay (Elecsys, Roch Diagnostics, Mannheim, Germany), TNF-alpha, immunometric essays (Immulite Diagnostic Products Corporation, Los Angeles, CA, USA), Aldosterone, radioimmunoassay kit (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistical analysis

When appropriate, data was $\log_{10}$-transformed to obtain approximately normal distribution. Results are expressed as mean (SD) for normally distributed data, otherwise the median (range) is shown. Paired data analysis was performed using the paired T-test. Comparisons between 2 groups were performed using the student T-test. Analysis of covariance was used for multiple group comparisons corrected for multiple testing by Bonferroni's method. Correlation coefficients were calculated using Spearman's method (r_s). Multiple linear regression analysis was used to study the association of neurohormonal and inflammatory makers with CMR measures and exercise capacity. Analysis was performed using the SPSS-PC statistical software package version 11.5 (SPSS, Chicago, Il, USA). A p-value < 0.05 was considered to indicate statistical significance.

Results

Fifty-three patients surgically repaired between 1980 and 1997 were included (median age at repair 0.8 (0.2 − 2.0) years, follow-up since repair 15 (6 − 23) years). No serious adverse effects to dobutamine were encountered. Two patients were excluded because of insufficient CMR stress data quality. Results relate to the remaining 51 patients. Patient characteristics are shown in Table 1.

None of our patients used cardiac medication. All were in sinus rhythm. Median QRS-duration was 111 ms (range 87 − 161 ms). One patient declined to perform a maximal exercise test. Exercise data from a second patient with severe obstructive abnormalities was excluded from analysis. Exercise results in Table 1 relate to the remaining 49(96%) patients.

Table 1. Patient characteristics

General parameters	**N = 51**
Gender (M/F)	37 / 14
Age at repair (years)	0.8 (0.2 – 2.0)
Age at study (years)	15 (7 – 26)
Interval since repair (years)	15 (7 – 23)
Body Surface Area (m^2)	1.6 (0.4)
Transannular patch repair	36
Blalock-Taussing shunt	2
Exercise Test	**N = 49**
Respiratory quotient at peak exercise	1.2 (0.1)
Peak oxygen consumption (ml/kg/min)	40 (8)
$VO2_{max}$ (%)	96 (18)
$Workload_{max}$ (%)	89 (13)

Data given are: number of patients (%), median (range) or mean (SD)

Table 2. Cardiac magnetic resonance imaging results: comparisons based on RVEDV groups

	Total Patients		Group I: < 108 ml/m²		Group II: 108 – 170 ml/m²		Group III: > 170 ml/m²	
	Rest	**Change**	**Rest**	**Change**	**Rest**	**Change**	**Rest**	**Change**
Right Ventricle								
EDV (ml/m²)	140 (38)	− 5 (9)‡	92 (8)*†	−3 (6)	135 (19)*	− 4 (9)	192 (22)	− 9 (13)
ESV (ml/m²)	73 (26)	− 17 (8)‡	43 (8)*†	−12 (6)	69 (14)*	− 16 (8)	109 (20)	− 22 (9)
SV (ml/m²)	67 (14)	12 (9)‡	49 (6)*†	10 (7)	66 (10)*	12 (8)	83 (10)	13 (12)
EF (%)	49 (6)	11 (5)‡	53 (6)*	12 (6)	49 (6)*	11 (5)	44 (5)	9 (4)
CI (L/min/m²)	5.0 (1.2)	1.8(1.0)‡	4.1 (0.6)*	1.4 (0.7)	5.0 (1.2)	1.8 (0.7)	5.8 (0.8)	2.1 (1.5)
Mass (g/m²)	24 (±6)	N.E.	18 (± 3)*†	N.E.	23 (± 4)*	N.E.	32 (± 5)	N.E.
Left Ventricle								
EDV (ml/m²)	81 (12)	− 3 (6)‡	74 (8)*	− 1 (5)	82 (12)	− 3 (7)	86 (11)	− 3 (6)
ESV (ml/m²)	36 (7)	− 11 (5)‡	30 (8)*	− 8 (4)	36 (6)	− 12 (6)	39 (8)	− 11 (5)
SV (ml/m²)	46 (7)	9 (6)‡	43 (4)	7 (6)	46 (8)	9 (6)	47 (8)	8 (5)
EF (%)	57 (9)	13 (6)‡	59 (8)	11 (5)	56 (4)	14 (6)	55 (7)	12 (5)
CI (L/min/m²)	3.5 (0.6)	1.3 (0.6)‡	3.7 (0.6)	1.2 (0.5)	3.5 (0.7)	1.3 (0.6)	3.2 (0.4)	1.3 (0.6)
Mass (g/m²)	53 (9)	N.E.	48 (6)	N.E.	54 (9)	N.E.	56 (12)	N.E.
Pulmonary Regurgitation								
PR−percentage	37 (0 − 57)	0 (6)	18 (2 − 27)*†	0 (5)	37 (0 − 57)*	0 (5)	48 (31 − 54)	1 (8)

Data given are mean (SD) and median (range), N.E. = not encluded

‡ Significantly different from zero (paired T-test),

* Significant difference ($p < 0.05$) with subgroup III (ANOVA, Bonferroni)

† Significant difference ($p < 0.05$) with subgroup II (ANOVA, Bonferroni)

Table 3. Neurohormones: comparisons based on RVEDV groups

Neuro–hormones	Total Population			Group I	Group II	Group III
	Median (range)	UL*	> UL†	Median (range)	Median (range)	Median (range)
N-ANP (nmol/L)	0.28 (0.07 – 0.52)	0.50	1 (2%)	0.29 (0.18 – 0.40)	0.29 (0.14 – 0.52)	0.29 (0.07 – 0.46)
NT-proBNP (pmol/L)	10 (2 – 42)	35	2 (4%)	13 (2 – 21)	12 (3 – 38)	8 (4 – 42)
Norepinephrine (pg/ml)	248 (106 – 508)	600	0 (0%)	219 (106 – 366)	247 (120 – 508)	292 (160 – 458)
Epinephrine (pg/ml)	37 (1 – 139)	100	6 (12%)	56 (24 – 139)	32 (1 – 103)	43 (12 – 131)
TNF–alpha (pg/ml)	7.0 (4.0 – 21.7)	8.1	1 (2%)	8.3 (4.8 – 15.7)	5.9 (4.0 – 21.7)	6.3 (4.6 – 9.7)
Endothelin (pg/ml)	1.1 (0.3 – 4.5)	2.5	2 (4%)	1.1 (0.6 – 1.9)	1.0 (0.3 – 4.5)	1.2 (0.7 – 2.8)
CRP (mg/L)	0.7 (0.2 – 17.5)	1.0	19 (38%)	0.6 (0.2 – 17.5)	0.6 (0.2 – 8.7)	0.9 (0.2 – 8.9)
Renin (ng/ml/u)	4.5 (1.0 – 15.8)	12	2 (4%)	5.9 (1.3 – 15.8)	4.4 (1.9 – 10.6)	3.8 (1.0 – 14.6)
Aldosteron (pg/ml)	52 (1 – 221)	250	0 (0%)	52 (1 – 150)	66 (1 – 209)	67 (26 – 221)

* UL = Upper limit of normal, † Number of patients (%) above UL

CMR results

Biventricular CMR results are shown in Table 2. With dobutamine-stress mean heart rate increased from 76 (13) to 88 (17) beats/min ($p < 0.001$). Both ventricles responded to stress with a significant increase in global systolic performance. Biventricular CR was preserved (positive) in all patients (Figure 1A and 1B).

We established 3 subgroups based on RVEDV: group I (n = 10) with RVEDV < 108 ml/m², group II (n = 29) with RVEDV 108 − 170 ml/m², and group III (n = 12) with RVEDV > 170 ml/m². CMR measurements for these subgroups are shown in Table 2. CMR parameter changes with stress were not significantly different between subgroups, nor were $VO2_{max}$ and $Workload_{max}$.

PR-percentage was also used to categorize patients. Three subgroups were established; mild PR (< 20%, n = 13), moderate PR (20 – 40%, n = 20) and severe PR (> 40%, n = 18). CMR parameter changes with stress were not significantly different between subgroups, nor were $VO2_{max}$ and $Workload_{max}$ (Data not shown).

Patients with a transannular patch (n = 36) showed more severe PR than those without (n = 15) a patch (median PR-percentage 41% (range 11 – 57) versus 16% (0 – 40), $p < 0.05$), had a larger RV (RVEDV 154 (34) ml/m² versus 105 (19), $p < 0.05$) and poorer RVEF (47 (6)% versus 53 (6), $p < 0.05$). CR of both ventricles was not different between patients with and without a transannular patch.

Twenty (39%) patients showed tricuspid regurgitation with a median TR-percentage of 3.6%. Patients TR showed comparable PR compared to those without TR (median PR-percentage 39% (range 1 – 57) versus 34% (0 – 54), $p = 0.21$), had a larger RV (RVEDV 155 (42) ml/m² versus 130 (33), $p < 0.05$) and tended to have poorer RVEF (47 (5)% versus 50 (7), $p = 0.06$). CR of both ventricles was not different between patients with and without TR.

Neurohormonal markers

Blood sample collection failed in two subjects. Measurements are shown in Table 3 with the large majority of values within normal limits. TNF-alpha significantly decreased with age ($r_s = -.57$, $p < 0.001$), hsCRP significantly increased with age ($r_s = 0.41$, $p < 0.05$) and $\log_{10}$NT-proBNP showed a significant non-linear relation with age (age²-factor required during analysis). No further

relations were found with age. Mean log_{10}NT-proBNP level was significantly higher in females (mean (±SE) difference log_{10}NT-proBNP (pmol/L) 0.34 (±0.08), $p < 0.001$). Mean log_{10} renine level was significantly lower in women (mean (±SE) difference –0.23 (±0.08), $p < 0.01$). No further gender determined differences were found.

No differences were found for any of the neurohormonal markers between subgroups based on RVEDV (Table 3) or subgroups based on PR-percentage (Data not shown). Neurohormonal marker levels were not different between patients with or without a transannular patch, or patients with or without tricuspid regurgitation.

In adulthood an NT-proBNP > 18 pmol/L in females and > 12 pmol/L in males indicate an increased risk for cardiac events such as heart failure.[15] Eight (62%) females and 14 (28%) males showed high-risk levels respectively. These 22 patients showed smaller RV-CR (9 (5) versus 12 (5) %, $p < 0.05$), smaller ΔRVESV (−14 (8) versus −19 (8) ml/m², $p < 0.05$) and smaller ΔLVESV (−9 (4) versus −13 (6) ml/m², $p < 0.05$) compared to patients without high-risk NT-proBNP levels.

The median hsCRP level was 0.7 mg/L (range 0.2 − 17.5). Mean interval since repair was longer in patients with levels > 0.7 mg/L compared to patients with hsCRP levels ≤ 0.7 mg/L (16 (5) versus 13 (5) years, $p < 0.05$). Patient with higher hsCRP levels tended to have worse $VO2_{max}$ (92 (17)% versus 86 (13)%, $p = 0.05$) and workload $_{max}$ (86 (13)% versus 92 (12)%, $p = 0.09$). No difference in any of the CMR parameters was found between both groups.

CMR stress response: relation to function and follow-up time

Relation to interval since repair: Biventricular CR did not correlate with interval since repair. Larger ΔESV and ΔCI correlated with a longer interval since repair (ΔRVESV: $r_s = 0.39$, $p < 0.01$, ΔRVCI: $r_s = 0.35$, $p < 0.05$, ΔLVESV: $r_s = 0.30$, $p < 0.05$, ΔLVCI: $r_s = 0.32$, $p < 0.05$).

Relation to exercise capacity: Larger ΔRVESV correlated with worse $VO2_{max}$ ($r_s = -0.29$, $p < 0.05$) and $Workload_{max}$ ($r_s = -0.35$, $p < 0.05$). RV-CR did not correlate with $VO2_{max}$ or $Workload_{max}$. Larger ΔLVSV correlated with worse $VO2_{max}$ ($r_s = -0.34$, $p < 0.05$). Larger ΔLVESV correlated with worse $Workload_{max}$ ($r_s = -0.34$, $p < 0.05$). Larger LV-CR correlated with worse $VO2_{max}$ ($r_s = -0.34$, $p < 0.05$) and $Workload_{max}$ ($r_s = -0.40$, $p < 0.05$).

Relation to RVEF and LVEF at rest: Larger ΔRVESV (r_s = −0.45, p < 0.001) and larger ΔRVSV (r_s = −0.35, p < 0.05) correlated with worse RVEF. Worse LVEF correlated with larger ΔRVESV (r_s = −0.38, p< 0.01), ΔRVSV (r_s=-0.41, p < 0.01), ΔLVESV (r_s = −0.36, p < 0.01), Δ LVSV (r_s = −0.49, p < 0.001) and LV-CR (r_s = −0.38, p < 0.01).

Discussion

At mid-term follow-up since surgical correction this study assessed levels of neurohormonal markers, biventricular systolic stress response and exercise performance in a relatively large population of TOF patients and related results to RV size and PR-percentage. This population generally is considered to have an increased risk for heart failure development.[1,7,12,16] Despite important dilatation of the RV in these patients with a median PR-percentage of 37%, the neurohormonal levels and biventricular CR were remarkably normal. Neurohormonal levels, biventricular CR and $VO2_{max}$ did not directly relate to amount of PR, RV size or longer duration of follow-up. The magnitude of the RV response was not different between patients with and without a transannular patch.

Neurohormonal markers and cardiac function

Increased levels of neurohumoral markers have been recognized as (early) signs of heart failure in acquired cardiac disease.[17-21] Elevated levels of these markers have prognostic value for decreased ventricular performance, functional class and survival.[2,17-21]

Adults with congenital heart disease, even when asymptomatic, were shown to have elevated levels of neurohormones, which related to decreases in NYHA class, systemic ventricular function and exercise capacity.[5] In children with various types of heart disease BNP levels correlated with clinical signs of heart failure and with systemic ventricular function.[22] In (asymptomatic) adults with isolated RV pressure (or volume) overload levels of natriuretic peptides inversely related to RVEF.[6] The large majority of our patients had normal levels of neurohormones. None of the markers showed significant relations to the degree of RV dilation, to biventricular systolic function (EF), or to the

magnitude of biventricular CR. A weak, but statistically significant positive association was established between NT-proBNP levels and the amount of PR measured, confirming stronger relationships assessed in adults.[6] Risk levels of NT-proBNP were found in 22(44%) patients.[15] These patients showed smaller biventricular ΔESV with stress and smaller RV-CR compared to other patients. Patients with hsCRP levels above the median tended to have worse exercise capacity compared to the others. Despite the overall normal CR, exercise performance and levels of neurohormones, the (limited) changes in biomarker levels found related to relevant RV loading condition abnormalities, decreased ventricular stress reserve and worse functional capacity. This can be interpreted as confirmation of the diagnostic potential of cardiac biomarkers, especially hsCRP and NT-proBNP, as early signs of activated compensatory mechanisms in abnormal ventricular loading conditions.[17,19] However, correlations were poor and these markers did not correlate with resting ventricular size and EF.

Ventricular stress response

Previous studies have documented an impaired RV systolic stress response in TOF patients.[23,24] In our study the changes of end-systolic volume, stroke volume and EF with stress were comparable to those commonly found in healthy young subjects.[23,24] The different results most likely reflect differences in populations studied. While most studies commonly include patients operated at various ages and with a variety of residual lesions, we selected patients treated according to recent surgical strategies, operated below the age of 2 years, and with few residual lesions.

The left ventricular analogue of PR is chronic aortic regurgitation. In asymptomatic patients with aortic regurgitation impaired LV stress reserve predicted LV dysfunction, development of symptoms and cardiac death.[11,25] Importantly, positive LV stress reserve before aortic valve replacement, predicted favourable post-operative LV function.[11] Data on RV stress reserve is limited. In patients with congenital heart disease and a negative CR, a higher CR (closer to zero) was associated with a higher $VO2_{max}$, while as in our patients there was no correlation between positive values of RV-CR and $VO2_{max}$.[10] Blunted response to beta-adrenergic stimulation in heart failure is considered an early sign of ventricular dysfunction.[11,25,26] Despite considerable RV dilatation our patients showed well preserved ventricular functional

reserve. Larger CMR parameter changes occurred in patients with a longer interval since repair, with worse $VO2_{max}$ and with poorer biventricular EF. It could be speculated this indicates up-regulation of pathways that promote ventricular contractility, such as the beta-adrenergic receptor pathway. This hypothesis is supported by recent findings in rats that showed up-regulation of the β-adrenergic receptor signal transduction pathway in failing hearts and an augmented inotropic response to isoproterenol.[27] Results on this subject however are equivocal, which calls for future studies on adaptations in the beta-adrenergic signalling pathway with progression of heart failure in TOF. Our data certainly do not support a PR or RV ventricular volume related blunting of stress response. Of note, Geva and co-workers in one of the largest studies in TOF so far, could not establish a relationship between PR fraction and RV dimensions with impaired clinical status.[28]

Limitations

We used pharmacological stress rather than physical stress because of the limited bore diameter of our MRI-scanner, preventing adequate physical stress. The ventricular response to physical exercise and to dobutamine stress corresponds well in healthy controls.[23,24] Ethical limitations prevented the inclusion of healthy children.

Compared to ischemic heart disease testing we used low dobutamine doses. In paediatric practice, doses above 10 microgram/kg/min are poorly tolerated.[29] For assessment of abnormal stress reserve, low dose dobutamine is sufficient.[29]

The cross-sectional study design prevented assessment of possible relations between our results and important outcome measures such as mortality, ventricular arrhythmia's or re-operation, including pulmonary valve replacement. In contrast to most studies in the field this study prospectively included a homogeneous patient population. Results therefore apply to a large set of the current population of Fallot patients, not confounded by a mix of different operative strategies and various types of residual lesions.

Clinical implications

Most studies on pulmonary valve replacement in TOF emphasize the importance of RV size as criterion for replacement and have used a mixture of additional criteria, acknowledging the limited value of clinical signs and symptoms in congenital heart disease.[7,12,16,30] Our study demonstrates that resting RV size and PR fraction do, at best, have poor correlation with impaired exercise capacity, biventricular stress response or neurohormonal activation, in a population operated according to current surgical strategies. In our opinion, this implies that patients should not undergo pulmonary valve replacement based on RV volume or PR fraction criteria.[16] Clear signs for structural heart disease resulting in neurohormonal activation and blunted stress response should be looked for.[3,4] Prospective longitudinal studies based on this concept, beneficially applied in LV disease states, should provide improved criteria for treatment strategies in the growing population of patients operated for tetralogy of Fallot.

Conclusions

In TOF repaired at young age overall neurohormonal markers are normal and cardiac functional reserve and exercise tolerance are well preserved, irrespective of PR-percentage and RV volume. This questions the validity of PR or RV volume criteria for pulmonary valve replacement in this age group. Low-dose dobutamine stress testing is well tolerated and may be a useful additional tool for clinical decision making.

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Changes during exercise of ECG predictors of ventricular arrhythmia in repaired Tetralogy of Fallot

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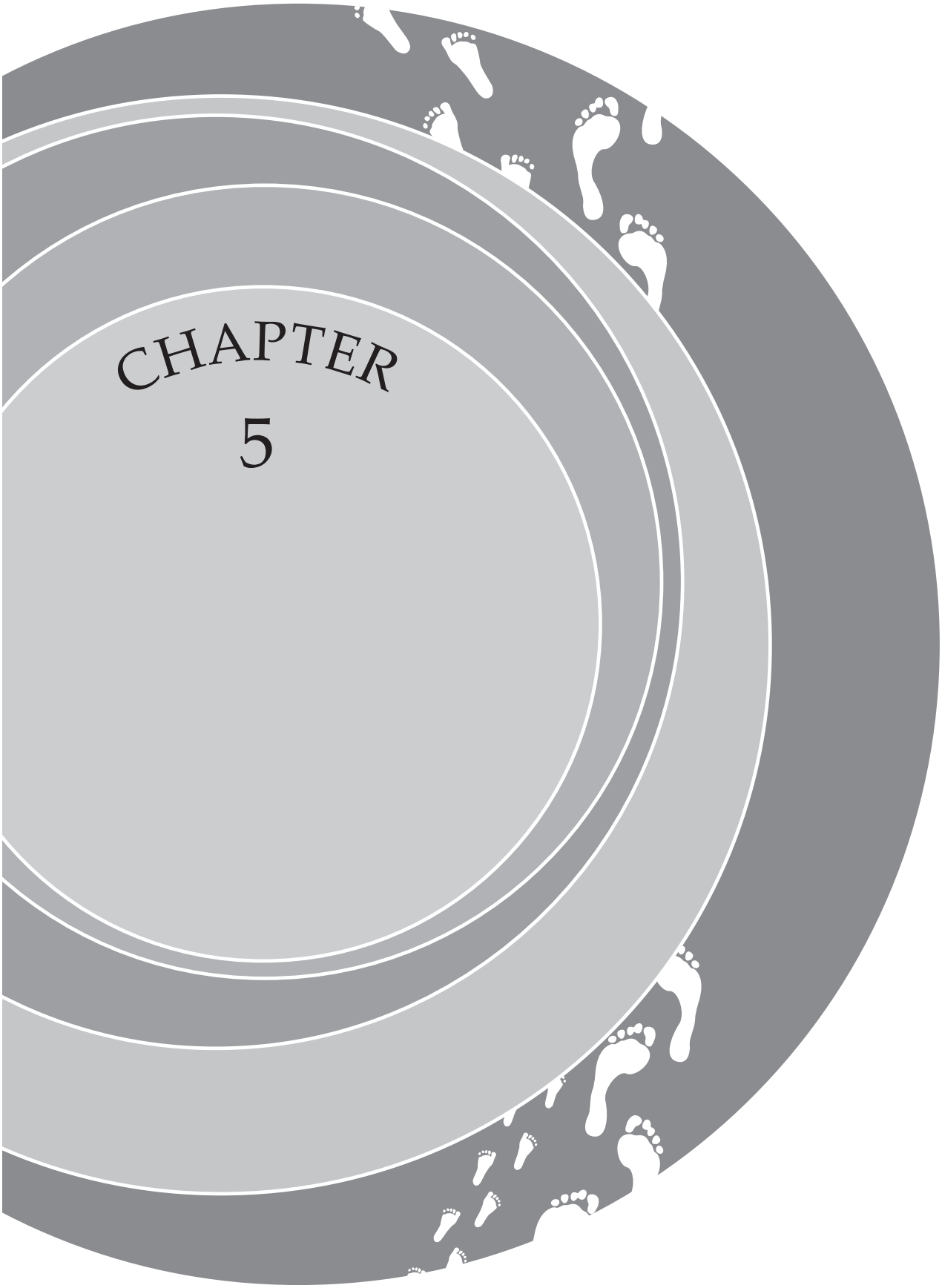
CHAPTER
5

Abstract

Purpose: Our study aimed to assess pro-arrhythmogenic electrocardiographic changes during maximal physical exercise in patients operated for Tetralogy of Fallot (TOF).

Methods: TOF patients prospectively underwent: 1) bicycle ergometry, 2) cardiac MRI, and 3) 24-hours Holter. ECG data was analyzed at rest, at 60% of peak exercise and at peak exercise. R-R duration, QRS-, QT- and JT-duration and dispersions were assessed. Changes of ECG parameters during exercise were calculated and correlated to RV volume, RVEF, RV wall-mass, PR-percentage and VO_{2max}. Exercise ECG data from healthy controls were used as reference.

Results: Thirty-one patients (mean age at repair (SD) 0.8 (0.5) years, age at study 16 (5) years) and 25 controls (age 12 (2) years) were included. With exercise mean QTc and JTc dispersions increased in patients ($p < 0.001$), but not in controls. At peak exercise JTc dispersion was larger in patients ($p < 0.01$). QTc did not change with exercise in patients ($p = 0.14$) and decreased in controls ($p < 0.05$). At all levels of exercise mean QTc, QRS and QRS dispersion were larger in patients (all $p < 0.001$). Significant associations were found for; 1) A larger increase of JTc dispersion with a higher PR-percentage, a larger RV volume, a larger RV wall-mass, 2) A larger QTc increase with a larger RV volume and worse RVEF.

Conclusion: During physical exercise inhomogeneity of repolarisation, known to predispose for re-entry ventricular arrhythmia, increases in repaired TOF. Larger inhomogeneity is found with more severe PR.

Introduction

Long-term survival after repair of tetralogy of Fallot (TOF) is good but below life expectancy in the general population.[1,2] Sudden cardiac death (SCD), a major cause of late mortality in repaired TOF,[1,2] often is attributed to ventricular arrhythmia.[3] Several factors have been associated with ventricular arrhythmia including elevated RV pressures, RV scarring, RV outflow tract patches, older age at repair, residual pulmonary regurgitation (PR), ventricular dilation and dysfunction.[3-6] Risk stratification for SCD in repaired TOF successfully focused on indicators of electrical inhomogeneity in the surface electrocardiogram (ECG) to predict ventricular arrhythmia.[3,5,7] QRS prolongation is considered the main marker associated with an increased risk of ventricular arrhythmia,[3,5,7-9] but other markers, such as prolonged QT-duration and increased dispersions of QT, JT and QRS have also been reported.[5,7,9] Residual PR appears the most important hemodynamic lesion associated with ventricular tachycardia (VT) and SCD in repaired TOF.[3] The contribution of PR to electrical inhomogeneity is reflected by prolonged QRS duration and increased QRS dispersion associated with RV dilation.[5,6,10,11] Exercise is considered a predisposing factor for ventricular arrhythmia in congenital heart disease.[12,13]

However, ECG markers for arrhythmia risk in TOF have all been established at rest in patients after (staged) transventricular repair performed at a relatively old age. Almost no data is available on electrocardiographic changes during physical exercise. One recent study showed that QRS shortening during exercise related to better exercise capacity.[14] Our study aimed to assess pro-arrhythmogenic electrocardiographic changes during maximal physical exercise in TOF repaired according to contemporary surgical techniques.

Methods

Patients

Between September 2002 and November 2004 a cross-sectional study was performed at our institution among 59 Fallot patients (41 males, 18 females; median age 15 years (range 6 − 23 years); median interval since repair 14 years (range 6 − 23 years). Patients prospectively underwent 1) bicycle ergometry, 2)

cardiac magnetic resonance imaging (CMR), and 3) 24-hours Holter monitoring. Patients were selected using the following criteria: 1) total surgical correction before the age of 2 years, 2) surgical correction by a transatrial-transpulmonary approach, 3) absence of residual intra-cardiac shunts, 4) a residual RV outflow tract Doppler gradient < 30 mmHg, 5) no associated cardiac anomalies. To be included in the present study a complete set of exercise ECG data, as defined in the 'ECG data analysis' section, was required. The local medical ethics committee approved the study protocol. Written informed consent was obtained from patients and/or parents (if patients were not the legal age to provide consent). Complete ECG data from 24 healthy controls that performed a maximal bicycle exercise test were retrospectively analysed for the present study.

Exercise testing

Patients performed a maximal bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany) allowing breath-by-breath monitoring. Workload was increased with 10 − 20 Watts/minute. Blood pressure, heart rate, oxygen saturation and a standardised 12-lead ECG (25 mm/s) were continuously monitored. Oxygen consumption (VO_2/kg) and carbondioxide excretion (VCO_2/kg) were measured. The respiratory exchange ratio (RER) was calculated (VO_2/VCO_2 = RER) to verify true maximal performance. The lower limit for RER was set at 1.0 in children and 1.1 in adults. Peak workload (Watts) and peak oxygen consumption (ml/kg) were compared to reference values, expressed as percentages of predicted, and are respectively referred to as W_{max} and VO_{2max}.[15]

ECG data analysis

ECG data were analysed by one observer at 3 predefined points of exercise: 1) at rest, 2) at the retrospectively determined 60% point of peak exercise, and 3) at peak exercise. ECG exercise data was defined complete when ≥ 10 out of 12 leads could be analysed at all predefined points. In every lead RR-interval, QRS-, QT- and JT-duration were manually measured. QT and JT duration were corrected for heart rate using Bazett's formula: QTc = QT/ √(RR-interval) and JTc = JT / √(RR-interval). Interlead dispersions of QRS, QTc, and JTc were

defined as the maximal minus the minimal interval. End of the T-wave was defined as the point where it crossed the iso-electric baseline, or where the tangent of it's downward slope crossed the iso-electric baseline. When the end of the T-wave was unclear QTc and JTc intervals were excluded from analysis for this lead. ECG parameter changes were calculated by subtraction of rest values from values at peak exercise.

Holter

A 24-hours Holter monitoring was performed. Patients were encouraged to participate normally in daily activities during the test.

Magnetic resonance imaging

Imaging was performed on a 1.5-Tesla Signa CV/i scanner using software releases V8.4 and V9.1 (GE Healthcare, Milwaukee, Wisconson, USA). Standardized localizer imaging planes were acquired for a flow-measurement of the pulmonary valve and a volumetric ventricular data set in short axis direction. Data was acquired during breath-holds at end-expiration. The volumetric data set was acquired using a 2D fast imaging employing steady-state free precession acquisition sequence (SSFP). Imaging parameters were: flip angle = 45º, TE set at min full, TR = 3.4 − 3.6 ms, 8 − 9 mm slice thickness, 0 − 1 mm inter-slice gap, 12 views/segment, readout bandwidth = 111Khz, a square FOV (30 − 34 cm), and a scanning matrix of 160 * 128. Twenty-four phases per cardiac cycle were reconstructed retrospectively.

Pulmonary valve flow measurements were performed perpendicular to flow using a standard 2D flow-sensitised retrospectively gated sequence starting the acquisitions on the R-wave. Flow sensitivity was set at 180 cm/sec and was increased if phase aliasing occurred. Thirty cardiac phases were reconstructed retrospectively. Imaging parameters were: 2D fast spoiled gradient echo, TR = 6 − 7 ms, TE = 3 ms, flip angle = 20º, readout bandwidth = 90 Khz, 6 mm slice thickness, 6 views/segment, a rectangular FOV and a scanning matrix of 256 *128.

CMR data analysis

CMR data analyses were performed by one observer on an Advanced Windows workstation (GE Healthcare, Milwaukee, Wisconson, USA). Flow images were quantitatively analysed using the Flow analysis software package V2.0 (Medis Medical Imaging Systems, Leiden, The Netherlands). Flow velocity curves were calculated by multiplying the manually drawn vessel area on each time frame with the spatial average flow velocities. The pulmonary regurgitant volume was divided by the systolic stroke volume in the main pulmonary artery to calculate PR-percentage. Patients were divided according to severity of residual PR: group A with mild PR (PR-percentage < 20%), group B with moderate-severe PR (PR-percentage 20 − 40%) and group C with severe PR (PR-percentage > 40%).[16]

The volumetric data set was quantitatively analysed using the Mass analysis software package V3.1 (Medis Medical Imaging Systems, Leiden, The Netherlands). End-diastolic and end-systolic time frames were used according to analysis techniques widely reported in literature to assess biventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and wall mass.[17] Volumes were indexed for body surface area (BSA) unless stated otherwise. Patient data were compared to published CMR reference values from healthy controls of the same age range.[18] Patient data outside the mean ± 2SD range found in controls were considered abnormal.

Statistical analysis

Results were expressed as mean (SD) unless stated otherwise. Electrocardiographic data was compared between patients and controls using analysis of covariance with adjustment for current age. Changes in ECG parameters with exercise in our population were found not to relate with age and therefore were compared using Student T-tests or Mann-Whitney U tests (in case of non-normal distributed data). Paired data analyses were performed using paired T-tests or Wilcoxon Signed rank tests. Spearman's correlation coefficients (r_s) were used to assess relations between two parameters. Subgroups based on PR-percentage were compared using analysis of variance with the Bonferroni method used to deal with multiple group comparisons.

Analyses were performed using the SPSS-PC statistical software package version 11.0 (SPSS, Chicago, Il, USA). A p-value < 0.05 was considered to indicate significance for patients characteristics. In view of the multiple comparisons made for the ECG parameters (table 2), $p < 0.01$ (two-sided), was considered the limit of significance.

Results

Patients

A complete ECG data set, as defined in the ECG data analysis paragraph of the methods section, was available in 31 (53%) out of the 59 Fallot patients. Results apply to patients with complete ECG data. Characteristics of patients and controls are shown in table 1.

Exercise test

Due to technical problems breath-by-breath measurements failed in one patient. This 10-year-old patient reached a peak heart rate of 194 beats/min and was considered to have performed maximally. Based on our RER criteria the remaining 30 patients and all controls performed a maximal exercise test. Patients reached a lower W_{max} ($p < 0.05$) and VO_{2max} ($p = 0.07$) compared to controls. No exercise induced ventricular arrhythmias were seen.

Holter

During 24-hours Holter monitoring 1 patient had 1 episode of VT (3 complexes at 174 beats/min) and 1 patient had 29 episodes of VT (all 3 complexes, maximal rate 166/min).

CMR examination

Due to claustrophobia CMR was terminated prematurely in 1 patient. A median PR-percentage of 33% was found (range 0 − 53%). Patients were grouped according to severity of residual PR. PR-percentage was mild in 8(27%) patients

(group A), moderate-severe in 14(47%) patients (group B) and severe in 8(27%) patients (group C).

Mean RV end-diastolic volume was 139(± 41) ml/m². Twenty-five (83%) patients had a dilated RV compared to published data on healthy controls (RV end-diastolic volume > 97 ml/m² or > mean +2SD).[18] Mean RV end-systolic volume was 73(±27) ml/m². Mean RVEF was 49(±6) %. Sixteen (53%) patients had a decreased RVEF compared to published data on healthy controls (RVEF < 49% or < mean –2SD).[18] RV free wall-mass was 24(±6) g/m².[18]

PR-percentage correlated positively with RVEDV (r_s= 0.59, $p < 0.01$) and negatively with RVEF (r_s= −0.48, $p < 0.01$).

Table 1. Patient characteristics

Baseline	**Patients (N = 31)**	**Controls (N = 24)**
Male / Female	22 (71%) / 9 (29%)	15 (63%) / 10 (40%)
Age at study (years)	16 (5)*	12 (2)
BSA (m^2)	1.6 (0.4)	1.5 (0.2)
Age at repair (years)	0.8 (0.5)	----------
Interval since repair (years)	15 (5)	----------
Staged repair†	2 (6%)	----------
Transatrial patch	20 (65%)	----------
Exercise	**Patients (N = 31)**	**Controls (N = 24)**
Peak heart rate (beats/min)	180 (12)	180 (12)
Peak workload (Watts)	158 (60)	152 (39)
W_{max} (%)	90 (13)*	99 (15)
Peak oxygen consumption (ml/kg/min)	39 (9)	42 (8)
VO_{2max} (%)	93 (17)	102 (20)
RER	1.20 (0.08)*	1.15 (0.08)

Data given are: number of patients (%) and mean (SD)

* Significant difference ($p < 0.05$) compared to controls

† Blalock Taussig shunt.

BSA= body surface area; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction, RER = respiratory exchange ratio, W_{max} = percentage of predicted peak workload, VO_{2max}= percentage of predicted peak oxygen consumption

ECG data analysis

ECG results are shown in Table 2. For ECG parameters that showed a significant change during exercise or a significantly different change with exercise compared to controls, relations were explored with: RVEDV, RV wall-mass, RVEF, PR-percentage and VO2max.

Ventricular depolarisation

Mean QRS duration and dispersion were significantly ($p < 0.001$) longer in patients than controls at all levels of exercise. QRS duration in none of the patients exceeded 170 ms. During exercise no significant change for mean QRS duration and dispersion were found within either patients (respective p-values; $p = 0.86$ and $p = 0.10$) or controls (respective p-values; $p = 0.18$ and $p = 0.26$). Mean changes for both parameters were also not different between patients and controls (respective p-values; $p = 0.43$ and $p = 0.14$).

Ventricular repolarisation

During exercise patients showed no mean change in QTc duration ($p = 0.14$), while in controls QTc tended to decrease ($p = 0.02$), which resulted in a significantly different mean change in QTc duration. In patients the change in QTc duration correlated positively with RVEDV ($r_s = 0.42$, $p = 0.02$) and RV wall-mass ($r_s = 0.43$, $p = 0.02$), and correlated negatively with RVEF ($r_s = -0.46$, $p = 0.01$).

Patients showed a significant increase of QTc dispersion ($p < 0.001$) with exercise, while in controls the increase in QTc dispersion approached the level of significance ($p = 0.02$). Mean QTc dispersion at peak exercise was not different at peak exercise ($p = 0.05$). Patients already showed a significant increase in QTc dispersion from rest to submaximal exercise ($p = 0.001$). The change in QTc dispersion showed no significant correlation with any of the clinical parameters.

Patients showed a significant increase in mean JTc dispersion ($p < 0.001$) while controls showed no change ($p = 0.07$). Mean JTc dispersion at peak exercise was larger in patients compared to controls ($p < 0.01$). In patients a larger increase of JTc dispersion correlated with a larger RVEDV ($r_s = 0.50$, $p = 0.005$), a larger RV wall-mass ($r_s = 0.47$, $p = 0.009$) and a larger PR-percentage ($r_s = 0.41$, $p = 0.03$).

Table 2. ECG data and changes during exercise

	Rest		Submaximal Exercise		Peak Exercise		Change§	
	Patients	**Controls**	**Patients**	**Controls**	**Patients**	**Controls**	**Patients**	**Controls**
QRS (ms)	113 (18)†	77 (3)	114 (18)†	78 (4)	113 (16)†	78 (4)	0 (6)	1 (3)
QT (ms)	336 (20)†	310 (30)	269 (22)†	244 (20)	246 (18)†	216(17)	−89 (17)*	−96 (29)*
QTc (ms)	409 (25)	386 (27)	415 (24)†	380 (22)	419 (35)†	373 (28)	10 (38)‡	−15 (29)
JT (ms)	222 (20)	232 (30)	155 (21)	165 (22)	132 (16)	137 (17)	−90 (18)*	−96 (29)*
JTc (ms)	270 (22)	289 (27)	238 (26)	257 (26)	225 (25)	238 (29)	−45 (27)*	−53 (29)
QRSd (ms)	25 (9)†	16 (6)	24 (10)†	13 (7)	26 (8)†	14 (6)	1 (8)	−2 (6)
QTcd (ms)	45 (10)	45 (11)	62 (23)	51 (16)	62 (20)	53 (11)	17 (22)*	9 (16)
JTcd (ms)	52 (14)	46 (11)	59 (20)	56 (19)	72 (23)‡	55 (16)	20 (26)*	9 (19)

Data given are: Mean (SD)

* Significant change ($p < 0.001$) from rest to peak exercise

† Significant difference ($p < 0.001$) between patients and controls (Ancova with adjustment for age)

‡ Significant difference ($p < 0.01$) between patients and controls

§ Change from rest to peak exercise

In addition differences among PR subgroups for ECG parameter changes from rest to peak exercise were explored. As is shown in Figure 1 the change in JTc dispersion with exercise was larger in group C (severe PR) compared to groups A (mild PR) and B (moderate PR). No further significant differences were found among subgroups. JTc dispersion at peak exercise was larger in group C compared to group A (88 (±27) ms versus 57 (±11), p = 0.03).

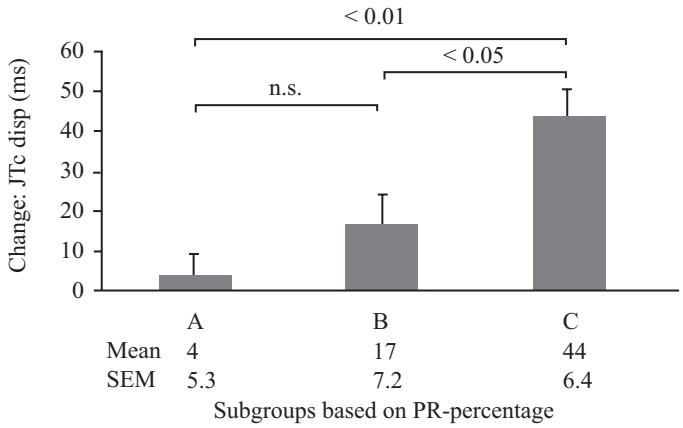

Figure 1. PR related changes of JTc dispersion from rest to peak exercise.
Data are expressed as mean ± SEM
PR subgroups; A – Mild PR (< 20%); B – Moderate PR (20 – 40%); C – Severe PR (> 40%)

Discussion

Our study assessed changes in the surface ECG of Fallot patients during maximal physical exercise to assess pro-arrhythmogenic electrocardiographic signs. Findings in patients were compared to findings in healthy controls. Differences found at rest between patients and controls confirmed those of earlier studies.[4,19,20] Differences in ECG changes with exercise between TOF patients and healthy controls pointed towards inhomogeneity of repolarisation, known to predispose for re-entry ventricular arrhythmia. During exercise both QTc and JTc dispersion increased in patients, while controls showed no change. At peak exercise this resulted in a significantly larger mean JTc dispersion in patients and the tendency for a larger mean QTc dispersion compared to controls. Furthermore patients showed significant lengthening of mean QTc

during exercise, while in controls QTc remained unchanged, which resulted in a significantly different change of mean QTc duration between patients and controls.

In addition our study explored possible relations of the observed ECG changes during exercise in patients with other parameters of clinical state. A larger increase in QTc correlated with a larger RV volume and worse RV systolic function. A larger increase in JTc dispersion correlated with more severe PR, a larger RV volume and larger RV wall-mass. In our population PR was the only residual defect of importance after correction. Therefore, patients were compared according to severity of PR. Patients with severe PR showed a significantly larger increase of JTc dispersion, and had a larger JTc dispersion at peak exercise compared to patients with mild PR.

Ventricular depolarisation

QRS duration and dispersion reflect ventricular depolarisation. Prolonged QRS duration, > 170 ms in children and > 180 ms in adults, is regarded the main risk factor for arrhythmia and SCD in repaired TOF.[3,5,7-9] As in previous studies mean QRS duration in our Fallot patients was significantly longer compared to controls.[4,6] However QRS duration did not exceed 170 ms in any of our patients. Previous papers reported a decrease of QRS duration with exercise in healthy subjects.[21-23] In coronary artery disease QRS prolongation during exercise indicated ischemia,[22,24] with the largest increase found in patients with documented exercise induced ventricular arrhythmia.[25] These observations have been explained by local exercise induced ischemia with subsequent local conduction delay.[25] We did not find evidence for altered conduction delay with exercise in repaired TOF or our controls. Recently, Budts et al. found QRS shortening with exercise relates to better exercise performance in repaired TOF. We did not find a relation of the change of QRS with VO_{2max}.[14] This may in part be explained by our relatively narrow range of QRS changes.

Like others we found that at rest TOF patients have significantly larger QRS dispersion than controls.[6] A larger QRS dispersion predicted (sudden) cardiac death in chronic heart failure.[26,27] In TOF a larger QRS dispersion was found in patients with VT compared to patients without VT.[7] A QRS dispersion > 35 ms (retrospectively) identified TOF patients with sustained VT.[7] Compared to patients with normal wall motion TOF patients with local RV wall-motion

abnormalities were shown to have larger dispersions of QRS, QT and JT.[28] This suggests a link between inhomogeneous RV mechanics (and possibly myocardial structure) and inhomogeneous RV conduction. Our range of findings for QRS dispersions at rest is comparable to the findings of Gatzoulis et al. in patients without VT.[7] In addition we showed QRS dispersion does not change during exercise in TOF repaired according to contemporary surgical techniques, even with PR fraction exceeding 40%. Based on our data, exercise does not seem to increase depolarisation inhomegeneity in these patients.

Ventricular repolarisation

QT(c) and JT(c) duration and dispersions represent ventricular repolarisation and can be used effectively to identify susceptibility for ventricular re-entry and sustained ventricular tachycardia.[4] As in previous reports we found mean QTc is prolonged in TOF ($p = 0.01$ at rest).[4,6] Gatzoulis *et al*. found that patients with documented sustained VT have a longer QT duration compared to other Fallot patients.[7] With exercise QTc shortened in our healthy subjects, while we found no mean change of QTc in Fallot patients. Nevertheless, a larger change in QTc duration with exercise correlated with more severe RV dilation and worse RV systolic function.

Larger dispersions of QTc and JTc represent inhomogeneity of repolarisation and increase the risk for ventricular arrhythmias.[29,30] Compared to controls a larger dispersion of ventricular repolarisation was found in patients with ventricular tachycardia/fibrillation.[29] QTc dispersion increased during exercise in patients with angina pectoris as well as in patients with isolated myocardial bridging,[31,32] while no change or a decrease was seen in healthy controls.[30-32] In chronic heart failure a larger QTc dispersion predicted SCD.[27] In TOF increased values for QT(c) and/or JT(c) dispersion were found.[4,6,33] Fallot patients with sustained VT had larger QT and/or JT dispersions than other Fallot patients.[7,33] In our patients QTc and JTc dispersions increased during exercise while controls showed no change for both parameters. Furthermore patients with severe PR showed a larger increase in JTc dispersion compared to those with mild or moderate residual PR. As such our findings indicate possible increased susceptibility to arrhythmia associated with physical exercise in Fallot patients, especially in those with severe PR.

Clinical relevance

We found mean QRS duration, QTc duration and QRS dispersion in our patients were significantly larger compared to controls. However individual values for QRS duration (considered the simplest and most practical predictor of sustained VT) remained well below the previously determined risk limits.[7] Our findings may reflect the positive influence of the surgical technique used, as less QRS prolongation and life threatening arrhythmia have been reported after transatrial-transpulmonary repairs of TOF compared to transventricular repairs.[4,34]

Physical exercise is considered a provocative factor for arrhythmia and SCD in a variety of congenital heart diseases.[12,13] Our study established an increase in electrical inhomogeneity of repolarisation with exercise, which is know to predisposes for ventricular re-entry arrhythmia.[4] Furthermore our data showed more severe PR and more severe RV dilation correlated with larger electrocardiographic abnormalities during exercise, although the relations found were generally weak. As such our study may contribute to an improved rationale for the recommendations made on exercise restriction in TOF patients with severe PR.[13] Our data may be interpreted as additional suggestion for the importance of correction of PR in arrhythmia management. Pulmonary valve replacement has been shown effective for elimination of PR and reduction of QRS-duration.[35,36] However effects of pulmonary valve replacement on long-term functional status and survival are not yet clear and criteria for optimal timing have not yet been established. To further determine the potential role of ECG changes with exercise in the management of patients with repaired TOF, we propose these measurements should be included in future studies on risk stratification for ventricular arrhythmia and/or optimal timing of pulmonary valve replacement.

Study design and limitations

We selected our TOF patients to represent the optimal result (no residual VSD or pulmonary stenosis of clinical importance) of generally accepted contemporary surgical techniques and focussed on PR related cardiac disease. We acknowledge our population represents only part to the total population seen in daily practice. However difficulties in data interpretation introduced

with various forms of ventricular overload, as apply to most studies in the field, are avoided by this study design. Furthermore residual PR is considered the most important hemodynamic lesion associated with both VT and SCD in repaired TOF.[3]

Our study does not contain longitudinal data and was not designed to determine cut off values for changes in ECG parameters with exercise predictive of ventricular arrhythmia or SCD.

Conclusions

During physical exercise inhomogeneity of repolarisation, known to predispose for ventricular arrhythmia, increases in repaired TOF. Larger electrical inhomogeneity is found with more severe PR.

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Aortic Distensibility and Dimensions and the Effects of Growth Hormone Treatment in the Turner Syndrome

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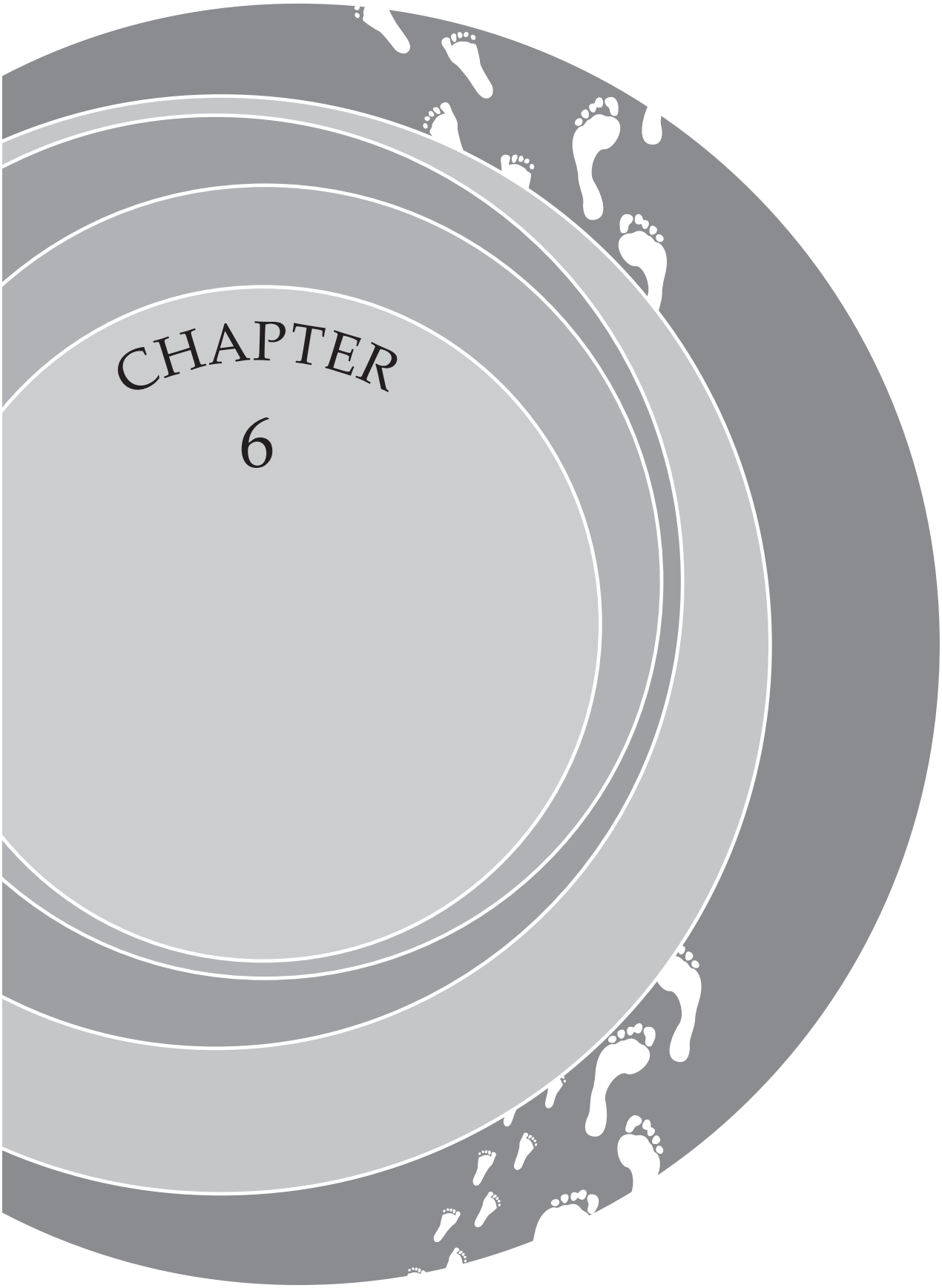

CHAPTER
6

Abstract

In the Turner syndrome (TS) an increased risk for cardiovascular malformations exists, including aortic dilation of unknown etiology. Abnormal biophysical wall properties may play an important role. Magnetic resonance imaging (MRI) has successfully been used to assess aortic size and wall distensibility. The aim of this study was to assess aortic biophysical properties and dimensions in the TS. We enrolled 38 former participants of our growth hormone (GH) dose-response study in the TS (age 12 ± 2, BSA 1.7±0.2), and 27 controls (age 21 ± 2, BSA 1.8 ± 0.1). Previously patients had been assigned to 1 of 3 groups, treated with different GH-dosages: group A – 0.045, B – 0.067 and C – 0.09 mg/kg/d. All underwent MRI at least 6 months after GH discontinuation to determine aortic dimensions and distensibility at 4 predefined levels: 1) ascending aorta, 2) descending aorta, 3) level of the diaphragm, 4) abdominal aorta. Patients had larger aortic diameters at all but level 4, and tended to have lower distensibility at level 3. Distensibility in group A was significantly lower compared to group C at level 4. Compared to controls group A had larger aortic diameters at all but level 4, and lower distensibility at level 4. Results in groups B and C were not different from controls. In conclusion, patients with the TS, formerly treated with GH, have a dilated aorta and signs of impaired wall distensibility. Severity of abnormalities seems related to GH dose, with a beneficial effect of a higher GH dose on the abnormalities.

Introduction

Structural cardiovascular malformations occur in up to 76% of patients with the Turner syndrome (TS).[1,2] Coarctation of the aorta and bicuspid aortic valve are most common and represent respectively 25 − 30% and 25 − 35% of cardiovascular malformations in the TS.[1-3] Aortic dilation has been regarded as less common (6.5%).[2] However, in recent studies using magnetic resonance imaging (MRI), aortic dilation was found in 25 − 50 % of patients with the TS and cardiovascular malformations.[1,3,4] The most common non-structural cardiovascular disease in the TS is arterial hypertension.[5] The number of reports on aortic dissection in the TS is increasing.[2,6] A function of the large arteries is the transformation of pulsatile flow into continuous flow, known as the "Windkessel" phenomenon. This phenomenon is determined by the biophysical properties of the aortic wall. Biophysical wall properties can be assessed using non-invasive imaging tools and allow in vivo quantification of the effects of altered arterial wall composition.[7] MRI has been proven accurate and reproducible for this purpose.[7] The aim of this study was to assess biophysical properties and dimensions of the aorta in TS.

Methods

For this prospective MRI-evaluation study we approached all 64 participants that completed our previous growth hormone (GH) dose response study in the TS.[8] Thirty-eight patients (59%) agreed to participate. During the GH-trial, biosynthetic human GH (Norditropin; Novo Nordisk A/S, Bagsvaerd, Denmark) was given in 3 different dosages; group A received 1.3 mg, B 2 mg, and C 2.7 mg GH/ m2 body surface area/ day (~ 0.045, 0.067, or 0.09 mg/kg/day), as described previously by van Pareren *et al*.[8] To induce puberty, micronized 17β-estradiol was given orally from the age of 12 years, after at least 4 years of GH-treatment. At start of GH-therapy diastolic blood pressure was significantly lower in group C compared to both other subgroups, resulting in a lower mean blood pressure in group C compared to group A. GH-therapy was continued until final height. All patients were at least 6 months after discontinuation of GH-treatment.

Twenty-seven healthy age, gender and body surface area (BSA) matched controls were included. Height, weight and blood pressures were measured, BSA was calculated. Besides the generally accepted contra-indications for MRI no exclusion criteria were used. The Medical Ethics Committee approved MRI-evaluation. Written informed consent was obtained from all participants.

MRI protocol

Imaging was performed on a General Electric 1.5 Tesla CV/i scanner (software release V9.1, Milwaukee, USA) using a 4-channel phased array torso coil. An anatomical overview of the area of interest was obtained in multiple directions using a bright blood imaging protocol, based on an ECG gated fat suppressed 2D single shot steady-state free precession technique. These images were used for planning subsequent scans. The aortic anatomy was imaged for reference using a high resolution magnetic resonance 3D angiography protocol and a double dose of Gd-DTPA (0.2 mmol/kg, Magnevist, Schering, Germany). Flow measurements were performed using a standard 2D flow-sensitized scan. The scans were planned perpendicular to the aorta at 4 predefined locations: 1) ascending aorta, level of the pulmonary artery bifurcation; 2) descending aorta, level of the pulmonary artery bifurcation; 3) descending aorta, diaphragm level; 4) abdominal aorta, level of the superior mesenteric artery (Figure 1A.). The flow sensitivity of the sequence was set to 180 cm/sec (increased if phase aliasing occurred) and the in-plane spatial resolution to 1 mm with a 256x256 scanning matrix.[7] Temporal resolution was approximately 50 ms and thirty cardiac phases were reconstructed retrospectively.[7] Breath-hold time varied between 25 − 40 sec per measurement depending on heart rate. Imaging parameters were: 2D FSPGR, TR = 6 − 7 ms, TE = 3 ms, flip angle = 20^{o}, readout bandwidth = 90 Khz, 6 mm slice thickness and 4 lines/segment. A fifth measurement was performed through the sinus of Valsalva to quantify aortic valve gradients. During each flow measurement, peripheral blood pressure was measured at the level of the brachial artery using a sphygmomanometer cuff.

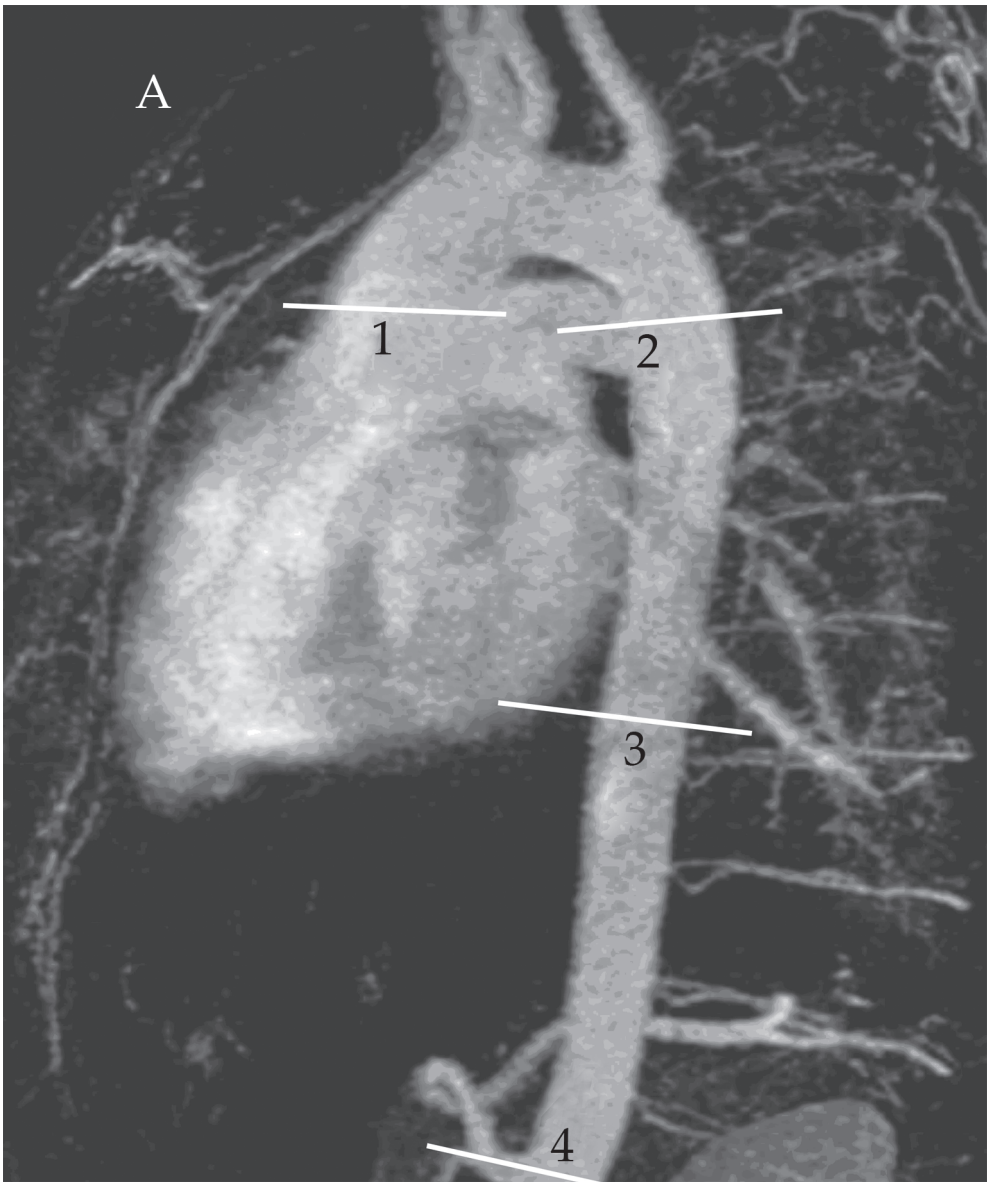
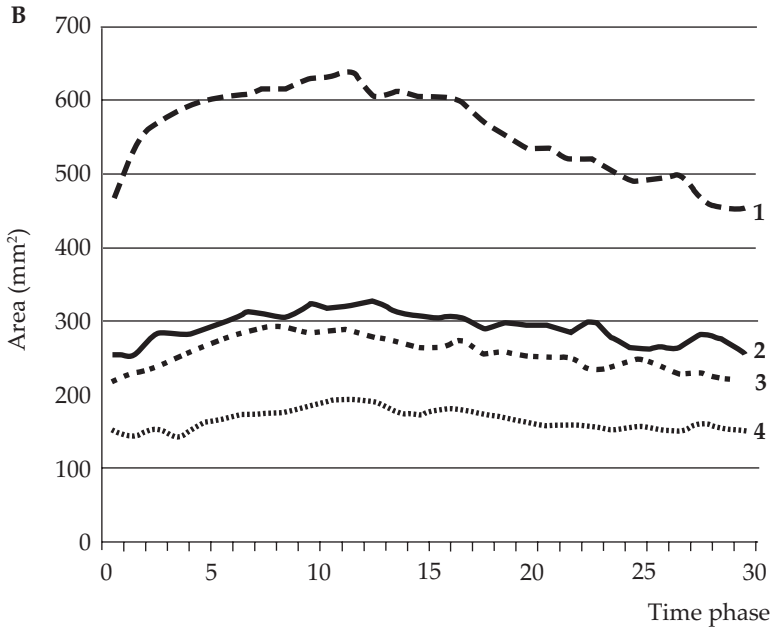


Figure 1. MRI angiography of the angiography of the in the Turner syndrome: a typical example.

A. The predefined levels of measurement

1. Ascending aorta. 2. Descending aorta. 3. Level of the diaphragm, and 4. Abdominal level



B. Aortic area (mm²) variation over the cardiac cycle

Image analysis and calculations

Flow images were quantitatively analyzed using the Flow analysis software package version 2.0 (Medis medical systems, Leiden, the Netherlands). Vessel areas were manually drawn for each cardiac phase (30 phases) and maximal and minimal aortic areas were selected (Figure 1B). Distensibility (10^{-3} $mmHg^{-1}$) defined as the relative area change for a pressure increment, was calculated by means of the following equation:[9]

D = (Amax−Amin) ÷ [Amin*(Pmax − Pmin)].

D = distensibility, Amax = maximal (systolic) aortic area (mm²), Amin = minimal (diastolic) aortic area, Pmax = systolic blood pressure (mmHg), and Pmin = diastolic blood pressure. Mean blood pressure was calculated using the equation:

Mean Blood Pressure = [(2*Pmin)+Pmax]/3.

Aortic diameters (mm²), aortic diameters indexed for BSA (mm/m²), and the ascending/descending aorta diameter-ratio were calculated using vessel areas. Patient values outside the mean ± 2SD range from our controls were considered abnormal. Pressure-gradients were calculated using the simplified

Bernoulli equation ($\Delta P = 4*Vmax^2$). At the sinus of valsalva, a maximal flow velocity of 3 m/s (gradient > 36 mmHg) was regarded to indicate an aortic valve stenosis of importance. A coarctation of the aorta was defined to be hemodynamically important in the presence of a pressure gradient > 20 mmHg (based on measurement of maximal flow velocity).

Statistical analysis

Analysis was performed using the SPSS-PC statistical software package version 11.5 (SPSS Inc, Chicago, Illinois). Results are expressed as mean ± SD. A P-value ≤ 0.05 was considered to indicate significance unless specified otherwise. Differences in aortic diameter and aortic distensibility between patients and controls were respectively tested using the independent t-test and analysis of covariance (with correction for systolic and diastolic blood pressures). To deal with multiple comparisons a p-value ≤ 0.0167 were considered to indicate significance when an individual GH-dosage group was compared to the controls. Differences between dosage groups were tested using analysis of variance for diameters and analysis of covariance (with correction for systolic and diastolic blood pressure) for distensibility. Two dummy variables were designed to distinguish between dosage groups. We corrected for multiple group comparisons by using the Bonferroni method. Spearman correlation coefficients were calculated for the assessment of bivariate correlations.

Results

Patients

The 38 TS patients included in the present study are a representative sample of the original population (see methods) based on voluntary participation in this MRI-evaluation. One patient previously received metal implants during scoliosis surgery and was excluded from final analysis because of substantial MRI artifacts**.** Characteristics of patients and controls are shown in Table 1. Between subgroups differences were only found for final height and blood pressure (Table 1). Mean plasma levels of high-density lipoproteins, low-density lipoproteins, triglycerides, Apolipoprotein A1, and Apolipoprotein B were normal and did not differ between subgroups (data not shown).

Cardiac history showed the following: bicuspid aortic valve in 10(26%), tricuspid aortic valve in 25(66%), and non-conclusive valve anatomy in the remaining 3 patients (one in each GH-subgroup). A bicuspid valve was diagnosed in 3 patients in group A, 5 patients in group B, and 2 patients in group C (n.s). In all but one patient the aortic valve pressure gradient was < 35 mmHg. One patient had severe aortic valve stenosis (Doppler peak velocity 5 − 6 m/s). One atrial septal defect type II had been surgically closed. Three other patients underwent surgical repair for aortic coarctation, with a residual but stable Doppler gradient of 15 − 20 mmHg in one.

Aortic anatomy

In 5 patients an anatomical aortic coarctation was diagnosed on MRI. Of these patients 2 had had a previous surgical coarctectomy. In 1 patient the aortic coarctation had not previously been diagnosed. A pressure gradient of importance was found in 2 of 5 patients (27 mmHg and 28 mmHg). In a sixth patient tapering of the descending thoracic aorta over a length of about 8 centimeters starting at the isthmus was observed. One patient had a right aortic arch. Peak velocity measurement at the sinus of Valsalva in the patient with known severe aortic valve stenosis was > 5.5 m/s (maximal setting) and < 3.0 m/s in all others. No pathology was found in controls.

Aortic diameters

The patient with severe aortic valve stenosis was excluded from analysis of ascending aorta diameters and the two patients with aortic coarctation with a gradient > 20 mmHg were excluded from the analysis of descending aorta diameters. All three were excluded from the analysis of the ascending/descending aorta diameter-ratio. Aortic diameters are shown in Table 2. The absolute ascending aorta diameter was dilated (> mean plus 2SD in controls) in 11(30%) patients, and the diameter indexed for BSA was dilated in 18(49%) patients. Ascending/descending aorta diameter-ratio was larger in patients (1.5 ± 0.3 in patients versus 1.4 ± 0.1 in controls, $p = 0.05$). In 13(35%) patients this ratio was abnormally high (> mean plus 2 SD in controls). No differences between subgroups were found.

Table 1. Characteristics of patients and controls

	Group A n = 13 (35%)	Group B n = 13 (35%)	Group C n = 11 (30%)	Total Patients n = 37 (100%)	Controls n = 27
Age (years)	20 ± 2	20 ± 2	19 ± 2	20 ± 2	21 ± 2
Height (cm)	158 ± 7*	164 ± 6*	165 ± 6*†	162 ± 7*	172 ± 7
Height standard deviation score ‡	−1.7 ± 1.2*	−0.7 ± 0.9*	−0.5 ± 1.0*†	−1.0 ± 1.2*	0.6 ± 1.1
Height gain (cm)§	12 ± 4	15 ± 4	18 ± 7	15 ± 5	-----
Height gain standard deviation score‖	1.7 ± 0.7	2.6 ± 0.8	2.0 ± 1.1	1.6 ± 0.9	------
BSA (m^2)	1.7 ± 0.2	1.8 ± 0.2	1.7 ± 0.1	1.7 ± 0.2	1.8 ± 0.1
Systolic blood pressure (mmHg)	129 ± 17*	116 ± 8†	113 ± 12†	119 ± 15	115 ± 10
Diastolic blood pressure (mmHg)	77 ± 12*	69 ± 8	64 ± 9†	70 ± 11*	64 ± 9
Mean blood pressure (mmHg)	94 ± 13*	84 ± 7	80 ± 10†	86 ± 12*	81 ± 9
Duration GH-Therapy (years)	9 ± 1	8 ± 3	9 ± 2	9 ± 2	-----
GH-discontinuation (years)	5 ± 2	5 ± 2	4 ± 2	5 ± 2	-----
Estrogen-Therapy (years)	8 ± 2	7 ± 2	6 ± 2	7 ± 2	-----

* Statistically significant difference compared to controls.
† Statistically significant difference compared to group A.
‡ Height for age: references healthy Dutch girls[24]
§ Final height − projected adult height at start of GH-treatment (calculated using the Lyon equation)[8]
‖ Final height standard deviation score − height standard deviation score at start GH therapy: references untreated Turner girls[25]

Table 2. Aortic diameters (mm/m^2)

	Controls	Total patients	Group A	Group B	Group C
Level 1	15.2 ± 1.2 n = 27 (100%)	17.6 ± 2.6*† n = 36 (97%)	17.4 ± 2.0† n = 13 (100%)	18.2 ± 3.3*† n = 12 (92%)	16.5 ± 1.6† n = 11 (100%)
Level 2	10.9 ± 1.2 n = 27 (100%)	11.8 ± 1.9† n = 35 (95%)	12.8 ± 2.2† n = 11 (85%)	10.9 ± 1.6 n = 13 (100%)	11.7 ± 1.4 n = 11 (100%)
Level 3	9.6 ± 0.7 n = 27 (100%)	10.4 ± 1.2* n = 36 (97%)	11.2 ± 1.4*† n = 13 (100%)	9.8 ± 0.6 n = 13 (100%)	10.3 ± 1.0 n = 10 (91%)
Level 4	8.5 ± 0.6 n = 27 (100%)	8.7 ± 0.9 n = 34 (92%)	9.1 ± 1.0 n = 13 (100%)	8.5 ± 0.7 n = 10 (77%)	8.6 ± 1.0 n = 10 (91%)

* Statistically significant difference compared to controls, absolute diameters (mm^2)

† Statistically significant difference compared to controls, diameters normalized for BSA (mm/m^2)

Table 3. Aortic distensibility (10^{-3} * mm Hg^{-1})

	Controls	Total patients	Group A	Group B	Group C
Level 1	5.3 ± 1.2 n = 27 (100%)	4.7 ± 2.3* n = 36 (97%)	4.1 ± 1.7* n = 13 (100%)	4.7 ± 2.5 n = 13 (100%)	5.5 ± 2.7 n = 10 (91%)
Level 2	5.2 ± 1.2 n = 27 (100%)	5.7 ± 2.4 n = 35 (95%)	5.0 ± 2.3 n = 11 (85%)	5.9 ± 2.4 n = 13 (100%)	6.3 ± 2.6 n = 11 (100%)
Level 3	7.5 ± 2.2 n = 27 (100%)	6.4 ± 1.9* n = 36 (97%)	5.4 ± 2.0* n = 13 (100%)	6.5 ± 1.5 n = 13 (100%)	7.4 ± 1.7† n = 10 (91%)
Level 4	8.4 ± 2.2 n = 27 (100%)	7.3 ± 2.5 n = 32 (86%)	5.8 ± 2.4*‡ n = 13 (100%)	8.1 ± 2.4 n = 10 (77%)	8.6 ± 1.9†§ n = 9 (82%)

* Statistically significant difference compared to controls

† Statistically significant difference compared to group A

‡ Statistically significant difference compared to controls with correction for diastolic blood pressure and systolic blood pressure

§ Statistically significant difference compared to group A with correction for diastolic blood pressure and systolic blood pressure

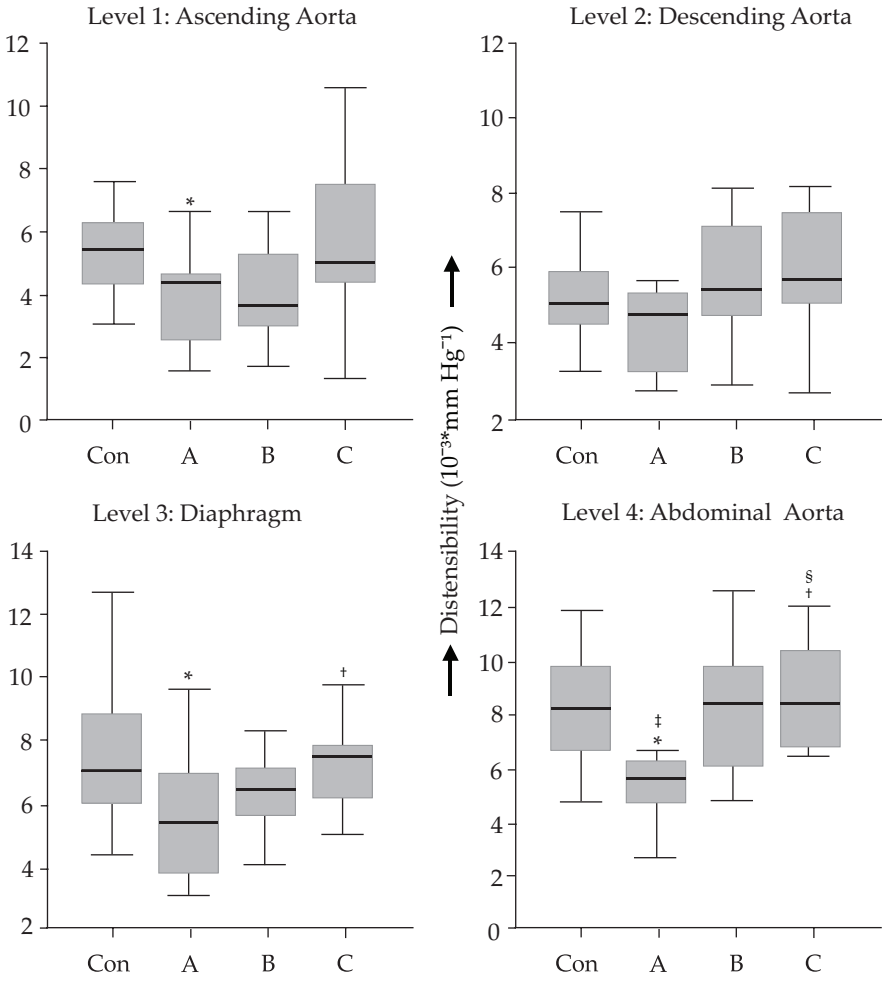
Aortic distensibility

The two patients with aortic coarctation were excluded from analysis of data for the descending aorta. Distensibility measurements are shown in Table 3 and Figure 2. Aortic distensibility correlated negatively with systolic and diastolic blood pressure at levels 3 and 4 (level 3: Systolic blood pressure $r = -0.67$, $p < 0.001$, Diastolic blood pressure $r = -0.39$, $p < 0.05$; level 4: Systolic blood pressure $r = -0.60$, $p < 0.001$, Diastolic blood pressure $r = -0.35$, $p < 0.05$). After correction for systolic and diastolic blood pressure patients still tended to have smaller distensibility at level 3 ($p = 0.07$). Analysis on GH subgroups showed aortic distensibility corrected for blood pressure in group A to be smaller at level 4, with a tendency for smaller distensibility at levels 1 ($p = 0.05$), and 3 ($p= 0.07$) compared to controls. Distensibility did not show a significant correlation with time duration since stop of GH-treatment at any of the levels of measurement.

Discussion

The present study shows that patients with the TS have larger aortic diameters (mm/m^2) at all thoracic levels of measurement and a larger ascending/descending aorta diameter-ratio compared to controls. Lower aortic distensibility was found at levels 1 and 3 before correction for blood pressure, and a tendency ($p = 0.07$) at level 3 after this correction in patients compared to controls. Therefore, we conclude the aorta in the TS shows abnormal dimensions and signs of impaired wall function. Furthermore we assessed the influence of received GH dose on aortic distensibility. We will discuss results corrected for blood pressure. Distensibility increased with increasing GH dose (Figure 2), which resulted in a significantly smaller distensibility in patients who received the lowest GH-dose compared to patients who received the highest dose at aortic level 4. Moreover we found group A to have lower aortic distensibility compared to controls at level 4 and a tendency towards lower distensibility at levels 1 ($p = 0.05$) and 3 ($p = 0.07$). No differences with controls were found in both other subgroups. Our results point towards normalization of aortic distensibility with increasing GH dose and suggest GH to have a beneficial influence on aortic wall properties in the TS.

Figure 2. Aortic distensibility per level of measurement



GH groups: Con = controls, A = 0.045 mg/kg/d
B = 0.067 mg/kg/d, C = 0.09 mg/kg/d

* Statistically significant difference compared to controls

† Statistically significant difference compared to group A

‡ Statistically significant difference compared to controls with correction for diastolic and systolic blood pressures

§ Statistically significant difference compared to group A with correction for diastolic and systolic blood pressures

Previous studies have shown mean aortic root diameter is larger in the TS compared to controls.[1,3,10] Dilation of the ascending aorta was found in 18 − 33% of patients.[1,10] Dilation and dissection most frequently (50 − 70% of cases), but not exclusively, occur in the ascending aorta.[(2,11)] We found ascending aorta diameter to be dilated in 11(30%) patients (> mean plus 2 SD in controls) and even in 18(49%) when diameter was indexed for BSA. In accordance with previous findings the ascending aorta/descending aorta diameter ratio was > 1.5 (a commonly used criterion for ascending aorta dilation) in 13(35%) of our patients.[1,4,12] In the TS the ascending/descending aorta diameter-ratio should be interpreted with some caution because of the frequently encountered abnormalities at the classical coarctation site that may influence this ratio.[1,6] Furthermore concurrent dilatation of ascending and descending aorta, like we found in TS, may result in false normal outcome of this ratio. We conclude that mean ascending aorta diameter is dilated in 30 to 50% of patients with the TS formerly treated with GH. Furthermore, we found dilation of the aorta is not limited to the aortic root and/or ascending aorta but is present throughout the entire thoracic aorta. Abnormalities were most prominent in patients that previously had received the lowest GH-dose.

The number of reports on aortic dissection in the TS, especially during pregnancy, is increasing.[2,6] Post-mortal findings similar to arterial cystic media degeneration seen in Marfan syndrome have been described in the TS.[2,13] Increased incidence of complications after surgery for coarctation has been reported in the TS as a result of apparent friability of the aortic wall.[2] A recent study showed increased carotid-femoral pulse wave velocity, increased carotid intima-media thickness, and a higher carotid augmentation index in TS.[10] These reports support the hypothesis that connective tissue abnormalities might play a role in Turner syndrome. Our findings, especially those in subgroup A, bear similarity with results found in Marfan syndrome on aortic wall distensibility and support the theory that connective tissue abnormalities play a role in aortic disease in the TS.[14,15] MRI-determined aortic distensibility has been shown to be decreased in a variety of cardiovascular diseases.[7] Our findings support the use of MRI-determined measurements for (early) detection of aortic wall dysfunction and quantification of intervention related effects on wall function.[7]

Aortic distensibility in normal subjects is negatively correlated with age, progression of atherosclerosis, an abnormal lipid profile and post-menopausal

state in women.[16,17,18] With increasing age plasma levels of anabolic hormones, such as GH and Insuline-like growth factor I, decline. GH replacement can reverse age related catabolic changes.[16] In women post-menopausal estrogen replacement therapy has been shown to reduce age associated increases in arterial stiffness.[17,18] Patients with GH deficiency show wall thickening of large arteries and a tendency towards decreased arterial wall compliance.[19,20] In response to GH treatment in GH deficiency arterial wall thickness decreased and compliance increased.[19,20] Our patient subgroups did not differ in 1) age, 2) plasma levels of cholesterol, triglycerides, Apolipoprotein A1 and Apolipoprotein B, or 3) estrogen treatment protocol. As all our patients were treated with GH we cannot quantify the sole effect of estrogen replacement therapy on aortic wall distensibility in the TS.

Elastic properties of the aorta depend on the presence, proportion and interaction of smooth muscles, collagen, and elastin proteins. This mixture of elements with different elastic properties results in a non-linear arterial pressure-volume relation. In rats, GH was found to influence collagen metabolism and change the mixture of fibrous elements in the aortic wall.[21] In young rats GH increased aortic extensibility.[21] In accordance with these findings our results in the TS indicate a positive effect of GH on aortic wall distensibility. Like others we found distensibility to negatively correlate with systolic blood pressure and diastolic blood pressure.[22] We therefore present distensibility results corrected for blood pressure. The aortic pressure-diameter curve has a linear, elastin-determined and an exponential, collagen-determined part. An increase in blood pressure within the exponential part results in a decrease of aortic distensibility.[23] With aging the curve shifts downward and to the right (age related aortic dilation), through what pressure-changes may occur in the exponential part.[23] In young subjects, like our patients, pressure changes are expected to occur in the linear part. However the degenerative aortic wall alterations described in the TS may change the age specific behavior. There is only little data on degenerative alterations in TS, no quantitative data on progression of such alterations over time, and no data on possible changes in wall composition in TS in relation to GH treatment.

Based on our data we think GH-treatment to have a (direct or indirect) beneficial effect on the biophysical properties of the aortic wall in TS. Further evaluation of the role of GH, arterial blood pressure, and their interaction on aortic distensibility in TS is required. Limitations of this study are that it

provides a cross-sectional evaluation in a population with a small age range, thus limiting analysis of age/time effects. This study was not designed to determine the optimal GH-dose leading to normal aortic function, or to determine the exact mechanism in which GH effects the aortic wall.

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Disproportionate cardiac size in adult Turner syndrome patients after growth hormone therapy during childhood

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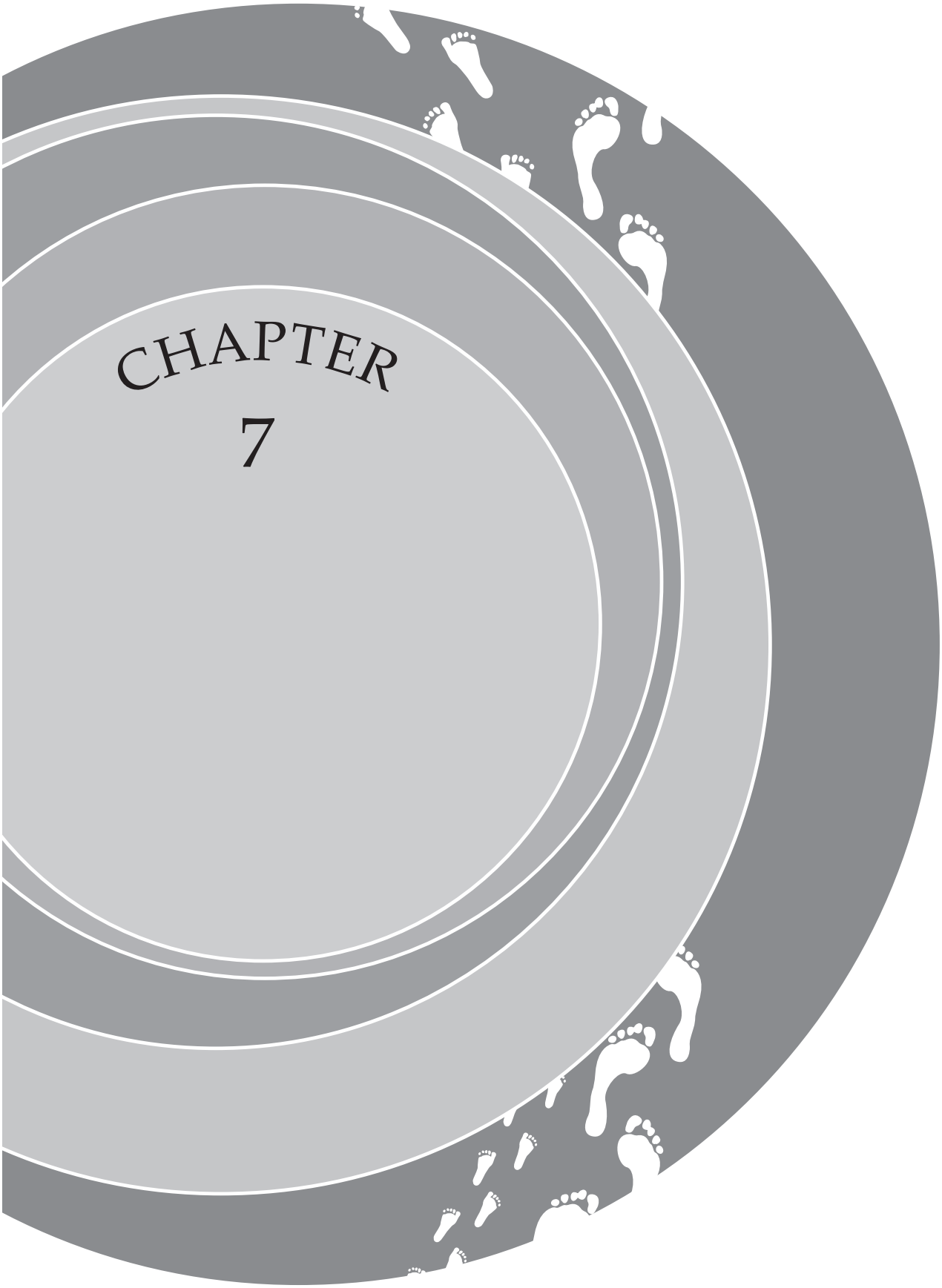
Submitted


CHAPTER
7

Abstract

Objectives: In Turner's syndrome (TS) growth hormone (GH) therapy is well established, but data on cardiac status following discontinuation of treatment are lacking. This study aimed to assess biventricular size and function in TS mid-term after discontinuation of GH-therapy.

Methods: TS patients (mean (SD) 5(2) years after GH discontinuation) and healthy women prospectively underwent cardiac magnetic resonance imaging (CMR). Ventricular 2D tomographic cine data was acquired to obtain biventricular volume, mass and ejection fraction. Mitral and tricuspid valve flow measurements were performed using a standard 2D flow-sensitized sequence. Flow velocity curves were calculated and indices of biventricular diastolic filling were derived.

Results: Thirty-three patients (mean (SD) age 20(2) years, BSA 1.75(0.15) m^2) and 23 controls (age 21(2) years, BSA 1.80(0.13) m^2) were included. Compared to controls patients had smaller mean end-diastolic volumes (RV, 84(11) ml/m^2 versus 79(11), p = 0.04; LV, 81(10) versus 72(10), p = 0.002), end-systolic volumes (RV, 38(7) ml/m^2 versus 36(6), p = 0.09; LV, 34(5) versus 28(6), p < 0.001) and stroke volumes (46(6) ml/m^2 versus 43(6), p = 0.06; LV, 47(7) versus 43(7), p = 0.07). Patients had a higher mean heart rate (79(13) beats/min versus 71(10), p < 0.05) and LVEF (61(5)% versus 58(4), p = 0.02). Biventricular mass, cardiac output and diastolic filling pattern were comparable.

Conclusion: Mid-term after discontinuation of GH therapy TS patients showed no myocardial hypertrophy and well-preserved biventricular function. Mean ventricular volumes in TS were smaller compared to controls, while comparable cardiac output was achieved at a higher resting heart rate, which may negatively impact long-term survival in TS.

Introduction

Turner's syndrome (TS) is characterized by a constellation of visible (dysmorphic) and non-visible physical findings caused by total or partial X-monosomy.[1] Common clinical findings is short stature. In northwestern Europe mean adult height in untreated TS is 142 to 147 cm, approximately 20 cm below normal average height in women.[2] Supra-physiological dosed growth hormone (GH) accelerates growth. In TS GH-treatment has been shown to normalize adult height in most patients and nowadays it is a well-established therapy.[2,3] In healthy controls supra-physiological dosed GH rapidly induces changes in left ventricular function (increased cardiac index) and size (hypertrophy and concentric remodeling).[4] Chronic GH excess in acromegaly is associated with increased cardiovascular morbidity and mortality.[5] Untreated acromegaly is associated with dynamic changes in cardiac structure and function that on the long-term may cause "acromegalic" cardiomyopathy and heart failure.[5,6] The GH dose normally used for treatment of short stature in TS is relatively high (1.4 mg/m² body surface area (BSA) /day in TS compared to 0.7 mg/m² BSA /day in GH deficiency). This raises concerns on possible cardiovascular side effects. We and others addressed these concerns in girls with TS during GH treatment and reported normal LV volumes without hypertrophy compared to controls.[7,8] However cardiac data mid- and long-term after discontinuation of GH treatment are lacking. Furthermore most previous studies focussed on LV size and function only. We hypothesize that myocardial effects of systemic GH treatment if present are biventricular. Cardiac magnetic resonance imaging (CMR) is the gold standard for determination of biventricular volumes, function and wall mass. The aim of his study was to prospectively assess biventricular size and function in TS mid-term after discontinuation of GH-therapy and compare results to healthy controls.

Methods

Thirty-three young women with TS, all former participants of our GH dose-response study, prospectively underwent CMR evaluation. The Medical Ethics Committee approved the study. Written informed consent was obtained from all participants. During the previous GH-trial, biosynthetic human

GH (Norditropin; Novo Nordisk A/S, Bagsvaerd, Denmark) was given. Patients were randomly assigned to 1 of 3 groups, treated with different GH-dosages: group I received 1.3, group II 2.0 and group III 2.7 mg/m² BSA /day as previously described by van Pareren *et al*.[3] To induce puberty, micronized 17β-estradiol was given orally from the age of 12 years, after at least 4 years of GH-treatment. At start of GH-therapy, there were no differences between groups in age, height or BSA. Diastolic blood pressure was significantly lower in group C compared to both other subgroups, resulting in a lower mean blood pressure in group C compared to group A. GH-therapy was continued until final height. At inclusion for CMR evaluation GH-treatment in all patients had been discontinued for at least 6 months. At our institution age-matched untreated TS patients are not available. Therefore 23 healthy age, gender and BSA matched controls were included. Height, weight, diastolic blood pressure and systolic blood pressure were measured. BSA, BMI and mean blood pressure were calculated. Besides the generally accepted contra-indications for MRI no exclusion criteria were used.

CMR protocol

Imaging was performed on a GE 1.5-T Signa CV/i scanner using software releases V8.4 and V9.1 (GE healthcare, Milwaukee, Wisconsin, USA) with a 4-channel phased-array coil. All images were acquired during breath-holds at end-expiration. A standardized multi-phase, multi-slice volumetric ventricular data set in short axis direction was acquired. Imaging was performed using a 2D fast imaging employing steady-state free precession acquisition sequence (FIESTA) with the following imaging parameters: flip angle = 45º, TE set at min full, TR = 3.4 − 3.6 ms, 8 − 9 mm slice thickness, 0 − 1 mm inter-slice gap, 12 views/segment, readout bandwidth = 111Khz, a square FOV (30 − 34 cm), and a scanning matrix of 160 * 128. Twenty-four phases per cardiac cycle were reconstructed retrospectively.

Mitral valve and tricuspid valve flow measurements were performed perpendicular to flow using a standard 2D flow-sensitized (phase velocity encoded) scan. Flow sensitivity of the sequence (VENC) was set at 120 cm/s. The VENC was increased with phase aliasing. Scans were retrospectively gated. Temporal resolution was approximately 35 − 50 ms per cardiac phase. Thirty phases were reconstructed retrospectively. Imaging parameters were:

2D FSPGR, TR = 6 − 7 ms, TE = 3 ms, flip angle = 20°, readout bandwidth = 90 Khz, 6 mm slice thickness, 6 views/segment, a rectangular FOV (75% in phase encoding direction), scanning matrix of 256 *128. Heart rate (beats/min) was assessed during each flow measurement.

CMR image analysis

CMR studies were analyzed on a commercially available Advanced Windows workstation (GE Healthcare, Milwaukee, Wisconson, USA). Volumetric data was quantitatively analyzed using the Mass analysis software package V3.1 (Medis Medical Imaging Systems, Leiden, The Netherlands). End-diastolic and end-systolic time frames from every slice were used for the assessment of biventricular end-diastolic and end-systolic volumes. Stroke volumes, ejection fractions and cardiac mass were assessed according to common analysis techniques.[9]

Flow images were quantitatively analyzed using the Flow analysis software package V2.0 (Medis Medical Imaging Systems, Leiden, The Netherlands). This package allows calculation of flow velocity curves by multiplying valve area (drawn on each of the 30 time frames) and spatial average flow velocities per time frame. From the resulting flow-velocity curves the following indices of biventricular diastolic filling were derived (Figure 1); 1) peak early filling rate (PeFR) (ml/s), 2) time to peak early filling rate (ttPeFR) (ms) measured from end-systole, 3) early filling fraction (FF) defined as volume increase (ml) during the first one-third of diastole normalized for ventricular stroke volume, 4) deceleration time (Dt) (ms), measuring the time from PeFR to the extrapolation point of deceleration of flow to the baseline, 5) peak atrial filling rate (PaFR) (ml/s), 6) time to peak atrial filling rate (ttPaFR) (ms) defined as time from end-systole to maximal increase in ventricular volume after atrial contraction, 7) atrial filling fraction (AFF) defined as the increase in ventricular volume after atrial contraction normalized for ventricular stroke volume, and 8) the ratio of peak early filling rate over peak atrial filling rate (PeFR/PaFR ratio).

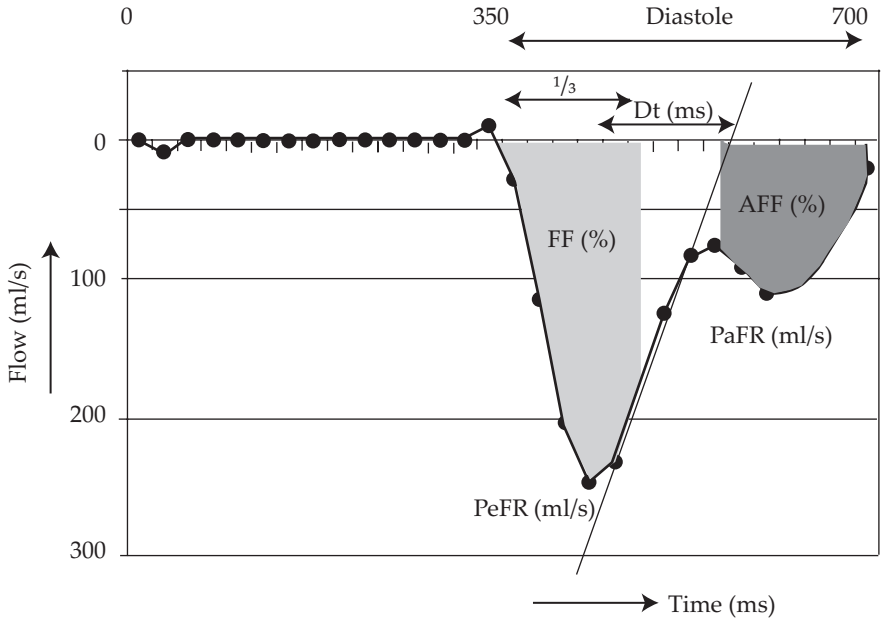


Figure 1. Phase velocity encoded AV-valve valve filling pattern: a typical example of the mitral valve

AFF = atria filling fraction (% of total diastolic filling during atrial contraction),

Dt = deceleration time, FF = early filling fraction (% of total filling during first ⅓ diastole),

PaFR = peak atrial filling rate, PeFR = peak early filling rate

Statistical analysis

SPSS-PC statistical software package version 11.5 was used for analysis (SPSS, Inc., Chicago, Illinois, USA). A p-value < 0.05 was considered to indicate statistical significance. Results are expressed as mean (SD). Characteristics and absolute CMR parameter values were compared between patients and controls using the two-sample T-test or Mann-Whitney U test. To deal with multiple comparisons according to Bonferroni's method a p-value ≤ 0.017 (i.e. 0.05/3) was considered to indicate significance when an individual GH-dosage group was compared to the controls. Bivariate correlation coefficients were calculated using Spearman's method (r_s).

Analysis of covariance with correction for BSA or weight and height was used to compare biventricular short axis data between patients and controls. Analysis of covariance with correction for HR was used to compare biventricular indices of diastolic filling between patients and controls. GH subgroups were

compared using analysis of variance. To deal with multiple group comparisons the Bonferroni method was used. RVEDV, RV-mass, LVSV and LV-mass were log_{10}-transformed before analysis of (co)variance was applied.

Results

Characteristics of patients, patient GH subgroups and controls are shown in Table 1. In all but 1 patient the Doppler-derived aortic valve pressure gradient was less then 35 mmHg. One patient (in group B) had severe aortic valve stenosis (Doppler peak velocity 5 − 6 m/s). Three other patients underwent surgical repair for aortic coarctation, with a residual but stable Doppler gradient of 15 − 20 mmHg in one.

Compared to controls patients were shorter (mean adult height, $p < 0.001$ and height SD score, $p < 0.001$), had a higher mean heart rate ($p = 0.006$) and higher diastolic blood pressure ($p = 0.05$). Heart rate positively correlated with mean blood pressure ($r_s = 0.53$, $p < 0.001$).

Significant positive correlations were found for GH dose with adult height $r_s = 0.44$, $p = 0.01$), and height SD-score ($r_s = 0.45$, $p = 0.01$). Negative associations of GH dose were found with systolic blood pressure ($r_s = -0.39$, $p = 0.02$, diastolic blood pressure ($r_s = -0.40$, $= < 0.02$) and mean blood pressure ($r_s = -0.43$, $p = 0.01$).

Aortic anatomy

In 4 patients an anatomical aortic coarctation was diagnosed on MRI. Of these patients 2 had had a previous surgical coarctectomy. A pressure gradient of importance was found in 2 (27 mmHg).

Biventricular size and ejection fractions

The biventricular CMR measures normalized or BSA of patients and controls are shown in Table 2. Compared to controls biventricular end-diastolic volume (RVEDV, $p = 0.04$ and LVEDV, $p = 0.001$), LV end-systolic volume ($p < 0.001$) and LV stroke volume ($p = 0.02$) were significantly smaller in patients. Patients had a higher LV ejection-fraction (EF) compared to controls ($p = 0.02$). Heart

rate (beats/min) negatively correlated with LVEDV (ml/m²) (r_s = −0.47, p = 0.001) and RVEDV (ml/m²) (r_s = −0.38, p = 0.003). At analysis of covariance with correction for height and weight the difference found for RVEDV no longer was present. For the LV a smaller end-diastolic volume (p= 0.03), a smaller end-systolic volume (p = 0.002) and a larger LVEF (p= 0.01) were found in TS patients compared to controls. There were no differences between GH dose subgroups, both without and with adjustment for BSA or weight and height.

Table 1. Patient characteristics

Parameter	Controls (n = 23)	Patients (n = 33)	Group I (n = 11)	Group II (n = 12)	Group III (n = 10)
Age (years)	21 (2)	20 (2)	21 (2)	20 (2)	19 (2)
Height (cm)	172 (8)	163 (7)*	159 (7)	164 (6)	166 (6)‡
Height SDS§	0.2 (1.2)	−1.1 (1.1)*	−1.8 (1.0)	−0.9 (1.0)	−0.6 (0.3)‡
Weight (kg)	68 (9)	71 (13)	69 (10)	75 (16)	65 (11)
BSA (m²)	1.80 (0.13)	1.75 (0.15)	1.71 (0.14)	1.82 (0.15)	1.72 (0.15)
Duration GH-Rx (years)	-----	8.6 (1.9)	8.3 (1.3)	8.1 (2.3)	9.4 (1.9)
Stop since GH-Rx (years)	-----	4.9 (2.0)	5.1 (1.4)	5.3 (2.2)	4.0 (2.0)
Duration E-Rx (years)	-----	7.2 (2.1)	7.7 (2.1)	7.2 (2.0)	6.6 (0.8)
Systolic Blood Pressure (mmHg)	115 (10)	118 (15)	128 (18)	116 (8)	112 (12)‡
Diastolic Blood Pressure (mmHg)	64 (9)	70 (12)	77 (14)†	69 (8)	63 (10)‡
Mean Blood Pressure (mmHg)	81 (9)	86 (12)	94 (14)†	85 (7)	80 (10)‡
Heart rate (beats/min)	71 (10)	79 (13) *	83 (14)†	78 (14)	75 (11)

Data are mean (SD), Group I received 1.3, group II 2.0 and group III 2.7 mg/m² BSA /day

* Significant difference (p < 0.05) between patients and controls (student T-test)

† Significant difference (p < 0.017) between patient subgroup and controls (student T-test)

‡ Significant correlation according to Spearman's method (p < 0.05) with GH dose

§ Height for age: references healthy Dutch girls[10]

BSA = body surface area, E-Rx = estrogen substitution therapy, GH-Rx = GH-therapy

Table 2. CMR short axis measurements: Patients versus controls.

	Right Ventricle			Left Ventricle		
	Controls	Patients	P-value	Controls	Patients	P-value
EDV (ml/m²)	84 (11)	79 (11)	0.04	81 (10)	72 (10)	0.002
ESV (ml/m²)	38 (7)	36 (6)	0.09	34 (5)	28 (6)	0.001
SV (ml/m²)	46 (6)	43 (6)	0.06	47 (7)	43 (7)	0.07
EF (%)	54 (4)	55 (4)	0.92	58 (4)	61 (5)	0.02
Mass (g/m²)	14 (3)	13 (2)	0.17	45 (6)	45 (6)	0.97
CO (L/min/m²)	3.4 (0.6)	3.4 (0.6)	0.87	3.5 (0.5)	3.5 (0.6)	0.71

Data are mean (SD) values for CMR values normalized for BSA
P-values are from analysis of covariance on original data with statistical adjustment for BSA; CO = cardiac output, EDV = end-diastolic volume, EF = ejection fraction, ESV = end-systolic volume, SV = stroke volume, Mass = wall mass.

Table 3. Biventricular diastolic filling characteristics: patients versus controls.

	Tricuspid Valve		Mitral Valve	
	Patient (n = 19)	Controls (n = 15)	Patient (n = 29)	Controls (n = 18)
TtPeFR (ms)	108 (19)	112 (16)	97 (37)	90 (22)
PeFR (ml/s)	337 (58)	317 (66)	396 (75)*	453 (83)
FF (%)	52 (14)	52 (9)	57 (14)*	64 (6)
Deceleration time (ms)	174 (43)	185 (48)	135 (32)	134 (26)
TtPaFR (ms)	361 (119)	427 (132)	361 (97)	398 (103)
PaFR (ml/s)	178 (69)	166 (48)	181 (38)	176 (36)
AFF (%)	23 (11)	23 (7)	24 (5)	22 (3)
E/A-ratio	2.2 (1.1)	2.1 (0.8)	2.3 (0.6)*	2.6 (0.4)
Heart rate (/min)	81 (13)*	71 (10)	80 (11)*	71 (10)

Data are mean (SD) values
* Significant difference ($p< 0.05$) between patients and controls (student T-test)
AFF = atrial filling fraction, E/A-ratio = PeFR/PaFR, FF = filling fraction first ⅓ diastole, PaFR = peak atrial filling rate, PeFR = peak early filling rate, TtPaFR = time to PaFR, TtPeFR = time to PeFR.

Atrioventricular (AV)-valve inflow

Results of the quantitative analysis of AV-inflow are shown in Table 3. For logistic reasons tricuspid valve measurements could no be completed in all patients. Mitral valve inflow in patients showed a smaller early peak filling rate ($p = 0.02$), a smaller early FF ($p = 0.03$), a smaller E/A-ratio ($p = 0.002$) and a larger AFF ($p = 0.07$). After correction for heart rate these differences no longer were present. Time to PaFR was longer in patients after adjustment for heart rate (adjusted difference 35 ms, standard error 12 ms).

No differences in indices of the tricuspid valve inflow pattern were present between TS patients and controls. After adjustment for heart rate FF was larger in patients (adjusted difference 8%, standard error 3%). No significant differences in tricuspid or mitral valve inflow indices were present between GH dose subgroups (neither with nor without adjustment for heart rate).

Discussion

In this study we prospectively assessed cardiac status in young adult women with TS, 5 (±2) years after discontinuation of GH therapy and compared results to those of a matched reference population. In contrast to previous studies analysis was not restricted to the LV. The most striking findings of this study were the smaller biventricular volumes in TS compared to controls. Patients showed no myocardial hypertrophy or systolic dysfunction and minor diastolic function changes compared to controls. Despite smaller stroke volumes patients showed comparable cardiac output to controls, by means of higher resting heart rate.

All our patients were former participants of a GH dose response study during which patients received supra-physiological dosed GH treatment.[3,7] During that trial GH dose ranged from 1 to 2 times the regularly used dose in TS and was given for a relatively long period of time (9 (±2) years). No differences were found for any of the CMR measures between GH dose subgroups.

GH and ventricular remodeling

The ability of GH to stimulate growth of cardiomyocytes has extensively been documented.[6] Effects of GH excess on cardiac size are staged.[6,11] Initially cardiomyocytes increase in cross-sectional area, resulting in concentric ventricular remodeling.[6] Myocardial hypertrophy induced by short term GH is has been shown reversible within 3 months in healthy controls.[4] In animal models of myocardial ischemia short-term GH excess reduced cell necrosis and apoptosis.[6] In heart failure models it induced myocardial hypertrophy without disproportional fibrosis and restored myocardial capillary density to normal levels.[6] As such, short-term GH induces the physiological type of myocardial hypertrophy. Myocardial hypertrophy in heart failure is characterized by cardiomyocyte lengthening, eccentric remodeling, decreased myocyte density and increased fibrosis.[5,6] This pathological type of hypertrophy is also seen in acromegalic cardiomyopathy and is a cause of concern in all (high dosed) GH treated patients.[5,6,11]

Data on cardiac status in relation to GH treatment during childhood is limited. All previous studies used echocardiography. During GH treatment no LV hypertrophy was found in TS,[7,8] Noonan syndrome,[12,13] GH deficiency[14] and idiopathic short stature,[15,16] During treatment Radetti *et al*. found patients with TS had smaller LV end-systolic volumes (ml/m²), but normal end-diastolic volumes compared to controls.[8] At the start of GH treatment in TS Sas *et al*. documented normal SD-scores for LV dimensions, that significantly decreased to values < 0 after 7 years of treatment.[7] In Noonan's Syndrome, Noordam et al. also found negative SD-score changes for LV dimensions during GH treatment.[12]

Data on cardiac status after discontinuation of high dosed GH treatment are even scarcer. Adults with childhood onset GH deficiency formerly treated with GH showed smaller LV dimensions, LV stroke volume and LV mass compared to controls.[17] However, in that study volumetric data were not normalized for body size while patients remained smaller than controls. We found wall mass in TS was comparable to controls, but biventricular volumes and stroke volumes were smaller. This strongly suggests that cardiac growth in our TS patients during childhood was disproportionally less than somatic growth. Studies among healthy children showed weight and height are important determinants of LV growth (indicated by LV mass) and found an important degree of

tracking for LV mass during childhood.[18,19] Analysis with correction for height and weight still resulted in smaller LV volumes in our patients compared to controls. We do not know of clinical studies that focussed on cardiac growth in relation to somatic growth during GH treatment. In experimental models of GH- and IGF1- deficiency disproportionate and differential effects on specific organ growth have been reported, but these studies do not explain our observations.[20,21]

GH and ventricular function

Initially GH excess is associated with normal to increased ventricular function.[4,6,11] Over time patients with acromegaly develop LV diastolic dysfunction.[22,23] In acromegaly diastolic dysfunction relates to disease activity and can be detected before evident systolic dysfunction or hypertrophy.[4,22] Compared to controls our TS patients showed normal RV diastolic filling and some shifting towards late diastolic LV filling. Previously Radetti et al. reported a higher A-peak, a smaller E/A-ratio and shortened deceleration time for LV filling in TS patients during GH treatment compared to controls.[8] Diastolic filling is known to be HR dependent.[24,25] In our patients correction for heart rate resulted in comparable biventricular diastolic filling pattern to controls. Like Radetti previously suggested, the changes seen LV diastolic filling in TS may result from adaptation to higher heart rates, rather than represent early signs of LV dysfunction as they do not entirely fit abnormalities of relaxation or compliance.

After discontinuation of GH for at least 6 months our TS patients showed a higher mean heart rate and increased LV ejection fraction compared to controls. During GH treatment Radetti et al. found signs of increased ventricular systolic performance in TS which was explained by decreased systemic vascular resistance and end-systolic meridional stress compared to controls.[8] We did not assess ventricular contractility in our patients. Compared to healthy controls our TS patients had higher mean blood pressure and comparable cardiac output. Therefore, afterload in our patients appeared not to be decreased. According to the formula of ejection fraction (EF = SV/EDV*100), a comparable stroke volume generated by a smaller ventricle automatically results in a higher ejection fraction. The higher LVEF in our TS patients compared to controls may be explained by this mathematical drawback of EF and does not

necessarily imply increased systolic LV performance. Overall our results lead to conclude that young adults with TS formerly treated with GH show normal biventricular function.

Clinical importance

So far data on cardiac status in TS after discontinuation of GH-therapy were lacking. Therefore, concerns on possible long-term cardiovascular side effects as seen in other situations with GH excess remained. To address these concerns we determined cardiac status mid-term after GH discontinuation in TS. With regard to the well-known complications of GH excess we found the following reassuring results: 1) absence of myocardial hypertrophy, 2) absence of diastolic dysfunction, generally considered an early sign of ventricular dysfunction, and 3) normal global biventricular systolic function. However, we did find our TS patients had smaller biventricular volumes and stroke volumes, especially for the LV, compared to controls and a higher mean resting heart rate. Evidence is increasing on the detrimental effect of higher resting heart rate on (cardiovascular) mortality.[26,27] Increased heart has repeatedly been found in TS.[28] A recent study described dysregulation of the sympathetic nervous system, leading to tachycardia, high blood pressure, increased resting norepinephrine levels, and a blunted cathecholinergic response to exercise in TS.[28] There is also evidence that resting heart rate negatively correlates with LV chamber size, which was what we found in our population.[29] The underlying mechanism for the increased resting heart rate in TS may well be multi-factorial. Considering the potential long-term (cardiovascular) mortality risk associated with this finding further research in TS is required, including research focussed on the disproportion between cardiac and somatic growth as described in this study.

Limitations

Our study is limited by its cross-sectional study design. Nevertheless we think our current data supplement the data previous published by Sas *et al.* on LV mass and volume during GH treatment and results point in the same direction.[7]

The absence of an untreated patient group precluded to distinguish between effects inherent to TS and effects related to GH treatment on our results. However we feel it's unethical to withhold GH treatment to TS patients.

One patient with severe aortic stenosis and 2 with residual aortic coarctation were included. If this would have influenced results, it would have been towards concentric LV hypertrophy, which was absent.

Conclusions

Mid-term after discontinuation of GH therapy TS patients show no myocardial hypertrophy and well preserved biventricular function. Ventricular volumes at adult age are smaller compared to controls. Comparable cardiac output to controls is achieved at a higher resting heart rate, which may have a negative impact on long-term survival.

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CHAPTER 8

General discussion

In the following section the most relevant findings and their practical implications are discussed. When applicable suggestions for future research are provided.

General consideration on the Fallot population studied

Because of a lack of studies on long-term follow-up in Fallot patients corrected according to contemporary surgical strategies, the common goal of chapters 2 to 5 was: to evaluate the different aspects of functional cardiovascular condition after optimal correction in the current surgical era using valid, quantitative diagnostic tools. Optimal surgical correction was defined as: a post-operative status without a residual VSD or clinically important RV outflow tract gradient. This resulted in the inclusion of a homogeneous population subjected to isolated pulmonary regurgitation (PR). Therefore, and in contrast to most previous studies, results were not confounded by a mixture of residual lesions, different types of cardiac overload, or different surgical approaches.

The population described represents an important part of daily clinical practice as residual PR is considered the most important hemodynamic lesion associated with both malignant ventricular arrhythmia and sudden cardiac death in corrected tetralogy of Fallot (TOF).[1] Although the number of patients remains relatively small, our population represents one of the largest series corrected by the transatrial transpulmonary approach described so far.[2-6]

Clinical condition after optimal surgical correction of TOF in the current surgical era

At mid to long-term follow-up the most important finding in our patients with TOF is that of well preserved clinical condition. This deduction is based on the following clinically relevant observations made in this thesis:

1) all patients were asymptomatic (86% in NYHA class I) or minimally symptomatic (14% in NYHA class II) (chapter 2)
2) all patients were without clinically important ventricular arrhythmia (chapter 2)
3) all patients had preserved biventricular contractile reserve (chapter 4)

4) mean oxygen consumption was not different from that in a reference population (mean (SD) 97 (17)% of predicted). In ¾ of patients a value > 85% was found (chapter 2)
5) neurohormonal activation was absent in the majority of patients (chapter 4)

These results support a conservative attitude towards treatment of chronic PR in corrected TOF during childhood. Nevertheless, we confirmed RV dilation (85% of patients) and global systolic dysfunction (49% of patients) are common in Fallot patients with residual PR, even in those patients corrected according to transatrial transpulmonary approaches (chapter 2). Furthermore deterioration of RV function and exercise capacity correlate with a longer interval since repair (chapter 2). The moderate associations found with time could however not be used to predict pace of decline in the individual patient.

Determinants of clinical condition

Despite the overall well preserved clinical condition in our patients we were able to identify risk factors associated with poorer clinical condition. Abnormal wall motion of RV outflow tract predicted a poorer RV ejection fraction. A higher PR-percentage predicted more severe RV dilation. As such chapter 2 leads to conclude further improvement of long-term clinical condition in the current surgical era may be obtained by improved preservation of RV outflow tract function, both in terms of normal wall motion and normal function of the pulmonary valve.

Following the above, the question how to improve RV outflow tract function arises. Previous studies stressed the negative impact of transannular patch repair on severity of PR, RV dilation, RV dysfunction and exercise capacity.[7-9] We found transannular patch repair was an independent predictor of a higher PR-percentage, but not of the other parameters of clinical condition. Furthermore transannular patch repair clearly related to abnormal RV outflow tract wall motion (chapter 2). As in TOF corrected by a transventricular approach, abnormal wall motion in the RV outflow tract contributed to global RV systolic dysfunction.[10] Therefore, the avoidance of a transannular patch may be expected to contribute to better preserved RV outflow tract function.

However, the use of a transannular patch may not be avoidable in all patients. Therefore alternative approaches were developed. Rao et al. reported a strategy aimed at the preservation of the native pulmonary valve, with excellent short term results regarding both residual PR and residual RV outflow tract gradients.[11] Nevertheless, the necessity to apply transannular patch repairs remained in patients with insufficient diameters of the pulmonary valve annulus.[11] An alternative may be a combined approach of annular enlargement combined with valve repair at the time of surgical correction. For this purpose several papers reported the use of so-called "cusped patches" to enlarge the RV outflow tract.[12-15] Despite good short-term results reported by some, the long-term functional gain with regard to residual PR was disappointing, or is still subject of ongoing investigation.[12-15] In our patients none of these strategies were applied. Still one could try and minimize the extent of the infundibular incision made and the size of the patch introduced. We found magnitude of right ventricular stress reserve was not effected by the presence of a transannular patch, or in other words the presence of a non-contractile wall section (chapter 4). This indicates patches in our patients generally had limited functional impact, which may refer to the use of relatively limited sized patches.

In contrast to our results, the incidence of abnormal wall motion in transventricular corrected TOF was comparable between patients with and without a transannular patch.[10] This may indicate transatrial transpulmonary approaches, by avoidance of a (large) ventriculotomy, result in less wall motion abnormalities. Both our and previous results show abnormal wall motion is not restricted to patients with a transannular patch, which implies other (non-) surgical factors, such as age at repair and extensiveness of the infundibulectomy, play a role in the development of wall motion abnormalities in the RV outflow tract. Severity of residual PR also seems to be affected by factors besides the use of a transannular patch, as a higher preoperative RV peak pressure in our series, independent of the presence of a transannular patch, predicted a higher PR-percentage at follow-up. This may be interpreted to indicate more extensive surgery needed to correct for more severe stenosis, results in worse RV outflow tract function at follow-up. In line with this hypothesis freedom of adverse effects after correction of pulmonary valve stenosis was better with isolated commisurotomy of the pulmonary valve compared to more extensive surgery.[16]

The debate on optimal age at repair is still ongoing. As all our patients were corrected after the age of 2 months we can only speculate on possible further improvement of clinical condition if patients were to be repaired in the neonatal period. We at least did not find important effects of age at repair on outcome in patients corrected between 2 and 24 months of age as is reported in chapter 2.

Restrictive RV physiology in TOF

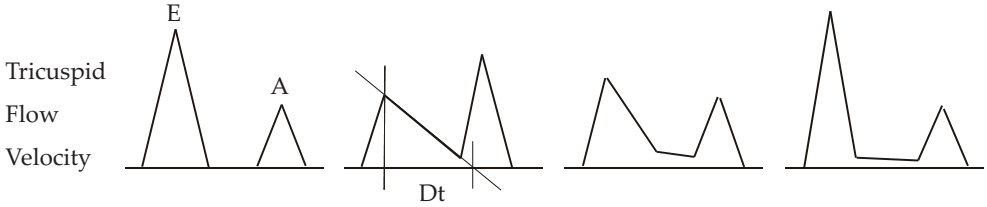
Several types of diastolic dysfunction have been reported in TOF among which restrictive RV filling.[17-21] Reports were equivocal on how restrictive RV filling, indicated by end-diastolic forward flow (EDFF) in the main pulmonary artery, affects long-term clinical condition.[17-21] Therefore, chapter 3 focused on differences between patients with and without EDFF. We concluded EDFF was associated with worse clinical condition at follow-up in corrected TOF.

Predominant or isolated diastolic dysfunction can cause the clinical syndrome of heart failure, including exercise intolerance.[22,23] To explain for the observed difference in clinical condition between our subgroups based on the presence of EDFF, we did not find significant differences in degree of RV dilation or global RV systolic function. Surprisingly, data on RV diastolic filling at rest appeared to contradict with our findings on exercise capacity, as most abnormal findings were found in patients without EDFF. Changes in the pattern of RV filling with stress so far had not been assessed in TOF. We hypothesized analysis during stress might reveal additional abnormalities, and therefore give additional information on RV function with chronic PR. Dobutamine stress imaging "unmasked" relaxation related diastolic dysfunction in patients with EDFF, while patients without EDFF showed no change in the RV filling pattern. Considering healthy subjects respond to dobutamine stress with improved ventricular relaxation, the observations made in patients with EDFF are highly abnormal.[24,25]

The observed fairly normal pattern of RV filling found at rest in patients with EDFF may be explained by so-called pseudo-normalization. Pseudo-normalization may mask diastolic dysfunction in patients that have both impaired and/or delayed ventricular relaxation and reduced effective chamber compliance.[23,26] With both types of diastolic dysfunction present, the characteristics of both ventricular filling pattern may be cancelled out

by accumulation, to result in an intermediate pattern that resembles normal ventricular filling (Figure 1). Results in chapter 3 showed Fallot patients as a group are characterized by impaired RV relaxation. EDFF in the main pulmonary artery, generally accepted to indicate restrictive ventricular filling or decreased RV compliance, was present in about ⅔ of patients. Our results at rest show that as with other cardiac conditions, relaxation related diastolic dysfunction may become masked in the presence of a less compliant ventricle. Instead of absent diastolic dysfunction at rest in patients with EDFF, it is more likely that these patients had both restrictive and relaxation related diastolic dysfunction, which may be graded to be a more severe form of diastolic dysfunction.[23]

Right ventricular diastolic filling pattern:



Filling characteristics:				
1. Relaxation	Normal	Impaired	Impaired	Impaired
2. Compliance	Normal	Normal	Midly Decreased	Severly Decreased
Descriptives:				
1. Functional Type	Normal (Young)	Impaired Relaxation	Pseudo Normal	Restrictive Physiology
2. Severity of dysfunction	None	Mild	Moderate	Severe

Figure 1. Diastolic ventricular filling in the normal heart and with cardiovascular disease.

A = peak atrial filling, DT = deceleration time, E = peak early filling

In summary chapter 3 showed stress imaging may unmask severe diastolic dysfunction not appreciated at rest in patient with restrictive RV physiology. Diastolic stress imaging proved useful, as it contributed to our understanding of decreased functional capacity in Fallot patients with EDFF compared to those without EDFF. Restrictive RV diastolic filling has been thought to act

beneficially in adults with TOF.[21] Our results show this is not the case in children and young adults corrected according to current surgical strategies and as such confirm earlier observations made in children.[17]

Recent insights on heart failure applied to TOF

Both a blunted response to beta-adrenergic stimulation[27-32] and elevated levels of neurohormonal are considered early signs of heart failure.[33-37] According to these recent insights neurohormonal activation and blunted ventricular stress response should be looked for during management of patients at risk for heart failure.[38,39] Moreover, ventricular stress reserve and level of neurohormonal activation have been used as prognosticators in heart failure.[31-37,40] The evaluation of contractile reserve appeared promising for optimisation of timing of surgery for mitral regurgitation,[30,41] and aortic regurgitation.[31] Trials with ACE-inhibitors and beta-blockers showed improved long-term outcome in heart failure patients.[40] Only little information is available in children and patients with congenital heart disease. Nevertheless, in these groups elevated levels of neurohormones related to worse NYHA class, decreased ventricular function and worse exercise capacity.[42-46]

Fallot patients subjected to chronic PR generally are considered to be at risk for the development of heart failure. Nevertheless, surprisingly few data is available on RV remodelling as a result of chronic PR and the associated level of neurohormonal activation or decline in functional reserve. The population presented in this thesis offered a unique opportunity to evaluate the above, which was done in chapter 4. In contrast with previous studies that analysed the type of ventricular response to stress in corrected TOF, chapter 4 described a normal biventricular response to stress, characterized by increased ventricular performance.[47-49] Moreover, patients uniformly showed a positive biventricular contractile reserve, irrespective of severity of PR, ventricular size or duration of follow-up since repair. Furthermore, the overall levels of neurohormonal markers in our series were normal (chapter 4). No significant relations were found for any of the neurohormonal markers with degree of RV dilation, biventricular systolic function at rest or exercise capacity. A weak positive correlation was found between NT pro-BNP and PR-percentage and risk levels of NT pro-BNP, found in 22 (44%) patients, related to smaller biventricular stress reserve.

In summary chapter 4 shows recent but generally accepted early indicators of heart failure are absent in our patients, which fits their asymptomatic to minimal symptomatic status. Nevertheless, the limited changes in biomarker levels found, especially those of NT pro-BNP, related to relevant RV loading and decreased ventricular stress reserve. This may be interpreted as a confirmation of the diagnostic potential of cardiac biomarkers as early signs of activated compensatory mechanisms with abnormal ventricular loading. The prognostic potential of ventricular stress reserve and level of neurohormonal activation on outcome measures such as mortality and freedom of reoperation, will have to be studied among patients with TOF and chronic residual PR.

Validity of criteria for timing of intervention for residual pulmonary regurgitation

This thesis did not aim to optimise timing of interventions for residual PR in corrected TOF. Nevertheless, results found may contribute to the discussion on validity of currently used criteria for timing of interventions. Most published series on pulmonary valve replacement for PR use occurrence of clinical symptoms as a primary indication for intervention.[50] Results from chapter 2 indicate TOF patients, like others patients with congenital heart disease, may not be aware of changes in clinical condition even in the presence of substantial ventricular remodelling and dysfunction.[9,51-53] This legitimates the fear in corrected TOF that by the time symptoms or exercise limitations become distinct irreversible ventricular damage may have occurred.[9,32,54-57] As such our results question the validity of occurrence of symptoms as a criterion for timing of intervention for PR in TOF.

Another frequently used criterion for pulmonary valve replacement, especially in recent studies using MRI techniques, is presence of RV dilation.[54,55,58-60] MRI derived criteria for RV size from recent studies applied to our population indeed identified patients with worse clinical condition (chapter 2). However, the prognostic value of volumetric criteria on long-term morbidity and mortality still has to be proven in prospective studies. As suggested earlier, ventricular stress reserve and the level of neurohormonal activation may be expected to bear prognostic value in patient subjected to chronic ventricular overload. These measures therefore may also proof useful in the process of decision making during the follow-up of Fallot patients with

chronic PR. In our series RV size and PR-percentage at best showed poor correlations with impaired exercise capacity, biventricular stress reserve and level of neurohumoral activation (chapters 2 and 4). Therefore our results not only show compensatory neurohormonal pathways associated with heart failure are not yet activated in our patients with considerable PR and RV dilation, but they may also indicate that TOF patients should not undergo pulmonary valve replacement solely based on RV volumetric or PR criteria. Future research on prognosticators for timing of pulmonary valve replacement should include neurohormonal cardiac biomarkers and ventricular functional stress reserve.

Role of bicycle ergometry

Sudden cardiac death, a major cause of late mortality in corrected TOF, often is attributed to the occurrence of ventricular arrhythmia.[1] Residual PR is the most important hemodynamic lesion associated with both ventricular arrhythmia and sudden cardiac death.[1] With several congenital heart diseases exercise is considered a provocative factor for ventricular arrhythmia.[61] So far all electrocardiographic arrhythmia risk predictors in TOF were established at rest and almost no data was available on ECG changes with physical stress.[1,62-65] Therefore, an extensive analysis of ECG changes with physical exercise was made in chapter 5.

The main finding was a significant increase of electrical inhomogeneity during repolarization with physical exercise. An additional observation of clinical interest was that more severe PR and RV dilation, related to larger electrocardiographic abnormalities with physical exercise. Inhomogeneity of repolarization is known to predispose for ventricular arrhythmia[66,67] and sudden cardiac death.[68] In line with this, Fallot patients with sustained ventricular tachycardia were shown to have larger QT and/or JT dispersions compared to other Fallot patients at rest.[63,69] Together with our data this may indicate patients with corrected TOF, especially those with severe PR, show increased susceptibility to arrhythmia with physical exercise. As such results presented in chapter 5 could be interpreted as to be in support of exercise restrictions in TOF patients with severe PR.[61,70] However, as none of our patients showed clinically important ventricular arrhythmia at any point during physical exercise, we can not prove this hypothesis based on the current data.

The role of QRS duration in the management of TOF

In corrected TOF QRS-duration (> 180 ms in adults and > 170 ms in children) is regarded the main predictor of malignant ventricular arrhythmia.[1,62-65] QRS-duration within the population described in this thesis did not exceed 170 ms. Moreover none of the patients showed clinically important ventricular arrhythmia on 24 hours Holter monitoring. Findings may reflect the positive influence of the surgical techniques used. In support of this assumption less QRS-prolongation and life threatening arrhythmia have been reported with transatrial transpulmonary repair for TOF compared to transventricular repair.[5,66] However, we should realize the critical values indicative of arrhythmia risk were mainly identified in patients corrected by a transventricular approach at a relatively old age. Secondly it should be noted that many comparisons on surgical approaches in Fallot literature are characterized by limited comparability between patient populations studied.[3,4,6,71-73]

Previously RV dilation has been associated with QRS prolongation.[62,74,75] Chapter 2 showed QRS prolongation in Fallot patients corrected according to contemporary surgical techniques predominantly related to worse functional condition. This predictive effect was present in a QRS range below the critical values reported to predispose for malignant ventricular arrhythmia. Pulmonary valve replacement has been shown to reduce QRS-duration proportional to the degree of RV volume reduction.[76,77] Therefore, a combined approach of pulmonary valve replacement with cryoablation was suggested for arrhythmia management in TOF.[78] Success rates of pulmonary valve replacement to improve RVEF on the other hand are inconsistent.[55,58,78,79] Cardiac resynchronization therapy in heart failure patients with prolonged QRS-duration has been shown beneficial for ventricular contractile function, symptomatic status, and mortality.[80,81] The relations found for QRS-duration with RVEF and exercise capacity in chapter 2 suggest functional gain may be achieved by cardiac resynchronization therapy in selective groups of patients with corrected TOF.

Final comments and future research perspectives in TOF

The generally well-preserved clinical condition in our series, combined with the cross-sectional study design, prevented determination of predictors of

important outcome measures such as mortality, ventricular arrhythmia or need for re-operation. Assessment of predictors of these "classic" outcome measures, requires longitudinal follow-up. The associations found with longer interval since repair in chapter 2 indicate clinical deterioration may still develop in our population. The diagnostic techniques applied throughout this thesis allowed us to acquire a quantitative assessment of the different aspects of functional cardiovascular condition. Although such quantitative tools are relatively expensive and time-consuming they are well suited for serial assessments of clinical condition.

The data from chapter 5 indicate electrocardiographic differences during repolarization between patients at variable risk for ventricular arrhythmia according to degree of hemodynamic overload (severity of PR) become distinct during physical exercise. Changes seen during repolarization, especially in patients with severe PR, may indicate increased susceptibility to arrhythmia. Longitudinal data is necessary to evaluate the suggested prognostic value of this observation. When proven valid, this knowledge is important considering the potential role in early detection of patients at risk for sustained ventricular arrhythmia.

Aortic disease in Turner's syndrome

In recent MRI studies aortic dilation was reported in up to 50% of patients with Turner's syndrome, which was far more than previously assumed from echocardiographic reports.[82-85] Aortic dilation may be complicated by dissection and rupture. In Turner's syndrome the number of reports on aortic dissections is increasing,[85,86] with the ascending aorta considered to be the location of preference.[85,87] Etiology of aortic disease in Turner's syndrome is unknown, but abnormal aortic wall composition may play a role. This "connective tissue hypothesis" gains support in literature on Turner's syndrome.[88,89]

Non-invasive measures of aortic wall stiffness indirectly reflect aortic wall composition.[90] These measures were shown to be abnormal in patients with connective tissue disease.[91,92] Although data on aortic wall stiffness may also contribute to our understanding of aortic disease in Turner's syndrome, they so far are missing. Therefore, we aimed to evaluate aortic diameters and regional distensibility in Turner's syndrome in chapter 6. We concluded that the aorta in Turner's syndrome shows abnormal dimensions and signs of

impaired wall function and abnormalities that stretch beyond the ascending aorta. Furthermore results showed normalization of aortic abnormalities with increasing growth hormone dose, which suggests a beneficial effect of growth hormone on aortic abnormalities in Turner's syndrome. Findings, especially those in the subgroup that received the lowest dose of growth hormone, bear similarity to results found in Marfan's syndrome and as such support the connective tissue hypothesis.

Abnormal aortic wall stiffness in Turner's syndrome

Aortic wall stiffness depends on the presence, proportion and interaction of smooth muscle cells, collagen, and elastin proteins, or in short wall composition. An explanation for the observed abnormal aortic wall stiffness in Turner's syndrome may be found in changed wall composition. Arterial cystic media degeneration similar to that in Marfan's syndrome has been observed in Turner's syndrome.[85,89] These changes do not essentially differ from the degenerative changes seen in the human aortic wall with aging.[93-95] In the theoretical model of aging, "wear and tear" of the aortic wall result in progressive fragmentation of the medial elastin network to be repaired by collagen, which results in changed relative concentrations of fibrillar material.[96,97] The breakdown of elastic fibers leads to aortic dilation with age and increased aortic stiffness.[97] The increase in aortic stiffness with aging is explained by a shift of the elastin determined part of the aortic pressure-diameter relation to the lower pressures range.[98] In the presence of degenerative like changes, the same mechanism may be assumed to play a role in Turner's syndrome.

Growth hormone and wall stiffness

An explanation for the observed beneficial effect of growth hormone on aortic wall stiffness may be that growth hormone effects aortic wall composition.[99] It is well established that aortic wall stiffness increases with age in both humans and animals,[96,100] while growth hormone secretion and serum IGF-I decline.[101] The increase in aortic stiffness is accompanied by increased cross-linking of collagen and elastin, gradual increased collagen content and decreased elastin content. Growth hormone administration to rats has been shown to change collagen content and composition of the aorta, and result in a decrease

of arterial wall stiffness especially in younger rats.[99,101] Moreover untreated patients with growth hormone deficiency have increased arterial wall thickness and increased arterial wall stiffness.[102,103] In such patients growth hormone replacement therapy reduces arterial wall thickness and stiffness.[102,103]

An alternative explanation for the observed beneficial effect of growth hormone on aortic wall stiffness may be a dose dependent effect of growth hormone on blood pressure. We found blood pressure to decrease with higher dose of growth hormone (chapter 6, table 1). According to the aortic pressure-diameter relation a decrease in blood pressure results in a decrease of aortic wall stiffness if changes occur in the exponential (non-elastin) part of the curve. Assuming degenerative changes are present in Turner's syndrome, pressure changes may now occur in the exponential part of the curve and result in changes of aortic wall stiffness. The effect of growth hormone on aortic distensibility may however also be the sum of multiple smaller effects, which requires further research to be revealed.

Long-term cardiac effects of growth hormone in Turner's syndrome

Growth hormone treatment nowadays is a well-established in Turner's syndrome.[104] Especially when started at young age and at supra-physiological doses excellent results on final height are reported.[105] However, based on knowledge of the cardiovascular effects of growth hormone excess in other situations, such as acromegaly, concerns have risen on the possible long-term cardiovascular side effects associated with high dosed growth hormone treatment.[106,107] So far data on cardiovascular condition after discontinuation of growth hormone therapy in Turner's syndrome are lacking.

We hypothesized side effects, if present, would be biventricular. Therefore, and in contrast to most previous studies we assessed biventricular size and function in young adult Turner patients formerly treated with growth hormone in chapter 7. Mid-term after discontinuation of growth hormone treatment we can conclude the feared deleterious type of cardiac remodelling associated with growth hormone excess (myocardial hypertrophy plus ventricular dysfunction) is absent in patients with Turner's syndrome. Furthermore, considering treatment had been discontinued for at least 6 months, this type of ventricular remodelling is not likely to develop in the future.

Chapter 7 showed Turner patients had smaller biventricular volumes compared to healthy controls. The previously studied Dutch Turner population from which our participants represent a non-selective subset, showed significant decreases of SD-scores for LV dimensions during active growth hormone treatment in childhood.[108] Together with our current results this strongly suggests disproportionate cardiac growth in Turner's syndrome, which can not be explained by observations from previous studies on organ specific effects of deregulation of the growth hormone / IGF-I axis.[109,110] As in previous studies, chapter 7 showed a higher mean resting heart rate in Turner patients compared to healthy controls.[111] Evidence is increasing on the detrimental effect of a chronic higher heart rate at rest on long-term (cardiovascular) mortality.[112,113] Heart rate has been shown to inversely relate to LV volume. The etiology of the increased resting heart rate found in Turner's syndrome may be multifactorial.[111]

Final comments and future research perspectives in Turner's syndrome

In summary, results on cardiovascular condition after discontinuation of high dosed growth hormone treatment in Turner's syndrome indicate this type of treatment is safe. Moreover, according to our results growth hormone acts beneficially on aortic abnormalities with increasing dose.

As described in this thesis aortic dilation is common among young adults with Turner's syndrome. The risk for aortic dissection is known to increase with larger aortic diameters, though dissection may also occur in the non-dilated aorta.[114] Besides aortic dilation, decreased aortic distensibility has been shown to predict progressive aortic disease in Marfan's syndrome.[114] We described signs of abnormal aortic wall function similar to those in Marfan's syndrome. The prognostic value of aortic diameter and decreased wall stiffness on progression of aortic dilation and occurrence of complications in Turner's syndrome should be evaluated. With regard to the observed beneficial effect of growth hormone on aortic distensibility our study design did not allow to determine the optimal dose needed to normalize wall function, nor to assess longevity of the observed beneficial effect after discontinuation of treatment. To answer these research questions dedicated longitudinal studies are required.

No untreated Turner patients were included in our study. Therefore a possible growth hormone related effect on ventricular growth and the

volumetric abnormalities observed in our study can not be excluded. The absence of differences between our growth hormone dose subgroups argues against this possibility. Nevertheless, further research is necessary to reach definitive conclusions. Serial follow-up of patients using the newer quantitative imaging tools, such as the MRI techniques applied in this thesis, should be able to satisfactorily address this problem. Quantitative diagnostic (imaging) tools in general would be helpful in the assessment of organ specific growth in response to growth hormone to evaluate the possibility of disproportionate cardiac growth in Turner's syndrome. The importance of such analysis lays in the possible association of smaller ventricular volumes with a higher resting heart rate. Considering the potential long-term mortality risks associated with the repeatedly reported higher resting heart rate in Turner's syndrome future research should focus on underlying etiology.

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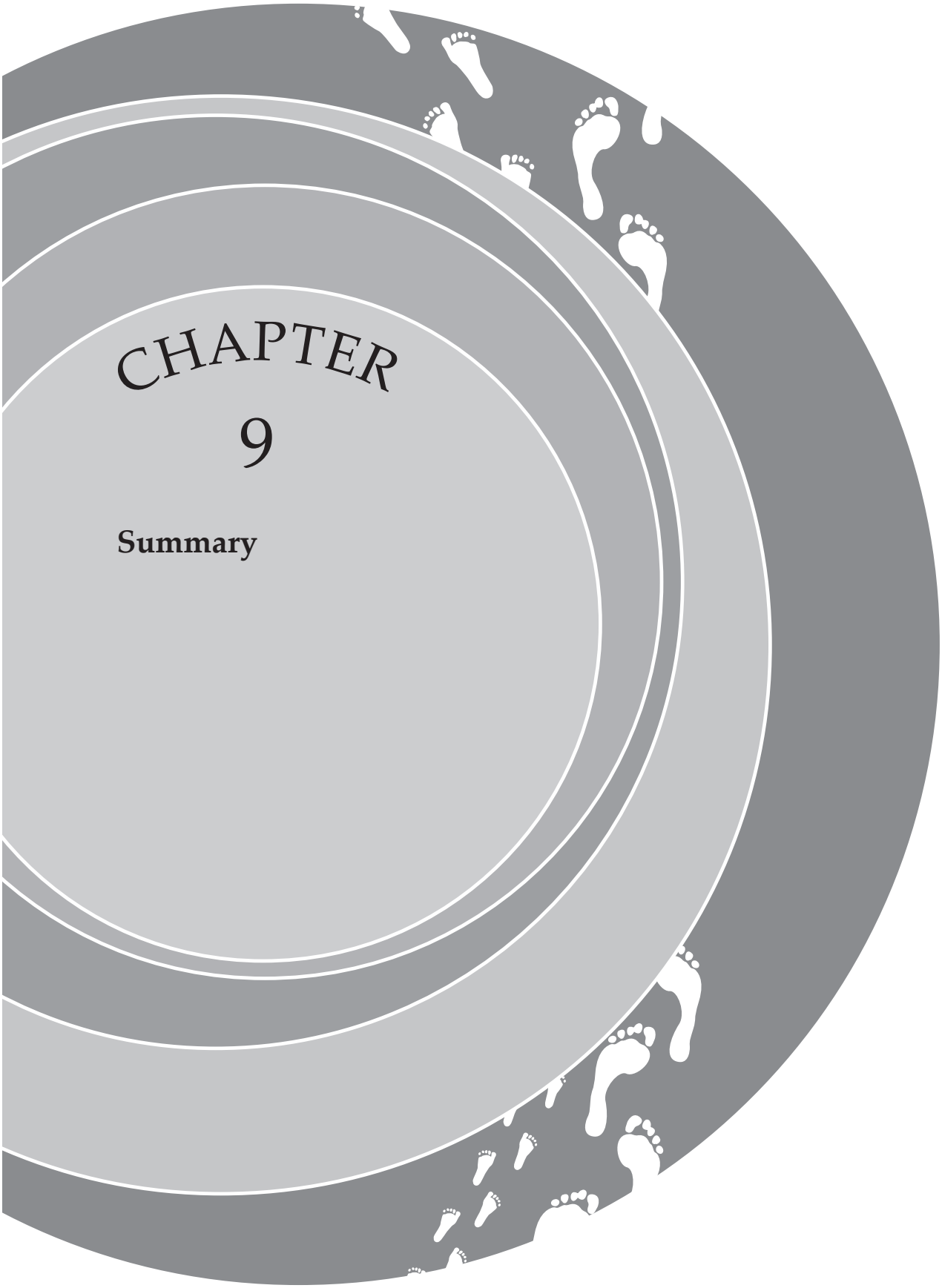


CHAPTER 9

Summary

Adequate and serial functional cardiovascular assessment is important in patients with congenital heart disease because many show disruption of normal myocardial geometry, which may or may not be accompanied with hemodynamic overload. We now know, that even after so-called "corrective surgery", total cure is only seldomly achieved. The presence of residual cardiac abnormalities may lead to malignant myocardial remodeling, which eventually may result in heart failure.

Surgical correction of tetralogy of Fallot (TOF), the most common cyanotic congenital heart lesion, has been performed since 1955. Literature on clinical condition following corrective surgery is extensive. Nevertheless, studies acquired with appropriate diagnostic tools, long-term after correction according to contemporary surgical strategies are lacking. The need for studies based on quantitative diagnostic tools for (repeated) documentation of clinical condition has been recognized, however such studies are expensive, time-consuming and therefore limited in number. Previous (MRI) studies often included a mixture of patients with regard to diagnosis at repair, age at repair, surgical techniques used for repair, and post-operative status, which complicates interpretation of results.

Therefore, the common purpose of the studies described in **chapters 2 to 5** was to evaluate different aspects of functional cardiovascular condition at mid- to long-term follow-up after optimal surgical correction of TOF in the current surgical era. Using a cross-sectional study design patients with the following characteristics were studied between September 2002 and November 2004: 1) total surgical correction performed before the age of 2 years, 2) interval since correction of at least 5 years, 3) total surgical correction performed by a transatrial transpulmonary approach, and 4) optimal correction of the initial lesions of TOF, defined as a post-operative status without residual VSD or residual outflow tract Doppler gradient > 30 mmHg

Based on cardiovascular side-effects of growth hormone excess in diseases such as acromegaly, concerns have risen on the possible long-term cardiovascular risks associated with high dosed growth hormone treatment. Turner syndrome is one of the currently well-established indications for growth hormone treatment during childhood. Data on cardiovascular condition after discontinuation of growth hormone therapy in Turner's syndrome are lacking.

Therefore the common purpose of **chapters 6 and 7** was to assess the different aspects of functional cardiovascular condition in young adult women with Turner's syndrome formerly treated with growth hormone. Participants represents a non-selective part of the Turner population from a previous Dutch growth hormone dose response study, based on voluntary participation in the described MRI-evaluation study. Patient data was compared to findings in healthy age, gender and body surface area (m^2) matched controls. MRI examinations were performed between May 2003 and June 2004.

Chapter 1 provides an introduction to 1) the general problems seen during the follow-up of congenital heart diseases, 2) the specific problems seen with corrected TOF, and with Turner's syndrome, and 3) diagnostic tools used throughout this thesis. At the end of the chapter (chapter 1.5) the specific study aims are presented.

The specific study aims in tetralogy of Fallot were:

- to assess clinical condition, including the assessment of biventricular volumes and function by cardiac MRI
- to identify factors associated with RV dilation, RV dysfunction and decreased exercise tolerance
- to assess RV diastolic function, in terms of RV filling pattern, at rest and during pharmacological stress
- to evaluate the effect of restrictive RV physiology, indicated by end-diastolic forward flow in the main pulmonary artery, on clinical condition
- to assess the level of 1) neurohormonal activity, 2) biventricular contractile reserve, and 3) maximal exercise capacity, in relation to the amount of residual PR and RV volume
- to assess pro-arrhythmogenic electrocardiographic changes in the surface ECG during maximal physical exercise
- to explore possible relations between electrocardiographic changes during physical exercise with other determinants of clinical condition

The specific study aims in Turner's syndrome were:

- to assess aortic dimensions and distensibility in young adults with Turner's syndrome formerly treated with growth hormone

- to assess the effect of growth hormone dose on aortic dimensions and distensibility
- to assess biventricular size and function in young adults with Turner's syndrome formerly treated with growth hormone
- to evaluate the effect of growth hormone dose on biventricular size and function

In **chapter 2** clinical condition was assessed in 59 patients with corrected TOF, and risk factors associated with RV dilation, RV systolic dysfunction and decreased exercise tolerance were identified. Despite the common findings of RV dilation (85% of patients) and RV systolic dysfunction (49% of patients), chapter 2 demonstrated symptomatic status, exercise performance and rhythm status were relatively normal at mid- to long-term follow-up since correction.

Severity of residual PR independently predicted the degree of RV dilation, but not of RV systolic dysfunction. Worse RVEF was independently predicted by abnormal wall motion of the RV outflow tract. Severity of both RV dilation and RV systolic dysfunction related to longer interval since repair, however the moderate associations found with interval since repair could not be used to predict the pace of decline in the individual patient. The most important predictor of worse exercise capacity was worse RVEF. Prolongation of QRS-duration, which was expected to predict larger RV volumes, also independently predicted worse RVEF and worse exercise capacity, or in short functional decline.

We suggest that further improvement of clinical condition may be obtained by improved preservation of RV outflow tract function (both in terms of preserved valvular function and in terms of preserved wall motion), and by a reduction of myocardial electrical inhomogeneity.

In **chapter 3** RV diastolic filling pattern at rest and during dobutamine stress were assessed in a non-selective subset of 36 patients. From previous studies the impact of restrictive RV physiology on clinical condition in corrected TOF remains unclear. End-diastolic forward flow (EDFF) in the main pulmonary artery, a generally accepted sign of restrictive RV filling, was shown to relate to worse exercise capacity at mid- to long-term follow-up. Furthermore patients with EDFF had a higher mean PR-percentage and tended to have a larger RV compared to patients without EDFF. These data are in contrast with the

previous concept that restrictive RV physiology acts protective against the detrimental effects of PR.

RVEF was comparable between patients with and without EDFF and could not be used to explain the observed difference in exercise capacity. Surprisingly, analyses of RV diastolic filling showed the RV filling pattern was most abnormal in patients without EDFF. We hypothesized stress imaging might provide additional information. Repeated measurements of RV diastolic inflow during low dose dobutamine stress showed no change in the RV filling pattern of patients without EDFF, while highly abnormal changes indicative of relaxation related dysfunction emerged in the RV filling pattern of patients with EDFF.

We concluded dobutamine stress MRI may be used to "unmask" abnormalities in RV diastolic filling not appreciated by rest imaging alone. Furthermore it was speculated that the highly abnormal RV filling pattern observed during stress in patients with EDFF contributed to our understanding of the observed difference in exercise limitation between subgroups.

The most recent guidelines for LV heart failure management are partly based on the neurohormonal concept. Surprisingly few data are available on RV remodeling as a result of chronic PR in relation to neurohormonal activation and/or functional ventricular stress reserve. **Chapter 4** describes studies in which 1) level of neurohormonal activation, 2) biventricular contractile reserve, and c) exercise performance were assessed in patients with TOF. In patients corrected at young age according to contemporary surgical strategies, overall levels of neurohormonal markers were normal and biventricular contractile reserve was preserved, irrespective of the amount of residual PR or the subsequent degree of RV dilation.

Only a weak significant positive relation was found between the level of NT pro-BNP and PR-percentage. Risk levels of NT-proBNP were found in 22 (44%) patients. These patients showed smaller biventricular ΔESV with stress and smaller RV-CR compared to other patients. Furthermore patients with hsCRP levels above the median tended to have worse exercise capacity compared to the others. These results can be interpreted as a confirmation of the diagnostic potential of cardiac biomarkers as early signs of activated compensatory mechanisms in case of abnormal ventricular loading conditions.

According to chapter 4, RV size and PR-percentage at best show poor correlations with impaired exercise capacity, biventricular stress response or neurohormonal activation, in a population operated according to current surgical strategies. We therefore question the validity of PR or RV volume criteria for pulmonary valve replacement in this group and suggest patients should probably not undergo pulmonary valve replacement solely based on RV volume or PR fraction criteria.

Previous studies successfully identified indicators of electrical inhomogeneity in the resting ECG of patients with TOF to predict ventricular arrhythmia. In congenital heart disease exercise is considered a predisposing factor for the development of ventricular arrhythmia. Exercise testing may be a useful diagnostic tool to detect such arrhythmia. An extensive analysis of ECG changes with exercise was not yet performed in corrected TOF. **Chapter 5** was used to assess pro-arrhythmogenic changes in the surface ECG of TOF patients and healthy controls during maximal physical exercise.

TOF patients showed significant lengthening of mean QTc duration during exercise, while in controls QTc remained unchanged. Furthermore both QTc and JTc dispersion increased in patients, while controls showed no change. At peak exercise mean JTc dispersion was significantly larger in patients compared to healthy controls and mean QTc dispersion tended to be larger. In addition a larger increase in QTc duration was found to correlate with a larger RV volume and with worse RV systolic function. Finally, a larger increase in JTc dispersion correlated with more severe PR.

Although TOF patient showed no arrhythmia it may be speculated that the increase in inhomogeneity of repolarization indicates increased susceptibility to arrhythmia associated with physical exercise, especially in patients with severe residual PR. As such the data support exercise limiting advices given to TOF patients with severe residual PR.

Using MRI aortic dimensions and distensibility at four predefined locations in young adult women with Turner's syndrome formerly treated with growth hormone were studied in **chapter 6**. During childhood the patients studied randomly received 1, 1.5 or 2 times the regularly used growth hormone dose in Turner's syndrome. In line with previous findings the ascending aortic diameter was enlarged in 30 − 50% of patients. In addition to previous data

Turner patients were shown to have larger mean aortic diameters at all sites of measurement along the thoracic aorta. Compared to healthy controls aortic distensibility in Turner patients was smaller at 2 out of 4 levels of measurement. From this it was concluded that Turner patients, besides aortic dilation, showed signs of impaired wall distensibility. Our findings in Turner's syndrome show similarity with results in Marfan's syndrome and as such are in support of the hypothesis that connective tissue abnormalities may play a role in aortic disease in Turner's syndrome.

Compared to healthy controls mean aortic diameters were larger at all thoracic levels of measurement in the subgroup of Turner patients that received the smallest dose of growth hormone. The other two subgroups only had a larger ascending aorta diameter compared to healthy controls. Compared to controls aortic distensibility was smaller at 3 out of 4 levels of measurement in the subgroup that received the smallest dose of growth hormone, while no differences were found for the other two subgroups. As such results suggest severity of aortic abnormalities in young adulthood relate to growth hormone dose received during childhood, with a beneficial effect of a larger dose on aortic abnormalities.

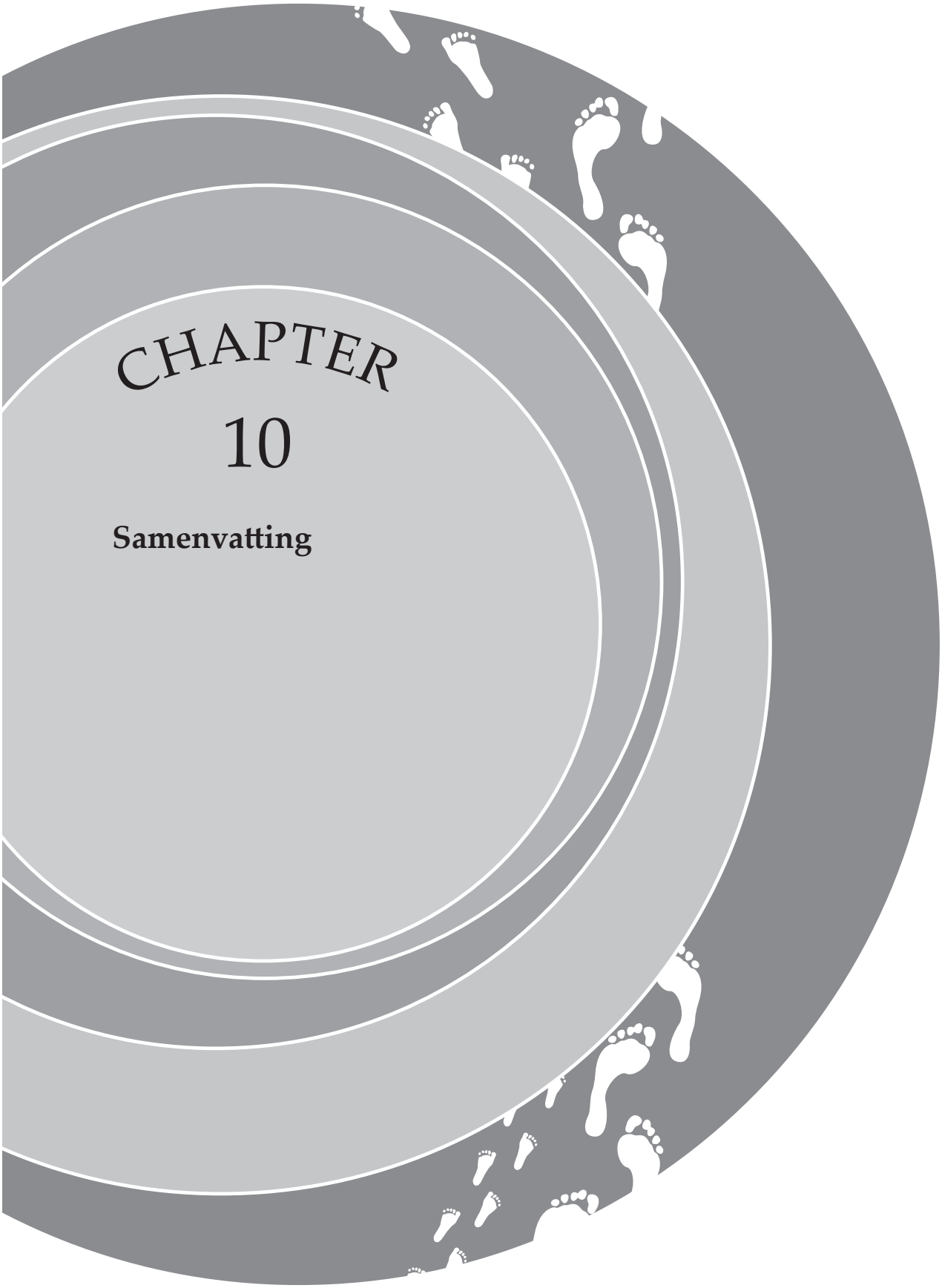
Chapter 7 of this thesis showed young adult women with Turner's syndrome formerly treated with growth hormone do not have myocardial hypertrophy, and show well preserved biventricular function. As such findings contradict the fear for pathologic myocardial remodeling with supra-physiologically dosed growth hormone treatment during childhood in Turner's syndrome.

Mean ventricular volumes, especially that of the left ventricle, were found to be smaller in patients compared to controls. Participants to the present study are a non-selective subgroup of a larger population that participated in a Dutch growth hormone dose-response study. Together with the cardiac findings from this larger cohort, the current data suggests disproportional cardiac growth in Turner's syndrome during childhood. No differences were found between growth hormone subgroups for indices of cardiac size or function.

Turner patients achieved comparable cardiac output to healthy controls, however at a higher mean resting heart rate. In Turner's syndrome a higher mean resting heart rate has repeatedly been found. Left ventricular size may play a role in the underlying aetiology of a higher resting heart. From previous findings in Turner's syndrome, aetiology may be expected to be multi-factorial.

Considering the potential long-term (cardiovascular) mortality risk associated with a higher resting heart rate, we suggest future research in Turner's syndrome to specifically address this topic.

Finally in **chapter 8** the main findings of this thesis are discussed. When applicable suggestions for future research are made.



CHAPTER 10

Samenvatting

Adequate en seriële bepalingen van de functionele cardiovasculaire conditie van patiënten met een aangeboren hartafwijking zijn van belang aangezien veel patiënten een abnormale geometrie van het hart en grote bloedvaten hebben, die al dan niet gepaard gaat met hemodynamische overbelasting. We weten nu dat zelfs na zogenaamde "correctieve hartchirurgie" slechts zelden een totaal normale situatie wordt bereikt. De aanwezigheid van cardiovasculaire restafwijkingen kan de aanleiding zijn van pathologische remodellering van hartspierweefsel, wat uiteindelijk kan resulteren in hartfalen.

Chirurgische correctie van tetralogie van Fallot, de meest voorkomende aangeboren cyanotische hartafwijking, is mogelijk sinds 1955. Er is veel literatuur verschenen met betrekking tot klinische conditie na chirurgische correctie. Desondanks is er een gebrek aan studies gebaseerd op adequate diagnostiek waarin lange termijn resultaten worden beschreven bij patiënten gecorrigeerd volgens de huidige chirurgische norm. De behoefte aan studies gebaseerd op kwantitatieve diagnostiek voor de (herhaaldelijke) bepaling van de klinische conditie van patiënten wordt onderkend. Dit type studies blijft echter beperkt in aantal omdat ze kostbaar en tijdrovend zijn. In eerdere studies werd vaak een niet homogene patiëntenpopulatie geïncludeerd wat betreft diagnose, leeftijd op moment van chirurgische correctie, de gebruikte chirurgische technieken en de postoperatieve conditie. Daardoor wordt de interpretatie van de resultaten uit deze studies bemoeilijkt.

Het gemeenschappelijk doel van de studies beschreven in de **hoofdstukken 2 tot 5** van dit proefschrift is daarom, de verschillende aspecten van functionele cardiovasculaire conditie te onderzoeken op midden tot lange termijn na optimale chirurgische correctie van tetralogie van Fallot volgens de huidige chirurgische norm. Gebruik makend van een crossectionele studieopzet werden tussen september 2002 en november 2004 Fallot patiënten met de volgende eigenschappen onderzocht: 1) totale chirurgische correctie voor de leeftijd van 2 jaar, 2) interval na correctie van minstens 5 jaar, 3) totale chirurgische correctie gebruik makend van een transatriaal transpulmonale benaderingswijze, en 4) optimale correctie van de initiële cardiale afwijkingen passend bij tetralogie van Fallot. Dit laatste werd gedefinieerd als een postoperatieve status zonder rest VSD en zonder rest gradiënt in de rechter ventrikel uitstroombaan > 30 mmHg.

Gedocumenteerde cardiovasculaire bijwerkingen in geval van een groeihormoon overschot, zoals in patiënten met acromegalie, zijn de aanleiding

geweest voor zorgen omtrent mogelijke cardiovasculaire risico's verbonden aan hooggedoseerde groeihormoonbehandeling. Het syndroom van Turner is op dit moment één van de indicaties voor groeihormoonbehandeling bij kinderen. Er is momenteel echter geen data voorhanden met betrekking tot cardiovasculaire conditie van patiënten met het syndroom van Turner na het stoppen van groeihormoonbehandeling.

Het gemeenschappelijk doel van de studies beschreven in de **hoofdstukken 6 en 7** van dit proefschrift is daarom om de verschillende aspecten van functionele cardiovasculaire conditie te onderzoeken bij jong volwassen vrouwen met het syndroom van Turner, die gedurende de kinderjaren werden behandeld met groeihormoon. De deelneemsters vormen een niet-selectieve afspiegeling van een grotere populatie die eerder deelnam aan een Nederlandse groeihormoon dose-response studie op basis van vrijwillige deelname aan de beschreven MRI studie. De bevindingen bij patiënten werden vergeleken met bevindingen bij gezonde vrouwelijke controles, met een vergelijkbare leeftijd en een vergelijkbaar lichaamsoppervlak (m^2). De MRI onderzoeken werden uitgevoerd tussen mei 2003 en juni 2004.

Hoofdstuk 1 bevat een inleiding betreffende 1) de algemene problematiek gezien tijdens het vervolgen van patiënten met een aangeboren hartafwijking, 2) de specifieke problematiek gezien bij patiënten na chirurgische correctie van tetralogie van Fallot en bij patiënten met het syndroom van Turner, en 3) de diagnostische middelen gebruikt in dit proefschrift. Aan het eind van dit hoofdstuk komen de specifieke studiedoelen van dit proefschrift aan de orde.

De specifieke studiedoelen in tetralogie van Fallot waren:

- het bepalen van de klinische conditie, inclusief de bepaling van het volume en de functie van beide ventrikels, gebruik makend van MRI
- de identificatie van risicofactoren voor het optreden van rechterventrikel dilatatie, rechterventrikel disfunctie en verminderde inspanningscapaciteit
- het bepalen van rechterventrikel diastolische functie op basis van vullingpatronen in rust en tijdens farmacologische stress
- de evaluatie van het effect van restrictieve rechterkamer fysiologie, aangeduid door einddiastolische voorwaartse flow in de arteria pulmonalis communis, op de klinische conditie van de patiënt

- het bepalen van de graad van 1) neurohormonale activiteit, 2) biventriculaire functionele contractiele reserve en 3) maximale inspanningscapaciteit, in relatie tot de mate van rest pulmonaalklep insufficiëntie (PI) en de ernst van rechterkamer dilatatie
- de bepaling van pro-arritmogene electrocardiografische veranderingen tijdens maximale fysieke inspanning in het oppervlakte ECG
- nagaan van de mogelijks aanwezige relaties tussen electrocardiografische veranderingen in patiënten tijdens fysieke inspanning en andere determinanten van klinische conditie

De specifieke studiedoelen in het syndroom van Turner waren:

- het bepalen van de dimensies en de distensibiliteit van de aorta in jongvolwassen patiënten die tijdens de kinderjaren werden behandeld met groeihormoon
- het effect nagaan van groeihormoon op de dimensies en de distensibiliteit van de aorta
- het bepalen van de afmetingen en de functie van beide ventrikels in jongvolwassenen patiënten die tijdens de kinderjaren werden behandeld met groeihormoon
- het effect nagaan van groeihormoon op de afmetingen en functie van beide ventrikels

In **hoofdstuk 2** werd in 59 patiënten na chirurgische correctie van tetralogie van Fallot de klinische conditie bepaald en werden risico factoren geassocieerd met rechterkamer dilatatie, rechterkamer systolische disfunctie en verminderde inspanningscapaciteit geïdentificeerd. Ondanks dat er frequent rechterkamer dilatatie (85% van de patiënten) en rechterkamer systolische disfunctie werd vastgesteld onder deze patiënten laat hoofdstuk 2 zien dat allen asymptomatisch tot minimaal symptomatisch zijn, een relatief normale inspanningscapaciteit hebben, zonder klinisch belangrijke ventriculaire ritmestoornissen.

De ernst van rest PI bleek een onafhankelijke voorspeller van rechterkamer dilatatie, maar niet van rechterkamer disfunctie. Abnormale wandbeweging in de rechterventrikel uitstroombaan bleek een onafhankelijke voorspeller van verminderde rechterkamer ejectiefractie. Ernst van zowel rechterkamer dilatatie als disfunctie waren geassocieerd met een langer interval sinds correctie.

Deze associaties konden echter niet worden gebruikt om achteruitgang in de individuele patiënt te voorspellen. De belangrijkste voorspeller van verminderde inspanningscapaciteit was een verminderde rechterkamer ejectiefractie. Zoals verwacht uit eerder onderzoek was een verlengd QRS-interval geassocieerd met een groter rechterkamer volume. Daarnaast vonden wij echter dat QRS verlenging ook een onafhankelijke voorspeller was van een verminderde rechterkamer ejectiefractie en verminderde inspanningscapaciteit, of in het kort van functionele achteruitgang.

Op basis van deze gegevens stellen wij dat verdere verbetering van de klinische conditie in patiënten met tetralogie van Fallot kan worden bereikt door te streven naar een verbeterde rest functie van de RV uitstroombaan na chirurgische correctie (zowel wat betreft minder rest PI als minder afwijkingen in wandbeweging), en door het reduceren van de elektrische inhomogeniteit in het hartspierweefsel.

In een niet-selectieve subgroep van 36 patiënten werd in **hoofdstuk 3** de diastolische functie van de rechterkamer in rust en tijdens dobutamine stress bepaald door middel van vullingpatronen. Op basis van eerder onderzoek was het effect van restrictieve vulling van de rechterkamer op klinische conditie onduidelijk. In hoofdstuk 3 werd aangetoond dat einddiastolische voorwaartse flow in de arteria pulmonalis communis (EDFF), een algemeen aanvaard teken van restrictieve rechterkamer vulling, gerelateerd is aan verminderde inspanningscapaciteit op midden tot lange termijn na correctie. Bovendien hadden patiënten met EDFF gemiddeld een hoger PI-percentage en neigden zij naar een gemiddeld grotere rechterkamergrootte in vergelijking tot patiënten zonder EDFF. Aldus zijn onze data in tegenspraak met de eerdere veronderstelling dat restrictieve rechterkamer fysiologie patiënten zou beschermen tegen de schadelijke effecten van pulmonaalklep insufficiëntie.

Er werd geen significant verschil gevonden in rechterventrikel ejectiefractie tussen patiënten met en zonder EDFF ter verklaring van het vastgestelde verschil in inspanningscapaciteit. Bovendien, en tot onze verrassing liet analyse van de rechterkamer vulling het meest abnormale patroon zien in patiënten zonder EDFF. Wij stelden de hypothese dat stress imaging aanvullende informatie zou kunnen verschaffen. Een herhaling van de meting van het rechterventrikel vullingpatroon tijdens dobutamine stress liet geen verandering zien in patiënten zonder EDFF, terwijl zeer abnormale veranderingen, wijzend op

relaxatie gebonden disfunctie, zichtbaar werden in het vullingpatroon van patiënten met EDFF.

We concludeerden dat dobutamine stress MRI gebruikt kan worden om afwijkingen in het diastolische vullingpatroon van de rechterkamer aan het licht te brengen die gemaskeerd worden in rust. Daarnaast stelden wij dat het vastgestelde abnormale patroon van rechterventrikel vulling in patiënten met EDFF tijdens stress bijdroeg aan ons begrip van het vastgestelde verschil in inspanningscapaciteit tussen patiënten met en zonder EDFF.

De meeste recente richtlijnen betreffende de behandeling van patiënten met linkerventrikel falen zijn gedeeltelijk gebaseerd op het zogenaamde "neurohormonale concept" (zie hoofdstuk 1.4.1). Er is verrassend weinig informatie beschikbaar over rechterkamer remodellering ten gevolge van chronische pulmonaalklep insufficiëntie in relatie tot neurohormonale activiteit en/of ventriculaire functionele stress reserve. In hoofdstuk 4 werden de volgende zaken daarom bepaald in patiënten met tetralogie van Fallot: 1) de neurohormonale activiteit, 2) de contractiele reserve van beide ventrikels, en c) de inspanningscapaciteit. In patiënten gecorrigeerd op jonge leeftijd volgens de huidige chirurgische norm werden normale waarden gevonden voor neurohormonale markers van hartfalen en bleek de contractiele reserve van beide ventrikels behouden, onafhankelijk van de ernst van insufficiëntie van de pulmonaalklep en de graad van rechter ventrikel dilatatie.

Er werd alleen een zwakke, positieve relatie gevonden tussen NT-proBNP en het PI-percentage. NT-proBNP waarden geassocieerd met een verhoogd risico op hartfalen werden vastgesteld in 22 (44%) patiënten. Tijdens dobutamine stress lieten deze patiënten een kleinere verandering in het eind-systolische volume van beide ventrikels zien, evenals een kleinere toename van de rechterkamer ejectiefractie. Tenslotte neigden patiënten met een hsCRP waarde boven de mediaan naar een gemiddeld lagere inspanningscapaciteit ten opzichte van de overige patiënten. Deze resultaten kunnen worden gezien als een bevestiging van het diagnostisch potentieel van cardiale biomarkers voor vroegtijdige onderkenning van activatie van compensatoire mechanismen bij abnormale ventriculaire belasting.

Volgens de bevindingen in hoofdstuk 4 correleren rechterventrikel grootte en PI-percentage matig met inspanningscapaciteit, functionele ventrikel reserve en mate van neurohormonale activatie in een populatie gecorrigeerd volgens

de huidige chirurgische norm. Daarom stellen wij de waarde van richtlijnen voor pulmonaalklepvervanging gebaseerd PI-percentage en rechterventrikel grootte in deze patiënten populatie ter discussie en opperen we dat de indicatie voor pulmonaalklepvervanging waarschijnlijk niet louter gesteld dient te worden op basis van PI-percentage en rechterkamer grootte.

Eerdere studies hebben met succes indicatoren gevonden van elektrische inhomogeniteit in het elektrocardiogram van Fallot patiënten tijdens rust, die ventriculaire ritmestoornissen kunnen voorspellen. In meerdere aangeboren hartafwijkingen wordt fysieke inspanning gezien als een uitlokkende factor voor het ontwikkelen van ritmestoornissen. Inspanningstesten kunnen nuttig zijn om dergelijke ritmestoornissen te documenteren bij risicopatiënten. Tot op heden werd geen uitgebreide analyse verricht van veranderingen in het elektrocardiogram van Fallot patiënten tijdens fysieke inspanning. In **hoofdstuk 5** werden pro-arritmogene veranderingen in het elektrocardiogram van Fallot patiënten en gezonde controles bepaald tijdens maximale fysieke inspanning.

Patiënten met TOF toonden een significante verlenging van de gemiddelde QTc-duur tijdens inspanning, terwijl er geen verandering werd gezien in gezonde controles. Bovendien was er sprake van een toename van de QTc en JTc dispersies tijdens inspanning in patiënten, terwijl geen veranderingen werden gezien in gezonde controles. Hierdoor was op het moment van maximale inspanning de gemiddelde JTc dispersie significant groter in patiënten. Bovendien correleerde een grotere toename in QTc duur met een groter rechterkamer volume en met een slechtere rechterkamer functie. Tenslotte werd vastgesteld dat een grotere toename in JTc dispersie correleert met meer PI.

Ondanks dat onze patiënten geen ritmestoornissen lieten zien, kan op basis van onze gegevens worden gespeculeerd dat de toename in elektrische inhomogeniteit tijdens ventrikel repolarisatie verwijst naar een verhoogde ontvankelijkheid voor het ontwikkelen van ritmestoornissen tijdens inspanning. Een verschijnsel dat in de grootste mate aanwezig lijkt in de subgroep patiënten met ernstige rest PI. Aldus steunen onze resultaten het gebruik van inspanningsbeperkende adviezen bij patiënten met een ernstige rest PI.

Gebruik makend van MRI technieken werd in **hoofdstuk 6** op vier vooraf vastgestelde meetpunten de dimensie en distensibiliteit van de aorta bepaald in jongvolwassen vrouwen met het syndroom van Turner. Gedurende de kinderjaren waren deze patiënten behandeld met groeihormoon, waarbij ad random 1, 1.5 of 2 maal de normaal gebruikte dosis werd gegeven. Overeenkomstig met eerdere resultaten werd in 30 − 50% van de patiënten een vergrote diameter van de aorta ascendens gevonden. In aanvulling op eerdere resultaten werd bij Turner patiënten een gemiddeld grotere diameter van de aorta gevonden ten opzichte van gezonde controles ter hoogte van alle meetpunten in de thoracale aorta. Ten opzichte van gezonde controles was de distensibiliteit van de aorta kleiner op 2 van de 4 meetpunten in patiënten. Op basis van deze gegevens werd geconcludeerd dat patiënten met het syndroom van Turner naast dilatatie ook tekenen van abnormale distensibiliteit van de aorta vertonen. Onze bevindingen vertonen overeenkomsten met bevindingen in patiënten met het syndroom van Marfan en steunen de hypothese dat aorta afwijkingen in het syndroom van Turner mogelijks gerelateerd zijn aan een afwijkende samenstelling van de aortawand.

Ten opzichte van gezonde controles waren de gemiddelde diameters van de aorta in de subgroep patiënten die de laagste dosis groeihormoon kreeg tijdens de kinderjaren groter ter hoogte van alle thoracale meetpunten. De andere twee subgroepen hadden alleen een grotere diameter ter hoogte van de aorta ascendens. Ten opzichte van gezonde controles was de gemiddelde distensibiliteit van de aorta kleiner op 3 van de 4 meetpunten in de subgroep die de laagste dosis groeihormoon kreeg tijdens de kinderjaren, terwijl er geen verschillen werden gevonden ten opzichte van controles in de andere 2 subgroepen. Aldus wekken deze resultaten de indruk dat de ernst van aorta afwijkingen bij jongvolwassen patiënten met het syndroom van Turner gerelateerd zijn aan de dosis groeihormoon ontvangen in de kinderjaren, waarbij er een heilzaam effect op de mate van afwijkingen lijkt uit te gaan van een hogere dosis groeihormoon.

Hoofdstuk 7 van dit proefschrift laat zien dat jongvolwassen vrouwen met het syndroom van Turner die eerder werden behandeld met groeihormoon, geen tekenen van myocard hypertrofie hebben en een goed bewaarde functie van beide ventrikels. Deze bevindingen weerleggen de angst voor pathologische remodellering van het myocard ten gevolge van supra-fysiologisch gedoseerde

groeihormoon behandeling tijdens de kinderjaren bij het syndroom van Turner.

De gemiddelde ventrikel volumes, en vooral die van de linker ventrikel, bleken kleiner in patiënten ten opzichte van gezonde controles. Deelneemsters aan deze studie zijn een niet-selectieve afspiegeling van een grotere populatie die eerder deelnam aan een Nederlandse groeihormoon dose-response studie. Samen met de cardiale gegevens afkomstig uit dit groter cohort, wekken de data beschreven in hoofdstuk 7 de indruk dat er disproportionele groei plaatsvindt van het hart tijdens de kinderjaren in patiënten met het syndroom van Turner. Er werden geen verschillen gevonden voor ventrikel grootte en functie tussen de verschillende groeihormoon subgroepen.

In rust hadden onze Turner patiënten een vergelijkbare cardiac output ten opzichte van gezonde controles, maar bereikten deze output aan een gemiddeld hogere hartfrequentie. Een hogere hartfrequentie in rust werd herhaaldelijk beschreven in het syndroom van Turner. Linker ventrikel afmetingen kunnen een rol spelen in de onderliggende etiologie van een toegenomen hartfrequentie. Echter gezien eerdere bevindingen in het syndroom van Turner kan worden verondersteld dat de etiologie multifactorieel bepaald is. Het potentieel lange termijn risico op toegenomen mortaliteit in ogenschouw nemend, stellen wij voor toekomstig onderzoek specifiek toe te spitsen op dit fenomeen.

Tenslotte worden de belangrijkste bevindingen van dit proefschrift in **hoofdstuk 8** besproken en worden suggesties gedaan voor toekomstig onderzoek.

Dankwoord

Het mag dan eindelijk gebeuren, het schrijven van mijn dankwoord. In de afgelopen 5 jaar zijn er heel wat mensen in meer of mindere mate betrokken geweest bij het tot stand komen van dit proefschrift. Daarvoor wil ik allen hartelijk danken. Hiermee mijn proefschrift af sluiten zou echter geen recht doen aan de inspanningen geleverd door een aantal mensen die ik hieronder persoonslijk wil noemen.

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Curriculum Vitae

Jochem van den Berg is geboren op 18 april 1976 in Eindhoven en groeide op in Best. In 1994 behaalde hij zijn VWO diploma aan het Jacob-Roelandslyceum te Boxtel. In dat zelfde jaar startte hij met de opleiding geneeskunde aan de Katholieke Universiteit van Leuven. In 1997 behaalde hij daar de graad kandidaat arts en in 2001 de graad arts. Gedurende het laatste, zogenaamde prespecialisatie jaar van de opleiding, was hij werkzaam als co-assistent op de afdeling kindergeneeskunde van het Universitair ziekenhuis Gasthuisberg te Leuven. In dat jaar was hij betrokken bij een effectiviteitstudie naar de rol van dexamethasone in de behandeling van RSV-brochiolitis bij kinderen met een onderliggende aandoening, uitgaand van de afdeling kinderlongziekten, onder leiding van Prof. dr. M. Proesmans.

Na het afronden van de opleiding geneeskunde was hij werkzaam als assistent kindergeneeskunde (AGNIO) in het Elkerliek ziekenhuis te Helmond.

In januari 2002 is hij gestart met zijn promotieonderzoek aan de afdelingen kindercardiologie (Prof. dr. W.A. Helbing) en radiologie (Prof. dr. P.M.T. Pattynama) van het Erasmus MC te Rotterdam. Hieruit zijn een aantal artikelen voortgekomen zoals beschreven in dit proefschrift.

Sinds juli 2006 is hij werkzaam als arts-assistent kindergeneeskunde in opleiding op de afdeling kindergeneeskunde van het St. Elisabeth ziekenhuis te Tilburg. In 2008 zal hij zijn opleiding vervolgen in het Wilhelmina Kinderziekenhuis te Utrecht.

Jochem woont samen met Marleen. Zij hebben een zoon, Brent.

List of Publications

- Jochem van den Berg, Ellen M. Bannink, Piotr A. Wielopolski, Peter M. Pattynama, Sabine M. de Muinck Keizer-Schrama, Willem A. Helbing. Aortic Distensibility and Dimensions and the Effects of Growth Hormone Treatment in the Turner Syndrome. *Am J Cardiology* 2006;97(11):1644-9.

- Jochem van den Berg, Piotr A. Wielopolski, Folkert J. Meijboom, Maarten Witsenburg, Ad J.J.C. Bogers, Peter M.T. Pattynama, Willem A. Helbing. Diastolic function assessed with magnetic resonance imaging in repaired tetralogy of Fallot at rest and during stress: restrictive right ventricular physiology is associated with worse clinical state at mid to long-term follow-up. In Press; *Radiology*.

- Jochem van den Berg, Wim C. Hop, Jan L.M. Strengers, Johan C. de Jongste, Lennie van Osch-Gevers, Folkert J. Meijboom, Peter M.T. Pattynama, Ad J.J.C. Bogers, Willem A. Helbing. Clinical condition at mid- to late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. Accepted; *The Journal of Thoracic and Cardiovascular Surgery*

- Jochem van den Berg, Jan L.M. Strengers, Piotr A. Wielopolski, Wim C. Hop, Folkert J. Meijboom, Yolanda B. de Rijke, Frans Boomsma, Ad J.J.C. Bogers, Peter M.T. Pattynama, Willem A. Helbing. In patients operated for tetralogy of Fallot at young age, impaired exercise capacity, biventricular stress response and neurohormonal levels are not related to RV volume and pulmonary regurgitant fraction. *Submitted*.

- Jochem van den Berg, Sandra de Bie, Folkert J. Meijboom, Wim C. Hop, Peter M.T. Pattynama, Ad J.J.C. Bogers, Willem A. Helbing. Changes during exercise of ECG predictors of ventricular arrhythmia in repaired tetralogy of Fallot. *Submitted*.

- Jochem van den Berg, Ellen M.N. Bannink, Piotr A. Wielopolski, Wim C. J. Hop, Lennie van Osch-Gevers, Peter M.T. Pattynama, Sabine M.P.F. de Muinck Keizer-Schrama, Willem A. Helbing. Disproportionate cardiac size in adult Turner syndrome patients after growth hormone therapy during childhood. *Submitted*.