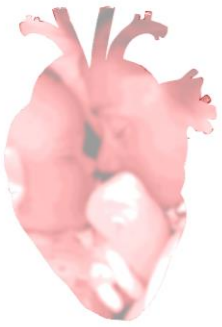
SYNDROMIC THORACIC AORTIC DISEASE

THE BICUSPID AORTIC VALVE, TURNER SYNDROME AND LOEYS-DIETZ SYNDROME TYPE III



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Syndromic Thoracic Aortic Disease

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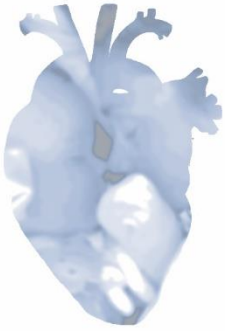
Voor Wianka en Jurriën

Contents



1

General introduction
Outline of the thesis

General introduction

Over the past decades the face of medicine has changed radically for patients with cardiac disease. Advances in research and developments in technology, coupled with a significant global increase in spending on health-related issues has caused a significant improvement in life expectancy [1-3]. This positive trend has impacted the lives of many, but especially of those suffering from congenital heart disease (CHD) (figure 1) [4]. The introduction of the heart-lung machine and other advance in the second half of the 20th century had a dramatic impact on the outcome of patients with severe congenital heart disease, where previously only 15% of patients reaching adulthood, now more than 90% of patients reach adulthood [5].

The Bicuspid aortic valve (BAV) is the most frequent congenital heart defect [6], with a prevalence of approximately 2% in the general population [6, 7]. Despite its frequent occurrence, we know relatively little about its etiology, natural history and optimal treatment. Importantly, in 50% of BAV patients dilatation of the ascending aorta occurs, adding to the elevated risk of aortic dissection. Turner syndrome (TS) is a genetic syndrome that is often associated with many different forms of CHD including a bicuspid aortic valve [8]. The risk of aortic dissection is elevated in patients with TS and reported to be 6 times or even 20 times higher compared with the normal population [9, 10].

A third group at risk of aortic dissection are the patients with a SMAD3 genetic mutation. This specific mutation was first described by our group in 2011 and the clinical entity was called the Aneurysm-Osteoarthritis syndrome. Recently, it became clear that there is overlap with other genetic syndromes and currently this syndrome is classified as Loeys-Dietz syndrome (LDS) type III. In this thesis we expand upon earlier efforts and describe long-term outcome and quality of life in these patients.

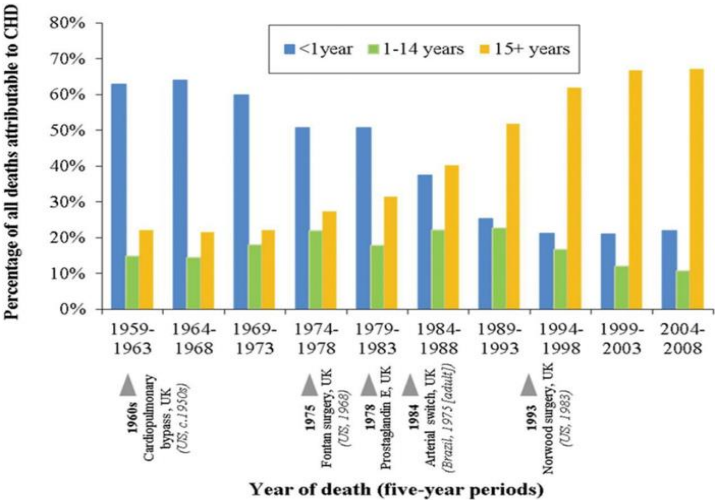


Figure 1. Trends in the percentage of all congenital heart defect–related deaths that occurred in England and Wales between 1959 and 2009, assessed at different ages. CHD indicates congenital heart disease (Knowles et al, 2012). *Reprinted with permission from BMJ Publishing Group Ltd. (License number: 4676510373318)*

Turner syndrome

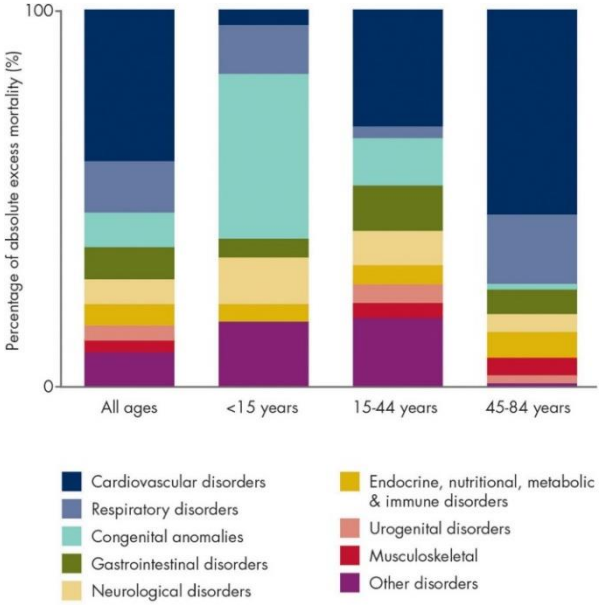


Figure 2. Differentiated mortality in TS for all ages and according to age groups. Categories were defined according to International Classification of Diseases. Numbers are adapted to express the percentage of total absolute excess risk caused by the group of disorders in question (8). *Reprinted with permission from Oxford University Press. (Licence number: 4676510824795)*

TS is a genetic disorder that is caused by a partial or complete monosomy of the X-chromosome, which occurs in 1 per 2500 live born females [11]and was first described by Henry Turner in 1938 [12]. TS patients may suffer from a multitude of disorders including short stature, estrogen deficiency, infertility and a 'webbed neck' [13]. Additionally, Diabetes, hypertension, ischaemic heart disease and stroke are prevalent and autoimmunity is increased, leading to thyroiditis (figure) 2 [8]. Care for Turner syndrome patients is generally provided by a multidisciplinary team in a tertiary centre; the standard composition of this team includes, at a minimum, a gynaecologist, endocrinologist-internist and cardiologist. Recently, the cardiovascular aspects of the syndrome have received more attention. Accordingly, current guidelines [14]dictate that every patient should consult a cardiologist specialized in congenital cardiology at least once every five years. This is especially important as an estimated 50% of women with TS will suffer from either congenital or acquired [15, 16]cardiovascular disease. These congenital abnormalities complicate care and are the main causes of morbidity and mortality in patients suffering from TS [8].

Often, these congenital heart defects (CHD) are left-sided, the most prevalent are: a bicuspid aortic valve (BAV, 15-30%), elongation of the transverse aortic arch (ETA, 49%) and coarctation of the aorta (CoA, 17%) [8, 16]. Additionally, bovine aortic arch, arteria lusoria may occur figure 3 [8]. Associated venous lesions frequently include partial abnormal pulmonary venous return (PAPVR) and persistent left superior vena cava (LSVC) [16, 17]. Other defects, such as a ventricular septal defect (VSD), are seen less often in TS [18]. Women with Turner syndrome also suffer from acquired heart diseases which mainly comprise hypertension, aortic dilatation, and dissection [9, 10].

Genetics of the cardiovascular pathology in TS

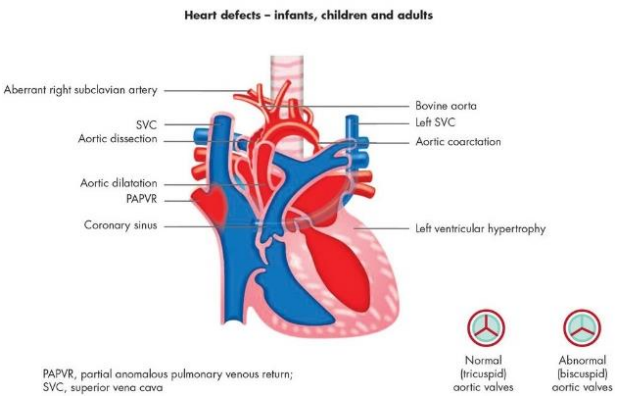


Figure 3. The most common congenital cardiovascular malformation seen in TS.PAPVR, Partial anomalous pulmonary venous return; SVC, superior vena cava (8).*Reprinted with permission from Oxford University Press. (Licence number: 4676511219970)*

On a genetic level TS and Bicuspid aortic pathology appear to exhibit some interesting similarities. Turner syndrome is an 'aneuploid' condition resulting from the complete or partial loss of the second sex chromosome [19]. It seems that the resulting 'deficiency' of sex chromosome genes predisposes individuals with Turner syndrome to diseases that are known to have a sex bias in the general population. Such a male predisposition is also present in patients with a bicuspid aortic valve. Together, the combination of the high incidence of BAV in women with Turner syndrome and the substantial sex bias towards males in the general 'euploid' population together suggest that there is a certain measure of 'protection' conferred by having a second X chromosome [19]. However, while all women with TS are by definition 'aneuploid' to a degree, certainly not all have a BAV. Consequently, one might deduce that a 'second hit', other than this monosomy, is necessary to cross the disease threshold (figure 4). Such a second hit, necessary for the aortic disease in TS women could be either environmental or epigenetic.

Recently an important role in BAV pathology has been described for matrix metalloproteinases (MMP's) and their inhibitor (tissue inhibitor of metalloproteinase, TIMP) enzymes that regulate extracellular matrix breakdown [20]. Especially interesting is TIMP-3, which was associated with BAV and aortic dilatation [21]. Downstream, MMP's, are

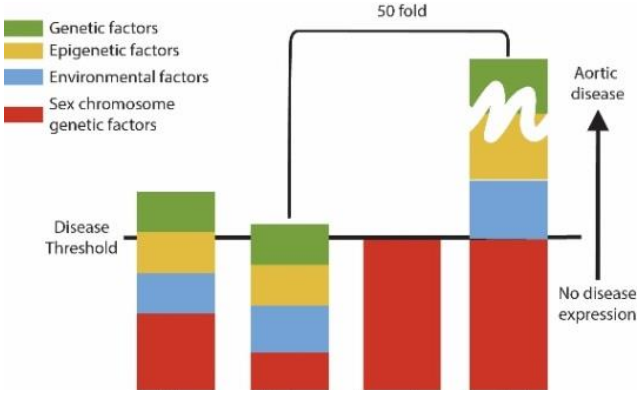


Figure 4. TS genetic hypothesis. The horizontal line represents a theoretical threshold of disease. In TS the loss of an X-chromosome alone is not sufficient alone to breach the disease threshold for BAV as not all women with TS have a BAV (17).

inhibited by TIMPs, where TIMP3 specifically controls MMP-2 and 9, which are highly expressed in thoracic aneurysm tissue. An unbalance between TIMPs and MMPs has been associated with aortic dilatation and dissection, as MMP activity in the tunica media of the aorta disrupts the elastin-based extracellular matrix [22-25].

This theory is supported by a recent study by Corbitt et al., which describes that TIMP3 exceeds genome-wide significance for the association with BAV and aortic root enlargement. However, the TIMP3 gene is located on chromosome 22, whereas previous literature suggested that a genetic factor would most likely be located on the short arm of the X chromosome (Xp), which has been associated with BAV and aortic aneurysms [26, 27]. Therefore Corbitt et al. hypothesize a second gene that has a pathogenic interaction with TIMP3, is unique to Xp, without a homolog elsewhere, escapes X-inactivation and is expressed in the developing aortic valve [19].

Corbitt el al., find that TIMP1, a functionally redundant paralogue of TIMP3, meets these criteria. Additionally, hemizygosity for TIMP 1 increased the chance of BAV aortoparthy, as its copy number is associated with BAV and dissection. This hemizygosity for TIMP 1 is exacerbated by TIMP3 risk alleles and subsequent loss of inhibition of MMP-2 and MMP-9 causes degradation of the extra cellular matrix (ECM) of the aortic wall. Subsequently ECM degradation leads to a release of active TGF-β which increases TGF-β signalling. In turn this increase in TGF-β signalling creates a positive feedback loop by increasing MMP expression and thereby aggravating the TIMP/MMP imbalance (29) and, eventually, aneurysm formation [19].This feedback loop may be the 'second hit' needed to progress from progenitor stages to the aortopathy often seen in Turner syndrome. This hypothesis provides an important foundation on which further studies can build.

Aortic dissection and dilatation

The frailty of the aortic wall that develops via the supposed pathophysiological mechanism described above may cause aortic dilatation, or even aortic dissection. This potential dilatation and dissection pose a serious clinical concern in patients with TS. The estimated prevalence of aortic dissection in women with TS varies greatly in literature, [9, 10] where the most recent and only prospective study estimates the incidence at 354 cases per 100 000 person-years. This is up to 12 times higher compared to the general female population [28]. And in TS aortic dissection is not exclusive to patients of old age, as peak incidence is observed in the third to fifth decade of life and dissection may even occur in the first decade of life [10, 29]. Additionally, in women with TS the diameter of the ascending aorta, where the dissection often originates [9, 10, 30], may be smaller on average than in those with other genetically triggered aortopathies [9, 30, 31], even when corrected for body surface.

Even more challenging than estimating the incidence of dissection, is discerning risk factors for dissection. Some classic risk markers include: hypertension, karyotype 45,X, and left-sided obstructive lesions including bicuspid aortic valves, coarctation of the aorta, and other obstructive arch lesions [8]. Aortic size is another important risk factor for dissection and aortic dilatation is quite common in TS women. As described above, the aetiology of the dilatation in TS is not yet fully understood. However, the histological changes such as cystic medial degeneration are reported in 42 to 72% of aortic dissections in TS [10, 32]. Additionally, collagen fiber composition may also be affected [10]. These changes in vascular smooth muscle cells, elastin, collagen, and other extracellular matrix components are not exclusive to TS as they are also encountered in other thoracic aneurysm diseases [32]. However, it is hard to discern a primary genetic cause from an environmental cause as aortic disease in TS is attenuated by common risk factors such as hypertension and hyperlipidaemia which end in mechanical and elastic failure of the aortic wall [33-35].

The Bicuspid aortic valve and aortic coarctation

Figure 5. Sketch of the aortic valve by Leonardo da Vinci

Leonardo da Vinci first described the bicuspid aortic valve [36], the most prevalent congenital heart defect in humans that affects 1-2% of the population [6, 7](BAV; figure 5), some five hunderd years ago. The number of publications on the bicupsid aortic valve increased exponentially over the past century (figure 6). A normal aortic valve consists of three leaflets and is therefore called tricuspid. Conversely, a bicuspid aortic valve exists in different configurations (figure 7) and consists of two leaflets. Depending on the raphe, different types can be discerned. The commissural fusion between the left and right coronary cusp (Type 1, LR-BAV) is the most common [37]. While the BAV anatomy may not intrinsically hamper valvular function, it is commonly associated with several adverse outcomes such as: valve dysfunction, (either stenotic or insufficient, requiring surgical intervention), bacterial endocarditis, and aortic dilatation and dissection [38-40]. The outcome differs substantially on a patient level and clinical predictors are difficult to discern, which is why the treatment of BAV patients is so challenging. Therefore discovering the etiology of BAV and

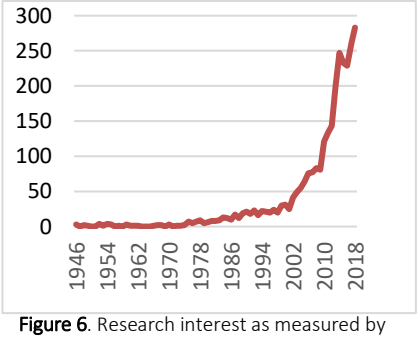


Figure 6. Research interest as measured by number of publications on the bicuspid aortic valve on www.ncbi.nlm.nih.gov/pubmed.

discerning moderators from disease mediators is paramoount in accurately predicting these morbidities and improving clinical outcome.

Aortic dilatation in bicuspid aortic valve

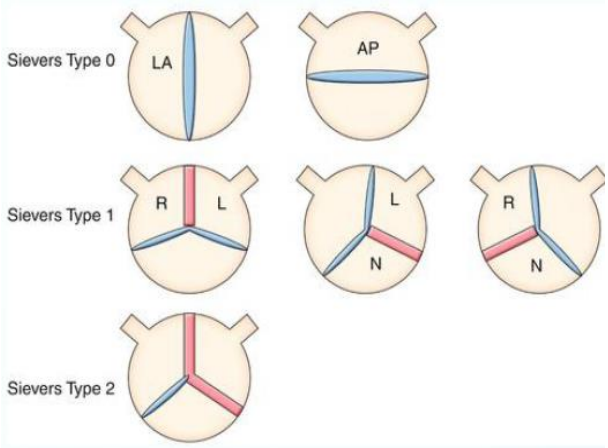


Figure 7. Classification of the bicuspid valve according to Sievers (39), Red lines indicate raphe between fused leaflets. *Reprinted with permission from Springer nature. (Licence number: 4676511219970*

There is much controversy around the aortic dilatation that is often seen in BAV patients. Generally three patterns of aoric dilatation can be discerned in BAV patients. Aortic dilatation of the aortic root and the tubular ascending aorta (type 1) has been associated with diagnosis at older age, aortic valve stenosis, and RL-fusion pattern of the aortic valve [41-43]. The second pattern, where only the tubular ascending aorta is involved, is often seen in co-occurrence with RN-fusion type [41-43]. The third type, where only the aortic root is affected is often considered the type where a genetic cause is most likely as it is associated with dilatation at young age, male sex, and aortic valve inssufficiency [41, 44, 45]. With respect to the etiology, two hypotheses exist. The first assumes the existence of common genetic defect that could potentially cause both the bicuspid leaflet configuration and the aortic wall frailty and subsequent dilatation. And indeed many genes have been associated with the occurence of BAV [46, 47]. More recently, MMP's and their inhibitor proteins TIMP's have been demonstraded to be of influence [20, 22]. The second hypothesis suposes a haemodynamic cause of the dilatation; abnormal BAV dynamics may cause perturbations on blood flow patterns and hemodynamic stress on the aortic wall, leading to aortic dilation [41, 48, 49].

The genetic hypothesis is supported by studies showing higher prevalence of aortopathy in relatives of BAV patients [50] and autosomal dominant, X-linked, and familial inheritance has been described [47]. However, no single gene model can clearly explain BAV inheritance. For example, difference in severity of aortic dilatation persist, even in BAV patients with normally functioning aortic valves or when aortic diameter is corrected for known risk factors such bloodpressure, peak aortic-jet velocity, and left ventricular ejection time [40]. Further histological changes, which are often erronously termed 'cystic medial necrosis' (seeing that they are neither cystic nor necrotic) are frequently found in BAV patients and negatively influence the structural integrity and flexibility of the aorta.

The hemodynamic theory is mainly supported by studies demonstrating regionally increased shear stress of the aortic wall depending on the type of bicuspid valve [41, 51, 52]. This hemodynamic hypothesis is gaining ground and is a promising area of research, especially 4D flow MR. However, mapping aortic wall stress is not without its difficulties, given that apart from technical challenges, data from healthy control populations is necessary in order to identify abnormal flow patterns [53].

SMAD3

In 2011 a new genetic mutation was found, these mutations appeared to cause a syndromic form of familial osteoarthritis and thoracic aortic aneurysms and dissections (TAAD) [54]. The SMAD3 gene encodes for a protein that is part of the transforming growth factor (TGF) β pathway. Nowadays, AOS is recognized by most to be a subtype of the Loeys-Dietz syndrome (LDS) [55]. Oftentimes patients first present with early-onset joint abnormalities, while other features include arterial aneurysms and tortuosity [54]. Mutations in the SMAD3 gene are thought to be responsible for 2% of familial TAAD [54, 56]. The underlying SMAD3 variant is responsible for some variation in the age of onset and penetrance [57]. Lower age of onset of the first aortic event is observed in individuals with a missense mutation in the MH2 domain than in those with halpoinsufficiency variants [57]. The aggressive aortic dilatation nessecitates vigilant follow-ups using yearly advance cardio-vascular imaging in these patients according to a dedicated AOS protocol that was devised in the Erasmus MC. However, the longterm outcomes of these patients and how their quality of life is affected by their affliction is unknown as of yet. Therefore, Part III of this thesis discusses those matters in two separate chapters.

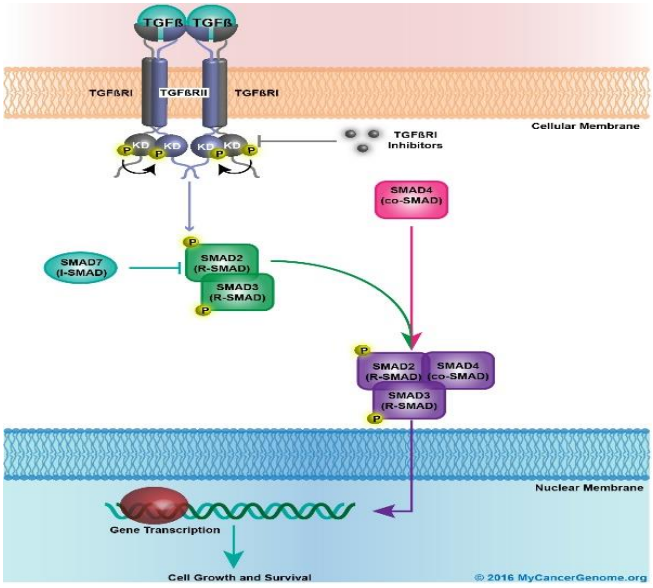


Figure 8.

TGF-β binds to the TGF-β receptor complex (TGFBR1 and 2). TGFBR1 then activates SMAD2 and SMAD3, which trimerize with a SMAD4. This SMAD trimer promote cell growth and survival after entering the nucleus and activating gene transcription and. Reprinted from: *mycancergenome.org/content/pathways/TGF-beta-signaling/*

This thesis: the BAV-study

This thesis covers aortic pathology in a broad perspective, but focusses on the pathology found in women with Turner syndrome and patients, with a SMAD3 mutation or a bicuspid aortic valve.

It centers around the BAV-study, funded by the Dutch Heart foundation, which was designed to find clinical risk markers that predict decline of cardiac function or complications in patients with BAV or TS. For that purpose, 187 patients with Turner syndrome or a bicuspid aortic valve were consecutively included in this prospective multicenter cohort study; a collaboration between the Radboud UMC, Leiden UMC ande the Erasmus MC. They either had a bicuspid aortic valve or Turner syndrome. The inclusion criteria for the BAV-patients were age ≥ 18 year and one of the following: [1] aortic stenosis (gradient >2.5 m/s), [2] aortic regurgitation (at least moderate) or [3] ascending aortic dilation ≥40 mm and/or aortic size index >2.1 cm/m2. At baseline and at three-year follow-up the study protocol included: blood sampling, cardiopulmonary exercise testing (CPET), twelve-lead electrocardiogram (ECG), trans thoracic echocardiography (TTE), CT and CMR on the same day (figure 8).

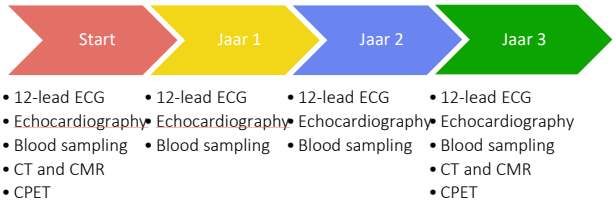


Figure 8. Schematic overview of the BAV-study.

This thesis aims to elucidate the etiologies and pathogenic mechanisms leading to BAV or aneurysm formation and find risk factors for disease progression. Furthermore, this thesis aims to explore the myriad of cardiovascular abnormalities associated with TS and to study their impact on the quality of life of the individual patient in addition to comprehensively describing the TS cardiovascular phenotype. This is done with a view to enabling the eventual individualization of current treatment protocols and to derive novel therapeutic strategies.

Part I focuses on Turner syndrome, its associated pathologies and the quality of life of TS women. The combination of imaging findings and clinical outcomes in patients with a bicuspid aortic valve is described in Part II. Finally, in Part III long-term follow-up of aortic diameters and the quality of life of patients with a SMAD-3 mutation is explored.

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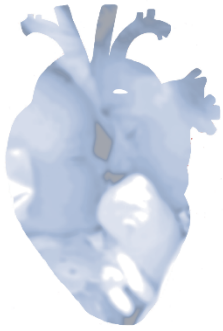
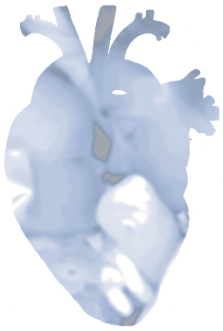


TURNER SYNDROME

TURNER SYNDROME



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Turner Syndrome and Cardiovascular Pathology

Aneurysms-Osteoarthritis Syndrome (book chapter)

Abstract

Turner syndrome is a complex and divers clinical entity that requires the cooperation of a myriad of specialist and allied health professions. One of the first concerns in these patients are the congenital and acquired cardiac and aortic pathologies. The cardiac pathology in these women ranges from benign to severe and life threatening disease. This chapter provides a narrative review of the known cardiovascular disease in women with Turner syndrome and describes several theories regarding its origin. Moreover, several of most frequently encountered clinical aspects are discussed.

Introduction

Turner syndrome (TS), a partial or complete monosomy of the X-chromosome, is a genetic disorder that occurs in 1 per 2500 live born females [1] and was originally described by Henry Turner in 1938 [2]. Patients may suffer from a multitude of disorders including short stature, estrogen deficiency, infertility and a 'webbed neck' [3]. The morbidity and mortality is significantly higher in these patients [1, 4]. Turner patients' care is given by a multidisciplinary team in a tertiary centre; such a team often comprises of a paediatrician, gynaecologist, endocrinologist-internist and cardiologist. In complex patients it may also be necessary to involve E.N.T. specialists, clinical-geneticists, ophthalmologists, psychologists, orthodontologists and orthopaedic surgeons. Recently the cardiovascular aspect of the syndrome has received more attention and according to current guidelines [5] every patient should be advised to visit a cardiologist specialized in congenital cardiology at least every five years. Due to increasingly complex patient care it is important that all patient care providers are aware of the cardiovascular phenotype associated with Turner syndrome. In this chapter the various cardiovascular manifestations that may occur in patients with Turner syndrome will be presented and the latest insights into the genetic aspects of the syndrome will be discussed.

Genetics

Females typically have two X-chromosomes, one paternally derived (X^p) and one maternally derived (X^m). However, in Turner Syndrome a *de novo* nondisjunction of the X-chromosome can lead to a female with a completely or partially absent X-chromosome, most often the paternal X-chromosome. This nondisjunction results in a diverse spectrum of karyotypes, of which the non-mosaic 45,X0 monosomy is the most well-known. Other Turner syndrome associated karyotypes known to cause are different forms of mosaicism (e.g. 45X/46XX) and structurally abnormal X-chromosomes such as iso-chromosomes (e.g. 46X,i(Xq)), ring chromosomes (e.g. 46X,r(X)), deletions (e.g. 46,X,del(X)) and even karyotypes with Y-chromosomal DNA (e.g. 45,X/46XY).

The suggestion that the non-disjunction in TS is the result of meiotic factors is unlikely since the number of 45,X conceptions is too high to be explained solely by the frequency of gametes hypo haploid for a sex chromosome. [6] A loss of sex chromosome after conception (a mitotic loss) would better explain the unequal ratio of the parental origin of the X-chromosome (male:female, 1:3). Due to the fact that a 46,XX conception would generate, upon loss of one X-chromosome during mitosis, a 45,X line with equal paternal and maternal origin of the remaining X-chromosome, whereas a 46,XY conception would generate a 45,X cell line of maternal origin. This explains a 1 to 3 male-to-female ratio.

An estimated 1 in every 100 pregnancies start as a Turner syndrome (45,X0) pregnancy. However, 99% of these pregnancies do not make it to full term [6]. In about 50% of the cases, analysis of peripheral lymphocytes indicates the complete loss of one X-chromosome, most often the paternal X-chromosome. However, most studies will have an inherent bias because 45,X0 will be over-represented in clinical populations since they are more prone to display the Turner phenotype. The frequency of the chromosomal pattern varies depending on the reason for karyotyping [7]. Karyotype determination that is carried out because of prenatal echo findings show a 45,X0 karyotype in 90% of cases, whereas it is only 63% in accidental findings.[5]

In addition, with the use of more sensitive genetic techniques such as fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase-chain-reaction (PCR) assays, non-mosaic 45,X0 prevalence rises to 60% and 74% respectively. This may suggest that the survival of non-mosaic karyotypes is an even rarer event than previously assumed. Thus, the hypothesis by Hook and Warburton that all Turner syndrome females might actually be 'cryptic mosaics' gains ground.

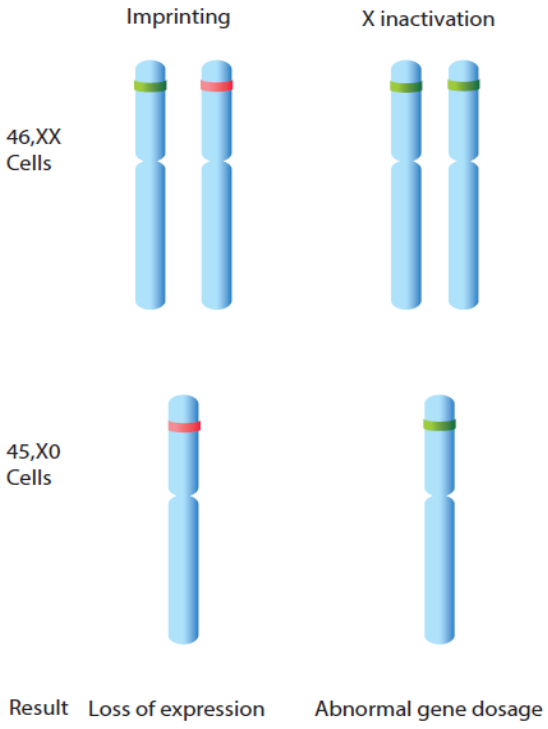

Figure 1. Genetic theory of Parental imprinting and X-inactivation.

However, the question of why the (in part) absence of an X-chromosome should be so invalidating when approximately 50% of the world population seems to do fine with one X-chromosome still remains.

Two main theories exist that try to explain the phenotypes found in Turner syndrome. A visual depiction of both theories is provided in figure 1.

For the first theory, the X-inactivation theory, it is important to understand the concept of X-inactivation: when fully transcribed somatic cells in 46,XX females would result in a surplus of transcriptional product. Therefore one X-chromosome has to be transcriptionally silenced to effectively reduce the transcriptional product to that of males. However, approximately 25% of genes on the inactive X-chromosome escape silencing [8].

These genes are predominantly located in two regions called pseudo-autosomal region 1 and -2 (PAR1 and -2). Of which PAR1 (2.6 Mbp) is located on the end of the p-arms of both X and Y chromosomes and PAR2 (320 kbp) is located on the q-arms end. Pseudo autosomal regions contain genes that normally escape X-inactivation have a Y-chromosome homolog and are inherited like autosomal genes.

The X-inactivation theory postulates [9] that the haploinsufficiency of these 'pseudo-autosomal genes' on the X-chromosome results in an insufficient dosage to ensure normal expression. Which exact genes are contributing to the Turner phenotype is not yet clear, but the diverse spectrum of features in TS suggests that multiple genes may contribute. Genes located in PAR-1, have already been found; the short-stature-homeobox (SHOX) gene is an example. Haploinsufficiency for this gene, one which escapes X-inactivation, appears to cause the short stature in TS. More recently a study by Urbach and Benvenitsy [10] discovered a gene necessary for placental function (PSF2RA), located in the pseudo autosomal region. According to this study deletion of this gene may cause placental malfunction leading to high fetal mortality in non-mosaic TS.

The second theory [11] suggests TS might be the effect of imprinted genes, expressed in a mono-allelic fashion, depending on a parental origin cause . Parental imprinting is a form of epigenetic regulation that results in parent-of-origin differential gene expression.[12] It has a crucial role in prenatal growth and placentation and will affect the development the musculoskeletal system and the brain. Hence, as displayed in figure 1, there is no expression when the X-chromosome containing the expressed allele is lost. The loss of these active alleles has also been implicated in Prader-Willi syndrome [13]. In non-mosaic TS it is often the maternal X-chromosome that is retained [14]. Phenotypical traits in TS have been associated with the parental origin of the remaining X-chromosome.

In conclusion, the genetic aspects of Turner syndrome are not yet fully unravelled. The role of imprinting and x-inactivation will have to be investigated further.

Cardiovascular disease

Introduction

An estimated 50% of women with TS will suffer from cardiovascular disease, be it congenital or acquired [15, 16]. Various congenital abnormalities complicate care and are likely to cause significant morbidity. The congenital heart defects (CHD) are mainly left-sided, of which a bicuspid aortic valve (BAV, 15-30%), elongation of the transverse aortic arch (ETA, 49%) and coarctation of the aorta (CoA 17%) are most prevalent [8, 16]. Associated venous lesions include partial abnormal pulmonary venous return (PAPVR) and persistent left superior vena cava (LSVC) [16, 17]. Other defects, such as a ventricular septal

defect (VSD), common in Down syndrome, are seen less often in TS [18]. The acquired heart diseases mainly comprise of hypertension, aortic dilatation, and dissection [19, 20].

Etiology

Genetic disorders such as TS are sometimes first noticed by a pre-natal ultrasound after detection of nucheal translucency. This collection of fluid under the skin in the neck region is supposed to be a precursor of the webbed neck, one of the classical traits of TS. Sixty-eight percent of infants with a webbed neck is affected by a genetic syndrome such as Down- (37%), Noonan- (5%) or Turner-syndrome (13%)[21]. CHD is detected in sixty percent of patients with a webbed neck and in TS a high prevalence of cardiac abnormalities, such as aortic coarctation, has also been observed [18, 21-23].

Therefore, a common causal mechanism from which the multiple CHDs arise has been suggested to lie in the disturbance of early lymphangiogenesis [24]. This co-occurrence does not necessarily imply a causal relation, since a single gene causing both lymphedema and CHDs could theoretically confound this causal relation [23]. And indeed haplo-insufficiency for the autosomal gene FOXC2;16q seems to cause lymphedema and cardiac defects independent of each other [22]. An attempt to further elucidate a causality, genetic or otherwise, between lymphangiogenesis and CHD will have to start with a thorough understanding of the cardiovascular phenotype.

Congenital Abnormalities

As noted above, a large number of cardiovascular malformations exist in TS. For some abnormalities the evidence is anecdotal and may not bear any particular association with TS. However, as the accuracy of imaging modalities and genetic techniques rises, an increasing number of abnormalities are detected in TS and genotype-phenotype correlations may become more evident.

Bicuspid Aortic Valve

The earliest description of the BAV dates back to the 15th century when Leonardo da Vinci sketched different variants of the aortic valve [25]. Furthermore, the association with aortic regurgitation and stenosis has been known for 150 years [26]. With a prevalence in the general population of about 0,5% to 2% [27] (males:females, 3:1), it is the most prevalent CHD. Approximately one third of these patients will develop serious complications that require treatment [28] since a BAV is likely to become stenotic or insufficient [29]. From a developmental viewpoint BAV is thought to be more than the mere fusion of two cusp leaflets; it is seen as a part of a developmental defect ranging from uni- to quadri-cuspid valves [6]. A true bicuspid valve is very rarely seen. More often it is a fusion of 2 cusps, resulting in two remaining cusps that are often unequal in size due to the

fusion. In this chapter we will focus on the BAV within Turner syndrome and we will discuss the BAV in the general population in more detail in a separate chapter.

The prevalence of BAV in Turner Syndrome ranges quite spectacularly, from as low 10% to as high as 39,2% [30], depending on the imaging modality and study population. Autosomal dominant, X-linked, and familial modes of inheritance have been reported in the general population [27]. BAV is associated with a monosomy 45,X0 and is often seen in combination with a coarctation of the aorta[31], but is also associated with acquired diseases, dilatation, aneurysm and dissection. Two dimensional and Doppler echocardiography is currently the most widely used and least demanding technique to assess valvular function. However, some studies suggest it underestimates the prevalence of BAV when compared to MRI [22]. Valves that are hard to asses seem to be bicuspid more often, resulting in an underestimation by echocardiography. [22]

Treatment for BAV in TS does not differ from normal, but it is important to note that the aorta of BAV patients dilates more quickly than in TAV in the general population, especially at the level of the ascendens and sinus [17]. Dilatation does clearly predict dissection, [19] however dissection may also occur at normal aortic diameters and it is therefore advisable to pay extra attention to TS patients when symptoms occur. The risk of dissection will be discussed further below.

Aortic coarctation

Aortic coarctation (CoA) is a congenital narrowing of the aorta, distal to the aortic annulus, that occurs in 3.4 per 10.000 live births and constitutes 5% of all CHD in the general population [32]. It is often seen in combination with a BAV, especially a left and right coronary cusp fusion.[22] In TS it is also seen very frequently, ranging from 12% to 17% [16].

The first successful surgical correction was performed in 1945 [33]. Nowadays, aortic coarctation is still preferably repaired surgically at an early age. However, lifelong surveillance is a necessity since patients remain at risk for re-coarctation and aneurysm formation [34-36]. Turner Syndrome (TS) has been associated with CoA and 17% of TS patients have a coarctation of the aorta [8]. Moreover, CoA in TS patients is often associated with the presence of a bicuspid aortic valve (BAV (RR, 4.6)) [22, 37]. Ho et al. recently found that aortic coarctation appeared to be associated with an elongated transverse aortic arch (ETA) [16]

Shinebourne and Elseed [38] hypothesize a haemodynamic pathogenesis of CoA. The altered flow patterns could be caused by a left-sided blockage within the fetal circulation, resulting in elevated pulmonary pressure and blood flow over the ductus arteriosus. They predict that abnormal flow via the ductus to the isthmic portion of the arch will produce

hypoplasia, tortuosity, or coarctation of the aorta in the juxtaductal region. These are all abnormalities that also appear in TS and some are predicted to be the result of left-sided lymphatic compression of the aortic arch, as hypothesized by Clark [24]. These abnormalities also include some right-sided defects (PAPVR, PLVCS), due to backpressure. However, we cannot rule out the contribution from genetic regulatory mechanisms to these malformations [8].
Stent implantation has been introduced as a treatment for CoA in the late 1980's [39], with good gradient relief and a low complication rate [39-41]. More recently the aortic arch and aortic wall composition in TS have received increasing attention. Changes in vascular smooth muscle cells, elastin and collagen fibre appear to contribute to the cardiovascular problems in TS [42]. Cystic medial wall necrosis, similar to what can be found in Marfan syndrome, has been described in TS and is suggested to be a causative factor of aortic dissection [43-45]. The aortic wall certainly appears to be fragile in TS as well. Stent implantation may therefore be associated with a higher risk of complications, especially aortic dissection. However, data on the ideal corrective technique of coarctation repair for patients with TS is limited, since it is largely based on small case series or case reports and are often contradictory [46, 47].

A recent study [48] has shown that stenting of aortic coarctation may be associated with increased risk of especially short term complications, such as aortic dissections.

Aortic arch abnormalities

Aortic Arch

Recently an elongated transverse arch (ETA) has been added to the Turner syndrome cardiac phenotype. It is defined by two criteria, firstly an origin of the left subclavian artery and secondly an inward indentation of the lesser curvature or kinking at the aortic isthmus. [16] It has been reported to occur in approximately half of the patients and is associated with a higher blood pressure, aortic coarctation an aberrant right subclavian artery and a left superior vena cava.

Aberrant right subclavian artery

The aberrant right subclavian artery, or arteria lusoria, is the most common anomaly of the aortic arch, which may occur in 0.4% to 2% of the population[49]. In TS however it can occur in as much as 8% in women. Its clinical significance lies in the fact that it can cause dysphagia [50] and mask the presence of a coarctation by altering the upper to lower blood pressure ratio, when measured at the right upper extremity [16]. Little is known about the aortic branching pattern in TS and its relation with other CHD seen in the cardiovascular phenotype.

Bovine arch

A common origin of the innominate artery and the left common carotid, also known as a 'bovine aortic arch', is seen in 8% of TS females, but has not yet been correlated with the syndrome [16]. It has been described in 13% of the general population

Venous abnormalities

In TS the cardiac defects are often left-sided and not many venous abnormalities are associated with the syndrome. As stated before, with more advanced imaging techniques, anatomy can be mapped in more detail, leading to the discovery of rarer cardiovascular malformations.

PAPVR

Partial anomalous pulmonary venous return (PAPVR), first described by Winslow in 1739 [51, 52], is often found by chance during routine check-up and can cause a hemodynamically significant left-to-right shunt. Significant shunts (Qp:Qs>1.5:1.0) can manifest as right heart volume overload, the onset of pulmonary hypertension [53] and can eventually result in right ventricular hypertrophy or failure [54]. Therefore, this necessitates early diagnosis and treatment. The prevalence of PAPVR in TS might be underestimated because it is difficult to diagnose via echocardiography. Previously, venous abnormalities in TS were relatively unknown and their occurrence was grossly underestimated due to this inadequate method of diagnosis. Prandstaller et al. reported in a study using echocardiography a PAPVR prevalence of 2.9% [55], however, since MRI and CT came in to regular use over the last 5 years, a prevalence of PAPVR in TS has been suggested to be as high as 15,7% by Ho et al. [16, 17]. And more recently detailed analyses finds PAPVR in almost 25% of Turner syndrome patients [56].

Persistent Left vena cava superior

A persistent left sided superior vena cava (PLVCS) is seen in 0.3–0.5% of the normal population, and in 4,4% of those with CHD [57, 58]. Most often, it is seen incidentally during CT scan of the thorax. In addition to the PLVCS (82%-90%), a normal VC can also be found[58]. Left to right shunting can be present, as the vein drains into the left atrium in 8% of cases, but is often not clinically significant. During fetal development the left anterior cardinal vein normally disintegrates, but in some cases this fails to take place. The failure of the left anterior cardinal vein to disintegrate results in connections with either the coronary sinus (92%) or the left atrium (8%) [58].

Interrupted inferior vena cava with azygous continuation

This venous malformality has been described anecdotally in case reports [59]and has been associated with CHD in the past. Very few cases are known in literature, but it can present as a dilated azygos vein or with pulmonary hypertension [60]If the diagnosis is missed it can

lead to problems during surgical procedures or percutaneous interventions. It is however unclear whether any causal relation is present since the prevalence in the general population is not known exactly. Larger cohorts with a control population will have to specifically be examined for this defect before we can draw any conclusions on its link with TS

Acquired Heart Disease

Acquired heart disease is a significant cause of morbidity and mortality in TS, as was revealed in an article by Mortensen et al [8]. Aortic dilation and dissection are for a large part the cause of absolute excess mortality amongst the TS population (SMR 23.6). Ischemic heart disease (SMR 2.8) is also a significant contributor to mortality in TS patients especially at older age.[8].

Aortic Dissection

Acute aortic dissection often presents with a sharp pain, but its clinical presentation is often more diverse [61]. The incidence is estimated at 36 per 100.00 TS-years, compared to 6 per 100.000 patient years in the general population (male:female, 2:1) [20]. Dissection also occurs much earlier than in the general population, with 56% of dissections between the age of 20 and 40 years, an incidence of 14 per 100.000 before 19 and an average dissection age of 35 years (4-64) [20]. However, it remains an infrequent event since TS occurs only in 1 per 2500 live-born females and only 1 or 2 of 100 females will develop a dissection over their lifetime [8]. Risk factors for dissection in TS include hypertension, karyotype 45,X0, BAV, CoA, age and pregnancy [8, 62]. It remains unclear however, whether this high rate of dissection can occur separately from the aforementioned risk factors, as it does in connective tissue disorders such as Marfan, Loeys-Dietz-syndrome or Aneurysms-Osteoarthritis syndrome. Some articles do suggest TS to be a separate risk factor for aortic dilatation [62].

There is no data on the outcome of the dissection in TS, but there is no reason to suspect it to be less severe than in the general population where mortality varies depending on the type: 26% for the type A dissection and 10,7% for a type B dissection respectively [61].

Aortic Dilatation

Aortic dilatation is very prevalent in TS and is estimated to occur in up to 42% percent of patients [15, 18, 43, 63]. Body size and age are the primary determinants of aortic size in TS [19] and since patients with TS are generally smaller and have a 'barrel shaped' chest, it is important to correct their aortic dimensions for body surface area (BSA). Several factors such as BAV, hypertension and vessel wall structure contribute to aortic dilatation. Presence of a BAV is associated with dilatation of the aortic root and proximal ascending aorta, this dilatation can be attributed to either changes in flow or to abnormalities of the

aortic media. Recent studies show a clear role for cellular mechanisms underlying the dilatation and its prevalence in first-degree relatives of BAV patients [64].

Therefore, it is particularly important to closely monitor aortic dimensions in females with TS. These dimensions should be corrected for body surface, because these females generally have a shorter height. Annual intensive follow-up may be justified when absolute ascending aortic diameters exceed 40 mm or 2.1cm/m^2 [27] and early surgical intervention might be necessary in this population. Dutch guidelines advise the use of MRI for the follow-up of the aortic diameters in these patients [5] and to use aortic size index (ASI) to determine correct therapy. The guidelines also state that frequent follow-up (1 per 1-2 years) is justified when ASI >2.0 cm/m2. It is also advisable to consider medicinal treatment with beta-blockers and angiotensin receptor blockers to control blood pressure. Elective surgery might even be considered when the ASI exceeds 2,5 cm/m2 or when rapid progression of the aortic diameter (0,5cm/y) is observed.

Hypertension

Aortic root dilatation is closely associated with blood pressure and left ventricular thickness and valve type, but does not seem to be affected by atherosclerosis [63]. Hypertension occurs in 7-17% of young girls with TS and in 50% of young adults, it can be secondary to an aortic coarctation or kidney disease but it is often primary [65]. Since it is a risk factor for dissection, guidelines advise blood pressure measurement 1-2 times per year and strive for a target blood pressure of <140mmHg and in case of a bicuspid valve for <120mmHg [5]. Hormone substitution therapy appears to positively influence blood pressure, or at least have no negative influence [65]

Pregnancy

Infertility is one of the important complications of TS affecting woman's life (ref). Patients with some mosaic karyotypes (45,X/46,XX) may be able to achieve spontaneous pregnancies (2-6%) [66], while others will only be able to conceive by oocyte donation. However, these assisted reproductive technologies may increase the risk of adverse events in TS patients , such as aortic dissection or rupture [67]. This risk seems to be augmented by hormonal influences on the vascular wall [67, 68]. Maternal death from aortic dissection in TS pregnancies is estimated at 2%, a 100-fold increased risk as compared to the general population. [68, 69]. The presence of hypertension, BAV and CoA are associated with an increased risk and pregnancy itself seems to be an additional, separate risk factor [70]. Therefore, treatment of hypertension, associated with poor fetal outcome such as prematurity and fetal growth retardation [71], is of great importance for both women and their children.

Special attention should also be given to the aortic diameter as an aortic size index (ASI) >2cm/m^2 and/or a significant abnormality is a strict contraindication for attempting pregnancy [68]. Aortic diameters should be measured at least once every four to eight weeks [72]. Consequently, deliveries should be in a medical center with cardiothoracic surgery facilities readily available.

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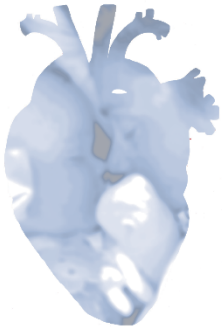
TURNER SYNDROME



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Partial anomalous pulmonary venous return in Turner syndrome

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Abstract

Objectives. The aim of this study is to describe the prevalence, anatomy, associations and clinical impact of partial abnormal pulmonary venous return (PAPVR) in the Turner population.

Methods. All Turner patients who presented at our Turner clinic, between January 2007 and October 2015 were included in this study and underwent ECG, echocardiography and advanced imaging such as cardiac magnetic resonance or computed tomography as part of their regular clinical workup. All imaging was re-evaluated and detailed anatomy was described.

Results. Partial anomalous pulmonary venous return was diagnosed in 24 (25%) out of 96 Turner patients included and 14 (58%) of these 24 partial anomalous pulmonary venous return had not been reported previously. Right atrial or ventricular dilatation was present in 11 (46%) of 24 partial anomalous pulmonary venous return patients.

Conclusions. When studied with advanced imaging modalities and looked for with specific attention, PAPVR is found in 1 out of 4 Turner patients. Half of these patients had right atrial and/or ventricular dilatation. Evaluation of pulmonary venous return should be included in the standard protocol in all Turner patients.

Introduction

Turner syndrome (TS) is a partial or complete monosomy of the X-chromosome, and was originally described by Henry Turner in 1938. It occurs in 1 per 2500 live born females (1-3). Turner syndrome is nowadays often diagnosed prenatally or during early childhood and patients present with a broad variety of disorders, including short stature, estrogen deficiency and cardiovascular abnormalities (4). Aside from a higher risk profile for ischemic heart disease, often congenital cardiac defects, located mainly on the left side, can be found in these patients. The most common lesions are: elongation of the aortic arch (49%), bicuspid aortic valve (14 - 30%), coarctation (7 - 18%), persistent left superior vena cava (13%), and atrial and ventricular septal defect (0-8%) (2, 5-9). PAPVR has been described to be more prevalent in TS patients, however knowledge about detailed anatomy and precise prevalence is scarce, partly because it is not routinely looked for at first recognition of the syndrome (6-9). However, PAPVR can cause an hemodynamically significant left-to-right shunt and subsequently, right chamber dilatation, arrhythmias and even pulmonary hypertension (10). This necessitates early diagnosis and, in case of a large shunt, treatment. In our tertiary centre for Turner syndrome all adult patients undergo a CT scan, while children and adolescents will have an MRI (11).

The aim of this study is to describe the prevalence, anatomy and clinical significance of PAPVR, in patients with Turner syndrome. Furthermore, factors, possibly related with PAPVR were studied.

Methods

Every Turner patient is enrolled into a prospective surveillance program according to a local standardized clinical protocol. This protocol includes clinical assessment by a cardiologist, ECG, echocardiography and cardiac CT (adults) or MR imaging (children and adolescents). For this study all adult patients, who were evaluated at the department of congenital cardiology between January 2007 and October 2015 with genetically proven Turner syndrome were included. We excluded patients with insufficient CT or MR imaging quality. The study was approved by the medical ethical committee of our center. Informed consent was waived.

Imaging

For this study all CT and MR-images were re-evaluated by two independent investigators (A.H. and R.C.), blinded to each other. When more than one scan (CT or MR) was available per patient, the most recent CT scan was used. Evaluation was done by multi planar reconstruction, using the AquariusNet (TeraRecon, Inc, San Mateo, CA) software. The connecting site was defined as the location where the anomalous pulmonary vein drained

into the systemic venous system. At this location vessel diameter and area were measured; perpendicular to the anomalous vein, as proximal to the vessel it feeds into as possible but where it was still discernable as a separate vessel (figure 1.) The anomalous vessel was then traced back to the lung lobe or lobes from which it originated; the site of origin. Right atrial and right ventricular dilatation was visually assessed on echocardiography images by two observers (A.T. and J.R.), blinded to CT/MR data, on apical 4-chamber view, parasternal long-axis and parasternal short-axis according to the latest guidelines (12). To assess global RV systolic function the right ventricular fractional area change (RV FAC) was calculated, where a RV FAC <32% was considered impaired (12).

Electrocardiography

ECG's were scored for signs of right atrial or ventricular abnormalities. Right atrial dilatation was defined as: a P-wave in lead II >0.25mV. Right ventricular hypertrophy was defined as: an R/S ratio in V1>1, R in V1>7mm, or a right bundle branch block RV1>15mm. Right axis deviation was defined as a QRS-axis of more than 90˚.

Karyotype analysis

For purpose of statistical analysis karyotypes were divided into one of seven different categories; monosomy (e.g. 45,X0), mosaicism for monosomy (e.g. 45,X/46,XX [9/41]), full or mosaic isochromosomes (e.g. 45,X0/46,i(Xq)), polyploidy (e.g. 45,X0/47,XXX (100/2)), ring chromosomes (e.g. 45,X0/46X,+r(X) [36/14]) and karyotypes with Y-material (e.g. 45,X0/46,XY/46,XX/47,XY [8/3/2/37]).

Statistical analysis

Continuous variables with a normal distribution were reported as mean ± standard deviation. We reported a median and range in case of non-normal distribution, checked using the Shapiro-Wilk test. Categorical variables were summarized as frequencies and percentages. The Chi squared test was used to detect associations between patient characteristics and imaging data, in case of an expected value <5 a Fischer's exact test was conducted. Independent sample t-tests and one-way ANOVA were used to compare means. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

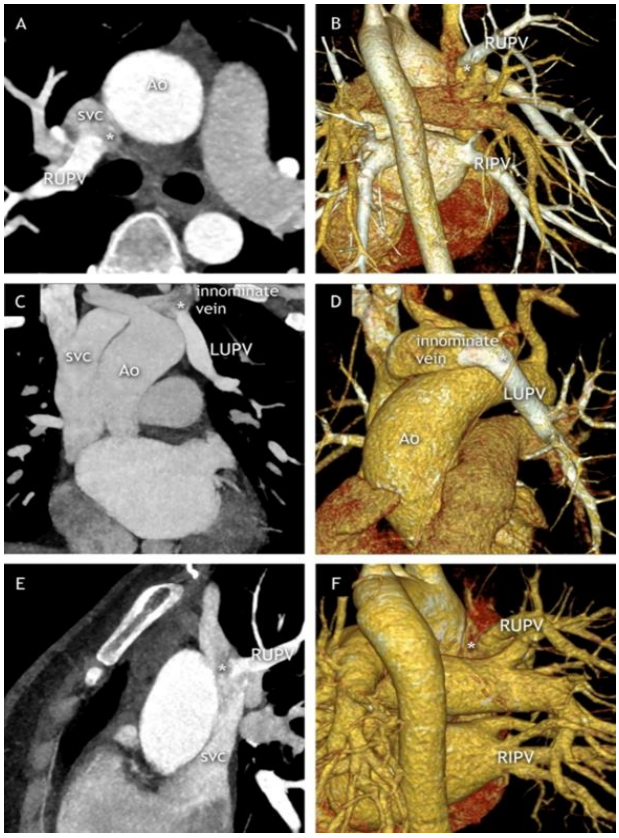

Figure 1. Measurement of PAPVR. Panel A) 3D volume rendered reconstruction showing a PAPVR (*), the Aorta (Ao), Pulmonary Artery (PA), innominate vein (IV). Panel B and C) Sagittal and coronal oblique views of how the connecting site area of the PAPVR (*) was measured. D) Cross section of the PAPVR (*) perpendicular to the vessel.

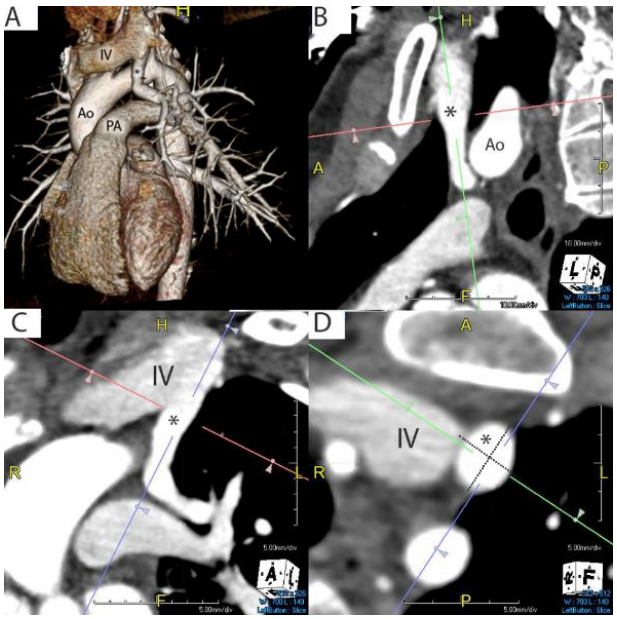

Figure 2. PAPVR as seen on CT. Panel A) Right upper pulmonary vein connecting to superior vena cava (*); Panel B,D,F) corresponding volume rendered image of the same patient. C) Coronal oblique view of the left upper pulmonary vein connecting to the innominate vein (*): E,F) Sagittal oblique image showing the right upper pulmonary vein connecting to the superior vena cava (*)

Results

Between January 2007 and October 2015, 104 patients with TS were referred to the outpatient clinic of our center for routine cardiac screening. In eight patients the image quality of the CT/MR was insufficient and these patients were excluded from further analysis. No differences in baseline characteristics were found between included and excluded patients. The baseline characteristics of the 96 patients included in our study are presented in table 1. At least one PAPVR was found in 24 of the 96 patients (25%) and had not been reported before in 14 (58%). In the majority of the patients a CT scan (n= 79, 82%) was performed, PAPVR was detected on 21 of these (27%). In the remaining 17 patients, an MR was performed and in 3 (18%) a PAPVR was found.

Echocardiographic imaging was of sufficient or good quality in all 96 patients. Right atrial (RA) and ventricular (RV) dimensions were measured and are reported in table 2. RA dilatation was found in 22 of the 96 patients (23%), and associated with the presence of PAPVR. In 7 of the 24 PAPVR patients the right ventricle was dilated compared to 7 of 72 in the non-PAPVR group (29% vs 10%, p=0.039). Adequate measurement of the RV FAC was possible in 73 patients and was considered impaired in 13 patients (19%). RA and RV area were measured in 75 patients, from which RV fractional area change was calculated (table 2). Both the RV end-diastolic area (EDA) and the end-systolic area (ESA) were enlarged in the PAPVR group (p<0.001 and p=0.001). The RV fractional area change (RV FAC) did not differ significantly between the groups.

The ECGs showed right axis deviation (6%) in 6 patients, all 6 had a PAPVR (p<0.001). Two ECG's showed signs of right atrial enlargement, one of the patients had a PAPVR, no signs of right ventricular hypertrophy or dilatation were found.

Anatomy

Details of the anatomy of the PAPVRs are presented in Table 3. The lung lobe of origin and the site where the PAPVR connects to the circulation could be determined in all 24 PAPVR patients. The most common site of origin was the left upper lung lobe (n=14, 58%) and the most common connecting site was the innominate vein (n=14, 58%). All PAPVRs were of the supra cardiac type, i.e. none of the PAPVRs connected to the coronary sinus or inferior caval vein. The median area of PAPVR was 38mm2 (inter quartile range: 83, range; 3-391mm2) with a median diameter of 8mm (inter quartile range: 8.7, range; 2-25mm). The vessel area correlated with the RV EDA (r=0.49, p=0.014). BAV was found in 18 (18.8%) patients and CoA in 10 patients (10.4%).

An arteria lusoria and a common origin of innominate and left carotid artery were found in 4 (4.2%) and in 1 (1%) patient respectively. BAV occurred more frequently in combination with PAPVR, (p=0.023). For CoA there was no clear association with PAPVR (p=0.115).

Table 1. Baseline characteristics

Patient characteristics (N=96)	Mean ± sd
Age, y	35 ±13
Height, cm	155 ±14
Weight, kg	65 ±17
Systolic BP, mmHg	124 ±19
Diastolic BP, mmHg	76 ±13
Body Surface Area, m2	1.6 ±0.25
Body Mass Index, kg/m2	27 ±6
Saturation,%O2 (N=49)	99 ±1.4

Table 1. Baseline characteristics, *saturation was available in 49 patients

Genetics

The information on the exact karyotype was available in 88 (92%) patients and shown in table 4. The most prevalent karyotype was a monosomy of the X-chromosome (45,X0), followed by a mosaic monosomy pattern . PAPVR was observed more frequently in patients with a 45,X0 monosomy or mosaic monosomy (19 in 55) when compared to the other karyotypes (3 in 33; 35% vs. 9%, p=0.008). Remarkably, PAPVR was not seen in any of the seventeen patients with an isochromosome (0% vs. 31%, p=0.005). Of the isochromosome karyotypes in this cohort all had deletion of the shorter p-arm (isochromosome-q), 11 were a mosaic form (e.g. 45,X0/46-X,i(X)(q10) [24/5]), the other were of the non-mosaic type (e.g. 46,X,i(Xq)).

Discussion

In this large group of Turner syndrome patients a surprisingly high prevalence of PAPVR (25%) was found. This percentage is markedly higher than in previous studies, where PAPVR prevalence, when reported at all, is found to be between 2.9 and 18% (2, 6, 7, 9, 13). The higher incidence may be explained by the careful attention in our study, but also by differences in imaging techniques. Echocardiography is probably less sensitive to pulmonary vein abnormalities than CT or MR, explaining a possible underestimation of

Table 2. Echocardiographic measurements.

Measurement	PAPVR N=24 (%)	Non-PAPVR N=72 (%)	Total N=96 (%)
Right Atrial Dilatation			P=0.004
No	13 (54.2)	61 (84.7)	74 (77.1)
Yes	11 (45.8)	11 (15.3)	22 (22.9)
Right Ventricular Dilatation			P=0.039
No	17 (70.8)	65 (90.3)	82 (85.4)
Yes	7 (29.2)	7 (9.7)	14 (14.6)
Right Ventricular measurements	N=22	N=51	p-value
EDA	22.5±6.3	16.4 ±6.8	<0.001
ESA	12.6±4.2	9.2 ±4.1	0.001
RV FAC	43.7±9.7	44.1±9.1	0.86

Table 2. Presented as N= (%) and mean ±sd, EDA: End diastolic Area, ESA: END systolic Area, RV FAC: Right ventricle fractional area change, RA: Right Atrial: RV: Right ventricle

PAPVR prevalence in earlier studies. Contrast-enhanced CT and contrast-enhanced 3D MR angiography are both adequate techniques to assess the presence of a PAPVR (14) where CT of course carries the disadvantage of radiation.

In this cohort none of the newly diagnosed PAPVRs needed immediate surgical intervention, but adequate follow-up of these patients is warranted to assess changes in right heart dimensions and pressures over time. PAPVR can become clinically relevant as adult-onset pulmonary hypertension has been reported in PAPVR patients (10, 15). We found some degree of right heart dilatation in half of the PAPVR patients. Therefore, we would like to stress the importance of including advanced imaging in the clinical protocol of Turner syndrome patients with specific attention for possible PAPVR and right heart dilatation.

Table 3. PAPVR, anatomy

	Site of Origin	Connecting site				
	Lung segments	SVC	IV	Left Subclavian Vein	PLVCS	Total
Right	Upper Lobe	2				2
	Upper Lobe/Middle Lobe	1			1	2
	Middle Lobe	2	2			4
	Middle Lobe/ Lower Lobe	2				2
	Lower Lobe	0				0
Left	Upper Lobe		10	1	1	12
	Lower Lobe		1			1
	Lower Lobe/lower lobe		1			1
	Total	7	14	1	2	24

Table 3. IVC: Inferior Vena Cava, IV: Innominate Vein, SCV: superior Vena Cava, PLVCS: Persistent Left Vena Cava

In addition to the clinical implications of having PAPVR , also some pathophysiological aspects warrant further investigation. This study was not designed to examine the PAPVR from a developmental aspect, but it is remarkable that only PAPVR of the 'supra cardiac type' (i.e. pulmonary veins draining into the superior caval vein or innominate vein) were observed, in concurrence with another study in a TS population (2). This is in contrast to what may be expected based on findings in non-Turner patients (16). It seems that the "supracardiac type" of PAPVR is an inherent part of the Turner cardiac phenotype, where in non-Turner cohorts this supracardiac type is relatively uncommon (17). Another remarkable observation is the absence of atrial septal defects, which are supposedly associated with PAPVR in the non-TS population, predominantly with right-sided PAPVR (17, 18). A single underlying cause for the wide spectrum of left-sided cardiac defects in TS, genetic or otherwise, has not yet been established. There are however several theories; cardiac abnormalities could be caused by either haemodynamical changes in utero or could have a multifactorial or genetic origin. It is suggested that either a jugular lymphatic obstruction may lead to compression of outflow structures (19), or that a left-sided blockage of the fetal circulation forms the explanation for the defects(20). The association

Table 4. Presence of PAPVR per karyotype.

Karyotype	PAPVR (N=, %)	Non-PAPVR (N=, %)	Total (N=, %)	p-value
(Mosaic) Monosomy X	19 (79,2)	36 (50)	55 (57.3)	0.008
Isochromosomes	0 (0)	17 (23.6)	17 (17.7)	0.005
Deletions	1 (4.2)	3 (4.2)	4 (4.2)	1
Polyploidy	1 (4.2)	4 (5.6)	5 (5.2)	1
Ring chromosomes	1 (4.2)	3 (4.2)	4 (4.2)	1
Y material	0 (0)	3 (4.2)	3 (3.1)	0.570
Missing	2 (8.3)	6 (8.3)	8 (8.3)	-
Total	24	72	96 (100.0)	-

Table 4. Presented as N= (%) and mean ±sd, PAPVR: partial abnormal pulmonary venous return

between TS genotype and PAPVR phenotype needs further study and knowledge about the various cardiac abnormalities and their interrelation might play a meaningful role in unravelling the etiology of the 'Turner cardiac phenotype'.

Limitations

A possible inclusion bias may have been in place as only TS patients from a tertiary center were included. However, we feel that this effect is likely to be very small as all TS patients are referred for follow-up irrespective of complaints or symptoms and follow-up is done according to a standard protocol.

Conclusion

PAPVR is present in one quarter of patients with Turner syndrome, and often missed at first diagnosis of the syndrome. Medical specialists involved in the care for TS patients, should include attention for PAPVR in their standard work-up.

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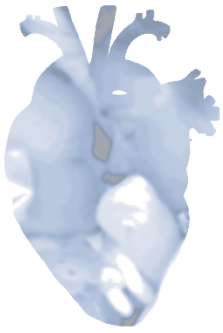
TURNER SYNDROME



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A Value-based Healthcare approach: Health Related Quality of Life and Psychosocial Functioning in Women with Turner Syndrome

Clinical Endocrinology, January 2020

Abstract

Objective: As part of the value-based health care program in our hospital a set of patient reported outcome measures was developed together with patients and implemented in the dedicated Turner Syndrome (TS) outpatient clinic. This study aims to investigate different aspects of health related quality of life (HR-QoL) and psychosocial functioning in women with TS in order to establish new possible targets for therapy.

Methods: A comprehensive set of questionnaires (EQ-5D, PSS-10, CIS-20, Ferti-QoL, FSFI) was developed and used to capture different aspects of HR-QoL and psychosocial functioning in a large cohort of adult women with Turner syndrome. All consecutive women, ≥18 years, who visited the outpatient clinic of our tertiary center were eligible for inclusion.

Results: Of the eligible 201 women who were invited to participate, 177 women (age 34 ±12 years, mean±SD) completed at least one of the validated questionnaires (88%). Women with TS reported a lower health-related quality of life (EQ-5D: 0.857 vs. 0.892, p=0.003), perceived more stress (PSS-10: 14.7 vs. 13.3; p=0.012) and experienced increased fatigue (CIS-20: p<0.001) compared to the general Dutch population. A relationship between non-cardiac comorbidities (e.g. diabetes, orthopedic complaints) and HR-QoL was found (R=0.508).

Conclusions: We showed that TS women suffer from impaired HR-QoL, more perceived stress and increased fatigue compared to healthy controls. A relationship between non-cardiac comorbidities and HR-QoL was found. Especially perceived stress and increased fatigue can be considered targets for improvement of HR-QoL in TS women.

Introduction

Turner syndrome (TS), first described by Henry Turner in 1938, is caused by a partial or complete monosomy of the X-chromosome, and occurs in 1 per 2500 live born females.[1, 2] Classic characteristics of TS include: short stature, webbing of the neck, estrogen deficiency and decreased fertility.[3-5] Moreover, significant morbidity in these patients is caused by the cardiovascular abnormalities of heart and thoracic vessels, which affect an estimated 50% of women with TS.[6] Of these congenital defects the bicuspid aortic valve (BAV: 15-30%), coarctation of the aorta (CoA 12-17%) and partial anomalous pulmonary venous return (PAPVR: 18-25%) are most prevalent.[2, 6-8] Additionally diabetes, obesity and hypertension are often seen in these women, adding to their cardiovascular risk.[9] Although cardiovascular and other physical morbidities of women with TS have already been described in detail, literature is still inconclusive or contradictory on the impact of TS on HR-QoL.[10] In addition to the physical factors, HR-QoL in these women is also affected by the mild neuropsychological deficits these patients may encounter, such as the relative weakness in visual–spatial, executive, and social cognitive domains.[11-13] Additionally, other factors such as lower socioeconomic status or impaired ability to work may affect QoL. Finally, fertility issues may also have impact on QoL in TS women. Since the phenotype is so multi-dimensional and heterogeneous, traditional psychometric tools, such as the SF-36, cannot completely capture the broad range of psychosocial problems in these patients.[14] Moreover, the importance of psychometrically sound disease-specific tools has been stressed in other chronic illnesses, where more generic tools often fail to capture loss of quality of life on disease specific domains.[15] In this study we describe the development and first results of a set of clinician and patient reported outcome set in Turner syndrome as part of the value-based health care programs in our hospital.[16] We aim to provide a comprehensive evaluation of HR-QoL and different domains of psychosocial functioning in women with TS in order to identify individual and disease-specific targets for effective improvement of their HR-QoL.

Methods

Development of the outcome set

For the development of such a set, out organization works according to a so called blueprint which is adapted to the specific situation of a disease team. This way of working is described in detail elsewhere. [16] In brief, a disease team is formed consisting of the most important disciplines involved in the treatment, in this case the departments of internal medicine, gynecology and cardiology. A representation of patients is invite to participate in this process. In our situation we had a 24 year old patient and the mother of a patient being also member of the national patient organization, they are volunteers for the Turner patients federation and have been in contact with and of support to many Turner women.

With this group and technically supervised by a value based healthcare expert, the team discussed in 4 sessions the following items: current care path, possible outcome measures from literature and complemented with topics from the patients that really matter to them. Consensus based this long list of outcome topics was decreased to a more discrete based on frequency and impact. Finally, the outcome topics were translated into validated outcome measures and built into our data capture tool in order to measure them electronically. Before every outpatient clinic visit, patients receive an email with a web link to the questions, so they were able to answer them at home before the visit. During the visit the result were discussed with them. Our tertiary care center has developed a 5- year VBHC-strategy to transform the institute into a true value innovator. An integrated, multidisciplinary Turner syndrome-care unit was already in place within our institute. The Turner team is composed of a cardiologist, endocrinologist, gynecologist, physiotherapist, psychologist and ENT specialist and other specialists are consulted upon indication.

For women with Turner syndrome, navigating the complex health-care pathway involving many specialties can be daunting. Therefore this path-way was redesigned analogous to the breast cancer-care path-way described earlier [ref 16]. A critical step within VBHC is defining an outcomes set, this was done with the described multi-disciplinary team. After both a literature survey and from experience, all participants worked on a long list of outcome domains and ranked based on prevalence, impact for the patient and relevance for quality of care. For sake of feasibility the final list was discussed and selected using a modified Delphi method, see figure. The PROMS selected are described below under 'instruments' and in more detail in the supplementary material.

As described earlier, PROMS in the VBHC-pathways in our institution are captured using an in-house developed open source electronical data collection tool, which allows the construction of data collection-forms and automatic distribution of PROMs. [16] Emails are sent to the patients in order to activate the distribution of PROMs. After the right treatment pathway is selected by the physician, all the following PROMs will be sent automatically by the tool at the right time-point. The tool was linked to the EHR enabling the review of the collected data for individual patients at the (outpatient) clinic. The secure platform is build up by two software programs, LimeSurvey[17] and GemsTracker[18]. The development team simultaneously developed a user-friendly interface to display the collected data. Longitudinal PRO data and data from the caregivers is collected in these pathways.

Setting and study design

All patients in our center of expertise are seen according to a new value-based healthcare clinical pathway which includes annual visits to the dedicated Turner outpatient clinic.[5, 19] Adult women with Turner syndrome who visited the outpatient clinic between

December 2015 and October 2018 were prospectively included. Cardiovascular examination was performed including electrocardiography (ECG) and transthoracic echocardiogram (TTE) and advanced cardiac imaging (CT or CMR). Karyotype was taken from the clinical genetics report. The study complied with the Declaration of Helsinki and was approved by the medical ethical committee of the Erasmus Medical Centre. Written informed consent was waived.

Instruments

As a part of a hospital wide value-based healthcare program patients were asked to complete 12 questionnaires: 5 standardized questionnaires: the EuroQol-5D (EQ-5D), Hospital Anxiety and Depression Scale (HADS), Checklist Individual Strength (CIS-20), Perceived Stress Scale (PSS-10), Fertility Quality of Life (Ferti-QoL), 4 questionnaires on sexual functioning (sexual activity question, brief sexual symptom checklist for women (BSSC-W), female sexual functioning index (FSFI) and the female sexual distress scale - revised (FSFD-R)) and 3 questionnaires on body image and the perceived burden questionnaires.[20-22] The questionnaires have been described in more detail in the supplementary methods. The sexuality questionnaires were offered to the women with TS aged 20 and 45 years because sexuality starts later in women with TS [23-26] and end earlier because of hormonal changes.

Statistics

Continuous variables were presented as mean ± standard deviation (SD) or as median with an interquartile range. Categorical variables were presented as frequencies and percentages. We examined distributions by visually assessing histograms of the data by calculating Z-values of skewness and kurtosis, and by tested for normality using the Shapiro-Wilk test. For comparison of normally distributed continuous variables between two groups the Student's t-test was used. Univariate linear regression analysis was performed. Subsequently, multivariate linear regression analysis was performed to identify patient characteristics that were significantly associated with different measures of HR-QoL or other psychosocial outcomes. In case of collinearity we entered the variable with the strongest correlation with the outcome into the multivariate linear regression analysis. As previously described the tri-modal distribution of the EQ-5D outcome measure hampers ordinary least squares (OLS) regression, three-part regression methods seem to have better prediction power than OLS with EQ-5D data, although OLS seems quite robust.[27] Therefore we conducted separate linear regression for the 0.5-0.99 range as an additional 'sensitivity analysis'. The statistical tests were two sided and a p-value below 0.05 was considered significant. The IBM SPSS® statistics 21.0 software was used to analyze the data.

Results

The questionnaires were offered to all 201 women with TS who visited our outpatient clinic between December 2015 and September 2018, of which 177 women completed at least one of the questionnaires (response rate: 88%) and were included in this study. Baseline characteristics of the 177 women are presented in table 1. The mean time to complete the questionnaires was 15 minutes. All women seen in our outpatient clinic between the age of 18 and 52 use HRT.

Table 1. Baseline characteristics.

Baseline characteristics	Women with TS Median [IQR]
Age, y	33 [18]
Height, cm	157 [11]
Weight, kg	64 [19]
Systolic BP, mmHg	125 [21]
Diastolic BP, mmHg	76 [17]
Body Surface Area, m2	1.65 [0.22]
Body Mass Index, kg/m2	25.4 [6.4]
Sinus Rhythm, n=167	167 (100)
Heart rate, bpm	75 (15)
Karyotype	171 (97)
Monosomy X	93 (52.5)
Mosaic	25 (14)
Isochromosomes	25 (14)
Deletions	6 (3.4)
Polyploidy	9 (5.1)
Ring chromosomes	5 (2.8)
Y material	8 (4.5)

Table 1. Continuous data are presented as mean ±SD. Categorical data are presented as n (%)

Table 2. Demographics

Demographics (N=177)	n=	%
Living situation	174	98
With a partner	50	29
Alone	47	27
Living with parents	44	25
Family	7	4
Friends	2	1
Children	30	16
Biological children	12	40
Foster or adopted children	11	37
After oocyte donation	7	23
Highest level of educational attainment	123	69
Pre-vocational secondary	14	11
Senior general secondary/pre-university	17	14
Intermediate vocational	51	41
Higher vocational	19	15
University education	13	11
Current occupation	90	51
Fulltime employed	23	26
Part-time employed	36	40
Still attend educational services	16	18
Unemployed	12	13
Sports participation	73	41
Jogging	19	26
Cycling	17	23
Fitness	16	22
Team sports	1	1

Table 2. Demographics. Completeness per domain (e.g. living situation) is presented as n (%) of the total cohort (n=177). Data per item is presented as n, % of the corresponding domain.

Demographics and morbidity

Many women indicated living with a partner (table 2; n=50, 28%). Of the women living with parents or family (n=51), 15 (29%) were older than 25 years of age. In total 29 women (16%) raised a total of 30 children. The highest level of educational attainment was known in 123 (69%) participants; most of who had finished intermediate vocational education in 51 (29%). Women were often employed, either fulltime (n=23, 13%) or part-time (n=26, 20%). Of the 90 participants less than half indicated to practice sports regularly, on average 3hours (median, IQR 3 hours) per week.

Noticeably all but 1 participant practiced individual sports. Data on morbidity is presented in table 3. Most frequently encountered problems included: ear and/or hearing problems (n=57; 32%) and cardiovascular disease (n=56; 32%). In the 56 women with cardiac disease several different structural heart defects were identified; of which a bicuspid aortic valve (BAV) was the most frequent (19%). Aortic dilatation was found in 10 patients (6%) and 1 patient had suffered from dissection (0.6%).

Table 3. Associated morbidity

Morbidity (n=177)	n=	%
Otological problems	57	32
Cardiovascular disease	56	32
BAV	34	19
PAPVR	12	7
CoA	9	5
bovine aortic arch	2	1
Persistent duct	2	1
PLSCV	2	1
ASD	1	0.6
VSD	1	0.6
Hypothyroidism	30	17
Dento-facial malformations	26	15
Orthopedic problems	21	12
Liver dysfunction	20	11
Renal malformations	13	7
Diabetes	6	3
Coeliac disease	3	2
Hyperthyroidism	1	1

Table 3. Associated diseases. Data per item is presented as n, %.

Primary outcome

EQ-5D

The EQ-5D was completed by nearly all patients (n=175, 99%). Women with TS scored lower compared to the general Dutch population (0.857 vs. 0.892; p=0.003) as shown in figure 1.[28] Women with TS scored significantly higher on the 'problems with daily activity' (p<0.001) and the 'fear and anxiety' (p<0.001) compared to healthy controls (supplementary figure 1). Finally the EQ-5D included a subjective 'health score' (EQ-VAS; supplementary figure 2), where the women with TS (n=176) scored significantly lower than healthy women (76.8 versus 82, p<0.001).

Figure 1. Total EQ-5D (HR-QoL) scores per age group in women with TS vs. the Dutch population.

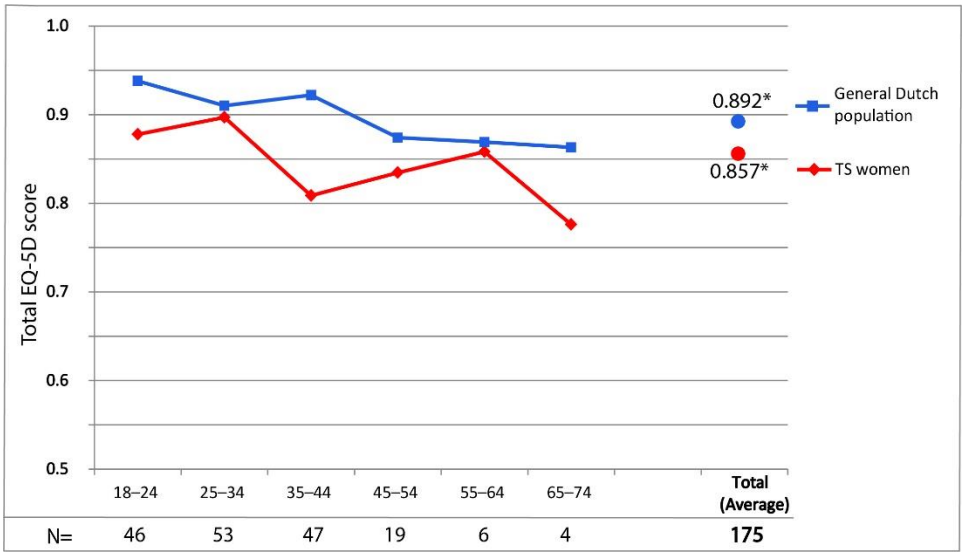


Figure 1. EQ-5D scores per decade of life. The red line depicts scores in women with TS. Blue line depicts scores in a cohort of healthy Dutch non- women with TS. *: average age groups ($p<0.003$).

Figure 2. Total CIS-20 (fatigue) scores in TS-women versus different non-Turner syndrome reference populations from literature.

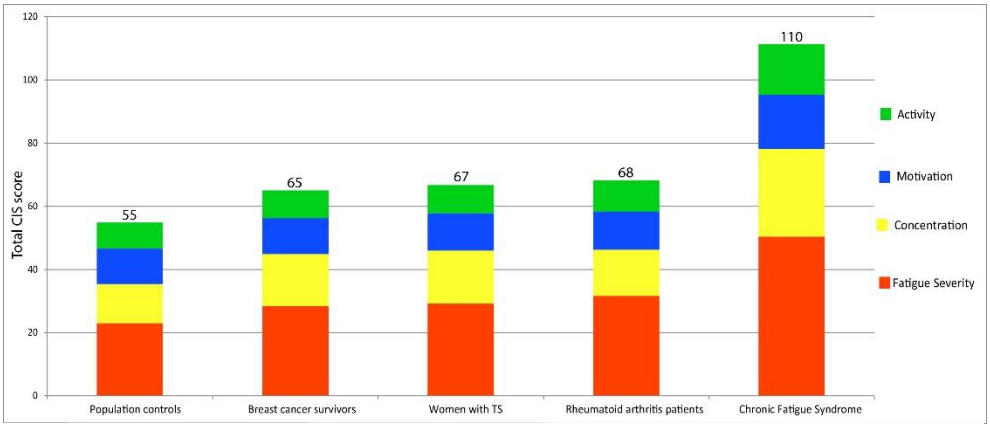


Figure 2. Total CIS-score per patient group colors indicates different subdomains, total CIS-20 scores are depicted on top of bars. Higher scores indicate more fatigue.

Secondary outcomes

PSS-10

Of the 176 women (99%) who completed the PSS-10 questionnaire more than half (n=90, 51%) indicated low or average stress (<13points), while 23% (n=41) experienced stress levels above average (between 13-20 points), and 25% (n=45) reported high stress levels (>20 points). Women with TS scored significantly higher than their non-TS peers, indicating a higher level of perceived stress. Especially women in the age group 45 to 59 years scored higher compared to their peers(n=45: 16.18 vs 12.99, p-value: 0.002), whereas higher but non-statically significant values where observed in the other age groups (18-39 years, n=124: 14.2 vs 13.34, p-value: 0.084) (≥60 years, n=7: 13.71 vs. 12.82, p-value: 0.403).

CIS-20

The CIS-20 was completed by 175 participants (99%). In our cohort 32% of patients (n=56) scored 76 or higher indicating increased fatigue. In figure 2 we compare our cohort of women with TS to reference populations from literature, showing that women with TS are significantly more fatigued than healthy controls, indicated by a higher total score (67 vs 55; p<0.001). They also score significantly worse on the sub scores of 'fatigue' and 'concentration' subscales compared to controls (29 vs 23; p<0.001 and 17 vs 12; p<0.001 respectively, figure 2)

HADS

The HADS measures fear and depression in patients under medical treatment. This questionnaire was offered to 27 who showed indications of emotional suffering on the EQ-5D and was completed by 20/27 eligible participants (74%). One of whom scored between 8 to 10 points, indicating a 'possible depression or anxiety disorder' while 19 women (95%) scored above 10 points, indicative of a 'probable depression or anxiety disorder'. Since this questionnaire was offered only to a subset of patients no comparison to a reference population could be made.

Fertility and Sexuality

The fertility-related quality of life (Ferti-QoL) was completed by 57 of the 140 eligible patients (41%). Women with TS scored significantly lower on the relational subscale (78 vs. 71; p=0.009) indicating more impact of fertility problems on the marriage or partnership (supplementary figure 3) compared to a reference population of women who underwent medically assisted reproduction.[29] Conversely, they scored better on the mind-body (90 vs 71; p<0.001), social (82 vs 74; p<0.001) and emotional sub scores (81 vs 60; p<0.001), indicating less impact of negative emotions on quality of life and impact of fertility problems, cognitions and behavior on physical health. On the total Ferti-QoL women with TS scored higher (82 vs 71; p=0.1467) indicating better fertility-related quality of life.

Additionally, the four questionnaires on sexual activity and sexual functioning in women (sexual activity question, BSSC-W, FSFI and FSFD-R) were completed by 57/140 (41%), 40/140 (29%), 8/9 (89%) and 2/5 (40%) participants respectively. On the 'sexual activity question' (mean age: 37.5±8.4years), 32 women (56%) indicated that they were sexually active. On the BSSC-W (mean age: 38±8.9years) 33 of the 40 respondents (82.5%) indicated that they were content with their sex life, 7 were not (17.5%). Causes for dissatisfaction with sex life included a lack of libido (n=3; 7%), reduced genital sensations (n=1; 2.4%), vaginal dryness (n=1; 2.4%) or pain during intercourse (n=2; 5%). As a part of the value-based healthcare program these women were then referred to a sexologist.

Body Image and Disease burden

The BCS questionnaire on body-image was answered by 175 (99%) women, of who 66 (37%) indicated to be discontent with their appearance. Scores of the body-image questionnaire on the 52 areas of physique are shown in supplementary figure 4. Women with TS were least content with their waist, build, belly, weight, and figure. Also reflected in this questionnaire is the discontent with their energy level. The burden questionnaire was completed by 177 women (100%) Self-reported burden scored on six domains is shown in supplementary table 1. The question which asked how much these issues on the different domains affected the participant on a scale from 0-10 was answered (n=161; 91%) with a mean score of 4.6 (SD±2.6). Of the physical complaints, fatigue was especially frequently reported by women in our cohort. Other physical problems (12%) often concerned joint and muscle pain (4%). The most frequently reported emotional complaint in the 'other emotional complaints' category (4%) was work related stress (2%). Problems in social interaction concerned the connection with peers (15%) or engaging in a romantic relationship (16%). In the 'work-related category' issues reported often included mild neuropsychological problems such as memory (19%), and concentration (20%) issues. The majority of other complaints in the work category (5%) specifically described the feeling of being overburdened by work (4%). Women with TS also frequently reported concerns about the future, often related to their education or work (30%).

Determinants of quality of life

Univariate linear regression showed age, diabetes, liver dysfunction, orthopedic problem, fatigue (CIS-20) and stress (PSS) to be associated ($p<0.2$) with worse quality of life (EQ-5D). Subsequent backward multivariate linear regression analysis revealed that higher fatigue ($\beta=-0.004$, $SE<0.001$, $p<0.001$), orthopedic complaints, defined as physical problems (e.g. scoliosis, leg length discrepancy or Madelung's deformity ($\beta=-0.049$, $SE=0.027$, $p=.072$) and diabetes ($\beta=-0.090$, $SE=0.047$, $p=0.056$) were associated with worse EQ-5D score (r-square: 0.508). Moreover, both PSS-10 score and CIS-20 score were independently associated with a lower EQ-5D outcome ($\beta=-0.014$, $p<0.001$ and $\beta=-0.005$, $p<0.001$, respectively). However, the PSS score was collinear with CIS-20 score ($\beta=-0.2454$, $p<0.001$, R square: 0.498) and

since CIS-20 had the strongest correlation PSS was removed from the analysis. Additional piece-wise separate linear regression for the 0.5-0.99 EQ-5D range improved the correlation, but did not change the outcome. Notably, the presence of cardiac disease or hearing impairment did not influence quality of life (EQ-5D). No significant difference was found between the different levels of educational attainment forEQ-5D (p=0.9156), CIS-20 (p=0.759) or PSS-10 (p=0.380) or for partnership status on EQ-5D (p=0.488), CIS-20 (p=0.055) or PSS-10 (p=0.265) . A summary of the questionnaires and their results has been provided in supplementary figure 5.

Discussion

In order to analyze the added value of our care for patients with TS we developed together with a small patients representation a set of clinician and patient reported outcome variables related to items that really matter to them in daily life. Subsequently we measured these outcome variables in a group of TS patients. This study describes the results of these measurements. In this large cohort of women with TS we found an impaired health related quality of life (HR-QoL), correlated to higher stress and more fatigue compared to control populations. When considering determinants for these results we found that especially having comorbidities such as diabetes and orthopedic complaints were related to lower HR-QoL. This impaired quality of life was reported before, in which at least some domains of QoL were found to be decreased in women with TS.[26, 30-36] However, three studies found QoL in women with TS to be comparable to non-TS controls,[37-39] or found even better scores by women with TS on some aspects such as social and emotional functioning.[38] Our study further determined in which domains Turner patients are especially experiencing difficulties and which factors contributed to their reduced mental health.

Moreover, in our cohort 'fatigue' as measured by the CIS-20 was strongly correlated with a lower quality of life. Fatigue is a complaint frequently encountered in the care for women with TS, often in absence of physical disease, with no clear cause for this debilitating complaint. We also found the increased score for fatigue to be correlated with high stress scores, and this was not sufficiently explained by any physical comorbidities. In literature it has been suggested that women with TS exhibit greater anaerobic stress during exercise, leading to increased muscle fatigue.[40] Also menopausal symptom may affect fatigue in TS women. However, such an effect cannot be determined from the results in the current study.

Another remarkable finding was that almost all women with TS engaged in sports chose an individual sports activity (e.g. running or fitness). It might be that a team sport is too demanding for these women as they have impaired performance across both verbal and visual–spatial domains,[41] or perhaps that they may feel more comfortable in an individual

setting because of their lower satisfaction with their body image. This clearly warrants further study.

We also consulted a 'Turner life coach' involved in the value-based health care program, for the interpretation of our results. Turner life coaches are women with TS who 'coach' Turner women in day-to-day problems. She suggested that the extreme fatigue may partially be explained by the mismatch that women with TS experience between what is expected of them by themselves and their environment and what they are capable of doing. This may result from the impaired concentration and attention leading to impaired executive function and subsequent fatigue. This is something that is also clearly reflected in the work domain of the burden questionnaire. Another potential explanation for these findings in women with TS is offered by Tancredi et al., who suggest that TS patients might have an overactive sympathetic nervous system (SNS).[42] Zuckerman et al. showed that TS patients have an increased resting norepinephrine level.[43] These TS women also had a lower response of catecholamines to exercise, which may be reflected in an increased basal tone of the SNS, resulting in high blood pressure, relative tachycardia, shorter conduction times and a decreased VO2max. This may culminate in the increased fatigue often experienced by these women.

Stress in women with TS has been investigated by Fjermestad et al. (n=57, mean age 40.6±11.1 years), showing that they experience more stress than healthy controls.[32] We also found an increased stress level in our cohort of Turner patients. In addition, we found that stress also negatively influenced HR-QoL. However, causality cannot be established based on this cross-sectional study, but stress reduction might be a tool for clinicians to improve QoL in women with TS.

From literature it is well-known that fertility issues play an important role in women with TS.[10, 36] Indeed the questionnaire on fertility was not well-responded to, showing that this issue might by a difficult topic for TS women. The results showed a lower relational quality of life but a higher score on the mind-body and emotional sub scores compared to a retrospective cohort of Dutch women who underwent medically assisted reproduction. The questionnaires used in this study are well validated in other populations and have been used in clinical setting. We have not evaluated the burden of filling out the questionnaire itself, but it takes approximately 15 minutes and we feel this is a relatively small effort. We do aim to evaluate the acceptability in future studies. Conversely clinicians are often time-pressed and the time it takes to fill in a questionnaire cannot be spent elsewhere. Therefore the set-up of automated sent questionnaires, providing so much important information is an important asset in the assessment for the clinician. In our study the feasibility was good as 177 out of the 201 women did fill in the questionnaires. An important hurdle is that some specific questionnaires such as the one on sexuality was only marginally filled in. This hurdle needs attention. Of the women that did fill in these

questionnaires just over half were sexually active and of these around 80% were content with their sex-life. There might be a selection bias of women feeling more comfortable completing these questionnaires being more positive on their sex-life, compared with women who feel uncomfortable, it may have been confronting or women may have considered questions not relevant.[44] Also, these questionnaires have not yet been validated specifically for the TS population which limits their interpretation. Therefore, future research should focus on developing disease specific tools, as previous studies show that disease specific HR-QoL instruments can contribute to more effective treatment interventions as they have more power to detect small differences and changes over time.[15, 45-47]

Clinical implications

We want to underline the need for screening with Turner specific questionnaires covering a broader range of HR-QoL and varying aspects of psychosocial functioning in women with TS. Reis et al. described 18 different instruments in a recent review, mostly the SF-36, used to assess QoL and related domains.[10] TS, however is a very heterogeneous syndrome that is not easily covered in a limited set of questions. However, a single validated TS specific questionnaire would in our opinion allow to more easily score QoL and act timely and appropriately. Considering our results, such a questionnaire would need to cover the HR-QoL aspects of the EQ-5D, stress, fatigue and sexuality. Indeed if all women with TS would fill in this questionnaire, problems could be identified timely and possible therapy can be offered and initiated. Once a common methodology has been established to investigate QOL in these women other possible sources of bias, such as ascertainment bias due to the tendency of TS women to give expected responses, could studied further. For some women group sessions may provide useful support, while others clearly need individual coaching or psychological therapy. In addition, a well-structured exercise program may be useful in selected women with TS. Finally, attention for and information on sexual functioning and fertility should be organized for all women with TS.

The main limitation of our study is that not all questionnaires were completed by all participants, which possibly introduced bias. Patient who experienced higher stress, more fatigue or lower QoL could have been less motivated to participate in this comprehensive set of questionnaires. A second limitation lies in the retrospective manner in which electronic patient records were searched for patient specific clinical information, which is sensitive to incompleteness. All women with TS are seen in our center and the current cohort should therefore be representative of the general TS population. Furthermore we had no data on the women who did not respond to the questionnaires, we were therefore unable to assess a potential difference between these groups. A final limitation is that there was no reference data on educational attainment and partnership status and therefore no

comparison on these aspects could be made. This would be an important aspect to take into account in designing future studies.

Conclusion

Value based healthcare means aiming at improving outcomes that really matter to patients. In order to do this, we should first measure these outcomes. By doing so, we showed that women with TS scored lower on HR-QoL and reported more stress and fatigue compared to healthy controls. Determinants which were found to affect HR-QoL were physical factors, such as diabetes and orthopedic complaints, but also stress and fatigue were clearly associated with lower HR-QoL.

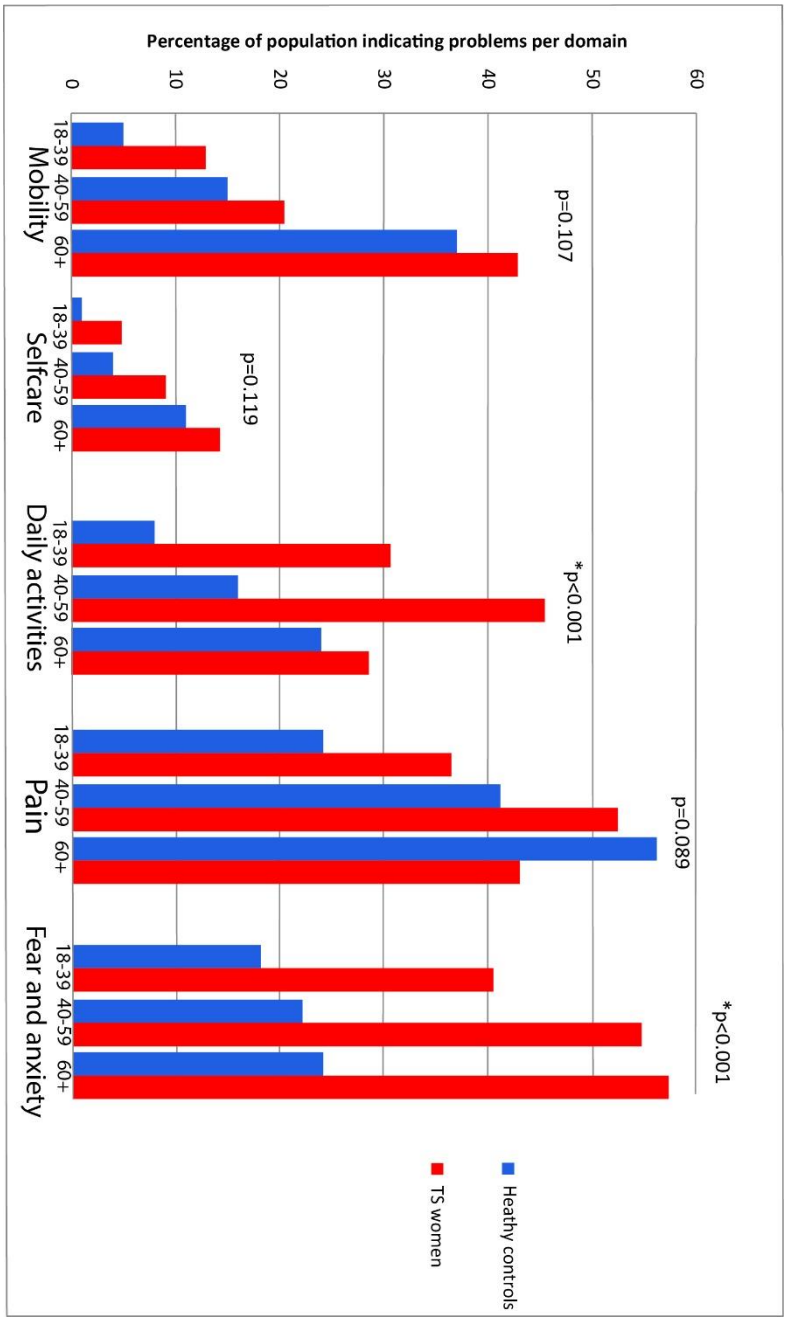
Supplementary Material

Supplementary table 1. Self-reported burden on six domains.

Self-reported Burden (N=177)	n=	%
Physical		
Obesity	59	33
Hearing	67	38
Fatigue	79	45
Emotional		
Anger	32	18
Sadness	34	19
Gloominess	48	27
loneliness	22	12
Low self-esteem	84	47
Anxiety	19	11
Practical concerns		
Trouble taking medication	15	8
Activities	21	12
Transportation to work	7	4
Social interaction		
Parents	18	10
Brothers or sisters	14	8
Family	6	3
Friends	18	10
Connection with peers	27	15
Romantic relationship	29	16
Work		
Absenteeism	3	2
Memory	33	19
Concentration	35	20
Relation with colleagues	35	20
Being bullied or excluded	7	3
Future		
Education or work	53	30
Uncertainty about physique	23	13
Aging	25	14

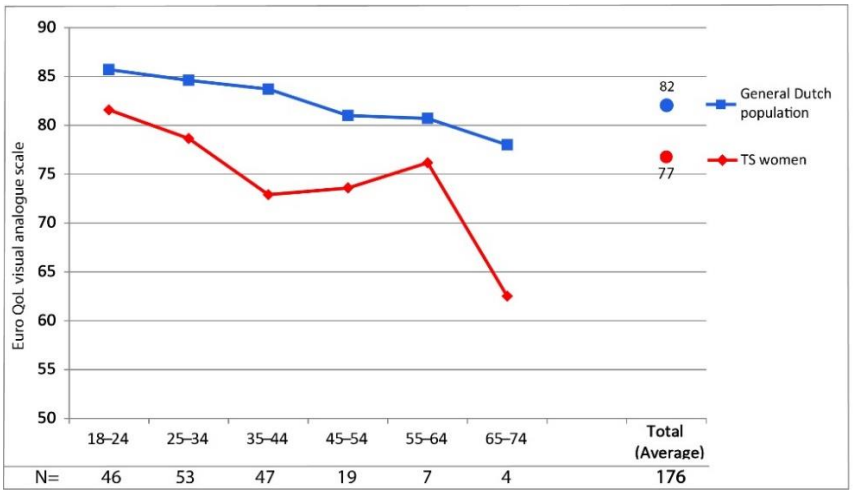
Supplementary table 1. Self-reported burden. Data per item is presented as n=, %.

Supplementary figure 1. EQ-5D (HR-QoL) scores per subdomain: TS women vs. Dutch population.



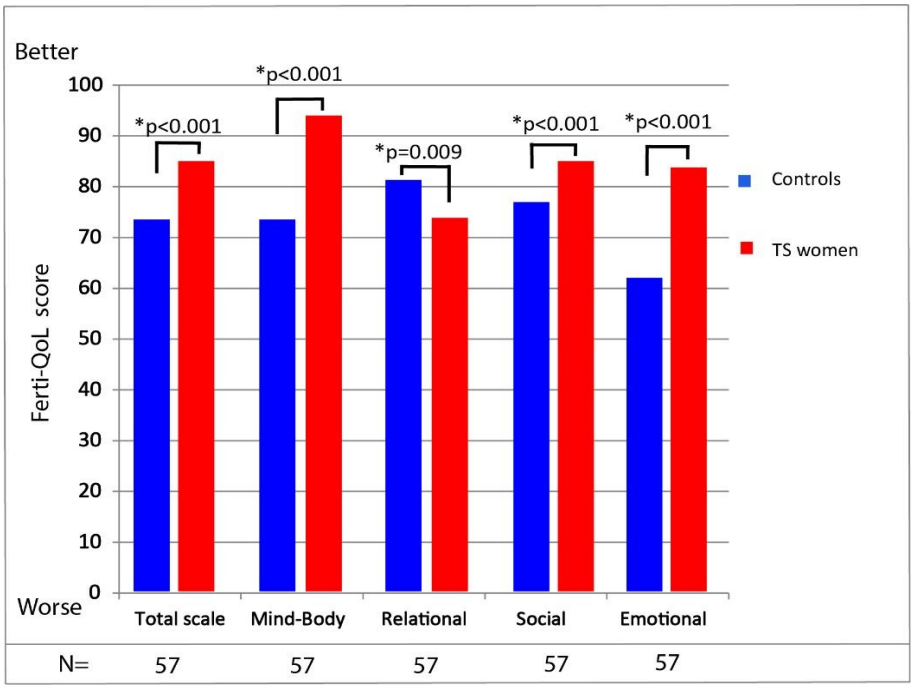
Supplementary figure 1. EQ-5D scores per subdomain. Scores in a cohort of healthy Dutch non- women (blue). The scores of women with TS (red). P values are calculated over the difference of the total cohort versus all controls.

Supplementary figure 2. Euro-QoL visual analogue scale (VAS): women with TS vs control population.



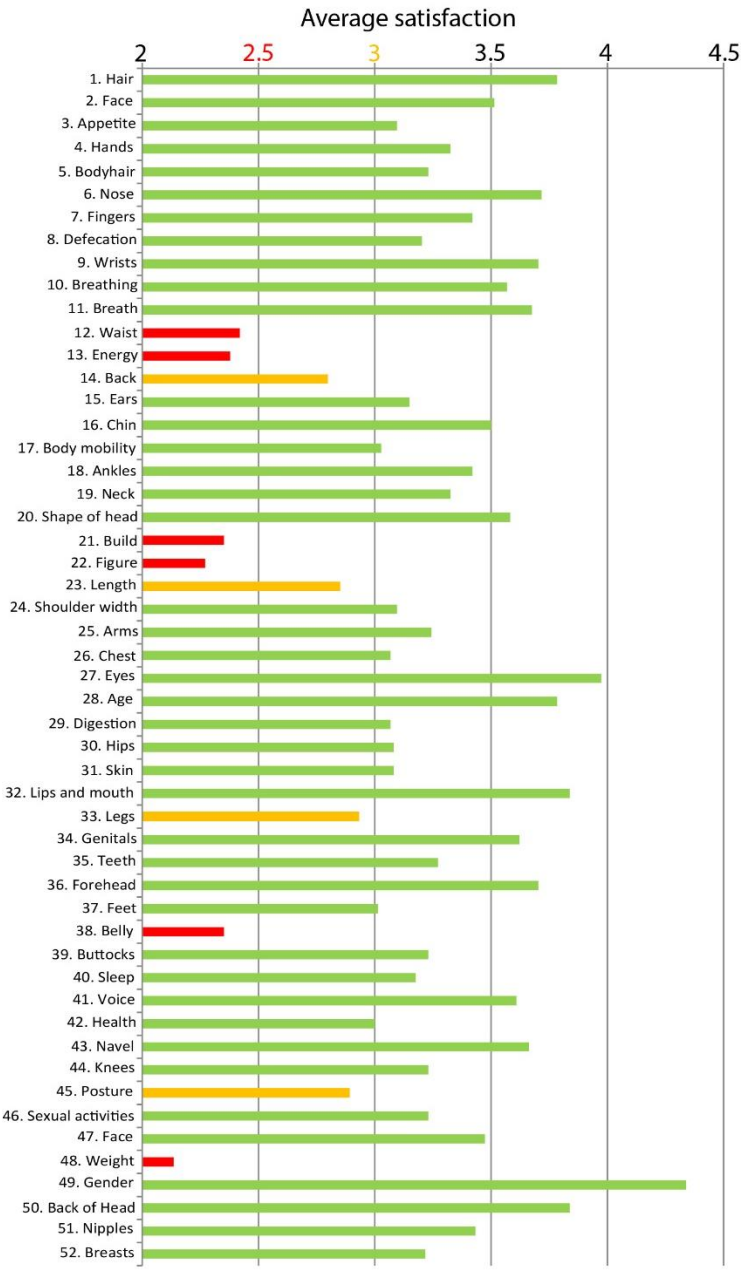
Supplementary figure 2. VAS-score per decade of life. Interpreted as a quantitative measure of health outcome as judged by the individual respondents. The red line depicts scores in women with TS. The blue line depicts scores in a cohort of healthy Dutch non- women with TS. *p-value

Supplementary figure 3. Ferti-QoL score per domain.



Supplementary figure 3 *p-value significant below p<0.05.

Supplementary figure 4. Body image



Supplementary figure 4. Body-image score on 52 items. Scored on a five point Likert-scale (1-5). Score below average (2.5) in red, scores below 3 in orange.

Supplementary methods

The HADS is an instrument to screen for anxiety and depression in patients under medical treatment using 14 statements on a four-point Likert scale.[48] The HADS was only offered after indication of emotional suffering on EQ-5D and therefore no comparison to a reference population can be made.

Ferti-QoL

The Ferti-QoL consists of 36 items that yield six subscales and three total scores, higher scores indicate a more favorable outcome.[49] It scores the fertility-related quality of life across the 'Emotional', 'Mind-Body', 'Relational', 'Social', 'Treatment Environment' and 'Treatment Tolerability' subscales. The emotional subscale score shows the impact of negative emotions related to fertility problems on quality of life. The Mind-Body subscale score shows the impact of fertility problems on physical health, cognitions and behavior. The relational subscale measures the impact of fertility problems on the marriage or partnership. The social subscale assessed the extent to which social interactions have been affected by fertility. The treatment environment subscale score covers the extent to which the accessibility and quality of treatment impacts quality of life. The treatment tolerability subscale score indicates the extent to which fertility medical services impact on daily life. We compare our data to a cohort of Dutch women who underwent screening for medically assisted reproduction.[29]

Sexuality questionnaires

All four questionnaires on sexual activity and sexual functioning in women (sexual activity question, BSSC-W, FSFI and FSFD-R) were offered to the women with TS aged 20 and 45 years.[50] These questionnaires were offered in a stepwise fashion; the FSFI and FSDS-R were offered only to women who had indicated sexual discontent on the BSSC-W.

Disease burden and body image

Furthermore a 'burden questionnaire' was offered which scored problems on six domains; 'physical', 'emotional', 'practical concerns', 'home and environment', 'work', and 'future'. And a separate score indicating how much they were bothered by the reported burden in their daily lives on a scale from 1-10. Finally, women who had indicated to be dissatisfied with their body were asked to fill out the Body Cathexis Scale (BCS),[51] a questionnaire about body image that assesses satisfaction on a five-point Likert-scale on 52 different areas of physique (e.g. length, breasts).

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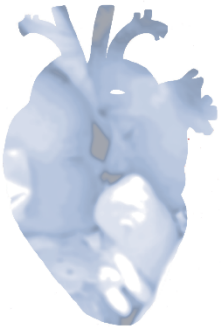
TURNER SYNDROME



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5

Systolic and diastolic strain measurements show left ventricular dysfunction in women with Turner Syndrome

Congenital heart disease 2021

Abstract

Objective: This study aimed to describe the systolic left ventricular global longitudinal strain (LvGLS) and left ventricular peak early diastolic strain rate (Sre) in adult women with Turner syndrome (TS) and to determine its relationship with exercise capacity and clinical parameters.

Methods: In this cross-sectional cohort study, consecutively included adult TS women underwent an electrocardiogram, transthoracic echocardiogram (TTE) and cardiopulmonary exercise test (CPET) on the same day. LvGLS and Sre were measured using 2D speckle tracking analysis (STE) and compared with age-matched healthy female controls.

Results: Ninety-four adult women (age 36±13 years) with TS and 32 healthy age-matched female controls were included. Women with TS had a significantly impaired/reduced systolic LvGLS (-17.82 ±2.98% vs. -21.80 ±1.85%, $p<0.001$) and Sre (0.98 ±0.32 s-1 vs. 1.27 ±0.19 s-1, $p>0.001$), compared to healthy female controls. Furthermore, TS women had reduced diastolic function as measured by conventional echocardiographic parameters: a higher A-wave ($p<0.001$), lower E/A-ratio ($p=0.001$), longer deceleration time ($p=0.006$), and a higher E/E'-ratio ($p<0.001$). Women with TS also had a significantly reduced maximal workload ($p=0.033$), reduced oxygen uptake ($p<0.001$) and a reduced maximal heart rate ($p<0.001$) during exercise. Multivariable linear regression analysis revealed that Age, karyotype and QT-duration were significantly associated with Sre, but not with LvGLS, in the TS population

Conclusions: Systolic and diastolic strain and exercise capacity were significantly reduced in TS women compared to healthy women. No correlation between strain itself and exercise capacity could be demonstrated, but correlations with conventional TTE parameters and baseline characteristics were found.

Introduction

Turner syndrome (TS) is caused by a partial or complete loss of the X chromosome and affects approximately 1 in 2000 live-born girls [1]. Besides the classical features, such as short stature and gonadal dysgenesis, these women have an increased risk of cardiovascular disease which is an important cause of morbidity and mortality among TS patients [1, 2]. Common congenital heart defects are bicuspid aortic valve (BAV; 25-39%) [3, 4], coarctation of the aorta (CoA; 12-16%)[3], and partial abnormal pulmonary venous return (PAPVR; 18-25%) [5, 6]. These congenital heart defects may affect left ventricular (LV) function [7] . However, TS has also been associated with increased LV mass and reduced LV dysfunction independent of congenital heart disease [8-10]. The etiology of this predominantly sub-clinical LV impairment that exists in absence of hypertension or poor metabolic control remains enigmatic [8, 9]. To date there is very little data on left ventricular global longitudinal strain (LV GLS) and LV diastolic strain rate (Sre) in adult women with Turner syndrome. And studies that did examine left ventricular function in TS patients were often done using conventional echocardiography [9, 11]. Where conventional echocardiography may not be able to detect early sub-clinical LV dysfunction and children may not have developed dysfunction yet. Therefore this study uses deformation measurements by 2D speckle-tracking echocardiography (STE) which may offer advantages, such as angle independency, over conventional echocardiographic markers for diastolic dysfunction [12-14]. Moreover, the myocardial deformation parameters as LvGLS and Sre have not yet been comprehensively described in adult women with TS. Furthermore the effect of sub-clinical LV dysfunction on exercise capacity has not yet been described in a TS population, whereas this effect is well-studied in non TS cohorts [15, 16]. While these effects may be clinically relevant, especially in a population that often struggles with unexplained fatigue[17]. Therefore, the aims of this study are threefold; firstly to comprehensively describe systolic (LvGLS) and diastolic LV function (Sre) using STE and compare it to age and gender matched controls. Secondly, to determine exercise capacity in women with TS. Finally, we aim to investigate possible relation between left ventricular function and exercise parameters.

Methods

Study population and design

In this multi-center, cross-sectional study 94 consecutive adult women with genetically proven TS were included from October 2014 to April 2016. All patients underwent a physical examination, transthoracic echocardiogram (TTE), electrocardiogram (ECG) and a cardio pulmonary exercise test (CPET) on a bike ergometer on the same day. Electronic patient records were used to collect medical history. A total of 32 age-matched healthy women were selected from a cohort study consisting of 155 healthy volunteers to serve as

control group. All healthy controls were free from a history of systemic disease, cardiovascular disease, renal dysfunction or cardiac medication use. Details of this control cohort have been described previously [7]. Hypertension was defined as the prescription of antihypertensive medication or an elevated blood pressure (systolic >140 mmHg and/or diastolic blood pressure >90 mmHg). Hypercholesterolemia and diabetes were defined as the requirement for treatment. Body surface area was determined using the DuBois formula [18]. This study was approved by the medical ethical committee of the Erasmus Medical Center. Written informed consent was obtained from all participants.

Echocardiography

Imaging acquisition

Two-dimensional greyscale images were obtained by two experienced sonographers using the ultrasound system iE33 (Philips Medical Systems, Best, The Netherlands) equipped with a S5-1 transducer (1-MHz to 5-MHz, frequency transmitted 1.7 MHz, frequency received 3.4 MHz). A minimum framerate of 60 Hz is obtained to optimize the speckle tracking echocardiograph. Digital images are stored in QLAB workstation (Philips Medical Systems) for further analysis.

Image analysis

Dimensional and functional measurements were done according to the recommendations for cardiac chamber quantification in adults [19]. The mitral- and aortic valve regurgitation were visually graded as none, mild, moderate or severe. Ejection fraction was visually graded as reduced, mildly reduced or good. Left ventricular strain analysis using STE was done by A.H. and S.Y, blinded to patient specific information. 2D-speckle tracking analysis was done using Tomtec Imaging Systems (2D Cardiac Performance Analysis). Feasibility was assessed by both observers, in case of insufficient imaging quality patients were excluded from further analysis. The peak systolic LV GLS, defined as the maximum strain value during the ejection, was calculated from the apical four-, three- and two-chamber views according to the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [19]. Also, LV global longitudinal early diastolic strain rate (Sre) was assessed as the maximum strain rate during early diastole. Sre was calculated for each apical chamber view by averaging the segmental Sre values. The myocardial contours, both end diastolic and end-systolic, are drawn automatically by the software. Contours were checked during the full cardiac cycle and manually adjusted if necessary.

Electrocardiogram and cardiopulmonary exercise test

Participants underwent a 12-lead standard resting electrocardiogram (ECG) and a symptom-limited cardiopulmonary bike exercise test (CPET) including a breath-by-breath

analysis. The diastolic and systolic blood pressure was measured at rest, and at maximal exertion. All parameters are determined according to the ATS/ACCP guidelines [20]. Individual standardized reference value are calculated according to the CPET-protocol used in our center using the formula for women: ((2*length-2.37*age-73)*1.01+16,6)*0.8. A workload or VO2max lower than 85% of the predicted value is considered as reduced exercise capacity. The reference group did not complete a bike ergometry as this was a retrospective cohort and this was not included in the protocol at the time of inclusion

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) when normally distributed, and as median and IQR in case of a non-normal distribution. Categorical variables are expressed in frequencies and percentages. Differences between two groups are compared by using the Student unpaired T-test when normally distributed and the Mann-Whitney U test in case of a non-normal distribution. Furthermore, differences between two measurements in a group were compared by using the paired T-test. Correlation analysis is performed by Pearson or Spearman correlation test, as appropriate. Univariable linear regression analysis and subsequent stepwise multivariable linear regression analysis ($p<0.10$) was performed to identify patient characteristics that are significantly associated with LV function and exercise capacity. In case of collinearity of variables, we entered the variable with the strongest correlation with the outcome into the multivariate linear regression analysis. A p-value of <0.05 is considered statistically significant. The inter-observer variability was analyzed by using the Bland-Altman analysis. The limits of agreement between two observers were defined as the mean of the differences ±1.96 SD. The coefficient of variation (COV) was calculated as the ratio of the standard deviation of the mean difference to the mean of the two measurements. All statistical analyses were performed with the Statistical Package for Social Sciences, version 21.0 (SPSS, Chicago, Illinois).

Results

Characteristics of the study population

Ninety-four adult women with TS (mean age 36 ± 13 years, all female) were included. The control group consisted of 32 healthy women (mean age 37 ± 6 years). Forty-four women had a monosomy X, 14 had a mosaicism, other karyotypes included isochromosome (n=14), polyploidy (n=5), ring chromosome (n=3), deletion (n=3), derivative (n=2).
Of these women, 41 (44%) were known with structural heart disease, such as BAV (n=27), PAPVR (n=13), CoA (n=9), persistent left vena cava superior (n=4), arteria lusoria (n=3), persistent ductus arteriosus (n=2), persistent foramen ovale (n=3), hypoplastic aortic arch

(n=1), aortic stenosis (n=1), pulmonary atresia (n=1), incomplete double aortic arch (n=1) or tetralogy of Fallot (n=1). Baseline characteristics for TS patients and healthy controls are shown in Table 1. There was no difference in baseline characteristics between TS women with and without structural heart disease. Moreover, eight TS women (9%) had underwent aortic intervention at moment of inclusion including: coarctation repair (n=6), coarctation repair and a graft replacement of the aortic root (n=1), and coronary artery bypass grafting (n=1). Furthermore, seven patients (7%) had underwent valve intervention. There were 23 (24%) TS women using cardiovascular medication: statin (n=8), angiotensin ll receptor blockers (n=6), beta-blockers (n=8) or angiotensin converting enzyme inhibitors (n=7).

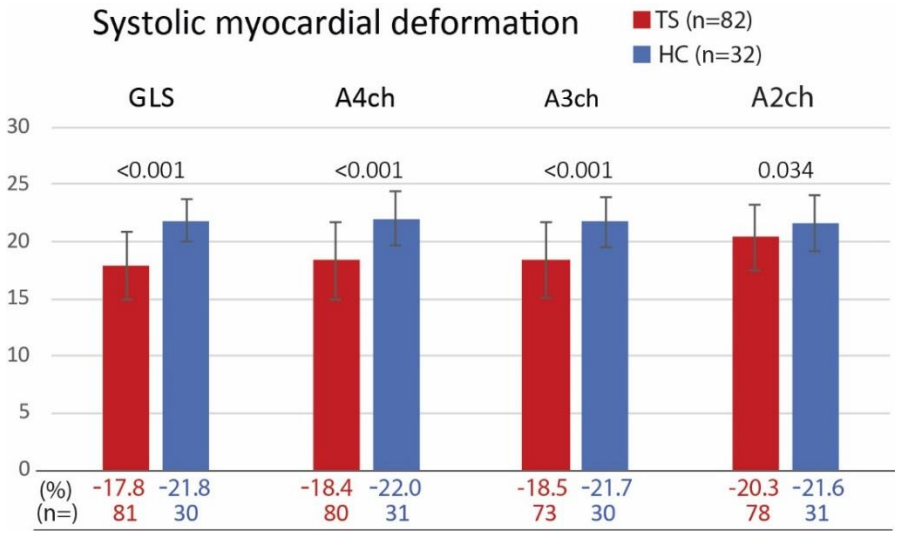
Systolic and diastolic myocardial deformation measurements

Twelve TS patients (13%) and one healthy control (3%) had to be excluded from strain analysis in advance because of poor imaging quality. Women with TS had a significantly impaired systolic LvGLS (-17.82 ±2.98% vs. -21.80 ±1.85%, p<0.001; figure 1A) and diastolic Sre (0.98 ±0.32 s-1 vs. 1.27 ±0.19 s-1, p>0.001; figure 1B) compared to healthy female controls. Furthermore, 28 TS women (30%) had a systolic LvGLS below normal (<17%, [19]). When compared with the lower limit of normal for their age group (<0.89s-1, [21]), 35 TS patients (37%) had a low Sre value. The intra-observer variability analysis showed low mean differences and good correlation for systolic LvGLS (0.31% ± 1.36, Pearson's R: 0.885, p-value<0.001, supplemental figure 1) and Sre (-0.07s-1 ±0.19, Pearson's R: 0.817, p-value<0.001, supplemental figure 1).

Table 1. Baseline characteristics

	Total TS (n=94)	Healthy controls (n=32)	P-value*
Baseline			
Age, years	36 ± 13	37 ± 6	0.674
Height, cm	155 ± 8	169 ± 6	**<0.001**
Weight, kg	62.9 ± 15.1	66.1 ± 9.8	0.171
BSA, m^2	1.61 ± 0.20	1.76 ± 0.13	**<0.001**
BMI, kg/m^2	26 ± 5.5	23± 3.3	**0.001**
SBP, mmHg	126 ± 15	118 ± 9	**<0.001**
DBP, mmHg	81 ± 12	75 ± 8	**0.001**
Hypertension	19 (20)	NA	
Hypercholesterolemia	10 (11)	NA	
Diabetes	4 (4)	NA	
HRT	94 (100)	NA	
Exercise		Completeness	n (%)
Workload, % of predicted	95 ± 23		92 (100)
Workload, watt	124 ± 39		92 (100)
Heart rate			
HR, % of predicted	89 ± 9		92 (100)
Heart rate, beats/ min	163 ± 23		92 (100)
O_2 pulse, ml/min/beat	9.31 ± 2.00		90 (98)
Blood pressure			
SBP, mmHg	155 ± 22		92 (100)
DBP, mmHg	80 ± 14		92 (100)
Ventilation			
VO_2, ml/ min	1555 ± 384		91 (99)
VO_2, % of predicted	89 ± 16		91 (99)
VO_2, ml/ min/ kg	25.16 ± 6.10		91 (99)
VCO_2, ml/ min	1819 ± 500		90 (98)
V'E, l/min	58.5 ± 16.6		91 (99)
V'E, l/ min/ kg	0.96 ± 0.29		91 (99)
PETO2, kPa	15.7 ± 0.9		91 (99)
$EqCO_2$	30.2 ± 4.6		90 (98)
EqO_2	35.4 ± 7.5		90 (98)
Peak RER	1.2 ± 0.1		91 (99)

Table 1. Continuous data are presented as 'mean ± SD' and categorical data as 'n= (%)'. *BSA:* body surface area, *SBP:* systolic blood pressure, *DBP:* diastolic blood pressure, HRT homone replacement therapy, *BAV:* bicuspid aortic valve, *NA:* not applicable, *: significance of the difference between patients with all Turner syndrome patients and healthy controls. Measurements at maximal exertion. *HR*: heartrate, *SBP*: systolic blood pressure, *DBP*: diastolic blood pressure, VO_2 : O_2 consumption, VCO_2: CO_2 production, *V'E:* minute volume, $PETO_2$: End tidal tension of oxygen, $EqCO_2$: ventilatory equivalent for CO_2, EqO_2: ventilatory equivalent for O_2, *RER*: respiratory equivalent ratio.



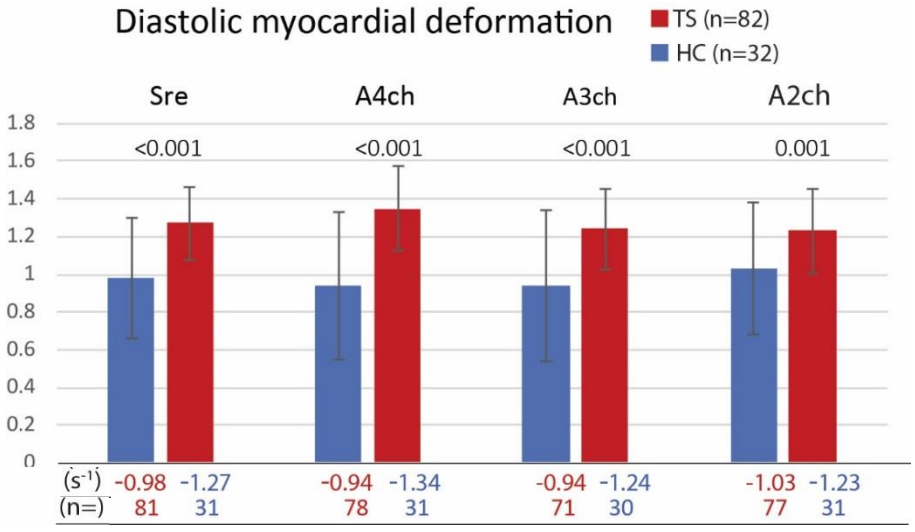


Figure 1. A) Systolic left ventricular global longitudinal strain (%, LVGLS); values for Turner syndrome patients (TS) are indicated in red, healthy controls (HC) in blue. B) Diastolic myocardial strain rate (S^{-1}, Sre). Apical (A) 4, 3 and 2 chamber (ch) views. Completeness is indicated (n=) for each view. P-values are shown above each column.

Conventional echocardiography

Echocardiographic measurements are shown in Table 2. All functional LV parameters, LV chamber function, E-wave, and E'-wave were significantly different in TS patients compared with healthy women. The absolute LV dimensions were not significantly different; however, when corrected for BSA, LV was significantly larger in TS women, both in end-diastole (LVEDd: 28mm/m2±3.6 vs. 26mm/m2±2.6, p= 0.002) and in end-systole (LVEDs: 18mm/m2 ±3.2 vs. 16mm/m2± 2.4, p=0.002). TS women may have higher BMI than their non-TS peers, which may influence their BSA. Therefore we also examined LV dimension corrected for height, where the same statistically significant difference was observed (LVEDd per meter: 29mm/m±2.9 vs. 27mm/m±2.1, p= 0.002) and in end-systole (LVEDs: 18mm/m ±3.2 vs. 16.5mm/m± 2.4, p=0.001).

Electrocardiography

Women with TS had significantly higher resting heart rate (77 bpm±13) compared to healthy controls (60 bpm±8, p<0.001). Also, conduction times differed between groups: the PR-duration was shorter (137ms±25 and 148ms±24, p=0.029), and QTc-duration was longer (420ms±31 and 395ms± 14, p<0.001) in women with TS compared to healthy women. None of the patients had signs of LV hypertrophy on the electrocardiogram and all TS patients, except one, were in sinus rhythm (n=92, 99%).

Table 2. Baseline characteristics

	Turner Syndrome (n= 94)	Completeness n (%)	Healthy controls (n= 32)	Completeness n (%)	P-value
Left ventricular function					
LVEF, %	53 ± 10	84 (89)	62±5	31 (97)	<0.001
E-wave, m/s	0.84 ± 0.21	90 (96)	0.81 ± 0.18	31 (97)	0.503
A-wave, m/s	0.66 ± 0.23	89 (95)	0.45 ± 0.12	31 (97)	<0.001
E/A-ratio	1.40 ± 0.55	89 (95)	1.95 ± 0.79	31 (97)	0.001
DET, ms	199 ± 53	88 (94)	177± 27	31 (97)	0.006
E'- wave, cm/s	10.1 ± 3.6	84 (89)	10.7 ± 2.0	30 (94)	0.968
E/e'- ratio	9.7 ± 4.0	84 (89)	7.5 ± 1.7	30 (94)	<0.001
Left sided dimensions					
LVEDd, mm	44.6 ± 4.6	93 (99)	45.6 ± 3.5	32 (100)	0.240
LVEDd per BSA, mm/m^2	27.9 ± 3.6	93 (99)	26.1 ± 2.6	32 (100)	0.002
LVEDs, mm	28.6 ± 4.6	93 (99)	27.9 ± 4.0	32 (100)	0.446
LVEDs per BSA, mm/m^2	17.9 ± 3.2	93 (99)	15.9 ± 2.4	32 (100)	0.002

Table 2. LVEF: left ventricular ejection fraction, BSA: body surface area, E-wave: mitral flow E velocity, A-wave: mitral valve A velocity, E/A- ratio: mitral flow E velocity/ A velocity, DET: deceleration time, E'- wave: early diastolic annular myocardial velocity (septal), E/E'-ratio mitral flow E velocity/ early diastolic annular myocardial velocity, LVEDd: left ventricular dimension at end-diastole, LVEDs: left ventricular dimension at end-systole,

Table 2 continued -Baseline characteristics

Valvular heart disease					
MV regurgitation		94 (100)	NA	-	-
None	78 (83)				
Mild	16 (17)				
Moderate	0 (0)				
AV regurgitation		94 (100)	NA	-	-
None	71 (76)				
Mild	22 (23)				
Moderate	1 (1)				

.**Table 2.**MV regurgitation: mitral valve regurgitation, AV regurgitation: aortic valve regurgitation, NA: not applicable

Cardio pulmonary exercise test

Cardiopulmonary exercise testing was performed in 92 (98%) patients and exercise parameters are shown in Table 1. Thirty-two TS women (35%) had a reduced workload and 33 women (36%) had a reduced VO2max (<85%). Moreover, TS women had a significantly reduced maximal heart rate (p<0.001), reduced oxygen uptake (p<0.001) and a reduced maximal workload (p=0.033) when compared with individual standardized reference values. Moreover, exercise capacity did not differ between women with and without cardiac defects (94% vs 96% of predicted, p=0.752).

Associations of systolic and diastolic myocardial deformation parameters

The results of the regression analysis are presented in table 3. In line with previous higher age was significantly associated with reduced Sre, and longer QTc times with a higher Sre. Also karyotype remained significantly associated with Sre (β-coefficient: 0.005, p-value <0.001; R2=0.445). For LvGLS no significant associations were found with baseline characteristics (Table 3). Although it was not the main objective of our study we did compare patients with and without cardiovascular disease. We did test for a possible difference in patients with or without structural heart disease. However, no such influence could be found for the main outcome measurements such as strain or exercise capacity. Moreover, some minor differences were observed that may point in the direction of minor

diastolic dysfunction in the patient group with cardiac disease. A higher a-wave was observed in (0.7 vs 0.6 m/s, p= 0.019), a lower e'-wave (9 vs. 11 cm/s, p=0.031). Patients with cardiac disease also had a larger 'LVED/BSA' both in systole and diastole (28.9 vs 27.2, p=0.19 and 18.6 and 17.3 p=0.49). However this was largely explained by them having a lower BSA (1.56 vs 1.65; p=0.02).

Discussion

This study demonstrates significantly lower myocardial deformation parameters (LvGLS and Sre) in women with TS Furthermore. Furthermore, TS women showed reduced conventional diastolic parameters, significantly different conduction times and a lower exercise capacity. Age, karyoptype and QTc-duration were significantly associated with Sre but not with LvGLS in the TS population. We did observe impaired diastolic function on conventional echocardiography compared to the healthy controls, mainly: lower A-wave and E/A-ratio, shorter DET, and higher E/e'-ratio.

LV myocardial deformation in women with TS

Although LV myocardial deformation measurement using STE is superior to tissue Doppler imaging (TDI), [22, 23] earlier studies have already described a higher A-wave and subsequently a lower E/A- ratio compared to healthy female subjects [8-11]. Our study supports these findings and adds a prolonged deceleration time and higher E/e'-ratio compared to healthy women.

Hypertension is an important risk factor for LV diastolic dysfunction and aortic dilatation. In line with previous studies, [24-27] we found an elevated diastolic and systolic blood pressure in women with TS. Therefore vigilant surveillance of not only systolic but also diastolic blood pressure in TS patients is important as described earlier [25]. We hypothesized that this difference in blood pressure may explain the difference in myocardial deformation parameters between TS and healthy controls. However, our current study shows no significant effect of blood pressure on the myocardial deformation parameters. This finding is in line with earlier studies that have shown that the changes in LV function seem to occur irrespective of hypertension or metabolic control in women with TS [9, 10].

An alternative explanation could lie in the increased prevalence of congenital heart disease in this population. Some congenital heart defects such as CoA and BAV are known to cause a reduced LvGLS, [7, 28] both of which occur frequently in women with TS. Unfortunately our study was not designed to and further studies are therefore needed to definitively confirm such a relation in TS women.

A third potential explanation could be offered by the decreased aortic distensibility that is described in women with TS [29-32]. Vascular stiffening reduces compliance and increases arterial pressure which augments overall vascular resistance. Subsequently the LV would

have to compensate for this pressure overload by increasing myocardial wall thickness, leading to reduced diastolic compliance or even increased end-diastolic volume. However, to our knowledge no longitudinal studies have been conducted that investigate a possible relation between diastolic function and aortic elasticity in women with TS. We found an indication of increased LV size when corrected for BSA or height in the TS population and a decreased exercise capacity. This could resemble the impaired diastolic reserve seen in HF with preserved ejection fraction (HFpEF) which leads to LV end-diastolic pressure (EDP) resulting in exercise intolerance [33]. However, a follow-up study would be needed to investigate if this holds any relation to the aortic distensibility.

Although hypertension, congenital heart disease and vascular compliance may all contribute to the observed LV dysfunction in women with TS, a common underlying cause could be assumed in TS. Recently, TS women were found to have increased cortisol levels [34]. Several aspects of the TS phenotype may well fit a 'hypercortisolism theory'. Like in patients with Cushing syndrome, long term exposure to increased levels of cortisol could lead to increased prevalence of left ventricular (LV) hypertrophy, higher frequency of concentric remodeling, and subsequent LV systolic and diastolic dysfunction, and left atrial systolic dysfunction, as well as increased regional LV wall thickness [35-38]. Possibly the electrophysiological changes [39], increased pulse wave velocity [40] and metabolic syndrome [37, 41] also fit such an explanation. Also the higher resting heart rate could fit in this hypothesis.

Limitations

The main limitation is the small sample size of the study, although this is one of the largest most comprehensive studies to date. Another shortcoming may be the lack of data on the coronary arteries of these patients. This study cannot fully discern the possible influence of the presence of structural heart disease on the cardiac function. We show that no significant difference on the main outcome parameter were found. However since this was not the primary objective of this study we suggest future studies to expand upon our current effort. A possible inclusion bias is unlikely as patients were consecutively included into this study. A possible source of bias is the time and effort taken by the study. This may cause only less affected patients to participate. As more severely affected patients may already be intensively monitored. Where less affected individuals may be tempted by a very comprehensive check-up. In this current study we have no information on the behavioral aspects of the deficit in exercise capacity. Future studies should therefore for example include a questionnaire to determine baseline activity levels of TS women.

Table 3. Linear regression analysis

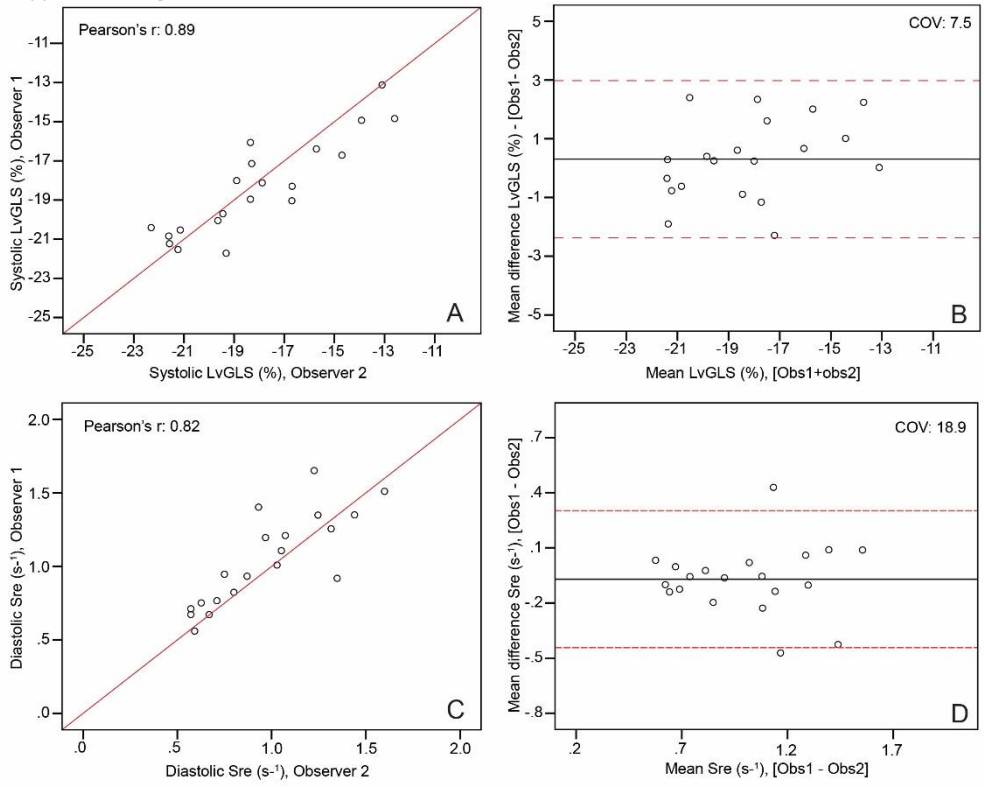
	Univariable regression				Multivariable regression			
	Left ventricular diastolic strain rate (SRe)							
		95% CI				95% CI		
Baseline characteristics	β-coefficient	Lower limit	Upper limit	p value	β-coefficient	Lower limit	Upper limit	p value
Age, years	-0,009	-0,014	-0,004	<0.001	-0.01	-0,14	-0,005	<0.001
BMI, kg/m^2	-0,005	-0,019	0,008	0.445				
Heart rate, beats/min	0,001	-0,004	0,007	0.632				
DBP, mmHg	0,004	-0,002	0,010	0.169				
SBP, mmHg	0,001	-0,004	0,006	0.610				
Karyotype*	0,142	-0,007	0,291	0.061	0.130	0,009	0,250	0.035
QT_c-duration, ms	0.004	0,002	0,007	<0.001	0.005	0,003	0,007	<0.001
PR-interval duration, ms	-0,001	-0,004	0,002	0.534				
	Left ventricular global longitudinal strain (LV GLS)							
Age, years	0.024	-0.025	0.074	0.335				
BMI, kg/m^2	0.064	-0.063	0.192	0.316				
Heart rate, beats/min	0.025	-0.028	0.079	0.342				
DBP, mmHg	-0.049	-0.103	0.005	0.074				
SBP, mmHg	0.013	-0.032	0.058	0.567				
Karyotype*	0.145	-1.623	1.333	0.845				
QT_c-duration, ms	0.014	-0.036	0.007	0.193				
PR-interval duration, ms	0.013	-0.012	0.038	0.315				

Table 3. Regression analysis. HR: heartrate, SBP: systolic blood pressure, DBP: diastolic blood pressure, * karyotype was dichotomized; monosomy (0) vs. other type (1) e.g. mosaic, NS: not significant.

Conclusion

Systolic LvGLS and Sre were both significantly lower in TS women compared to healthy females and exercise capacity was found to be reduced in TS women. Reduced LVGLS and Sre were not associated with exercise capacity, but correlation with conventional TTE parameters and baseline characteristics were observed.

Supplemental figure 1



Supplemental figure 1. Inter-observer agreement and identity line for LvGLS (A) and Sre (B). Bland-Altman plot for LvGLS (B) and Sre (D). Dashed red lines indicate ±1.96 SD. LvGLS: left ventricular global longitudinal strain, Sre diastolic strain rate. COV: coefficient of variation. Both Pearson's r's are significant with a p-value <0.001

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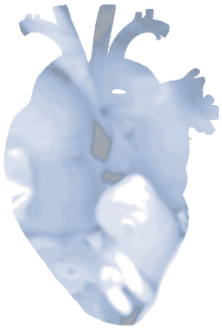
TURNER SYNDROME



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6

Coronary anatomy in Turner syndrome versus patients with isolated bicuspid aortic valves

Heart, May 2019

Abstract

Objectives. Variations in coronary anatomy, like absent left main stem and left dominant coronary system, have been described in patients with Turner syndrome (TS) and in patients with bicuspid aortic valves (BAV). It is unknown whether coronary variations in TS are related to BAV and to specific BAV subtypes. To compare coronary anatomy in patients with TS with/without BAV versus isolated BAV and to study BAV morphology subtypes in these groups.

Methods. Coronary anatomy and BAV morphology were studied in 86 patients with TS (20 TS-BAV, 66 TS-tricuspid aortic valve) and 86 patients with isolated BAV (37±13 years vs 42±15 years, respectively) by CT.

Results. There was no significant difference in coronary dominance between patients with TS with and without BAV (25% vs 21%, p=0.933). BAVs with fusion of right and left coronary leaflets (RL BAV) without raphe showed a high prevalence of left coronary dominance in both TS-BAV and isolated BAV (both 38%). Absent left main stem was more often seen in TS-BAV as compared with isolated BAV (10% vs 0%). All patients with TS-BAV with absent left main stem had RL BAV without raphe.

Conclusions. The equal distribution of left dominance in RL BAV without raphe in TS-BAV and isolated BAV suggests that presence of left dominance is a feature of BAVs without raphe, independent of TS. Both TS and RL BAV without raphe seem independently associated with absent left main stems. Awareness of the higher incidence of particularly absent left main stems is important to avoid complications during hypothermic perfusion.

Introduction

Turner syndrome (TS) is caused by complete or partial monosomy of the X chromosome in all or part of the cells and affects 1 in 2500 women [1]. The mortality rate in patients with TS is around three times higher than in the general female population, mainly as a result of cardiovascular disorders [2]. This includes coronary artery disease (CAD) [3], the presence of a bicuspid aortic valve (BAV, 12%–30%), coarctation of the aorta (CoA, 7%–18%), partial anomalous pulmonary venous return (1%–25%) [4-6] and hypoplastic left heart syndrome[7]. Also coronary anomalies are reported frequently in patients with TS (20% vs 5% in the general population), although data are scarce [7]. These coronary anomalies mainly seem to involve the left coronary artery (LCA) system, with immediate bifurcation of the two major branches of the LCA (i.e., absent main left coronary stem) being the most common anomaly reported with an incidence of 14%[7]. A higher prevalence of left coronary dominance has also been noted in patients with TS (28% vs 20% in healthy controls) [7]. Furthermore, the prevalence of BAV is common in TS, described in 12%–30% of patients with TS [5, 8, 9] vs 1%–2% in the general population [10, 11].

BAV is the most common congenital cardiac abnormality and variations in coronary anatomy, such as an absent main left coronary stem [12], have been described. The incidence of a left dominant coronary artery system in patients with BAV is reported to be 25%–29%, [13, 14] much higher than the reported incidence of 10%–12% in the general population with tricuspid aortic valves (TAV) [15, 16]. Interestingly, a left dominant coronary artery system as well as immediate bifurcation of the LCA appears to be associated to the left-right fusion BAV without a raphe (ie, strictly bicuspid) [17].

Thus, patients with TS are reported to have an increased prevalence of coronary anomalies, increased left coronary dominance and increased prevalence of BAV, but data on these issues are limited. Furthermore, little is known about the relation between coronary anomalies, left coronary dominance and BAV, and the various morphologies of BAV in patients with TS. In addition, the relation with the BAV-associated aortic disease (mainly aortic coarctation) is unclear. The current study will focus on these issues in patients with TS in comparison to patients with isolated BAV. The aims of the current study are: (1) to investigate coronary anatomy in patients with TS; (2) to study coronary anatomy in patients with TS in relation to the presence of BAV and BAV morphology subtypes; (3) to compare coronary anatomy in patients with TS with BAV versus isolated BAV; (4) to investigate the relation with aortic pathology, mainly CoA, in patients with TS versus patients with isolated BAV; and (5) to evaluate the potential role of gender on coronary anatomy in the different groups.

Methods

Study population

This is a multicenter study performed in three different academic medical centers in the Netherlands. The study population consisted of 89 patients with TS and 89 non-TS patients with isolated BAV, who were regularly visiting the outpatient clinics of the Erasmus Medical Center, the Radboud University Nijmegen Medical Center or Leiden University Medical Center, The Netherlands.

The inclusion criteria were: age ≥18 years and no prior aortic valve surgery for all patients. In addition, genetic confirmation of chromosome XO was an inclusion criterion for patients with TS. Patients with non-determinable aortic valve morphology were excluded from the analysis, leaving a total number of 172 patients included in the study. In included patients, multiphase CT scanning was performed to assess the aortic valve morphology and coronary artery anatomy. The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO). The medical ethical committee of the participating centers approved the study (P15.167). All patients provided informed consent in writing. The current study is conducted by the research consortium 'Unravelling etiology and risk factors in patients with Bicuspid Aortic valves', conducted by the Erasmus Medical Center, Rotterdam; the Radboud University Nijmegen Medical Center, Nijmegen; and the Leiden University Medical Center, Leiden, The Netherlands.

CT coronary angiography data acquisition and image analysis

ECG-triggered multiphase CT scanning was performed in the three centers according to a standardized imaging protocol with local adjustments (Erasmus Medical Center: Siemens Medical Systems, Germany; Radboud University Nijmegen Medical Center: Toshiba Medical Systems; Leiden University Medical Center: Toshiba Medical Systems, Otawara, Japan). Dose-modulated ECG pulsing was employed. Pitch was adjusted to the heart rate and if necessary beta blockers were administered prior to the scan. Iodinated contrast material was administered through an antecubital vein followed by a mixture of contrast and saline. Imaging started using bolus tracking in the aorta. Images were reconstructed at 1.0mm with a 0.4mm interval. Aortic valve morphology was evaluated and identified as RL with 'fusion' of right and left coronary leaflets; RN with right and non-coronary fusion; and as LN with left and non-coronary fusion. In addition to this, presence or absence of a raphe was described (figure 1).

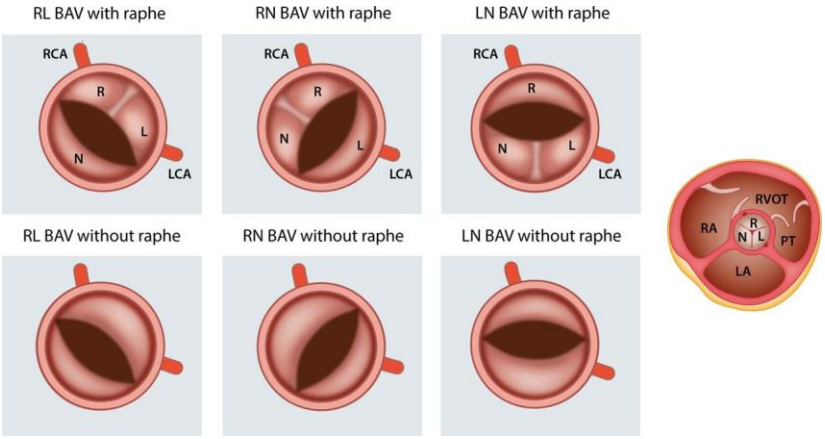

Figure 1. Schematic overview of different BAV morphologies. Upper panel: BAVs with a raphe; top left: BAV with fusion of right and left (RL) coronary leaflets; middle: BAV with fusion of right and non-coronary (RN) leaflets; right: BAV with fusion of left and non-coronary (LN) leaflets. Lower panel: strictly bicuspid valves (without a raphe). Leaflet size and symmetry, as well as the position of the commissures, may vary from the schematic overview depicted here. BAV, bicuspid aortic valve; L, left coronary leaflet; LA, left atrium; LCA, left coronary artery; N, non-coronary leaflet; PT, pulmonary trunk; R, right coronary leaflet; RA, right atrium; RCA, right coronary artery; RVOT, right ventricular outflow tract. (Modified after Schaefer et al 20).

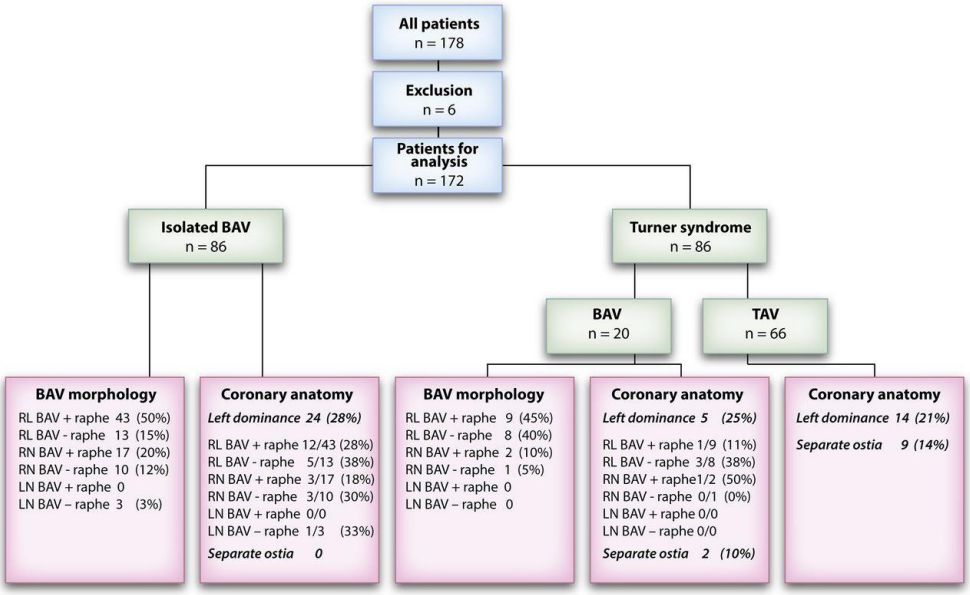

Figure 2. Flow chart indicating the study groups. BAV, bicuspid aortic valve; LN, left and non-coronary leaflets; RL, right and left coronary leaflets; RN, right and non-coronary leaflets; TAV, tricuspid aortic valve.

Coronary anatomy and coronary vessel dominance were assessed in a standardized manner by dividing the coronary artery into 17 segments according to the guidelines of the American Heart Association[18]. The coronary artery system was classified as right dominant when the posterior descending artery (PDA) originated from the right coronary artery (RCA) and considered left dominant if the PDA originated from the left circumflex artery (LCX). The coronary artery system was classified as balanced, when the PDA originated from the RCA in combination with a large posterolateral branch originating from the LCX, reaching to or close to the posterior interventricular groove. Subsequently, the presence of a left main stem and localization of the coronary ostia were assessed. If there was no left main stem, the LCA was designated as having separate ostia of the left anterior descending coronary artery (LAD) and LCX. A selection of representative CT scans was three-dimensionally reconstructed using the AMIRA V.4.0 software package (Template Graphics Software, San Diego, CA, USA).

Statistical analysis

Continuous variables are presented as mean±SD or as median and IQR. Categorical variables are presented as numbers and percentages. Cross-tabulations were made for binary categorical data, on which X2 goodness-of-fit tests were performed to test for independence. Statistical analysis was performed using SPSS software (V.23.0, SPSS). A p value <0.05, by a two-sided test, was considered statistically significant.

Results

Patient characteristics

The study population comprised 172 patients with a mean age of 39±14 years, 65 patients (38%) were male, 107 female (62%). Eighty-six patients (50%) had TS, inherently all female. Out of 172 patients, 106 (62%) had a BAV, of which 20 had TS (figure 2). Baseline patient characteristics are depicted in table 1.

BAV morphology

BAV morphology was studied in patients with TS and BAV (TS-BAV) and in patients with isolated BAV.

TS and BAV

In the group of patients with TS-BAV (n=20), 11 (55%) had a BAV with raphe vs 70% in the isolated BAV group. In 9/20 patients (45%), the raphe was located between the left and right coronary cusps (RL BAV). In two patients (10%) the raphe was located between the right and non-coronary cusps (RN BAV). BAVs without raphe were observed in 9/20 patients (45%, as compared with 30% in the isolated BAV group), eight patients had an RL BAV, one patient had an RN BAV (figure 2).

Isolated BAV

In the group of patients with isolated BAV, the majority of patients (60/86 (70%)) had a BAV with a raphe. In 43/86 patients (50%), an RL BAV with raphe was present, in accordance with the prevalence in previous studies in patients with isolated BAV [17, 19, 20] In 17/86 patients (20%), an RN BAV with a raphe was present. In 26/86 patients (30%), no raphe was identified. In this group of strictly BAVs, 13 patients had RL BAV, 10 an RN BAV and 3 an LN BAV.

Table 1. Patient characteristics

	Total (n=172)	Isolated BAV (n=86)	TS-BAV (n=20)	TS-TAV (n=66)
Age (years)	39±14	42±15	37±12	37±13
Gender, male (%)	65 (38)	65 (76)	0 (0)	0 (0)
CoA (%)	20 (12)	11 (13)	5 (25)	4 (6)
Length (cm)	168±15	180±11	154±7	156±9
Weight (kg)	71±16	79±14	57±10	65±16

Table 1. BAV, bicuspid aortic valve; TS-BAV, Turner syndrome and bicuspid aortic valve; TS-TAV, Turner syndrome and tricuspid aortic valve.

Coronary anatomy

Of all 172 patients analyzed, 43 (25%) had a left dominant coronary artery system and 122 (71%) had a right dominant coronary artery system; in one patient there was a balanced coronary artery system and in six patients dominance was not clear. Separate ostia of the LCA (i.e., no left main stem) were seen in 11 patients (6%).

Table 2A. BAV morphology subtypes in relation to coronary anatomy; TS-BAV versus TS-TAV

	TS-BAV	TS-TAV	P values
Left dominance	5/20 (25%)	14/66 (21%)	0.933
Type 1A	1/9 (11%)		
Type 1B	3/8 (38%)		
Type 2A	1/2 (50%)		
Type 2B	0		
Type 3B	0		
Separate ostia	2/20 (10%)	9/66 (14%)	0.655
Type 1B	2/2 (100%)		

Table 2A. BAV, bicuspid aortic valve; CoA, coarctation of the aorta; TS-BAV, Turner syndrome and bicuspid aortic valve; TS-TAV, Turner syndrome and tricuspid aortic valve

Coronary anatomy in patients with TS with and without BAV

There was no significant difference in presence of left dominant coronary artery systems between patients with TS-BAV and patients with TS with a TAV (25% vs 21%, p=0.933, table 2A). In addition, no significant differences were noted in the occurrence of separate ostia between patients with TS-BAV and patients with TS-TAV (10% vs 14%, p=0.655).

Coronary anatomy in TS patients with BAV vs patients with isolated BAV

There was no significant difference in prevalence of left dominant coronary artery systems between patients with isolated BAV and patients with TS and BAV (28% vs 25%, p=0.517, table 2B). Separate ostia were more often observed in patients with TS and BAV as compared with patients with isolated BAV, although numbers were low (2 vs 0 patients, respectively, table 2B)

Table 2B. BAV morphology subtypes in relation to coronary anatomy; isolated BAV versus TS-BAV

	TS-BAV	Isolated BAV	P values
Left dominance	5/20 (25%)	24/86 (28%)	0.517
Type 1A	1/9 (11%)	12/43 (28%)	
Type 1B	3/8 (38%)	5/13 (38%)	
Type 2A	1/2 (50%)	3/17 (18%)	
Type 2B	0	3/10 (30%)	
Type 3B	0	1/3 (33%)	
Separate ostia	2/20 (10%)	0	<0.05
Type 1B	2/2 (100%)		

Table 2B. BAV, bicuspid aortic valve; TS-BAV, Turner syndrome and bicuspid aortic valve.

BAV morphology subtypes in relation to coronary anatomy

BAV morphology in patients with TS-BAV and patients with isolated BAV is summarized in table 2B. In both groups, RL BAVs without raphe showed a relatively high percentage of left dominant coronary artery systems (38% in both groups, table 2B), as compared with the general population. In the TS-BAV group, both patients with separate ostia had an RL BAV without raphe (table 2B). Separate ostia were not observed in the group with isolated BAV in this cohort.

Aortic pathology in patients with TS versus patients with isolated BAV

Nineteen out of 172 (11%) patients had CoA. Of these 19 patients, 6 (32%) showed a left dominant coronary artery system. No significant difference in occurrence of left coronary dominance was found between patients with CoA and patients without CoA (32% vs 25%). In addition, there was no difference in the presence of left dominance between patients with CoA and TS and those without TS (33% vs 30%). A representative example of a patient with TS with CoA and RL BAV without a raphe is shown in figure 3.

Figure 3.

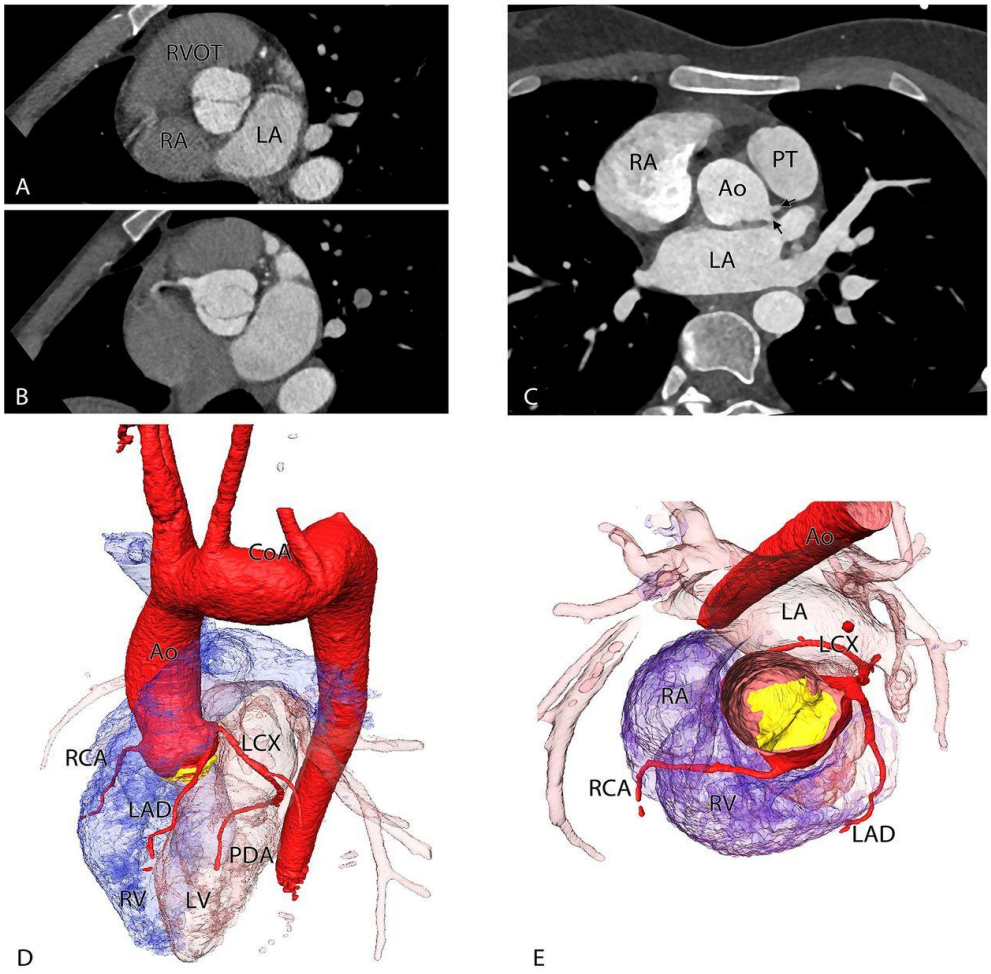

Figure 3. Example of bicuspid aortic valve with fusion of right and left coronary leaflets (RL BAV) without raphe, closed (A) and open (B), with separate ostia (arrows) of the left anterior descending coronary artery (LAD) and left circumflex artery (LCX) (C). (D, E) Three-dimensional reconstruction of a heart with RL BAV without raphe, aortic coarctation (CoA), a left dominant coronary artery system and separate ostia of the LAD and LCX. The aortic valve is indicated in yellow. Ao, aorta; LA, left atrium; LV, left ventricle; PDA, posterior descending artery; PT, pulmonary trunk; RA, right atrium; RCA, right coronary artery; RV, right ventricle; RVOT, right ventricular outflow tract.

Role of gender

Finally, the role of gender was evaluated. Naturally, all patients in the Turner group were female. In the group with isolated BAV, 65 patients (76%) were male, 21 patients (24%) were female. Twenty of 65 (31%) men in this isolated BAV group had a left dominant coronary artery system. Of the 21 women with isolated BAV, 4 (19%) showed left dominance as compared with 25% in the TS-BAV group and 21% in the TS-TAV group. In summary, there was no significant difference in presence of left dominancy between women in the different groups.

Discussion

The key findings of this study were:

- No significant differences in coronary anatomy with regard to coronary dominance or absence of left main stem were found between patients with TS with and without BAV. In addition, no significant differences in prevalence of left dominant systems between patients with BAV with TS versus without TS were observed.
- Patients with RL BAVs without raphe showed a high prevalence of left coronary dominance in the group of TS-BAV as well as in isolated BAV.
- Separate ostia were more often seen in patients with TS and BAV as compared with patients with isolated BAV. No significant differences in the occurrence of separate ostia between patients with TS-BAV and patients with TS-TAV were observed.
- There was no significant difference in occurrence of left coronary dominance between patients with CoA and without CoA and between patients with CoA and TS and those without TS.

Coronary anatomy: dominance

As previously described, there is an association between BAV and the presence of a left dominant coronary artery system [17]. Whether this also applies to BAV in TS was to date unknown. One previous study described a higher prevalence of left dominant coronary artery systems in TS, however this was not specified to aortic valve morphology (BAV vs TAV) [7]. The current study shows that patients with TS and BAV do not show significantly more left dominant coronary artery systems as compared with patients with TS with TAV (25% vs 21%). The higher prevalence of left dominance in TS therefore does not seem to be attributed to the presence of BAV, suggesting that the presence of TS may be an independent factor associated with LCA dominance, regardless of valve morphology. If there was a cumulative effect of TS and BAV, we would have expected the group of TS-BAV to have a much higher prevalence of left dominance, but this was not the case (25% vs 21%).

In general, patients with isolated BAV showed more left dominant coronary artery systems (28%) than reported in the general population. This is in accordance with our previous study, in which we found a higher prevalence of left dominance in RL BAV without raphe in patients with isolated BAV[17], and it is in line with the literature[16, 17].16 17 Identical results were obtained in the current study for both patients with TS-BAV and isolated BAV. The equal percentages of this distribution in both TS and isolated BAV groups suggest that the presence of left dominance is a feature of BAVs without raphe and not affected by the presence of TS. In summary, both TS and RL BAV without raphe seem to be independently associated with left coronary dominance.

Coronary anatomy: separate ostia

Separate ostia or absent left main trunk has been described in 14% of patients with TS compared with less than 1% in the general population, which was not specified to aortic valve morphology [7, 21]. The current study shows comparable results, showing separate left-sided coronary ostia in 13% of patients with TS. No significant differences in absence of main stem with regard to valve morphology (BAV or TAV) were found. Remarkably, in the current study, separate ostia were not observed in patients with isolated BAV, whereas separate ostia were previously observed in patients with isolated BAV in 11%–15% [12, 17]. Within the TS-BAV group, both of the separate coronary ostia occurred in RL BAV without raphe, which corresponds to previous data in isolated BAV [17]. Therefore, we postulate that, as observed in the analysis of coronary dominance, both TS and RL BAV without raphe are independently associated with absent left main stems. The fact that RL BAVs without raphe often showed a left dominant coronary artery system and separate ostia of the LAD and LCX may be explained by molecular mechanisms guiding the ingrowth of coronary arteries [22, 23]. It is tempting to speculate that in patients with BAV, where strict bordering of the cusps is hampered, variations in coronary anatomy occur more often. This might be more outspoken in patients with strictly bicuspid valves, where a raphe is missing and no valvar commissures can be determined.

Coarctation of the aorta

TS is associated with aortic pathology, especially CoA and (tubular) hypoplasia [24, 25]. In contrast to previous results in isolated BAV [17], patients with TS with CoA did not show more left dominant coronary artery systems as compared with patients without CoA. In addition, there was no difference in the presence of left dominance between patients with CoA and TS and those without TS.

Role of gender

The role of gender in distribution and outcome of heart disease has received more attention in recent years. Gender differences play a role in CAD. Cardiovascular risk factors are similar among women and men, but it is only the male sex that comprises a risk factor

for CAD. In young women, the first symptoms of CAD develop years later than in men, related to the benefit of the protective effect of oestrogens [3]. Previous studies have reported a higher incidence of CAD (obstructive and non-obstructive) in patients with left dominant coronary anatomy [26, 27].In addition, patients with RL BAVs without raphe have been reported to be more at risk of developing significant CAD [17]. BAV is almost three times more common in men than women[10], which might be related to the increased risk of men for CAD, although the mechanism of such a relation is to date unresolved [17]. Patients with TS are more at risk of CAD as well, probably due to the lack of oestrogens, but possibly also due to the fact that there's more left dominance in patients with TS. Whether or not this is related to strictly bicuspid (no raphe) is yet to be explored.

Conclusions and clinical relevance

This study shows that there are no differences in coronary artery dominance between patients with TS with and without BAV and between patients with TS-BAV and isolated BAV.

Patients with RL BAVs without raphe show a high prevalence of left coronary dominance in the group of TS-BAV as well as in isolated BAV. The equal distribution in both TS and isolated BAV groups suggests that both TS and RL BAV without raphe are independently associated with left coronary dominance.Patients with TS-BAV show more separate ostia of the LAD and LCX as compared with patients with isolated BAV. In addition, separate ostia were more often observed in patients with TS with RL BAV without raphe, suggesting that both TS and RL BAV without raphe are independently associated with absent left main stems.Patients with TS are more prone to develop CAD at a younger age due to lack of oestrogens. The presence of a left dominant coronary artery system and CoA, exposing to early hypertension, carry an additional risk of premature CAD. In case of the need for diagnostic coronary angiography or surgery, it is important to be aware of the higher incidence of particularly separate left coronary ostia, to avoid complications during hypothermic perfusion.

Study limitations

This study was conducted in a relatively small group of patients, bearing the risk of overestimation of results. Although we found an association of BAV subtypes with some variations in coronary anatomy in this descriptive study, this does not mean that there is a causal relationship. However, as limited data are currently present on coronary anatomy in patients with TS in different BAV morphologies, the current study adds insight into this issue with respect to the general, non-syndromal, population and could raise awareness of potential variations in coronary anatomy in different subgroups of patients with BAV.

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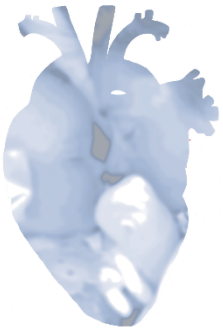
TURNER SYNDROME



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7

Aortic dilatation and outcome in women with Turner syndrome

Heart, May 2019

Abstract

Background Women with Turner syndrome (TS) are at increased risk of aortic dissection, which is related to ascending aortic diameter. However, the relation between aortic diameter and outcome is not well determined. This study evaluates the prevalence of aortic dilatation, the growth rate of the aorta and the risk of aortic complications in adults with TS.

Methods Single centre, retrospective study of all women with TS followed with a strict protocol in an outpatient TS clinic. Aortic diameters were analysed using advanced imaging. The primary outcome was a combined endpoint of aortic-related mortality, aortic dissection and preventive aortic surgery. The secondary endpoint was aortic growth and prevalence of aortic dilatation, defined as an aortic size index >20 mm/m2 at baseline.

Results At least one cardiac MR/CT was available in 268 women with TS, having median age of 28.7 (IQR: 21.3–39.7) years. Aortic dilatation was present in 22%. Linear regression identified independent factors associated with larger aortic diameters: age (coefficient=0.23; p<0.001), hypertension (coefficient=2.7; p<0.001), bicuspid aortic valve (coefficient=3.3; p<0.001), 45XO karyotype (coefficient=1.7; p=0.002), weight (coefficient=0.075; p<0.001) and growth hormone treatment (coefficient=1.4; p=0.044). During follow-up (6.8±3.2 years), five women (2%) reached the primary endpoint (two dissections, three aortic surgery). Women withmore than one scan (n=171; 1015 patient-years follow-up), the median aortic growth was 0.20 (IQR: 0.00–0.44) mm/year. In multivariate analysis, aortic growth was not associated with baseline aortic diameter or other variables.

Conclusions Aortic dilatation is common and known associations were confirmed in large adult TS cohort However, aortic dissection, related mortality and preventive aortic surgery are rare. Growth hormone treatment in childhood was associated with aortic dimensions.

Introduction

Turner syndrome (TS) is a rare disorder, caused by partial or total absence of an X-chromosome. Prominent features are short stature, gonadal dysgenesis and congenital heart defects. Most commonly seen cardiovascular abnormalities are bicuspid aortic valve (BAV), partial anomalous pulmonary venous return, elongation of the transverse aortic arch, aortic coarctation and ascending aortic dilatation[1-3]. Depending on the definition, the prevalence of aortic dilatation ranges from 4% to 42% [4, 5]. In patients with TS, aortic dissection is reported to occur six times more often compared with the general population [1]. Reported associated factors of aortic dissection are the presence of BAV, aortic coarctation, dilatation of the aorta, hypertension and pregnancy. Dilatation of the aorta occurs predominantly at the level of the ascending aorta and is associated with dissection [6, 7]. European Society of Cardiology guidelines advise to correct for body surface area (BSA) in small body size patients[8]. For the ascending aortic diameter, this index is called the aortic size index (ASI). Preventive aortic surgery is advised when the ASI exceeds 27.5 mm/m2, but this cut-off value is mainly derived from extrapolation of thoracic aortic dissection in women with non-TS with mostly normal height and higher age[8]. Other guidelines advise preventive surgery even with lower ASI (>25 mm/m2), mainly based on registries of aortic dissection [9]. The relation between aortic diameters and clinical outcome in patients with TS is not studied in large prospective studies. Increase in aortic diameters over time is theoretically expected to be more rapid in patients with a dilated aorta based on Laplace's law and is also expected to be associated with the same factor that also are associated with aortic dilatation, but whether this is true for patients with TS is also not well investigated[10].

In this cohort study of women with TS, we describe the prevalence of ascending aorta dilatation, growth of the aorta over time and sought to identify factors associated with clinical outcome.

Methods

Population

In March 2003, a dedicated multidisciplinary adult TS outpatient clinic was established at Radboud University Medical Centre and a standard protocol for assessment and follow-up was initiated [11]. The diagnosis of TS was made based on karyotyping of at least 30 blood lymphocytes. All TS karyotypes were included and divided in two main groups 45X0 and mosaicism (non-45X0), in which the mosaicism group is divided in six groups (online supplementary 1). A strict follow-up protocol was followed [8]. As part of their multidisciplinary evaluation, patients were routinely investigated by a cardiologist with ECG, echocardiography and cardiac MRI (CMR) or when contraindicated CT and by an

endocrinologist and gynaecologist. The yield of this standardised health screening in the initial 100 patients of our cohort was published previously [11]. All women with TS visiting this specialised outpatient clinic were eligible for inclusion. For this retrospective study, we included all women with TS who had at least one CMR/CT at adult age and the images had to be available for review. For the study on aortic growth, all patients with at least two CMR/CT were included. BSA was calculated using the Dubois formula [12]. Ascending aortic dilatation was defined as an ASI≥20mm/m2. Z-scores for every patient were calculated based on the formula published by Campens et al [13]. Hypertension and hypercholesterolaemia were defined following guidelines and 'requiring medical therapy'. The Institutional Ethical Board (CMO Arnhem-Nijmegen) approved this study and concluded that no informed consent was needed as the treating doctors performed the study and the institution adopted an opt-out policy on scientific medical file research. All data were handled carefully and confidentially.

Advanced imaging

Baseline and follow-up aortic diameters were measured by a dedicated radiologist using CMR or when contraindicated CT. In all CMR/CT a standard imaging protocol was used. An Avanto 1.5T whole-body MRI system was used (Siemens). Dedicated phased-array cardiac surface coils were placed over the thorax. All images were acquired with breath-hold. The ascending aorta was measured on axial TRUFI images in the axial plane.

For CT acquisition, a 320 slice scanner (Aquilion one, Toshiba) was used. The heart was fully covered within a wide volume scan with ECG gating during the whole heart cycle. The ascending aorta was measured in the axial plane, during diastolic phase. In both modalities, an inner edge to inner edge method was used to measure the ascending aortic diameter at the height of the right pulmonary branch [11]. Both the absolute measurements and measurements corrected for BSA (ASI) were collected.

Endpoints

The primary endpoint was an aortic event, defined as aortic-related mortality (proven or high suspicion of dissection or rupture), aortic dissection or (preventive) aortic surgery. Information on the vital status of all participants was obtained from the municipal base administration of personal data (GBA) of the Netherlands on 1 February 2017.

The secondary endpoint was the increase in ascending aortic diameters which was assessed in the patients with more than one CMR/CT. Patients who reached the primary endpoint before having the second CMR/CT were excluded from this analysis. The annual change of the aortic diameter was calculated based on the aortic diameter measurements of the first and last scan, divided by the time span between these scans. Because of this, negative aortic diameter change could occur [14].

Statistical analysis

Results are expressed as mean±SD or as median±IQR if the distribution was skewed or the Shapiro-Wilk test showed abnormal distribution. A p≤0.05 was defined to be statistically significant. The independent samples t-test was used to compare means (eg, aortic growth/year) between groups. In case of a skewed distribution, the Mann-Whitney test was used. The paired sample t-test was used to compare ascending aortic diameter change in time within cases. Univariate and multivariate linear regression analyses were used to explore associations with aortic diameter and aortic growth, or logistic regression analysis was used to explore associations with aortic dilatation and aortic growth using the same variables. Survival analysis could not be performed due to the limited number of events.

Results

In total, 270 patients with TS were eligible, of whom 2 had to be excluded due to poor-quality aorta images. The remaining 268 patients, median age of 28.7 (IQR: 21.3–39.7) years and mean height of 155.2±7.2 cm, had at least one CMR/CT with adequate imaging and were included in the current study. During follow-up, 171 patients with TS had at least one other CMR/CT (figure 1). For the other patients, additional CMR/CT imaging was not available due to various reasons (eg, care transfer, refusal by patient, lost to follow-up, short period since first scan). No differences were found in baseline characteristics between the patients with versus without more than one scan.

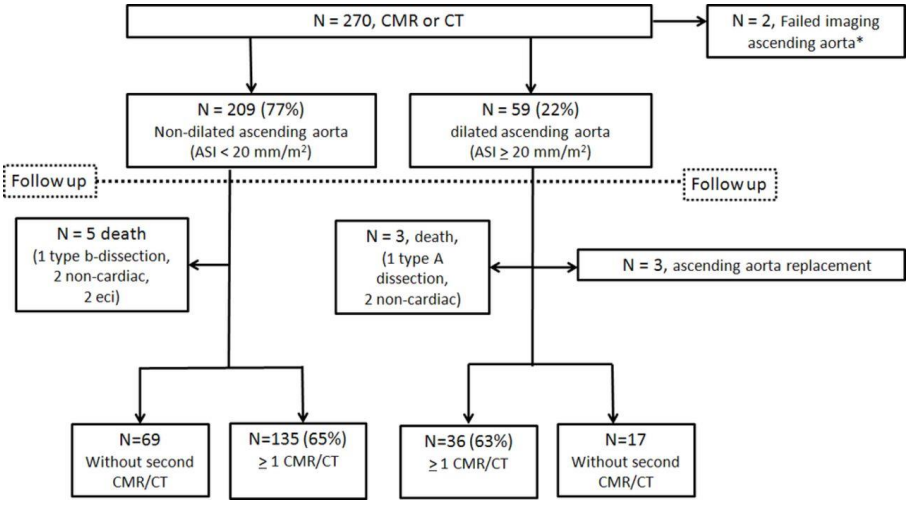

Figure 1. Flow diagram of patient inclusion. *Due to artefacts, the CMRs were not suitable for measuring the diameter of the ascending aorta. ASI, aortic size index; CMR, cardiac MRI.

Baseline

Characteristics of all 268 included patients at baseline are shown in table 1. Dilatation of the ascending aorta (ASI>20 mm/m2) was present in 59 (22%) patients. Mean z-score was 0.91±1.50 and 22.8% had an z-score ≥2. The mean age of the patients with TS and a dilatated ascending aorta was significantly higher compared with patients with TS without dilatation 40.9 (IQR: 29.0–47.3) versus 25.9 (IQR: 20.5–34.8) years, p<0.001. The prevalence of hypertension was significantly higher in the women with dilatation (33.9% vs 12.1%; p<0.001). Figure 2 shows the uncorrected and corrected ascending aortic diameters at baseline for all patients according to age. At the age of 35 years, the upper 95% line crosses the ASI=25 mm/m2 line. In total, 13 patients had an ASI>25 mm/m2, mean age of 44.3±7.7 years versus 30.4±10.8 years in ASI<25 mm/m2. Baseline uncorrected ascending aortic diameter was independently associated with age, hypertension, BAV, 45X0 karyotype, weight and growth hormone treatment (table 2). Although the p-value for aortic coarctation in univariate analysis was <0.10, we excluded it from the model. The reason for this were: the SE was larger than the coefficient, the number of women with aortic coarctation was low and multivariate analysis using backward selection with p<0.1 excluded coarctation out of the model.

Table 1. Characteristic of patients with TS with or without aortic dilatation at baseline

	Total (N=268)	ASI <20 mm/m² (n=209)	ASI >20 mm/m² (n=59)	P-value
Age, years (IQR)	28.7 (21.3–39.7)	25.9 (20.5–34.8)	40.0 (29.0–47.3)	<0.001
Height, cm (SD)	155.1 (±7.2)	156.5 (±6.7)	150.4 (±6.9)	<0.001
Weight, kg (IQR)	59.0 (51.3–67.8)	60.0 (53.0–70.0)	53.0 (48–59)	<0.001
BSA, m^2 (IQR)	1.57 (1.47–1.70)	1.60 (1.51–1.71)	1.47 (1.37–1)	<0.001
BMI, kg/m^2 (IQR)	24.7 (22.0–27.7)	25.1 (22.2–28.0)	23.5 (21.5–26.0)	0.048
45X0 Mosaicism	40.0% 60.0%	36.7% 63.3%	51.9% 48.1%	0.052
BAV	22.0%	15.5%	45.8%	<0.001
CoA	3.4%	2.9%	5.1%	NS
Growth Hormone*	61.0%	66.8%	40.7%	0.001
Active smoking	9.5%	9.3%	10.2%	NS
Hypertension	16.9%	12.1%	33.9%	<0.001
Dyslipidaemia	4.5%	3.4%	8.5%	NS
Diabetes	3.8%	2.4%	8.5%	0.032

Table 1. ASI: Aortic size index BAV: bicuspid aortic valve, CoA: coarctation of the aorta. 45X0 and mosaicism refers to the karyotype; aortic size index (mm/m2) is the ascending aortic diameter divided by BSA.*Patients treated during childhood with growth hormone. ↵BMI, body mass index; BSA, body surface area; NS, non-significant; TS, Turner syndrome.

A history of growth hormone treatment during childhood was reported in 161 (60%) patients. Compared with patients who were treated with growth hormone, the non-treated group was significantly older (mean age 39.3±10.7 vs 25.0±6.8 years; p<0.001). As a consequence of the relative recent introduction of synthetic growth hormone treatment, younger age patients were more likely to have been treated with growth hormone. The mean aortic diameter and ASI unadjusted for age were smaller for patients who were treated compared with the non-treated group (27.2±4.8 vs 29.1±5.2 mm; p=0.004 and 16.9±3.1 vs 18.9±4.1 mm/m2; p<0.001). However, after correcting for variables shown in table 2, previous growth hormone treatment was still associated with a larger ascending aortic diameter.

Table 2. Univariate and multivariate linear regression analysis for the association of absolute ascending aortic diameter at baseline

	Univariate		Multivariate*		
	Coefficient	P values	Coefficient	P values	95% CI for coefficient
Age (years)	0.209	<0.001	0.230	<0.0001	0.17 to 0.29
Hypertension	4.024	<0.001	2.677	<0.0001	1.24 to 4.12
Bicuspid aortic valve	3.254	<0.001	3.307	<0.0001	2.07 to 4.55
Karyotype 45X0	1.823	0.005	1.702	0.002	0.64 to 2.77
Weight (kg)	0.056	0.014	0.075	<0.0001	0.04 to 0.11
Growth hormone treatment†	−1.879	0.003	1.404	0.044	0.04 to 2.77
Diabetes‡	3.96	0.015			
Aortic coarctation	3.1	0.076			
Height (cm) §	−0.07	0.115			
Active smoking	0.36	0.74			
Dyslipidaemia	1.77	0.24			
Body surface area	2.76	0.119			

Table 2. *R^2=39.1%, indicating that only 39% of the aortic diameter differences could be explained by this model; coefficient=regression coefficient also called estimate; analysis of the residuals showed a normal distribution. †Multicollinearity between age and history of growth hormone therapy (correlation −0.637). ‡In the best fit model, diabetes was excluded as it was not significant in multivariate analysis. §Small differences in height in this cohort, mean 155.1 (±7.2) cm.

Follow-up

Survival status was available for all patients. In total, eight patients died during a mean follow-up of 6.8±3.2 years. These eight cases are described in table 3. In two patients, the cause of death was assumed to be related to aortic dissection (case 129; case 4). Case 129 was a 44-year-old patient with TS with an ascending aortic diameter of 65 mm (ASI=39.2 mm/m2), who delayed her operation to get married and died suddenly. No

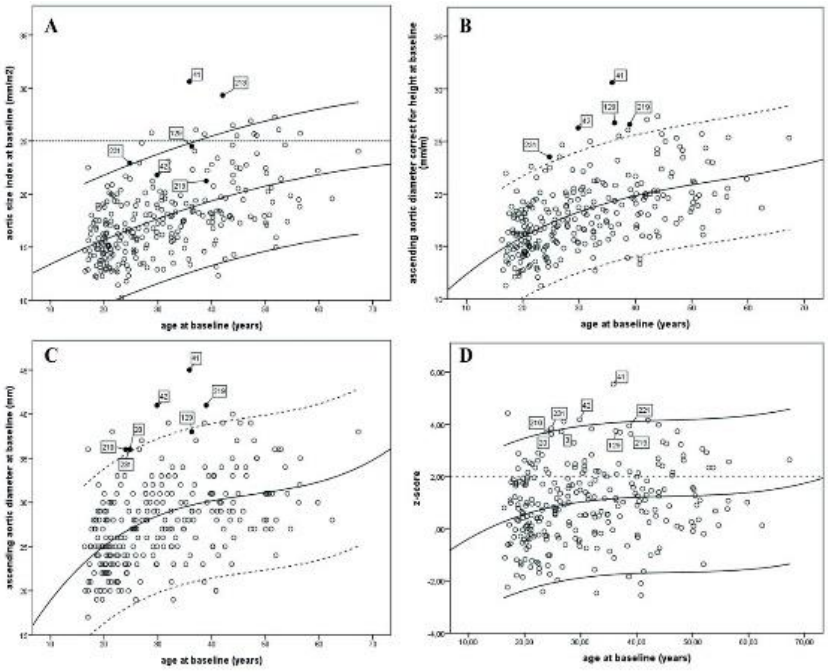

Figure 2.Ascending aortic diameter at baseline corrected and uncorrected versus age. (A) Aortic size index versus age; (B) ascending aorta diameter corrected for height versus age; (C) absolute ascending aortic diameter versus age; (D) z-score at baseline versus age. Cases 41, 42 and 231 underwent aortic preventive surgery. Case 231 had aortic valve dysfunction as primary indication. Case 129 is a patient who had presumably a type A dissection. Case 219 had a body mass index of 40.5 kg/m2 and an ascending aorta of 41 mm. Case 213 is a patient who has an ascending aortic diameter of 39 mm and a body surface area of 1.33 kg/m2. The centre line represents the mean of y-axis variable and the upper and lower line represent the 95% limit of the mean of y-axis variable.

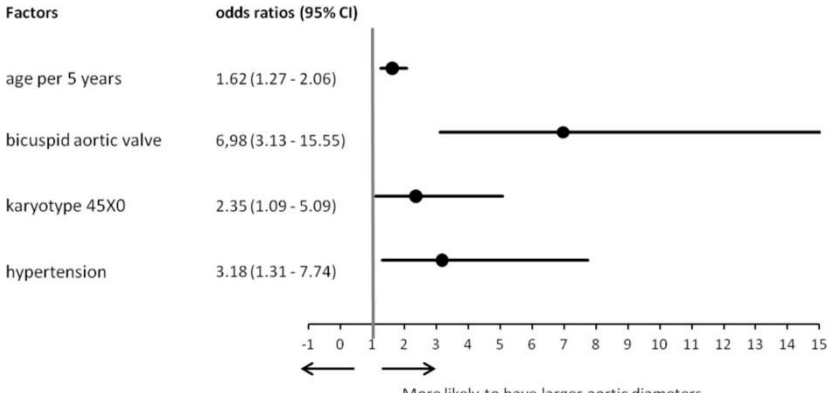

Figure 3. Forest plot of adjusted odds ratios for aortic dilatation at baseline in women with Turner syndrome. R2=38.1%. Aortic dilatation was defined as an aortic diameter >20 mm/m2 body surface area.

autopsy was performed. Case 4 was also 44 years old and died from acute dissection of the descending aorta. This patient had normal ascending (30 mm; ASI=18.4 mm/m2) and descending (25 mm) aortic diameters on CMR 3.5 years prior to this event. Preventive ascending aortic surgery was performed in three patients. In two patients, the indication for surgery was ascending aortic dilatation (45 mm; 48 mm or ASI=28 mm/m2; ASI=25.5 mm/m2, respectively) and in one patient the indication was severe aortic valve regurgitation with concomitant moderate ascending aortic dilatation (36 mm; ASI=22.9 mm/m2). The primary endpoint was therefore reached in five patients. Because of the limited number of events, no analysis on predictors could be performed.

Table 3. Causes of death in women with TS

Case no	Probable cause	Age of death years	Corrected aortic diameter mm/m²	BAV	GH	Karyotype	CoA	HT
129	Type A AoD*	44	39.2	Yes	No	45X0	Yes	Yes
2	Cancer	53	27.9	No	No	Unknown	No	Yes
3	Cachexia and dementia	58	27.0	no	No	Non-45X0	No	Yes
4	Type B AoD	44	18.4	No	No	45X0	No	No
5	Intestinal ischaemia	67	19.4	No	No	Non-45X0	No	Yes
6	Cancer	50	19.7	No	No	Non-45X0	No	No
7	Unknown†	33	19.5	No	Yes	Non-45X0	No	No
8	Unknown	38	20.1	No	Yes	45X0	No	No

Table 3. AoD: aortic Dissection, BAV: bicuspid aortic valve, GH: Growth Hormone, CoA: coarctation of the aorta, HT: hypertension*Case 129 is also shown in figure 2A. This woman with TS was on waiting-list for preventive aortic surgery. †History myocardial infarction on the age of 30 years; the corrected aortic diameter also called aortic size index (mm/m2) is the ascending

Aortic growth

In total, 171 (64%) patients had more than one CMR/CT during follow-up (figure 1). There was a significant increase in ascending aortic diameter per patient (1.2±2.3 mm; p<0.001) in a mean follow-up time of 5.9 (range: 1.1–11.3) years and a total of 1015 patient-years. Ascending aortic diameter increase per year was 0.20 (IQR: 0.00–0.44) mm/year.

The median ascending aortic diameter change in the whole cohort was 0.43 (IQR: 0.00–0.43) mm/year. The mean time between the first and last CMR/CT was not significant different between the women with TS who had a dilated and non-dilated ascending aorta (6.2±2.4 vs 5.9±2.1; p=0.51). The median ascending aortic diameter change in the dilated

group was 0.00 (IQR: −0.20 to 0.31) mm/year and 0.24 (IQR: 0.00–0.44) mm/year in the non-dilated group (p=0.021). No significant difference was found in ascending aortic diameter change between patients with (n=38) or without BAV (n=133) 0.16 (IQR: −0.02 to 0.37) mm/year versus 0.22 (IQR: 0.00–0.44) mm/year, p=0.75). There was a difference in patients with (n=29) or without (n=142) hypertension 0.00 (IQR:−0.22 to 0.30) mm/year versus 0.23 (IQR: 0.00–0.44) mm/year, p=0.04). Eight women showed an increase in ascending aorta diameter of ≥1 mm/year. Of the nine women who had an ASI>25 mm/m2 at baseline, one underwent preventive aortic surgery and one experienced an aortic complication during follow-up.

During the study period, four women became pregnant, and median change in aortic diameter was 0.05 (IQR: −0.17 to 0.97) mm/year versus 0.20 (IQR: 0.0– 0.43) mm/year for the other women (p=0.84).

Figure 4 shows the change in ascending aortic diameter for all 171 patients, related to baseline ascending aortic diameter (both uncorrected and corrected for BSA). The three operated cases had a growth varying between 0.33 and 1.22 mm/year and the woman with presumed type A dissection had an ascending aortic growth of 3.25 mm/year (not presented in figure 4). Univariate linear regression identified two associations with aortic growth, hypertension, and aortic dilatation at baseline, which were not significant in multivariate analysis. Based on the upper quartile of ascending aortic change (0.43 mm/year), the TS cohort was divided in two groups. Logistic regression did not identify significant associations for aortic growth ≥0.43 mm/year. Figure 5 shows the unadjusted HRs in a forest plot of all tested variables.

Discussion

This study describes one of the largest TS cohorts to date, in which aortic dimensions are measured using advanced imaging during a relative long follow-up time. Aortic dilatation was present in one-fifth of women with TS at a mean age of 29 years. Classical factors associated with larger aortic diameters were age, hypertension, BAV, 45X0 karyotype, weight, and growth hormone treatment. During almost 7 years of follow-up, only 2% of the women suffered an aortic event and no unexpected ascending aortic complications occurred. The aortic growth rate was low (0.20 mm/year), but higher than reported in the normal population (0.12 mm/year)[13] [14]. Classical factors associated with larger aortic diameters, such as a BAV, were not associated with faster growth of the ascending aortic diameter. Also, an initial larger aortic diameter was not associated with faster growth

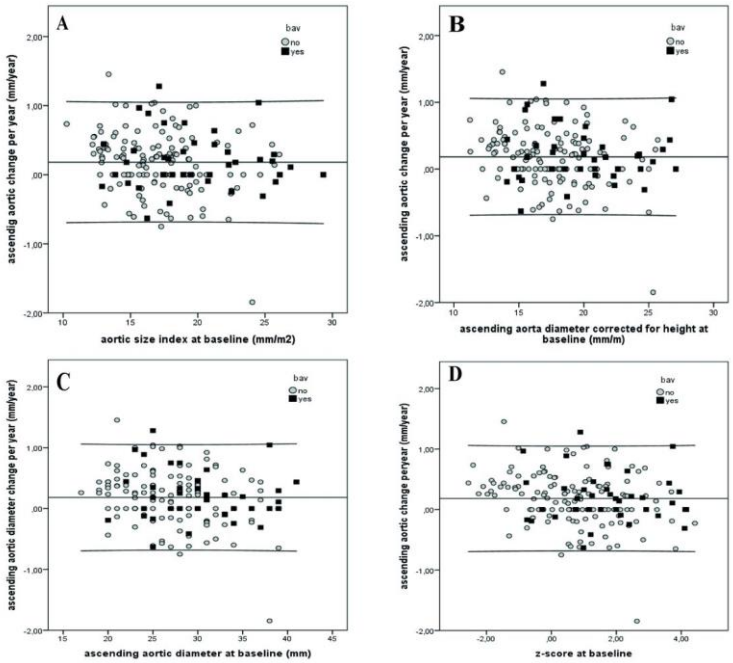

Figure 4. Corrected and uncorrected ascending aortic diameter change versus baseline corrected and uncorrected ascending aortic diameter. (A) Ascending aortic change versus aortic size index at baseline; (B) ascending aortic change versus ascending aorta diameter corrected for height at baseline; (C) ascending aortic change versus absolute aortic diameter at baseline; (D) ascending aortic change versus z-score at baseline. Case 129 (diameter change of 3.25 mm/m2) is not presented in these figures.

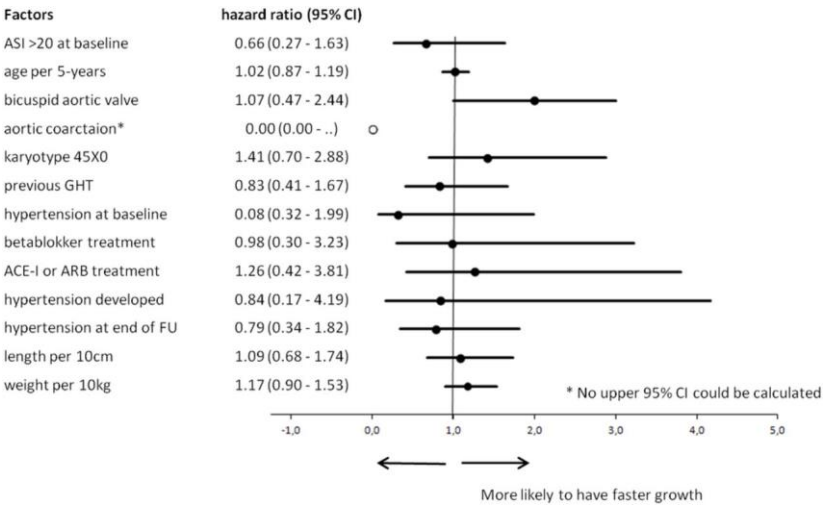

Figure 5. Forest plot of unadjusted HRs for aortic growth. Aortic growth was defined as aortic diameter increase >0.42 mm/year. ACE-I, ACE inhibitors; ARB, angiotensin II receptor blockers; ASI, aortic size index; FU, follow-up; previous GHT, previous growth hormone treatment during childhood.

Ascending aortic dilatation

As shown by others, current study shows that also in women with TS age has a clear impact on aortic diameter [15]. This association with age is also observed in the general population [13, 16]. This relation is not linear but rather more curved and levelling-off at older age. In the current TS guidelines, no correction is made for age, which seems indicated. At a median age of 29 years, 22% of the women with TS have a dilated aorta (ASI>20 mm/m2). Maybe this high prevalence is partly caused by the ASI method. One of the pitfalls of the ASI method is that the ASI becomes lower in obese patients (case 219) and relative larger in slim patients (case 213). Due to this 'overcorrection' of the aortic diameter, some women with TS will be labelled as having a normal aortic diameter. Correcting the aortic diameter using height instead of BSA could partly solve this problem. This is especially important when realising that ASI is the main indicator for preventive surgery. Recent publications have shown that z-scores used for people with a normal height are also fit for women with TS [13, 15].The z-score was ≥2 in 22.8% of the women in this cohort. This is comparable with the ASI method. Indeed, both the z-score method and the ASI method correct for weight and height. It seems more appropriate to use ASI or z-score in women with TS with a normal BMI and be cautious in women with a very low or very high BMI. The cross-sectional analysis confirmed the known factors associated with aortic dilatation [4]. In addition to these known associations, our data suggest that growth hormone treatment during childhood is associated with larger aortic diameter even after correcting for age and height. Due to multicollinearity with age and the chance of having being treated with growth hormone, this effect should be interpreted with caution. Dedicated research is warranted to investigate the long-term effect of growth hormone treatment on aortic diameters, aortic wall composition and vulnerability. Olivieri et al found that a partial cusp fusion was associated with larger aortic diameters [17]. In the current study, we did not use this partial cusp fusion.

Aortic growth

Even though older patients with TS generally have a larger ascending aorta, we do not know if these larger dimensions also lead to higher risks of aortic complications. It seems logical that dilatation occurring at younger age is associated with more aggressive aortic pathology. In the literature, the mean age at which patients with TS present with aortic dissection is 32 years[4] [18-20]. The age of both patients with dissection in our series was 44 years, so also still relatively young. Others showed that especially younger adult women with TS who had a dilatated aorta are vulnerable and that after a certain age the risk of aortic dissection decreases [7].

Limited publication on aortic growth in women with TS are available. A prospective study would be the best study design. Our study is retrospective, but because of the standardised follow-up, the use of CMR/CT scans and the inclusion of all patients referred to our hospital

without selection bias, we believe this to be the second-best option to study aortic growth. The observed increase in aortic diameters in the current study is low, but higher than reported in the general population[13]. Univariate analysis suggested that hypertension and baseline aortic dilatation were associated with aortic growth, but in multivariate analysis they were no longer significant. Possibly that treatment of hypertension protected these women against accelerated aortic growth. The low increase in aortic diameter and the relative short follow-up time could be an explanation for not finding any independent associations for aortic diameter change. Mortensen et al developed an aortic diameter prediction model using complex mathematical processing based on the follow-up of 78 women with TS over a period of almost 5 years. These cohesive models identified predictors of accelerated aortic growth (aortic coarctation, BAV, age, diastolic blood pressure, BSA and antihypertensive treatment)[7]. In our study, we could not confirm these findings. Heterogeneity of karyotypes present in patients with TS has been shown. In most cases, blood lymphocytes are used for the diagnosis and sometimes additional buccal cells are used. Different cell lines can show different karyotypes, making it possible that the karyotype of the aortic wall differ from the cell line used for diagnosis[21]. The aortic wall properties may therefore be not well presented by the used karyotypes.

Outcome

In 7years of follow-up, the incidence of aortic complications was 2%. This low incidence of 0.3%/year immediately illustrates the difficulty of identifying risk factors of aortic complications in women with TS. On the other hand, it is important information that the absolute risk is very low, although still higher than in women with non-TS [1]. Our data certainly do not support a more aggressive approach towards surgery. The indication for surgery is still matter of debate. Pape et al showed, in a large cohort of patients, that in 50% of the patients with a dissection, the aortic diameter was below the advised surgical aortic diameter threshold.[22]. This clearly shows that, aortic diameter as sole parameter on which preventive aortic surgery is advised in current guidelines is not sufficient enough to prevent future aortic dissections.[8, 9, 23] [24]. Future research should focus on other parameters to better predict future aortic dissection risk.

Limitations

Although we have included all patients, selection bias due to referral cannot be excluded. However, if selection bias has taken place, the more severe cases would have been sent to our tertiary clinic and therefore the relatively positive and reassuring results would only have been more positive. Indeed, information on survival and events was 100% complete. The used z-score is based on echocardiographic measurements and could differ from a z-score based on CMR/CT measurements.

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Supplement 1

Mosaicism group division

1) mosaicism 45,X/46,XX

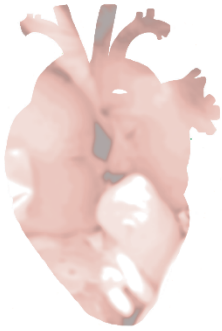
2) isochromosome (45,X/46,X,i(Xq), 46,X,i(Xq) or 45,X/46,X,i(Xq)/47,X,i(Xq))

3) deletion (45,X/46,X,del(X) or 46,X,del(X))

4) polyploidy (45,X/46,XX/47,XXX or 45,X/46,XXX)

5) ring X material (45,X/46,X,r(X))

6) Y-material (45,X/46,XY, 45,X/46,XX/46,XY or 45,X/48,XXYY)



II

BICUSPID AORTIC VALVE AND AORTIC COARCTATION

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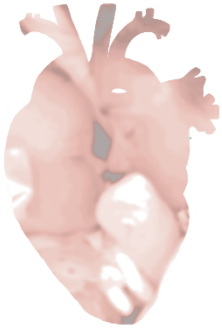

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8

Aortic Coarctation

Abstract

Aortic coarctation is a narrowing of the aorta, usually in juxta-ductal position which warrants life-long clinical follow-up. In this chapter the etiology, anatomy, natural history, diagnosis and treatment of this congenital heart disease will be comprehensively discussed. Additionally a non-exhaustive overview of genetic syndromes and associations is provided.

Introduction

Aortic coarctation, a congenital stenosis usually located in juxta-ductal position [1-3], has been recognized since its first description in 1760 by Morgagni during his autopsy of a monk [4]. It was more formally recognized as a clinical entity after its description in 1928 [5], and it has been surgically corrected since 1945 [6]. Nowadays it is generally accepted to be part of a general aortopathy, linked with other left-sided heart defects such as bicuspid aortic valve (BAV) [7]. The coarctation can vary in severity from quite discrete to a severe long hypoplastic segment. The incidence of CoA is approximately 4 per 10,000 live births and constitutes 5-8% of all congenital heart disease (CHD) [8]. Nowadays, aortic coarctation is preferably repaired surgically at an early age, but catheter intervention has become a valid alternative, especially in outgrown children and adults. Lifelong surveillance is warranted, also after successful repair, since patients remain at risk for hypertension, re-coarctation and aneurysm formation [9-11]. When left untreated, most patients die before the age of 50 mainly due to coronary artery disease, stroke or intracranial hemorrhage. And even in patients with satisfactory repair major complications still occur. In this chapter we discuss the etiology, pathophysiology and the clinical aspects of aortic coarctation.

Pathogenesis, epidemiology and Anatomy

Anatomy

Aortic coarctation is defined as a narrowing of the aortic isthmus, often juxta ductal in position. Three main types can be distinguished depending on the anatomical position of the infolding of the aortic wall relative to the ductus arteriosus (DA); pre-, post or at the site of the ductus (figure 1) In 90% of cases the infolding is directly opposite to the DA. These variants present at different ages due to their difference in pathophysiology. The post – ductal, also called the adult type, variant will have to develop collaterals pre-natally, and will therefore often present at adult age. Whereas the pre-ductal or infant-type is a cyanotic and duct dependent-lesion because no collaterals develop. Therefore, after birth

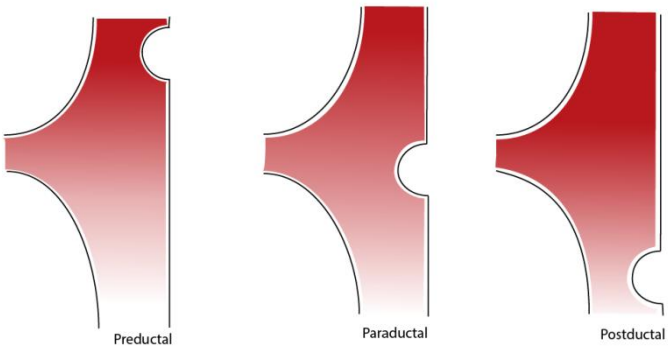

Figure 1: schematic depiction of the three possible locations of the infolding relative to the patent ductus arteriosus (PDA). With blood flowing from top to bottom and the PDA entering from the left.

the closure of the DA will result in hypoperfusion of the lower extremities. However, there is no evidence that these subtypes differ from each other in etiology. Also, coarctation has been described in anecdotal cases to present in the abdominal aorta, which is however more likely to be inflammatory, or auto-immune in origin. Aortic coarctation can even be traumatic when aortic dissection compromises the true lumen of the aorta.

Epidemiology

Aortic coarctation is a relatively frequent congenital heart defect (CHD) and is found in approximately 3-4 per 10.000 live births and constitutes 5% of all CHD [8]. It occurs more often in males than in females in a ratio between 1.27 to 1.74 to 1 [12, 13]. In most patients it is diagnosed shortly after birth, depending on the subtype and clinical symptoms.

Etiology

There are three possible theories explaining the development of coarctation. There is the ductal tissue theory, which suggests that ductal muscular tissue extends into the wall of the thoracic aorta, causing the aorta to constrict postnatally simultaneous with the ductus arteriosus. Several studies have confirmed the presence of ductal tissue in the aortic wall [14, 15].

Another theory is the developmental theory, which suggests coarctation formation starts with a fault in early fetal development. A part of the fetal circulation involutes to form the separate dorsal aorta and right subclavian artery. A small segment of the fetal dorsal aorta will erroneously involute and will subsequently move cranially with the left subclavian artery [16]. This would then form the coarctation.

The third theory is based on hemodynamical changes. During fetal development the aortic isthmus is a naturally occurring narrow segment because it doesn't have to conduct a large flow of blood. This segment will then later be widened to facilitate the increased blood flow. If the increase in blood flow remains absent this narrow area will persist and a coarctation will be formed. This could also partly explain the association with BAV, as a diminished forward flow and increased post ductal flow can predispose to development of CoA as well.

The etiology of CoA remains enigmatic, but it is generally assumed that coarctation is in fact part of a general aortapathy, linked with bicuspid aortic valve, aortic dissection and even intracranial aneurysms [7]. The underlying cause of these histological abnormalities remains largely undiscovered although cystic media necrosis has been reported. More research is clearly needed to discern cause and effect.

Clinical picture

Pathophysiology

The main pathophysiological mechanism by which aortic coarctation causes morbidity and mortality is the afterload increase of the left ventricle (LV). This occurs when the arterial duct closes post-natally and starts a causal chain in which increased left ventricular pressures lead to compensatory hypertrophy and eventually dysfunction. When the coarctation is severe enough this can be an acute process, leading to hypoperfusion distal to the coarctation, presenting in neonates with signs of shock. But also to a 'backward failure'; where the rapid increase in LV systolic afterload, increased wall stress and compensatory left ventricular hypertrophy may cause increased pulmonary venous pressures with pulmonary congestion, followed by elevated pulmonary arterial pressures, right ventricular pressure overload and subsequently heart failure. The foramen ovale might be opened by the sudden increase in pressure causing left to right shunting of blood.

In less pronounced cases this process will be less rapid and collaterals can develop, bypassing the coarctated segment and delaying the onset of clinical signs

In addition to ductal tissue in the aortic wall other histological wall changes are present in CoA patients. Wall stiffness is increased and distensibility is decreased [17]. There is more collagen but less smooth muscle tissue in the prestenotic aortic wall when compared to post stenotic aortic wall. And cystic medial necrosis, the depletion or disarray of elastic tissue, is also seen.

The effects of coarctation are not yet fully explained, as patients with a relieved coarctation often still suffer from hypertension, requiring pharmacological treatment. No clear association could be established between the remaining gradient over the CoA and the occurrence of hypertension. Therefore the involvement of the renin-angiotensin-aldosterone-system is supposed, although also other mechanisms may be involved.

Complications

The natural history has been described in coarctation patients before correction became imperative. These patients often suffered from left heart failure, intracranial hemorrhage, infective endocarditis, aortic dissection and rupture and coronary and cerebral heart disease [2, 10]. Nowadays after intervention the most common complications are hypertension, recurrent coarctation, aortic rupture or aneurysm, early coronary artery disease and cardiomyopathy. Risk for complications increases with age, and BAV is an independent additional risk factor for complications as is age [18]. BAV itself is associated with aortic weakness, higher risk ok aortic dissection and rupture, which possibly explains the increased risk when present in addition to CoA.

Diagnosis

The clinical presentation of CoA varies greatly with age. When CoA becomes evident shortly after birth it presents as a severe cyanotic heart defect, with poor feeding, tachypnea, lethargy, symptoms of congestive heart failure or shock. The onset of symptoms will coincide with closure of the ductus arteriosus. When CoA presents later during childhood or even in adulthood, the clinical symptoms will be due mainly to high blood pressure in the upper extremities and may include: nosebleeds, intracranial hemorrhage, dizziness, tinnitus, shortness of breath. Also symptoms from low blood pressure in the lower extremities may become evident including abdominal angina, claudication, leg cramps, exertional leg fatigue and cold feet [19]. A blood pressure gradient can often be seen as a high upper body systolic hypertension, in combination with a relative lower body hypotension. However, when large collaterals exist, this may be more difficult to determine.

There are different diagnostic techniques used to objectify the presence and severity of CoA.

Inspection and patient history might reveal some of the symptoms mentioned above. A telltale sign would be differential cyanosis where the upper extremities are normally perfused and the lower extremities are hypo perfused.

On palpitation a weak or absent femoral pulse may be noted, which may have a prognostic value, especially in combination with a prominent brachial pulse [20]. Both a radio femoral pulse delay and palpable collaterals on palpation are both pathognomonic for CoA. Of note is that an origin of the right subclavian artery distal to the coarctation might mask this difference, as it would also be decreased and therefore the carotid pulse should be palpated as well. In addition ventricular dysfunction may decrease pulses both in the upper and lower extremities which may reduce the gradient.

On auscultation a supra sternal thrill, vascular murmur (often systolic) on the back, or a continuous vascular murmur can be heard.

An electrocardiogram may reveal signs of left ventricular hypertrophy with or without secondary ST-segment abnormalities. On chest X-ray rib notching as a result of dilated intercostal arteries, a dilated ascending aorta, kinking or double contouring in the ascending aorta (figure 3'sign) and a dilated left subclavian artery can be found. Also cardiomegaly in the infant can be a sign of a coarctation.

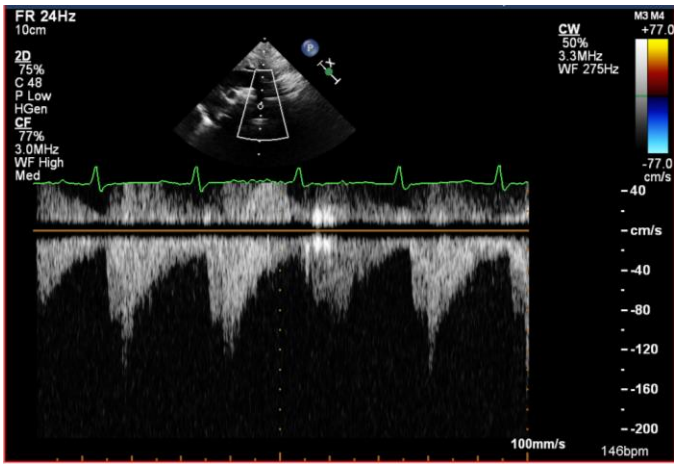

Figure 2. serrated diastolic runoff pattern in the aorta

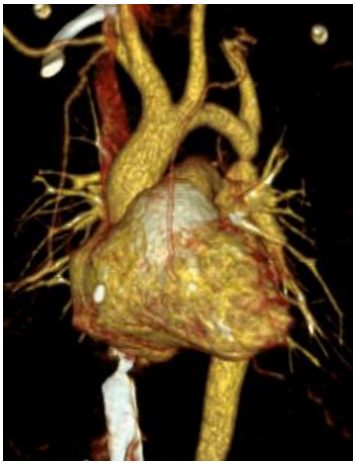

Figure 3. 3D reconstruction (CT) of aortic coarctation in a 6-month old child. Very prominent A. Anonyma and late branching a. subclavia sinistra.

Echocardiography is of great value in estimating site, structure and severity of the CoA. Especially in newborns this technique gives excellent opportunities as the entire aortic arch, isthmus, arterial duct and descending aorta are imaged from the suprasternal notch and from the right and left infraclavicular windows. It can also provide information on the function and severity of left ventricular hypertrophy as well as associated cardiac abnormalities and vessel diameters. In adolescents and adults echocardiography of the isthmus and descending aorta may become difficult as the distance from the transducer increases and the airways may form a more prominent barrier. High systolic velocities are generally found, but a diastolic run-off phenomenon in the descending or abdominal aorta is presumably the most reliable sign of significant coarctation. Doppler flow tracing can show a "serrated" pattern with a rapid acceleration and a high velocity systolic peak, followed by a gradual deceleration throughout diastole (figure 2).

However CMR and CCT are the preferred non-invasive imaging techniques because these allow for the entire aorta to be assessed. It allows for the precise location and collateral anatomy to be imaged. Also cardiac catheterization and manometry or angiography, are important diagnostic modalities. And 3D reconstructions can provides insightful visual aid to the surgeon when planning reconstruction (figure 3).

Treatment

In case of severe coarctation there is clear evidence that treatment of CoA, will reduce left ventricular afterload and will improve the long-term outcome of the patient. There are

however different treatment options with pro's and con's for all techniques and there is no clear superior technique.

Indication for intervention

The decision to intervene is preferably taken in a multidisciplinary setting where careful evaluation on the level of the individual patient is possible. According to the most recent guidelines a pressure gradient between the upper and lower body extremities of >20 mmHg in combination with an upper body hypertension (>140/90mmHg in adults) is a class I, level C indication for intervention [19]. Also, an abnormal blood pressure response during exercise or significant left ventricular hypertrophy are class I indications for intervention.

In other cases the indication for intervention is less clearly defined. When there is hypertension in combination with a relative coarctation (>50% narrowing) compared to the aortic diameter at the level of the diagram as measured on CT, MR or invasive angiography an intervention should be considered for intervention (Class IIa, level C). And finally, in case of an anatomical narrowing (>50%) in the absence of hypertension or a significant pressure gradient an intervention may be considered (Class IIb, level C). This will in practice however not often be the sole reason for intervention. After intervention endocarditis prophylaxis is advised for 6 months.

Choice of intervention

There are two main therapies for the relief of CoA: surgical and interventional. When considering surgery there are several operative techniques to choose from; (extended) end-to-end anastomosis, patch aortoplasty, subclavianflap aortoplasty and resection with interposition graft. All techniques have different advantages and disadvantages. With patch angioplasty for example there is a higher incidence of aneurysm formation, while in subclavian flap aortoplasty a higher incidence of recoarctation has been found. The incidence of dissection is approximately equal amongst all modalities. [21] The (extended) end-to-end anastomosis is the most widely used technique and generally regarded as the safest and most effective method. However, this technique is not feasible in every situation.

The other option for gradient relief: catheter intervention, is used more often in full-grown children and adults. A balloon is used to disrupt the intimal and medial layers of the narrowed segment. Generally a covered stent is deployed to prevent recoarctation and aneurysm formation.

Catheter intervention is a safe and effective alternative to surgery, with good gradient relief. Stenting has a lower acute complication rate when compared to surgery or balloon angioplasty alone [22], but more often needs elective re-intervention than surgery. There is however little evidence regarding the long-term outcome of the effectiveness of the blood

pressure reduction and late complications after stenting. No randomized trials have compared stenting to surgery [23], and it is therefore hard to objectively compare the two modalities. And the choice is best made on the basis of individual patient characteristics.

Conservative treatment

The acute medical treatment of CoA in the neonate is focused on maintaining patency of the ductus arteriosus. This is mainly done by administering a prostaglandin E1 inhibitor and diuretics can be given to alleviate symptoms of heart failure. In the adult patient treatment is mainly focused on blood pressure control. This is normally achieved using: beta-blockers, ACE inhibitors and angiotensin-receptor blockers [24]. The use of ACE-inhibitors has however been associated with renal failure, especially when renal perfusion cannot be sustained [25].

In case of a less severe coarctation or increased intervention risk the choice between intervention and conservative treatment is especially important. For example in patients with Turner syndrome more complications are seen after intervention than in the normal population [26], and the balance may shift towards a more conservative approach.

Long term outcome

Patients with CoA historically had a reduced long-term survival, mainly influenced by early interventional and the late hypertensive complications. Until the 1980s patients still only had an average life expectancy of 38 years [10], as patients often died before the age of 50. Nowadays patients, who have been operated using the most recent techniques, have a good medium- to long-term survival with actuarial survival of 98% at 40, 98% at 50 and 89% at 60 years of age respectively [27]. But still atherosclerotic cardiovascular disease and cerebrovascular events contribute significantly to late morbidity and mortality. An important risk factor is late repair which associates with hypertension, but even patients with early repair have a 30% 10-year incidence of hypertension [28]. Also re-intervention and descending aortic aneurysms occur in 34% and 18% respectively and are lowest in patients treated using end-to-end repair [27]. Vigilant blood pressure control is therefore indicated even in corrected patients.

Pregnancy

Cardiac output increases by almost 50% during the second trimester of pregnancy, and rises even further during labor. There are cases of aortic dissection during pregnancy in woman with CoA [29, 30]. However, in general pregnancy is well tolerated in women with repaired CoA. However, there seems to be an excess of miscarriages and hypertensive disorders. In the normal population these hypertensive disorders of pregnancy occur in approximately 8% of all pregnancies, whereas in CoA patients hypertension and pre-eclampsia probabilities are estimated to be 0.183 (SE 0.285) and 0.061 (SE 0.211)

respectively [31]. Woman with CoA are more likely to deliver by Caesarean section and have longer hospital stays. They had more cardiovascular accidents as a composite endpoint , there is however no evidence of increased maternal mortality or miscarriage [32].

Quality of life

A topic receiving little attention in the medical field is the health perception of patients with congenital heart disease (CHD). No specific research on the psychological function of CoA patients has been done, but there are studies into other less severe CHD such as uncomplicated septal defects which are in part also applicable to CoA patients. These studies show that although patients scored significantly better on physical or emotional problems, bodily pain, social functioning compared to normative data [33, 34], patients do show clearly reduced sexual functioning. This occurs especially around the age of 20, when patients actively engage in relationships and feel hampered for example by their scar tissue [35]. Sexuality is often ignored by physicians despite a clear demand on information by patients. Patients often grow-up in a very protective environment where “risky behavior” such as sport participation is discouraged. Whilst even for complex CHD sport can have a positive influence on exercise capacity and subjective physical function without an increased risk of sudden death or cardiac arrhythmias. Unfortunately many of these topics such as contraceptives, sexuality and pregnancy and sport participation are often insufficiently addressed by medical specialist and caregivers.

Associations

In this paragraph we will discuss a number of syndromes and less well-known congenital cardiovascular defects that are seen in combination with CoA.

There is no known causal genetic defect for CoA, but it often occurs together with several other left-sided defects such as BAV. It is seldom associated with right-sided defects. There is a myriad of genetic syndromes which are known to have a relatively frequent occurrence of CoA and genetic abnormalities occur in 6,2% of patients with a CoA. They have however different genetic origins and therefore a single genetic cause for CoA is improbable. Almost all syndromes described below have a frequent occurrence of several congenital heart defects and therefore it seems plausible that there is a common developmental pathway. A patent arterial ductus is found in almost half (43%) of CoA patients and also septal defects are very common (39% ventricular, 20% atrial septal defects and atrioventricularseptal defects in 4,4%). We will discuss the aortic valve separately but also the mitral, tricuspid and pulmonary valves are found to be abnormal in respectively 4,9%, 2.4% and 1% of CoA-patients. In this paragraph we will discuss a number of the syndromes and less well-known congenital cardiovascular defects that are seen in combination with CoA.

Bicuspid aortic valve

The aortic valve is normally made up of 3 cusps, however in 1-2% of the general population abnormal cusp formation during valvulogenesis leads adjacent cusps to fail to segregate and form one single cusp. BAV can cause significant morbidity as the valve is prone to leakage or stenosis and is often accompanied by aortic dilatation and dissection. Histo-pathological changes of the aortic media such as loss of smooth muscle and medial layer elastic fibers can be seen in the ascending aorta of BAV patients and it has been argued that BAV and CoA are part of the same aortopathy. BAV is, as CoA, more often seen in males than in females (2:1, male:female). Of the patients who have a CoA between 50% and 75% also have BAV [36]. The prevalence of CoA in BAV patients is less well studied but is approximately 7% [37]. Aortic dilatation is more severe in patients with both BAV and CoA than in patients with an isolated CoA [38]. The dilatation varies from patient to patient, and clear associations with age and hypertension could not be shown. A current parameter in BAV research is the cusp anatomy; different valve types are discerned [39], based on their morphological cusp phenotype. Of which the type with fusion of the left and right coronary cusp is associated with CoA. [7].

Hypoplastic Left-Heart Syndrome

The hypoplastic left heart syndrome (HLHS) occurs in 0.016% to 0.036% of live births and occurs more often in males [40]. It is the clinical presentation in 11% of CoA patients. It entails severe left-sided outflow obstruction due to an abnormal development of the left-sided cardiac structures; a predominant underdevelopment of the left ventricle, aorta and sometimes also mitral atresia or stenosis. The degree of left ventricular outflow obstruction can vary from patient to patient [40], and the right heart is often enlarged and hypertrophic. Coarctation of the aorta in juxta position is commonly present [41-43]. It is a duct-dependent lesion and therefore needs a series of univentricular surgical palliations or a heart transplantation. The coarctation of patients with HLHS is histologically similar to isolated coarctation as ductal tissue has been shown. [44]

Taussig-Bing anomaly

In 1949 Helen Taussig and Richard Bing described the first case of what is now known as the Taussig-Bing anomaly (T-Ba); an uncommon form of a double outlet right ventricle (DORV) in which both the aorta and pulmonary artery arise from the right ventricle [45]. The pulmonary artery overrides a subpulmonary ventricular defect. It is associated with additional aortic arch obstruction in 39% to 52% of patients, substantially complicating the surgical management [46, 47]. Approximately 6,7% of coarctation patients have this anomaly. Also a complete transposition of the great arteries and transposition complexes are found to be associated with an aortic obstruction at subaortic level or in the aortic arch [48, 49].

Kabuki syndrome

This syndrome with an estimated prevalence of 1 in 32000 received its name from the supposed resemblance of its typical facial features to make-up worn by the artists in a traditional Japanese dance-drama called 'Kabuki'. In Kabuki syndrome patients 69 to 91% of patients has a congenital heart defect, most of these lesions are left-sided obstructions of which 29% an aortic coarctation[50, 51]. It is caused by a mutation of two genes located on the short arm (or p-arm) of the X-chromosome KMT2D or KDM6A (or MLL2) and inherits in an autosomal dominant fashion. In a study describing the KMDA6A knocked down zebrafish, prominent defects in heart development were found [52].

Shone's Syndrome

Shone's complex or Shone's syndrome, first described in eight cases in 1963, includes a supravalvular mitral valve membrane, a 'parachute mitral valve', a subaortic stenosis and coarctation of the aorta (CoA). [53]. In addition BAV was also present in 30-83% of these patients. [53-55] CoA is seen in approximately 96% of patients, however only 63% patients exhibit all four symptoms. It is managed surgically, where the level of involvement of the mitral valve and presence of secondary pulmonary hypertension is the main determinant of clinical outcome in these patients [56].

Myhre syndrome

Myhre syndrome is a very rare syndrome (prevalence <1/1.000.000), caused by a heterozygous mutation in the SMAD4 gene on chromosome 18q21. [57] A study of 32 patients describes congenital heart defects in 17 patients, including patent ductus arteriosus , aortic coarctation (12,5%) mild-to-moderate valvular aortic stenosis (12,5%) and one membranous ventricular septal defect.

Williams-Beuren syndrome

Williams-Beuren syndrome is caused by a deletion on chromosome 7q11.23 and occurs in approximately 1 in 10 000 live births [58]. One of the deleted genes is the ELN gene which codes for the protein elastin [59]. The syndrome was first described by Williams et al. in 1961 in four patients, and then in the following year also by Beuren et al. in an additional five patients. Congenital cardiovascular defects occur in about 80% of all patients where some form of arterial stenosis is the predominant form occurring in 40-75% of patients [60]. It differs however from the typical juxta ductal CoA in that its preferred location is at the sinotubular junction (supravalvular aortic stenosis) and is also often seen as an elongated hypoplastic segment [59], of which the first is the most common, occurring in approximately 75% of the children.

Noonan syndrome

Noonan syndrome (NS) occurs in approximately 1/1000 to 1/2000 live births [61] and it is one of the most common syndromic causes of congenital heart disease second only to Downs syndrome [62]. It inherited in an autosomal dominant manner, although many individuals have a de novo mutation. Mutations recognized to cause the syndrome include mutations in the *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS* and *BRAF* genes. The congenital heart disease occurs in between 50 and 80% of patients, with pulmonary valve stenosis and hypertrophic cardiomyopathy being the most common (50-60% and 20% of patients respectively). However, other structural defects such as: atrial septal defect, patent ductus arteriosus, and tetralogy of Fallot have also been described [62]. The left-sided outflow obstructions can occur at the valvular or supravalvular level or as classic aortic coarctation [63, 64]. CoA itself is seen in approximately 8,8% of patients [63], and is more often seen in patients with a PTPN11 mutation [62].

Alagille syndrome

Alagille syndrome (AGS) is a multisystem disorder affecting the liver, heart, eyes, face, skeleton, and other systems occuring in 1 in 70.000 newborns. Up to 70% of patients have a mutation in the Jagged1 gene, which fulfills a function in the Notch signaling pathway. The remaining 30% is probably also caused by a mutation in this large gene, but not yet found due to testing limitations [65]. The cardio vascular defects are predominantly of the pulmonary arteries (67%) [66] In a study describing 268 individuals with AGS aortic coarctation was only found in 3 cases (1.1%), still substantially higher than in the normal population.

The 22q11.2 deletion syndrome

The 22q11.2 deletion syndrome is the most common microdeletion syndrome and is known for its wide variety of signs and symptoms. It has been described under many different names of which some well-known include; the Sphrintzen syndrome, DiGeorge syndrome and the velo-cardiofacial anomaly. Its incidence is approximately 1 in 3000 persons and 75% of patients has a form of CHD. A common 3 Mb hemizygous deletion of 22q11.2 is detected in the majority of patients. Smaller deletions within this 3 Mb region together with rare deletions outside of the region account for the other 30% [67]. This syndrome occurs in 0.9% of patients with a CoA. Other CHD's are tetralogy of Fallot, pulmonary stenosis, pulmonary stenosis and septal defects.

Turner syndrome

Of the aforementioned syndromes Turner syndrome (TS) is probably the most well-known, with a prevalence of approximately 1 in 2500 live born girls [68]. It has a broad variety of features, amongst which short stature, infertility and a webbed neck. Aortic pathology is seen quite frequently in TS. Aortic dilatation and especially aortic dissection are seen more often, but also BAV and CoA are associated with the syndrome. [1, 68] In up to 17% of

patients a CoA is found the presence of CoA in TS patients is often associated with BAV (RR, 4.6) [69, 70]. More recently Ho et al. found that in 50% of Turner patients aortic coarctation appeared to be associated with an elongated transverse aortic arch [1]. Supposedly other abnormalities such as an aberrant right subclavian artery (8%), and common origin of the innominate and left carotid artery (8%) belong to the same cardiovascular phenotype [68].

Miscellaneous

In addition to the syndromes and associations mentioned above there are other associations with CoA; congenital rubella syndromes are known to cause cardiac and cardiovascular disease especially pulmonary artery stenosis and patent ductus arteriosus in 50% of patients [71]. But also aortic coarctation has been reported in these children. Intracranial Berry aneurysms occur often in patients with coarctation. It is however unclear if there is a common pathophysiological ground to this association and whether it is due to secondary modifiable risk factors, such as blood pressure.

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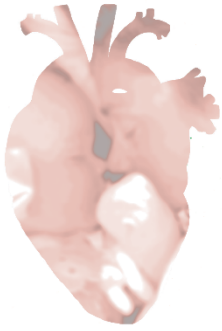
BICUSPID AORTIC VALVE AND AORTIC COARCTATION



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Left ventricular global longitudinal strain in bicuspid aortic valve patients: head-to-head comparison between computed tomography, 4D flow cardiovascular magnetic resonance and speckle-tracking echocardiography

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Abstract

Objectives. Left ventricular global longitudinal strain (LVGLS) analysis is a sensitive measurement of myocardial deformation most often done using speckle-tracking transthoracic echocardiography (TTE). We propose a novel approach to measure LVGLS using feature-tracking software on the magnitude dataset of 4D flow cardiovascular magnetic resonance (CMR) and compare it to dynamic computed tomography (CT) and speckle tracking TTE derived measurements

Methods. In this prospective cohort study 59 consecutive adult patients with a bicuspid aortic valve (BAV) were included. The study protocol consisted of TTE, CT, and CMR on the same day. Image analysis was done using dedicated feature-tracking (4D flow CMR and CT) and speckle-tracking (TTE) software, on apical 2-, 3-, and 4-chamber long-axis multiplanar reconstructions (4D flow CMR and CT) or standard apical 2-, 3-, and 4-chamber acquisitions (TTE).

Results. CMR and CT GLS analysis was feasible in all patients. Good correlations were observed for GLS measured by CMR (-21 ± 3%) and CT (-20 ± 3%) versus TTE (-20 ± 3%, Pearson's r: 0.67 and 0.65, $p<0.001$). CMR also correlated well with CT (Pearson's r 0.62, $p<0.001$). The inter-observer analysis showed moderate to good reproducibility of GLS measurement by CMR, CT and TTE (Pearsons's r: 0.51, 0.77, 0.70 respectively; $p<0.05$). Additionally, ejection fraction (EF), end-diastolic and end-systolic volume measurements (EDV and ESV) correlated well between all modalities (Pearson's $r>0.61$, $p<0.001$).

Conclusions. Feature-tracking GLS analysis is feasible using the magnitude images acquired with 4D flow CMR. GLS measurement by CMR correlates well with CT and speckle-tracking 2D TTE. GLS analysis on 4D flow CMR allows for an integrative approach, integrating flow and functional data in a single sequence.

Introduction

For decades left ventricular (LV) ejection fraction (EF) has been the gold standard for quantification of systolic LV function. [1] It has been a key metric in therapy and prognostication, in particular in patients with valvular heart disease. However, more sensitive methods have since been in development; [2] of which LV global longitudinal strain (GLS) is currently accepted as a more sensitive measurement, that may already be reduced before a decrease in LV EF can be observed. Moreover LV GLS allows for quantitative assessment of global and segmental ventricular function by measuring myocardial deformation, largely independent of angle and ventricular geometry. [3-5] GLS is defined as the percentage of shortening between the end-diastolic and end-systolic length of the myocardium. This technique of deformation measurement has been validated in different populations using speckle-tracking echocardiography. [5-15] More recently it was shown that GLS can also be derived from multiphase Computed Tomography (CT) datasets and conventional Cardiovascular Magnetic Resonance (CMR) steady state free-precession (SSFP) cine imaging using feature-tracking algorithms. [16, 17] However, these techniques, especially GLS measurement using CT are still new and not yet very well validated. In this study we propose a novel method that uses this feature-tracking algorithm on magnitude images acquired during 4D flow CMR to quantify LV volumes and GLS. 4D flow CMR allows for comprehensive post-hoc evaluation of blood flow patterns by 3D blood flow visualization and quantification of flow parameters. [18] Previous studies have shown that quantification of ventricular volume and function can be accomplished with 4D flow MRI with precision and inter-observer agreement comparable to that of SSFP cine imaging. [19, 20] Strain analysis would be a valuable additional feature of 4D flow CMR, as this would allow for integrative analysis of flow and function in one sequence.

Methods

In this prospective cohort study, adult patients with a bicuspid aortic valve (BAV) were included [21, 22]. The study protocol consisted of TTE, CT and CMR on the same day. The inclusion criteria were age ≥ 18 year and one of the following: [1] aortic stenosis (gradient >2.5 m/s), [2] aortic regurgitation (at least moderate) or [3] ascending aortic dilation ≥40 mm and/or aortic size index >2.1 cm/m2. Patients with contra-indications to CT, CMR or contrast agents were excluded. For the current study we only included patients who underwent at least two of the three imaging modalities. The study complied with the Declaration of Helsinki and was approved by the medical ethical committee of the Erasmus Medical Center (MEC14-225). Written informed consent was provided by all patients.

Echocardiography

One of two experienced sonographers performed a standard two-dimensional transthoracic echocardiogram. All studies were acquired using harmonic imaging on an EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with an x5–1 matrix-array transducer (composed of 3040 elements with 1-5 MHz). A non-foreshortened apical (A) four-chamber (ch), A3ch and A2ch were recorded with manual rotation. All echocardiographic images were obtained with a frame rate >60 frames per second.

Computed Tomography

Acquisition was performed using a dual-source CT (Somatom Force or Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). Retrospective ECG-gated spiral acquisition was applied, and kV was modulated to patient size and a vascular exam type. Dose modulated ECG-pulsing was employed with nominal tube current during the 0 to 40% window of the R-R interval, and tube current reduced to 20% of the nominal output for the remainder to reduce the radiation dose. Reference tube current was set at 150 mAs per rotation. The pitch was adapted to increase proportionally with higher heartrates. No beta blockers were administered prior to the scan. Reconstructions were made with a medium smooth kernel. In total 20 different reconstructions with a slice thickness of 1.5mm and 1.0-mm overlap were made in each patient at every 5% of the R-R interval. The mean dose length product (DLP) was 362mGy-cm (estimated effective dose 5mSv, using a conversion factor of k=0.017). A 65 ml bolus of iodinated contrast material (Iodixanol 320, Visipaque, GE Healthcare, Cork, Ireland) was administered through an antecubital vein followed by a 40 ml 70/30% saline/contrast medium bolus, both at 5 ml/s.

Cardiovascular Magnetic Resonance imaging

Image acquisition was performed using a 1.5T clinical MRI scanner (Discovery MR450, GE Medical Systems, Milwaukee, WI, USA) using a 32-channel phased-array cardiac surface coil. The imaging protocol consisted of black blood TSE aorta, 2D phase contrast images for pulse wave velocity measurements, SSFP for aortic distensibility measurements, contrast enhanced MR angiography and 4D flow CMR of the entire heart and aorta. The 4D flow CMR was acquired immediately after the bolus injection of 0.1–0.2 mmol/kg gadolinium-based contrast agent (Gadovist 1 mmol/ml, Bayer, Mijdrecht, The Netherlands). The 4D flow sequence has been described before. [23] In short the sequence was prescribed in axial plane, including the entire thorax in the field of view. The k-space was filled with variable-density Poisson-disc under sampling with acceleration factors of 1.8×1.8 (phase×slice) and the parallel imaging algorithm used was ESPIRiT. Typical scan parameters were: matrix 192×160×78, acquired resolution 2.1×1.8×2.8 mm, reconstructed resolution 2.1×1.8×1.4 mm, flip angle 15°, views per segment 4, bandwidth 63 kHz, number of reconstructed phases 20 per cardiac cycle, and a velocity encoded value set at 250 cm/s. Due to restricted scan time per patient no SSFP cine images were acquired.

Image analysis

All images (CMR, CT and TTE) were analyzed by one observer (A.T.), who had 6 years of experience in cardiovascular imaging, in a random order and blinded to the results of the other image modalities. The TTE, CT, and CMR data was then re-measured by a second observer (S.Y.), who has one year of experience, blinded to the results of the first observer and to the corresponding measurements of the other modalities. For 2D TTE, speckle tracking analysis was performed using dedicated commercially available software (2D Cardiac Performance Analysis, Tomtec Imaging Systems). End-systolic and end-diastolic frames were identified manually; additionally the annulus and apex were identified manually in end-systole (Figure 1). Subsequently, the software semi-automatically detected the end-diastolic and end-systolic myocardial contours. These contours were visually checked and corrected if necessary. This process was performed in all apical views (A2ch, A3ch, and A4ch).

Figure 1. Left ventricular parameters by three different modalities in the same patient

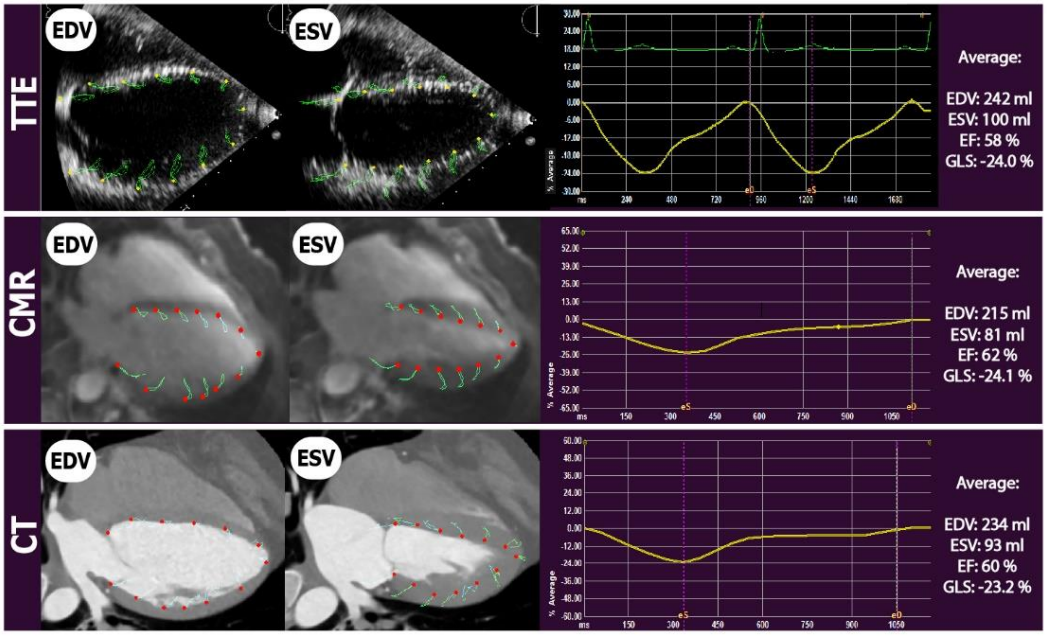

Fig 1. Transthoracic Echocardiography (TTE), Computed Tomography (CT) and Cardiovascular Magnetic Resonance (CMR) EDV: end-diastolic volume, ESV: end-systolic volume, EF: Ejection Fraction, GLS: Global Longitudinal Strain. Yellow lines depict GLS during the cardiac cycle. eS: end-systolic phase, eD: End-diastolic phase.

All CT and CMR images were analyzed semi-automatically using commercially available software from Medis Medical Imaging Systems, Leiden the Netherlands. All images were loaded into the Medis Suite software (version: 3.1.16.6). A2ch, A3ch, and A4ch reconstructions were made from the 3D data sets using Medis 3D View (version: 3.1.18.1). For the CMR analysis only the magnitude images, which contain the anatomical data, of the 4D flow data set were used. All cardiac phases were included in the multi-plane reconstructions and endocardial contours were drawn manually at both end-diastole and end-systole using Medis QMass software (version: 8.1.30.4) where the papillary muscles and trabeculations were included in the LV lumen. Subsequently GLS, ejection fraction (EF), end-diastolic and end-systolic volume (EDV and ESV) were calculated using QStrain software (version: 3.1.16.6). Volumes were corrected for body surface area (BSA). BSA was calculated according to the Dubois formula. [24] In QMass LV contours were drawn manually and focused on adequate tracking of the myocardium for precise strain analysis. However, changes to the contours necessary for optimal tracking of the myocardium caused an underestimation of the ESV. Therefore, in order to provide data on the inter-modality variability of the volumes, a second set of separate endocardial contours had to be drawn for the measurement EDV, ESV and EF. The second trace of endocardial contours, drawn for the volumetric analysis, used standard anatomical landmarks (supplemental video 1). However, for adequate strain analysis the left ventricular outflow tract (LVOT) had to be excluded, and the first trace therefore started more apically in both end-systole and end-diastole, (supplemental video 2) to prevent highly positive segmental strain disturbing GLS measurement. For the inter-observer variability, twenty patients were chosen at random.

Statistical analysis

The IBM SPSS® statistics 21.0 software was used to analyze the data. Continuous variables were presented as mean ± standard deviation (SD) or as median with an interquartile

range. Categorical variables were presented as frequencies and percentages. We tested for normality by calculating Z-values of skewness and kurtosis, using the Shapiro-Wilk test and by visually assessing the data. For comparison of normally distributed continuous variables between two groups the student's t-test was used. To quantify correlations the Pearson correlation test was applied. Inter-observer agreement between two investigators was assessed using Bland-Altman analysis. [25] The bias was defined as the mean absolute difference (i.e. the average absolute difference between two modalities). The limits of agreement between two measurements were determined as the mean of the difference ±

1.96 SD. Additionally, the coefficient of variation (COV) was provided to compare the dispersion of two variables. The COV was defined as the SD of the differences of two measurements divided by the mean of their means. The statistical tests were two sided and a p-value <0.05 was considered significant.

Results

Fifty-nine patients were included, of whom 37 men (63%). Their baseline characteristics are presented in table 1. In 56 patients (95%) echo measurements could be performed, two patients did not undergo echocardiography due to organizational reasons and one patient was excluded because of insufficient image quality. In total 53 patients underwent a CT scan, of which one patient was excluded due to technical limitations, therefore 52 (88%) patients were included for CT analysis. In six patients no CT scan was done due to organizational reasons. In 48 patients (83%) 4D flow CMR was performed. In

Table 1. Baseline characteristics

Baseline characteristics, n=59	Median [IQR]
Age, years	34 [19]
Height, cm	180 [23]
Weight, kg	75 [19]
BMI, kg/m^2	24 [3]
BSA, m^2	1.9 [0.4]
SBP, mmHg	123 [17]
DBP, mmHg	79 [16]
Aortic valve	
Vmax, m/s	2.2 (1.6)
Peak Gradient, mmHg	19 (32)
AoI grade - none	12 (20)
AoI grade - moderate	34 (58)
AoI grade - severe	13 (22)
Sievers type*	
Type 0 – lat	6 (10)
Type 0 – ap	7 (12)
Type 1 - LR	23 (49)
Type 1 - RN	7 (12)
Type 1 - LN	1 (2)
Type 2 – LR/RN	7 (12)

Table 1. Data are presented as median [IQR] or n (%), BSA: body surface area, SBP and DBP: systolic and diastolic blood pressure, Vmax: peak aortic valve velocity, AoI: aortic valve insufficiency, *Valve type according to Sievers

eleven patients 4D flow CMR was missing due to organizational reasons (scan time per patient was restricted and therefore 4D flow could not always be performed in all patients). The results of all measurements are presented per modality in table 2. The results of the inter-modality agreement are presented in table 3. All CT and MR scans were included. No scans (CT or CMR) were excluded because of insufficient image quality. A sensitivity analysis was conducted which showed that the there was no significant difference when only the patients who underwent
all three modalities were considered (n=39) (tables 2 and 3).

Table 2. Left ventricular parameters per imaging modality.

	All patients*			All three modalities completed†		
	CT (n=52)	**CMR** (n=48)	**TTE** (n=56)	**CT** (n=39)	**CMR** (n=39)	**TTE** (n=39)
GLS (%)	-20 ± 3	-21 ± 3	-20 ± 3	-21 ± 2	-21 ± 3	-20 ± 3
EF (%)	58 ± 6	54 ± 7	55 ± 6	58 ± 5	55 ± 7	55 ± 5
EDV (ml)	192 ± 65	203 ± 62	185 ± 64	183 ± 58	193 ± 62	180 ± 57
EDV/BSA (ml/m^2)	99 ± 26	105 ± 26	95 ± 26	95 ± 24	100 ± 24	94 ± 24
ESV (ml)	82 ± 33	94 ± 34	83 ± 33	77 ± 28	87± 32	81 ± 29
ESV/BSA (ml/m^2)	42 ± 13	48 ± 15	42 ± 15	40 ± 12	45 ± 13	42 ± 12

Table 2 *In this analysis all patients that completed 2 or more imaging modalities were considered. † In this sensitivity analysis data is shown when only patients are considered that completed all three imaging modalities. Data are presented as mean ± standard deviation. EDV: end-diastolic volume, ESV: end-systolic volume, EF: Ejection Fraction, GLS: Global Longitudinal Strain, BSA: Body Surface Area. Transthoracic Echocardiography (TTE), Computed Tomography (CT) and Cardiovascular Magnetic Resonance (CMR).

Left ventricular global longitudinal strain and ejection fraction

When comparing CMR and CT versus TTE, strong correlations (table 3: Pearson's r: 0.67, p<0.001 and Pearson's r: 0.65, p<0.001 respectively) were found for GLS. However, especially CMR seemed to slightly overestimate GLS with a mean difference -2% and a bias of 3% when compared to TTE (figure 2). The results of the EF measurements per modality are presented in table 2; results for the agreement analysis of EF are shown in table 3 and figure 3. Of all three modalities EF, measurement by CT yielded the highest mean EF: 58±6%, where CMR yielded the lowest mean EF of the three modalities (54±7%).

Volume measurement

Correlations for LV end-diastolic volumes (supplemental figure 4) were strong for both CMR and CT compared to TTE (table 3, Pearson's r: 0.84 and 0.85, both p<0.001 respectively), where the mean difference was smallest between CT and TTE. As shown in table 2, EDV

Table 3. Inter-modality agreement.

	All Patients					All three modalities				
	Pearson's r[†]	**Bias**[‡]	**Mean difference**	**Lower LOA**	**Upper LOA**	**Pearson's r**[†]	**Bias**[‡]	**Mean difference**	**Lower LOA**	**Upper LOA**
	CMR vs. TTE (n=45)					**CMR vs. TTE** (n=39)				
GLS (%)	0.67	3	-2	-7	3	0.69	2	-2	-6	3
EF (%)	0.61	4	0	-11	10	0.62	4	0	-10	11
EDV (ml)	0.84	31	16	-53	85	0.86	28	13	-50	75
ESV (ml)	0.82	17	8	-32	47	0.85	15	6	-28	40
	CT vs. TTE (n=49)					**CT vs. TTE** (n=39)				
GLS (%)	0.65	2	-1	-5	4	0.65	2	-1	-5	3
EF (%)	0.67	4	2	-6	11	0.69	4	3	-5	11
EDV (ml)	0.85	26	8	-61	77	0.88	23	3	-54	59
ESV (ml)	0.83	13	0	-36	36	0.87	12	-4	-33	25
	CT vs. CMR (n=42)					**CT vs. CMR** (n=39)				
GLS (%)	0.62	2	1	-4	6	0.56	2	1	-5	6
EF (%)	0.68	5	3	-8	14	0.56	5	3	-8	14
EDV (ml)	0.93	19	-11	-56	35	0.93	18	-10	-54	33
ESV (ml)	0.90	14	-11	-40	19	0.90	13	-10	-38	18

Table 3. [†]: all significant with a p<0.001. [‡] Defined as the mean absolute difference, LOA: Limit of agreement. EDV: end-diastolic volume, ESV: end-systolic volume, EF: Ejection Fraction, GLS: Global Longitudinal Strain. Transthoracic Echocardiography (TTE), Computed Tomography (CT) and Cardiovascular Magnetic Resonance (CMR).

measurements were larger on CMR (203±62ml) compared with TTE (185±64ml), which resulted in the largest bias of 31ml and limits of agreement ranging between -53ml and 85ml. Correlations for ESV were comparable to those found for EDV (supplemental figure 5). ESV measured by CMR and CT correlated strongly with TTE (Pearson's r: 0.82 and 0.83 respectively, both p<0.001). Here too CT compared best with TTE with a mean difference of -0.3ml (bias: 13ml) versus 7.8ml on average for CMR compared with TTE (bias: 17ml).

Figure 2. Inter-modality agreement for global longitudinal strain

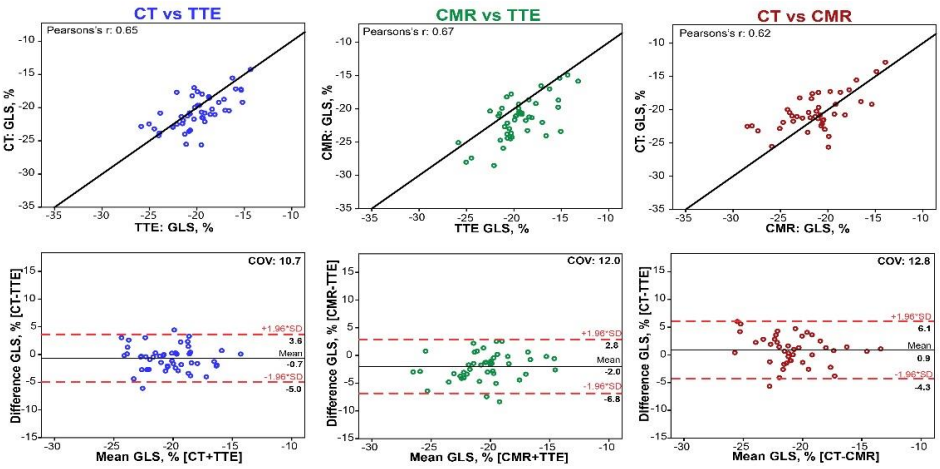

Fig. 2. Agreement between Transthoracic Echocardiography (TTE), Computed Tomography (CT) and Cardiovascular Magnetic Resonance (CMR) for global longitudinal strain (GLS). Bland-Altman plots and identity line (black) for CT versus TTE (blue) and CMR versus TTE (green) and CT versus CMR (red). Dashed red lines indicate ±1.96 SD. COV: coefficient of variation.

Figure 3. Inter-modality agreement for ejection fraction

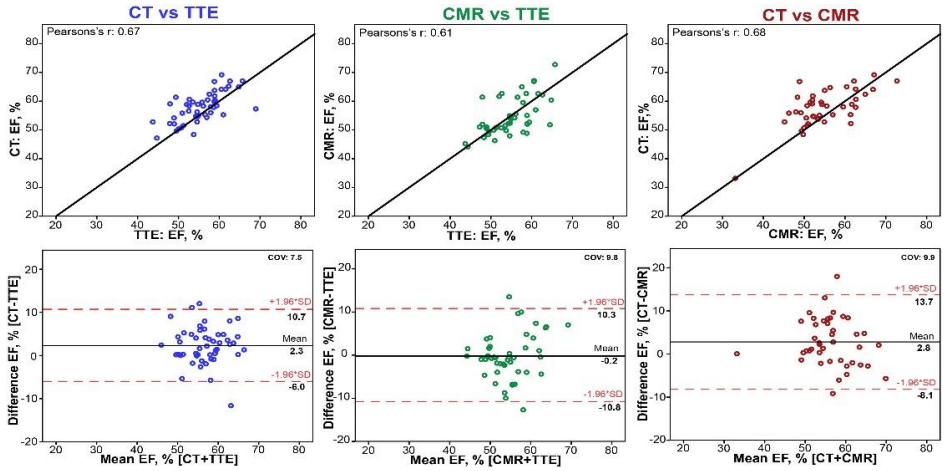

Fig. 3. Agreement between Transthoracic Echocardiography (TTE), Computed Tomography (CT) and Cardiovascular Magnetic Resonance (CMR) for ejection fraction (EF). Bland-Altman plots and identity line (black) for CT versus TTE (blue) and CMR versus TTE (green) and CT versus CMR (red). Dashed red lines indicate ±1.96 SD. COV: coefficient of variation.

Inter-observer variability

Inter-observer variability was assessed for all three modalities; the results of the second observer agreement analysis for TTE are presented in supplemental figure 6. Both for GLS and EF good inter-observer agreement was found (Pearson's r: 0.70, p<0.001 and 0.60, p=0.006 respectively), and also for EDV and ESV (Pearson's r: 0.96 and 0.90, p<0.001 respectively). The relatively large mean difference for EF (-9.4%) for TTE, was mainly driven by observer 1 overestimating both EDV (mean difference: 13.7ml) and ESV, with a tendency towards a more significant overestimation of the ESV (mean difference: 27.2ml) relative to the EDV. Inter-observer variability for CT is presented in supplemental figure 7, where a strong correlation between observers was found for GLS with a mean difference of -1.8% on average. Finally, inter-observer variability for CMR is presented in supplemental figure 8, where a moderate correlation for GLS (Pearson's r: 0.51, p=0.023) was found.

Discussion

In this prospective cohort study we demonstrated for the first time that the assessment of GLS is feasible using a feature-tracking algorithm on the magnitude images acquired by 4D flow CMR directly after gadolinium contrast. This opens the way for an integrative one-sequence approach in which both flow and functional information can be acquired simultaneously. Moreover, in this study functional LV parameters measured by CMR correlated well with 2D TTE, with a mean difference comparable to that found in other studies using 'conventional' SSFP cine CMR images. [26-29] On average GLS in our cohort of BAV patients was similar to that found using SSPF CMR images in a healthy adult population. [30]

Although LV functional analysis by CT has been possible for a number of years there is limited data available on the value of CT in GLS assessment. [16, 31-33] CT has been shown to correlate closely with CMR and TTE for left ventricular assessment, [27] and more recently also for GLS analysis. [28] Additionally, studies have described good correlations between CT and TTE. [16, 32] Our study confirms these correlations with TTE and CMR for both GLS and EF. Furthermore, CT had the best reproducibility of all three modalities, reflected in the lowest coefficient of variation in the second-observer analysis. The observed overestimation of EF by CT compared to CMR could be explained by the fact that, especially on the long axis A3ch-view, papillary muscles are often difficult to discern resulting in a smaller ESV and subsequent high EF. Furthermore, unlike TTE and CMR, CT has the disadvantage of significant radiation exposure for the patient, since imaging of the complete cardiac cycle is necessary for GLS analysis. CT and CMR correlated well both for GLS and EF. Based on the high spatial resolution CT could have been expected to outperform CMR, as CMR may require more observer interpretation in determining the endocardial contour. Indeed we observed a lower coefficient of variation for CT versus TTE

(COV: 10.7) compared to CMR versus TTE (COV: 12.0) for both GLS and for EF (COV: 7.5 vs 9.8). Additionally, second observer analysis for CT showed a lower COV for all LV measurements.

A clear limitation of this study is the need for separate contours for the GLS and volumes, caused by the frequent inadequate tracking of the basal and mid and anterior septal segments by the feature-tracking algorithm on CT and CMR (supplemental figure 9). Tracing the endocardial contour in the apical three chamber view from the mitral valve to the aortic valve orifice (supplemental video 1) often resulted in positive strain values in these segments, lowering the GLS. This could be resolved by placing the endocardial marker more apically (supplemental video 2) resulting in an underestimation of the EDV and ESV. A third video shows the same process for MR in apical three and 4 chamber views (supplemental video 3 and 4 respectively). The difficulty here is that when abandoning the anatomical landmark there is no clear alternative, which introduces possible inter-observer variability. Although more time consuming we chose to draw a second endocardial tracing focusing on the volume quantification when this problem occurred. With regard to the post-processing process, we found the TTE workflow to be significantly less time intensive compared to CT and CMR, partly because with TTE the sonographer directly acquired the apical 2-, 3-, and 4-chamber views. Both with CT and CMR the observer had to create these views retrospectively. This may allow for more precise reconstruction and analysis, but it is also more time intensive as it increases workflow complexity, and creates a possible source of bias between observers. It has been shown that both observer experience and the software used for analysis can have a significant influence on the agreement for CMR (30, 31) as for TTE (32). And although outside the scope of this study we agree that user experience is an important factor in LV functional analysis. This is perhaps best reflected in the second observer analysis for TTE, where a small but consistent difference in EDV and ESV resulted in a systematically lower EF for the second observer. Another limitation is that we did not have SSFP CMR cine images available for these patients, which would have allowed to also compare 4D flow CMR with the 'gold standard' for volume quantification and feature-tracking strain analyses on SSFP images. We feel that part of the variation between CMR and the other modalities could be explained by the inferior spatial resolution of the magnitude image datasets. Furthermore, the standard deviation of GLS and EF in this patient cohort is small, as all patients had relatively preserved LV function. A future study could evaluate how this technique performs in patients with a reduced LV function.

Conclusion

Feature-tracking GLS analysis is feasible using the magnitude images acquired by 4D flow CMR with adequate imaging quality. GLS measurement by CMR correlates well with CT and speckle-tracking 2D TTE. GLS analysis on 4D flow CMR allows for an integrative approach in

which flow and functional data can be acquired in one sequence. Future studies should aim to validate these findings in a healthy control population, preferably compared with SSPF cine imaging.

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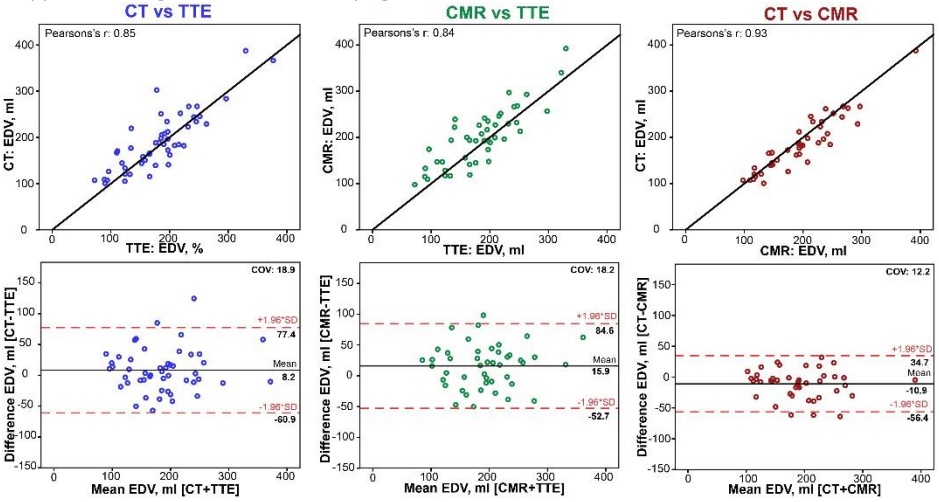
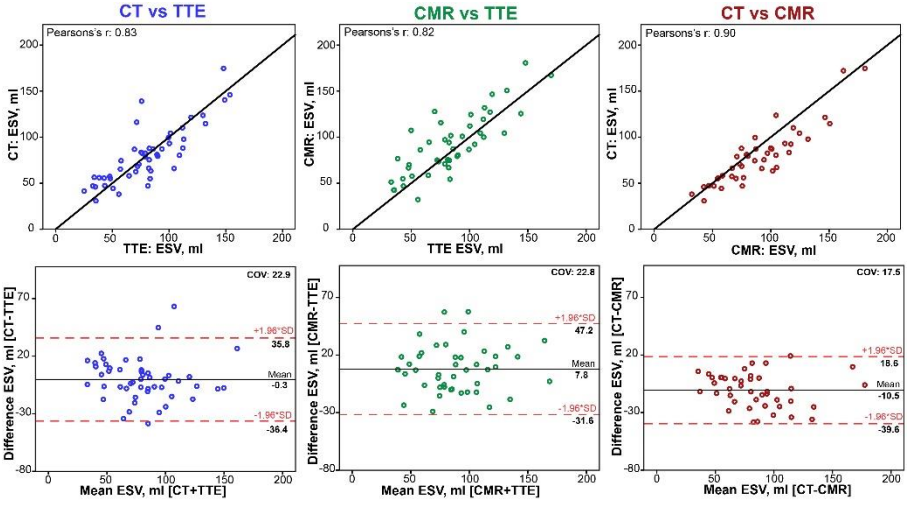
Supplementary figures

Supplemental figure 4: Inter-modality agreement for end–diastolic volume.



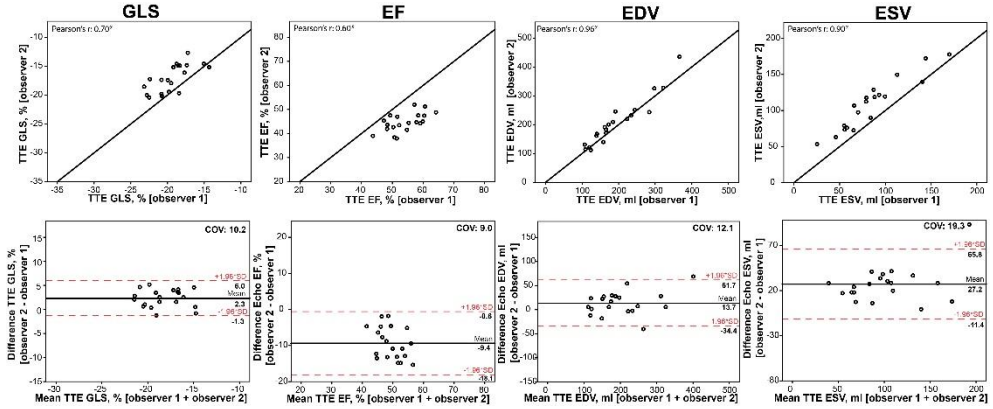
Supplemental figure 4. Agreement between transthoracic echocardiography (TTE), Transthoracic Echocardiography (TTE), Computed Tomography (CT) and Cardiovascular Magnetic Resonance (CMR) for end-diastolic volume (EDV). Bland-Altman plots and identity line (black) for CT versus TTE (blue) and CMR versus TTE (green) and CT versus CMR (red). Dashed red lines indicate ±1.96 SD. COV: coefficient of variation.

Supplemental figure 5: Inter-modality agreement for end-systolic volume.



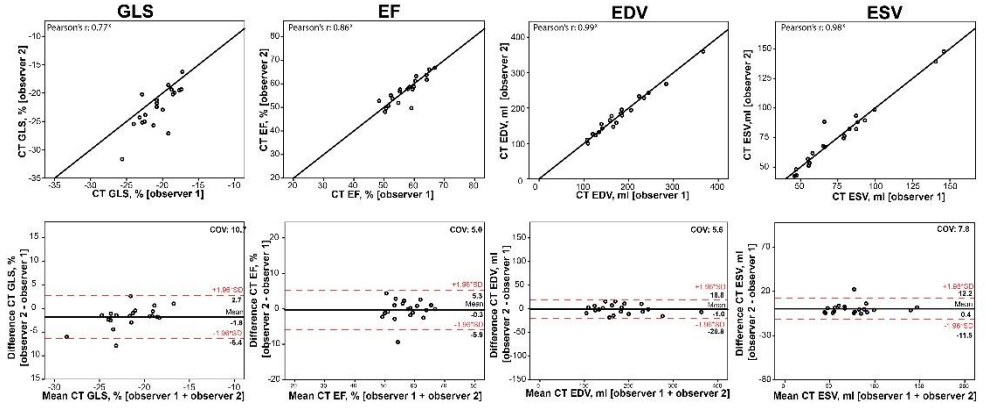
Supplemental figure. 5: Agreement between transthoracic echocardiography (TTE), Computed Tomography (CT) and Cardiovascular Magnetic Resonance (CMR) for end-systolic volume (ESV). Bland-Altman plots and identity line (black) for CT versus TTE (blue), and CMR versus TTE (green) and CT versus CMR (red). Dashed red lines indicate ±1.96 SD. COV: coefficient of variation.

Supplemental figure 6: Inter-observer agreement for Transthoracic Echocardiography.



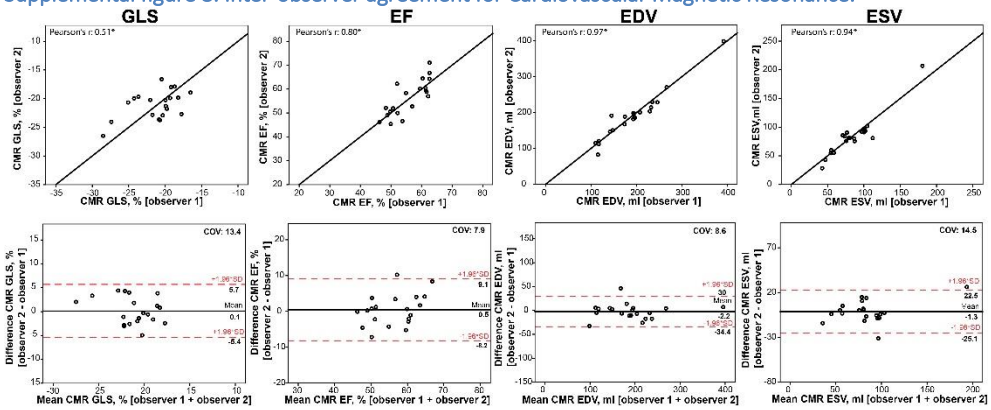
Supplemental figure 6: Inter-observer agreement for Transthoracic Echocardiography (TTE) (n=20). Bland-Altman plots and identity line (black) for global longitudinal strain (GLS), ejection fraction (EF), end-diastolic volume (EDV) and end-systolic volume (ESV). Dashed red lines indicate ±1.96 SD. COV: coefficient of variation. *All Pearson's r's are significant with a p<0.01

Supplemental figure 7: Inter-observer agreement for Computed Tomography.



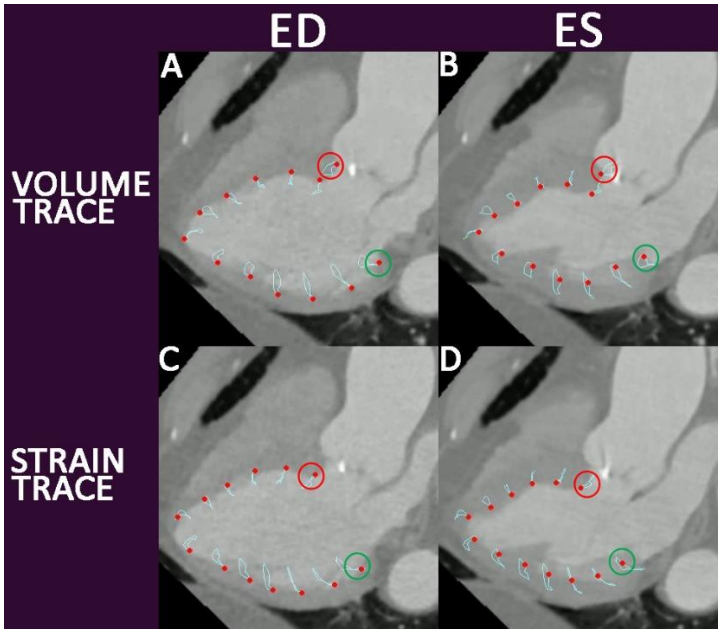
Supplemental figure 7: Inter-observer agreement for Computed Tomography (CT) (n=20). Bland-Altman plots and identity line (black) for global longitudinal strain (GLS), ejection fraction (EF), end-diastolic volume (EDV) and end-systolic volume (ESV). Dashed red lines indicate ±1.96 SD. COV: coefficient of variation. *All Pearson's r's are significant with a p-vale of p<0.001

Supplemental figure 8. Inter-observer agreement for Cardiovascular Magnetic Resonance.



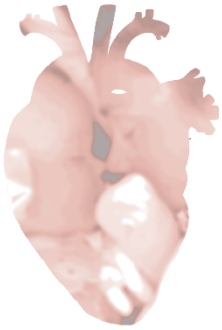
Supplemental figure 8. Inter-observer agreement for Cardiovascular Magnetic Resonance (CMR) (n=20). Bland-Altman plots and identity line (black) for global longitudinal strain (GLS), ejection fraction (EF), end-diastolic volume (EDV) and end-systolic volume (ESV). Dashed red lines indicate ±1.96 SD. COV: coefficient of variation. *All Pearson's r's are significant with a p-value <0.05

Supplemental figure 9. Separate contours for the volume and strain traces.



Supplemental figure 9. contours as drawn for the volume trace (A and B) and the contours as drawn for the strain trace more apically (C and D). In both end-diastole (ED, A and C) and end-systole (ES, B and D).

BICUSPID AORTIC VALVE AND AORTIC COARCTATION



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10

Transthoracic 3D echocardiographic left heart chamber quantification in patients with bicuspid aortic valve disease

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Abstract

Objectives. Integration of volumetric heart chamber quantification by 3D echocardiography into clinical practice has been hampered by several factors which a new fully automated algorithm (Left Heart Model, (LHM)) may help overcome. This study therefore aims to evaluate the feasibility and accuracy of the LHM software in quantifying left atrial and left ventricular volumes and left ventricular ejection fraction in a cohort of patients with a bicuspid aortic valve.

Methods. Patients with a bicuspid aortic valve were prospectively included. All patients underwent 2D and 3D transthoracic echocardiography and computed tomography. Left atrial and ventricular volumes were obtained using the automated program, which did not require manual contour detection. For comparison manual and semi-automated measurements were performed using conventional 2D and 3D datasets.

Results. 53 patients were included, in four of those patients no 3D dataset could be acquired. Additionally, 12 patients were excluded based on poor imaging quality. Left ventricular end-diastolic and end-systolic volumes and ejection fraction calculated by the LHM correlated well with manual 2D and 3D measurements (Pearson's r between 0.43 and 0.97, $p<0.05$). Left atrial volume (LAV) also correlated significantly although LHM did estimate larger LAV compared to both 2DE and 3DE (Pearson's r between 0.61 and 0.81, $p<0.01$).

Conclusions. The fully automated software works well in a real-world setting and helps to overcome some of the major hurdles in integrating 3D analysis into daily practice, as it is user-independent and highly reproducible in a group of patients with a clearly defined and well-studied valvular abnormality.

Introduction

Left atrial and ventricular volumes and ejection fraction are important diagnostic and prognostic parameters, widely used in daily practice. Indication for cardiac surgery in patients with valvular abnormalities such as bicuspid aortic valve disease, rely heavily on accurate left ventricular (LV) volume and function assessment. For many years, two-dimensional echocardiography (2DE) has been the most widely used modality for LV volumetric assessments; however, it relies on geometric assumptions which cause inaccuracy and the reproducibility remains suboptimal. Three-dimensional echocardiography (3DE) has largely overcome these drawbacks as it has the ability to visualize cardiac structures from any perspective, entailing an accurate quantitative and more reproducible evaluation of cardiac chambers. However, the use of 3DE in daily clinical practice has been hampered, because there is a learning curve for data acquisition, and 3D data analysis can be a time-consuming process, moreover there is need for experienced observers.

A fully automated and user-interference free algorithm may improve the feasibility of 3DE in daily clinical practice. Such a method has now been proposed in the new 'Heart Model' Software (LHM), which promises a rapid and accurate automated quantification of left atrial (LAV) and LV volumes and ejection fraction (LVEF). The feasibility and accuracy of the new "Heart Model" was recently compared to cardiac magnetic resonance by Tsang et al who concluded that this technique is strongly correlated with CMR, with a high reproducibility and short analysis time [34, 35]. However, it has not been reported whether this also applies to patients with valvular heart disease where high reproducibility and feasibility is very important.

Therefore, this study aims to assess feasibility and reproducibility of the 'Heart model' software in a prospective cohort study by comparing the results between echo and CT using conventional 2D, 2D-xPlane, 3D transthoracic echocardiography TTE (3DE) techniques in patients with a bicuspid aortic valve (BAV) with moderate to severe aortic valve stenosis or regurgitation.

Methods

Patients selection

Patients with a BAV who visited the outpatient clinic between October 2014 and March 2016 were prospectively included. All patients underwent the full study protocol on the same day. The study protocol consisted of physical examination, electrocardiography (ECG), 2D and 3D echocardiography and a cardiac CT scan. The study was approved by the medical

ethical committee of the Erasmus medical center and informed consent was given by all patients who participated in the study.

Echocardiography

Image acquisition

Two experienced sonographers (J.S.M., W.B.V.) performed a standard two-dimensional transthoracic echocardiogram (2DE). All studies were acquired in the left lateral decubitus position, in harmonic imaging using an EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands) equipped with a x5 – 1 matrix-array transducer (composed of 3040 elements with 1-5 MHz) A non-foreshortened apical four-chamber view (A4C) and two-chamber view (A2C) were recorded with manual or electronic rotation (iRotate) followed by a focused LV, A4C and A2C image. From the focused LV- A4C a true perpendicular image view (A2C) was acquired with xPlane mode, in order to retrieve both views from the same heart-beat. This was repeated with the focus on the true long axis of the LA [36]. Real-time 3D-TTE was performed immediately after the 2D-TTE with the same ultrasound unit and transducer. A four-or six-beat full volume dataset of the LV and LA was acquired from the apical window during a single breath hold. Two extra datasets were acquired from the A4C view in the dedicated 'Heart Model' acquisition mode.

Image analysis

Analysis was performed by A.T.H. and J.S.M. All measurements were blinded to patient specific information. Before measurements were performed, the quality of each dataset was evaluated by both observers. Patients were excluded from further analysis in cases of poor image quality (e.g. poor endocardial visualization).

2D Echocardiography

LV end diastolic volume (LVEDV), LV end systolic volume (LVESV) and LVEF were calculate using the Simpsons bi-plane method of disk summation, as stated in the guidelines, from the standard A4C and A2C and apical xPlane images [37]. LAV was calculated using the area length method.

3D Echocardiography

Manual: LV volumes and LVEF were measured using commercially available software (QLab-3DQ, Philips medical systems). The user aligned the mutiplanar view to obtain the true long axis of the LV in the A4C and A2C view. Landmarks were placed on the mitral annulus and apex. The endocardial border was traced automatically and adjusted manually where needed. For the LA volume, the true long-axis was aligned using the multiplanar mode in the end-systolic frame and the contour traced as mentioned above. The 3D dataset was scored feasible when the entire cardiac contour could be traced.

Automatic: Offline fully automatic analysis of the datasets was performed using the Q Lab advanced 'Heart Model' analysis software. This software has previously described in detail before by Tsang et al [34, 35]. In brief, this software detects the endocardial surfaces by using an adaptive algorithm. This identifies a global end-diastolic shape which it uses in combination with motion detection to determine an end-systolic cavity [34, 35]. The program combines information from a database of 1000 3D TTE studies and its endocardial surface detection to model the LA and LV. Afterwards it matches features from the known datasets to the current patient for which it needs, much like manual measurements, a minimum of approximately 14 or 15 LV segments. The final model (figure 1) is displayed with the possibility to manually edit the contours if the user deems this necessary. To better estimate the added value over existing 3D techniques we chose not to manually edit the contours.

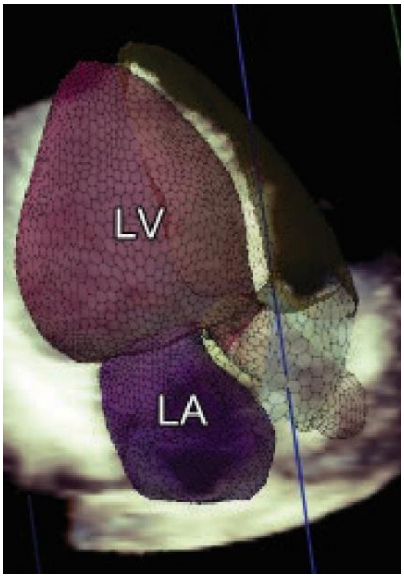

Figure 1. The model as generated by the LHM of left atrial (LA and left ventricular (LV) volumes.

Cardiac Computed Tomography

Data acquisition

Acquisition was performed on a 3rd generation dual-source CT (Somatom Force, Siemens Healthcare, Forchheim, Germany). Retrospective ECG gated spiral acquisition was used, with a mean dose length product (DLP) of (estimated effective dose 5mSv, using k=0.017) 362mGy-cm kVp was modulated to patient size. Besides patient size and the selected kV the mA was modulated to the heartrate to provide a high mA pulse during 1-40% of the RR interval. The pitch was adapted to increase proportionally with higher heartrates. Reconstructions were made with a medium smooth kernel, with a slice thickness of 1.5mm at an increment of 0.4mm at every 5% of the RR interval.

Image processing

Images were analyzed semi-automatically using Syngo Via software (vb 10., Siemens, Forcheim Germany). Image analysis was performed by AC, with 1 year of cardiac CTexperience. All cardiac phases were analyzed the software automatically detects the ED and ES phase, this was manually changed if needed. The endo and epicardial contours are automatically placed by the software and manually adjusted were need. The papillary muscles and if present trabeculations were included into the LV lumen. The basal plane was selected perpendicular to the short axis at the level of the mitral valve. Care was used to make sure the basal plane was on the same level in the ED and ES phase.

Statistics

The IBM SPSS® statistics 21.0 software was used to analyze the data. Continuous variables were presented as mean ± standard deviation (SD) or as median with an interquartile range. Categorical variables were presented as frequencies and percentages. We tested for normality by calculating Z-values of skewness and kurtosis, using the Shapiro-Wilk test and by visually assessing the data. For comparison of normally distributed continuous variables between two groups the student's t-test was used. To quantify correlations the Pearson or Spearman correlation test was applied. Intra-observer and inter-observer agreement between two investigators (A.T.H, J.S.M.) were assessed by repeated analysis of the same images in a third of the dataset a month after initial analysis at the same images and blinded to the initial results. The limits of agreement between two measurements were determined as the mean of the differences (bias) ± 1.96 SD and presented in a Bland-Altman plot [25]. Additionally, the coefficient of variation (COV) was provided to compare the dispersion of two variables. The COV was defined as either the SD of the differences of two measurements divided by the mean of their means. The statistical tests were two sided and a p-value below 0.05 was considered significant.

Results

Fifty-three patients with a BAV were included; baseline characteristics are presented in table 1. Eight patients also had Turner syndrome. Four patients previously underwent aortic coarctation resection and three patients underwent a balloon dilatation of their stenotic aortic valve. One patient underwent closure of a type II atrial septal defect. In all 53 patients, 2DE measurements could be performed and functional echo parameters were measured, as presented in Table 1. In four patients, no 3D dataset could be acquired. Additionally, 12 patients were excluded based on poor imaging quality.

Left ventricle

LHM versus manual 2D measurements

There was a good correlation between the LHM and the manual bi-and xPlane measurements for LVEDV, LVESV, and LVEF. In table 2 the measurements of LV volumes and function and LA maximal volume are presented for all different methods. Figure 2a and 2b show the Bland-Altman plots for EF by 2DE bi-plane and xPlane compared to the LHM. The results of the agreement analysis between the LHM and the measurements based on the 2DE are shown in table 2. For clarity purposes, we did not include mutual correlations between the different echo modalities; however, Bi-plane and xPlane had a high correlation for LVEDV (r=0.977), LVESV (r=0.978) and LVEF (r=0.702). Additionally, both methods correlated strongly with conventional 3D as expected.

LHM versus manual 3D measurements

The LHM correlated strongly with the 3D LV measurements as shown in table 2. The LHM seems to estimate slightly larger LVEDV and LVESV and a smaller LVEF compared to manual 3D (table 2). Figure 2c shows the Bland-Altman plot for EF measured by 3DE. 16 patients (30%) had to be excluded due to poor imaging quality, which is considered acceptable in routine setting for 3DE.

Table 1. Baseline characteristics of the study population (n=37).

		Parameter	Median (IQR)
Baseline		Men, n (%)	25 (68)
		Age, years	35.2 (23)
		Height, cm	178 (26)
		Weight, kg	72 (24)
		BMI, kg/m^2	23.9 (3.0)
		SBP, mmHg	122 (20)
		DPB, mmHg	80 (19)
Mitral valve		E-wave, m/s	0.70 (0.2)
		A-wave, m/s	0.50 (0.2)
		E/A-ratio	1.2 (0.9)
		DT, ms	209 (67)
		E' septal, cm/s	7.8 (3.1)
		Ee'-ratio	9.0 (3.6)
Aortic valve	BAV (n=32)	No AoI, n= (%)	5 (16)
		Mild AoI , n= (%)	21 (66)
		Moderate AoI, n= (%)	5 (16)
		Severe AoI, n= (%)	1 (3)
		Peak velocity, m/s	2.65 (1.6)
		VTI, cm	52.8 (45)
		Gradient, m/s	28 (33)
	TS* (n=5)	No AoI, n= (%)	4 (80)
		Mild AoI, n= (%)	1 (20)
		Moderate, AoI n= (%)	0 (0)
		Severe AoI, n= (%)	0 (0)
		Peak velocity, m/s	1.4 (0.6)
		VTI, cm	28.4 (12)
		Gradient, m/s	8 (6.5)

Table 1. Data are expressed as median and IQR or as 'n=, (%)' for gender and aortic insufficiency. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; DT: deceleration time. * Subgroup of patients with Turner syndrome (TS) and a bicuspid aortic valve (BAV).

Table 2. Correlations between LHM and four different methods of volumetric chamber quantification.

Method	Phase	Mean, SD	Pearson's r†	Bias	Lower LOA	Upper LOA
LHM (n=37)						
	EDV (ml)	146 ±48				
	ESV (ml)	77 ± 29				
	EF (%)	47 ±5				
	LA (ml)	61 ±19				
LHM 2nd dataset (n=12)						
	EDV (ml)	143±61	0.99**	-0.8	-9	7
	ESV (ml)	78±34	0.99**	1	-7	9
	EF (%)	45±4	0.58*	-1.5	-7	4
	LA (ml)	57±19	0.98**	-1	-9	7
2DE Bi-plane (n=37)						
	EDV (ml)	145 ±54	0.93**	0.06	-41	41
	ESV (ml)	77 ±31	0.88**	0.2	-29.1	29.4
	EF (%)	47 ±8	0.63**	0.5	-11.8	12.8
	LA (ml)	43 ±16	0.61**	17	-13.6	47.4
2DE xPlane (n=37)						
	EDV (ml)	143 ±52	0.94**	2	-32	36.4
	ESV (ml)	77 ±30	0.88**	0.8	-27.1	28.8
	EF (%)	47 ±8	0.43**	0.6	-13	14.2
	LA (ml)	42 ±16	0.69**	18	-8.8	45.2
3D (n=37)						
	EDV (ml)	143 ±50	0.97**	2	-23	27.6
	ESV (ml)	71 ±26	0.91**	6	-16.9	29.8
	EF (%)	50 ±7	0.51**	-3	-15.5	9.8
	LA (ml)	53±19	0.81**	9	-13.1	32.1
CT (n=37)						
	EDV (ml)	185±63	0.88**	-42	-102.3	18.9
	ESV (ml)	67±24	0.81**	10	-24.1	43.6
	EF (%)	64±5	0.24	16	-28.3	-4.7

Table 2. Data are presented as mean and SD. EDV: end-diastolic volume, ESV: end-systolic volume, EF: Ejection Fraction, LA: Left atrium, LOA: Limit of agreement, COV: coefficient of variation. †: compared with the LHM, **: $p<0.01$ *: $p<0.05$. A negative mean implies a smaller value was given by the LHM.

Figure 2. Bland-Altman plots demonstrating inter-modality agreement of EF and LAV in 2DE biplane (panel A and B), 2DE xPlane (panel C and D), 3DE (panel E and F) and CT (panel G) compared to LHM.

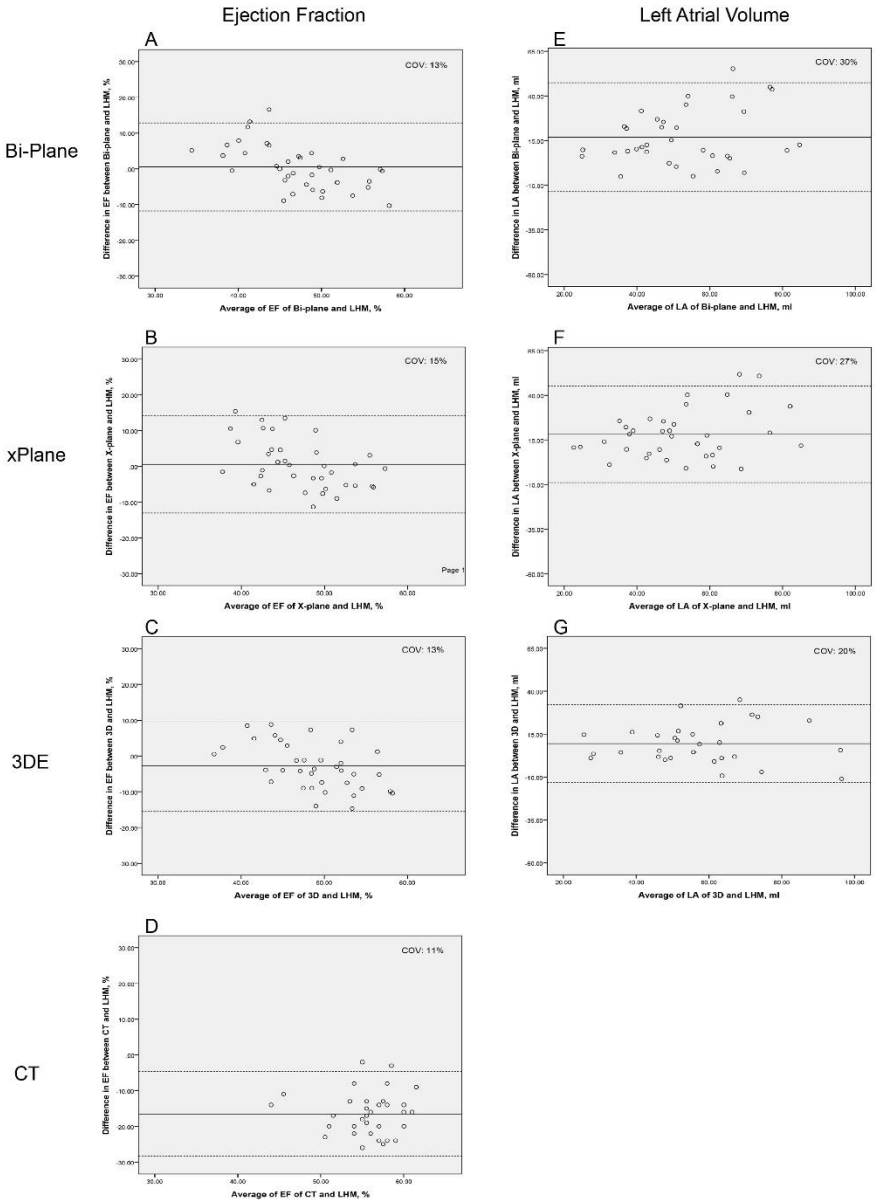

Figure 2. Left atrial volume measured by bi-plane 2DE (A). Ejection fraction measured by bi-plane 2DE (B). Left atrial volumes measured by xPlane 2DE (C). Ejection fraction measured by xPlane 2DE (D). Left atrial volumes measured by 3DE (E). Ejection fraction measured by 3DE (F). Ejection fraction measured by CT (G). The solid lines depict the mean difference of the two measurements; the dashed lines depict the limits of agreement. COV: coefficient of variation.

Inter- and intra-observer variability

LHM versus CT

Although the CT measurements correlated with the LHM for EDV and ESV (r=0.88 and r=0.81); mean differences were 42ml (23%) and 10ml (15%) respectively (p<0.001 and p=0.002). Compared to CT the LHM seems to estimate smaller LVEDV (table 2) and consequently also produces a smaller LVEF (mean difference 16%, p<0.001) as shown in figure 2d. The correlations for Bi-plane, xPlane and conventional 3D with CT for LVEF were comparable; a low correlation due to the relatively small LVEDV compared to CT.

The LHM has no intra-, or inter-observer variation as the model produced the exact same measurements when the same dataset is used (mean difference: 0±0, p<0.001). In addition, when the measurements were repeated on a second acquisition of the same patients (n=12) there was some variation but generally there was good agreement reflected by a small bias and narrow limits of agreement (table 2). The inter-observer variability for the LVEDV and LVESV on conventional 3DE was calculated (r=0.909, p<0.001 and r=0.862, p<0.001) in 14 (38%) patients.

Left atrial volume

The LAV was estimated consistently significantly larger by the LHM (table 2) compared with on both 2DE and 3DE as is shown in figure e, f and 2g. This 'overestimation' was the most evident comparing to the 2D methods and less pronounced compared with manual 3D measurements. The correlation between 2D Bi-plane and 2D xPlane measurements of the LA volume was very high (r= 0.946, p<0.001). When comparing the LAV measured on 2D with the LA volume measured on 3D, xPlane outperforms Bi-plane (r= 0.632, p<0.001 and r= 0.551, p=0.002 respectively).

Discussion

The main findings of this study can be summarized as follows:

- Automated chamber quantification is feasible in patients with bicuspid aortic valve disease in a routine clinical setting.
- The 'Heart Model' provides accurate automatic measurements of LVEDV, LVESV and LVEF and LAV compared to 2D and 3D echocardiography.
- There is no inter or intra-observer variability and very little 'inter-dataset' variability.

Left ventricular assessment

In daily clinical practice LV function is routinely estimated by bi-plane Simpson method of disk-summation; however, this requires sufficient experience and has limitations in accuracy and reproducibility, especially due to the geometric assumptions of the shape of

the ventricular or atrial cavity inherent to 2DE [37]. Moreover, the lack of a third dimension is generally considered to result in high inter-measurement variability and limits endocardial visualization, predominantly of apical lateral segments. Foreshortening of the LV often performed in an attempt to alleviate this shortcoming causes reduced accuracy and reproducibility [38]. Volumetric quantification from 3D data sets allows frame-by-frame detection of endocardial surface and does not require manual image plane positioning or geometric assumption [39] and has furthermore been shown to have a higher reproducibility than 2DE [40-42].

The bias of CT and 3D echocardiography is approximately as low as the bias of MRI when estimating LVEF [43]. Additionally, previous studies showed that for LVEF CT has the best correlation with MRI. In this light it is remarkable that in our study the correlation with CT is weak, as the EDV seems to be systematically estimated to be larger by CT than by the LHM or other echo modalities [27, 43]. This systematic underestimation may in part reflect an inter observer variability, as more of the trabeculations were included in the LV cavity for CT, entailing a larger EDV. Also, the trabeculations in this population may be more pronounced than in healthy subjects, adding to the observed difference.

Left heart chamber quantification by 3DE is hampered by several factors, mainly the ease with which these techniques can be used in daily clinical practice. A 3D learning curve is often time consuming and a degree of experience is required. Especially in the growing and aging population of patients with valvular and congenital heart disease, where patients regularly undergo extensive echocardiographic evaluation, user-independent and non-invasive follow-up imaging is much needed.

Added value of LHM

Accurate and reproducible measurements of left chamber volumes are very important in clinical practice, as they correlate with prognosis and determine treatment strategies. Moreover, in order to test new therapies, changes in these parameters must be accurate to demonstrate the efficacy of medical therapy or intervention. Our results indicate that intra-observer, inter-observer, and test-retest reproducibility of this method are very high and even exceptionally for intra-observer variability (0%) since this algorithm has no human interaction (i.e. phase selection and contouring are automatic).

We had to exclude 16 patients (30%) in total due to imaging quality limitations which is comparable to conventional 3DE in a routine clinical setting.

The main concern with 3D echocardiography is the accessibility in terms of time and skill required to produce accurate and reproducible results. The algorithm described in this study promises to improve on these points. This study demonstrates a high feasibility and

accuracy in in a population of patients with BAV disease, a population where fast, reliable, user-independent and non-invasive follow-up imaging by echocardiography is imperative.

Left Atrial Volume

Another remarkable finding is the relatively large LA volume estimated by the LHM compared to 2DE measurements. First, we suggested that this could be explained by the inclusion of the pulmonary vein orifice into the left atrial cavity by the algorithm. However, when carefully re-evaluating the LA contours, most seemed to adequately follow the left atrial walls. Another explanation could be that it is actually an underestimation of the 2DE measurements. This can partly be explained by the use of the length area formula which assumes the LA to be ellipsoid, which is evidently not always the case [37]. The correlation of LA volume measurements with 3D TTE was better. Still, inherent flaws of 2D imaging in combination with LA anatomy could contribute to this discrepancy. In the standard 2DE the LA measurements are performed on the A4C and A2C views which are focused on the true long axis of LV. The true long axis LA may not be in the same plane as the LV and therefore may appear foreshortened on the apical four chamber view. In xPlane a special focus view on the true LA long axis was acquired which better correlated with the LHM.

Limitations

The golden standard for quantitative volumetric heart chamber assessment is cardiac magnetic resonance imaging (MRI). Unfortunately, no cine cardiac images were available in this study. Therefore, no comparison with MRI could be made; consequently, we used volumetric data from CT as an additional source of validation. Additionally, we feel that EDV by 2DE has been slightly underestimated and therefore 3DE is best used as a reference modality. We were strict when it came to image quality therefore we had to exclude 12 patients from analysis. However, a sufficiently large cohort could be analyzed. Eight patients had Turner syndrome, patients affected with this genetic disorder are notoriously hard to echo, mainly because of a wide 'barrel-shaped' thorax and often a high BMI. Three of these patients were excluded due to low imaging quality.

Conclusion

Automated chamber quantification is feasible and accurate in patients with bicuspid aortic valve disease in a routine clinical setting. The 'Heart Model' provides accurate automatic measurements of LVEDV, LVESV and LVEF and LAV and has a high reproducibility between dataset and no inter or intra-observer variability. It does however seem to underestimate end-diastolic volume compared to CT.

Acknowledgements

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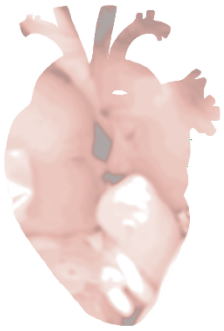
BICUSPID AORTIC VALVE AND AORTIC COARCTATION



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11

Multi-Center Experience with Endovascular Treatment of Aortic Coarctation in Adults

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Abstract

Objective The objective of this study was to evaluate outcomes of endovascular treatment of aortic coarctation in adults.

Methods Clinical data and imaging studies of 93 consecutive patients treated at nine institutions from 1999 to 2015 were reviewed. We included newly diagnosed aortic coarctation (NCO), recurrent coarctation, and aneurysmal/pseudoaneurysmal degeneration (ANE) after prior open surgical repair (OSR) of coarctation. Primary end points were morbidity and mortality. Secondary end points were stent patency and freedom from reintervention.

Results There were 54 (58%) male and 39 (42%) female patients with a mean age of 44 ± 17 years. Thirty-two patients had NCO (mean age, 48 ± 16 years) and 61 had endovascular reinterventions after prior OSR during childhood (mean, 30 ± 17 years after initial repair), including 50 patients (54%) with recurrent coarctation and 11 (12%) with ANE. Clinical presentation included asymptomatic in 31 patients (33%), difficult to control hypertension in 42 (45%), and lower extremity claudication in 20 (22%). Endovascular treatment was performed using balloon-expandable covered stents in 47 (51%) patients, stent grafts in 36 (39%) patients, balloon-expandable uncovered stents in 9 (10%) patients, and primary angioplasty in 1 (1%) patient. Mean lesion length and diameter were 64.5 ± 50.6 mm and 19.5 ± 6.7 mm, respectively. Mean systolic pressure gradient decreased from 24.0 ± 17.5 mm Hg to 4.4 ± 7.4 mm Hg after treatment ($P < .001$). Complications occurred in nine (10%) patients, including aortic dissections in three (3%) patients and intraoperative ruptures in two patients; type IA endoleak, renal embolus, spinal headache, and access site hemorrhage occurred in one patient each. The aortic dissections and ruptures were treated successfully by deploying an additional covered stent proximal to the site of dissection or rupture. Two patients died within 30 days of the index procedure. After a mean follow-up of 3.2 ± 3.1 years, nearly all patients (98%) were clinically improved and all stents were patent. Reintervention was needed in 10 (11%) patients. Freedom from reintervention at 5 years was 85%. Two additional patients died during follow-up of coarctation-related causes, including rupture of an infected graft and visceral ischemia. Patient survival at 5 years was 89%.

Conclusion Endovascular repair is effective with an acceptable safety profile in the treatment of NCO and postsurgical complications of coarctation after initial OSR. Aortic rupture is an infrequent (2%) but devastating complication with high mortality. Balloon-expandable covered stents are preferred for NCO, whereas stent grafts are used for ANE. The rate of reinterventions is acceptable, with high procedural and long-term clinical success.

Introduction

Coarctation of the aorta (CoA) is a common congenital heart defect and affects 5% to 8% of live births with congenital heart disease [1-4]. Open surgical repair (OSR) continues to be the “gold standard” for its treatment, with excellent operative and long-term outcomes[5] since the first successful operation by Crafoord in 1945 [6]. Throughout the years, advancements in surgical technique and medical therapy have allowed a dramatic improvement in patients' survival, matching the expected survival for the general population [3, 7-9]. The introduction of endovascular balloon angioplasty in 1982 and stenting 10 years later also offered a less invasive alternative in selected cases[10, 11]. Currently, given the expected longevity of this population of patients, emphasis has been placed on management of late complications from prior OSR, including recurrent coarctation (RCO), aneurysm/pseudoaneurysm formation (ANE), and valve dysfunction. In addition, a small number of patients develop symptoms and are newly diagnosed with CoA (NCO) in adulthood [12-15].

The clinical data on use of endovascular treatment of CoA in adults remain scarce. The largest experience includes 59 patients, although larger reports have shown successful results in pediatric patients [12, 16]. These studies have shown a low rate of complications and reintervention in the range of 9% to 12%. The aim of our study was to review a multi-institutional experience and outcomes in adult patients with only endovascular treatment of NCO and patients with late complications from OSR in the form of RCO and ANE.

Methods

Cohort of patients

We retrospectively reviewed the clinical data of all consecutive adult patients (older than 18 years) treated between January 1, 1999, and June 30, 2015, by angioplasty or stenting at nine participating institutions (Supplementary Table, online only). The reporting standards of the Society for Vascular Surgery were used for definition of stent graft complications after thoracic endovascular aortic repair [17]. Indications for endovascular treatment included NCO or a late complication from initial OSR, which included RCO and ANE adjacent to the initial anastomosis. Technical success was defined by successful angioplasty with or without stent placement with no evidence of significant residual stenosis (>30%), pressure gradient (>10 mm Hg), type IA endoleak, rupture, or dissection. Consent of individual patients for study inclusion was obtained, and the study received approval from each of the Institutional Review Boards including the Human Research Protection Program. The data collection method was by review of medical records and imaging when available. Data were entered into a standardized database by the staff physician or research assistant. To ensure

patients' confidentiality, no patient-identifying information was shared between participating institutions.

Data collection included patients' demographics, cardiovascular risk factors, operative reports, and radiologic studies. Baseline clinical information at the time of presentation and other comorbidities were also recorded. Preoperative computed tomography angiography (CTA), magnetic resonance angiography, angiography, and transthoracic echocardiography data were also recorded.

Definitions

NCO in the adult was defined by imaging evidence of aortic narrowing with resistant systemic hypertension, lower extremity claudication, or ischemic nephropathy. Presence of end-organ damage (e.g., ventricular dysfunction, stroke, retinopathy) was evaluated. Anatomic analysis of the NCO was obtained by cross-sectional noninvasive imaging whenever possible, with contrast-enhanced angiography used selectively. Patients with late complications after prior OSR during childhood were diagnosed during surveillance studies. ANE was defined by fusiform or saccular dilation of at least 1.5 times the diameter of the aorta adjacent proximal to the anastomosis. RCO was defined as re-narrowing of the previously repaired area causing a pressure gradient measured during angiography and signs or symptoms, such as systemic hypertension, lower extremity claudication, and ischemic nephropathy. In NCO and RCO patients, technical success after intervention was defined with a post intervention pressure gradient of <10 mm Hg and a residual stenosis of <30%.

Adjunctive procedures included carotid to subclavian artery bypasses to increment the proximal landing zone, spinal drains to ameliorate the potential for spinal cord ischemia, creation of iliac artery conduit for inadequate femoral artery access, and rapid ventricular pacing for accurate stent graft deployment.

Statistical analysis

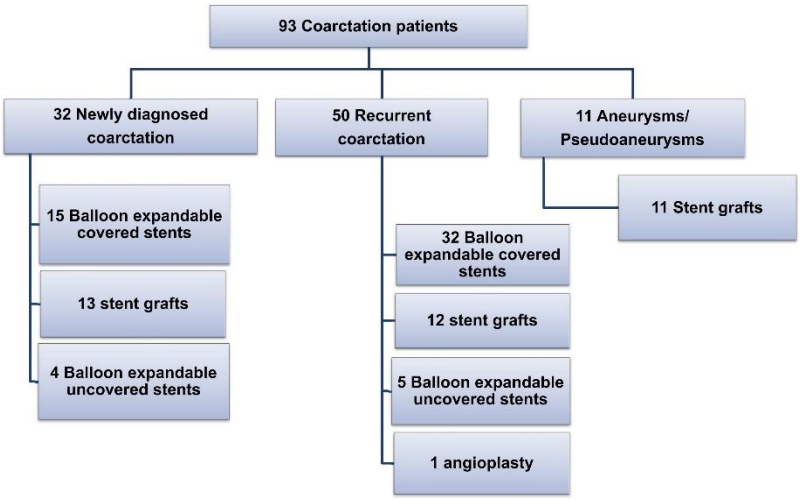
Three-way analysis of variance was used for the analysis of primary outcomes, including operative morbidity and mortality. Secondary outcomes included stent or stent graft patency and freedom from reintervention. Time-dependent outcomes (e.g., survival, patency, and reintervention) were analyzed using Kaplan-Meier survival estimates, and differences were determined using log-rank test. Data were reported using means and standard deviations for continuous variables or as frequencies for categorical variables. Differences between categorical variables in two groups were tested using the χ^2 test, and differences between continuous variables were tested using Student t-test. Analyses were performed using SAS version 9.1.3 and JMP version 8.0 (SAS Institute, Cary, NC).

Results

Patients

There were 93 patients treated with endovascular interventions, including 54 (58%) male and 39 (42%) female patients with a mean age of 44 ± 17 years (Table I). Thirty-two (34%) patients were NCO with a mean age of 48 ± 16 years. Sixty-one (66%) patients who had a prior OSR during childhood presented with postsurgical complications at a mean age of 42.7 ± 17.4 years (Fig 1). In this group, the mean and median age at the initial OSR were 14 years and 10 years, respectively. The mean time from OSR to endovascular intervention was 30 ± 17 years.

Fig 1. Etiology of coarctation repair with mode of treatment (N = 93)



Clinical presentation

At the time of presentation, 62 patients (67%) were symptomatic. There were 30 (94%) in the NCO group and 32 (64%) in the RCO group, respectively. The symptomatic patients in the NCO group included 22 (69%) with resistant hypertension and 8 (25%) with bilateral lower extremity claudication. Eleven (34%) of these patients also had echocardiographic evidence of left ventricular hypertrophy.

The patients with prior OSR included 50 (54%) in the RCO group and 11 in the ANE group. There were 32 (64%) in the RCO group who were symptomatic, and those included 20 (40%) with resistant hypertension and 12 (24%) with bilateral lower extremity claudication. Eleven (22%) of these RCO patients also had echocardiographic evidence of left ventricular hypertrophy. Patients in the ANE group were all asymptomatic (Table I).

Table 1. Patients' demographics , comorbidities, imaging studies, and anatomic measurements

	All CoA (n = 93)	NCO (n = 32)	RCO (n = 50)	ANE (n = 11)	P
Demographic information					
Age, years	44 ± 17	48 ± 16	39 ± 16	59 ± 14	NS
Male	54 (58)	17 (53)	30 (60)	8 (73)	NS
Comorbidities					
Hypertension	84 (90)	31 (97)	42 (84)	11 (100)	NS
Hypercholesterolemia	23 (25)	6 (19)	9 (18)	8 (73)	
Left ventricular hypertrophy	22 (24)	11 (34)	11 (22)	0 (0)	NS
Diabetes mellitus	4 (4)	3 (9)	1 (2)	0 (0)	NS
Symptomatic	62 (67)	30 (94)	32 (64)	0 (0)	NS
Resistant hypertension	42 (45)	22 (69)	20 (40)	0 (0)	NS
Claudication	20 (22)	8 (25)	12 (24)	0 (0)	NS
Anatomic measurement					
Diameter of narrowest area of CoA, mm	10.1 ± 4.7	9.1 ± 5.2	10.1 ± 4.4	15.0 ± 5.0	NS
Length of CoA, mm	19.1 ± 14.6	16.4 ± 9.9	17.5 ± 10.9	33.3 ± 27.6	NS

	All CoA (n = 93)	NCO (n = 32)	RCO (n = 50)	ANE (n = 11)	P
Normal aortic diameter proximal to CoA, mm	19.8 ± 5.8	21.2 ± 6.9	18.7 ± 5.1	22.1 ± 4.4	NS
Normal aortic diameter distal to CoA, mm	21.6 ± 5.9	23.5 ± 6.9	20.5 ± 5.5	23.3 ± 2.8	NS
Distance from left subclavian artery to area of CoA, mm	18.3 ± 18.2	23.7 ± 11.4	15.4 ± 15.2	16.0 ± 34.7	NS
Imaging study					
CTA only	40 (43)				
CTA and MRA	34 (37)				
MRA only	12 (13)				
Angiography	5 (5)				
Transthoracic echocardiography	2 (2)				

Table 1. ANE, Aneurysm/pseudoaneurysm formation; CoA, coarctation of the aorta; CTA, computed tomography angiography; MRA, magnetic resonance angiography; NCO, newly diagnosed aortic coarctation; NS, not significant; RCO, recurrent coarctation. Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

Endovascular treatment of ANE

All 11 (12%) patients in this group had a previous CoA repair in childhood, and the ANE was treated using stent grafts (Fig 1). Across the board, among all institutions, there was consensus in the decision to use stent grafts under aneurysmal circumstances. A wide variety of different stent grafts were used across institutions, which included brands such as Gore Medical (Flagstaff, Ariz), Cook Medical (Bloomington, Ind), and Medtronic Medical (Minneapolis, Minn) stent grafts. The normal aortic diameters proximal and distal to the area of enlargement were 22.1 ± 4.4 mm and 23.3 ± 2.8 mm. The stent graft diameter and length were 23.7 ± 6.9 mm and 81.7 ± 43.0 mm. Total adjunct procedures included two spinal drains, one iliac artery conduit, and one rapid ventricular pacing for accurate stent graft deployment. Furthermore, there were four patients with a concomitant left carotid to left subclavian artery bypass (Fig 2) and two with a right carotid to left carotid to left subclavian artery bypass (Table 2).

Fig. 2 Intraoperative angiograms of a patient undergoing pseudoaneurysm repair.

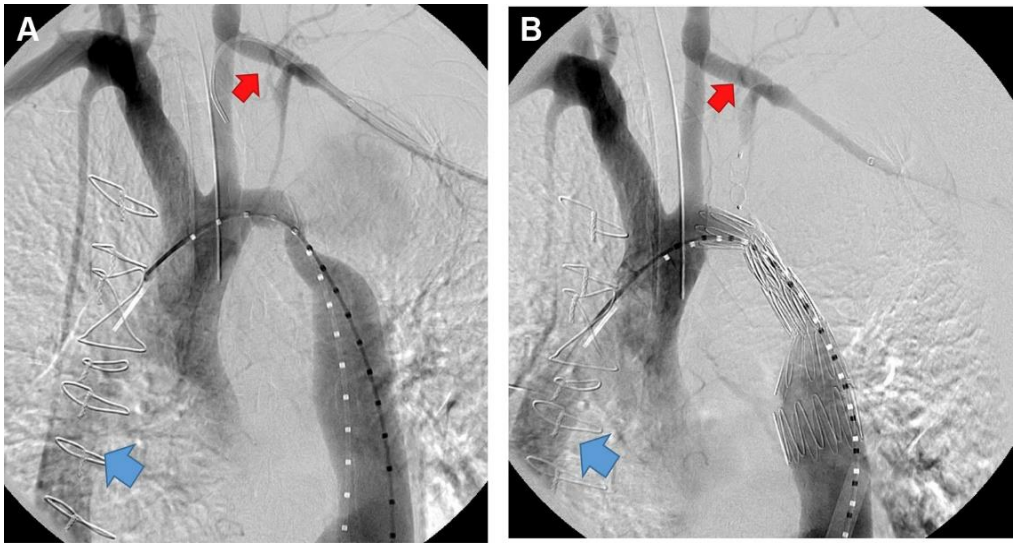


Fig 2. (A) before stent deployment (notice the left common carotid artery to left subclavian artery bypass [red arrow] and the ascending aorta to descending aorta bypass to relieve the pressure gradient [blue arrow]) and **(B)** after stent graft deployment.(Reprinted by permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Endovascular treatment of NCO and RCO

There were 82 patients in this category, 50 (53%) with RCO and 32 (34%) with NCO (Fig 1). The decision among institutions on how to treat these patients was diverse; however, there seemed to be a degree of consensus regarding the treatment of RCO patients, which was significant in the use of balloon-expandable covered stents ($p = .043$) as opposed to the treatment of patients in the NCO and ANE groups. There was no difference in the use of stent grafts and balloon-expandable bare-metal stents among NCO and RCO patients. A variety of different brands for stents were also used in this group. The balloon-expandable covered stents included the Cheatham-Platinum stent (NuMED, Hopkinton, NY) and Atrium Advanta stent (Maquet, Wayne, NJ), and the balloon-expandable uncovered stents included the Palmaz stent (Cordis, Milpitas, Calif) and the Covidien LD stent (Medtronic).

For the RCO patients, there were 32 (33%) patients treated with balloon-expandable covered stents, 12 (13%) patients treated with stent grafts, 5 (5%) treated with balloon-expandable bare-metal stents, and 1 treated with angioplasty alone. The diameter and length of the area of CoA were 10.1 ± 4.4 mm and 17.5 ± 10.9 mm, respectively. The normal aortic diameter proximal and distal to the area of CoA was 18.7 ± 5.1 mm and 20.5 ± 5.5 mm, respectively. The stent diameter and length were 18.4 ± 5.7 mm and 61.9 ± 54.8 mm, respectively. The angioplasty balloon's diameter used to treat this group was 19.0 ± 4.4 mm. The pretreatment and post-treatment pressure gradients were 23.4 ± 14.1 mm Hg and 4.6 ± 8.8 mm Hg ($p < .0001$). Adjuncts for the endovascular procedure included five inductions of hypotension(four rapid ventricular pacing and one inferior vena cava occlusion) and one spinal drain placement. Furthermore, there were three patients with a right carotid to left carotid to left subclavian artery bypass and one with a left carotid to left subclavian artery bypass (Table 2).

For the NCO patients, there were 15 patients treated with balloon-expandable covered stents, 13 patients treated with stent grafts, and 4 treated with balloon-expandable bare-metal stents. The diameter and length of the CoA were 9.1 ± 5.2 mm and 16.4 ± 9.9 mm. The normal aortic diameter proximal and distal to the area of enlargement was 21.2 ± 6.9 mm and 23.5 ± 6.9 mm, respectively. The stent graft diameter and length were 20.5 ± 7.3 mm and 65.1 ± 43.4 mm, respectively. The angioplasty balloon's diameter used to treat this group was 18.6 ± 3.7 mm. The pretreatment and post-treatment pressure gradients were 29.4 ± 19.8 mm Hg and 4.6 ± 4.7 mm Hg ($p < .0001$). Adjuncts for the procedure included 10 inductions of hypotension (7 rapid ventricular pacing, 1 inferior vena cava occlusion, 1 infusion of adenosine, and 1 proximal in-flow occlusion using a Coda balloon [Cook Medical]) and 1 iliac artery conduit. Furthermore, there was one left carotid to left subclavian artery bypass (Table 2).

Table 2. Procedure details including adjuncts (n = 93)

	All CoA (n= 93)	NCO (n = 32)	RCO (n = 50)	ANE (n = 11)	P
Stent information					
Balloon-expandable covered stent (NuMED, Maquet)	47	15	32	0	.043
Balloon-expandable bare-metal stent (Cordis, Medtronic)	9	4	5	0	NS
Stent graft (Gore Medical, Cook Medical, Medtronic Medical)	36	13	12	11	NS
Angioplasty	1	0	1	0	NA
Length, mm	64.5 ±50.6	65.1±43.4	61.9±54.8	81.7±43.0	NS
Diameter, mm	19.5 ± 6.7	20.5 ± 7.3	18.4 ± 5.7	23.7 ± 6.9	NS
Largest angioplasty balloon diameter, mm	19.6 ± 5.5	18.6 ± 3.7	19.0 ± 4.4	27.1 ± 8.5	NS
Residual stenosis, %	6.5 ± 14.8	5.8 ± 12.3	9.2 ± 18.1	–	NS
Pretreatment gradient, mm Hg	24.0 ± 17.5	29.4±19.8	23.4±14.1	–	NS
Post-treatment gradient, mm Hg	4.4 ± 7.4	4.6 ± 4.7	4.6 ± 8.8	–	NS
Adjunct					

Table 2. ANE, Aneurysm/pseudoaneurysm formation; CoA, coarctation of the aorta; NCO, newly diagnosed aortic coarctation; NA, not applicable; NS, not significant; RCO, recurrent coarctation. Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

	All CoA (n= 93)	NCO (n = 32)	RCO (n = 50)	ANE (n = 11)	P
Induction of hypotension					
Rapid ventricular pacing	12	7	4	1	
Inferior vena cava occlusion	2	1	1		
Adenosine infusion	1	1			
Proximal balloon occlusion	1	1			
Spinal drain	3		1	2	
Cervical debranching					
Right carotid to left carotid to left subclavian artery bypass	5		3	2	
Left carotid to left subclavian artery bypass	6	1	1	4	
Temporary iliac artery conduit	2	1		1	

Procedural success and complications

Technical success was achieved in 100% of the patients. There were in total nine procedure-related complications including four that required immediate attention, which included two aortic ruptures, one type IA endoleak, and one access vessel hemorrhage. One aortic rupture belonged to the NCO group and one to the RCO group (2% rupture rate). Each one of them was treated with stent grafts, and they required the deployment of an additional stent graft to seal the rupture. The type IA endoleak patient belonged to the RCO group repaired with a stent graft, which also required the deployment of an additional stent graft to successfully seal the endoleak. This patient had a left carotid to left subclavian artery bypass, and therefore circulation to the left arm was not affected by the additional

stent graft. The right common femoral artery hemorrhage occurred in a patient in the RCO group, and this was treated successfully by an open arterial repair. In addition, three aortic dissections (3% dissection rate) were recognized at the distal end of the stent, which were nonflow-limiting and therefore followed up with serial cross-sectional imaging. In the perioperative period, two additional complications were recognized, including a patient with left renal artery embolization and a second patient with a spinal headache due to cerebrospinal fluid leak who required a blood patch.

The mean length of hospitalization was 5 ± 26 days, and there were two deaths including one of the ruptured patients and one of the dissection patients. These deaths occurred on the same day of the operation and included cardiopulmonary arrest and hemorrhage.

Follow-up

Our cohort of patients was observed for a mean of 3.2 ± 3.1 years. During this time, nearly all patients (98%) demonstrated improvement of their presenting signs and symptoms. Two patients had residual claudication with long walking distances. All stents on imaging follow-up in the form of CTA were patent. Ten (11%) patients required 11 reinterventions. Five patients with RCO underwent angioplasty alone; three patients with RCO underwent angioplasty and stenting (two stent grafts and one balloon-expandable covered stent). One patient with a proximal pseudoaneurysm underwent coverage of this pseudoaneurysm with a stent graft successfully. One patient with a type IA endoleak underwent cervical debranching (left carotid artery to left subclavian artery bypass) and stent graft placement. This last patient returned after 22 months with a pseudoaneurysm at the distal anastomosis from the debranching graft and underwent a left carotid to left axillary artery bypass (Fig 3). On Kaplan-Meier survival analysis, the freedom from reintervention at 5 years was calculated to be 85% (Fig 4)

There were in total eight deaths during our follow-up period. Four patients died of unknown causes and two were directly related to the CoA repair. One patient ruptured after a stent graft infection with Coxiella burnetii. A second patient with prior mesenteric bypass developed mesenteric ischemia from a reoperation for a stenotic mesenteric bypass. Additional known causes of death included exacerbation of chronic obstructive pulmonary disease and cardiac arrest after aortic valve surgery. On Kaplan-Meier survival analysis, the overall survival at 5 years was calculated to be 89% (Fig 5).

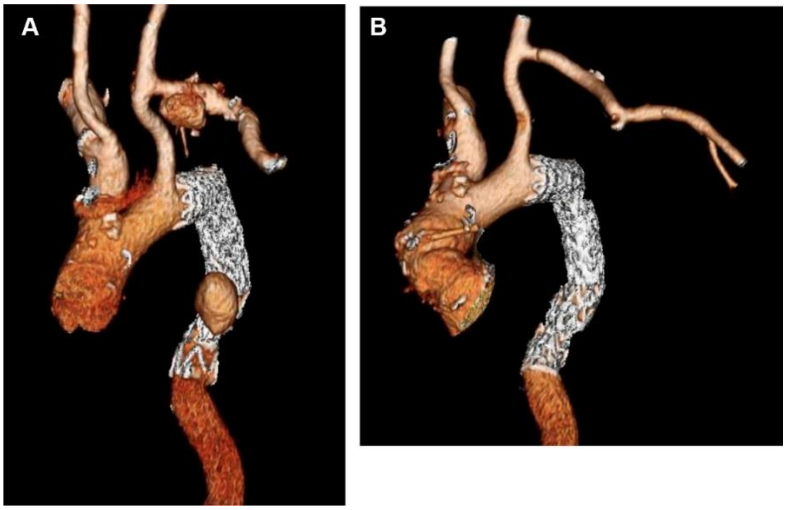


Fig 3. A) Pseudoaneurysm of the left carotid to left subclavian artery bypass before repair. B) Left carotid to left axillary artery bypass. (Reprinted by permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

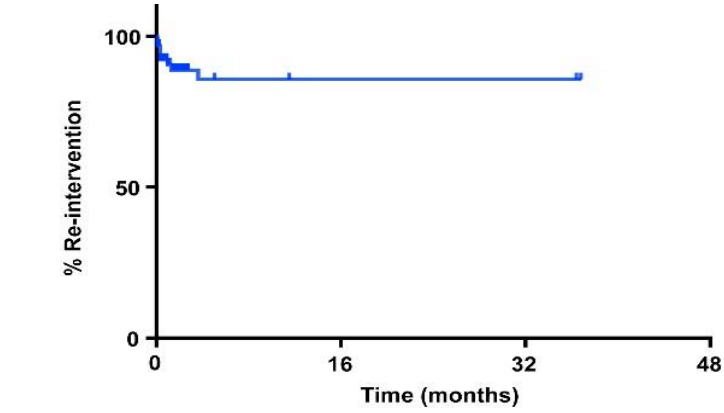


Fig 4. Kaplan-Meier estimate of freedom from reintervention in 93 patients treated for coarctation.

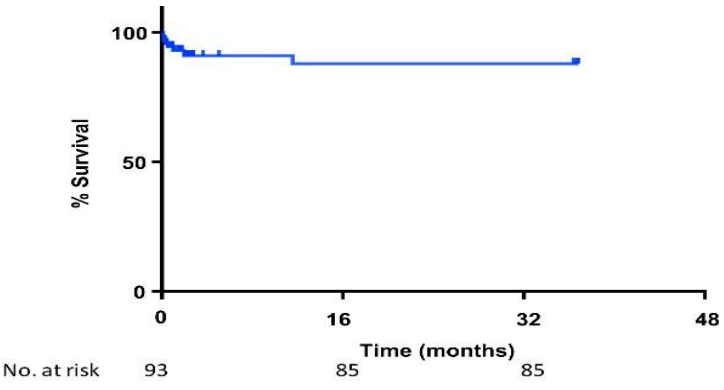


Fig 5. Kaplan-Meier estimate of survival in 93 patients treated for coarctation (note that only 2 are directly related to coarctation repair).

Discussion

CoA of the aorta is a common congenital heart defect and affects 5% to 8% of live births with congenital heart disease [1-4]. Advancements in surgical techniques and medical therapy in the past 50 years have dramatically improved survival in this population of patients [18]. These patients are now at risk for late complications associated with their OSR, which include ANE and RCO. There is also a small number of patients who become symptomatic in adulthood, NCO [12-15]. Our study addresses the importance of lifelong surveillance of all CoA patients. Our mean time from OSR to reintervention was 30 ± 17 years.

In review of other series for the treatment of coarctation including both adults and children, such as the ones by Forbes et al [16] and Roselli et al, [12] it has been reported that intravascular stent placement, although a technically demanding procedure, has an acceptable rate of complications and reinterventions. Furthermore, it has been successful at reducing the aortic gradient and relieving symptoms in these patients. Morbidity and mortality are comparable to our results at 14.3% and 0.4%, respectively (Table 2). Our Kaplan-Meier survival analysis demonstrated an 89% survival rate at 5 years.

Our review is a multicenter series that observed only adults with NCO or patients with prior coarctation repair with complications from the previous OSR in childhood. These endovascular repairs with our currently available endovascular devices seem safe and feasible with good periprocedural outcomes (5% rate of rupture and dissection), good long-term outcomes, and a freedom from reintervention of 85% at 5 years, which has also been demonstrated by Forbes et al [16]. The intermediate outcomes from the Coarctation of the Aorta Stent Trial (COAST) published by Meadows et al [19] seem encouraging for the treatment of CoA in all patients (adults and children), with excellent technical success (99%) and good midterm outcomes at 2 years. Their preferred method of treatment was the use of balloon-expandable covered stents, which provided excellent results in this population of patients. We were able to observe in our cohort that also the preferred stent was the balloon-expandable covered stent in the setting of RCO and stent grafts in ANE. Stent grafts seem logical in the treatment of ANE for obvious reasons related to the length of the repair necessary to cover the entire diseased aorta, which has also been demonstrated in other reports [12].

Table 3.Endovascular coarctation repairs reported in the literature

Author	Year	Treated n=	Treated Endovascularly n=	Cohort	Follow-up, months	Morbidity%	Reintervention %	Mortality %
Forbes et al	‘07	565	565	Adult and children	–	14.3	Not reported	0.4
Musto et al	‘08	21	21	Adults	6	0	Not reported	0
Canaud et al	‘11	7	7	Adults	44.8	0	0	0
Zipfel et al	‘11	8	8	Adults	36	0	0	12.5
Roselli et al	‘12	110	59	Adults	96	14	12 (endovascular)	0
Juszkat et al	‘13	37	6	Adults and children	292.8	14	16 (open)	0
Sohrabi et al	‘14	120	120	Adults and children	31.1	0	5 (endovascular)	0
Ostovan et al	‘14	33	33	Adults and children	–	3	0	3

Author	Year	Treated n=	Treated Endovascularly n=	Cohort	Follow-up, months	Morbidity%	Reintervention %	Mortality %
Butera et al	‘14	143	143	Adults and children	58.1	14.7	24 (endovascular)	0.7
Meadows et al	‘15	105	105	Adults and children	24	0	18 (endovascular)	0
Erben et al	‘17	93	93	Adults	38.1 ± 37.2	10	11 (endovascular)	2

The need for reintervention during the follow-up period in the COAST trial was acceptable at 8.6%, and the clinical success was also encouraging at 90% in regard to the systolic blood pressure difference between upper and lower extremities. In our cohort, the freedom from reintervention at 5 years was calculated to be 85%, which is reassuring regarding the endovascular treatment of CoA. Furthermore, the risk of death was also extremely low from both the procedural and long-term follow-up standpoint.

Although our study is unique by observing adults with coarctation, it also bears limitations. It is a retrospective review of a low-incidence surgical disease with multiple adjuncts used at the time of intervention, which limits our ability to draw firm conclusions about the most optimal surgical approach. Furthermore, techniques and interventional approaches were center specific, which reflects the center's level of comfort using specific devices. Therefore, a generalization of the best repair approach would not be accurate without larger numbers and a more diverse experience. Adjuncts to the procedure have been previously reviewed in other series, [20-27] and they seem reasonable options aiding in the process of stent graft deployment and helping avoid potential paraplegia in the postoperative period. Last, there are four deaths in our cohort that we could not account for as far as the reason of death. Therefore, we should assume that they could have been related to CoA. Overall, acceptable clinical outcomes have been demonstrated in the management of this population of complex patients, which further encourages the use of endovascular techniques for the long-term treatment of CoA.

Conclusions

NCO of the aorta and postsurgical complications of CoA are rare in adults. In the current era, endovascular treatment is effective with an acceptable safety profile. Balloon-expandable covered stents are preferred in the setting of NCO. Stent grafts are preferred for ANE. Aortic rupture is infrequent (2%) but carries a high mortality rate. The rate of reinterventions was acceptable, with high procedural and long-term clinical success.

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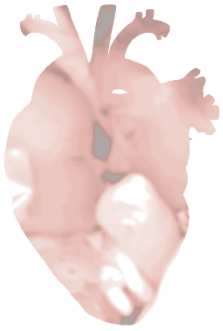
Appendix

Supplementary table. Patients included in the study from each participating institution (N = 93)

Institution	No. of patients (%)	NCO, No. (%)
1	33 (36)	8 (8)
2	30 (32)	8 (8)
3	7 (7)	5 (5)
4	7 (7)	5 (5)
5	6 (6)	1 (1)
6	3 (3)	2 (2)
7	3 (3)	2 (2)
8	2 (2)	1 (1)
9	2 (2)	0 (0)
Total	93 (100)	32 (34)

Supplementary table. NCO, Newly diagnosed aortic coarctation.

BICUSPID AORTIC VALVE AND AORTIC COARCTATION



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12

Adverse outcome of coarctation stenting in patients with Turner syndrome

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Abstract

Objectives. This study examines the outcome and procedural outcomes of percutaneous stent angioplasty for aortic coarctation in patients with Turner syndrome (TS). TS occurs in 1 in 2500 live-born females and is associated with aortic coarctation.

Methods. In this multicenter, retrospective cohort study, all patients with TS and a coarctation of the aorta, treated with percutaneous stent implantation were included. The procedural strategies were dictated by local protocols. Adverse events at short and long-term follow-up and qualitative parameters concerning the stent implantation were assessed.

Results. In the largest study to date of TS patients receiving aortic stents, a total of 19 patients from 10 centers were included. Twelve patients were treated for native and 7 for recurrent coarctation. Age at intervention was 16.9 (7-60) years (median; min-max). The coarctation diameter increased significantly from 8.0mm (2-12) pre-intervention to 15.0mm (10-19) post-intervention ($p<0.001$). Three (15.8%) adverse events occured within 30 days of the procedure, including two dissections despite the use of covered stents, one resulting in death. At long-term follow-up (6.5 years, min-max: 1 to 16), two additional deaths occured not known to be stent-related.

Conclusions. Though percutaneous treatment of aortic coarctation in TS patients is effective, it is associated with serious morbidity and mortality. These risks suggest that alternative treatment options should be carefully weighed against percutaneous stenting strategies.

Introduction

Aortic coarctation (CoA) is a congenital narrowing of the aorta and is usually located in the juxta-ductal position (1-3). The incidence is approximately 4 per 10,000 live births and constitutes 5-8% of all congenital heart disease (CHD) (4). It is more common in males and usually occurs sporadically (5, 6). If untreated, most patients die before 50 years of age from coronary artery disease, stroke or intracranial hemorrhage caused by arterial hypertension (2, 3, 7). The first successful surgical correction was performed in 1945 (8). Surgical repair of CoA is still performed today; however, percutaneous treatment has become a valid alternative with good gradient relief and a low complication rate both for native and recurrent CoA (9).

Turner syndrome (TS) is characterized by a partly missing X-chromosome. It is associated with aortic pathology in approximately half of the patients, including bicuspid aortic valve (BAV; ~30%), elongation of the transverse aortic arch (49%) and CoA (~17%)(1), and the risk of aortic dissection is well recognized (10). More recent studies describe the presence of histological abnormalities of the aortic wall in some TS patients, including cystic medial wall necrosis, changes in vascular smooth muscle cells and elastin or collagen fibres, occurring seemingly independently from any haemodynamic changes (11-14). These changes, possibly inherent to TS, might increase aortic wall fragility and contribute to the increased risk of dissection (10). Because of these vessel wall abnormalities, percutaneous treatment of CoA in TS patients may be associated with a higher risk of complications, especially aortic dissection and rupture. Data on outcome and procedural results of CoA stenting in TS patients is based on small case series or case reports, and the results are contradictory.

In this report, we describe the outcome and procedural results of percutaneous intervention for CoA in patients with TS and review the current literature on this topic.

Methods

Tertiary centers specializing in care for patients with CHD were asked to contribute patients to this study. The ethics committees and/or institutional review boards of the participating centers gave permission to access and use patient data. In this retrospective study, all TS patients with a history of percutaneous intervention for CoA from the participating centers were included. Anonymized patient data were entered into a digital format and included baseline patient characteristics, medical history, procedure –details, results and complications. Pre-procedural parameters included: peak and mean pressure gradients, coarctation diameter, aortic diameters proximal and distal to the CoA and, when available, aortic diameter at the level of the diaphragm as measured on the angiogram. Post-procedural results included: peak and mean pressure gradients at the end of the intervention and the diameter of the treated coarctation segment. Hypertension was

defined as a blood pressure >140/90 mmHg or treatment with anti-hypertensive drugs. Short-term complications were defined as complications within 30 days from the procedure. All adverse cardiac events noted in the patient history during or after the intervention were analyzed. We subdivided the adverse events according to two levels of severity (15): (1) adverse event (AE): any complication causing no harm; resulting in clinically important transient impairment of a body function or transient damage to a body structure, requiring more than minor intervention to prevent permanent impairment of a body function or damage to a body structure. (2) Serious adverse event (SAE): any complication which results in death, is life-threatening, requires hospitalization or causes prolongation of existing hospitalization, resulting in permanent impairment of a bodily function or permanent damage to a body structure and/or requiring major intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

Statistics

The IBM SPSS® statistics 21.0 software was used to analyze the data. Descriptive characteristics are presented as median and minimum and maximum values due to small sample size and skewed data for some parameters. We tested for normality using the Shapiro-Wilk test. The chi-squared test or Fischer's exact test were used to compare between groups, and the students T-test was used to compare means. Missing values are reported in the results tables and were not taken into account in analyses. A two-sided p-value below 0.05 was considered significant.

Results

Ten centers contributed 19 patients with TS and percutaneous treatment of CoA. None of these patients have been previously reported in literature. Relevant demographics and medical history are presented in Table 1. Median age at the time of percutaneous intervention was 16.9 (min-max: 7-60) years, and the median follow-up duration was approximately 6 years (min-max: 1-16). Ten patients (53%) were under 18 years of age at the time of the procedure. The karyotype of 12 patients was known; 10 had a full monosomy X (45,X: 83%), and 2 had an isochromosome. BAV was present in 11 patients (58%), and often occurred in association with other types of CHD (see Table 1). Eigth patients (42%) who had previous surgical repair of CoA (median age 0.36 years, 1 day-27 years), all done using end-to-end anastomosis.

Table 1: Baseline characteristics

Patient	Karyotype	Age at intervention (years)	Length (cm)	Weight (kg)	SBP/DBP (mmHg)	Hypertension	Anti-Hypertensive Medication	Associated heart disease
1	–	47	138	49.0	165/49	+	β-b	▪
2	45,X/46,XX	32	151	59.0	150/104	+	β-b, AI, diuretic	BAV, PLSVC
3	–	21	153	57.0	100/60	+	β-b	BAV, VSD
4	–	60	145	37.0	111/78	+	ARB, β-b	BAV, PAPVR with severe PH, chronic AF, PE
5	45,X	13	132	42.3	140/80	+	none	BAV
6	45,X	10	127	22.0	112/69	+	+†	BAV
7	45,X	7	116	22.0	80/49	+	+†	BAV
8	45,X	17	161	68.5	120/62	+	+†	▪
9	45,X	48	150	55.0	145/78	+	none	PLSVC draining into LA
10	45,X	12	139	36.0	160/70	+	none	▪
11	45,X	13	160	45.4	111/67	▪	None	BAV, Dextrocardia
12	45,X	37	147	60.0	123/62	+	+†	Sub aortic membrane
13	45,X	35	140	58.2	150/90	+	None	BAV, PAPVR: RUPV into SVC
14	46,Xi(X)	12	136	31.1	111/73	+	AI	BAV
15	–	7	113	22.0	89/61	+	+†	Aberrant subclavian artery
16	–	12	130	40.0	–	+	AI	LA enlargement. Bilateral SVC with left SVC to CS.
17	46 Xi (Xq)	12	132	33.7	95/56	▪	none	BAV
18	–	48	140	46.0	88/58	▪	β-b, AI, Diuretic,	BAV, PAPVR, restrictive cardiomyopathy
19	45,X	29	138	84.7	128/68	+	β-b	PAPVR
Median		16.9	139	45.4	112/65	▪		
Min-max		7-60	113-161	22-84.7	80-165/49-104	84%*		

Table 2: Intervention characteristics

		Coarctation Diameter		Gradient Mean (peak)		Aortic diameter (pre-procedure)		Stent			Adverse events		Most Recent follow-up imaging		
Pt	Indication	Pre mm	Post mm	pre mmHg	Post mmHg	prox mm	distal mm	Type	Covered	Length mm	Early <30d	Late	Type	Date	Findings
1	Recurrent	11	16	14 (34)	– (4)	16	25	Numed CCPS	+	–	Dissection/ Death *	▪	CT	12-2009	Aortic rupture
2	Native	12	17	– (25)	–	17	22	Numed CCPS	+	45	▪	▪	MR	09-2015	LV dilatation
3	Recurrent	12	17	– (35)	–	35	34	Numed CCPS	+	45	▪	▪	CT	10-2004	none
4	Native	9	19	5 (15)	0 (0)	20	16	Gore TAA CTAG (2)	+	50(2 x)	▪	death	-	-	-
5	Recurrent	6	10	24	0 (0)	12	11	Numed CCPS	+	28	▪	▪	-	-	-
6	Recurrent	6	13	22	0 (0)	11	13	Palmaz 308	o	30	▪	▪	-	-	-
7	Native	5	–	12	0 (0)	11	14	Advanta Atrium V12	+	26	▪	Re-CoA	Re-Cath	07-2014	Gradient 2mmHg
8	Native	8	–	41	0 (0)	15	16	MaxLD 26 EV3	o	26	▪	▪	-	-	-
9	Native	11	–	20 (45)	0 (9)	21	24	Numed CCPS	+	34	Dissection	▪	CT	2009	dissection
10	Recurrent	8	12	– (30)	0 (3)	13	17	Numed CCPS	+	39	▪	▪	-	-	-

11	Native	–	–	3 (10)	– (0)	–	–	–	o	–	▪	▪	MR	01-2014	RA dilatation
12	Residual	6	14	10 (29)	0 (0)	14	14	–	o	34	▪	▪	CT	11-2015	residual narrowing
13	Native	–	–	8 (19)	–	–	–	Numed CCPS	+	30	▪	death	-	-	-
14	Native	2	11	9 (22)	0 (0)	13	–	Numed CCPS	+	39	▪	▪	Echo + CT	09-2015	BAV + Ao dil
15	Recurrent	–	–	–	–	–	–	–	o	–	▪	▪	-	-	-
16	Native	–	–	– (24)	– (20)	–	16	–	o	–	▪	▪	MR	10-2015	none
17	Native	11	12	9 (19)	0 (0)	16	20	Advanta Atrium V12	+	29	▪	Re-CoA▪	MR	01-2013	none
18	Native	8	16	6 (10)	0 (0)	20	19	Numed CCPS	+	34	Death **	▪	-	-	-
19	Native	9	18	– (15)	0 (0)	18	25	Numed CCPS	+	34	▪	▪	CT	11-2014	none
Median		8	14	10 (23)	0 (0)	16	16		68%	34	16%	24%	n=11	3†	
Min-max		2-12	10-19	5-41 (10-45)	0 (0-20)	11-35	11-34			26-100				0-16	

Table 1. +: Present, ▪: Absent, –: no data, *percentage with hypertension, †: no details available, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BAV: Bicuspid Aortic Valve, PSLVC: Persistent Left Superior Vena Cava, VSD: Ventricular Septal Defect, PAPVR: Partial Anomalous Pulmonary Venous Return, PH: Pulmonary Hypertension, a-fib: atrial fibrillation, LA: Left Atrium, RUPV: Right Upper Pulmonary Vein, CS: Coronary Sinus, PE: pericardial effusion β-b: Beta-blocker ARB: angiotensin receptor blocker, AI: ACE-inhibitor

Table 2: – no data, ▪ Not Applicable, CoA: coarctation of the Aorta, Native: no previous intervention, recurrent: previous intervention, residual: stented but re-coarctation, * dissection of the descending aorta (figure 1), ** heart failure 15 days after procedure, † median years since procedure.

Outcome – procedural and short-term

No procedural complications were observed, however five of the 19 patients had a serious or somewhat serious adverse event during follow-up (26%). Three occurred within 30 days of the procedure. All three (table 2: 1, 9 and 18) had been treated with a covered stent. Two patients (table 2: 1 and 9) had a dissection of the descending aorta, these patients also had high gradients and systolic blood pressures. "One dissection with entry point just distal of the stent, included the descending and abdominal aorta until the superior mesenteric artery and was treated conservatively with spontaneous resolution after a few days (table 2: 9).

The other dissection (table 2: 1) was fatal, and the patient died shortly after stenting of a residual coarctation from end-to-end anastomosis performed eighteen years earlier. The procedure was uneventful without detection of a dissection or rupture by angiography immediately post-stent placement. The patient was admitted to the cardiology ward when she reported pain in the back several hours after the procedure. Her hemoglobin concentration was low but stable (106.3 g/L or *6.6 mmol/*), but the back pain worsened, followed by hypotension. A computed tomography scan showed an active massive hemorrhage in the mediastinum, medio-caudal of the stent (Figure 1). Before surgery could be performed, the patient suffered a cardiac arrest and could not be resuscitated.

Another patient (table 2: 18), diagnosed with restrictive cardiomyopathy, in addition to the coarctation, presented with signs of heart failure 15 days after the stent procedure. She was treated with diuretic and inotropic agents. On the 24th day after the stent placement, she developed cardiogenic shock with refractory hypotension. She went into cardiac arrest with unsuccessful resuscitation. As no autopsy was performed, the exact cause of death could not be determined, and, therefore, a direct causal relationship to the stenting procedure is not certain. While no procedural deaths were observed, the 30-day mortality was 11%.

Outcome – Long-term

In 11 of the 19 patients (58%) follow-up imaging had been performed. In none of these patients signs of subclinical stent related pathology was detected (table 2). However, in patient 2 LV dilatation has been observed.Two deaths (12%) occurred >30 days after stent implantation (table 2: 4 and 13). One patient died at 61 years of age one year after stent implantation, due to progressive heart failure, without a clear cause. The second patient died at 39 years of age 4 years after stent implantation. At autopsy, a large thrombus was discovered near the mitral valve, suggesting that this death likely was not related to the stent procedure. Two other patients (table 2: 7 and 17) developed a significant re-coarctation after stent implantation, requiring re-intervention.

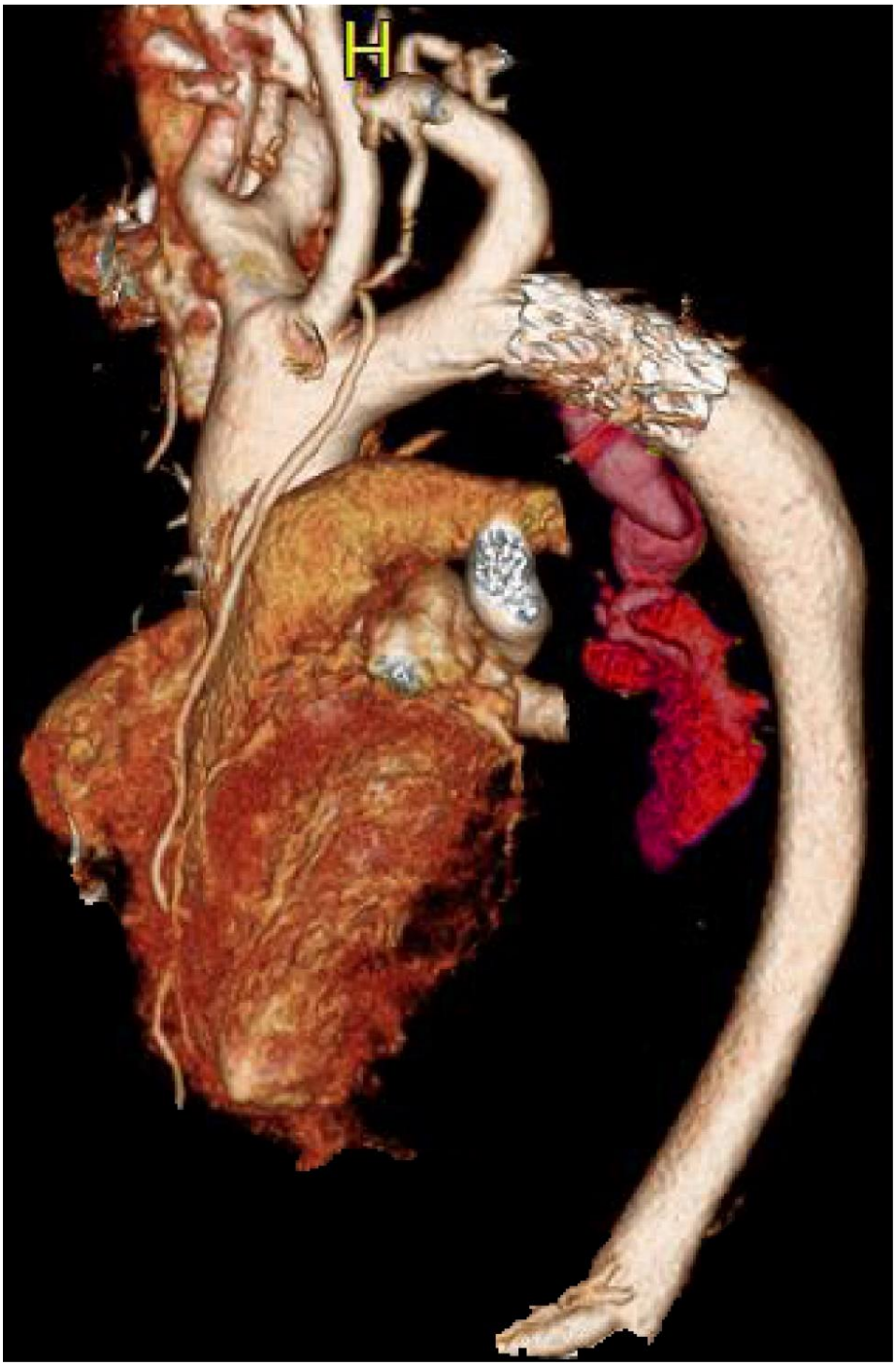

Fig. 1. Aortic rupture (in patient 1). A computed tomography scan showing an active massive hemorrhage in the mediastinum, medio-caudal of the stent site. Adobe Photoshop CS6 was used to correct color for clarity purposes.

Discussion

The complications from stenting in the coarctation population is low (~1% AE) (17).In studies conducted in non-TS populations major complications for stenting of CoA ranged from 0 to 7% (15, 18, 19). In our cohort of TS patients however, we found a high risk of adverse events; two of the three patients had a proven aortic dissection, fatal in one of them. In the third patient vascular injury as a cause of death was implied, but could not be proven.. This study illustrates that non-stent related fatal cardiovascular events may occur during long term follow-up. However, spontaneous dissection as may occur in TS patients, was not seen in this cohort. These long-term results have to be interpreted with caution as TS patients have a high cardiovascular risk profile. In this population hypertension and diabetes are more prevalent, which may result in a higher risk of dissection and heart failure.

Etiology

A possible mechanism responsible for the apparently high risk of arterial complications in the TS population is not easy to provide, but some processes in TS, like cystic medial necrosis, are similar to those seen in thoracic aortic aneurysm and might provide a basis for understanding the observed aortic wall fragility.". Changes have been described in the collagen fiber composition and intima-media with cystic medial degeneration of the aorta (20, 21). TGF-β signaling may also play a role, as its disruption is observed in other genetic disorders that result in aneurysm formation and increased risk for dissection and rupture (22). Aortic frailty may also occur when molecules such as biglycan and vascular endothelial growth factor (VEGF) are decreased (23, 24), as shown in non-TS aortic aneurysmal tissue. These factors were not assessed in this retrospective study, but, in future efforts, histological analyses of aortic tissue might prove valuable. In this series of TS patients a high risk of complications was observed, which could be due to an inherent aortopathy in TS similar to that in Marfan syndrome (MFS). In MFS, because of this associated elastopathy, thoracic endovascular aortic repair (TEVAR) is contraindicated (25).

Procedural results

The two post-procedural aortic dissections occurred in patients who were treated with covered stents, and these events illustrate that the use of covered stents does not prevent the occurrence of dissection. In addition, the two patients who developed dissections had the highest gradients and also had high blood pressures. Other studies have reported hypertension as a risk factor for complications in Turner patients. (26)

One of the patients in the series (patient 4), did not receive a traditional balloon expandable stent, e.g. covered or uncovered CP or Advanta V12 stents, instead received a self-expanding vascular stent graft, followed by balloon angioplasty of the now completely

covered coarctation segment. In TS patients it may be safer to use self-expanding nitinol-based stent grafts which are designed to treat aortic aneurysms, as they cover a larger area of tissue around the coarctation. The left subclavian artery, however, limits the degree to which the stent can be extended proximally in the arch.

Furthermore, the positive effect of covered stents is still under discussion. In at least one of the cases with a dissection, the entry point was known, and it was at the distal edge of the stent. If a mechanism of aortic injury is related to the ends of the stents, a covered stent may not be effective at preventing the dissection or leakage. Conceptually positioning of a longer endovascular stent graft and a subsequent expansion of a stent within the lumen of the graft may provide a better alternative. Still, these results in this study are in contrast with what is suggested in literature in for example the COAST II trial, where a possible advantage for the use of covered stents compared to bare metal stents is suggested when examining aortic wall injury (15). However no protective effect was shown and especially when looking at aneurysm formation long term results are needed (15).

Literature Review

Our literature search yielded one case series and four case reports regarding stenting in TS patients. Zanjani et al. describe a series of 10 TS patients with CoA treated with stent implantation, of which 7 patients have been treated with a bare metal stent (BMS) versus 3 with a covered stent (27). There were no dissections or deaths within a follow-up of 2.5 years, however, 2 (20%) late aneurysms at the coarctation site occurred. Two case reports describe uncomplicated stent implantations in patients with TS (28, 29), while two other case reports describe dissections of the aorta (14, 30) (Table 3). The two late deaths in our study could have had a cause not directly related to the stent implantation. Excluding these two cases, the results of the pooled studies show dissection and/or death occurring in 5 out of a total of 35 cases (14%). However, Including case-reports may overestimate incidence of for example dissection. Although the complication rate is high, the stent angioplasty itself is effective. We found a significant increase in coarctation diameter and a clear reduction in the gradient over the stented segment in all patients. Our results are in that aspect comparable with published results for the non-TS population (31). TS patients with severe CoA should be counselled not only about the advantages of this treatment, but also about the risk of dissection and death with this treatment. Whether surgical treatment for CoA in TS is a safer alternative remains unclear. Two studies suggest that surgical repair by end-to-end anastomosis also shows an increased risk, especially of perioperative hemorrhage (32, 33). These studies, however, are dated and probably not valid for comparison. Although conservative medical management is an option, long-standing ascending aortic and upper extremity hypertension in these patients with known aortopathy is not necessarily a lower-risk option. Further study is needed to understand the optimal management of this high-risk group of patients.

Table 3. Literature overview

Author	Ref.	Year	procedures	Serious AE's	Somewhat serious AE's	Resulted in death	Mean age (years)	Mean follow-up (months)	Monosomy %
Zanjani et al.	[1]	2010	10	0	2	0	12 (9-24)	30.5	70
Kataoka et al.	[2]	2006	2	0	0	0	14.5	42	–
Thanopoulos et al.	[3]	2000	2	0	0	0	9.5	30.5	–
Fejzic and van Oort	[4]	2005	1	1 (type B diss.)	0	1	19	0.25	–
Lin et al.	[5]	1986	1	1 (type A diss.)	0	0	8	42	100
Present study		2015	19	3 (2 type B diss.)	1	2	17	72	77
Total			35	5 (14%)	3 (9%)	3 (9%)			

Table 3. Data are presented as n=, mean ± SD or %, –: no data

1 Zanjani KS, Thanopoulos BD, Peirone A, Alday L, Giannakoulas G. Usefulness of stenting in aortic coarctation in patients with the Turner syndrome. Am J Cardiol. 2010;106(9):1327-31.

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Limitations

This study is limited by its sample size: TS is a relatively uncommon disorder, and in these women stenting procedures are not frequently performed. It is also limited by its retrospective nature without consistent clinical follow-up and therefore late aneurysms, dissection, or other complications may have been missed. The long-term results and causes of death are to be interpreted with care, especially in the cases where no autopsy could be done. Patient selection bias cannot be excluded, as only patients from tertiary care centers with expertise in CoA stenting were included in this study; hospitals with less stenting experience may experience an even higher complication rate.

Conclusions

In this series of TS patients, stent treatment for coarctation of the aorta was effective but was associated with dissection or death in several cases. The advantages and disadvantages of conservative medical management, end-to-end anastomosis surgery, and percutaneous stent treatment should be separately considered and discussed with the individual patient. Additional studies are needed to determine the best treatment strategy for TS patients with CoA and to determine the etiology of the histologic abnormality.

To our knowledge, we present the largest study of CoA stenting in TS patients to date. Our study reinforces the concern of potential aortic dissection with stenting in TS patients which appears not to be prevented by the use of covered stents.

Acknowledgements

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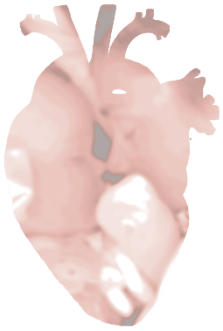
BICUSPID AORTIC VALVE AND AORTIC COARCTATION



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13

Differences in Aortopathy in Patients with a Bicuspid Aortic Valve with or without Aortic Coarctation

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Abstract

Objectives. The combination of aortic coarctation (CoA) and bicuspid aortic valve (BAV) is assumed to be associated with a higher risk of ascending aortic dilatation and type A dissection, and current European Society of Cardiology (ESC) guidelines advise therefore to operate at a lower threshold in the presence of CoA. The aim of our study is to evaluate whether the coexistence of CoA in BAV patients is indeed associated with a higher risk of ascending aortic events (AAE).

Methods. In a retrospective study, all adult BAV patients visiting the outpatient clinic of our tertiary care center between February 2003 and February 2019 were included. The primary end point was an ascending aortic event (AAE) defined as ascending aortic dissection/rupture or preventive surgery. The secondary end points were aortic dilatation and aortic growth.

Results. In total, 499 BAV patients (43.7% female, age 40.3 ± 15.7 years) were included, of which 121 (24%) had a history of CoA (cBAV). An aortic event occurred in 38 (7.6%) patients at a mean age of 49.0 ± 13.6 years. In the isolated BAV group (iBAV), significantly more AAE occurred, but this was mainly driven by aortic valve dysfunction as indication for aortic surgery. There was no significant difference in the occurrence of dissection or severely dilated ascending aorta (>50mm) between the iBAV and cBAV patients ($p = 0.56$). The aortic diameter was significantly smaller in the cBAV group (30.3 ± 6.9 mm versus 35.7 ± 7.6 mm; $p < 0.001$). The median aortic diameter increase was 0.23 (interquartile range (IQR): 0.0-0.67) mm/year and was not significantly different between both groups ($p = 0.74$).

Conclusions. Coexistence of CoA in BAV patients was not associated with a higher risk of aortic dissection, preventive aortic surgery, aortic dilatation, or more rapid aorta growth. This study suggests that CoA is not a risk factor in BAV patients, and the advice to operate at lower diameter should be reevaluated.

Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect with a prevalence of 0.5–1.3% [1]. In about half of all BAV patients, ascending aortic dilation develops, predisposing for life-threatening complications such as aortic dissection [2]. BAV can occur isolated (iBAV), but also in combination with additional heart defects or in the context of a syndrome.Depending on age groups studied, the prevalence of aortic coarctation (CoA) in BAV patients varies between 22% and 36% and is increased in younger age groups [2,3,4,5]. Whether there is a difference in prevalence of aortopathy between BAV patients with (cBAV) or without a CoA remains unknown.After CoA correction, many patients suffer from hypertension, which is a known risk factor for aortic dissection and higher mortality, especially in BAV patients [4,6]. In a pediatric cohort of BAV patients, CoA was associated with smaller ascending aortic diameters, while in adults, contradicting studies about CoA in BAV patients have been published, with some showing a higher risk of ascending aortic events (AAE) when CoA was present in these patients, while others found no relation [4,7,8].The aortopathy in BAV patients is generally assumed and feared, and although the incidence of type A aortic dissections is low, it is clearly higher compared with the general population with BAV patients having an estimated 6 times higher risk [9]. Although only a few studies have investigated the impact of CoA in BAV patients on the incidence of aortopathy, current ESC guidelines on aorta pathology advise to consider preventive aortic surgery at a lower aortic diameter in BAV patients when a history of CoA is present [10].

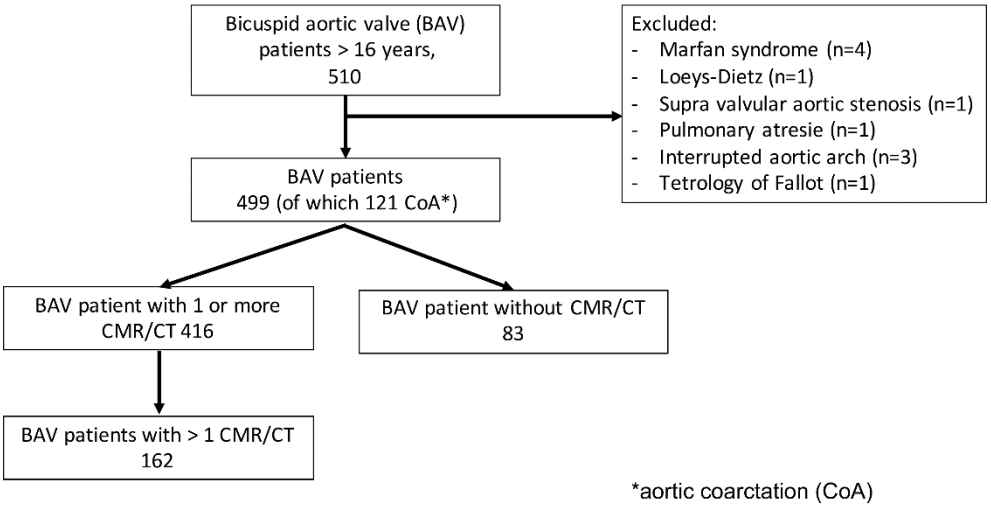
The aim of this study is to investigate whether the coexistence of CoA in BAV patients is associated with ascending aortic events (AAE), aortic dilatation and aortic diameter increase.

Method

Medical ethical committee region Arnhem–Nijmegen approved this study under file number CMO: 2017-3599. In this retrospective study, we included all BAV patients who visited the adult outpatient clinic between February 2003 and February 2019. Exclusion criteria were presence of an associated complex congenital heart disease (e.g., tetralogy of Fallot) or a hereditary thoracic aorta disease (e.g., Marfan syndrome) (Flow diagram Figure 1) and incomplete data. Hemodynamic unimportant small defects or corrected defects were not excluded (e.g., ventricular septal defect, atrial septal defect, persisting left cava vein, persisting ductus arteriosus, subaortic membrane, abnormal pulmonary venous return). BAV presence was diagnosed on echocardiography or on cardiac magnetic resonance imaging (CMR) or by the surgeon during aortic valve surgery. Patients with a hemodynamic important CoA (gradient >20 mmHg across the isthmus stenosis invasively measured or hypertension in presence of a >50% aortic narrowing compared with aortic

diameter at the diagram) were assigned to the BAV with CoA group (cBAV). All patients with a hemodynamic important CoA underwent an intervention (surgery or percutaneous). Patients without CoA were assigned to the isolated BAV group (iBAV).

Figure 1: Inclusion flow chart



Following our standard protocol, during each visit all patients underwent an electric cardiography (ECG) and echocardiography. Cardiologists with expertise in congenital heart disease and echocardiography evaluated the echocardiographic images. Quantification of valve dysfunction severity was done according to current guidelines [11,12]. Moderate to severe stenosis or regurgitation was defined as significant aortic valve dysfunction.

BAV morphology was classified following the Sievers classification [13]. Frequency of follow-up was determined depending on the severity of valve dysfunction and other relevant comorbidities. In most cases, this was either annually or biannually. Hypertension was defined as a blood pressure above 140/90 mmHg on several measurements, all these patients were treated with antihypertensive medication [14].

The primary end point of this study was an ascending aortic event (AAE), defined as the occurrence of acute dissection of the ascending aorta or the occurrence of (preventive) ascending aortic surgery. The secondary end points were aortic diameter on CMR or CT at age >16 years of age and aortic growth during follow-up using CMR or CT during adulthood.

Advanced aortic imaging

Aortic diameters were measured on advanced imaging by experienced radiologists. Cardiac Magnetic Resonance Imaging (CMR) was preferably used and in case CMR was not possible or contra-indicated, an ECG-triggered CT scan was performed. The ascending aorta was

measured in the axial plane, during diastolic phase. In both modalities, the inner edge to inner edge method was used to measure the ascending aortic diameter at the height of the right pulmonary branch [15]. Ascending aortic diameter was defined as dilated when the ascending aorta >40 mm or aortic size index >20 mm/m2 [10]. Frequency of advanced imaging was based on indication, but performed at least once during the first visit to the adult outpatient clinic and typically repeated every 5 years.

The aortic diameter change (in mm) between two CMR/CT ascending aortic measurements was divided by the time between the two measurements, which had to be at least one year apart. For every successive scan, the aortic diameter change was calculated. This implies that multiple "means" could be present in one patient, in that case the means were added up and divided by the number of means for that specific patient, resulting in one mean aortic diameter change per patient.

Statistical analysis:

Statistical analysis was performed using Statistical package for social sciences, version 25 for Windows (SPSS, Chicago, IL, USA). Results are expressed as mean ± standard deviation or as median 25% and 75% interquartile range (IQR) if the distribution was skewed. A p-value <0.05 was defined to be statistically significant. The independent samples T-test was used to compare means between groups. In case of a skewed distribution, the Mann–Whitney U test was used. To evaluate a significant difference between proportions, a chi-square test was used. Univariate and multivariate logistic regression was used to correct for important determinants of AAE, for example, age, aortic valve dysfunction, and hypertension.

Results

Baseline

A total of 499 BAV patients were identified, of which 121 (24.2%) were diagnosed to have CoA (cBAV). Baseline characteristics of all included BAV patients are shown in Table 1.

Aortic events

The median age of coarctation repair was 10 month (IQR: 2 months; 7.9 years), of which 107 had a surgical repair. Balloon angioplasty of descending aorta was performed in 14 patients, at a median age of 13.5 (IQR: 3.8; 31.5) years, and a stent was implanted in 12 of them.

The prevalence of aortic valve regurgitation was significant higher in the iBAV group (p = 0.006). There was no age difference between patients with (41.6 ± 16.2 years) or without (40.4 ± 15.7 years) a significant aortic valve regurgitation in total group or in the iBAV group

(42.6 ± 16.1 years in no significant versus 44.0 ± 16.9 years in significant aortic valve regurgitation).

presents the percentage of each age group with an event for the iBAV and CoA-group. Only age was related to the occurrence of an aortic event and was still significant after correction for CoA. In the multivariate analysis CoA was not associated with aortic events. Due to the low event rate a limited number of variables could be tested.

Table 1: baseline characteristics of all included patients

	All BAV patients (n =499)	Isolated BAV (n=378)	BAV + Aortic coarctation (n=121)	p-value
Female (%)	43.7	44.2	42.1	0.695
Age at end of study (years)	40.3±15.7	42.5±16.1	33.6±12.2	<0.001
Weight (kg)	72.0 (62.0-82.0)	72.0 (62.0-82.0)	71 (60.0-81.3)	0.519
Height (cm)	172.8±12	172.7±12.6	173.5±11.4	0.482
Turner (%)	14.9	16.9	5.0	0.001
Hypertension (%)	19.8	28.9	28.9	0.005
Smoking (%)	10.7	10.4	11.6	0.713
Diabetes (%)	2.0	1.9	2.5	0.683
Hypercholesterolemia (%)	7.6	9.4	3.3	0.031
Other congenital defect* (%)	22.9	17.2	38.8	<0.001
Aortic sinus of Valsalva (mm)**	33.4±8.9	33.8±6.2	32.3±5.8	0.026
Ascending aorta (mm)**	34.4±7.2	35.3±7.2	31.6±6.5	<0.001
Aortic regurgitation moderate/severe (%)	17.9	20.7	9.2	0.006
Aortic valve stenosis moderate/severe (%)	5.7	5.7	5.5	0.924

Table 1. * persisting left cava vein (n=4), persisting ductus arteriosus (n=16), ventricular septal defect (n=23), atrial septal defect (n=10), subaortic membrane (n=6), abnormal pulmonary venous return (n=4).**echocardiographic measurement at first visit adult outpatient clinic

Events Analysis

Table 2 shows the ascending aortic events (AAE) for the total group and iBAV and cBAV groups separately. The mean age at AAE was not significantly different between both groups. Aortic dissection occurred in two iBAV patients and in one cBAV patient, who was also a Turner patient; none of these three patients survived. No aortic ruptures occurred. There was a significant difference in AAE between iBAV group and cBAV group (p = 0.016). This was mainly driven by aortic valve dysfunction as primary indication for aortic valve replacement in combination with ascending aorta replacement. When patients with aortic

valve dysfunction as primary indication were excluded, there was no significant difference in prevalence of AAE between iBAV and cBAV groups (p = 0.743). There was no significant difference (p = 0.711) in the prevalence of high-risk BAV patients (ascending aortic diameter >55 mm and ascending aortic dissection).

Table 2: characteristics of patients with an aortic event

	All	iBAV	CoA-group	p-value
Number of events (% of event in group)*	38 (7.6%)	35 (9.3%)	3 (2.5%)	0.016
Age at event	49.0 ± 13.6	49.3 ± 13.6	46.4 ± 19.2	0.821
Type of event				
Dissection (% of total in group)*	3 (0.06%)	2	1	NA
Surgery indication:	35	33 (8.7%)	2 (1.7%)	0.007
Valvular dysfunction (% of total in group)*	21 (4.2%)	21 (5.6%)	0	0.004
Aortic dilatation (% of total in group)*	13 (2.6%)	11 (2.9%)	2 (1.7%)	0.743
Unknown	1	1	0	

Table 2. NA: not applicable. *events divided by total patients in the group

Figure 2: aortic events in 499 BAV patients as percentage of total in each age group and iBAV or BAV+CoA-group.

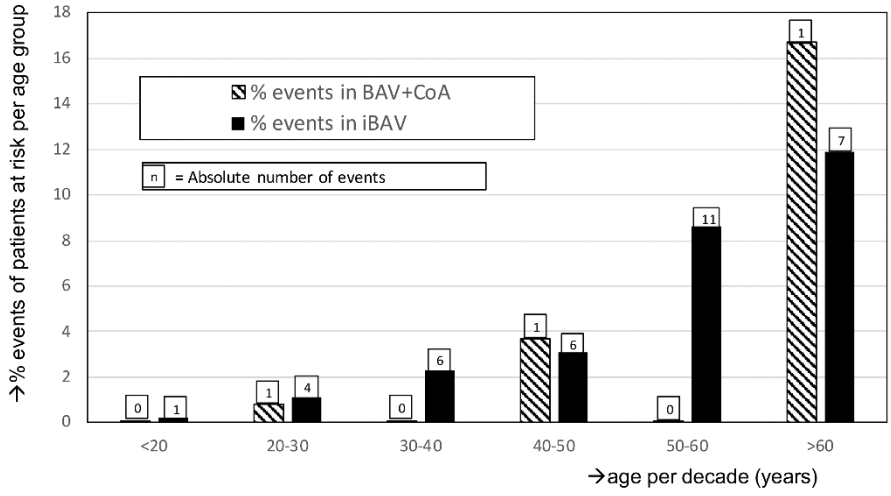


Figure 2 illustrates the age distribution at which the AAE occurred for both groups. For each age group, the patients with an AAE were divided by the total patients in this age group. In the age groups <20 years, 30–40 years, and 50–60 years, no AAE were observed. In the

other age groups, the percentages were comparable. Table 3 show the univariate and multivariate analysis of AAE. Due to the low event rate, a limited number of variables could be tested (CoA, hypertension, age, aortic regurgitation).

Table 3. Predictors of acute aortic events.

	Univariate Analysis Odds Ratio (95% CI)	*p*-Value	Multivariate Analysis, Odds Ratio (95% CI)	*p*-Value
Age	1.063 (1.041–1.086)	<0.001	1.054 (1.029–1.080)	<0.001
Aortic coarctation	0,249 (0.075–0.825)	0.023	0.410 (0.117–1.441)	0.164
Hypertension	2.664 (1.316–5.391)	0.006	1.329 (0.589–2.998)	0.494
Moderate to severe aortic regurgitation	1.364 (0.922–2.017)	0.120		

Ascending aortic diameter on CMR/CT.

At least one CMR/CT was available in adulthood in 416 BAV (83%) patients. The mean aortic diameter at first CMR/CT was 34.4 ± 7.8 mm, at a median age of 27.2 (20.2–43.1) years. There was a significant difference in age between the 312 patients in the iBAV group (median age of 30.5 (21.0–47.5)) and the 104 patients in the cBAV group (median age 21.9 (18.4–30.8)) ($p < 0.001$) and a significant difference in aortic diameter between iBAV (mean diameter of 35.7 ± 7.6 mm) and cBAV group (mean diameter 30.3 ± 6.9 mm) ($p < 0.001$). The aortic diameter in the cBAV group was still significantly smaller (coefficient = −3.42; $p < 0.001$) after correcting for age (coefficient = 0.23; $p < 0.001$). The mean aortic size index (absolute diameter divided by body surface area) was 18.6 ± 4.0 mm/m2 and was significant lower in the cBAV group compared with the iBAV group (16.2 ± 3.7 versus 19.4 ± 3.9 mm/m2; $p < 0.001$). After correcting for age, cBAV patients had still a smaller aortic size index (coefficient of −2.6; $p < 0.001$).Ascending aortic dilatation defined as a diameter >40 mm was significant more prevalent in the iBAV group compared with the cBAV group (31.1% versus 9.8%; $p < 0.001$).Ascending aorta dilatation when defined as aortic size index >20 mm/m2 was also significant more prevalent in the iBAV group (45.0% versus 13.7%; $p < 0.001$). In Turner women, the aortic size index was significantly larger compared with the rest of the group (19.9 mm/m2 versus 18.6 mm/m2; $p = 0.043$). cBAV was present in 8.6% of all Turner women and in 1.2% of all BAV patients.All patients with an ascending aortic diameter >55 mm were operated. There was no significant difference between the iBAV and cBAV groups (2.6% versus 1.0%; $p = 0.46$) in the prevalence of nonoperated patients with an ascending aortic diameter >50 mm.Aortic diameter increase during follow-up

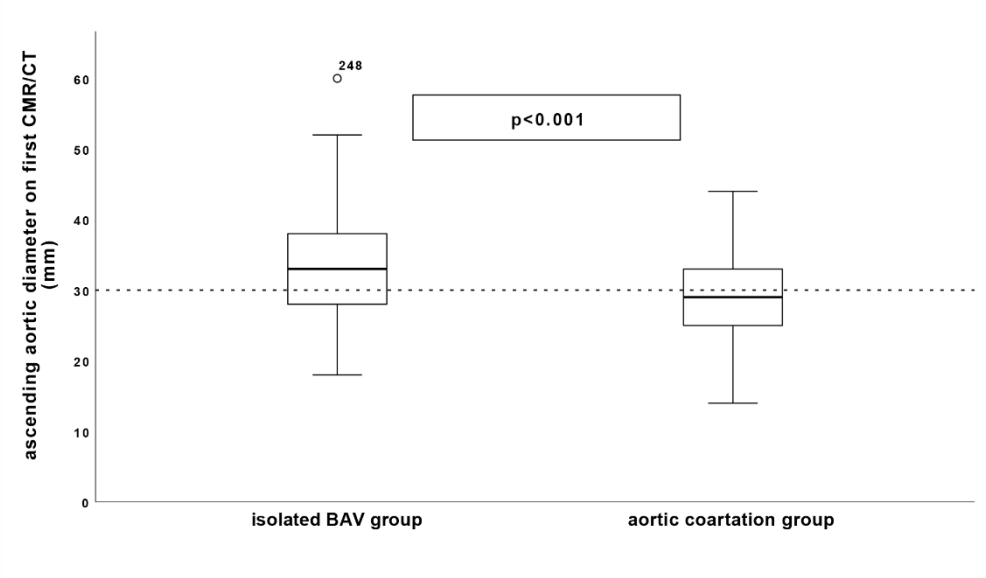
Aortic Diameter Increase during Follow-up

In 162 patients (49 cBAV, 30%), more than one CMR/CT was available. The mean follow-up time was 6.0 ± 2.9 years, the median ascending aortic diameter change was 0.23 (0.0–0.67)

mm/year. Figure 3 shows the boxplot of the median ascending aortic diameter change of the iBAV group (median age at first CMR/CT 28.6 (20.3–45.0) years) and the cBAV group (median age at first CMR/CT 21.2 (18.0–29.9) years. There was no significant difference (p = 0.74) in median aortic diameter change between the iBAV group (0.24 (−0.02–0.76) mm/year; n = 114) and the cBAV group (0.20 (0.00–0.57) mm/year; n = 49). None of the patients had an aortic diameter increase of >3 mm/year.

In the 162 patients with two or more CMR/CT scans (follow-up group), 22.7% had hypertension, this was not significantly different in the iBAV and cBAV groups (20.2% versus 28.6%; p = 0.241). Of the 14 patients with an ascending aortic diameter of >50 mm at first CMR/CT (1 cBAV patient), four patients were operated before the second CMR/CT was performed. The remaining 10 patients had a median ascending aortic change of −0.13 mm (−0.85–0.14).

Figure 3: boxplot of mean ascending aortic diameter change (mm/year) for iBAV and CoA-group.



Discussion

The presented data in this large study of relative young BAV patients suggest that patients with and without aortic coarctation are both similarly associated with aortic events and show a comparable increase in ascending aortic diameter. The current idea is that large ascending aortic diameters are associated with a higher risk for future AAE. In this study, ascending aortic diameter was significantly higher in the iBAV group, probably due to higher age. Nevertheless, the prevalence of preventive ascending aortic surgery was comparable to the cBAV group, when the primary indication was ascending aortic dilation.

The current ESC aortic guideline and ESC valve guideline both state that ascending aortic surgery should be advised (class IIa, level C) at a lower ascending aortic diameter (50 mm instead of 55 mm) in BAV patients with a (history of) CoA [10,16]. In this study, no evidence to substantiate this recommendation is found. In fact, the results points towards a more favorable course in cBAV patients, and therefore the recommendation of the ESC should be revisited.

Eleid et al. presented a small cohort of aortic dissection in BAV patients, in which they concluded that cBAV was associated with dissection, since they found that 23% of the BAV patients had a CoA [5]. This conclusion is debatable because the normal prevalence of CoA in BAV is about 23% and, therefore, represents a normal distribution of iBAV and cBAV [5].

Oliver et al. described a group of BAV patients (n = 341), in which they found that the coexistence of CoA was associated with more ascending aortic events. They defined an event as a dissection or rupture of the sinus of Valsalva or an aortic dilatation > 55 mm [4] They experienced the same problem as the current study of a low event rate and a younger-aged cBAV group with a mean age of 18 (16–23) years [4]. The difference with the current study can partly be explained by a slightly different AAE definition (in this study, also preventive aortic surgery patients were included), which could have caused a higher event rate in the current study.

Michelena et al. reported 416 BAV patients, in whom they found no increased AAE in cBAV patients during a mean follow-up time of 16 ± 7 years [6]. Tzemos et al. showed that a history of CoA was associated with a lower event rate [17].

The fact that this study and other studies did not find significant differences in AAE between iBAV and cBAV suggest that the recommendation of earlier preventive surgery in cBAV patiënts needs to be reconsidered [6,17].

Aortic diameter is the most important parameter on which the indication for preventive aortic surgery is based, although some other factors are important too, such as hypertension [18]. In the current study, as in other studies, it was observed that

coexistence of CoA was associated with smaller aortic diameters [6,19,20]. This implies that cBAV patients are less likely to develop an aortic aneurysm needing preventive aortic surgery. On the other hand, a higher prevalence of hypertension was observed in the cBAV group, and hypertension has been associated with AAE, especially dissection [21]. The development of hypertension could be induced by the relative aortic hypoplasia after CoA correction. The definition of aortic hypoplasia is guided by the application of the Z-score for the aortic arch, but at which z-score hypertension develops is not clear.

Rapid aortic growth (>3–5 mm/year) is a risk factor for future AAE and is an indication to consider preventive surgery [10].

The ascending aortic diameter increase was slow (0.20–0.23 mm/year) and not different between the iBAV and cBAV groups in the current study, and this is in line with previous reports (Oliver 2009). This suggests that CoA is not associated with increased growth rates in BAV patients and thus probably not associated with a higher risk of AAE, also after longer follow-up.

In this study, only patients with a BAV were analyzed, and whether these data also apply to patients with an aortic coarctation and a normal aortic valve was not investigated

Limitations

Several potential limitations must be noted. All limitations associated with retrospective research apply to this study. Due to the low number of events, no hard conclusions can be drawn from this paper, only suggestions, but for now it is the best we have. Our study population consisted of patients receiving care in a specialized center and may therefore be less generalizable. The age difference between the two groups was partly caused by referral bias, since BAV was, especially in the older patients, more often diagnosed during aortic surgery. This problem was largely corrected by conducting a multivariate analyses in which we corrected for age. A potential limitation is also caused by the fact that CMR/CT was not performed in every patient at a fixed time interval. Finally, we did not evaluate specific aortic dilatation patterns.

Conclusion

This study suggests that the ascending aortic event rate is not different between BAV patients with or without a history of aortic coarctation. Implying that a difference in indication for ascending aortic surgery is not justified in BAV patients based on a history of aortic coarctation alone.

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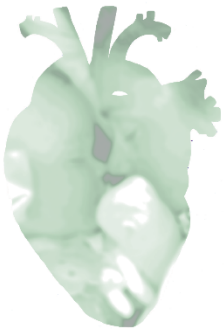

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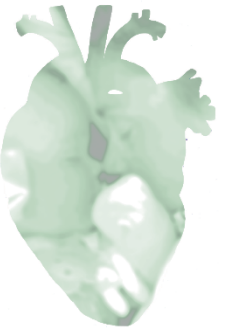

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14

Long-term follow up of aortic dimensions in patients with SMAD3 mutations

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Abstract

SMAD 3 mutations cause an aggressive form of aortic aneurysms, vascular tortuosity and osteoarthritis which has a profound effect on the lives of patients. The clinical phenotype is encapsulated in the aneurysm-osteoarthritis syndrome (AOS) which is now often recognized as a separate type (III) of Loeys-Dietz syndrome (LDS). Our researchgroup has previously described the aortic dilatation and clinical outcomes in this patient group. This chapter describes the long-term follow-up.

Pathogenic SMAD3 mutations are a known cause of early aortic dilatation and dissection. In combination with osteoarthritis at young age this is encapsulated in the Aneurysms-Osteoarthritis Syndrome (AOS) [1]. AOS has many similarities with Loeys-Dietz Syndrome (LDS), and is recognized by some as part of LDS [2]. It is currently unknown how the rate of aortic dilatation in SMAD3 patients compares to other syndromic causes of aortic dilatation.

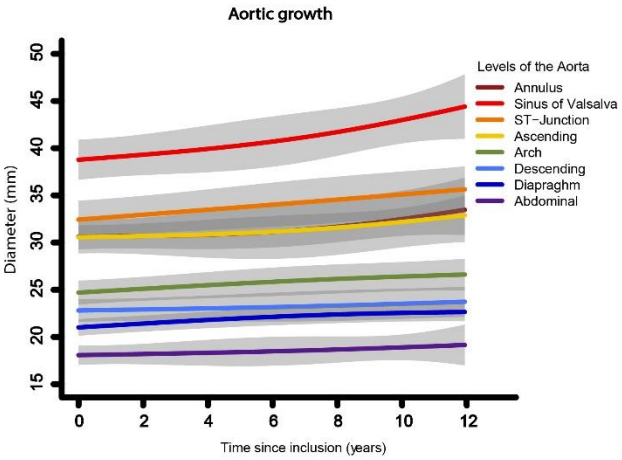
We have followed SMAD3 mutation carriers in our center per in-house protocol since December 2011. This protocol includes yearly ECG-gated contrast enhanced thoraco-abdominal computed tomography angiography (CTA). In ten patients earlier scans were available (2003 to 2011), which were included only when aortic diameters could be reliably measured according to protocol standards. Aortic dimensions were repeatedly measured perpendicular to the vessel at 8 standardized levels using double-oblique multi planar reconstruction by an experienced cardiovascular radiologist, blinded to clinical data and to previous measurements. To account for correlations between multiple measurements within each patient, average time trends were estimated using linear mixed models. Cubic splines were used to model non-linear growth curves. Patient-specific intercepts and slopes allowed for individual deviations from the average growth. As described in our in house protocol patients with an aortic diameter of 42mm or above are considered in the interdisciplinary heart team for intervention. The study protocol was approved by the medical ethics committee of our center.

Baseline characteristics are shown in figure 1 (Panel A). When looking at the average increase per year (figure 1: Panel B), significant growth was seen at three levels: the sino-tubular junction (STJ), the ascending aorta and the level of the diaphragm. The average growth was largest at the STJ with 0.4mm/year (95%CI: 0.12-0.62, p=0.005), followed by the ascending aorta and diaphragm with 0.2mm/year (95%CI: 0.04-0.38, p=0.018 and 95%CI: 0.10-0.27, p<0.001 respectively). The aorta did not show significant growth at the level of the annulus, sinus of Valsalva, aortic arch, the descending and the abdominal aorta. Age had an impact especially at the level of the aortic arch and abdominal aorta. During follow-up no mortality occurred; however, 14 (50%) patients needed elective valve sparing root replacement (VSRR). The median age at time of operation was 40.6 years (IQR: 22.76). Additionally, fourteen vascular interventions, most often embolization of a side branch aneurysm, were needed in nine patients. Five of these patients also underwent a VSRR. In total 18 patients (64%) underwent at least one cardiovascular intervention during the duration of this study. Interventions were done at the discretion of the vascular surgeon, as there are no clear guidelines for intervention in this patient group.

Baseline Characteristics

SMAD-3 patients (n=28)	
Age, years	34 (15-69)
Gender (female)	17 (61)
Follow-up duration, years	10 (3-14)
Blood pressure medication	6 (21)
Most frequent genetic mutation*	9 (32)
Baseline aortic diameters, mm	
Annulus	31±5
Sinus of Valsalva	39±6
ST junction	33±6
Ascending aorta	31±4
Aortic arch	25±4
Decending aorta	23±3
Diaphragm	21±2
Abdominal aorta	18±3

Panel A



Panel B

Figure 1. Baseline characteristics and aortic growth. A, baseline characteristics, *most patients shared the same heterozygous mutation R287W, 859C>T, SMAD3 ex 9. Data are shown as mean±SD, median (25%–75%), or n (%). B, aortic growth: average of all aortic measurements per level of the aorta, shaded gray areas indicate the 95% CI for the estimate. ST: indicates sino-tubular

The mean rate of increase in aorta diameter in the normal population is 0.07mm and 0.09mm per year of life in women and men respectively[3]. The natural course of this process is influenced by many factors such as: age, sex and blood pressure. In the last decade much attention has been paid to genetic aortopathies. In Marfan syndrome for example the aorta dilates fastest at the level of the sinus of valsalva with a rate of approximately 0.49mm±0.5mm per year [4]. In comparison to LDS, where the aorta can grow at rates of up to 10mm/year, dilatation in our cohort may seem relatively mild [5]. However, in earlier studies mortality was high, and although no deaths occurred during our follow-up, it should be noted that this could be explained by the intensive management and preventive surgery at relatively mild dilatation of the aorta.

The current results differ from a previous report from our group especially in growth rate and location of fastest growth, which can be explained by longer follow-up duration, inclusion of milder cases discovered by family screening, and by using different analysis methods. Still, we can appreciate that SMAD3 mutation carriers show aortic dilatation at a rate similar to other genetic aortopathies, dilatation occurs predominantly at the STJ and ascending aorta, but also in all other parts of the aorta and large arteries. With this study we provide evidence that SMAD3 mutations cause an aggressive form of aortic dilatation, warranting vigilant follow-up. The fastest growth rate (0.4mm/year) was observed at the level of the sino-tubular junction. In 64% (18/28) of the patients in this study a potentially fatal arterial pathology was discovered. However, for the management of SMAD3 patients this implies that the current protocol adequately addresses the clinical problem in these

patients as no patients died from aortic rupture or suffered from aortic dissection during follow-up. Additionally this study provides an important measure of reference to other known causes of genetic aortopathies. More research is needed to determine predictors for fast growth and possible medical therapies in SMAD3 patients hopefully resulting in a better understanding and improved outcome.Source of funding:

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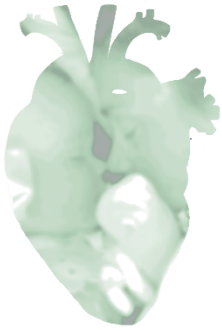
SMAD3



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15

Psychological well-being in patients with aneurysms-osteoarthritis syndrome

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Abstract

Objectives. Aneurysms-Osteoarthritis Syndrome (AOS) is characterised by arterial aneurysms and dissection in combination with early-onset osteoarthritis, which can impact quality of life.

Methods. We describe the subjective quality of life and investigate anxiety and depression in 28 AOS patients aged 15 to 73 years. Three questionnaires were used: (SF-36), Hospital Anxiety and Depression Scale (HADS) and Rotterdam disease specific questionnaire. Results of the SF-36 and HADS were compared to a reference Dutch cohort and the SF-36 questionnaire also to patients with Marfan syndrome.

Results. Compared to the general population, AOS patients scored significantly lower on the following SF-36 domains: physical functioning, vitality, social functioning, bodily pain and general health. Physical functioning was also lower than in Marfan patients. Patients with AOS scored higher on the HADS depression scale, while anxiety did not show a significant difference compared to the general population. No difference in SF-36 and HADS domain scores were found between patient with and without orthopaedic symptoms or patients with or without previous aortic surgery. Additionally, we found that patients' worries for their future and heredity of their disease are important factors for anxiety, which should be addressed in clinical practice.

Conclusions. In conclusion, our population of AOS patients showed reduced quality of life in comparison with the general population on physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, and social functioning. Physical functioning was also lower than in Marfan patients.

Introduction

An aneurysm or dilatation of the thoracic aorta can cause aortic dissection, which is a potentially life threatening event as over half of all patients with an acute thoracic aortic dissection die within 30 days (1). In 20% of the patients an aortic aneurysm results from a heritable thoracic aortic disease (HTAD) (2, 3). In 2011, a new HTAD was described, the so-called "Aneurysms-Osteoarthritis Syndrome (AOS)", caused by a pathogenic variant in the SMAD3 gene(4), which is part of the TGF-β pathway. Aneurysms-Osteoarthritis Syndrome has many similarities with Loeys-Dietz syndrome (LDS), and is therefore also referred to as LDS type 3. In AOS, aneurysms can occur within the aorta and other arteries (among which the splenic, iliac, hepatic and intracranial arteries). Furthermore, the arteries show tortuosity and aortic dissections or ruptures already occur in a mildly dilated aorta. In 18% of the patients aortic dissection is even the first manifestation of the disease(5). In addition to the vascular findings, joint abnormalities are an important feature of this syndrome, which are often the reason for first presentation. These joint abnormalities include osteoarthritis and osteochondritis dissecans at a relatively young age(6). Other characteristics associated with pathogenic variants in the SMAD3 gene are widely spaced eyes, bifid uvula, umbilical or inguinal hernias varices, velvety skin and striae(4). These physical symptoms and the risk of life threatening dissection of the arteries might cause reduced quality of life, anxiety and depression. Anxiety in AOS patients can also be caused by experiencing the consequences of the disease through relatives, since this autosomal dominant genetic disorder is often diagnosed in multiple family members. Therefore knowledge about psychological well-being and causes of impaired quality of life and anxiety or depression in AOS patients is important in order to develop specific management strategies. Although psychosocial well-being has been investigated for other vasculopathies such as Marfan syndrome(7) and Ehlers-Danlos(8), no attention has been paid yet to the quality of life and occurrence of depression or anxiety in patients with this life-threatening syndrome. Therefore, the aim of this study was to comprehensively describe the subjective quality of life and investigate anxiety and depression in AOS patients.

Materials and methods

Study population

All carriers of a pathogenic variant in the SMAD3 gene undergoing follow-up in our tertiary center per in-house protocol since January 2009 were invited for this study. Family members which were 50% risk carriers with obvious AOS related symptoms (aortic dilatation or osteoarthritis at an early age) were also included. Demographic and clinical data were obtained from the electronic patient files. Diabetes mellitus was defined as current use of medication. As part of our protocol, all patients underwent echocardiography and whole-body computed tomography angiography (CTA). The aortic

measurements of the sinus of Valsalva, ascending aorta, aortic arch and descending aorta were measured using the inner edge-to-inner edge method on the most recent CTA. Aneurysms and dissections were categorized by the following locations and definition: head and neck, thoracic, coronary, abdominal, leg and/or arm or pulmonary artery. Information on the following valvular, ventricular and arrhythmic abnormalities was collected: bicuspid aortic valve, aortic stenosis (Vmax >2.5 m/s), aortic regurgitation (at least moderate)(9), valvular disease other than from the aortic valve, congenital heart disorders, ventricular hypertrophy (septal wall>13 mm), left ventricular dilatation (diastolic diameter >60 mm) and atrial fibrillation (former, paroxysmal or current). The study complied with the Declaration of Helsinki and was approved by the medical ethical committee of the Erasmus Medical Centre (MEC17-057). Written informed consent was provided by all patients.

Questionnaires

All participants received three questionnaires: the Short Form-36 Health Survey (SF-36)(10), the Hospital Anxiety and Depression Scale (HADS)(11) and the Rotterdam disease specific questionnaire. The questionnaires were sent at first on the 14th of November 2017 and were collected until the 1st of February 2018. If participants did not respond at first, they received a maximum of two reminders. The SF-36 was used to determine patient-reported quality of life. It covers the following eight domains: physical functioning, role limitations due to physical health, bodily pain, general health, mental health, role limitations due to mental health, vitality (energy or fatigue related) and social functioning. The scale ranges from 0 through 100 points. A lower score per subcategory, reflects a lower quality of life on that life domain. In addition, two sum scores, the mental component summary (MCS) and physical component summary (PCS), were calculated(12). These summary scores are standardized according to the general Dutch population(13), which means that all scores above and below 50 are above and below the average in the Dutch population. The HADS questionnaire determines the levels of anxiety and depression on two subscales with a total score ranking from 1 to 21. A score of 0 to 7 for either subscale is in the normal range, a score of 8 to 10 is possible abnormal and 11 or higher indicates the probable presence of anxiety or depression. The “Rotterdam disease specific questionnaire” was developed by our multidisciplinary team in the Erasmus Medical Center (supplemental file A) to investigate the impact of having AOS related aortic aneurysm on daily life, work participation, sexual functioning, pregnancy wish and sports participation. Patients received 18 statements and were asked to grade how they felt on a continuous scale from 0 to 10, 0 being ‘I completely disagree’ and 10 being ‘I completely agree’.

Comparison with the general population and other aortic disease patients (Marfan syndrome)

For the HADS and SF-36 questionnaires we compared our data to the reference values of the age-matched general Dutch population(13, 14). For the SF-36, a cohort of age and sex matched Marfan patients was also available, which allowed us to compare AOS with another syndromic HTAD(15). For the results of the Rotterdam disease specific questionnaire, there are no reference values available yet because this questionnaire was newly developed for this study's aim.

Table 1. Results of SF-36 and HADS in patients with AOS

	Domain/scales	Score	Summary measures[†]	Score
SF-36	Physical functioning	45.0 (30.0-78.8)	PCS	34.3 (25.0-48.2)
	Role limitations due to physical health	37.5 (0.0-100.0)		
	Bodily pain	57.5 (35.0-75.0)		
	General health	40.0 (25.0-55.0)		
	Mental health	76.0 (57.0-88.0)	MCS	50.4 (39.4-59.9)
	Role limitations due to mental health	100.0 (33.3-100.0)		
	Vitality	50.0 (20.0-63.8)		
	Social functioning	62.5 (50.0-87.5)		
HADS	Depression scale	5.0 (2.0-9.8)		
	Anxiety scale	5.0 (2.0-7.8)		

Table 1. Note: Data is shown as median (25–75%). Abbreviations: AOS, aneurysms-osteoarthritis syndrome; HADS, hospital anxiety and depression scale; MCS, mental component summary; PCS, physical component summary. [a] Standardized scores with use of the general Dutch population (Aaronson et al., 1998).

Statistical analysis

Continuous variables with a normal distribution were reported as mean with ± standard deviation and the median and interquartile range was reported in case of non-normal distribution. Categorical variables were summarized as frequencies and percentages. Data distribution was checked using histograms. Because of the non-normally distribution of the values in the domains of the SF-36 and HADS questionnaires, the median and interquartile ranges are presented in the table and the p-value of the one-sample Wilcoxon signed rank test was presented in the text and figures. With the one-sample Wilcoxon signed rank test the median of a continuous variable in our cohort was compared with a hypothesized median of a reference group. Since our reference article showed their values only with mean ± S.D., we assumed that the variables were distributed normally. Because mean and median are comparable in normally distributed variables, we used the mean of the reference as hypothesized median in our non-parametric test. To visually compare our data

with reference data presented as mean ± SD, also our data were presented as mean ± SD in the figures although we could not proof normal distribution. However, only small differences were found between the calculated mean and median of the HADS and SF-36 domain scores. To further investigate if patients with orthopaedic symptoms or previous aortic surgery had higher levels on the SF-36 and HADS domains, we performed the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

Results

Study population

Of the 31 patients with AOS in our centre, 28 patients (90%) agreed to participate and returned the questionnaires. The other three patients were approached two times, but could not be reached (n=2) or decided not to participate due to time-constraints (n=1). There were no major differences between the 28 responders and 3 non-responders. The baseline characteristics of the 28 study patients are presented in Table 1. Our cohort contained 23 participants with a confirmed SMAD3 mutation representing 10 different genetic mutations with the most common heterozygous mutation (R287W, 859C> T, SMAD3 ex 9) present in 9 patients. The mean age was 44.0±17.3 years with an age range from 15 to 73 years. Of the 28 patients, 17 (61%) were women. Cardiac or vascular abnormalities were present in 22 (79%) patients and orthopaedic symptoms were present in 24 (86%) patients. In 18 (64%) of the 28 patients both cardiovascular manifestations and orthopaedic symptoms were reported.

Quality of life, anxiety and depression

The median values with interquartile range of the domains from the SF-36 and HADS questionnaires are presented in Table 2. Our cohort scored significantly lower compared to the age-matched reference group of 1742 Dutch citizens(13) on the following domains: physical functioning ($p<0.001$), role limitations physical health ($p=0.001$), bodily pain ($p=0.001$), general health ($p<0.001$), vitality ($p<0.001$), and social functioning ($p=0.002$). AOS patients showed a standardized PCS score of 34.3 (25.0-48.2) and a MCS score of 50.4 (39.4-59.9). When comparing the SF-36 with age-matched Marfan patients, only physical health was lower in patients with AOS ($p=0.005$). The mean values with standard deviation of the domains from the SF-36 questionnaire for AOS patients, Marfan patients and the reference group are visualized in Figure 1. The HADS questionnaire showed no differences in anxiety (median 5.0 versus 5.1, $p=0.569$) between AOS patients and the general population. However, patients with AOS scored higher on the depression subscale (median 5.0 versus 3.4, $p=0.036$) compared to a sample of 199 Dutch adults (14). In our population of AOS patients, 2 patients (7%) scored above the cut-off, indicative for clinical depression,

while 1 patient (4%) scored in the range for clinical anxiety. The mean values with standard deviation of the domains from the HADS questionnaire are shown in Figure 2 for the AOS patients and the reference group. No significant differences in SF-36 and HADS domain scores were found between patient with and without orthopaedic symptoms or patients with or without previous aortic surgery.

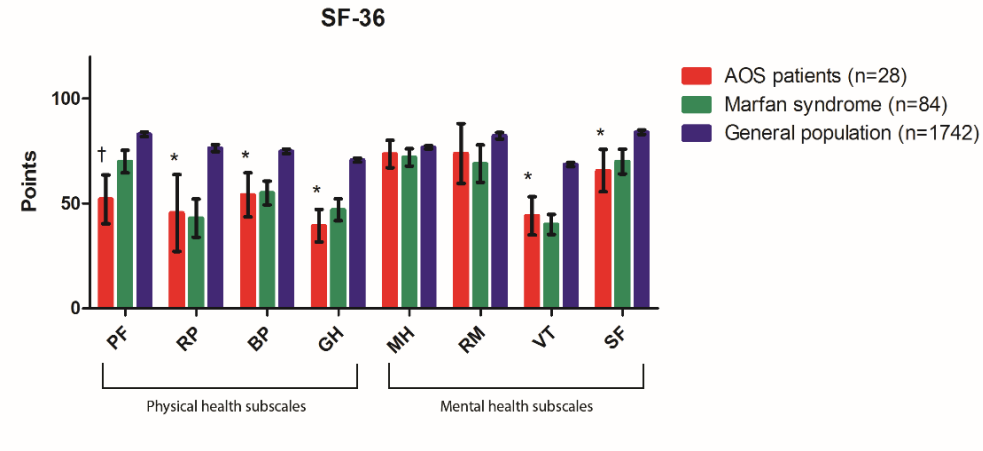

Fig 1. Comparison of eight SF-36 domains between AOS patients, Marfan patients and healthy control. Data is shown as mean (incl. 95% CI). The SF-36 scale ranges from 0 through 100 points. The lower the point count per subcategory, the more prevalent it is that the individual has a negative effect of that sub scale's premise. For social functioning and general health one patient was missing, because he forgets to fill in one page of the questionnaire. * Significant lower compared to the mean of the general population (One-sample Wilcoxon signed rank test). † Significant lower compared to both the mean of the general population and the mean of patients with Marfan syndrome (One-sample Wilcoxon signed rank test). AOS, aneurysms-osteoarthritis syndrome; BP, bodily pain; GH, general health; HADS, hospital anxiety and depression scale; MH, mental health; PF, physical functioning; RM, role limitations due to mental health; RP, role limitations due to physical health; SF, social functioning; VT, vitality

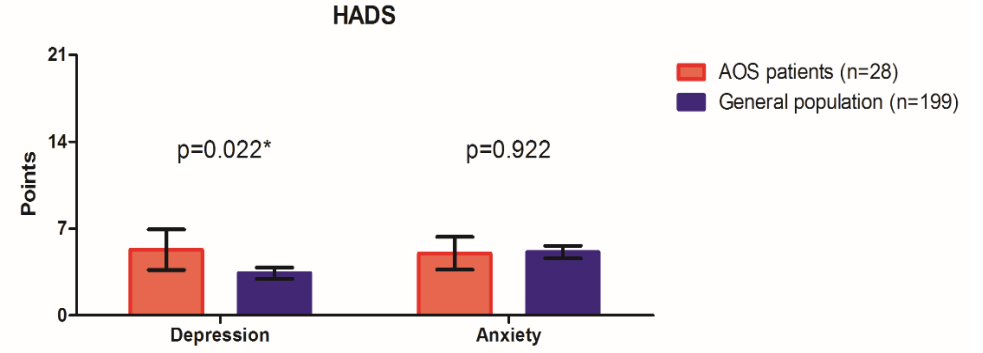

Fig. 2 Comparison of two HADS domains between AOS patients and healthy control. Data is shown as mean (incl. 95% CI). The anxiety and depression sub scales have a point system of 0 through 21 points total. The higher the point count for any sub scale, the more likely that the individual suffers from anxiety or depression. *Significant higher compared to the general population (one-sample Wilcoxon signed rank test)

Table 2. Baseline characteristics

Baseline characteristics	AOS patients (N=28)
Sex (female)	17 (61%)
Age (years)	44.0 ± 17.3
Confirmed SMAD3 mutation carriers (a)	23 (82%)
BMI (kg/m2)	24.9 ± 3.4
Smoking (currently)	2 (7%)
Systolic blood pressure (mmHg)	128.2 ± 16.9
Diastolic blood pressure (mmHg)	80.4 ± 9.5
Medication use	14 (50%)
- Beta-blocker	8 (29%)
- Diuretics	0 (0%)
- ACE inhibitors	4 (14%)
- Angiotensin receptor blocker	2 (7%)
- Calcium channel blocker	0 (0%)
- Cholesterol lowering drugs (statins or other)	3 (11%)
- Platelet inhibitor	6 (21%)
- Oral anticoagulant	2 (7%)
Comorbidity	4 (14%)
- Diabetes Mellitus	0 (0%)
- Coronary artery disease	1 (4%)
Aortic aneurysm or dissection	19 (68%)
- History of aortic surgery	9 (32%)
- Thoracic aortic aneurysms (>40 mm) (b)	5 (18%)
- Head and neck arterial anomaly	6 (21%)
- Coronary arterial anomaly	0 (0%)
- Abdominal arterial anomaly	5 (18%)
- Leg or arm arterial anomaly	0 (0%)
- Pulmonary artery dilatation (>40mm)	2 (7%)
Aortic diameter (b)	
- Sinus of Valsalva	36.0 ± 3.5 (range 30-44)
- Ascending aorta	30.6 ± 3.6 (range 25-40)
- Aortic arch	26.5 ± 3.7 (range 21-34)
- Descending aorta	24.9 ± 3.4 (range 19-33)
Cardiac anomalies	9 (32%)
- Bicuspid valve	0 (0%)
- Aortic stenosis (Vmax > 250 m/s)	0 (0%)
- Aortic regurgitation (at least moderate)	0 (0%)
- Valve disease other than aortic (at least moderate)	1 (4%) (c)
- Congenital heart disease (i.e. VSD)	1 (4%)
- Ventricular hypertrophy (>13 mm)	2 (7%)
- Left ventricular dilatation (>60 mm)	2 (7%)

Table 2 continued

- Atrial fibrillation (former/paroxysmal or currently)	4 (14%)
Age first vascular or cardiac abnormalities (in years)	38.0 (26.5-56.0)
Orthopaedic abnormalities (d)	24 (86%)
Age first orthopaedic abnormalities (in years)	20.0 (13.8-46.0)

Table 2. Data is shown as median (25–75%), mean±SD or as N (%). Missing values for BMI (n = 2).a Five patients have a 50% chance of having AOS, since they are not yet genetically tested. They are included because they showed significant aortic, cardiac or orthopaedic symptoms associated with AOS.b Aortic diameters of the sinus of Valsalva and ascending aorta and prevalence of thoracic aortic aneurysm (>40 mm) are presented for patients who have not undergone aortic surgery.c This patients showed moderate mitral valve regurgitation.d Orthopaedic abnormalities such as arthritis, arthrosis, osteochondritis dissecans, orthopaedic surgeries, osteosarcomas, instability of the joints, joint or muscle pain.

Disease specific anxieties/concerns

In the Rotterdam disease specific questionnaire, the majority of the patients reported fear and/or anxiety according to their future or the future of their siblings or offspring's (Figure 3). Concerns about dying at an early age (median 3.5, IQR 1.0-7.0), future health (median 5.0, IQR 2.3-7.0), future surgery (median 6.5, IQR 1.0-9.0) and heredity of their disease (median 7.0, IQR 4.3-10.0) were mentioned. The risk of developing aortic dilatation or dissection or already having aortic pathology did not have a significant impact on participation in work, hobbies, sexual activities and physical activities.

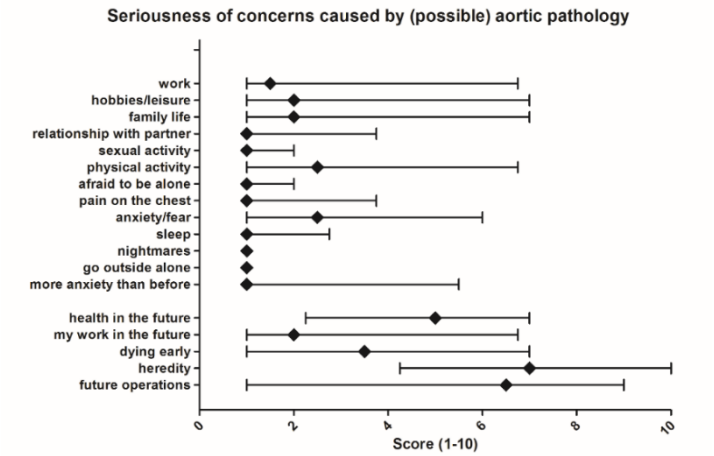

Figure 3. Results of the Rotterdam disease specific questionnaire. This figure shows the influence of (possible) aortic dilatation or dissection on different aspects of life. Data shown as median with interquartile range 25–75%

Discussion

The results of our study show that patients with AOS report a lower quality of life, mainly on the physical health subscales, and higher scores on the depression subscale compared to the general Dutch population. Disease specific anxiety was most often related to the future of their own health or the health of their close relatives. Although anxiety, depression and quality of life have been described in other patients groups with aortic pathology (16-18), specifically after thoracic aortic surgery(19), it has not yet been described in AOS patients or Loeys-Dietz syndrome. In general, AOS is not a very well-known syndrome among cardiologist and other specialists, while pathogenic variants in the SMAD3 gene are responsible for 2% of familial thoracic aortic disease (20). This patient group is of great interest, because of their recently discovered extensive presentation including severe joint abnormalities and most importantly aggressive cardiovascular phenotype requiring vigilant follow-up (5). Therefore it is important for all clinicians involved in the care for these patients to be aware of the psychological aspects in order to provide adequate care. We showed lower SF-36 scores, on almost all domains compared to the general population (13). The median PCS score of our patients with pathogenic variants in the SMAD3 gene was 34.3, which means a much lower physical health than the general population, while the median MCS score (50.4) showed that mental health was comparable with the general population. However, on two subscales of mental health, namely vitality and social functioning, AOS patient did score lower than the general population. We know that middle aged Dutch patients with congenital heart disease show similar or even more favorable levels compared to normative data using the SF-36 survey (21). This difference between patients with congenital heart disease and AOS patients can be explained by the moment at which the symptoms are present. Orthopedic and cardiovascular symptoms associated with AOS start at a median age of 22 and 38 years respectively, which cause an acute change in patients' health with clear impact on quality of life. Whereas the patient with congenital heart disease are known with their defect from birth, AOS patients need to adapt and accept that they have this disease at later age. Compared to patients with Marfan syndrome (15), AOS patients scored only lower on the SF-36 questionnaire for the domain of physical functioning. This can be a result of the more extensive presentation of musculoskeletal complaints in patients with AOS including osteoarthritis, osteochondritis dissecans, scoliosis and pectus excavatum (6, 22). This assumption is supported by data from patients with Ehlers-Danlos syndrome, a connective tissue disorder which presents with extreme musculoskeletal symptoms including hypermobility (23). Ehlers-Danlos patients report even lower physical function score (39.6) and general health score (26.8) compared to AOS patients (8, 24). We did not find a difference between patients with and without orthopedic symptoms. However, this should be tested in larger cohorts, since our cohort might be too small to prove the association between orthopedic symptoms and reduced quality of life. In conclusion, AOS patients and probably also patients with other

heritable thoracic aortic disease, have lower quality of life than the general population, but there seem to be some differences between syndromes. By assessing quality of life, anxiety and depression, we found unfavorable outcomes and impairments, warranting attention and in some cases treatment. In our population of patients with pathogenic variants in the SMAD3 gene, 4% scored above the cut-off for clinical anxiety, while 7% scored in the range for clinical depression. These percentages are comparable to or even slightly lower than the prevalence's in the general German population, which are 5.2% for anxiety and 9.6% for depression based on the HADS questionnaire (25). However, the median of the continuous outcome of the depression scale was higher in OAS patients than in the general population. With the development of our own Rotterdam disease specific questionnaire, we were able to identify patients concerns due to their disease. Most importantly, patients report worries concerning the future of their own health or the health of their close relatives. These results emphasize the need for physicians to discuss patient's future and risk for family members and check in each patient whether someone is concerned about this. This is not only important for AOS, but for all inherited syndromes. Generic questionnaires such as SF-36 or EuroQol (EQ-5D) are commonly used for quality of life assessment. Although the use of validated questionnaires is extremely important, these questionnaires do not distinguish between quality of life based on the disease itself or as a result of other problems like small or short-term injuries and life events. With the use of more disease-specific questionnaires, such as the Rotterdam disease specific questionnaire, in larger cohorts we will be able to identify the cause of physiological burden in a disease more precisely in the future. Nevertheless, before using these questionnaires in clinical practice, they should be validated.

In this study, we used questionnaires to measure self-reported quality of life, anxiety and depression, which may have caused documentation of more complaints than patients would have mentioned spontaneously. Also, it may cause some information bias, although we assume that the high response rate of 90% reduced the chance of bias. Because of our single center design, we included a small cohort, which prevented us from extensive identification of factors associated with quality of life, anxiety or depression.

Conclusion

In conclusion, our population of AOS patients showed reduced quality of life in comparison with the general population on physical functioning, role limitations due to physical functioning, bodily pain, general health, vitality, and social functioning. Physical functioning was also lower than in Marfan patients. Although the prevalence of depression was similar to the general population, patients with AOS scored significantly higher on the depression scale, which physicians must be aware of to provide good medical care. Additionally, we

found that patients' worries for their future and heredity of their disease are important factors for anxiety, which should be addressed in clinical practice.

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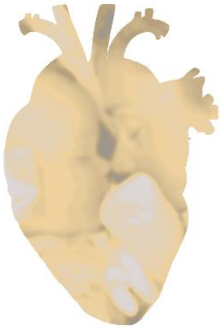
IV

EPILOGUE



16

Summary and General Discussion

Summary

Chapter 1 provides a general introduction and overview of the studies included in this thesis.

Part I Turner syndrome

Chapter 2 is based on a book chapter and introduces the phenotype associated with Turner syndrome (TS); its genetic etiology is discussed and the known associated pathologies are described. It provides the foundation on which the rest of 'Part I' of this thesis builds. In Chapter 3 we describe a retrospective cohort of 96 patients with TS patients with detailed imaging of the pulmonary vasculature. Earlier studies indicated that TS patients may have an increased incidence of partially abnormal pulmonary venous return (PAPVR). Which was confirmed as 1 out 4 TS patients had such a PAPVR. This study changed clinical practice, as advanced imaging in these patients is now routinely checked for presence of PAPVR. In Chapter 4 we describe the health-related quality of life of 177 women with TS and investigate the factors that influence it. This study is a part of the value-base healthcare program in the Erasmus MC. Value-based healthcare entails aiming at improving outcomes that matter most to patients in their everyday lives. In order to do this, these outcomes should first be measured. In this study we showed that TS women suffer from impaired QoL, more perceived stress and increased fatigue compared to healthy controls. A relationship between non-cardiac comorbidities and HR-QoL was found. Furthermore, TS women appeared to practise individual sports, like running, almost exclusively. In addition to this, we also examined how content TS women were with their body on the 'body satisfaction' scale. TS women were most dissatisfied with their waist, build, figure, belly, and weight. These results, especially those of perceived stress and increased fatigue, can be considered targets for improvement of HR-QoL in women with TS. In Chapter 5 we describe systolic left ventricular global longitudinal strain (LvGLS) and left ventricular peak early diastolic strain rate (Sre) in 94 adult women with TS and relate it to clinical outcome. Women with TS had a significantly lower systolic LvGLS (-17.82 ±2.98% vs. -21.80 ±1.85%, $p<0.001$) and Sre 0.98 ±0.32 s-1 vs. 1.27 ±0.19 s-1, $p>0.001$) compared to healthy females' controls. Furthermore, TS women had reduced diastolic function as measured by conventional echocardiographic parameters. Moreover, LvGLS and Sre were comparable between TS patients with and without structural heart disease. Women with TS also had a significantly reduced maximal workload, reduced oxygen uptake and a reduced maximal heart rate during exercise. In Chapter 6 the coronary anatomy of patients with TS is compared to that of patients with a BAV. This study shows that patients with BAV with fusion of right and left coronary leaflets (RL BAV) without raphe have a high prevalence of left coronary dominance in the group of TS-BAV as well as in isolated BAV (both 38%) and that absent left main stem was more often seen in patients with TS and BAV (13%) as

compared with patients with isolated BAV (0%). Aortic dilatation is a significant concern in TS women. Often the aortic diameter increases faster compared to the general population and elective surgery is needed. Therefore, we studied a large retrospective cohort of 268 TS women with advanced imaging of the aorta. Chapter 7 discusses the outcome and aortic dilatation in these women with TS. This is a much-debated topic within the TS literature as dilatation is common and many associations, such as growth hormone treatment during childhood, are described. In this study we confirmed some of these associations. Fortunately aortic dissection and preventive aortic surgery were rare.

Part II the Bicuspid Aortic Valve and Aortic Coarctation

Chapter 8 is based on a book chapter and serves as an introduction to 'Part II' of this thesis. In this chapter the aortic coarctation is discussed, which is a form of aortic pathology that is interwoven with Both Turner syndrome (discussed in Part I) and the bicuspid aortic valve (which is also discussed in Part II). In Chapter 9 we evaluated a novel method of strain analysis using 4D flow CMR. We showed that GLS analysis is possible using the magnitude datasets produced by 4D flow CMR with adequate imaging quality in BAV patients. GLS measurement by CMR correlated well with CT and speckle-tracking 2D TTE. Chapter 10 focuses on volume quantification of the left ventricle using a novel algorithm on 3D echocardiography datasets. In theory, use of a fully automated method of volume quantification allows for a user-independent and thereby highly reproducible measurement. Left ventricular end-diastolic and end-systolic volumes and ejection fraction was calculated by the software and correlated well with manual 2D and 3D echocardiographic measurements. Left atrial volume also correlated significantly, although LHM did estimate larger left atrial volume compared to both 2D and 3D echocardiography. Software like this may help to overcome some of the major hurdles in integrating 3D analysis into daily practice, as it is user-independent and highly reproducible in a group of patients with BAV. Bicuspid aortic valve is often seen together with aortic coarctation. Chapter 11 describes the outcomes of 93 patients who underwent aortic coarctation stenting. Complications occurred in nine patients (10%), including aortic dissections in three patients (3%) and intraoperative ruptures in two patients. The aortic dissections and ruptures were treated successfully by deploying an additional covered stent. Two patients died within 30 days of the index procedure. After a mean follow-up of 3.2 ± 3.1 years, nearly all patients (98%) were clinically improved and all stents were patent. Reintervention was needed in 10 (11%) patients. Freedom from reintervention at 5 years was 85%. Two additional patients died during follow-up of coarctation-related causes, including rupture of an infected graft and visceral ischemia. Patient survival at 5 years was 89%. This study demonstrates that endovascular repair of aortic coarctation is effective and has an acceptable safety profile in the treatment of newly diagnosed CoA and after initial surgical repair. Additionally, it was demonstrated that aortic rupture is an infrequent (2%) but devastating complication with high mortality. The rate of reinterventions is acceptable, with high procedural and long-term clinical success. Chapter 12 builds on the previous chapter in the sense that the outcome of coarctation stenting might be safe for the average CoA patient, but in women with TS a vasculopathy of the aorta exists, with a frailer aortic wall as a result. In women, CoA is one of the most prevalent congenital heart diseases (7-18%). Resolution of the aortic narrowing is generally considered to be a safe alternative for the surgical approach in selected cases. However, the inherently weaker aortic wall of TS patients may expose them to greater risk than their non-TS peers. Therefore, our hypothesis for this multi-centre retrospective study was to investigate the safety of

coarctation stenting in a cohort of TS patients. However, TS is a relatively rare disease and CoA treated using stenting in these patients therefore is even more rare. Consequently, we had to do our utmost to find the 19 patients with TS, from different 10 centres, who had been treated using percutaneous stent angioplasty for aortic coarctation. Three (15.8%) adverse events occurred within 30 days of the procedure, including two dissections (despite the use of covered stents), one of which resulted in death. At long-term follow-up (6.5 years, min-max: 1-16), two additional deaths occurred that are not known to be stent-related. Thereby, we showed that although percutaneous treatment of aortic coarctation in TS patients is effective, it is associated with serious morbidity and mortality. These risks therefore suggest that alternative treatment options should be carefully weighed against percutaneous stenting strategies. Chapter 13 seeks to put an end to the controversy around whether having a CoA is associated with larger aortic diameters and higher complication rates. In order to do so, this study describes the outcome of 483 BAV patients and evaluates whether the coexistence of CoA is associated with aortic events, aortic dilatation and aortic diameter growth. We concluded that the coexistence of CoA was not associated with a higher aortic event rate, a higher prevalence of aortic dilatation, or faster ascending aorta growth. CoA should thus not be seen as a risk factor that justifies earlier preventive aortic surgery in BAV patients.

Part III SMAD3

In 2011, our study group described the aneurysm–osteoarthritis syndrome (AOS) caused by a mutation in the SMAD-3 gene for the first time. Chapter 14 describes the long-term follow-up of outcome and aortic diameters in patients with AOS. We demonstrate that, although these patients remain high-risk, when they are screened according to the intensive clinical follow-up protocol there was no mortality. Analogous with patients with TS, quality of life is affected in AOS patients. Therefore, Chapter 15 studies, for the first time, how the subjective quality of life is affected in (28) AOS patients and investigates how the levels of anxiety and depression are affected by the burden of this disease. Compared to the general population, AOS patients scored significantly lower on the following SF-36 domains: physical functioning, vitality, social functioning, bodily pain, and general health. Patients with AOS scored higher on the HADS depression scale, while anxiety did not show a significant difference compared to the general population. This study emphasizes that patients' worries for their future and heredity of their disease are important factors for anxiety and should therefore be addressed in clinical practice.

General Discussion

This thesis focusses on three specific forms of aortopathies: women with Turner syndrome, patients with a bicuspid aortic valve, and patients with a SMAD3 gene mutation. At the most favourable end of the spectrum we find the BAV aortopathy, which is relatively common and can follow a benign course in most cases, where mere watchful waiting can be appropriate. Other aortopathie may be rare rare but can be very aggressive and require vigilant follow-up, such as the Aneurysm-osteoarthritis syndrome (AOS) caused by mutations in the SMAD-3 gene we discussed in 'Part III'. However, the dilemma shared between the patients who suffer from these diseases is that an optimal treatment approach for them is still unclear, and many etiological questions remain. This thesis attempts to find answers to these questions by retrospectively reviewing data from our own centre and contributing to the research efforts of other centres. Moreover, we also included BAV and TS patients in the new multi-centre prospective cohort study designed for this purpose: the BAV-study. This thesis describes the answers that were found as a result of those studies and reflects on the challenges that still remain for future consideration.

Turner Syndrome

Women with TS experience an overall threefold increase of mortality [1-3], and a 13-15 year reduction in life expectancy [2, 4]. Especially women with a 45,X0 monosomy, who are more prone to have congenital heart disease, are adversely affected [1, 5]. Therefore, cardiovascular disease is an important factor as cardiovascular pathology such as: aortic disease, valvular pathology, hypertension and ischaemic heart disease contribute to nearly half of this excess mortality [1, 6]. Careful documentation of the TS cardiovascular phenotype is essential discovering its cause.

Congenital heart disease

The etiology of Turner syndrome (TS) is still unknown and, as discussed previously in this thesis, several theories exist. A genetic cause, probably located on the X chromosome is suspected [5, 7]. TS women typically face a lifelong heavy burden of congenital and acquired cardiovascular disease, with increased mortality and morbidity [1, 4]. The most frequent cause of early mortality is congenital heart disease, occurring in approximately 23–50% of patients [4, 8-10]. Especially prevalent congenital heart diseases are a bicuspid aortic valve (BAV: 15-30%) and the coarctation of the aorta (CoA 12-17%). In this thesis, a relatively unknown vascular anomaly is described in more detail, the partial abnormal pulmonary venous return (PAPVR). We found that it occurred even more frequently in TS women than previously thought (Chapter 3). The prevalence of PAPVR is estimated to be 0.1% (18) In the general population, where we found an estimated prevalence of 25% in the cohort we studied. Therefore, it could be supposed that PAPVR may be an independent

marker for the TS diagnosis, as CoA [11]and BAV are [12]. Consequently, women with TS will have to be systematically screened to detect such anomalies, preferably using advanced imaging techniques, such as cardiac CT or MRI. The high spatial resolution of ECG-triggered cardiac CT may have the highest sensitivity to detect the sometimes small PAPVRs. However, CMR allows for shunt size quantification, which is ultimately needed for clinical decision making. In addition to the clinical relevance to the individual patient, the discovery of new aspects of the TS phenotype may provide valuable information about the etiology of CVD in TS women.

Another addition to the TS cardiovascular phenotype this thesis has made are the congenital morphological coronary artery anomalies described in chapter 6. Variations in coronary anatomy, like absent left main stem and left dominant coronary system, had already been described in women with TS and in BAV patients [13, 14]. However, such variations in coronary anatomy in TS women had not yet been related to the presence of BAV or even specific to BAV morphotypes. Therefore, we compared coronary anatomy between patients with TS and patients with an isolated BAV. We observed no difference in coronary dominance between patients with TS with and without BAV. Furthermore, bicuspid valves with fusion of right and left coronary leaflets, but without raphe, showed a high prevalence of left coronary dominance in both women with TS and isolated BAV. Absent left main stem was seen only in TS patients with RL- type BAV without raphe, which may be an important insight for the cardiothoracic surgeon to avoid complications during hypothermic perfusion. However, whether these coronary malformations increase mortality risk is unknown and is an important subject for further studies.

The third, and perhaps the most interesting addition to the TS phenotype, is the systolic and diastolic left ventricular dysfunction we described in Chapter 5 of this thesis. There seems to be a decrease in ventricular function in women with TS compared to healthy controls. We did not find an obvious reason for such a decrease in ventricular function. It would be logical to expect a connection to the high prevalence of congenital heart disease in this population. However, we could not establish such an association. The impaired LV function seemed to exist independently of traditional causes such as hypertension or CoA. An alternative explanation may lie in the disturbed hemodynamics in TS women via ventricular-arterial coupling [15]. TS women are known to have decreased aortic distensibility [16-19], and both systolic and diastolic hypertension are prevalent in these women. Increased vascular resistance could decrease the efficiency of the ventricular-arterial coupling. Reduced vascular compliance and increased arterial pressure may increase vascular resistance. The LV of TS women may subsequently compensate by increasing end-systolic volume and lengthening contraction, which in turn may cause hypertrophy [20]. Future studies will have to investigate a possible relation between diastolic function and aortic elasticity. Although the ventricular-arterial coupling may

potentially provide a pathophysiological basis on which we can understand and predict the disease process that takes place in TS, it does not provide information as to its etiology. A common underlying cause could be supposed.

Role for Cortisol?

Such a primary causative mechanism could lie in glucocorticoid metabolism; a recent study showed that long-term cortisol concentrations in scalp hair were elevated in patients with TS when compared to matched control subjects. [21]. Several aspects of the TS phenotype may well fit an important role for Cortisol.

Cortisol acts through both the glucocorticoid receptor and the mineralocorticoid receptor, the latter of which is expressed in the myocardium, endothelial cells, and the vascular smooth muscle [20]. The high cortisol level in TS patients was associated with short stature, total cholesterol levels, and a worse cardio metabolic profile in terms of fasting glucose and triglyceride levels [21]. It could be supposed that long-term exposure to increased cortisol levels is also related to the diastolic dysfunction in women with TS. Such dysfunction is for example frequently seen in populations of patients that are exposed to high levels of cortisol, such as patients with Cushing's syndrome (CS). It is well-known that the high cortisol in CS has multiple effects on the heart; increased prevalence of left ventricular (LV) hypertrophy, higher frequency of concentric remodeling, LV systolic and diastolic dysfunction, and left atrial systolic dysfunction, as well as increased regional LV wall thickness [22-25]. Additionally, subtle ECG-changes, such as prolonged QT-corrected dispersion, have also been described in CS patients [26]. In CS, the hypothesis is that not the severity of the excess, but rather the duration of hypercortisolism relates to the level of cardiac dysfunction [23]. Moreover, these negative cardiac effects are reversed upon initiation of treatment [27]. Pulse wave velocity was also increased in a cohort of pediatric patients with CS and was positively associated with midnight Cortisol [28]. Cortisol has also been associated with aortic pathology; mainly as a factor in aortic aneurysm formation [29] and aortic dissection [30]. Additionally, it is also found to be predictive of outcome in heart failure patients [31]. Moreover, individuals who are chronically exposed to elevated cortisol levels are prone to develop metabolic syndrome, including central obesity, insulin resistance, hyperglycemia, and dyslipidemia [24, 32].

These cardiac, aortic and metabolic effects strongly resemble those described in women with TS, especially those with a 45,X monosomy compared to other genotypes [33]. In our current study we also find a negative effect of the 45,X monosomy on diastolic function compared with other genotypes. This raises the question whether an underlying genetic cause of TS observed hypercortisolism could be supposed. And, indeed, such a gene, 5-HT2RC, located on the X-chrome is involved in the cortisol regulation. Studies by Brummett et al., suggest that functional polymorphism (rs6318) in this 5HTR2C gene is associated with

increased incidence of death or MI, independent of several traditional risk factors and two conventional markers of CVD severity [34, 35].

Despite these interesting similarities found in literature, such an association is still highly speculative and further studies are needed to confirm a possible causative relation between hormonal influences and the TS cardiovascular phenotype.

Aortic dilatation and dissection

Aortic dilatation poses a challenging dilemma in the clinical care of TS women. It is currently not well understood what its etiology is and what factors aggravate it. Moreover, it is not evident in which way we should measure it, absolute diameters or relative to body size or to the relevant population reference. This hampers establishing an optimal treatment strategy. Currently, it is considered to be appropriate to intervene earlier in the disease process than in dilated non-TS aortas.

In chapter 7 we described a TS cohort, in which aortic dimensions are measured using advanced imaging during a relatively long follow-up time. Aortic dilatation was found in 22% of women. Factors that are typically associated with large aortic diameters were hypertension, BAV, 45X0karyotype, weight, and growth hormone treatment. These women were followed-up for 7-years during which 2% had an aortic event. The aortic growth rate was low (0.20mm/year) but still exceeds that in the general population (0.12mm/year) [36, 37]. No associations for faster aortic growth could be determined upon long-term follow-up.

Another important aspect that comes into clearer view with the results of this study is the correction of the aortic diameter using the aortic size index in TS patients. The ASI corrects the Aorta for BMI, as it is based on the idea that relative aortic size is more important than absolute aortic size in predicting complications [38]and that a disproportionally large aorta, though 'small' in absolute terms, in a small female may still expose her to an increased risk for complications. This may, however, cause an 'overcorrection' of aortic diameter in some TS women, who are prone to be overweight and thus underestimate the risk these women are exposed to. The use of Z-score may be a valid alternative for ASI as this may take into account a TS-specific population mean. The Z-score, or standardized score, is the number of standard deviations that an individual's aortic diameter is above or below the mean value of a reference population. Z-score is a reliable method to evaluate the severity of the aortic diameter in women with TS [37, 39], especially in TW women >15 of age [40].

Especially the possible unfavourable effects on the aortic wall of growth hormone treatment are controversial. In animal and human cell models, treatment with GH has been observed to directly influence the homeostasis within the media layer of the aortic wall (27, 28).

Recently, Mortensen et al. have described comparable or smaller aortic growth rates as compared to age and gender matched healthy controls [41]. They confirm the adverse influence of BAV and CoA on aortic diameter in this population. These results reflect the difficulty of this research topic and there remains a need for validation by prospective studies in larger cohorts

Quality of life

In addition to comprehensive description of the TS phenotype a second aim of this thesis was to add value to the care of the individual TS patient. Often the quality of life (QoL) is not affected not only affected by disease severity or general health [42], but also by other socioeconomic factors such as the ability to take on life insurance or to find full-time employment [43]. Consequently, improvements in understanding of, for example, disease etiology may not always translate well to an actual increase in the perceived quality of life. More recently, 'value-based competition in health care' (VBHC) has become a guiding principle in the quest for high quality health care for acceptable costs [44]. It aims at achieving high value for patients, where value is defined as the health outcomes per dollar spent [45]. This introduces efficiency into the equation of healthcare, given that value is defined here as outcomes relative to costs. However, measuring these outcomes, which are inherently condition-specific and multidimensional, is difficult. This is particularly difficult given that for the majority of medical conditions, no single outcome captures the results of care. Therefore, as part of the corporate value-based health care program we developed, we report on a set of clinician and patient reported outcome measures in Chapter 4. Moreover, we described the health-related quality of life of women with Turner syndrome, because in order to improve health-related QoL (HR-QoL), we should first comprehensively measure outcome. By doing so, we showed that TS women suffer from impaired QoL, more perceived stress and increased fatigue compared to healthy controls. Such outcomes are important because perceived stress and increased fatigue can be considered targets for improvement of HR-QoL in TS women. Furthermore, a relationship between non-cardiac comorbidities and HR-QoL was found, which demonstrates that adequate multidisciplinary care for these women is vital to their perceived quality of life. However, more studies will be needed to establish cost-effective new targets for intervention that improve health care for women with Turner syndrome.

A paradigm shift towards VBHC means aiming at improving outcomes that really matter most to patients' lives. Before the introduction of this concept healthcare providers often tended to measure only what they could directly control in a particular intervention or what was easily measured, rather than the outcomes that effectively improved the standard of care as perceived by the patients [45]. However, we will also need to acknowledge some shortcomings of VBHC. Although VBHC improves many aspects of healthcare, its concepts, mainly taken from business strategy, cannot be unequivocally

translated to the context of health care. Groenewoud et al. [44] have recently discussed what they deem to be the four significant challenges of VBHC posed to ethics. Firstly, they argue that VBHC tends to neglect patients' personal values [1] by its narrow framing of the concept of 'value'. It simply assumes a certain hierarchy in values that may not be representative for every individual patient. Secondly, VHBC arguably ignores the intrinsic value of the 'caring act' [2] as it reduces it to its cash equivalent. Furthermore, VHBC is said to disproportionately replace *trust* in professionals with *accountability*, which has led to soaring bureaucracy and tightening organizational control over daily medical practice. Some authors argue we should not throw away the child with the bathwater, but rather a form a notion of 'intelligent accountability' that may alleviate the heavy administrative burden and secure the patient-doctor relationship [46]. Finally, VHBC may undermine solidarity, as it encourages patients to leave [3] if they feel that they may receive better healthcare elsewhere [44]. This consequently may create differences between rich and poor due to variances in access to information and access to alternative (private) healthcare options. To overcome these shortcomings, we will need to focus on increasing personal value by ensuring the outcome relates well to the values of each individual by providing both comprehensive and comprehensible information. This should entail increasing allocative value by equally distributing health-care assets amongst different subgroups by increasing health-care budget in a fair manner. This could for example be done by shifting allocated budget populations from evident overuse of low value to more high value interventions. Finally, we will need to develop systems on a population level that stimulate shift from low to high value interventions.

In short, the QoL of women with TS is compromised by several factors which we studied in Chapter 4. Knowledge of the factors that determine QoL in these women is essential in developing patient-centred health care. Whereas knowledge of these factors will not replace the need for an individual approach to patient-care, it will be a useful addition to the current tools at the clinicians' disposal.

Bicuspid aortic valve and Aortic Coarctation

Novel imaging techniques in bicuspid aortic valve patients

This thesis focused on different aspects of the bicuspid valve. One of them being the development of new imaging techniques that may facilitate the workflow of the caregiver. In Chapter 9 and 10 we described two novel methods, the measurement of GLS in 4D flow MR images and left-heart model based on speckle-tracking echocardiography, both of which have the potential to significantly reduce the effort and time spent per patient. Such techniques may also reduce inter- and intra-observer biases. Workflow automation is a double-edged sword, with benefits for both patient and physician. On the one hand, a more efficient, less user-dependent workflow may add value for the patient as it may potentially reduce medical errors and improve patient outcome [47]. On the other hand, these new techniques, using fully automated software based on artificial intelligence and big data have the potential to improve workflow efficiency for the physician tremendously [48]. By doing so, the time spent by physicians analyzing images could then be spent elsewhere and so such findings can be seen as of high value.

Aortic coarctation

The final three chapters of Part II (Chapter 11, 12 and 13) focus specifically on a problem that is related to the BAV: the aortic coarctation. BAV can be found in 70–75% of patients with the coarctated aorta (CoA) [49-51]. Conversely, approximately 7% of BAV patients have CoA [50]. Both lesions are part of the same diffuse arteriopathy [52]. Chapter 8 provides a comprehensive picture of this serious defect that warrants lifelong vigilant follow-ups. Several questions in the treatment of patients with CoA still remain. One of which concerns the optimal treatment of the defect; therefore, in Chapter 11 we described a cohort of adult patient with a CoA and chapter 12 specifically focuses on women with Turner Syndrome with concomitant coarctation of the aorta. Traditionally, since 1944, CoA has been treated surgically [53], which provides long-term follow-up and although it has significant risks it is considered a safe treatment option, as is described in chapter 8. Endovascular treatment of adult aortic coarctation has been developed in the early 90's [54]and is thus a relatively new alternative compared to surgery, and therefore the long term outcome is less well known [55]. We described 93 patients who were treated using stenting and primary angioplasty. We described 2 perioperative deaths and a 5-year survival of 89%. This adds important information to the existing evidence that percutaneous treatment is a safe and effective treatment as an alternative to CoA surgery for adults in the general population. However, women with TS differ from the general population in a key aspect for this discussion: fragility of the aortic wall. As described earlier, TS patients have a generalized aortopathy, which leads to increased prevalence of aortic dilatation and dissection. Our hypothesis was that this fragility may also potentially affect the outcome of the treatment. A frail coarctated aorta may be more safely corrected

using open surgery, where complications may be more readily dealt with. Therefore, we have performed our own multi-center study that aimed to retrospectively include only women with TS who had also been percutaneously treated for CoA. In total, 19 such patients were found in 10 centers. Twelve patients were treated for native and 7 for recurrent coarctation. Three (15.8%) adverse events occurred within 30 days of the procedure, including two dissections, one resulting in death. After 6.5 years, two additional deaths occurred, not known to be stent-related. This event-rate is markedly higher than in the general population, especially when considering the literature review of smaller similar cohorts. These risks suggest that alternative treatment options should be carefully weighed against percutaneous stenting strategies. Such decisions should be carefully made, preferably in a multi-disciplinary team with ample expertise in treatment of TS women.

The interrelation between BAV and CoA is further explicated in Chapter 13 which investigates the influence of a history of CoA on aortic events and dilatation in BAV patients. The current ESC guidelines advise ascending aortic surgery at a lower ascending aortic diameter in BAV patients with a history of CoA (50mm instead of 55mm, class IIa, level C) [51, 56]. An earlier study did find a higher aortic event rate in BAV with a history of CoA patients [57]; however in our cohort of 483 BAV patients we could not find evidence to substantiate this claim. Our study differed in the definition of primary endpoint event and study groups. Similar results to our study have been found [58, 59]with no significant difference or even lower event rates in non-CoA BAV patients. We also did not find a difference in aortic growth rates, which may suggest that preventative surgery is necessarily indicated earlier in these patients. However, hypertension is more prevalent in CoA patients, which is a risk factor for dissection, and therefore careful individual decision-making is advised.

SMAD3

Aortic dilatation

Part III of this thesis focusses on the most aggressive aortic pathology, that caused by pathogenic SMAD3 mutations. Together with osteoarthritis at young age this is encapsulated in the aneurysms-osteoarthritis syndrome or AOS [60, 61]. AOS has many similarities with Loeys-Dietz syndrome and is recognized by some as part of Loeys-Dietz syndrome [62]. Short-term follow-up showed fast and unpredictable aortic growth with high morbidity [61]. However long-term follow-up had not yet been described and it was yet unknown how the rate of aortic dilatation in SMAD3 patients compares to other syndromic causes of aortic dilatation. Therefore, we described all patients who had been under frequent follow-up in our center. This resulted in a small cohort of 28 patients, which is still relatively large for such a rare disease, with a follow-up duration of 10 years. What

could be appreciated is that although the growth is fast, it is currently adequately monitored using our in-house protocol which includes yearly full-body advanced imaging, as no mortality occurred during this follow-up period. In our cohort aortic growth rates were lower than expected, although clearly higher than in the general population: 0.07 and 0.09 mm per year of life in women and men respectively [63]. The highest growth rate was observed at the sinotubular junction, 0.4mm/year, which resembles other aortopathies such as Marfan syndrome [64]. Obviously, from a patient-perspective not the growth of the aorta but the zero deaths are the most important finding. Moreover, half of patients needed very invasive surgery of the aorta and another 14 vascular interventions were done. Future research will have to show whether less frequent follow-up may be appropriate for a sub-set of the patients.

Quality of Life

Another question in this patient group is how the impending high risk of aortic dissection or rupture affects the psychological well-being in SMAD3 patients. It is known already that their orthopedic complaints have a significant influence on day-to-day life and may influence their feeling of well-being even more. Therefore, we described the psychological well-being of the 28 patients under follow-up in our center. We found significantly decreased health-related quality of Life, as scored by the SF-36, compared to the general population. This difference was mainly driven by the lower physical component summary compared to the mental component summary. There is, however, a marked discrepancy with congenital heart disease patients, who have as described earlier, similar or even more favorable levels compared to healthy controls [42]. We suggest that this difference between patients with congenital heart disease and AOS patients is most likely due to the timing of the onset of the complaints. Congenital heart disease by definition starts at birth, meaning that patients learn to cope with their limitations early on, and perhaps look at life as a glass that is half full. AOS patients, however, typically develop symptoms between the age of 22 to 38years old, which cause a sharp decrease in their perceived health. In addition to this decreased perception of health due to being diagnosed with a heart disease, these patients often experience the accompanying osteoarthritis as most debilitating. This creates the need for them to adapt to these new 'patient ship' with all the challenges this presents.

Future directions

During this thesis we encountered several limiting factors, not due to shortcomings in study design but due to the nature of the defects we were studying. The first limitation is study size; Turner syndrome is a relatively rare and very heterogeneous disease. Often the complications we want to study in these women, such as aortic dissections, are rare. Therefore, close cooperation between academical medical centers involved in the care for these women is vital. Preferably on an international level, but we can start closer to home

and organize and standardize the TS research nationally. We are under way with such an effort in the cooperation between the university hospitals of Nijmegen and Rotterdam and the Dutch-Flanders collaboration. The second obstacle is standardization, with variability between methods being a problematic source of bias. It hampers clinical interpretation of the, often small, differences between outcomes. Also, the method of defining aortic dilatation and with use of ASI or Z-score needs more attention and standardization. The third and final task for future researchers is patience; if we want to study processes such as aortic dilatation, we need time. The pathophysiological changes in the aorta do not happen overnight and if we want to understand what is happening, we will need to observe these patients very closely over the decades to come.

Conclusions

The aims of this thesis were to elucidate the etiologies and pathogenic mechanisms leading to BAV or aneurysm formation and unravel risk factors for disease progression. To explore the myriad of cardiovascular abnormalities associated with TS and study their impact on the quality of life of the individual patient. We found PAPVR to be prevalent among TS women, providing important information on the TS phenotype. We showed that the health-related quality of life in the women was impaired compared to relevant controls, driven by increased fatigue and stress. This may offer opportunities for therapeutic interventions in the future. We showed that systolic and diastolic left ventricular function is reduced in TS women compared to age and gender matched controls in TS women. We studied coronary anomalies in TS and BAV patients and found presence of left dominance to be a feature of BAVs without raphe, independent of TS. Both TS and RL BAV without raphe seemed independently associated with absent left main stems. Awareness of such anomalies may be important to avoid complications during surgical procedures in these patients. We showed that aortic dilatation is common in TS patients; however, aortic dissection, related mortality, and preventive aortic surgery are rare. Finally, we found that SMAD3 patients had a reduced quality of life compared to the general population, with their worries for the future and heredity of their disease constituting particularly important factors for anxiety. This is an important insight and should be addressed in clinical practice. Regarding their aortic pathology we showed that although many need invasive preventative aortic surgery, no mortality occurred. The observed aortic growth was highest at the sino-tubular junction and comparable to other genetic aortopathies, such as Marfan syndrome.

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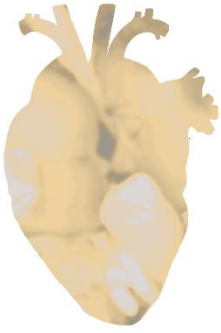

17

Postscript

Nederlandse samenvatting

Deel I Het syndroom van Turner

Hoofdstuk 2 is gebaseerd op een boekhoofdstuk en introduceert het fenotype dat wordt geassocieerd met het syndroom van Turner (TS). In dit hoofdstuk wordt de genetische etiologie van het syndroom besproken, het is de basis waarop 'Deel I' van dit proefschrift voortbouwt. In hoofdstuk 3 beschrijven we een retrospectief cohort van 96 patiënten met TS met gedetailleerde beeldvorming van de longvasculatuur. Eerdere studies suggereerden dat TS-patiënten een verhoogde incidentie van gedeeltelijk abnormale pulmonale veneuze terugkeer (PAPVR) kunnen hebben. Dit vermoeden wordt bevestigd in hoofdstuk 3 waar we aantonen dat circa 1 op 4 van al onze TS-patiënten een dergelijke PAPVR had. Met deze studie veranderde ook de klinische praktijk, aangezien geavanceerde beeldvorming bij deze patiënten nu routinematig wordt gecontroleerd op aanwezigheid van PAPVR. In hoofdstuk 4 beschrijven we het begrip 'health-related quality of life' (HR-QoL): de gezondheid gerelateerde kwaliteit van leven. We beschrijven deze HR-QoL van 177 vrouwen met TS en onderzoeken de factoren die deze kwaliteit van leven beïnvloeden. Deze studie maakt deel uit van het 'value-based health-care programma' in het Erasmus MC. Value-based healthcare betekent gericht zijn op het verbeteren van resultaten die er het meest toe doen voor patiënten. Om dit te doen, moeten we eerst deze resultaten meten. In deze studie hebben we aangetoond dat vrouwen met TS een verminderde kwaliteit van leven ervaren, meer stress hebben en vermoeider zijn in vergelijking met gezonde controles. Wat daarnaast opviel is dat vrouwen met TS vaker individuele sporten te beoefenen, het vaakst hardlopen. We hebben ook onderzocht hoe tevreden TS-vrouwen waren met hun lichaam op een speciale schaal van 'lichaamstevredenheid'. TS-vrouwen waren het meest ontevreden over hun taille, lichaamsbouw, figuur, buik en gewicht. Deze resultaten, vooral ervaren stress en verhoogde vermoeidheid, kunnen nu als specifieke doelen voor verbetering van kwaliteit van leven worden gebruikt. In hoofdstuk 5 beschrijven we de systolische linkerventrikel globale llongitudinale strain (LvGLS) en linkerventrikel diastolische strain (Sre), een maat voor de functie, bij 94 volwassen vrouwen met TS en relateren deze aan hun klinische uitkomsten. Vrouwen met TS hadden een significant lagere systolische LvGLS (-17,82 ± 2,98% versus -21,80 ± 1,85%, p <0,001) en Sre 0,98 ± 0,32 s-1 versus 1,27 ± 0,19 s-1, p> 0,001) in vergelijking met gezonde vrouwen. Bovendien hadden TS-vrouwen een verminderde diastolische functie, hoewel LvGLS en Sre vergelijkbaar waren tussen TS-patiënten met en zonder structurele hartziekte. Vrouwen met TS hadden ook een aanzienlijk lagere maximale inspanningscapaciteit, verminderde zuurstofopname en een verminderde maximale hartslag tijdens inspanning. In hoofdstuk 6 wordt de anatomie van kransslagvaten van patiënten met TS vergeleken met die van patiënten met een bicuspide aorta klep (BAV). Deze studie toont aan dat patiënten met BAV met fusie van rechter en linker klepblaadjes zonder raphe een hoge prevalentie

hebben van linker coronaire dominantie in de groep van TS-BAV evenals in geïsoleerde BAV (beide 38%). Daarnaast wordt afwezigheid van de linker hoofdstam vaker gezien bij patiënten met TS èn BAV (13%) in vergelijking met patiënten met geïsoleerde BAV (0%). Aortadilatatie is een belangrijke zorg bij TS-vrouwen. Vaak neemt de aortadiameter sneller toe in vergelijking met de algemene bevolking en is electieve chirurgie nodig. Daarom hebben we een groot retrospectief cohort van 268 TS-vrouwen bestudeerd met geavanceerde beeldvorming van de aorta. Hoofdstuk 7 gaat over aortadilatatie bij deze vrouwen met TS, een veelbesproken onderwerp in de TS-literatuur omdat het veel voorkomt en er veel factoren zijn, zoals groeihormoonbehandeling tijdens de kindertijd, die er mee in verband worden gebracht. In deze studie hebben we sommige van deze associaties bevestigd. Bovendien waren gelukkig aortadissectie en preventieve aorta-chirurgie zeldzaam.

Deel II De Bicuspide Aorta Klep en Coarctatie van de Aorta

Hoofdstuk 8 is gebaseerd op een boekhoofdstuk en dient als een inleiding tot 'Deel II' van dit proefschrift. In dit hoofdstuk wordt de-coarctatie van de aorta besproken, een vorm van aortapathologie die verweven is met zowel het syndroom van Turner dat in deel I is besproken als met de bicuspide aortaklep die in deel II wordt besproken. In hoofdstuk 9 evalueerden we een nieuwe methode voor strainanalyse met behulp van 4D flow CMR. We tonen aan dat GLS-analyse mogelijk is met behulp van de magnitude datasets geproduceerd door 4D flow CMR met adequate beeldkwaliteit bij BAV-patiënten. GLS-meting door CMR correleerde goed met CT en spikkelsporen 2D TTE. Hoofdstuk 10 richt zich op volumekwantificatie van de linker hartkamer met behulp van een nieuw algoritme op 3D echocardiografie datasets. In theorie maakt het gebruik van een volledig geautomatiseerde methode voor volumekwantificatie een gebruiker-onafhankelijke en daardoor zeer reproduceerbare meting mogelijk. Linker ventriculaire eind-diastolische en eind-systolische volumes en ejectiefractie berekend door de software en goed gecorreleerd met handmatige 2D en 3D echocardiografische metingen. Het linker atriumvolume correleerde significant, hoewel LHM het grotere linker atriumvolume schatte in vergelijking met zowel 2D- als 3D-echocardiografie. Dergelijke software kan helpen bij het overwinnen van enkele van de belangrijkste hindernissen bij het integreren van 3D-analyse in de dagelijkse praktijk, omdat het gebruikers-onafhankelijk is en zeer reproduceerbaar in een groep patiënten met BAV. Bicuspide aortaklep wordt vaak gezien samen met aorta-coarctatie. Hoofdstuk 11 beschrijft de resultaten van 93 patiënten die stenting in de aorta-coarctatie hebben ondergaan. Complicaties traden op bij negen (10%) patiënten, waaronder aortadissecties bij drie (3%) patiënten en intraoperatieve breuken bij twee

patiënten. De aortadissecties en -breuken werden met succes behandeld door een extra bedekte stent in te zetten. Twee patiënten stierven binnen 30 dagen na de indexprocedure. Na een gemiddelde follow-up van 3,2 ± 3,1 jaar waren bijna alle patiënten (98%) klinisch verbeterd en waren alle stents gepatenteerd. Herinterventie was nodig bij 10 (11%) patiënten. De vrijheid van herinterventie na 5 jaar was 85%. Twee extra patiënten stierven tijdens de follow-up van coarctatie-gerelateerde oorzaken, waaronder het scheuren van een geïnfecteerd transplantaat en viscerale ischemie. De overleving van de patiënt na 5 jaar was 89%. Deze studie toont aan dat endovasculair herstel van aorta-coarctatie effectief is en een acceptabel veiligheidsprofiel heeft bij de behandeling van nieuw gediagnosticeerd CoA en na eerste chirurgische reparatie. Het voegt eraan toe dat aortaruptuur een zeldzame (2%) maar verwoestende complicatie is met hoge mortaliteit. Het aantal herinterventies is acceptabel, met hoog procedureel en langdurig klinisch succes.

Hoofdstuk 12 bouwt voort op het vorige hoofdstuk, waar stenten van een aorta coarctatie vaak veilig is kan dit bij vrouwen met TS (met een vasculopathie van de aorta), met een frailer aortawand als gevolg. Bij vrouwen is CoA een van de meest voorkomende aangeboren hartziekten (7-18%). Het oplossen van de aorta-vernauwing wordt in het algemeen beschouwd als een veilig alternatief voor de chirurgische aanpak in geselecteerde gevallen. De inherent zwakkere aortawand van TS-patiënten kan hen echter blootstellen aan een groter risico dan hun niet-TS-leeftijdsgenoten. Daarom was onze hypothese voor deze multicenter retrospectieve studie om de veiligheid van coarctatiestenting in een cohort van TS-patiënten te onderzoeken. TS is echter een relatief zeldzame ziekte en CoA bij deze patiënten is daarom nog zeldzamer. We hebben echt ons best gedaan om 19 patiënten met TS uit 10 centra te verzamelen die waren behandeld met percutane stent angioplastiek voor aorta-coarctatie. Drie (15,8%) bijwerkingen traden op binnen 30 dagen na de procedure, inclusief twee dissecties ondanks het gebruik van bedekte stents, waarvan één resulteerde in overlijden. Bij langdurige follow-up (6,5 jaar, min-max: 1-16) traden twee extra sterfgevallen op waarvan niet bekend was dat ze stent-gerelateerd waren. Daarbij hebben we aangetoond dat, hoewel percutane behandeling van aorta-coarctatie bij TS-patiënten effectief is, dit gepaard gaat met ernstige morbiditeit en mortaliteit. Daarom suggereren deze risico's dat alternatieve behandelingsopties zorgvuldig moeten worden afgewogen tegen percutane stentstrategieën. Hoofdstuk 13 probeert een einde te maken aan de controverse over de vraag of het hebben van een CoA geassocieerd is met grotere aortadiameters en hogere complicaties. Deze studie beschrijft de uitkomst van 483 BAV-patiënten en evalueert of de coëxistentie van CoA geassocieerd is met aorta-gebeurtenissen, aortadilatatie en aortadiametergroei. We concludeerden dat het naast elkaar bestaan van CoA niet was geassocieerd met een hoger percentage aorta-gebeurtenissen, een hogere prevalentie van aortadilatatie of een sneller oplopende aortagroei. Daarom moet CoA niet worden gezien als een risicofactor die eerdere preventieve aorta-chirurgie bij BAV-patiënten rechtvaardigt.

Deel III SMAD3

In 2011 beschreef onze studiegroep voor het eerst het aneurysma-osteoartrose syndroom (AOS) veroorzaakt door een mutatie in het SMAD-3-gen. Hoofdstuk 14 beschrijft de lange termijn follow-up van uitkomst en aortadiameters bij deze patiënten. We tonen aan dat, hoewel deze patiënten nog steeds een hoog risico lopen, er geen sterfte was bij screening volgens het intensieve klinische follow-up protocol. Net als bij TS wordt de kwaliteit van leven bij deze patiënten aangetast. Hoofdstuk 15 onderzoekt voor het eerst bij 28 AOS-patiënten hoe de subjectieve kwaliteit van leven en het onderzoeken van angst en depressie wordt beïnvloed door de last van deze ziekte. In vergelijking met de algemene bevolking scoorden AOS-patiënten aanzienlijk lager op de volgende SF-36-domeinen: fysiek functioneren, vitaliteit, sociaal functioneren, lichamelijke pijn en algemene gezondheid. Patiënten met AOS scoorden hoger op de HADS-depressieschaal, terwijl angst beleving geen significant verschil vertoonde in vergelijking met de algemene bevolking. Deze studie benadrukt dat de zorgen van patiënten voor hun toekomst en de erfelijkheid van hun ziekte belangrijke factoren voor angst zijn en daarom in de klinische praktijk moeten worden aangepakt.

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PhD Portfolio

Name	Allard van den Hoven
Department	Cardiology
Research School	COEUR, Erasmus MC
PhD period	October 2014 – May 2016 And May 2018 – 01 October 2019
Title Thesis	Syndromic thoracic aortic disease
Promotor	Prof dr. J.W. Roos-Hesselink
Co-promotor	Dr. A.E. van den Bosch (copromotor)

PhD training

	Year	Workload (ECTS)
General academic skills and research skills		
Biostatistical methods I (CC02)	2014	5.7
Cursus Openclinica	2014	0.3
Research Integrity	2015	0.3
Biomedical English Writing and Communication	2015	3.0
Workshop on Photoshop and Illustrator	2015	0.3
In-depth courses		
New imaging strategies for the detection of atherosclerosis	2014	0.3
Cardiovascular clinical epidemiology	2014	0.5
COEUR PhD Day	2014	0.3
COEUR Congenital heart disease	2015	1.5
Annual Intensive exam orientated congenital echocardiography course	2015	1.5
COEUR Congenital heart disease	2018	1.5
Annual Intensive exam orientated congenital echocardiography course	2018	1.5
Dutch Heart Foundation Papendal course	2018	2.1

	Year	Workload (ECTS)
(International) Conferences and symposia		
NVVC Autumn conference, Papendal	2014	0.6
NVVC Spring congress, Noordwijkerhout	2015	0.6
AEPC Congress, Prague	2015	0.9
NVVC Autumn congress, Papendal	2015	0.6
EuroEcho, Sevilla	2015	1.2
ESC congress , Rome	2016	1.5
Davos Winter meeting	2016	1.2
Euroguch, Lausanne	2017	0.6
ESC congress, Barcelona	2017	1.5
Davos Winter meeting	2018	1.2
ESC congress, Munchen	2018	1.5
RV Failure symposium, Rotterdam	2018	0.3
ACHD congress, Toronto	2018	0.3
Seminars and workshops		
Junior Kamer dag, Gouda	2014	0.6
TED-talk masterclass, Delft	2018	0.5
EACP Course on Sports Cardiology, Munich	2018	0.6

Presentations

Oral presentations		
NVVC autumn conference, Papendal, The Netherlands	2014	0.6
Turner patient verenigings dag, Amersfoort	2014, 2015	0.2
BAV-consortium research meetings	2014-2018	0.6
Aorta symposium, Rotterdam	2015	0.3
EuroEcho, Sevilla	2015	0.6
NVVC Autumn congress, Papendal	2015	0.6
Journal club, Erasmus MC, Rotterdam	2016	0.1
Hartstichting dag	2017	0.1
Davos Winter meeting	2016	0.6
Research meetings, department of congenital cardiology, Rotterdam	2014-2018	0.4
Davos Winter meeting	2018	0.6
Journal club, Erasmus MC, Rotterdam	2019	0.1

	Year	Workload (ECTS)
(Moderated) Poster Presentations		
NVVC Spring congress, Noordwijkerhout	2015	0.3
AEPC Congress, Prague	2015	0.3
Euroguch Congress, Lausanne	2017	0.3
ACHD congress, Toronto	2018	0.3
Dutch Heart Foundation PhD course: Cardiac Function & Adaptation, Papendal.	2018	0.6

Teaching activities

Lecturing		
Minor CHD, Aortic pathology and CHD	2014	0.1
Supervising		
Master's thesis: strain imaging in Turner syndrome	2018	0.9
Systematic review, 2nd year medical students	2015, 2016, 2018	0.3

About the author

Allard Tiberius van den Hoven, born on October 2nd 1990 in Rotterdam in the Netherlands, graduated high school in 2009.

Van den Hoven started medical school at the Erasmus University Rotterdam in 2009. As a Master's student he worked as a research student for the department of 'Clinical Epidemiology'. For his Master thesis he studied pulmonary vascular return in women with Turner syndrome. This resulted in his first publication and was also the start of his PhD research at the department of Cardiology (Erasmus MC, Rotterdam).

Under the supervision of prof. dr. Roos Hesselink and dr. van den Bosch he was involved in the management of a large multicenter study funded by the Dutch Heart Foundation: the Bicuspid Aortic Valve (BAV) Study. After completing the patient inclusion he started his clinical rotations at the Erasmus Medical Center which he finished in 2018, obtaining his Master's degree. After his Medical training he returned to PhD research and completed the three-year follow-up of the BAV-study.

In October 2019 he started working as a clinical resident (ANIOS) at the department of Internal Medicine at the Sint-Franciscus Gasthuis & Vlietland Rotterdam. He is currently employed in the Erasmus MC as a cardiology resident (ANIOS).

Van den Hoven has always been active in sports. He started rowing at KR&ZV de Maas in Rotterdam where he joined the competitive team and competed at (inter)national championships, culminating in several national championship titles, and a bronze medal at the World Rowing Junior Championships. During his Bachelor studies he competed three consecutive years in the World Rowing Under 23 Championships.

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If you can force your heart and nerve and sinew
To serve your turn long after they are gone,
And so hold on when there is nothing in you
Except the will which says to them: 'Hold on!'

If you can fill the unforgiving minute
With sixty seconds' worth of distance run,
Yours is the Earth and everything that's in it,
And - which is more - you'll be a Man, my son!"

– Rudyard Kipling, If –

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