Congenital Aortic Stenosis and Aneurysms

Denise van der Linde

Congenital Aortic Stenosis and Aneurysms

Congenitale aorta stenose en aneurysmata

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam

op gezag van de rector magnificus
Prof.dr. H.G. Schmidt
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 19 april 2013 om 11.30 uur

door

Denise van der Linde

geboren te Rotterdam

ERASMUS UNIVERSITEIT ROTTERDAM

Colofon

Van der Linde, D.
Congenital aortic stenosis and aneurysms.
ISBN: 978-90-5335-585-5

Lay-out by: Nikki Vermeulen, Ridderprint BV, Ridderkerk, the Netherlands
Cover by: Robert Kanters, Ridderprint BV, Ridderkerk, the Netherlands
Printed by: Ridderprint BV, Ridderkerk, the Netherlands
Number of copies: 650

Promotiecommissie

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"It is a sign of strength, not of weakness,
to admit that you do not know all the answers."

John P. Loughrane

Financial support for the publication of this thesis was generously provided by:

Erasmus University Rotterdam	Biotronik Nederland B.V.
J.E. Jurriaanse Stichting	Servier Nederland Farma B.V.
Stichting Lijf en Leven	St. Jude Medical Nederland B.V.
Cardialysis	Edwards Lifesciences
Roche Diagnostics Nederland B.V.	Boehringer Ingelheim B.V.
Merck Sharp & Dohme B.V.	GE Healthcare B.V.

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

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Abbreviations and acronyms

- **2D** = two-dimensional
- **3D** = three-dimensional
- **AF** = atrial fibrillation
- **ACE** = angiotensin-converting enzyme
- **AHA** = American Heart Association
- **AOS** = Aneurysms-Osteoarthritis syndrome
- **AoS** = aortic stenosis
- **aPWV** = aortic pulse wave velocity
- **AS** = aortic stenosis
- **ASD** = atrial septal defect
- **ASE** = American Society of Echocardiography
- **AR** = aortic regurgitation
- **ARB** = angiotensin receptor blocker
- **AR-CL** = autosomal recessive cutis laxa
- **ATS** = arterial tortuosity syndrome
- **ASTRONOMER** = Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin
- **AV** = atrioventricular
- **AVA** = aortic valve area
- **AVR** = aortic valve replacement
- **β-MHC** = beta-myosin heavy chain
- **BAV** = bicuspid aortic valve
- **BMI** = body mass index
- **bpm** = beats per minute
- **BSA** = body surface area
- **CHD** = congenital heart disease
- **CI** = 95% confidence interval
- **CMR** = cardiac magnetic resonance
- **CO** = cardiac output
- **Coarc** = coarctation of the aorta
- **COL3A1** = collagen type III alpha 1
- **CONCOR** = CONgenital CORvitia
- **CT** = computed tomography
- **CTA** = computed tomography angiography
- **CV** = coefficient of variation
- **DSS** = discrete subaortic stenosis
- **EAE** = European Association of Echocardiography
- **ECG** = electrocardiogram
- **EDS** = Ehlers-Danlos Syndrome
- **EDV** = end-diastolic volume
- **ESV** = end-systolic volume
- **EF** = ejection fraction
- **ESC** = European Society of Cardiology
- **FBLN-4** = fibulin-4
- **FBN1** = fibrillin-1
- **FTAAD** = familial thoracic aortic aneurysm-dissection
- **FS** = fractional shortening
- **GLUT10** = glucose transporter type 10
- **GUCH** = grown-up congenital heart disease
- **HDL** = high-density lipoprotein
- **HOCM** = hypertrophic obstructive cardiomyopathy
- **HR** = hazard/heart rate
- **HS-CRP** = high-sensitivity C-reactive protein
- **IQR** = interquartile range
- **KM** = Kaplan-Meier
- **LDS** = Loeys-Dietz syndrome
- **LDL** = low-density lipoprotein
- **LV** = left ventricular
- **LVH** = left ventricular hypertrophy
- **LVOT** = left ventricular outflow tract
- **MFS** = Marfan syndrome
- **MMP** = matrix metalloproteinase
- **MRA** = magnetic resonance angiography
- **MRI** = magnetic resonance imaging
- **MV** = mitral valve
- **MYLK** = myosin light chain kinase
- **NOTCH 1** = neurogenic locus Notch homolog protein 1
- **NT-proBNP** = N-terminal pro brain natriuretic peptide
- **NYHA** = New York Heart Association class
- **OCD** = osteochondritis dissecans
- **PDA** = patent/persistent ductus arteriosus
- **PEFR** = peak early filling rate
- **PKD** = polycystic kidney disease
- **PLFR** = peak late filling rate
- **Pmax** = peak transaortic gradient
- **PROCAS** = Prospective randomized trial of the effects of Rosuvastatin on the progression of stenosis in adult patients with Congenital Aortic Stenosis
- **PS** = pulmonary stenosis
- **PTPN11** = tyrosine-protein phosphatase non-receptor 11
- **ROI** = regions of interest
- **SALTIRE** = Scottisch Aortic Stenosis and Lipid Lowering Trial, Impact on Regression
- **SD** = standard deviation
- **SEAS** = Simvastatin and Ezetimibe in Aortic Stenosis
- **SLC2A10** = solute carrier familiy 2, facilitated glucose transporter member 10
- **SOS1** = son of sevenless homolog
- **SPSS** = Statistical Package for the Social Sciences
- **SSFP** = steady state free precision
- **SV** = stroke volume
- **TAA** = thoracic aortic aneurysm
- **TAAD** = thoracic aortic aneurysms and dissections
- **TASS** = Tyrolean Aortic Stenosis Study
- **TAV** = tricuspid aortic valve
- **TAVI** = transcatheter aortic valve implantation
- **TGA** = transposition of the great arteries
- **TGF-β** = transforming growth factor beta
- **TGF-βR** = transforming growth factor-β receptor
- **TOF** = tetralogy of Fallot
- **TTE** = transthoracic echocardiography
- **UTRs** = untranslated regions
- **Vmax** = peak aortic velocity
- **VSD** = ventricular septal defect
- **VSRR** = valve sparing aortic root replacement

PART I

Introduction

General introduction

1

Introduction

Due to improvements in pediatric cardio-thoracic surgery, anesthesia and diagnostics over the past decades, the number of adult patients with congenital heart disease (CHD) is growing. This causes an increasing demand in clinical practice for insight in long term outcome in both non-operated and operated adult CHD patients. Furthermore, knowledge about etiology and genetics of CHD is rapidly expanding. Every day new genes and syndromes are identified.

In order to grasp the exact nature of the pathologies described in this thesis, the epidemiology of CHD and the functional anatomy of the left ventricular outflow tract and aorta will first be delineated. Thereafter, the congenital aortic disorders investigated in this thesis will be introduced individually. Finally, the aim and outline of this thesis will be presented.

Epidemiology of congenital heart disease

CHD is the most common type of birth defect, accounting for 28% of all major congenital anomalies.[1] Of the 150 million babies born around the globe annually, more than a million are affected by CHD.[2] This represents an enormous global health burden, not only in developed countries, but certainly also in developing countries. In developing countries, CHD is probably an underestimated cause of mortality and morbidity due to lack of resources.

Birth prevalence of CHD is generally considered to be around 8 per 1000 live births, but varies widely between published reports.[2] The eight most common congenital heart defects are: ventricular septal defect (37%), atrial septal defect (10%), persistent ductus arteriosus (8%), pulmonary stenosis (8%), tetralogy of Fallot (4%), coarcatation of the aorta (4%), aortic stenosis (4%) and transposition of the great arteries (3%).[2]

The growing adult population

Massive breakthroughs in cardiovascular diagnostics and cardio-thoracic surgery in recent decades have led to a reduction in infant mortality.[3-4] Nowadays the vast majority of babies born with CHD can expect to reach adulthood, and with continued improvements in surgery and care this number will only increase further in the upcoming decades.[5] Consequently, a new and steadily growing patient population is emerging: grown-up congenital heart disease (GUCH) patients. Furthermore, some defects may be diagnosed for the first time in adulthood. The prevalence of CHD is estimated to be 4 per 1000 adults.[6] GUCH patients require long term expert medical care in specialized centers to deal with the unique health care needs in this population, such as psychosocial issues, pregnancy risk, recurrence risk, career planning and re-operations. Successful transition from pediatric cardiology into the adult health care system is crucial to maintain adequate care and follow-up in these patients.[7]

Epidemiology of congenital aortic disorders

One of the most common congenital pathologies affecting the aortic valve is congenital aortic stenosis (AS), which accounts for approximately 4% of all congenital heart defects.[2]

Congenital AS can occur at a valvular, subvalvular or supravalvular level.[8] In this thesis, only sub- and valvular congenital AS are topics of investigation.

Another frequent, and often feared, aortic abnormality is a thoracic aortic aneurysm. The greatest danger is that an aortic aneurysm may rupture - causing severe, life-threatening bleeding**.** Various underlying disorders, ranging from hereditary syndromes to congenital heart defects, can cause the aorta to dilate. These disorders will be described extensively in the last parts of this thesis.

From left ventricular outflow tract to aorta: functional anatomy

Travelling back in time to January 9th 1513, a manuscript of Leonardo da Vinci appears with rather precise descriptions and drawings of the aortic valve complex (Figure 1).

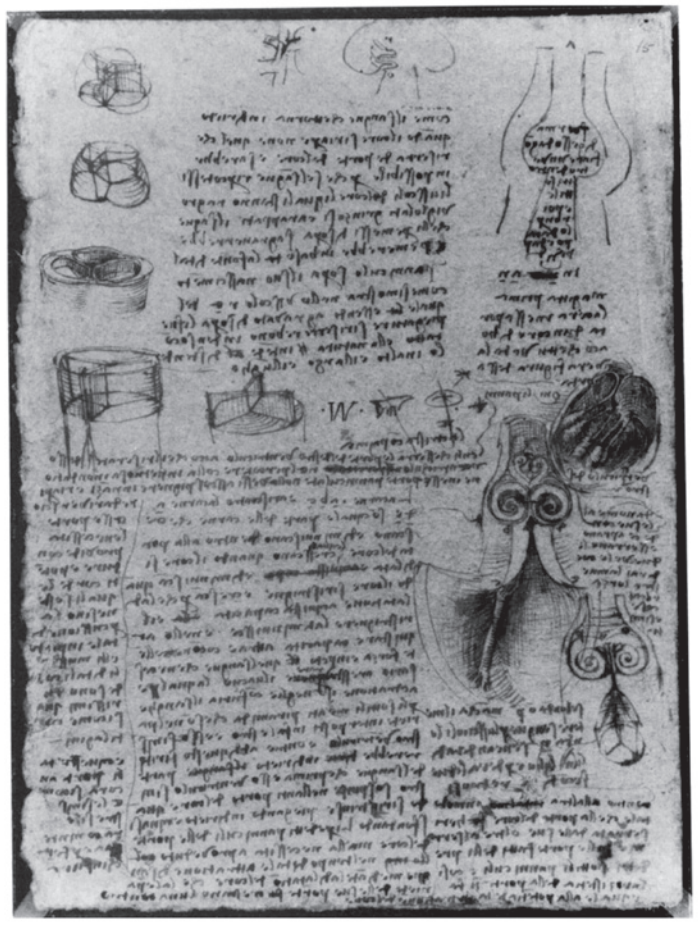

Figure 1. *A page in Leonardo da Vinci's notebook (Recto 19082) demonstrating sketches of the left ventricular outflow tract and aortic root. (Brown ink on paper, The blood flow through the aorta, brown ink on paper, The Royal Collection 2009, Her Majesty Queen Elizabeth II, RL 19082r).*

Although a bovine heart was used to create these drawings, he clearly illustrates remarkable insight in the aortic valve structure and the hemodynamics in the sinuses of Valsalva. In his notes he writes: *"on the reopening [diastole] of the left ventricle the blood contained in it ceases to escape from the ventricle, and at that time the escaping blood would attempt to return into this ventricle together with that which lies above it, but the remainder of the revolving impetus which still exists in the escaping blood is that which with this revolving beats against the sides of the three valves and closes them so that the blood cannot descend"*.[9] Hereafter, he elegantly notes that the current of the blood which closes the aortic valve has to be lateral and not perpendicular, because otherwise the cusps would get wrinkled.[9]

The left ventricular outflow tract (LVOT) is considered to be that region of the left ventricle that lies between the anterior cusp of the mitral valve and the ventricular septum.[10] The smooth anteromedial wall of the LVOT is formed by the ventricular septum. The upper medial part just beneath the junction of the right coronary and noncoronary cusps of the aortic valve is formed by the membranous ventricular septum. This structure is surgically important, as the bundle of His courses beneath the membranous septum and may be injured in the course of resection or suture placement, resulting in complete heart block.[11]

The aortic root is a highly complex structure that forms the transition from the fibromuscular LVOT to the fibroelastic wall of the aorta. As the aortic valve leaflets are incorporated into the cardiac skeleton, all chambers of the heart are directly related to the aortic valve complex.[12-13] The aortic valve normally consists of 3 semilunar leaflets, which meet centrally along a line of coaptation when the valve is closed. Each leaflet has attachments to the aorta and within the left ventricle (LV). Behind each leaflet, the aortic wall bulges outward to form the sinuses of Valsalva. The left and right aortic sinuses give rise to the coronary arteries and contain ventricular musculature at their base structure. Taking all these facts into account, we reach the conclusion that the annulus has a crown-like circlet shape extending all the way up to the sinotubular junction, rather than being just a flat ring (Figure 2).

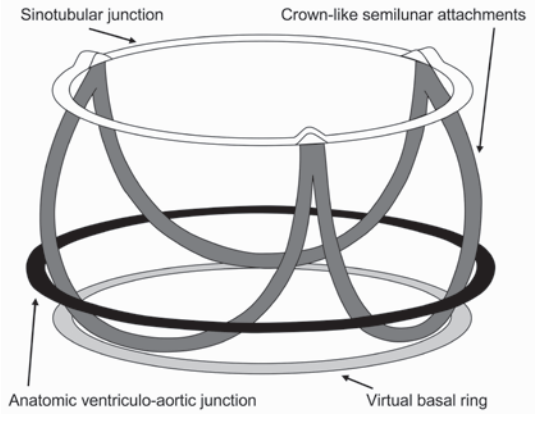

Figure 2. *Complex crown-like structure of the aortic valve annulus.*

The aorta is the largest artery in the body, originating from the aortic valve and extending throughout thorax and abdomen (Figure 3). The best known function of the aorta is distributing oxygen rich blood to all major organs. However, another important function of the aorta is to reduce LV afterload and facilitate diastolic perfusion of the coronary arteries.[14] In order to perform this task, the aorta has to be able to distend and recoil in response to pulsatile flow without rupturing. Therefore the aortic vascular wall consists of a complex composition of multiple layers: tunica adventitia, tunica media and tunica intima. Within the tunica media, smooth muscle cells facilitate vasodilatation and vasoconstriction, while collagen provides strength and elastin enables distensibility.[14]

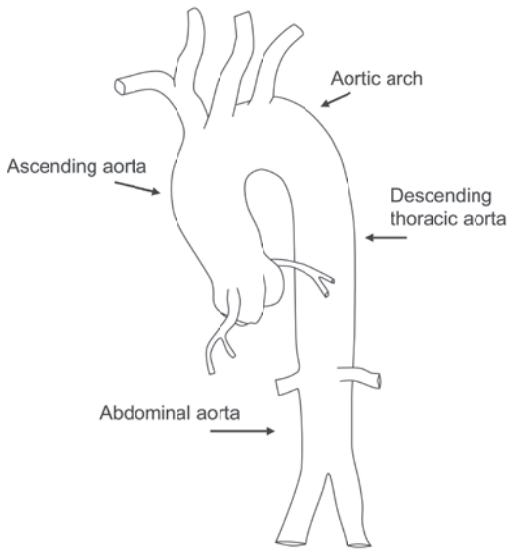

Figure 3. *Aorta.*

Discrete subaortic stenosis

Subaortic stenosis is a narrowing in the LVOT just underneath the aortic valve, creating an outflow obstruction for the blood flowing from the LV into the aorta. It is an important condition, with an estimated prevalence of 6.5% in the GUCH population.[8,15] Although it can occur as an isolated lesion, in the majority of patients other CHD lesions coexist, such as a ventricular septal defect (VSD), valvular aortic stenosis and coarctation of the aorta.[8,15-18] Furthermore, some outflow obstruction may develop after correction of another CHD.[8]

Several anatomic variants can be distinguished within the spectrum of subaortic stenosis.[8,19] The most frequent anatomic variant is discrete subaortic stenosis (DSS), which is caused by a membrane or fibromuscular ring beneath the aortic valve (Figure 4). Less common is tunnel subaortic stenosis, which is a more complex form of LVOT obstruction caused by a tunnel-like or diffuse ring-like stenosis resulting in a centimeters-long narrowed segment of the LVOT.

Lastly, the dynamic form of LVOT obstruction must be recognized, which is seen in for example hypertrophic obstructive cardiomyopathy (HOCM). The dynamic aspect refers to an obstruction which changes in severity during ventricular ejection, with the most severe obstruction in mid-to-late systole. Regarding subaortic stenosis, this thesis will only focus on DSS.

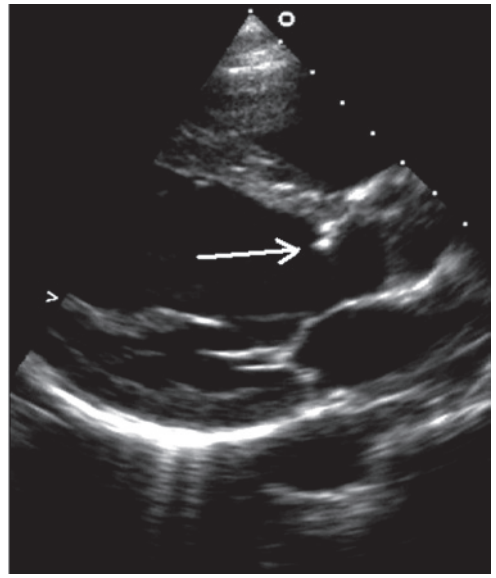

Figure 4. *Discrete subaortic stenosis on transthoracic echocardiogram.*

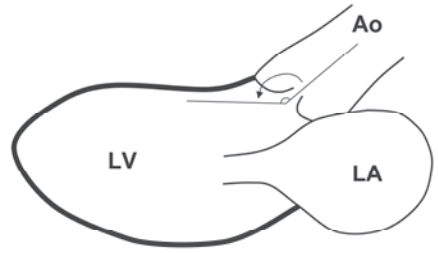

Figure 5. *Measurement of the aortoseptal angle.*
Ao = aorta; LA = left atrium; LV = left ventricle.

Truly congenital or not? Rheology of DSS

"Rheology, the science of deformation and flow of matter", is a term once introduced by Eugene C. Bingham (1878-1945, professor of chemistry at Lafayette College, Pennsylvania, USA).[17] This terminology perfectly applies to the poorly understood etiology of DSS.[17] Since DSS does not appear during embryologic development of the heart and infrequently occurs in the neonatal period, it is generally considered to be an acquired cardiac defect of postnatal development rather than a true congenital defect.[17-18,20-22] So how can this defect be acquired? Several hypotheses regarding this question exist.[17]

Turbulence theory

In patients with DSS abnormal flow patterns are present.[23] Several anatomic substrates that have been found in DSS patients may induce the flow disturbances: apically situated muscular ventricular bands, malalignment of the interventricular septum and increased mitral-aortic separation.[17,24-26] Chronic flow disturbances stimulate the endothelium and cause development of DSS and its recurrence after surgery.

Geometric theory

Several studies demonstrated an increased prevalence of steepened aortoseptal angle (Figure 5), malaligned VSD with anterior deviation of the infundibular septum and mitral-aortic separation in DSS patients.[24-29] These abnormal geometric arrangements in the LVOT cause a site of increased shear stress, where DSS can then develop.

Four stage mechanical stress and genetics theory

Mechanical stresses can alter the structural and functional properties of cells by mechanotransduction.[30] Thereafter proliferation and adaptation of the cells to the external forces can occur by altered gene expression.[31] Genetic predisposition and familial occurrence of development of DSS have been suggested.[32-40] These arguments combined lead to the four stage etiology proposed by Cape et al.[30]: genetic predisposition → geometrical abnormalities → mechanical stresses → cellular proliferation and formation of DSS.

Natural history of DSS

DSS is notable for its rapid hemodynamic progression in childhood and its association with aortic regurgitation (AR), which is found in 30-80% of patients.[15,18,20,41-46] Development of AR is thought to be secondary to the aortic valve damage as a consequence of the high velocity subvalvular jet.[15,30,46-50] In children, several predictors for hemodynamic progression have been identified such as younger age at diagnosis, higher gradient at diagnosis, presence of AR, initial aortic valve thickening, distance from membrane to aortic valve and anterior mitral valve leaflet involvement.[51-54]

Although natural history in children is extensively described, little is known about the evolution of DSS in adulthood.[15-16,50,55-56] In contrast to children, adults with DSS seem to have a slow progression rate over several decades.[15] However, no study in adults has ever focused on elucidating factors predicting DSS progression or associated AR in DSS patients, or predictors for timing of surgery.

Postoperative outcome of DSS

Surgery for DSS has not always been performed with a stable strategy. Therefore it is not surprising that postoperative results and outcome vary widely and are not always satisfactory. Reported early postoperative complications include mortality (0-6%), mitral valve damage, AR, VSD creation, or conduction problems such as bundle branch block and complete heart block.[19,47,52,57-61] Furthermore, DSS recurrence is frequent (27-41%)[47,49,61-65] and re-operation is frequently required (4-36%).[16,19,47,52-54,57,61-75] Two hypotheses exist about the cause of recurrence, namely either regrowth of tissue originating from the original site of obstruction, or scar formation in the subvalvular area during the healing process.[76-77] Several predictors for re-operation in children have been established: high pre-operative gradient or post-operative residual gradient, younger age at surgery, short distance between membrane and aortic valve, and anterior mitral valve leaflet involvement.[47-48,61-63,67,69] In adults, the only identified factor shown to predict re-operation is post-operative residual gradient, thus complete relief of the LVOT obstruction seems essential.[19]

Diagnostic work-up in DSS patients

Typical findings during physical examination include a systolic ejection murmur at the left sternal border without radiation into the carotids and without systolic ejection click. If AR is present, a diastolic murmur may be heard. The electrocardiogram may show signs of LV hypertrophy.

Echocardiography

Two-dimensional (2D) transthoracic echocardiography is the imaging modality of first choice to visualize LVOT anatomy, identify associated lesions and assess AS and AR severity, LV function and LV hypertrophy. Severity and exact location of the subvalvular obstruction are determined using color or pulsed Doppler.[78] The degree of AR can be graded as mild, moderate or severe.[79] In addition, 3D transthoracic echocardiography or 2D/3D transesophageal echocardiography may be useful to gain insight in the complex LVOT anatomy and visualize the membrane.[8]

Treatment modalities for DSS

Although surgery is the treatment of choice for DSS, a recent study introduced transluminal balloon tearing as a possible alternative for surgery in patients with isolated thin DSS.[8,80] However, long-term results of this new treatment modality have to be awaited. There is no role for medical therapy. Endocarditis prophylaxis is only recommended for patients with a prosthetic valve or previous infective endocarditis.[8]

Indications for surgery in DSS patients

Controversy exists about the timing of surgical treatment, ranging from early (mild to moderate obstruction) to late (severe or symptomatic) repair. Early repair has been advocated to prevent aortic valve damage and thus progressive AR.[41,46-49,53-54,74,81-82] However, early repair is associated with a high risk of recurrence and need for re-operation.[16,19,47,52-54,57,61-75] According to the 2010 ESC guidelines for the management of grown-up congenital heart disease, surgery is indicated in symptomatic patients with a mean Doppler gradient ≥50 mmHg and/or severe AR.[8] Furthermore, surgery should be considered in asymptomatic patients with a Doppler gradient <50 mmHg when LV ejection fraction is <50%, AR is severe and LV end-systolic diameter >50 mm, marked LV hypertrophy is present or blood pressure response is abnormal on exercise testing.[8]

Surgical treatment options for DSS

A major factor in recurrent LVOT obstruction is believed to be inadequate relief of the obstruction at surgery. Although the fibrous membrane is universally excised, some groups advocate concomitant myectomy to achieve full relief of the LVOT obstruction,[74,83] whereas others have reported that myectomy adds little to the procedure.[53,61,67,75-76,84-85] In case of moderate-to-severe AR, the aortic valve should be replaced or repaired at time of surgery.[8]

Congenital valvular aortic stenosis

The most common left heart obstructive lesion at young adult age is congenital valvular aortic stenosis (AS).[86] In >90% of the cases, a bicuspid aortic valve (BAV) can be identified as the underlying cause.[87-88] BAV is the most common congenital heart defect, with a prevalence of 1-2% in the general population.[89-90] BAV is approximately three times more frequent in males than in females.[91] The BAV typically consists of 2 unequal-sized leaflets, while the larger leaflet often has a central raphe resulting from fusion of the commissures (Figure 6).[91] In 80% of cases there is a fusion of the right and left coronary cusp, creating a larger anterior cusp giving rise to both coronary arteries and smaller posterior cusp.[92-94] Fusion of the right and non-coronary cusp is found in almost 20% of cases, resulting in a larger right cusp, but normal coronary artery origins.[92-94] Fusion of the left and non-coronary cusps is less frequent. Complications associated with BAV include AS, AR, infective endocarditis and dilatation of the ascending aorta.[91]

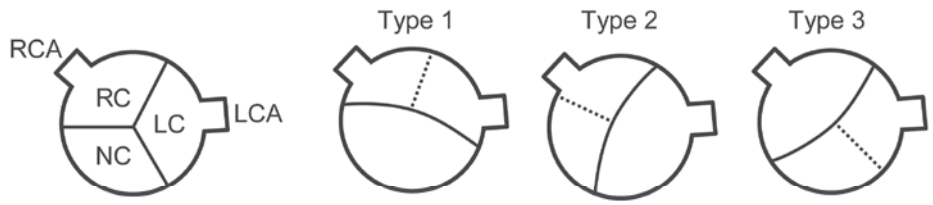

Figure 6. *Bicuspid aortic valve leaflet morphology.*

Type 1 = fusion between right and left coronary cusps. Type 2 = fusion between right and non-coronary cusps. Type 3 = fusion between left and non-coronary cusps. Adapted from Schaefer et al.[94] LC = left coronary cusp; LCA = left coronary artery; NC = non-coronary cusp; RC = right coronary cusp; RCA = right coronary artery.

Natural history of congenital AS

Natural history of congenital AS can be variable, ranging from lifelong asymptomatic to rapidly progressive disease in childhood, potentially life threatening and requiring several interventions. Catheterization studies from the 1960s – 1980s suggested that congenital AS is a rapidly progressive disease in children with a high-risk of sudden cardiac death.[95-100] However, more recent longitudinal studies using echocardiography as diagnostic tool state that congenital AS in children shows limited progression over time, except for neonates.[101-105] Data regarding the natural history of congenital AS in adulthood are scarce.[86,106] In these small studies, progression rate in adults was found to be slow.[86,106] Faster progression was dependent on the position and eccentricity of the cusps and older age.[86,106] Although progression rate does not seem to be high, many congenital AS patients require aortic valve interventions at some point in their life. In fact, congenital AS is the most important indication for aortic valve replacement (AVR) in adults aged <60 years old.[107]

Associated aortic dilatation

Prevalence of aortic dilatation in BAV patients is high, ranging from 15% to 79%.[92-93,108-118] BAV associated aortic dilatation is predominantly located in the tubular ascending aorta.[113,119] Age, hypertension, male sex, valve morphology and significant valve dysfunction (aortic regurgitation in particular) are risk factors associated with aortic dilatation.[93,109,111,114,117-118] Progression rate of aortic dilatation varies from 0.2 to 1.9 mm/year.[113-116,120] Fusion of the right and left valve leaflets yields an almost 3 times increased risk at rapid aortic dilatation.[114]

The most feared complication of aortic dilatation is aortic dissection, due to the high associated mortality.[91] In the past, the prevalence of aortic dissection associated with BAV was estimated to be around 4%.[91] However, recently two large studies reported a low rate of aortic dissection (0.1% per patient-year of follow-up) and no dissections at all.[108-109] Despite the low rates of dissection, this complication might still affect many patients, since BAV disease is common in the general population. Risk factors for dissection include aortic size, family history, male sex, aortic stiffness, and presence of other diseases affecting the aorta, such as Turner syndrome.[121-127]

Why does aortic dilatation occur in BAV patients?

Perhaps the most important question that needs to be addressed in order to gain insight in risk of dissection and accomplish treatment recommendations is: what causes the aortic dilatation in BAV patients? Nowadays two theories are proposed regarding the pathogenesis of dilatation of the aorta: the hemodynamic theory and the genetic theory.[128]

According to the hemodynamic theory, turbulent flow due to abnormal valve morphology and cusp orientation in BAV, induces abnormal hemodynamic stress on the aortic wall, thereby causing aortopathy.[94,128-131] Recently four-dimensional cardiac magnetic resonance studies showed an abnormal systolic helical flow in BAV patients which was not found in any of the healthy volunteers or patients with tricuspid aortic valves.[132-133] Furthermore, a positive correlation between the degree of AS and aortic size was found, supporting the theory that dilatation is dependent on hemodynamics.[117]

The genetic theory on the other hand assumes that the aortic wall fragility is secondary to a common developmental defect involving both the aortic valve and the aortic wall.[128] Many studies have identified several structural abnormalities at the cellular level in the aorta of BAV patients: fragmentation and loss of elastic fibers, increased expression and activity of matrix metalloproteinases, cystic medial necrosis, decreased fibrillin and apoptosis of vascular smooth muscle cells.[134-144] Furthermore, some studies report that aneurysms and progression occur irrespective of hemodynamic valvular function.[110,113] Mutations in the *NOTCH1* gene have been related to BAV.[145] However, an argument against the genetic theory is the fact that there is evidence that the anatomic pattern of the aortic dilatation in BAV and Marfan syndrome is different. Whereas BAV associated aortic dilatation is predominantly present in the tubular ascending aorta, in Marfan syndrome and other connective tissue disorders a focal dilatation at the sinuses of Valsalva is seen (Figure 7).[113,119,146-147]

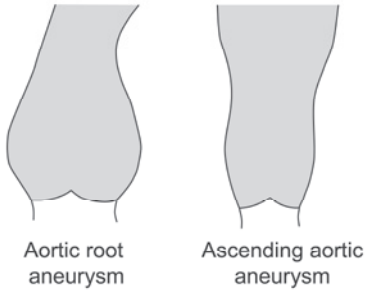

Figure 7. *Types of aortic dilatation.*

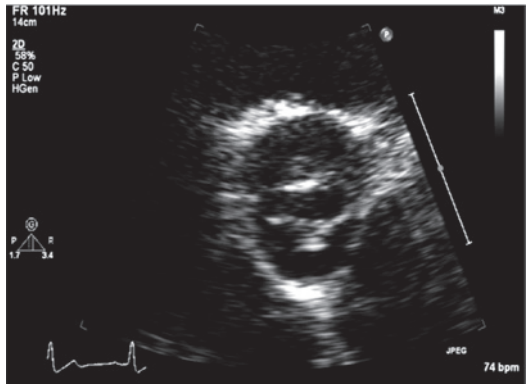

Figure 8. *Typical "fish-mouth like" opening of a bicuspid aortic valve on transthoracic echocardiogram.*

Diagnostic work-up in congenital AS patients

Typically a systolic ejection murmur over the aortic valve, radiating into the carotid arteries can be found during clinical examination. Sometimes a thrill may be palpable. The electrocardiogram may show signs of LV hypertrophy.

Echocardiography

Two-dimensional transthoracic echocardiography (TTE) is the gold standard for evaluation of AS severity.[78] In addition, TTE is useful to assess LVOT and valve anatomy, exclude presence of concomitant CHD and quantify LV hypertrophy and LV function. Short and long axis images are used to identify the number leaflets and to describe leaflet mobility, thickness and calcification.[78] Identification of a BAV is most reliable in systole, when the two commissures create a "fish-mouth like" opening (Figure 8).

The primary hemodynamic parameters recommended for clinical evaluation and grading of AS severity are: peak aortic velocity (Vmax), mean transaortic gradient and aortic valve area (AVA) (Table 1).[78]

Table 1. *Severity grading of aortic stenosis*

	Mild	Moderate	Severe
Peak aortic velocity (m/s)	2.0-2.9	3.0-3.9	≥4.0
Mean aortic gradient (mmHg)	<30	30-49	≥50
Aortic valve area (cm^2)	>1.5	1.0-1.5	<1.0

Vmax has been shown to be the strongest predictor of clinical outcome.[86,148] Adequate measurement of Vmax is performed with continuous wave Doppler in multiple acoustic windows to determine the highest velocity.[149-150] Vmax is measured at the outer edge of the dark signal (Figure 9).

Parallel alignment of the ultrasound beam is required, otherwise Vmax is underestimated. Furthermore, Vmax may be underestimated if cardiac output is low and may be overestimated if severe concomitant aortic regurgitation is present.

Peak transaortic gradient (Pmax) is directly calculated from Vmax using the simplified Bernoulli equation (Pmax = 4*$Vmax^2$) and thereby does not add additional information.[78] However, mean transaortic gradient is the average gradient across the valve during the entire systole and thus dependent on the shape of the velocity curve, which varies with AS severity and flow rate.[151] Calculation of the mean gradient requires averaging of instantaneous mean gradients over the ejection period and cannot be calculated from the mean velocity.

Calculation of AVA can be helpful when flow rates are very low or very high.[78] AVA is calculated using the continuity equation and requires 3 measurements: AS velocity, LVOT diameter for calculation of the circular area and LVOT velocity.[152-153] Because AVA calculation is dependent on 3 different measurements, it is most prone to variability and error.[78]

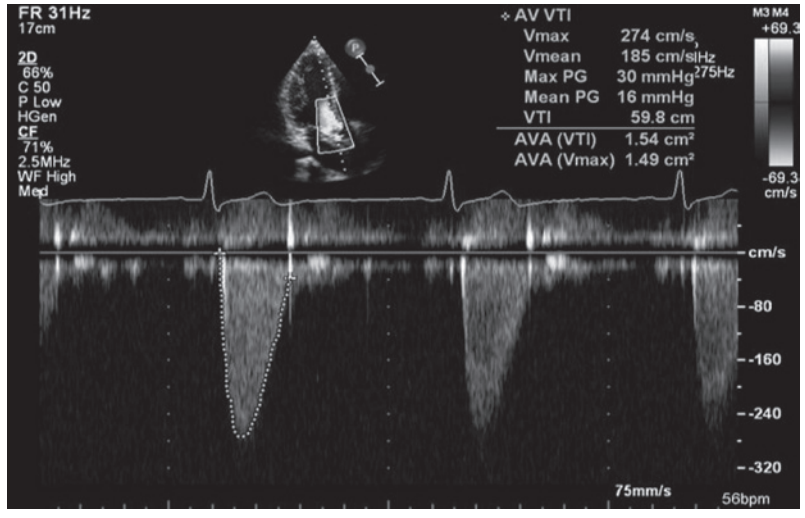

Figure 9. *Measurement of peak aortic velocity (Vmax) with transthoracic Doppler echocardiography.*

Cardiac magnetic resonance and computed tomography angiography

Since BAV disease affects both the aortic valve and the ascending aorta, active surveillance of both structures is necessary. Ascending aortic diameter should be measured at 4 levels: aortic valve annulus, sinus of Valsalva, sinotubular junction and proximal ascending aorta (Figure 10). Since TTE may not be able to detect aneurysms distal to the sinotubular junction, cardiac magnetic resonance (CMR) or computed tomography angiography (CTA) may provide valuable additional information.[8] Recent guidelines consider CMR superior to TTE for aortic imaging, however there is a lack of data comparing both imaging modalities.[8]

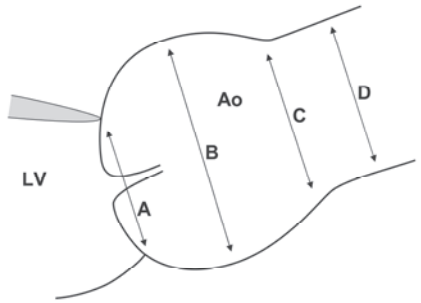

Figure 10. *Measurement of the aortic diameter at four levels: (A) aortic valve annulus, (B) sinus of Valsalva, (C) sinotubular junction and (D) proximal ascending aorta.*

Ao = aorta; LV = left ventricle.

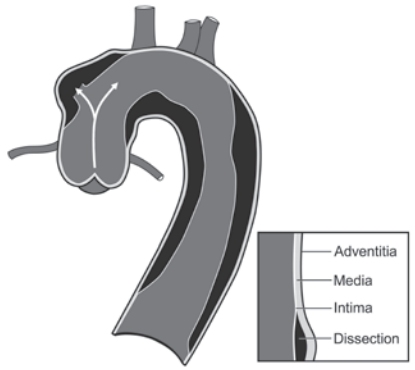

Figure 11. *Aortic dissection*

Treatment modalities for congenital AS patients

Currently, there is no accepted pharmacological treatment to halt or reduce AS progression, and thus the only therapeutic option is an intervention. Endocarditis prophylaxis is only recommended for patients with a prosthetic valve or positive history for infective endocarditis.[8]

Are statins the Holy Grail?

BAV is associated with calcification at early age, from the fourth decade in life.[106] Calcification of the aortic valve appears to result from an active disease process reminiscent of atherosclerosis, with chronic inflammation, accumulation of lipids and calcification.[154-155] Many studies show that the risk factors associated with aortic stenosis are the same as the risk factors of atherosclerosis, e.g. smoking, diabetes, hypertension and hypercholesterolemia.[156-160] Despite a better insight in the pathophysiology of the valve calcification, there is currently no accepted pharmacologic treatment.

Theoretically, statins might be beneficial in patients with AS due to their low-density lipoprotein (LDL)-cholesterol lowering effect and anti-inflammatory actions.[161] Experimental and observational studies have demonstrated that the level of LDL-cholesterol plays a role in AS progression and statin therapy is associated with reduced AS progression and slower calcification.[160,162-166] However, in recent clinical trials performed in elderly patients with already calcified valves no effect of statin therapy was found.[167-172] The use of statins in congenital AS patients is investigated in this thesis.

Indications for intervention in congenital AS patients

In general, asymptomatic patients with mild-to-moderate AS and normal LV function should be managed conservatively and monitored regularly. Aortic valve replacement (AVR) is indicated in patients with severe AS in one of the following circumstances:

valve-related symptoms (angina pectoris, dyspnoea, syncope), exercise induced symptoms, exercise induced fall in blood pressure below baseline, systolic LV dysfunction (LV ejection fraction <50%), Vmax progression >0.3 m/s/year or concomitant if there are other indications for cardiac surgery.[8,173]

Regardless of symptoms or valve function, aortic surgery should be considered if the ascending aorta is >50 mm (>27.5 mm/m^2 BSA) to prevent acute dissection or rupture.[8,174] Patients undergoing AVR should be considered for concomitant aortic surgery when the aortic diameter is >45 mm.[174]

Interventional/surgical treatment options in congenital AS patients

Balloon valvuloplasty may be considered in adolescents and young adults with non-calcified valves, however re-intervention rate is reported to be high.[175-176] For adult patients, especially those with calcified valves, AVR is the treatment of choice. Several factors, such as age, life expectancy, wish to become pregnancy, lifestyle, comorbidity and patient preference, are important to consider when choosing the type of prosthetic valve.[8,177] Mechanical valves are more durable than bioprotheses and homografts, but are associated with risk at thromboembolism and require lifelong anticoagulation.[178-180] The downside of implantation of a bioprothesis or homograft at young adult age is the increasing re-operation risk in the second decade after operation due to degeneration of biological valve substitutes.[179-182] The Ross procedure may be another alternative for patients at childbearing age and those who are engaged in high impact sports activities, but is associated with progressive neo-aortic root dilatation and reoperations.[178,183] Simulation models might be useful to predict outcome after aortic valve replacement.[107,184] Extensive patient counseling and clinical decision making weighing technical options, patient characteristics and patient preferences are essential to determine an optimal and individualized treatment strategy. Aortic surgery with AVR can be performed using Bentall procedure or separate valve and graft replacement.[185-188] Despite good results with valve-sparing operations, there is controversy about leaving behind an abnormal BAV.[91,189-192]

Familial thoracic aortic aneurysms and dissections

"There is no disease more conducive to clinical humility than aneurysm of the aorta", William Osler once quoted (Canadian Physician, 1849-1919). These words still resonate today, when many patients with ruptured aortic aneurysms die before reaching the hospital and the mortality rate among those who reach the hospital is still very high.[193] Since aortic aneurysms are often asymptomatic, *"silent killer"* might be a suitable synonym. In 2007, aortic aneurysms and dissections ranked as the 19th common cause of death in the USA (Figure 11).[133,194]

Aortic aneurysms most commonly occur in the abdominal aorta and are typically associated with atherosclerosis and advanced age.[195] So far, no single major gene has been identified to cause isolated abdominal aortic aneurysms.[195] In contrast, thoracic aortic aneurysms and dissections (TAAD) can occur in every age group without obligate association with cardiovascular risk factors.[195] Histologically, TAADs most often result from cystic medial degeneration characterized by loss of smooth muscle cells and elastic fiber degeneration.[196]

Table 2. *Syndromic and non-syndromic forms of familial TAAD with identified genes.*

Disease or phenotype	Gene	Protein	Chromosome
Syndromic forms			
Marfan syndrome[198]	*FBN1*	Fibrilin-1	15q21.1
Loeys-Dietz syndrome[147,199]	*TGFBR1* *TGFBR2*	TGF-βR1 TGF-βR2	9q33-34 3p24-25
Aneurysms-Osteoarthritis syndrome[200]	*SMAD3*	SMAD3	15q22.2-24.2
Ehlers-Danlos syndrome type IV[201]	*COL3A1*	Type III collagen	2q24.3-31
Cutis laxa type 1[202-203]	*FBLN-4*	Fibulin-4	11q13
Arterial tortuosity syndrome[204]	*SLC2A10*	GLUT10	20q13.1
Noonan syndrome[205]	*PTPN1*	PTPN11 (SHP2) SOS1 GTPase K-Ras	12q24.1
Polycystic kidney disease[206]	*PKD1* *PKD2*	Polycystin 1 Polycystin 2	16p13.3-p13.12 4q21-22
Turner syndrome[127]	--	--	45, X0
Non-syndromic forms			
TAA + BAV[145,207]	*NOTCH1*	Notch 1	9q34-35
TAAD + PDA[208-209]	*MYH11*	β-MHC	16p122-p13.13
TAAD[210]	*ACTA2*	Smooth muscle actine	10q22-q24
TAAD[211]	*MYLK*	MYLK	3q21.1

** Table adapted from article by Moltzer et al.[194]*

Abbreviations: ß-MHC, ß-myosin heavy chain; BAV, bicuspid aortic valve; COL3A1, collagen type III alpha 1; FBLN-4, fibulin-4; FBN1, fibrillin-1; GLUT10, glucose transporter type 10; MYLK, myosin light chain kinase; NOTCH 1, neurogenic locus Notch homolog protein 1; PDA, patent ductus arteriosus; PKD, polycystic kidney disease; PTPN11, tyrosine-protein phosphatase non-receptor 11; SLC2A10, solute carrier familiy 2, facilitated glucose transporter member 10; SOS1, son of sevenless homolog; TAA, thoracic aortic aneurysm; TAAD, thoracic aortic aneurysm dissection; TGF-ß, transforming growth factor-ß; TGF-βR, transforming growth factor-ß receptor

TAAD often affects multiple family members and can be inherited in an autosomal dominant pattern with variable age of onset and decreased penetrance.[197] Familial TAAD is subdivided into non-syndromic forms, which can be associated with CHD, and syndromic forms, with prominent features of connective tissue disorders (Table 2).[127,145,147,194-195,198-211] The syndromic forms are caused by genes encoding for proteins involved in the transforming growth factor (TGF)-β signalling pathway and are characterized by increased TGF-β signalling in the arterial wall.[195] Increasing evidence has led to the conclusion that TGF-β signaling plays a central role in the pathogenesis of arterial aneurysms (Figure 12).[195]

A new syndrome?

Recently a new syndromic form of familial TAAD was described: the Aneurysms-Osteoarthritis Syndrome (AOS), caused by mutations in the *SMAD3* gene.[200] This gene encodes the SMAD3 protein, which is a member of the TGF-β pathway that is essential for TGF-β signal transmission.[212-214] AOS is inherited in an autosomal dominant manner and is found to be responsible for 2% of familial TAAD.[200,215]

Key features of this syndrome include arterial aneurysms and tortuosity, early-onset joint abnormalities and mild craniofacial features. Patients with AOS show aneurysms throughout the arterial tree, although most commonly in the sinuses of Valsalva, and a high risk of early dissection/rupture, thereby resembling patients with Loeys-Dietz syndrome.[147,199-200] In contrast to other familial TAAD forms, early-onset osteoarthritis is present in nearly all patients and is often the first reason to seek medical advice.[200] Craniofacial abnormalities include hypertelorism (widely spaced eyes) and a bifid uvula. Furthermore, features of connective tissue disorders, such as umbilical and/or inguinal hernias, varices, velvety skin and striae, are present in the majority of AOS patients.

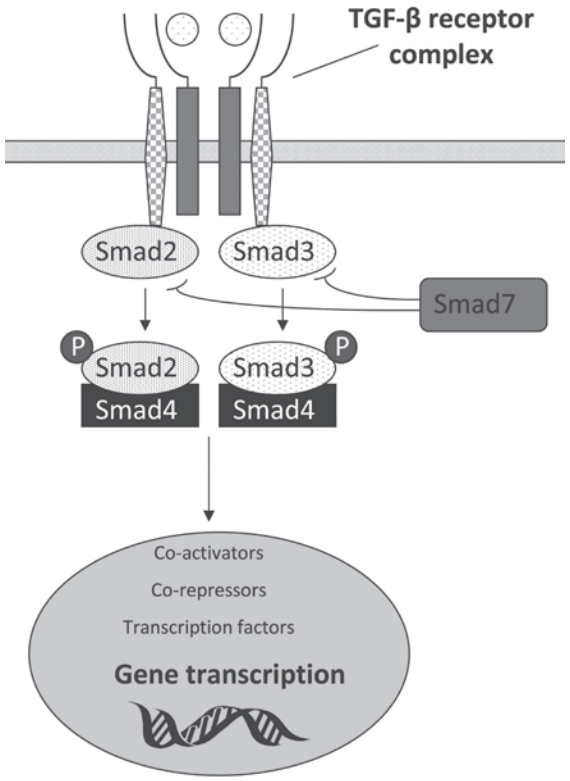

Figure 12. *The transforming growth factor (TGF) ß signalling pathway. TGF-ß binds to the TGF-ß receptors and activates Smad2 and Smad3 by phosphorylation (P). This process is inhibited by Smad7. Activated Smad2 and Smad3 form heterodimers with Smad4 and regulate gene transcription in the nucleus.*

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Aim and outline of the thesis

Congenital heart disease is the most common type of birth defect, affecting over a million newborns worldwide every year. Improvements in cardio-thoracic surgery, anesthesia and diagnostics have lead to an increasing number of patients surviving into adulthood. This requires adjustment of clinical care and insight in the long term outcome of these patients. The aim of this thesis is to investigate epidemiology, natural history, treatment, prognostic factors and genetic aspects of congenital aortic stenosis and aneurysms.

The following research questions are addressed:

- *How to identify the "true" birth prevalence of congenital heart disease?*
- *Which prognostic determinants are related to the long-term outcome of discrete subaortic stenosis, in both conservatively managed as well as operated patients?*
- *What is the natural course of congenital valvular aortic stenosis and associated aortopathy, and is there a role for statin therapy to reduce progression?*
- *Which cardiovascular consequences are associated with Aneurysms-Osteoarthritis Syndrome and can we establish preliminary clinical recommendations?*

Epidemiology of congenital heart disease

Although the birth prevalence of congenital heart disease is generally considered to be 8 per 1000 live births, estimates vary widely. As information about congenital heart disease birth prevalence is important to gain insight in etiology and to plan care, it is essential to have a reliable estimate of congenital heart disease birth prevalence. A systematic review and meta-analysis aims to provide a complete overview of the reported congenital heart disease birth prevalence and the eight most common subtypes over time in the period from 1930 until 2010. Furthermore, geographic and economical differences in congenital heart disease birth prevalence are explored **(Chapter 2)**.

Discrete subaortic stenosis

Discrete subaortic stenosis is a fibrous obstruction in the left ventricular outflow tract beneath the aortic valve. Whereas natural history and post-operative outcome are well known in children, little data exist about adults with discrete subaortic stenosis. We aim to elucidate the natural history and risk factors for progression and need for surgery in adulthood **(Chapter 3)**. Since recurrence and re-operation rates are high after surgery for discrete subaortic stenosis, we also explore long-term surgical outcome and factors predicting that course **(Chapter 4)**.

Congenital valvular aortic stenosis

A bicuspid aortic valve is the most common congenital heart defect, and it is associated with several complications such as progressive aortic stenosis, regurgitation and ascending aortic dilatation. However, longitudinal data regarding the natural history of congenital aortic stenosis and associated aortopathy in adulthood are scarce. We aim to describe the natural course of congenital aortic stenosis and identify factors related to prognosis in a large cohort of adult congenital aortic stenosis patients **(Chapter 5)**. The effect of statins on the progression of congenital aortic stenosis is investigated in a randomized controlled trial **(Chapter 6)**. Next, the association between hemodynamic progression and ascending aortic dilatation is assessed using cardiac magnetic resonance **(Chapter 7)**. Last of all, cardiac magnetic resonance and transthoracic echocardiography are compared as imaging tools for aortic dilatation **(Chapter 8)**.

Familial thoracic aortic aneurysms; a new syndrome

Recently *SMAD3* gene mutations were found to be responsible for the Aneurysms-Osteoarthritis Syndrome. This syndrome is characterized by arterial aneurysms and tortuosity, early-onset osteoarthritis and mild craniofacial abnormalities. We aim to extensively outline all cardiovascular features and the phenotypic spectrum of Aneurysms-Osteoarthritis Syndrome **(Chapter 9-10)**. Thereafter, short-term outcome and early surgical experience are explored **(Chapter 11)**. Finally, consequences of Aneurysms-Osteoarthritis Syndrome in other arteries than the aorta are described **(Chapter 12-13)**.

PART II

Epidemiology of congenital heart disease

2

Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis

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J Am Coll Cardiol. 2011;58:2241-7.

Abstract

Congenital heart disease (CHD) accounts for nearly one-third of all major congenital anomalies. CHD birth prevalence worldwide and over time is suggested to vary; however, a complete overview is missing. This systematic review included 114 papers, comprising a total study population of 24,091,867 live births with CHD identified in 164,396 individuals. Birth prevalence of total CHD and the 8 most common subtypes were pooled in 5-year time periods since 1930 and in continent and income groups since 1970 using the inverse variance method. Reported total CHD birth prevalence increased substantially over time, from 0.6 per 1,000 live births (95% confidence interval [CI]: 0.4 to 0.8) in 1930 to 1934 to 9.1 per 1,000 live births (95% CI: 9.0 to 9.2) after 1995. Over the last 15 years, stabilization occurred, corresponding to 1.35 million newborns with CHD every year. Significant geographical differences were found. Asia reported the highest CHD birth prevalence, with 9.3 per 1,000 live births (95% CI: 8.9 to 9.7), with relatively more pulmonary outflow obstructions and fewer left ventricular outflow tract obstructions. Reported total CHD birth prevalence in Europe was significantly higher than in North America (8.2 per 1,000 live births [95% CI: 8.1 to 8.3] vs. 6.9 per 1,000 live births [95% CI: 6.7 to 7.1]; $p < 0.001$). Access to health care is still limited in many parts of the world, as are diagnostic facilities, probably accounting for differences in reported birth prevalence between high- and low-income countries. Observed differences may also be of genetic, environmental, socioeconomical, or ethnic origin, and there needs to be further investigation to tailor the management of this global health problem.

Introduction

Congenital heart disease (CHD) is the most common cause of major congenital anomalies, representing a major global health problem. Twenty-eight percent of all major congenital anomalies consist of heart defects (1). Reported birth prevalence of CHD varies widely among studies worldwide. The estimate of 8 per 1,000 live births is generally accepted as the best approximation (2). CHD, by definition, is present from birth. The most practical measurement of CHD occurrence is birth prevalence per 1,000 live births (3).

Massive breakthroughs have been achieved in cardiovascular diagnostics and cardiothoracic surgery over the past century, leading to an increased survival of newborns with CHD. Consequently, more patients with CHD reach adulthood, creating a completely new and steadily growing patient population: patients with grown-up congenital heart disease (GUCH). The prevalence of CHD is estimated to be 4 per 1,000 adults (4). Patients with GUCH often need long-term expert medical care and healthcare-related costs are high (5). Therefore, the global health burden as a result of CHD increases quickly.

It is important to have reliable information about worldwide CHD birth prevalence because this may lead to better insight into its etiology. In addition, dedicated care could be better planned and provided. Variation in CHD occurrences over time and worldwide has been suggested, but a complete overview is missing. In this systematic review and meta-analysis, we provide a complete worldwide overview of the reported birth prevalence of total CHD and the 8 most common subtypes of CHD from 1930 until 2010.

Methods

Search strategy

We conducted a PubMed literature search on September 23, 2010, using the following search terms: “heart defects, congenital/epidemiology,” and “incidence” or “prevalence.” The search was limited to original research papers with English abstracts. No time restriction for publication dates was used. Reports of large governmental birth registries were searched online.

All titles and abstracts were screened for study population (live births, children), type of CHD, and birth prevalence. Studies were eligible if they reported the birth prevalence of total CHD or 1 of the 8 most common CHD subtypes: ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary stenosis (PS), patent ductus arteriosus (PDA), tetralogy of Fallot (TOF), coarctation (Coarc), transposition of the great arteries (TGA), and aortic stenosis (AoS). CHD was defined according to the definition of Mitchell et al. (6); namely, “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance.” This definition excludes PDA in premature infants, Marfan syndrome, bicuspid aortic valve, mitral valve prolapse, cardiomyopathies, and congenital arrhythmias. Papers studying only specific groups (e.g., only Down syndrome), rheumatic heart disease, or case studies of rare defects were excluded. Papers focusing on etiology, (pre-natal) diagnosis, treatment, prognosis, or animal research were also excluded.

After exclusion on the basis of the title and abstract, full papers were carefully read and reconsidered according to all abovementioned inclusion and exclusion criteria. Studies focusing on CHD prevalence in schoolchildren age >5 years or including only severe forms of CHD were excluded. When a study was eligible for inclusion, we verified the denominator and numerator and recalculated the estimated birth prevalence to check accuracy. Studies with incorrect or missing denominators or numerator were excluded. Three authors performed the search independently using these inclusion and exclusion criteria. In case of disagreement, an agreement was negotiated. References of selected papers were crosschecked with the same inclusion and exclusion criteria.

Data extraction

Selected papers were reviewed and study characteristics were tabulated in a MS Excel for Windows (Microsoft Corporation, Redmond, Washington) and Review Manager version 5.0 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The following study characteristics were registered: time period during which the study was performed, country, study design (retrospective or prospective), age of patients, diagnostic method, number of live births, number of patients with CHD, and birth prevalence of total CHD and 8 CHD subtypes. Studies were grouped according to 5-year time periods since 1930 to demonstrate time trends. Time period is taken as the period in which the study was performed. Before 1970, many differences in availability of diagnostic and registration facilities between the continents existed, so we used only those studies performed after 1970 to compare continents and income groups. World Bank Income groups based on gross national income per capita in 2008 were defined as: low income (≤$975), lower-middle-income ($976 to $3,855), upper-middle-income ($3,856 to 11,905), and high income (≥$11,906) (7).

Statistical analysis

Statistical analyses were done in Review manager 5.0, MS Excel, and SPSS version 15.0 (SPSS, Chicago, Illinois). Birth prevalence of total CHD and the 8 most common subtypes were pooled using the inverse variance method. Pooled group estimates were compared with a chi-square test. Time trends were plotted by using the Savitzky-Golay smoothing technique. Heterogeneity on basis of study design (retrospective vs. prospective), study size, continents, income groups and time periods was explored by using the Q and the I^2 statistics and by means of funnel plots.

Results

Search results

The systematic literature search yielded 1,136 potential eligible studies. After exclusion, cross-referencing, and reaching agreement on 3 studies, 114 studies were included in this systematic literature review and meta-analysis (Figure 1, Online Table 1). This resulted in a total study population of 24,091,867 live births with CHD identified in 164,396 individuals. There were 12 reports of prospective birth defect registries. Seventy-six studies used echocardiography as the main diagnostic tool; the rest used combinations of diagnostic tools, such as death certificates, autopsy and surgical reports, physical examination, x-rays, and catheterization.

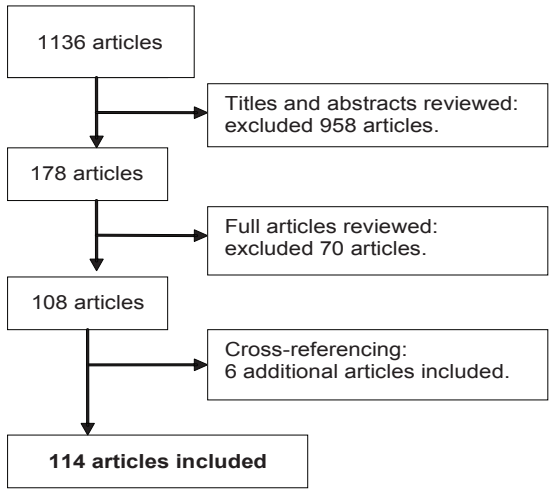

Figure 1. *Flow chart of study selection.*

Flow chart representing the selection of studies during the systematic literature search. Initial search yielded 1,136 potential eligible studies. After reading titles and abstracts, 958 articles were excluded on basis of exclusion criteria named in the search strategy paragraph of the Method section. Another 70 articles were excluded after evaluation of full text and recalculating denominators and nominators. Cross-referencing let to inclusion of 6 additional articles, after which 114 articles were included in this systematic review.

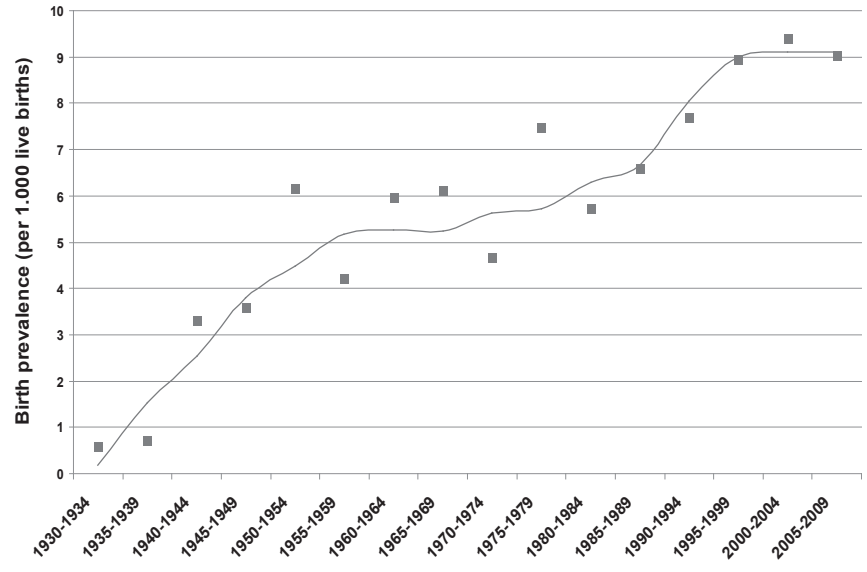

Figure 2. *Total CHD birth prevalence over time.*

Time course of reported total congenital heart disease (CHD) birth prevalence from 1930 until 2010. The blue line shows the time trend, while the squares represent the calculated birth prevalence values for each time period.

Total CHD birth prevalence

Over time, the reported total CHD birth prevalence increased substantially (Figure 2), from 0.6 per 1,000 live births (95% confidence interval [CI]: 0.4 to 0.8) in 1930 to 1934 to 9.1 per 1,000 live births (95% CI: 9.0 to 9.2) after 1995. The increase over time was S-shaped, with a first steep increase from 1930 to 1960, followed by stabilization around 5.3 per 1,000 live births from 1961 to 1975, a second steep increase from the late 1970s until 1995, and eventually stabilization around 9.1 per 1,000 live births in the last 15 years.

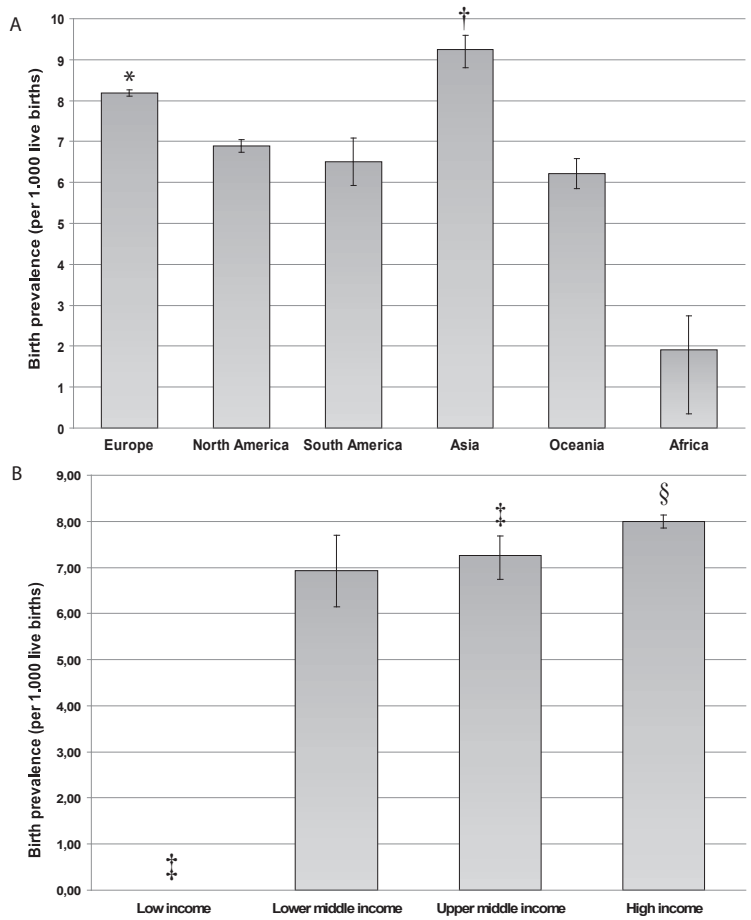

Figure 3. *Total CHD birth prevalence per continent and world bank income group since 1970.*

*(**A**) Reported total CHD birth prevalence per continent. * Reported total CHD birth prevalence in Europe was significantly higher than in North America (p<0.001), South America (p<0.001), Oceania (p<0.001) and Africa (p<0.001). † Reported total CHD birth prevalence in Asia was significantly higher than in Europe (p<0.001), North America (p<0.001), South America (p<0.001), Oceania (p<0.001) and Africa (p<0.001).*
*(**B**) Reported total CHD birth prevalence per World Bank Income Group. ‡ Reported total CHD birth prevalence in upper-middle income countries was significantly higher than in lower-middle income (p<0.013). No data were available for low-income countries. § Reported total CHD birth prevalence in high-income countries was significantly higher than in upper- and lower- middle-income countries (p<0.001).*

Significant geographical differences were found (Figure 3A). The highest reported total CHD birth prevalence was found in Asia (9.3 per 1,000 live births [95% CI: 8.9 to 9.7]) and the lowest in Africa (1.9 per 1,000 live births [95% CI: 1.1 to 3.5]). Reported total CHD birth prevalence in Asia was significantly higher compared with all other continents (all, $p < 0.001$). Europe had the second highest reported total CHD birth prevalence (8.2 per 1,000 live births [95% CI: 8.1 to 8.3]).

Significant differences between World Bank income groups were found (Figure 3B), with the highest reported total CHD birth prevalence in high-income countries (8.0 per 1,000 live births [95% CI: 7.9 to 8.1]; all, $p < 0.001$). Reported total CHD birth prevalence in upper-middle-income countries was 7.3 per 1,000 live births (95% CI: 6.9 to 7.7) and 6.9 per 1,000 live births (95% CI: 6.1 to 7.7) in lower-middle-income countries ($p = 0.013$). No data from low-income countries were available.

Birth prevalence of the 8 most common subtypes of CHD

Reported birth prevalence of the 8 most common CHD subtypes since 1945 is shown in Figure 4.

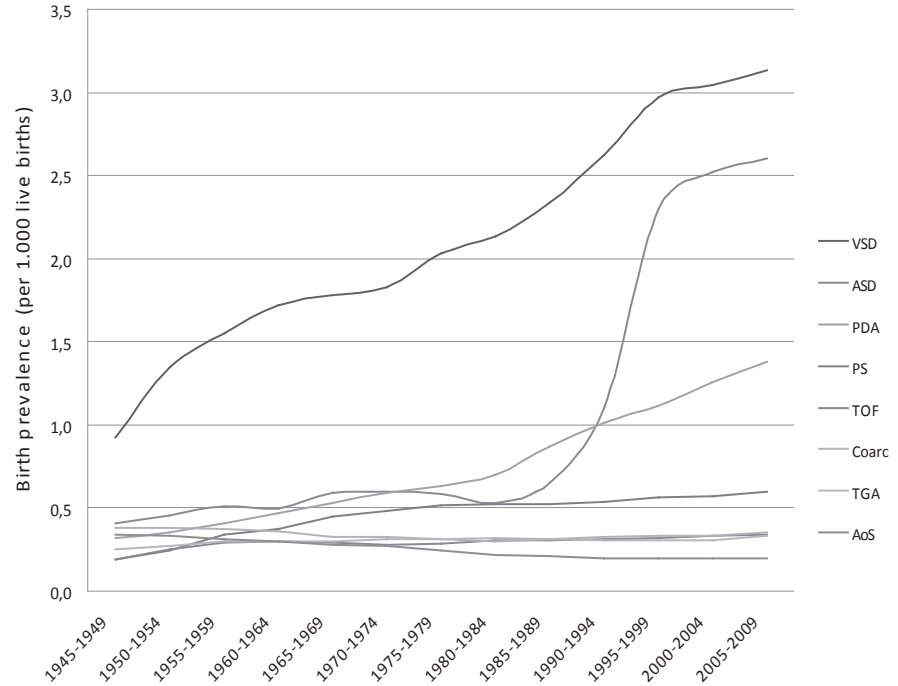

Figure 4. *Birth prevalence of CHD subtypes over time.*

Time course of birth prevalence of the 8 most common CHD subtypes from 1945 until 2010. AoS = aortic stenosis; ASD = atrial septal defect; Coarc = coarctation; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

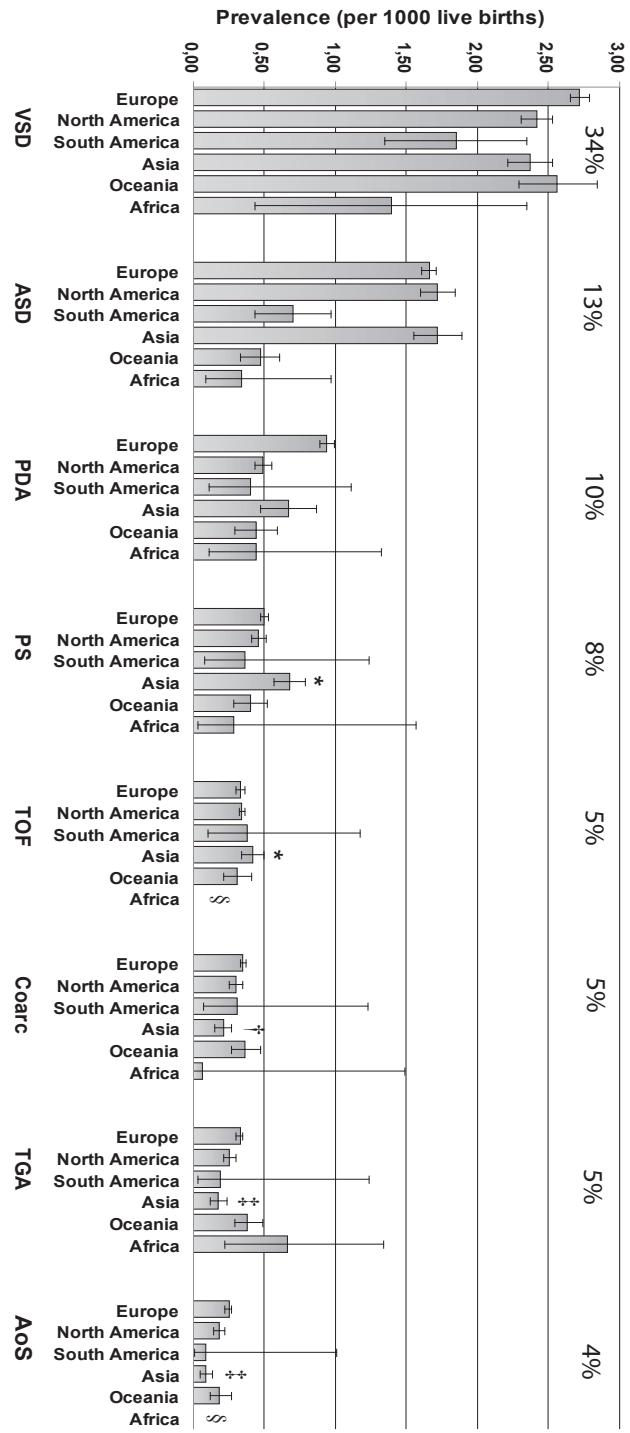

Figure 5. *Birth prevalence of CHD subtypes.*

*Reported birth prevalence of the 8 most common CHD subtypes per continent. Distribution of subtypes within total CHD is mentioned as percentages above bars. Abbreviations of subtypes as in Figure 4. * Reported PS and TOF birth prevalence in Asia was significantly higher than in Europe (p<0.001) and North America (p<0.001). † Reported Coarc birth prevalence in Asia was significantly lower than in Europe (p<0.001). ‡ Reported TGA and AoS birth prevalence in Asia was significantly lower than in Europe (p<0.001), North America (p<0.001) and Oceania (p<0.001). § No data on TOF and AoS birth prevalence in Africa were available. Abbreviations as in Figure 4.*

Distribution of the 8 most common CHD subtypes worldwide is shown with percentages in Figure 5. Worldwide reported birth prevalence of the CHD subtypes (per 1,000 live births) was: VSD, 2.62 (95% CI: 2.59 to 2.65); ASD, 1.64 (95% CI: 1.61 to 1.67); PDA, 0.87 (95% CI: 0.83 to 0.91); PS, 0.50 (95% CI: 0.48 to 0.52); TOF, 0.34 (95% CI: 0.31 to 0.37); Coarc, 0.34 (95% CI: 0.32 to 0.36); TGA, 0.31 (95% CI: 0.28 to 0.34); and AoS, 0.22 (95% CI: 0.20 to 0.24).

Significant geographical differences in reported birth prevalence of the 8 most common CHD subtypes were detected (Figure 5). Asia reported relatively more pulmonary outflow obstructions (PS and TOF) and fewer left ventricular outflow tract obstructions (Coarc and AoS). Furthermore, Asia reported a lower TGA birth prevalence compared with Europe, North America, South America, and Oceania ($p < 0.001$).

Heterogeneity, subgroup analyses, and publication bias

Significant heterogeneity was observed within pooled estimates for all time periods, continents and income groups (all I^2 statistic = 100%; Q statistic, $p < 0.001$). Birth prevalence estimates did not differ significantly between prospectively and retrospectively designed studies or between large and small studies. Funnel plots were symmetrical.

Discussion

This meta-analysis is the first to systematically compile the available published evidence on worldwide CHD birth prevalence over the past century.

Changes over time in CHD birth prevalence

Over time, the reported total CHD birth prevalence increased substantially, from <1 per 1,000 live births in 1930 to 9 per 1,000 live births in recent years. With a worldwide annual birth rate around 150 million births (8), this corresponds to 1.35 million live births with CHD every year, representing a major public health issue.

The increase in reported total CHD birth prevalence over time may be caused by changes in diagnostic methods and screening modalities rather than representing a true increase. Over the past century, knowledge about diagnostics and treatment of CHD increased considerably. Survival increased dramatically due to improvements in the field of cardiothoracic surgery and anesthesia. Specialized pediatric cardiologists were trained, and large prospective birth defect registries became available. Before the era of echocardiography, detection of CHD was dependent on autopsy reports, death certificates, physical examination, x-rays, catheterization, and surgical reports. Therefore, only severely affected subjects could be detected. In the 1970s, echocardiography was widely introduced into clinical practice, making it possible to also diagnose asymptomatic patients as well as patients with mild lesions (9). This development probably explains the increased birth prevalence of total CHD in the 1970s, as well as the increase in specific groups, such as patients with VSD, ASD, and PDA.

Furthermore, echocardiography currently is often used as a screening tool before (noncardiac) surgery or full assessment in case of noncardiac disease, causing an increase in diagnoses of minor lesions such as a small VSD or ASD. Our results confirm findings from the Metropolitan Atlanta Congenital Defects Program that routine use of echocardiography has increased diagnosis of minor defects (10). The relative stability of the estimation of birth prevalence of complex CHD subtypes also argues for a merely methodological increase.

Nonetheless, there are arguments that not only the reported but also the true CHD birth prevalence changed over time. Survival of premature infants has improved over the last century, attributing to an increase in total CHD and especially VSD birth prevalence (4). Because increasing numbers of women in developed countries are delaying childbearing to an older age, maternal age has increased in the last decades, consequently causing a higher birth prevalence of congenital abnormalities (11,12). In addition, the patient population with GUCH is steadily increasing and their offspring is at increased risk of having a congenital abnormality (13). Furthermore, one might hypothesize that changes in environmental exposures—for example, due to industrialization and urbanization— over the past century have had effects on CHD birth prevalence. However, only maternal pre-gestational diabetes mellitus, phenylketonuria, febrile illness, infections, various therapeutic drug exposures, vitamin A use, marijuana use, and exposure to organic solvents have been proven to be associated with increased risk of CHD (14). Exposure to ionizing radiation in occupational settings or in clinical practice did not show any associations with CHD birth prevalence (14). Data about alcohol consumption, hard drugs, or cigarette smoking during pregnancy are insufficient to determine risk for CHD. The impact of increased use of fetal echocardiography and pregnancy termination on reduction of CHD birth prevalence is expected in the next time periods (15). Furthermore, in the upcoming decades we will probably see the effect of improving figures on infant survival and socioeconomical circumstances in developing countries on CHD birth prevalence.

Geographical and income group differences in CHD birth prevalence

Important geographical differences were found. Asia reported the highest total CHD birth prevalence (9.3 per 1,000 live births). This finding could in part be attributed to high consanguinity rates in some study populations (e.g., in Iran and India) (16,17). CHD birth prevalence among children with consanguineous parents was found to be considerably higher than in nonconsanguineous parents, suggesting an important genetic influence (16). Very interesting is the relatively high birth prevalence of pulmonary outflow tract obstructions (PS and TOF) and low birth prevalence of left ventricular outflow tract obstructions (Coarc and AoS) in Asia. These findings confirm the results of Jacobs et al. (18), who found that white children seem to have more left ventricular obstructive lesions, whereas Chinese children have more right ventricular outflow tract lesions. A possible explanation could be found in genetic origin.

Interestingly, Europe had the second highest reported total CHD birth prevalence. The difference between Europe and North America (8.2 vs. 6.9 per 1,000 live births; $p < 0.001$) was unexpected because the study populations and design of the studies in these 2 continents are quite comparable.

This difference might be attributed to ethnic, socioeconomical, and environmental differences. North America has a relatively larger population of African-American inhabitants and, as previously described, CHD is less common in this population (19). Part of the difference might also be explained by differences in healthcare and referral systems. In the United States, as was noted in the Baltimore-Washington Infant Study (20), referral of infants with developmental abnormalities, such as Down syndrome and other trisomies, for cardiac evaluation can be inhibited, whereas these societal factors probably are of less importance in most European countries. Moreover, the fact that we found important differences in CHD birth prevalence according to income status also argues in favor of the fact that lack of resources, medical insurance, screening programs, and referral systems probably lead to an underestimation of the true birth prevalence.

Heterogeneity in this meta-analysis

Obviously, reported birth CHD prevalence reflects the true CHD birth prevalence but also depends on the study design of the original papers, study population selection, and diagnostic tools used. CHD prevalence highly depends on age and gestational age. For example, PDA in preterm babies is a functional abnormality, whereas it is an abnormality in term infants (21). Furthermore, CHD prevalence highly depends on the sensitivity and specificity of the detection method. Differences in study population selection and inclusion and exclusion criteria of included studies attributed to heterogeneity in this meta-analysis. Tests for heterogeneity showed high heterogeneity in continents, income groups, and time periods, but this finding can be explained by the fact that, due to the very large sample sizes, point estimates were very precise and SEs very small, and therefore heterogeneity was expected and inevitable. We did not find bias caused by the design (prospective or retrospective nature) or size of included studies.

Study limitations

Even though we investigated all available reports of total CHD and CHD subtype birth prevalence worldwide, checked for bias caused by study design, and adjusted comparisons to the era of echocardiography, some residual bias may be present in our estimates (e.g., caused by differences in quality of the papers). It remains difficult, as stated by others, to determine whether detected differences in CHD birth prevalence are real or merely methodological (22). Another inevitable limitation of this meta-analysis is that it does not really cover the entire world population. Data from developing countries were scarce, and studies often do not include indigenous inhabitants and tribes. Population-wide prospective birth defect registries are necessary to determine the true birth prevalence, including economically developing parts of the world.

Conclusions

Reported total CHD birth prevalence increased substantially over the last century, reaching a stable estimate of 9 per 1,000 live births in the last 15 years. This corresponds to 1.35 million newborns with CHD every year, representing a major global health burden. Significant geographical differences were found. It remains uncertain whether detected differences in CHD birth prevalence represent true or merely methodological differences. In the future, the etiology of CHD needs to be further clarified and population-wide prospective birth defect registries covering the entire world population are needed to determine the exact birth prevalence.

Acknowledgment

The authors thank Helena Heuvelman, MD, for her support in data analysis.

@ **For supplementary Table 1, please see the online version of this article available at:** *http://www.sciencedirect.com/science/article/pii/S0735109711030798.*

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PART

III

Discrete subaortic stenosis

3

Natural history of discrete subaortic stenosis in adults: a multicentre study

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Eur Heart J. E-pub 13 Dec 2012.

Abstract

Aims

Discrete subaortic stenosis (DSS) is often diagnosed early in life and known for its sometimes rapid haemodynamic progression in childhood and strong association with aortic regurgitation (AR). However, data about the evolution of DSS in adulthood are scarce. Therefore we aimed to evaluate the natural history of DSS, and identify risk factors for progression of DSS, AR, and intervention-free survival.

Methods and results

Conservatively managed adult DSS patients were included in this retrospective multicentre cohort study. Mixed-effects and joint models were used to assess the progression of DSS and AR, and intervention-free survival.

Longitudinal natural history data were available for 149 patients [age 20 (IQR 18-34) years, 48% male]. Sixty patients (40.3%) had associated congenital heart defects (CHDs). The median follow-up duration was 6.3 (IQR 3.0-12.4) years. The baseline peak left ventricular outflow tract (LVOT) gradient was 32.3±17.0 mmHg and increased by 0.8±0.1 mmHg/year. While the baseline LVOT gradient (p=0.891) or age (p=0.421) did not influence the progression rate, the presence of associated CHD was associated with faster progression (p=0.005). Mild AR was common (58%), but did not significantly progress over time (p=0.701). The median intervention-free survival was 16 years and associated with the baseline LVOT gradient [hazard ratio (HR) =3.9 (95%CI 2.0-7.6)], DSS progression [HR=2.6 (95%CI 2.0-3.5)] and AR [HR=6.4 (95%CI 2.6-15.6)].

Conclusions

In contrast to children, DSS progresses slowly in adulthood. In particular patients with associated CHD are at risk for faster progression and should be monitored cautiously. Discrete subaortic stenosis progression is not influenced by the LVOT gradient or age. Mild AR is common, but nonprogressive over time.

Introduction

Fibromuscular discrete subaortic stenosis (DSS) is often diagnosed early in life and notable for its unpredictable, but sometimes rapid haemodynamic progression during childhood.[1-4] Aortic regurgitation (AR) is present in 30-80% of patients and thought to develop secondary to aortic valve damage caused by the high-velocity subvalvular jet.[1-11] In children, the natural history is well established and several predictors for haemodynamic progression have been identified such as younger age or a higher gradient at diagnosis.[1,12-14] Despite the fact that DSS is a relatively frequent abnormality (6.5%) in adults with congenital heart defects (CHD), data about DSS in adulthood are scarce.[7,8,15-18] In contrast to infants and children, adults with DSS seem to have a slower progression rate.[7] However, there is a lack in studies focusing on the elucidation of factors that predict DSS or AR progression in adults. Therefore, the main purpose of this study was to evaluate the natural history of DSS in a large cohort of adults and identify risk factors for DSS progression, AR progression and the need for surgery.

Methods

All adult patients (18 years or older) with a pre-existing diagnosis of fibromuscular DSS seen between January 1980 and October 2011 at the Congenital Cardiac Centre for Adults of one of the participating centres (Erasmus University Medical Centre, Rotterdam, The Netherlands; University Hospital Gasthuisberg, Leuven, Belgium; Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; Toronto Congenital Cardiac Centre for Adults located at Peter Munk Cardiac Centre, Toronto, Canada) were evaluated for eligibility. Fibromuscular DSS was defined as: "encirclement of the left ventricular outflow tract (LVOT) by a membrane or short-segment stenosis consisting of fibrous or fibromuscular tissue". Eligible patients were selected from the CONCOR database,[19] the Dutch registry for adult patients with CHD, and the Leuven and Toronto database for adults with CHD. Exclusion criteria were: prior surgical resection of subaortic tissue, lack of serial echocardiographic examinations, predominant dynamic subaortic obstruction due to hypertrophic cardiomyopathy, subvalvular obstruction caused by accessory mitral valve tissue or the support system of mitral valve prosthesis, complex LVOT obstruction (tunnel-like subaortic narrowing), concomitant moderate-to-severe valvular aortic stenosis, transposition of the great arteries or univentricular connections. This retrospective study was approved by the institutional review board and ethical committee of the participating centres. Informed consent was waived.

Demographic, clinical and surgical data were obtained from medical charts and electronic health records. All available transthoracic echocardiograms, electrocardiograms and exercise tests were collected. Baseline was defined as entry of the study (first available echocardiogram in adulthood). Follow-up was defined as the time between the first and last available echocardiogram. Peak systolic instantaneous LVOT gradient was derived from the continuous wave Doppler LVOT peak flow velocity from the apical three- or five-chamber views. The degree of AR was graded by experienced echocardiographers and cardiologists as mild, moderate, or severe.[20] The left ventricular (LV) mass was calculated using the modified Devereux formula.[21] The aorto-septal angle was measured in the parasternal long-axis view at end-diastole, as previously described.[22,23]

Statistical analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for descriptive data-analysis. Normally distributed continuous variables were summarized using the mean ± standard deviation (SD). Non-normally distributed continuous variables were summarized using the median and the interquartile range (IQR). Categorical variables were summarized using the frequency and percentage. Group differences in baseline variables were assessed using the two-sample *t* test, the χ^2-square test, or the Mann-Whitney *U* test. All statistical tests were two-sided; a *P*-value <0.05 was considered statistically significant.

For advanced statistical analyses of the longitudinal and survival data, the R statistical software (version 2.15.0, available at: *www.r-project.org*) was used. To assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient mixed-effects model analyses were used. In particular, for the LVOT gradient progression rate a linear mixed-effects model was used, whereas for AR progression a mixed-effects continuation ratio model was employed.[24] The following factors were included in the models as covariates: age at baseline, age at diagnosis, gender, prior intracardiac surgery, additional CHDs, baseline LVOT gradient (< or ≥ 50 mmHg), aortic valve morphology, LV mass, ventricular septal defect (VSD), AR, aorto-septal angle and smoking. For each of the covariates in the model its main effect and interaction with time was added, allowing for different average longitudinal evolutions per covariate. Residual plots were used to validate the models' assumptions, and when appropriate, transformations of the outcome variables were used in the analysis. Furthermore, to account for missing covariate data a multiple imputation approach was used. Wald tests were used to assess which prognostic factors were most associated with the progression of the LVOT gradient and AR.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of DSS patients was compared with the expected survival of the normal Dutch population.[25] Patients were censored at the end of follow-up or classified as event (surgery for DSS or death). A penalized likelihood approach was employed for the Cox regression model with baseline data, to account for the low number of events compared with the number of covariates. A joint modelling approach and time-dependent Cox model were respectively used to investigate the effect of the LVOT gradient and AR on the hazard ratio (HR).[26]

Results

Out of 427 identified patients with fibromuscular DSS, longitudinal natural history data were available for 149 patients (Figure 1). Baseline characteristics are summarized in Table 1. Sixty patients (40.3%) had associated CHD. The median follow-up duration was 6.3 (IQR 3.0-12.4) years, yielding a total of 1191 patient-years. On average 2.7 ± 0.9 (range 2-9) echocardiographic studies were available for each patient.

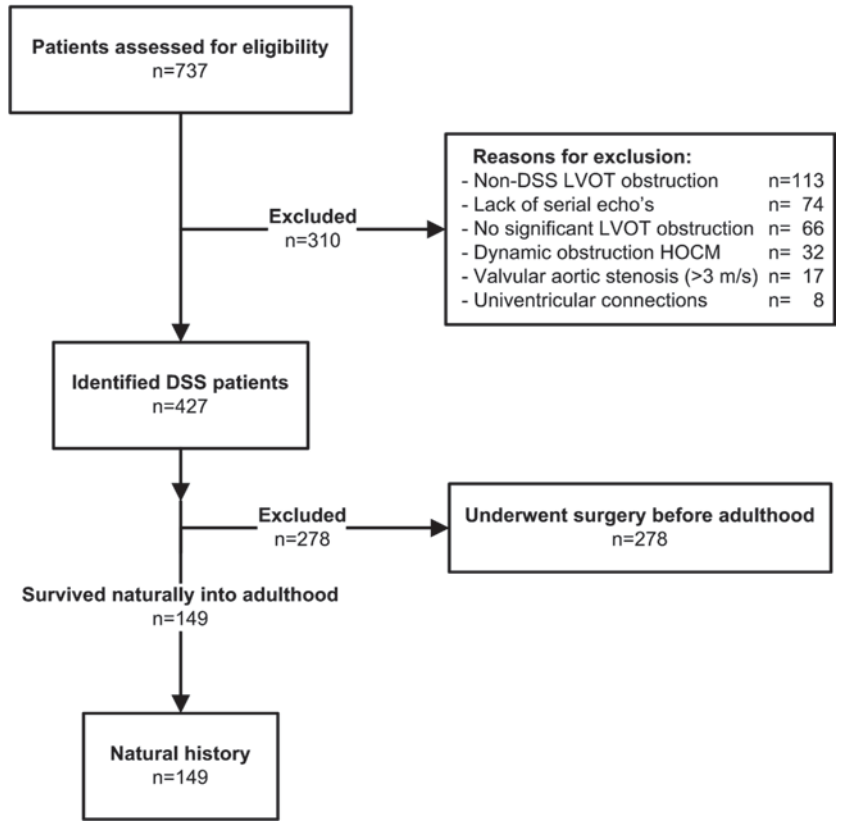

Figure 1. *Flowchart of patient inclusion.*

DSS = discrete subaortic stenosis; HOCM = hypertrophic obstructive cardiomyopathy; LVOT = left ventricular outflow tract.

Progression of left ventricular outflow tract gradient over time

The peak systolic instantaneous LVOT gradient was 32.3 ± 17.0 mmHg at baseline and linearly increased over time with a rate of 0.8 ± 0.1 mmHg per year. Six patients demonstrated a progression rate >5 mmHg/year. The presence of an associated CHD was associated with faster progression of the LVOT gradient (p=0.005; Figure 2), in particular a VSD (p=0.035). The LVOT gradient progression rate was not influenced by the age at baseline (p=0.421), age at time of diagnosis (p=0.273), gender (p=0.960), prior intracardiac surgery (p=0.162), baseline LVOT gradient ≥50 mmHg (p=0.891; Figure 2), current smoking (p=0.282) or aortic valve morphology (p=0.240) (see Supplementary material online, Table S1).

Table 1. *Baseline characteristics.*

	Discrete subaortic stenosis patients (n=149)	Intervention-free survival group (n=106)	Patients with an event (surgery or death) (n=43)	p-value
Male	72 (48.3)	52 (49.1)	20 (46.5)	0.778
Age at baseline, years	20.4 (17.6-33.8)	20.2 (17.5-33.6)	20.5 (17.8-34.2)	0.701
Age at DSS diagnosis, years	17.0 (7.5-30.5)	18.8 (7.4-31.8)	16.7 (5.9-29.0)	0.810
Body mass index, kg/m^2	25.4 ± 5.5	25.8 ± 6.1	24.6 ± 3.9	0.251
Systolic blood pressure, mmHg	125.6 ± 16.6	125.9 ± 16.6	125.1 ± 16.6	0.787
Diastolic blood pressure, mmHg	74.9 ± 10.3	75.5 ± 10.2	73.5 ± 10.6	0.282
Peak systolic instantaneous LVOT gradient, mmHg	32.3 ± 17.0	28.4 ± 14.1	41.9 ± 19.9	<0.001
≤30 mmHg	76 (51.0)	64 (60.4)	12 (27.9)	<0.001
30-50 mmHg	51 (34.2)	33 (31.1)	18 (41.9)	
≥50 mmHg	22 (14.8)	9 (8.5)	13 (30.2)	
Aortic regurgitation				
None / trivial	57 (38.3)	44 (41.5)	13 (30.2)	0.085
Mild	86 (57.8)	61 (57.5)	25 (58.1)	
Moderate	5 (3.4)	1 (9.4)	4 (9.3)	
Severe	1 (0.7)	0 (0.0)	1 (2.3)	
Associated CHD / repaired *				
None	89 (59.7)	63 (59.4)	26 (60.5)	0.961
Ventricular septal defect	24 (16.1) / 7 (4.7)	17 (16.0) / 5 (4.7)	7 (16.3) / 2 (4.7)	0.971
Atrial septal defect	11 (7.4) / 6 (4.0)	9 (8.5) / 5 (4.7)	2 (4.7) / 1 (2.3)	0.417
Valvular aortic stenosis (< 3 m/s)	7 (4.7) / 0 (0.0)	2 (1.9) / 0 (0.0)	5 (11.6) / 0 (0.0)	0.011
Coarctation of the aorta	15 (10.1) / 6 (4.0)	10 (9.4) / 4 (3.8)	5 (11.6) / 2 (4.7)	0.687
Persistent ductus arteriosus	6 (4.0) / 4 (2.7)	4 (3.8) / 3 (2.8)	2 (4.7) / 1 (2.3)	0.805
Shone's complex	2 (1.3) / 0 (0.0)	0 (0.0) / 0 (0.0)	2 (4.7) / 0 (0.0)	0.025
Aorto-septal angle, º #	138.2 ± 16.2	138.8 ± 16.8	133.6 ± 11.0	0.423
Left atrial diameter, mm	36.6 ± 8.4	35.9 ± 7.7	40.1 ± 10.8	0.058
Indexed for BSA, mm/m^2	20.1 ± 5.2	19.5 ± 4.8	22.6 ± 6.4	0.028

Table 1. *Baseline characteristics. (Continued)*

	Discrete subaortic stenosis patients (n=149)	Intervention-free survival group (n=106)	Patients with an event (surgery or death) (n=43)	p-value
LV mass, gram	174.0 ± 65.0	164.9 ± 55.8	215.6 ± 86.8	0.003
Indexed for BSA, gram/m^2	94.6 ± 35.1	88.6 ± 27.9	121.5 ± 49.8	<0.001
LVOT diameter, mm	16.5 ± 3.3	16.4 ± 3.4	17.0 ± 3.0	0.640
LV end-diastolic diameter, mm (IQR)	46.8 ± 6.7 (41.0 – 51.0)	46.1 ± 6.2 (40.0-50.0)	50.1 ± 8.0 (46.5-56.3)	0.059
Indexed for BSA, mm/m^2	25.8 ± 4.3	25.2 ± 3.9	28.4 ± 5.3	0.004
LV end-systolic diameter, mm (IQR)	28.3 ± 5.6 (25.0 – 32.0)	27.8 ± 5.3 (24.3-31.0)	30.6 ± 6.8 (24.8-35.0)	0.053
Indexed for BSA, mm/m^2	15.6 ± 3.5	15.2 ± 3.1	17.4 ± 4.6	0.013
Fractional shortening, %	39.7 ± 7.2	39.8 ± 7.1	38.9 ± 7.9	0.641
Maximum exercise capacity, % from norm	86.3 ± 22.3	86.6 ± 21.8	85.8 ± 23.4	0.256
Sinus rhythm	146 (98.0)	104 (98.1)	42 (97.7)	0.283
Heart frequency, beats per minute	71.9 ± 14.5	72.5 ± 14.6	70.3 ± 14.5	0.487
QRS duration, ms	101.8 ± 20.8	98.7 ± 17.5	110.8 ± 26.6	0.005
PR time, ms	154.6 ± 34.3	153.6 ± 35.8	157.0 ± 30.3	0.640
NYHA class I	144 (96.6)	104 (98.1)	40 (93.0)	0.118
Smoking				
Never	112 (75.2)	84 (79.2)	28 (65.1)	0.323
Former	11 (7.4)	6 (5.7)	5 (11.6)	
Current	26 (17.4)	16 (15.1)	10 (23.3)	

Values are expressed as n(%), median (IQR) or mean±SD.
**Diagnoses are not mutually exclusive (one patient could have multiple associated CHD).*
 # This variable was only available for 82 patients.
BSA = body surface area; CHD = congenital heart defects; DSS = discrete subaortic stenosis; IQR = interquartile range; LV = left ventricular; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

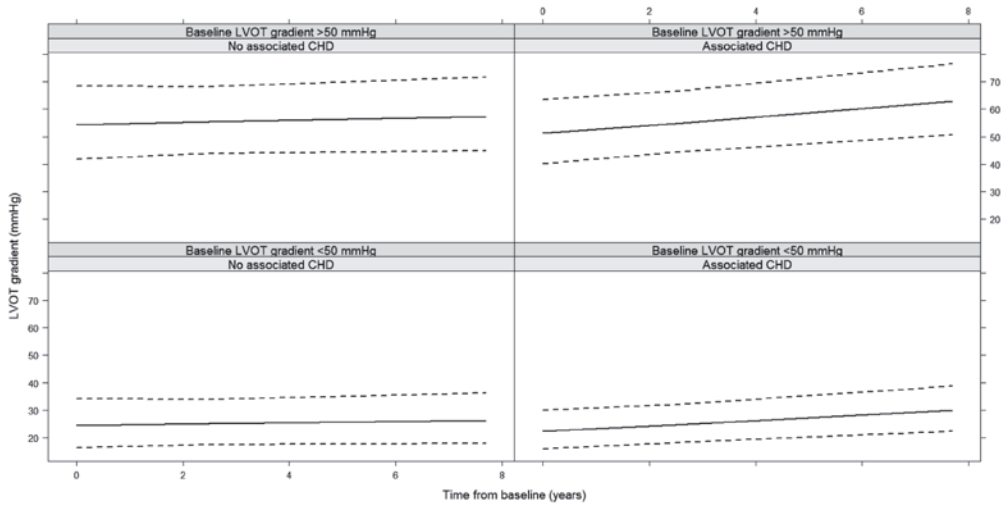

Figure 2. *Evolution of discrete subaortic stenosis over time.*

Progression of the left ventricular outflow tract gradient over time by the baseline left ventricular outflow tract gradient (<50 mmHg and ≥50mmHg; p=0.891) and by the presence or absence of an associated congenital heart defect (p=0.005). The dashed lines denote 95% confidence intervals.
LVOT = left ventricular outflow tract; CHD = congenital heart defect.

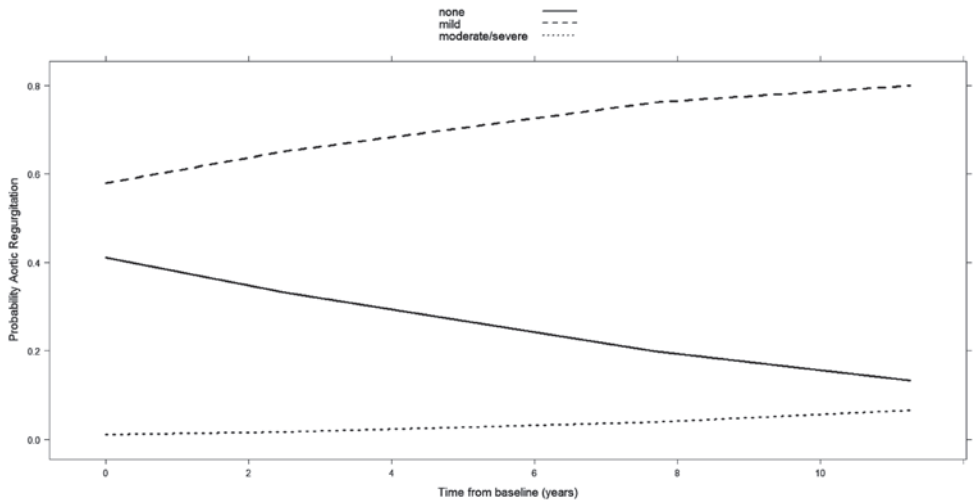

Figure 3. *Evolution of aortic regurgitation over time.*

No significant progression in the severity of aortic regurgitation over time (p=0.747).

Progression of aortic regurgitation over time

A LVOT gradient ≥50 mmHg (p=0.007) was independently associated with a higher probability of having AR (see Supplementary material online, Table S2). Although Figure 3 demonstrates that over a period of 10 years the probability of not having AR decreases from approximately 40% to approximately 20%, progression to moderate-to-severe AR was rare. Overall, the AR severity did not significantly progress over time (p=0.747). A baseline peak LVOT gradient ≥50 mmHg did not influence the progression of AR (p=0.999).There were no factors significantly associated with progression from mild to moderate-to-severe AR (see Supplementary material online, Table S2).

Clinical outcome

Two patients died suddenly 4 and 16 years after entry in the study (37 and 39 years old, LVOT gradients before death 63 and 85 mmHg, respectively, no associated CHD, no left ventricular hypertrophy). The cause of death was unknown in both patients (no autopsy). The cumulative survival was 94% at 20 years (0.17% per patient-year; Figure 4A). One patient was successfully resuscitated after an episode of ventricular fibrillation (36 years old, LVOT gradient before the event 49 mmHg, associated repaired VSD and left ventricular hypertrophy). Two patients (22-year old male and 52-year-old female, LVOT gradients 21 and 64 mmHg, respectively, both had an associated unrepaired VSD and mild AR) had an episode of endocarditis (0.17% per patient-year).

During follow-up 41 patients required surgery for DSS according to the clinical practice guidelines (5.9% per patient-year). The median intervention-free survival was 16 years (Figure 4A). The mean age at the time of DSS surgery was 35.1 ± 14.0 years. The pre-operative LVOT gradient was 75.3 ± 3.6 mmHg and 17 of the 41 patients (41.5%) had moderate-to-severe AR. The type of DSS surgery was enucleation in 20 patients (48.8%) and enucleation with additional myectomy in 21 patients (51.2%). Nineteen patients (46.3%) underwent concomitant surgery: aortic valve replacement or repair (n=16) or VSD closure (n=3). Post-operative complications included bleeding requiring rethoracotomy (n=1), atrial fibrillation (n=4), complete AV block requiring permanent pacemaker implantation (n=3), and heart failure (n=1).

Independent predictors for impaired intervention-free survival were the baseline LVOT gradient ≥50 mmHg [HR 3.9 (95%CI 2.0-7.6); Figure 4B], LVOT gradient progression over time [HR 2.6 (95%CI 2.0-3.5)] and moderate-to-severe AR [HR 6.4 (95%CI 2.6-15.6)] (see Supplementary material online, Table S3).

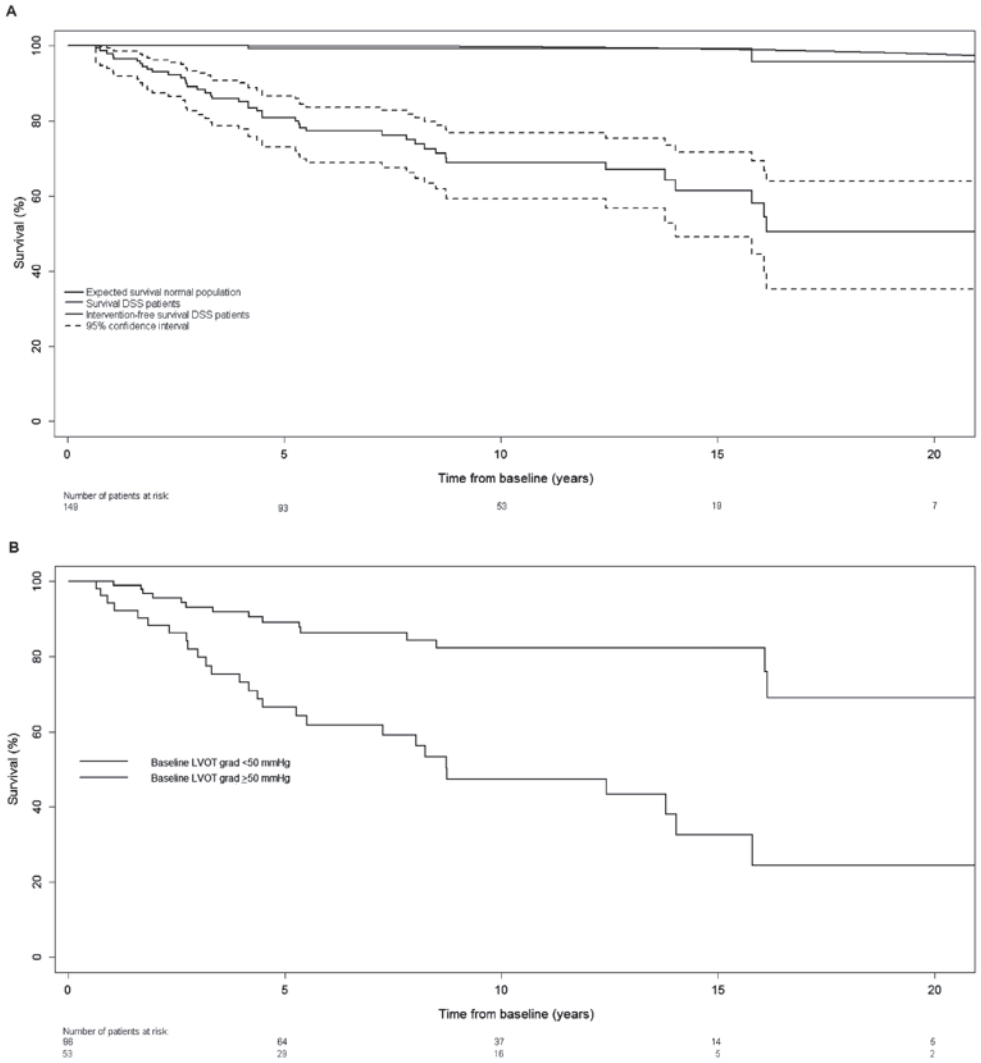

Figure 4. *Kaplan-Meier plots.*

(A) Cumulative Kaplan-Meier survival and intervention-free survival for discrete subaortic stenosis patients and expected survival for the normal Dutch population.
(B) Cumulative Kaplan-Meier intervention-free survival for discrete subaortic stenosis patients with a baseline peak systolic instantaneous left ventricular outflow tract gradient <50 mmHg compared with ≥50 mmHg (p<0.001).
DSS = discrete subaortic stenosis; LVOT = left ventricular outflow tract.

Discussion

This study is the first large longitudinal study focusing on the natural course of DSS over time and risk factors influencing the clinical outcome in adult patients. Given the scarcity of data about the natural evolution of DSS in adults, these results will contribute to our understanding of the clinical course of DSS in adulthood and guide clinical management.

Progression of discrete subaortic stenosis

Interestingly, the present study demonstrates that DSS in adulthood progresses very slowly, with < 1 mmHg gradient increase per year. These results confirm the findings of a series published by Oliver et al.[7] that showed a similar slow progression rate in only 25 patients with sequential echocardiographic studies. Remarkably, the slow progression rate along several decades in adults contrasts to the progressive nature of DSS described in children.[1-4] This phenomenon might be explained by the fact that adults who survived into adulthood without an intervention compile a highly selected subgroup and represent a mild phenotype within the spectrum of DSS.

The study by Oliver et al.[7] suggested that age influences DSS evolution, since they found significant correlations between age and LVOT gradient and progression.[7] To evaluate if age was not only correlated but could actually significantly predict DSS disease progression, we explored age as a covariate in longitudinal echocardiographic models in this large population. However, neither age at the study baseline nor age at the time of diagnosis significantly influenced LVOT progression over time. Furthermore, in contrast to paediatric populations, we did not find an association between DSS severity at baseline and the progression rate in adults who naturally survived into adulthood.[1,12-14] Thus, patients with LVOT gradients ≥50 mmHg were not at risk for faster progression of the LVOT obstruction.

With respect to the prevalence of associated CHD, our population was comparable with those described in other studies.[7,8,15] Notably, the presence of an associated CHD, particularly a VSD, was the only independent predictor for DSS progression. Many previous studies have tried to elucidate the poorly understood aetiology of DSS.[3,27,28] It has been demonstrated that abnormal geometric arrangements in the LVOT, such as steepened aorto-septal angle, malaligned VSD, and mitral-aortic separation, may induce increased shear stress.[22,23,29-31] Cellular flow studies have shown that increased shear stress triggers growth factors and cellular proliferation, eventually stimulating development of the subaortic membrane and progression of the LVOT obstruction.[11] Our findings suggest that adult DSS patients with associated CHD and those without additional CHD compile two different subgroups within the DSS spectrum. We hypothesize that the presence of associated CHD, particularly a VSD, causes more abnormal hemodynamic forces at the LVOT level, which could be caused either by the CHD itself or by prior intracardiac surgery for that defect. The abnormal hemodynamic forces might cause increased shear stress, thereby evoking a more intense response on a cellular level and faster progression of the LVOT obstruction. We tried to elucidate whether the aorto-septal angle influenced LVOT progression over time, but unfortunately there were too many missing values for this covariate. Future rheological studies in adult DSS patients are certainly warranted to test this hypothesis.

Aortic regurgitation

The most commonly described hemodynamic sequel in DSS patients is AR, which is thought to evolve secondary to the high velocity subvalvular jet produced by the LVOT obstruction.[5-11] In an attempt to prevent damage to the aortic valve, early surgical resection of the subaortic membrane has been advocated.[32,33] However, Oliver et al.[7] demonstrated in 25 adults that AR is common, and usually mild and nonprogressive over time.[7] Similarly, our study clearly showed that AR is only haemodynamically relevant (moderate-to-severe) in a minority of patients although mild AR is found in the majority of adult DSS patients. More importantly, while about 20% of patients developed mild AR during the study period, progression to moderate-to-severe is rare. In the total group, the AR progression was not statistically significant and we could not identify a subgroup of patients at a higher risk for progression. Therefore, the fear of development of progressive AR seems to be overestimated and early surgical repair of DSS in adult patients with a low LVOT gradient and no/mild AR is not justified.

Survival

Overall, the cumulative 20-year survival of patients with DSS is comparable with the survival of the age-matched normal Dutch population.[25] Since the life expectancy of Canada, the Netherlands and Belgium is comparable, this probably does not influence our survival results at young adult age.[34] However, the rate of (near) sudden death (0.17-0.25% per patient-year) in our study of young adult patients with DSS is worrisome. This seems to be higher than the generally estimated 0.09% per patient-year in adult patients with any type of CHD.[35,36] Moreover, it represents a 30-125 times increased risk of sudden death compared with the general population with a similar age range.[37-41] Unfortunately the absolute number of events was too small to identify any risk factors for sudden death in patients with DSS.

Clinical implications

Discrete subaortic stenosis progresses very slowly in adulthood; however, patients with associated congenital lesions, particularly a VSD, are at risk for faster disease progression and should be monitored cautiously. Furthermore, this large study shows that AR is usually mild and does not progress over time, thereby rejecting the hypothesis that early repair is required to prevent development of progressive AR.

According to the present study, prophylactic surgery in asymptomatic adult DSS patients is not indicated solely to prevent rapid progression of the LVOT obstruction or progressive AR. Our data do not support the current North American guidelines that state that surgical intervention should be recommended in any DSS patient with a peak LVOT gradient ≥50 mmHg, but are more in line with the European and Canadian guidelines.[42-44] However, the timing of surgical intervention is a highly complex issue compiling various factors in an individual patient-based approach: the peak LVOT gradient, progression rate of the LVOT gradient, severity and progression of AR, presence of associated CHD, LV diameter and function, and risk of sudden death. Postponing surgery to higher LVOT gradients might increase the chance of requirement of concomitant aortic valve repair or replacement and increase the risk of sudden death. On the other hand, until now it is unclear whether surgery will prevent or at least minimize the risk of sudden death.

Unfortunately, the optimal timing of surgical intervention in adult patients with DSS cannot yet be derived from the present study.

Since endocarditis only occurred in two patients with a concomitant unrepaired VSD, it is likely that these cases were related to the unrepaired VSD rather than DSS. Thus, the risk of endocarditis in patients with isolated DSS seems to be low and endocarditis prophylaxis should only be indicated in high-risk patients.[44]

Since the LVOT gradient progression is generally slow and AR is usually mild, echocardiographic follow-up can probably be limited to 3-5-year intervals for the majority of patients. However, for patients with associated congenital lesions (particularly a VSD), peak LVOT gradient ≥50 mmHg, or moderate-to-severe AR more frequent echocardiographic follow-up evaluations seem reasonable, for example every 1-2 years.

Study limitations

This retrospective study inheriting all limitations of a retrospective study design included patients monitored in adult congenital clinics at tertiary care centres, and therefore a referral bias may exist. Inclusion of deceased patients from the databases limited survival bias. Unfortunately, some echocardiographic parameters could not be retrieved for all patients, but this was dealt with by using the multiple imputation approach for missing values. The fact that echocardiography was not performed precisely every year, was accounted for by the use of mixed-effects models that take different lengths of follow-up into account. Furthermore, by using the joint modelling approach we allowed for the dependency and association between the longitudinal echocardiographic data and survival data. Finally, we have to acknowledge that the median follow-up duration of 6.3 years was relatively short. For definitive conclusions regarding the long-term outcome of DSS in adulthood, a longer follow-up period is required.

Conclusions

Conservatively (non-surgically) managed DSS progresses slowly in adulthood, though patients with associated congenital lesions, especially a VSD, are at risk for faster DSS progression and should be monitored cautiously. The baseline LVOT gradient does not influence DSS progression over time, and thus should not be used as the sole indication to proceed to surgery. AR is usually mild and does not progress over time, indicating that prophylactic surgery to prevent AR progression is not justified.

Acknowledgements

We thank Angela Oxenius, MD from the Toronto Congenital Cardiac Centre for Adults, Division of Cardiology, Peter Munk Cardiac Centre, and University of Toronto, Toronto, Ontario, Canada, for her extensive contribution to the data collection of this manuscript. Furthermore, we would like to thank the medical teams, technicians and sonographers at the participating centres.

@ **Supplementary material is available at European Heart Journal online:** *www.eurheartj.oxfordjournals.org.*

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4

Surgical outcome of discrete subaortic stenosis in adults: a multicenter study

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Circulation. 2013; In press.

Abstract

Background

Discrete subaortic stenosis (DSS) is notable for its unpredictable hemodynamic progression in childhood and high re-operation rate, however data about adulthood are scarce.

Methods and results

Adult patients who previously underwent surgery for DSS were included in this retrospective multicenter cohort study. Mixed-effects and joint models were used to assess postoperative progression of DSS and aortic regurgitation (AR), and re-operation.

A total of 313 patients at 4 centers were included (age at baseline 20.2 years (Q1 to Q3, 18.4-31.0), 52% male). Median follow-up duration was 12.9 years (Q1 to Q3, 6.2-20.1), yielding 5617 patient-years. The peak instantaneous left ventricular outflow tract (LVOT) gradient decreased from 75.7±28.0 mmHg pre-operatively to 15.1±14.1 mmHg postoperatively (p<0.001), and thereafter increased over time at a rate of 1.31±0.16 mmHg per year (p=0.001). Mild AR was present in 68%, but generally did not progress over time (p=0.76). A pre-operative LVOT gradient ≥80 mmHg was a predictor for progression to moderate AR postoperatively. Eighty patients required at least one re-operation (1.8% per patient-year). Predictors for re-operation included female gender (HR=1.53, 95%CI 1.02-2.30) and LVOT gradient progression (HR=1.45, 95%CI 1.31-1.62). Additional myectomy did not reduce the risk for re-operation (p=0.92), but significantly increased the risk of a complete heart block requiring pacemaker implantation (8.1% versus 1.7%; p=0.005).

Conclusions

Survival is excellent after surgery for DSS, however reoperation for recurrent DSS is not uncommon. Over time the LVOT gradient slowly increases and mild AR is common, though generally nonprogressive over time. Myectomy does not show additional advantages and as it is associated with an increased risk of complete heart block, it should not be performed routinely.

Introduction

Discrete subaortic stenosis (DSS) is notable for its unpredictable and sometimes rapid hemodynamic progression in childhood and its association with aortic regurgitation (AR), which is found in 30-80% of patients.[1-7] Different strategies exist for the timing of surgical treatment, ranging from early (mild to moderate obstruction) to late (severe or symptomatic) repair. Early repair has been advocated to prevent aortic valve damage and thus AR progression.[5-12] Nevertheless, it remains unclear whether surgery can actually alter the course of progressive AR. Furthermore, surgery is associated with a high recurrence risk and need for re-operation (8-34%).[12-18] A major factor in DSS recurrence is believed to be inadequate relief of the obstruction.[19] Therefore some groups advocate concomitant selective myectomy to achieve complete relief of the LVOT obstruction,[8,18-21] whereas others have reported that the addition of myectomy does not reduce the number of recurrences.[16,17,22-27]

While postoperative outcome and risk factors for re-operation in children are well established, postoperative data for the adult population are limited.[15,27,28] Therefore, the aim of this study was to identify risk factors for postoperative DSS recurrence, AR progression and re-operation in a large cohort of adult patients who previously underwent surgical treatment for DSS.

Methods

All adult patients who previously underwent surgery for fibromuscular DSS and were seen between January 1980 and October 2011 at the Congenital Cardiac Center for Adults of one of the participating centers (Erasmus University Medical Center, Rotterdam, and Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; University Hospital Gasthuisberg, Leuven, Belgium; and Toronto Congenital Cardiac Centre for Adults located at Peter Munk Cardiac Centre, Toronto, Canada) were evaluated for eligibility for this study.

Fibromuscular DSS was defined as a complete or incomplete encirclement of the LVOT by a membrane or short-segment stenosis consisting of fibrous or fibromuscular tissue. Baseline of this study was defined as time of first adult outpatient clinic visit. Eligible patients were selected from the CONCOR database (the Dutch registry for adult patients with congenital heart disease (CHD)),[29] and from the Leuven and Toronto local database for adults with CHD. Although all patients followed in Congenital Cardiac Centers for Adults were ≥17 years old, the first surgery for DSS could have been performed in childhood. Exclusion criteria were: lack of serial echocardiograms, non-DSS causes for subaortic obstruction (tunnel-like subaortic narrowing, hypertrophic cardiomyopathy, accessory mitral valve tissue or mitral valve prosthesis), concomitant moderate-to-severe valvular aortic stenosis, transposition of the great arteries and univentricular connections. This retrospective study was approved by the institutional review board and ethical committee of participating centers. Informed consent was waived.

Demographic, clinical and surgical data were obtained from medical charts and electronic health records. All available transthoracic echocardiograms, electrocardiograms and exercise tests were collected.

Peak systolic instantaneous LVOT gradient was derived from the continuous wave Doppler LVOT peak flow velocity. The degree of AR was graded by experienced echocardiographers and cardiologists as mild, moderate, or severe.[30] Left ventricular mass was calculated using the modified-Devereux-formula.[31] In the parasternal long-axis view at end-diastole, we measured the aorto-septal angle, which is the angle formed by the plane of the ventricular septum and the ascending aorta, as previously described.[32,33]

Statistical analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc., Chicago, Illinois) was used for descriptive data-analysis. Continuous variables were summarized using mean ± standard deviation (SD) and median and 25th percentile (Q1) to 75th percentile (Q3). Categorical variables were summarized using the frequency and percentage. The paired t-test, paired Wilcoxon and McNemar's test were used to compare pre- and postoperative measurements. All statistical tests with a p-value <0.05 were considered significant.

For advanced statistical analyses of the longitudinal and survival data, the R statistical software (version 2.15.0, available at: *www.r-project.org*) was used. To assess changes in echocardiographic measurements over time while accounting for the correlation between repeated follow-up measurements in each patient, mixed-effects models analyses were used. In particular, for the postoperative LVOT gradient progression rate a linear mixed-effects model was used, [34] whereas for postoperative AR progression a mixed-effects continuation ratio model was employed. To allow for flexibility in the modeling of the patient-specific longitudinal trajectories, we used natural cubic splines of time in the specification of the mixed-effects models, both in the fixed- and random effect part of the models. The following variables were included in the models as covariates: age at time of surgery, age at diagnosis, gender, pre-operative peak instantaneous LVOT gradient, difference between pre- and postoperative gradient (delta), type of surgery (isolated enucleation or additional myectomy), associated CHD and smoking. For each of the covariates in the model its main effect and interaction with time was added, allowing for different average longitudinal evolutions per covariate. Residual plots were used to validate the models' assumptions, and when appropriate transformations of the outcome variables were used in the analysis. Furthermore, to account for missing covariate data a multiple imputation approach was used for the covariates pre- and postoperative LVOT gradient (missing for 42 patients). Five generations of 'complete' data sets were realized. Wald tests were used to assess which prognostic factors were most associated with the progression of peak instantaneous LVOT gradient and AR.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of DSS patients was compared to the expected survival of the age-matched normal Dutch population.[35] Patients were censored at end of follow-up or classified as event (surgery for DSS or death). A penalized likelihood approach was employed for the Cox regression model with baseline data, to account for the low number of events compared to the number of covariates.

A joint longitudinal and survival model and the time-dependent Cox model were respectively used to investigate the effect of peak instantaneous LVOT gradient and AR on the hazard ratio (HR) for intervention-free survival.[36]

Table 1. *Baseline characteristics.*

	Operated DSS patients
Male	163 (52.1)
Age at baseline, years	20.2 (18.4-31.0)
Age at DSS diagnosis, years	8.0 (4.0-15.0)
Body surface area, m^2	1.8 ± 0.2
Body mass index, kg/m^2	25.9 ± 5.4
Systolic blood pressure, mmHg	125.6 ± 19.4
Diastolic blood pressure, mmHg	72.6 ± 10.9
Associated CHD anomalies; previously repaired *	
None	150 (47.9)
Ventricular septal defect	72 (23.0); 15 (4.8)
Atrial septal defect	18 (5.8); 4 (1.3)
Valvular aortic stenosis	29 (9.3); 2 (0.6)
Coarctation of the aorta	48 (15.3); 10 (3.2)
Persistent ductus arteriosus	20 (6.4); 8 (2.6)
Shone complex	10 (3.2); 0 (0.0)
Aortoseptal angle, º	124.7 ± 15.9
Left atrial diameter, mm (indexed for BSA, mm/m^2)	42.4 ± 11.7 (22.8 ± 5.3)
Left ventricular mass, gram (indexed for BSA, mm/m^2)	222.0 ± 86.3 (120.1 ± 42.8)
LV end-diastolic diameter, mm (indexed for BSA, mm/m^2)	49.1 ± 7.5 (27.1 ± 4.4)
LV end-systolic diameter, mm (indexed for BSA, mm/m^2)	29.5 ± 7.4 (16.3 ± 4.3)
LV fractional shortening, %	40.3 ± 9.0
E/A ratio	1.5 ± 0.6
E/E' ratio	11.9 ± 6.0
Maximum exercise capacity, % from norm	82.1 ± 20.4
Sinus rhythm	295 (94.2)
Heart frequency, beats per minute	72.5 ± 14.5
QRS duration, ms	114.9 ± 28.9
PR time, ms	160.5 ± 30.9
NYHA class I	290 (92.9)
Smoking	
Never	211 (67.4)
Former	26 (8.3)
Current	64 (20.4)
Unknown	12 (3.8)

Values are n(%), median (Q1 to Q3) or mean±SD.
** Diagnoses are not mutually exclusive.*
BSA = body surface area; CHD = congenital heart disease; DSS = discrete subaortic stenosis; LV = left ventricular; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

Results

A total of 737 patients were assessed for eligibility to participate in this study. Inclusion criteria were met by 313 patients. Four hundred twenty-four patients were excluded, mainly due to LVOT obstruction due to another cause (n=145), no history of DSS surgery (n=149) or lack of serial echocardiography examinations (n=74).

Baseline characteristics of the 313 patients are summarized in Table 1. One hundred sixty-three patients (52.1%) had one or more associated CHD. Baseline LVOT diameter was 14.5±3.8 mm in women and 15.7±4.2 mm in men (p=0.19). Follow-up ranged from 1 to 31 years (median 12.9, Q1 to Q3 6.2-20.1 years), yielding a total of 5617 patient-years. On average 2.3 ± 1.4 (min. 2, max. 8) echocardiographic studies were available for each patient.

Operative outcomes

The 313 included patients underwent a total of 412 operations for DSS. The peak instantaneous LVOT gradient decreased from 75.7 ± 28.0 mmHg pre-operatively to 15.1 ± 14.1 mmHg postoperatively (p<0.001). The LVOT diameter increased from 14.5 ± 3.8 mm to 19.0 ± 3.7 mm (p<0.001). In 251 patients (61%) the first surgery was performed in childhood (mean age 12.9±6.7 years). Table 2 shows the surgical details, including concomitant surgery and postoperative complications. In those patients who did not undergo concomitant aortic valve repair or replacement during surgery for DSS, the severity of AR was unchanged postoperatively (p=0.60). Seventeen patients (4.4%) suffered from a complete heart block postoperatively, requiring pacemaker implantation. Patients who underwent an additional myectomy more frequently developed a complete heart block than patients who underwent isolated enucleation (respectively 8.1% versus 1.7%; p=0.005).

Mortality and morbidity

One death occurred within 30 days after surgery for DSS due to heart failure. Ten patients (mean age 49.1 ± 16.5 years) died during follow-up (0.18% per patient-year) (Figure 1A). Five deaths were for cardiac reasons (4 heart failure and 1 septic shock after endocarditis). In 2 patients the cause of death was metastasized cancer. Three patients died suddenly during follow-up (unknown cause of death, no autopsy; age 19, 30 and 48 years old, all had an LVOT gradient <30 mmHg at last follow-up visit, 2 had an associated ventricular septal defect, no left ventricular hypertrophy). The cumulative survival of DSS patients after surgery was 97% at 20 years.

During follow-up 34 patients (age 29.9 ± 15.1 years) were hospitalized for various reasons (0.61% per patient-year): heart failure (n=13), endocarditis (n=12), ventricular fibrillation followed by successful resuscitation (n=2), cardioversion for atrial fibrillation (n=5), stroke (n=1) and pericarditis (n=1).

Table 2. *Surgical details for 412 DSS operations.*

	First operation (n=313)	Second operation (n=80)	Third operation (n=19)
Age at time of surgery, years	17.1 ± 14.9	22.9 ± 13.9	32.1 ± 10.4
Pre-operative peak LVOT gradient, mmHg	74.7 ± 28.9*	79.3 ± 22.2	76.6 ± 36.3
Postoperative peak LVOT gradient, mmHg	14.6 ± 13.8*	17.6 ± 16.2	10.9 ± 9.2
Pre-operative aortic regurgitation			
None	84 (26.8)	15 (18.8)	1 (5.3)
Mild	173 (55.3)	26 (32.5)	5 (26.3)
Moderate	44 (14.1)	15 (18.8)	4 (21.0)
Severe	12 (3.8)	24 (30.0)	9 (47.4)
Postoperative aortic regurgitation			
None	87 (27.8)	18 (22.5)	5 (26.3)
Mild	208 (66.4)	59 (73.8)	13 (68.4)
Moderate	18 (5.8)	3 (3.8)	1 (5.3)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Type of surgery			
Isolated enucleation	189 (60.4)	31 (38.8)	8 (42.1)
Additional myectomy	122 (39)	43 (53.8)	9 (47.4)
Unknown	2 (0.6)	6 (7.5)	2 (10.5)
Concomitant surgery †			
Aortic valve bioprosthesis	8 (2.5)	7 (8.8)	2 (10.5)
Aortic valve mechanical prosthesis	10 (3.2)	12 (15.1)	8 (42.1)
Aortic valve repair	18 (5.8)	7 (8.8)	2 (10.5)
Ross procedure	2 (0.6)	12 (15.0)	2 (10.5)
Coarctation repair	4 (1.3)	0 (0.0)	0 (0.0)
Supravalvular aortic repair	3 (1.0)	1 (1.3)	1 (5.3)
Persistent ductus arteriosus ligation	9 (2.9)	0 (0.0)	0 (0.0)
Mitral valve replacement or repair	8 (2.5)	3 (3.8)	0 (0.0)
Ventricular septal defect closure	46 (14.7)	1 (1.3)	0 (0.0)
Atrial septal defect closure	6 (1.9)	0 (0.0)	0 (0.0)
Postoperative complications †			
New left bundle branch block	36 (3.2)	8 (10)	0 (0.0)
New right bundle branch block	33 (3.2)	3 (3.8)	1 (5.3)
New complete heart block requiring pacemaker	12 (3.8)	3 (3.8)	2 (10.5)
Atrial fibrillation	6 (1.9)	2 (2.5)	2 (10.5)
Heart failure	3 (1.0)	1 (1.3)	0 (0.0)
Mortality	1 (0.3)	0 (0.0)	0 (0.0)
Neurological complication (stroke or neuropathy)	1 (0.3)	2 (2.5)	0 (0.0)

Values are n(%) or mean±SD.
**Only available for 298 patients.*
† Overlapping categories.
DSS = discrete subaortic stenosis; LVOT = left ventricular outflow tract obstruction.

Re-operations

During follow-up, 80 patients (25.6%) underwent at least one re-operation for recurrent DSS, of whom 19 patients required a third operation (re-operation rate 1.76% per patient-year) (Table 2). The mean time interval between initial operation and re-operation was 12.0 ± 7.6 years. Median intervention-free survival was 17 years (Figure 1A). Independent predictors for impaired intervention-free survival were female gender (HR=1.531 (95%CI 1.018–2.302); Figure 1B), peak instantaneous LVOT gradient progression over time (HR=1.454 (95% CI 1.308–1.616)), pre-operative peak instantaneous LVOT gradient ≥80 mmHg (HR=1.016 (95% CI 1.004–1.028)) and difference between pre- and postoperative peak instantaneous LVOT gradient (HR=1.021 (95% CI 1.007–1.035)) (Online Supplement Table 1).

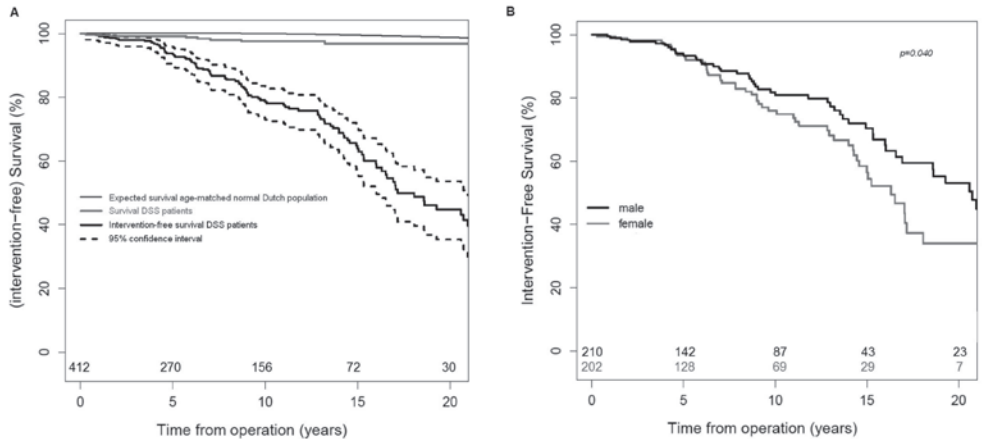

Figure 1. *Kaplan-Meier plots.*

(A) Survival and intervention-free survival for DSS patients and expected survival for the normal age-matched Dutch population. (B) By gender. DSS = discrete subaortic stenosis

Recurrence of LVOT gradient postoperatively

Postoperative peak instantaneous LVOT gradient was 15.1 ± 14.1 mmHg, which linearly increased over time at a rate of 1.31 ± 0.16 mmHg per year (p=0.001). Independent risk factors for faster postoperative peak instantaneous LVOT gradient progression were increased age at time of DSS diagnosis (p=0.048) and female gender (p=0.059, trend) (Figure 2). A higher pre-operative LVOT gradient was associated with an overall higher residual postoperative peak instantaneous LVOT gradient (p<0.001), but did not significantly influence the postoperative peak instantaneous LVOT gradient progression rate (p=0.74). Peak instantaneous LVOT gradient progression rate was not influenced by type of surgery (enucleation +/- myectomy) (p=0.85), age at time of surgery (p=0.21), presence of associated CHD (p=0.12) or smoking (p=0.24) (Online Supplement Table 2).

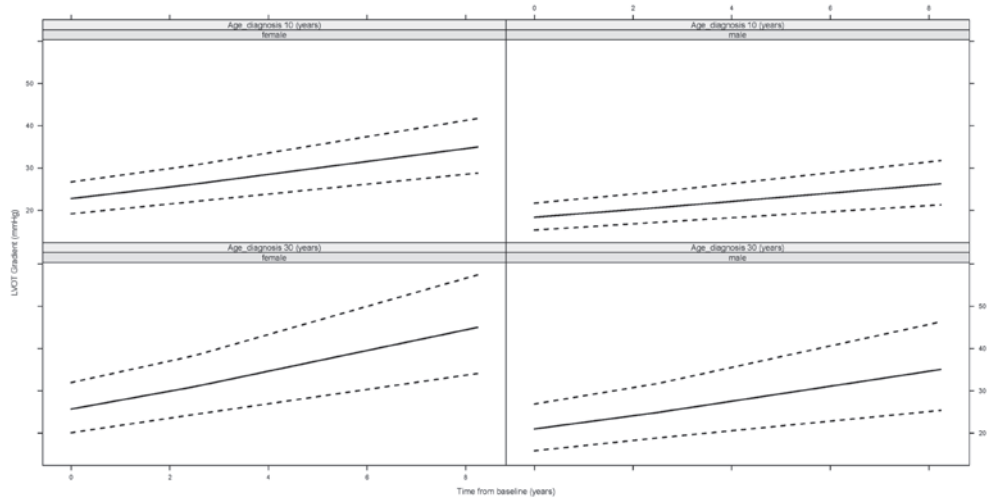

Figure 2. *Discrete subaortic stenosis over time.*

Evolution of discrete subaortic stenosis over time postoperatively by age at time of diagnosis (p=0.048) and gender (p=0.059).

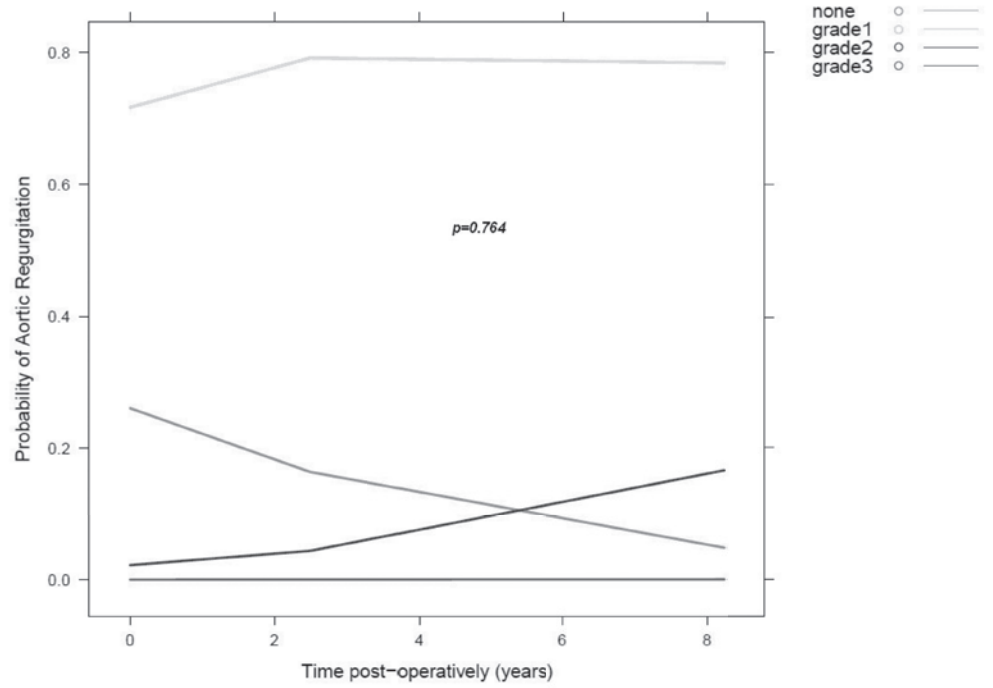

Figure 3. *Aortic regurgitation over time.*

Probability of postoperative aortic regurgitation over time.

Progression of AR postoperatively

Immediately postoperatively mild AR was present in 68% of patients and moderate AR in 5%, no patients exhibited severe AR. Over time, AR severity did not significantly progress in the total study population (p=0.76; Figure 3). Approximately 10% of patients, however, progressed from having no AR to mild AR, and another 10% of patients developed moderate AR during the first 8 years after surgery (Figure 3). None of the patients progressed to severe AR. A pre-operative peak instantaneous LVOT gradient ≥80 mmHg was an independent risk factor for development of moderate AR postoperatively (p=0.008; Figure 4). We could not identify any other factor that was significantly associated with postoperative development of mild AR or progressive AR (Online Supplement Table 3).

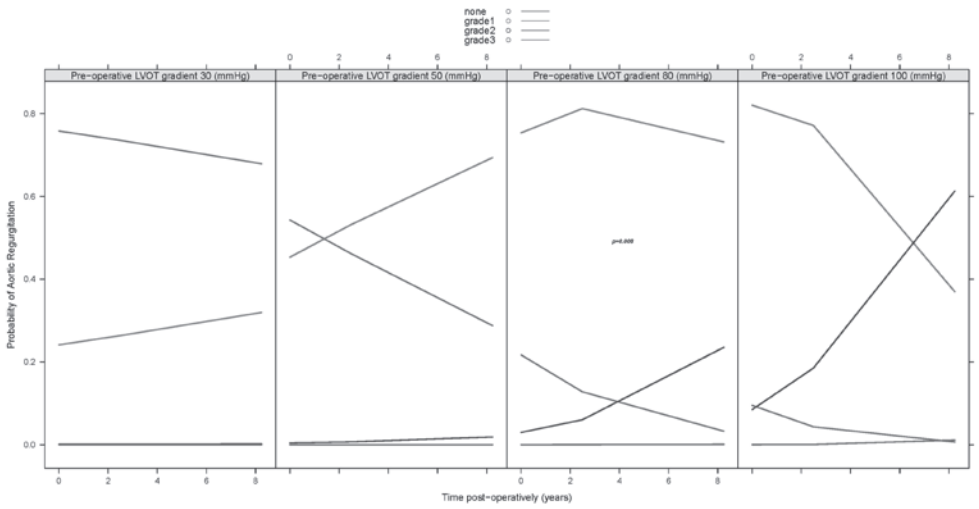

Figure 4. *Pre-operative LVOT gradient versus postoperative aortic regurgitation.*

Association between various levels of pre-operative peak LVOT gradient and probability of postoperative aortic regurgitation progression over time. LVOT = left ventricular outflow tract

Discussion

In this multicenter study, we have analyzed data on a large cohort of adult patients who underwent surgical DSS resection with 13 years postoperative follow-up (range 1 to 31 years) to determine predictors for DSS recurrence, AR worsening and re-operation. The results of the present study may be the basis for modification of the current strategies for management of DSS patients.

DSS recurrence and re-operations

In the total study population, postoperatively the peak instantaneous LVOT gradient increased slowly, though significantly, over time with 1.3 mmHg per year. This finding confirms a smaller study that previously reported a slight increase in postoperative gradient at late follow-up.[27]

Surprisingly, increased age at time of diagnosis (>30 years old) was a risk factor for faster postoperative LVOT gradient progression. This phenomenon might be explained by the fact that when DSS was discovered late in adulthood, patients were more likely to present with symptoms and thus might be in an advanced stage of the disease. Another hypothesis is that aging itself is related to faster postoperative progression.

In this study we used re-operation as an objective clinically relevant outcome, rather than recurrence only because of lack of a universal definition for recurrence. We do acknowledge that the indication for reoperation is also not concrete and universal. Our re-operation rate for recurrent DSS (1.8% per patient-year) was comparable to two other adult surgical series, which reported re-operation rates of 0.5% and 2.6% per patient-year.[15,27] As reported in several studies in children with DSS, a higher peak instantaneous gradient across the LVOT at the final pre-operative echocardiogram was an independent predictor for re-operation in our adult patient population.[10,12,16,17,24] Testing various cut-off points, we found that a peak instantaneous LVOT gradient ≥80 mmHg is most predictive for the need of re-operation. In addition, incomplete removal of the LVOT obstruction, reflected in a smaller difference between pre- and postoperative gradient, was found to be a risk factor for re-operation. This has previously been demonstrated in several previous studies.[12,15,20,22,26,37] Furthermore, as expected, LVOT gradient progression postoperatively is a strong predictor for re-operation. In addition to the echocardiographic parameters to monitor and predict LVOT gradient progression, perhaps biomarkers might be useful to identify those with more rapidly progressing disease. Further research in this area is warranted.

Surprisingly, women carry a 1.5 times elevated risk for re-operation compared to men. In addition, female patients tended to have a more rapid postoperative LVOT gradient progression rate than male patients. These gender differences in re-operation or recurrence risk have not been reported previously. This phenomenon might be explained by the fact that women are likely to have a smaller LVOT. In our cohort the LVOT diameter tended to be smaller in women compared to men, although not statistically significant. Perhaps pregnancy might have been a confounding factor, but unfortunately we did not collect information about pregnancies during follow-up, and there is a lack of studies investigating the consequences of pregnancy in DSS patients. Furthermore, transcriptional regulation of genes related to myocardial hypertrophy and fibrosis might be gender dependent, as has been shown after aortic valve replacement for valvular aortic stenosis.[38] Pathophysiological studies are required to explore the underlying mechanisms for these gender differences.

Isolated enucleation versus additional myectomy

Several hypotheses regarding DSS recurrence have been proposed. Recurrence may result from regeneration of tissue from the same region or from scar formation in the subvalvular area during healing.[19,39] Furthermore, turbulence due to incomplete removal of the LVOT obstruction has been postulated to promote fibrosis and subsequent restenosis.[12] Although some previous studies have suggested that additional myectomy during the first operation reduces the incidence of recurrence, other authors have questioned this finding.[8,16-27]

Our results do not support the benefit of additional myectomy, neither for the risk of re-operation, nor for the LVOT gradient progression rate postoperatively. A trade-off when performing aggressive surgical resection to potentially lower the recurrence rate is the risk of a complete AV-block, which was significantly higher in the patients who underwent additional myectomy compared to those who underwent isolated enucleation (8% versus 2%). In previous studies the risk of a postoperative complete AV-block is typically 1% to 5%, however this might be up to 14% when a more aggressive surgical approach is performed.[6,7,12,17,20] Of course the results of a myectomy and risk of heart block are operator dependent, but this study included patients from four different centers over a time span of 30 years making it impossible to study this factor adequately. Therefore, from our study we conclude that an additional myectomy may be justified when a substantial degree of septal hypertrophy is detected, but should be discouraged in the majority of patients.

Aortic regurgitation after DSS surgery

While most DSS patients exhibited mild (non hemodynamically relevant) AR both pre- and postoperatively, our study shows that in the majority of patients AR is not progressive over time. Approximately 10% of patients who did not have AR before, however, developed mild AR relatively shortly after surgery. Furthermore, another 10% of patients progressed from mild to moderate AR, but progression to severe AR was very rare. We identified a pre-operative peak instantaneous LVOT gradient ≥80 mmHg as a risk factor for progressive AR after surgery. Previous studies in children with DSS have also demonstrated the association between a high pre-operative LVOT gradient and progressive AR postoperatively.[40,41] In order to prevent progressive AR postoperatively, it may be wise to perform re-operation before the peak LVOT gradient reaches 80 mmHg. In conclusion, we agree with the statement made by Stassano et al. that resection of the subaortic membrane cannot improve AR, but we disagree with their suggestion that resection can entirely "stabilize" the grade of regurgitation.[27]

Clinical implications

Postoperative long-term survival after surgical treatment of DSS is excellent and comparable to the normal population. The rate of reoperation is considerable (approximately 2% per year), and given the excellent survival of these young adult patients, the majority of patients will require a reoperation for recurrent DSS at some point in their life. Post-operatively the peak instantaneous LVOT gradient progresses slowly, though steadily, over time in adults. Therefore lifelong regular follow-up, including echocardiography, is required after surgery, but since the LVOT progression is generally slow this can probably be limited to 2-4 year intervals in the majority of patients. Women and patients >30 years old at time of diagnosis are at risk for faster LVOT gradient progression after surgery, and should thus be monitored more frequently. Of course patients with decreased LV function or severe/progressive AR should also be followed more frequently. Additional myectomy did not reduce DSS recurrence or re-operation risk, and significantly increased the risk of a complete heart block.

Therefore myectomy should not be encouraged in the majority of patients, and only be performed in case of marked LV hypertrophy. Postoperative AR is common, however generally mild and non-progressive over time in the majority of patients. Patients with a pre-operative Doppler derived peak instantaneous LVOT gradient ≥80 mmHg, however, are at increased risk for development of moderate AR, but progression to severe AR is rare.

The current ESC and ACC/AHA guidelines for adults with CHD do not provide specific recommendations for re-interventions in DSS patients.[42,43] The Canadian guidelines state that a peak instantaneous LVOT gradient >50 mmHg is an indication for re-operation when patients have symptoms.[44] The timing of re-operation is a highly complex issue that should take various factors into account: the peak LVOT gradient, progression rate of the LVOT gradient, severity and progression of AR, LV volume and function, the presence of (exercised induced) symptoms, and the risk of sudden death. Unfortunately, the optimal timing of re-operation, combining all these factors, in adult patients with DSS cannot yet be derived from the present study.

Study limitations

Several limitations of this study merit attention. This retrospective study included patients monitored in adult congenital clinics, and therefore referral bias may exist. One of the major study limitations was the fact that indications for (re-)operation were not standardized, because of the multicenter approach and broad time period. By using prospective databases to identify eligible patients and therefore also including deceased patients, we aimed to limit survival bias. Unfortunately, some echocardiographic parameters could not be retrieved for all patients, but this was dealt with by using the multiple imputation approach for missing values. The fact that echocardiography was not performed precisely every year, was accounted for by the use of mixed-effects models that take different lengths of follow-up into account. Furthermore, by using the joint modeling approach we allowed for the dependency and association between the longitudinal echocardiographic data and survival data. Ideally, our findings need to be validated by a large prospective cohort study.

Conclusions

Although survival is excellent after surgery for DSS, the majority of patients will require a reoperation for recurrent DSS throughout life. Postoperatively the LVOT gradient progresses slowly and mild AR is common, but non-progressive over time in the majority of patients. Myectomy should not be performed routinely, since it does not reduce the risk of recurrence or re-operation and increases the risk of a complete heart block.

Clinical perspective

Discrete subaortic stenosis (DSS) is a narrowing of the left ventricular outflow tract (LVOT) just beneath the aortic valve. In childhood, DSS is known for its unpredictable and sometimes rapid hemodynamic progression. Furthermore, aortic regurgitation is present in 30-80% of patients. Since re-operation rates have been reported to be high (8-34%), there is an ongoing debate about the timing of surgical intervention and type of surgery. This is the first large study that evaluates the surgical outcome in adult patients. In contrast to children, in adults the LVOT gradients progresses slowly. Mild aortic regurgitation is common, but nonprogressive over time in the majority of patients. Patients with a pre-operative peak LVOT gradient ≥80 mmHg, however, are at risk for progression to moderate aortic regurgitation. Survival after surgery for DSS is excellent, with survival rates comparable to the normal population. The re-operation rate in young adult patients, however, is high (2% per year). Given the excellent survival in this young patient population, the majority of patients face a reoperation for recurrent DSS throughout life. Additional myectomy does not reduce the risk for re-operation, but significantly increases the risk of a complete heart block requiring pacemaker implantation. Therefore myectomy should not be performed routinely.

Acknowledgements

We would like to thank the medical teams, technicians and sonographers at the participating centers.

@ **Supplementary tables can be found online at:**
http://circ.ahajournals.org/

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PART

IV

Congenital valvular aortic stenosis

5

Congenital valvular aortic stenosis in young adults: Predictors for rate of progression of stenosis and aortic dilatation

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Int J Cardiol. E-pub 16 Nov 2012.

Abstract

Background

Congenital aortic stenosis (AS) is the most common obstructive left sided cardiac lesion in young adults, however little is known about the natural history in adults. Therefore, we aimed to evaluate the progression rate of AS and aortic dilatation in a large multicenter retrospective cohort of asymptomatic young adults with congenital valvular AS.

Methods

Data were obtained from chart abstraction. Linear mixed-effects models were used to evaluate the progression of AS and aortic dilatation over time. A joint model combining longitudinal echocardiographic and survival data was used for survival analysis.

Results

A total of 414 patients (age 29±10 years, 68% male) were included. Median follow-up duration was 4.1 (2.5-5.1) years (1587 patient-years). Peak aortic velocity was 3.4±0.7 m/s at baseline and did not change over time in the total patient population (-0.01±0.03 m/s/year). Increased left ventricular mass was significantly associated with faster AS progression ($p<0.001$). Aortic dilatation was present in 34% at baseline and 48% at follow-up ($p<0.001$). The aortic diameter linearly increased over time with a rate of 0.7±0.2 mm/year. Rate of aortic dissection was 0.06% per patient-year. Seventy patients required an aortic valve intervention (4.4% per patient-year), with AS progression rate as most powerful predictor (hazard ratio 5.11 (95%CI 3.47-7.53)).

Conclusions

In the majority of patients with mild-to-moderate congenital AS, AS severity does not progress over time. However patients with left ventricular hypertrophy are at risk for faster progression and should be monitored carefully. Although aortic dissections rarely occur, aortic dilatation is common and steadily progresses over time, warranting serial aortic imaging.

Introduction

Congenital valvular aortic stenosis (AS) represents 4% of all congenital heart defects (CHD) [1]. It is the most frequent indication for aortic valve replacement (AVR) in adults under the age of 60 years, with subsequently a restraint life expectancy [2]. Clinical outcome of congenital AS considerably varies, and includes a wide spectrum ranging from a lifelong asymptomatic course to progressive disease in childhood requiring repeated interventions. So far, research on evolution of AS and predictors of progression mainly focused on calcified aortic stenosis, or congenital AS in childhood [3-5]. Only limited serial echocardiographic data are available describing the natural course of AS and identifying predictors of progression and outcome of AS in young adults [6,7].

The underlying cause for congenital AS is often a bicuspid aortic valve (BAV), which is strongly associated with aortic dilatation [8,9]. Several studies report about the progression rate of aortic dilatation and associated predictors in mixed-groups of BAV patients (normally functioning, regurgitant and stenosed valves), but none of these studies specifically focus on patients presenting with AS [10-14]. Continuing controversy still exists as to whether BAV-associated proximal ascending aortic dilatation is caused by intrinsic aortic wall pathology or hemodynamic factors, or perhaps a combination of both [15,16].

The aim of the present study was to determine the stenosis and aortic dilatation progression rate and identify risk factors for fast disease progression in a large cohort of asymptomatic young adult patients with congenital valvular AS.

Methods

All adult patients with congenital valvular AS, who attended the outpatient clinic for adult CHD of a participating centre, between January 2005 and October 2011, were identified. Eligible patients were selected from prospective databases: the CONCOR database (the Dutch registry for adult patients with CHD) [17], and the Leuven and Toronto database for adults with CHD. Inclusion criteria were: age 18-55 years old and a baseline peak aortic velocity >2.5 m/s. Patients had to have serial echocardiographic examinations at least 1 year apart. Exclusion criteria included subvalvular or supravalvular AS, previous AVR, history of acute rheumatic fever, or mitral valve condition (mitral insufficiency >2+ or mitral valve area <1.5 cm^2). Demographic, clinical and surgical data were obtained from chart abstraction. All available transthoracic echocardiograms, electrocardiograms and exercise tests were collected. The collected information was registered in a dedicated research database. Indications for surgery included severe AS with any valve-related symptoms, symptoms during exercise testing and left ventricular (LV) ejection faction <50%, or an ascending aortic diameter >50 mm.

The study protocol was approved by the Medical Ethical Committee of the participating centres, and conducted according to the Helsinki Declaration. Informed consent was waived. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [18].

Echocardiographic data

AS severity was objectified by measurements of peak aortic velocity, mean gradient and continuity equation aortic valve area [19]. The degree of aortic regurgitation was graded by experienced sonographers and cardiologists as mild, moderate, or severe [20]. LV mass was calculated using the modified Devereux formula [21]. Left ventricular hypertrophy (LVH) was defined by a body surface area (BSA)-indexed threshold of >115 g/m^2 for men and >95 g/m^2 for women [22]. BSA was calculated with the Mosteller formula [23]. We defined the aortic valve as calcified if there was calcified thickening and increased echogenicity of the cusps in the parasternal long or short axis views. The ascending aorta diameter was measured at end-diastole from leading edge to leading edge at four levels: annulus, sinus of Valsalva, sinotubular junction (STJ) and proximal ascending aorta. If the aortic diameter was more than two standard deviations (SD) above normal values by gender, the aorta was considered dilated [24].

Statistical analysis

The Statistical Package for Social Sciences, version 19.0 (SPSS, Inc., Chicago, Illinois) was used for descriptive data-analysis. Normally distributed continuous variables were summarized using the mean ± SD. Non-normally distributed continuous variables were summarized using the median and interquantile range (IQR). Categorical variables were summarized using the frequency and percentage. The McNemar test was used to compare the frequency of aortic dilatation at baseline and follow-up. p-Values *<0.05* were considered statistically significant.

For advanced statistical analyses, R (version 2.14.1, available at: *www.r-project.org*) was used. Linear mixed-effects models were used to assess changes in peak aortic velocity and proximal ascending aortic diameter over time while accounting for the correlation between repeated follow-up measurements in each patient. Annual progression rates were calculated while taking into account all echocardiograms for each patient. The following covariates were included in the models: baseline peak aortic velocity, age, gender, prior aortic valve intervention (balloon valvuloplasty or open valvulotomy), smoking, aortic valve calcification, LV mass, total LV load (peak aortic valve gradient + systolic blood pressure), aortic regurgitation and baseline aortic diameter. Residual plots were used to validate the models' assumption. Wald tests were used to assess which parameters were most associated with the progression over time.

Probabilities of intervention-free survival from baseline were obtained by the Kaplan-Meier method. Survival of the congenital AS patients was compared to the expected survival of the age-matched general Dutch population [25]. An event was defined as AVR or death. The linear mixed-effects model predicting peak aortic velocity progression was inserted into a Cox regression survival model as a time-varying covariate. The purpose of this joint modelling approach is to account for any biological variation in aortic valve function and repeated measurements within patients. Benefits of joint modelling include reduction of bias and improvement of efficiency, and resulting in more precise estimates [26].

Results

A total of 1318 patients were assessed for eligibility to participate in this study. Nine hundred and four patients were excluded, mainly due to previous AVR (n=484), peak aortic velocity <2.5 m/s (n=374), or lack of serial echocardiographic examinations (n=31). A total of 414 patients were included in this study.

Baseline characteristics are shown in Table 1. All patients were asymptomatic at baseline and 98% was in sinus rhythm. Associated CHD were encountered in 45 patients (11%): aortic coarctation (n=37, repaired in 34 patients), ventricular septal defect (n=7), patent ductus arteriosus (n=6), and atrial septal defect (n=2) (not mutually exclusive). Aortic valve calcification was present in 91 patients (22%). Five patients (1.2%) were known with the diagnosis diabetes mellitus.

Median follow-up duration was 4.1 (2.5-5.1) years, yielding a total of 1587 patient-years. On average 3.3 ± 1.8 echocardiographic studies were available for each patient.

Progression rate of aortic stenosis severity and its predictors

Peak aortic velocity was 3.4 ± 0.7 m/s at baseline and did not progress significantly over time in the total study population (-0.01 ± 0.03 m/s per year; p=0.774). However, fast progression (≥0.2 m/s/year) was noted in 56 patients (13.5%). In 13 patients (3.1%) the progression was even ≥0.5 m/s per year. An increased LV mass was the only independent factor associated with faster progression of peak aortic velocity (p<0.001). The presence of an aortic coarctation was not significantly related to an increased LV mass (200.3±89.5 g versus 204.6±65.4 g; p=0.720).

Progression rate was not influenced by prior intervention (p=0.892), gender (p=0.430), age (p=0.717), smoking history (p=0.082), aortic valve calcification (p=0.471), baseline peak aortic velocity (p=0.521), total LV load (p=0.860) or aortic regurgitation (p=0.413) (Online Supplement Table 1). The effects of LV mass and age on peak aortic velocity progression over time are demonstrated in Figure 1.

Progression rate of aortic dilatation and its predictors

Aortic dilatation mainly occurred at the level of the proximal ascending aorta: 142 patients (34%) showed dilatation at baseline, rising to 197 patients (48%) at follow-up (p<0.001). Increased age (p<0.001), prior intervention (p=0.019), presence of moderate-to-severe regurgitation (p=0.004) and increased LV mass (p<0.001) were associated with an overall larger proximal ascending aorta (Online Supplement Table 2).

The proximal ascending aortic diameter significantly increased over time with a rate of 0.66 ± 0.23 mm per year (p=0.005). Fast progression (≥3 mm/year) was noted in 12 patients (2.9%), while 6 patients (1.4%) showed very fast progression (≥5 mm/year). The aortic dilatation progression rate tended to be faster in men compared to women (p=0.089; Figure 2). Age (p=0.316), prior intervention (p=0.659), smoking (p=0.275), presence of moderate-to-severe regurgitation (p=0.212), baseline aortic dilatation >40 mm (p=0.181) and LV mass (p=0.728) did not influence aortic dilatation progression rate (Online Supplement Table 2). Furthermore, aortic growth was not influenced by baseline peak aortic velocity (p=0.201; Figure 3).

Table 1. *Baseline characteristics.*

	Total group (n=414)	Men (n=281)	Women (n=133)
Age at baseline, years	29.3 ± 10.0	29.5 ± 10.2	28.9 ± 9.8
Body surface area, m^2	1.9 ± 0.2	2.0 ± 0.2	1.7 ± 0.2
Body mass index, kg/m^2	25.0 ± 4.4	25.0 ± 4.2	24.8 ± 4.9
Blood pressure, mmHg			
Systolic	124.3 ± 15.8	126.8 ± 15.4	119.1 ± 15.4
Diastolic	74.8 ± 10.3	75.7 ± 10.3	72.8 ± 10.0
Prior intervention	124 (30.0)	91 (32.4)	33 (24.8)
Balloon aortic valvuloplasty [a]	87 (21.0)	61 (21.7)	26 (19.5)
Open aortic valvulotomy [a]	55 (13.3)	43 (15.3)	12 (9.0)
Aortic stenosis severity			
Peak aortic velocity, m/s	3.4 ± 0.7	3.4 ± 0.7	3.4 ± 0.7
Mean aortic gradient	25.5 ± 10.8	26.0 ± 11.2	26.1 ± 11.5
Aortic valve area, cm^2	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.4
Bicuspid aortic valve	391 (94.4)	269 (95.7)	122 (91.7)
Aortic diameters, mm (indexed for BSA) → % dilated			
Annulus	22.9 ± 3.5 (12.2 ± 2.0) → 8 (1.9)	23.8 ± 3.5 (12.1 ± 2.1) → 5 (1.8)	21.1 ± 2.8 (12.2 ± 1.9) → 3 (2.3)
Sinus of Valsalva	30.7 ± 5.2 (16.2 ± 2.8) → 20 (4.8)	31.5 ± 5.1 (15.9 ± 2.7) → 14 (5.0)	29.1 ± 5.0 (16.8 ± 3.1) → 6 (4.5)
Sinotubular junction	27.6 ± 4.9 (14.6 ± 2.7) → 28 (6.7)	28.1 ± 4.8 (14.3 ± 2.5) → 19 (6.8)	26.7 ± 5.1 (15.4 ± 3.0) → 9 (6.8)
Proximal ascending aorta	34.7 ± 6.9 (18.4 ± 3.8) → 142 (34.3)	35.3 ± 6.9 (17.9 ± 3.5) → 95 (33.8)	33.5 ± 6.7 (19.4 ± 4.3) → 47 (35.3)
Aortic regurgitation			
None/Mild	235 (56.8)	152 (54.1)	83 (62.4)
Moderate	133 (32.1)	94 (33.5)	39 (29.3)
Severe	46 (11.1)	35 (12.5)	11 (8.3)
Left atrial diameter, mm	33.9 ± 6.7	34.9 ± 5.9	31.7 ± 7.6
LV hypertrophy	173 (41.8)	116 (41.3)	57 (42.9)
Interventricular septal thickness, mm	10.8 ± 2.3	11.1 ± 2.3	10.2 ± 2.4
Left ventricular posterior wall thickness, mm	10.3 ± 2.1	10.7 ± 2.0	9.5 ± 2.0
Left ventricular mass, g (indexed for BSA)	201.4 ± 64.0 (106.9 ± 32.2)	222.5 ± 66.1 (112 ± 32.2)	165.2 ± 53.3 (94.9 ± 28.6)

Table 1. *Baseline characteristics. (Continued)*

	Total group (n=414)	Men (n=281)	Women (n=133)
LV end-diastolic diameter, mm (indexed for BSA)	50.5 ± 6.7 (26.7 ± 3.8)	52.0 ± 6.4 (26.5 ± 3.8)	47.1 ± 6.1 (27.2 ± 3.7)
LV end-systolic diameter, mm (indexed for BSA)	30.8 ± 6.0 (16.3 ± 3.2)	32.0 ± 6.0 (16.3 ± 3.2)	28.3 ± 5.2 (16.4 ± 3.0)
LV fractional shortening, %	39.0 ± 7.6	38.5 ± 7.7	40.0 ± 7.5
E/A ratio	1.7 ± 0.6	1.7 ± 0.6	1.65 ± 0.7
Maximum exercise capacity, % from norm	90.4 ± 18.4	91.2 ± 17.9	88.7 ± 19.6
Heart frequency, beats per minute	70.1 ± 12.6	68.3 ± 12.2	74.0 ± 12.6
QRS duration, ms	99.5 ± 14.8	102.6 ± 14.5	93.1 ± 13.4
PR time, ms	153.4 ± 25.9	156.9 ± 26.7	146 ± 22.3
Smoking			
Never	298 (72.0)	118 (66.9)	110 (82.7)
Former	25 (6.0)	18 (6.4)	7 (5.3)
Current	91 (22.0)	75 (26.7)	16 (12.0)

Values are expressed as n(%), or mean ± SD. BSA = body surface area; LV = left ventricular.

[a] Eighteen patients had an open aortic valvulotomy and balloon aortic valvuloplasty.

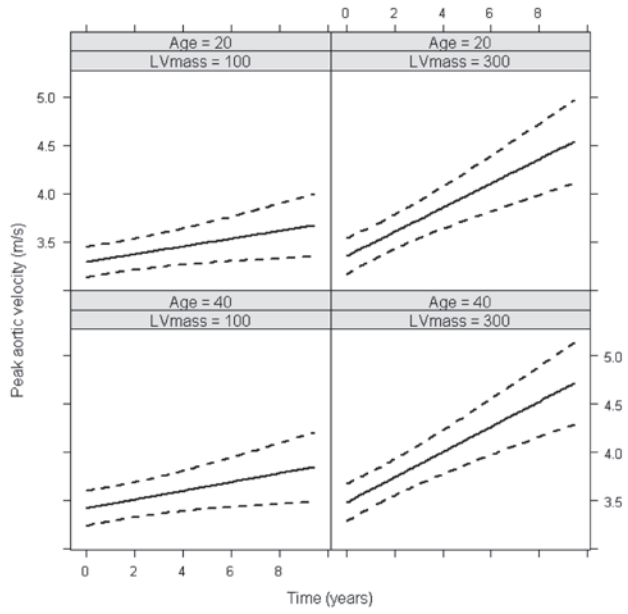


Figure 1. *Progression of congenital aortic stenosis over time by left ventricular mass (p<0.001) and patient age (p=0.717).*

The dashed lines denote 95% confidence intervals. LV = left ventricular.

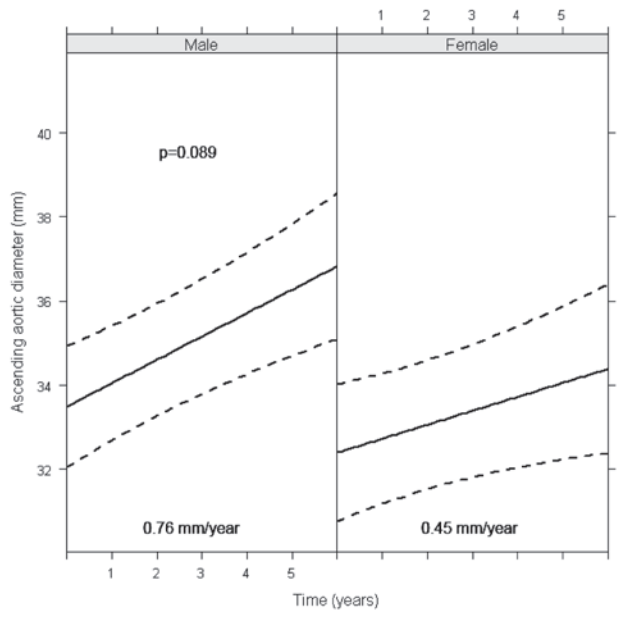


Figure 2. *Proximal ascending aortic dilatation progression rate over time by gender.*

The dashed lines denote 95% confidence intervals.

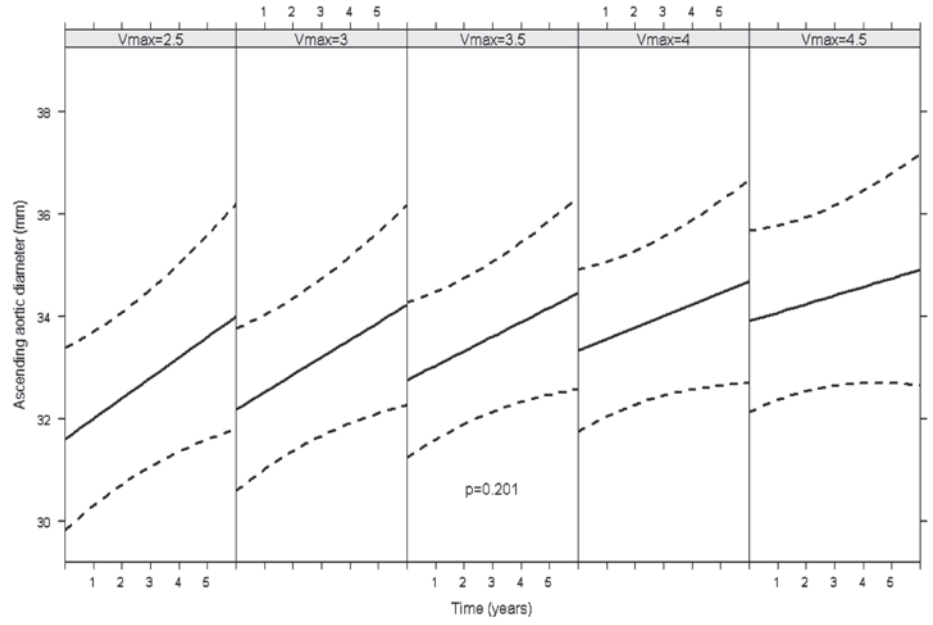


Figure 3. *Proximal ascending aortic dilatation progression rate over time by AS severity.*

The dashed lines denote 95% confidence intervals. Vmax = peak aortic velocity in m/s.

Clinical outcome

During the follow-up period 5 deaths occurred at a mean age of 48 ± 10 years (0.32% per patient-year). Clinical cause of death was: 1 leukemia, 3 sudden deaths and 1 arrhythmia (no detailed information available). No autopsies were performed. A 36-year-old patient presented in the emergency room with a Type A aortic dissection (last measured proximal ascending aortic diameter 51 mm), but was operated on successfully (rate 0.06% per patient-year of follow-up). In addition, 4 patients experienced an episode of endocarditis at a mean age of 27 ± 6 years (0.25% per patient-year). Three patients were hospitalized for left-sided heart failure due to severe AS at a mean age of 32 ± 8 years (0.19% per patient-year).

Seventy patients underwent AVR at a mean age of 36 ± 10 years (4.4% per patient-year). Peak aortic velocity at the final echocardiographic study before intervention was 4.4 ± 0.7 m/s. Performed operations included: 25 mechanical valves (35%), 25 Bentall procedures (35%), 10 tissue valves (14%), 5 Ross procedures (7%), 4 balloon valvuloplasties (6%) and 1 surgical valvulotomy (1%). In addition, 2 patients underwent aortic valve-sparing operations.

Overall estimated intervention-free survival was 87±2% at 3 years and 78±4% at 5 years (Figure 4A). Median intervention-free survival for patients with an aortic peak velocity >4 m/s was 5 years (Figure 4B). AS progression rate was the most powerful predictor for AVR (Table 2). Increased age (>30 years) and prior aortic valve intervention were also found to be significant predictors of outcome (Table 2; Figure 4C and 4D). In addition, an increased LV mass tended to influence intervention-free survival (Table 2).

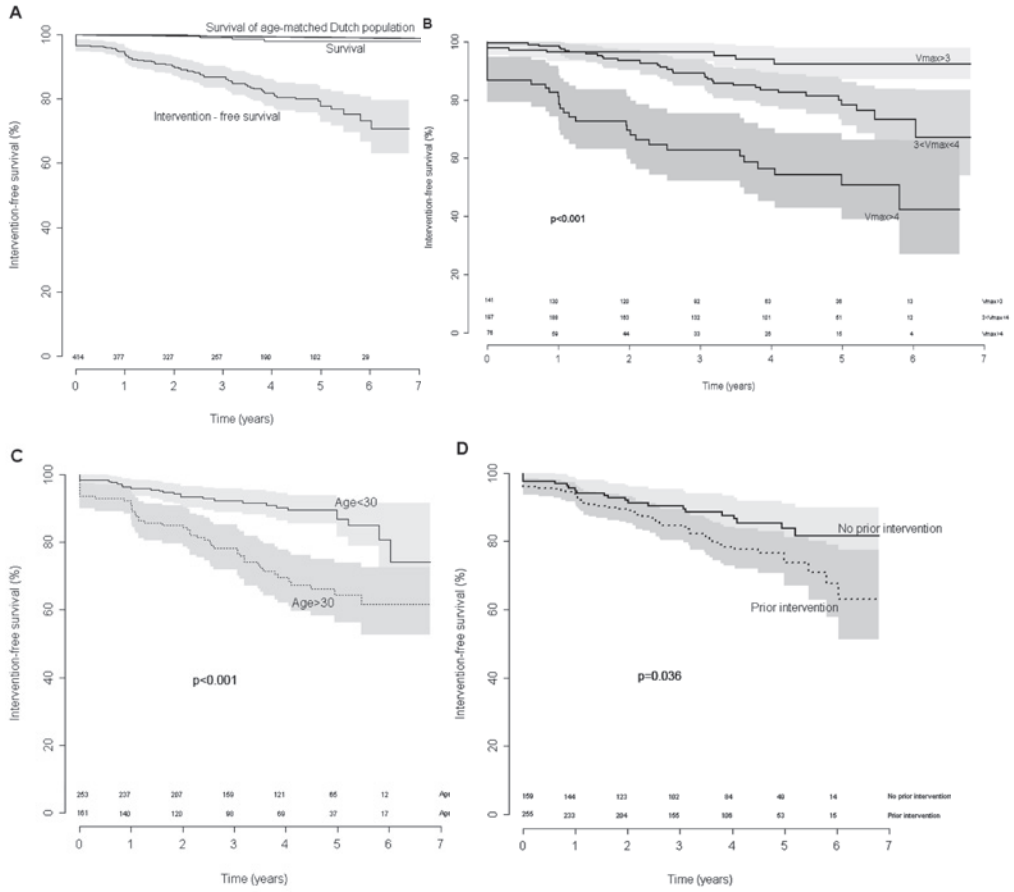


Figure 4. *Kaplan-Meier curves.*

(A) Cumulative Kaplan-Meier survival and intervention-free survival for the congenital AS patients and expected survival of the age-matched Dutch population.
(B) Cumulative Kaplan-Meier intervention-free survival for congenital AS patients according to baseline peak aortic velocity (p<0.001).
(C) Cumulative Kaplan-Meier intervention-free survival for congenital AS patients aged according to age at baseline (p<0.001).
(D) Cumulative Kaplan-Meier intervention-free survival for congenital AS patients with and without prior aortic valve intervention (p=0.036).
The grey-toned areas denote the 95% confidence intervals. The numbers above the x-axis reflect the numbers at risk. AS = aortic stenosis; Vmax = peak aortic velocity in m/s.

Table 2. *Joint model (combining longitudinal and survival data) for intervention-free survival.*

	Hazard ratio	p-value
Age (>30 years)	1.04 (1.02-1.07)	<0.001 *
Gender	1.51 (0.86-2.63)	0.150
Prior aortic valve intervention	1.77 (1.04-3.02)	0.036 *
Left ventricular mass	1.01 (0.99-1.02)	0.084
Former smoking	1.17 (0.48-2.85)	0.726
Current smoking	0.91 (0.50-1.65)	0.751
Aortic stenosis progression rate (mixed-effects model)	5.11 (3.47-7.53)	<0.001 *

Hazard ratios are expressed with 95% confidence intervals.
** p<0.05.*

Discussion

To our knowledge this is the first large multicenter cohort study evaluating the progression rate of asymptomatic congenital valvular AS in young adults. Given the scarcity of data about the progression of congenital AS in young adults, these results will contribute to our understanding of the clinical course of congenital AS in adulthood and guide clinical management.

Progression of AS severity

Overall, peak aortic velocity did not change over time in our cohort during the median follow-up of 4.1 years, though a subset of patients did show fast progression. This seems to be comparable to previously reported slow progression rates around 0.08 m/s per year in young adults with congenital AS [6,7,27]. This accumulated evidence shows that in general the progression rate in congenital AS is lower than in degenerative calcific AS with reported progression rates around 0.3 m/s per year [28]. In contrast to the study by Yap et al.[6] according to our results older age is not associated with faster progression in these young adult patients.

Interestingly, we identified LV mass to be strongly associated with progression of congenital AS, irrespective of total LV load or the presence of an aortic coarctation. Ventricular remodelling and development of LVH have classically been interpreted as a physiological mechanism used by the LV to compensate for the chronic pressure overload [29]. However, recent insights have questioned whether this hypothesis is true. Perhaps LVH is not just a consequence of AS, but otherwise involved in the disease mechanism. Many studies have reported that the hypertrophic response to AS is not uniform in patients with comparable AS severity and regression of LVH after surgical correction is also variable [30-33]. Perhaps other factors than the pressure overload play a role in the adaptive hypertrophic response, for example gender and genetic predisposition [32-34]. Furthermore, one might even argue whether evolution of LVH is adaptive or inappropriately maladaptive. Recently, the unfavourable prognostic implications of LVH were elegantly demonstrated in patients with severe degenerative AS [35,36].

In our young adult patients with congenital AS, the association between increased LV mass and faster AS progression emphasizes the unfavourable impact of LVH on clinical outcome. Nowadays controversy exists about how the degree of LVH should influence timing of surgery. The current European guidelines carefully state that asymptomatic patients with severe congenital AS and excessive LVH (≥15 mm), unless this is due to hypertension, may be considered for AVR; while the North American guidelines do not mention LVH as consideration for AVR [37-39]. Basic research is warranted to elucidate the mechanisms behind the development of LVH in order to identify those patients that are at risk of LVH-related worse outcome and will benefit from more aggressive thresholds to proceed to surgery.

Progression of aortic dilatation

As expected, proximal aortic dilatation was present in almost half of our study population. Older age, history of prior aortic valve intervention, moderate-to-severe aortic regurgitation and LVH were all associated with the presence of proximal aortic dilatation, but none of these factors influenced the rate of aortic dilatation. Since previous studies only investigated aortic dilatation in mixed groups of BAV patients (inclusion not restricted to patients presenting with AS), it is incorrect to directly extrapolate those findings to our study group. However, these studies agree regarding the fact that patients of older age or with moderate-to-severe aortic regurgitation are more likely to have a dilated aorta [13,40,41].

We found that proximal aortic dilatation steadily progressed with a rate of 0.7 mm per year. This seems to be comparable to other studies in BAV patients, which report rates ranging from 0.2 to 1.9 mm/year [10-14]. Furthermore, our results are in line with the rate of progression (0.4 mm per year) reported in a small prospective study of adult congenital AS patients [27]. Interestingly, the rate of progressive aortic dilatation was faster in male than in female patients. When we indexed the aortic diameter for BSA (Online Supplement Table 3), this gender difference no longer existed and no other risk factors for faster aortic dilatation were identified. Therefore we speculate that the faster aortic growth in men is associated with their larger absolute aortic size. Despite evidence supporting the use of relative rather than absolute aortic size [42], our results suggest that absolute aortic size is an important predictor for aortic growth and might be the preferred measurement for clinical management of adult congenital AS patients. In addition, the gender difference in aortic growth rate might be explained by hormonal differences, genetic predispositions, hypertension or other gender differences, as remains to be elucidated in the future.

Surprisingly, the presence or progression of aortic dilatation was not related to AS severity in this large cohort of adult congenital AS patients. This argues against the so called haemodynamic theory, stating that aortopathy in BAV is caused by abnormal haemodynamic stress on the aortic wall due to turbulent flow as a result of abnormal valve morphology and cusp orientation [43]. There are conflicting data on this topic, since some studies did find a correlation between the degree of AS and aortic size [40], whereas other did not [10,44].

Our data strengthen the upcoming theory that aortic dilatation in BAV patients is not solely dependent on haemodynamics, but rather is a result of aortic wall fragility secondary to genetic factors and a common developmental defect involving both the aortic valve and the aortic wall [43].

Aortic dissections

Aortic dissection is, without any doubt, the most feared complication of BAV-associated aortic dilatation. Therefore it is remarkable that only 1 case of aortic dissection occurred in our large cohort with almost 1600 patient-years of follow-up. This converts to an aortic dissection risk of 0.06% per patient-year of follow-up in asymptomatic young adult patients with congenital AS. Although the prevalence of aortic dissection was estimated to be much higher in the past, two other large cohort studies with BAV patients also reported a low rate of aortic dissections (respectively 0.09% and 0.06% per patient-year of follow-up) [45,46]. Whether these low rate estimates indicate that we really do not have to fear aortic dissections, or reflect that prophylactic aortic surgery >50 mm efficiently prevents aortic dissections, remains a point of debate.

Survival

Survival was good compared to the expected survival of the general population, but the 3 sudden deaths remain worrisome. Unfortunately no autopsy was performed to establish the cause of death. A close look at the last available data before sudden death suggests that these patients were slightly older and had a slightly higher peak aortic velocity, greater LV mass and lower LV fractional shortening than the total cohort, but had a normal aortic diameter. However, these 3 cases do not allow statistical assessment of risk factors for sudden death.

Clinical implications

In the total study population of patients with predominantly mild-to-moderate AS, AS severity remained stable over time. However, patients with LVH showed faster disease progression, and should be monitored cautiously. In addition, LVH might be useful as an indicator for timing of earlier aortic valve intervention. Furthermore, while proximal ascending aortic dilatation was common, the risk for aortic dissection in adult congenital AS patients was low (0.06% per patient-year of follow-up). Noteworthy, proximal ascending aortic dilatation progressed steadily over time, and faster in male than in female patients. Consequently, these results stress the importance of careful and serial monitoring of the aorta patients with congenital AS. Aortic valve intervention rate is high, in particular in patients with progressive AS and history of prior aortic valve intervention.

Study limitations

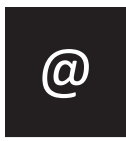
This study inherits all limitations of a retrospective study design. A selected group of patients was included: patients with prior AVR and those without serial echocardiographic measurements were excluded. By including patients with a history of balloon valvuloplasty and open valvulotomy in childhood, one might question whether this is truly a natural history study. Furthermore, our study population consisted of patients receiving care in specialized CHD centres and might not be representative owing to referral bias. The use of prospective databases has limited the survival bias and extent of missing data. A potential limitation caused by the fact that echocardiography was not performed precisely every year, was dissolved by the use of the linear mixed-effects models that take different lengths of follow-up into account. We admit that echocardiography might not have been the best tool for aortic diameter follow-up; however availability of computed tomography or magnetic resonance in this large cohort was limited. Finally, we did not assess the impact of BAV morphology or pregnancy on progression.

Conclusions

In patients with mild-to-moderate congenital AS, AS generally does not progress over time. However patients with LVH are at risk for fast disease progression and should be monitored cautiously. Aortic dissections were rare despite the presence of proximal ascending aortic dilatation in half of the patients. The aorta grows steadily over time and thus needs to be monitored repeatedly. Despite an excellent overall survival, intervention-free survival is impaired, particularly in patients >30 years old with a history of prior aortic valve intervention and severe or fast progressing AS.

Acknowledgements

We would like to thank the medical teams, technicians and sonographers at the participating centres.



Supplementary data to this article can be found online at:
http://dx.doi.org/10.1016/j.ijcard.2012.10.027.

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6

Effects of rosuvastatin on the progression of stenosis in adult patients with congenital aortic stenosis (PROCAS Trial)

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Am J Cardiol. 2011;108:265-71.

Abstract

Recent trials have failed to show that statin therapy halts the progression of calcific aortic stenosis (AS). We hypothesized that statin therapy in younger patients with congenital AS would be more beneficial, because the valve is less calcified. In the present double-blind, placebo-controlled trial, 63 patients with congenital AS (age 18 to 45 years) were randomly assigned to receive either 10 mg of rosuvastatin daily (n = 30) or matched placebo (n = 33). The primary end point was the progression of peak aortic valve velocity. The secondary end points were temporal changes in the left ventricular mass, ascending aortic diameter, and N-terminal pro-brain natriuretic peptide (NT-proBNP). The median follow-up was 2.4 years (interquartile range 1.9 to 3.0). The mean increase in peak velocity was 0.05 ± 0.21 m/s annually in the rosuvastatin group and 0.09 ± 0.24 m/s annually in the placebo group (p = 0.435). The annualized change in the ascending aorta diameter (0.4 ± 1.7 mm with rosuvastatin vs 0.5 ± 1.6 mm with placebo; p = 0.826) and left ventricular mass (1.1 ± 15.8 g with rosuvastatin vs −3.7 ± 30.9 g with placebo; p = 0.476) were not significantly different between the 2 groups. Within the statin group, the NT-proBNP level was 50 pg/ml (range 19 to 98) at baseline and 21 pg/ml (interquartile range 12 to 65) at follow-up (p = 0.638). NT-proBNP increased from 40 pg/ml (interquartile range 20 to 92) to 56 pg/ml (range 26 to 130) within the placebo group (p = 0.008). In conclusion, lipid-lowering therapy with rosuvastatin 10 mg did not reduce the progression of congenital AS in asymptomatic young adult patients. Interestingly, statins halted the increase in NT-proBNP, suggesting a potential positive effect of statins on cardiac function in young patients with congenital AS.

Introduction

The Progression of Stenosis in Adult Patients With Congenital Aortic Stenosis (PROCAS) trial was designed to study the effect of long-term lipid-lowering therapy with daily use of rosuvastatin on the echocardiographic and neurohumoral outcomes in asymptomatic young adult patients with congenital aortic stenosis (AS). We hypothesized that statins prevent calcifications and halt the progression of congenital AS.

Methods

The PROCAS study was a prospective, double-blind, randomized, placebo-controlled, multicenter trial that evaluated the effect of rosuvastatin on the progression of asymptomatic congenital AS in young adult patients. The study was conducted at 6 tertiary referral centers for congenital heart disease in The Netherlands and Belgium. Enrollment occurred from December 2005 to December 2007. The intended follow-up duration was 3 years. Annually, patients underwent transthoracic echocardiography, laboratory testing, and electrocardiography. After the baseline assessment and randomization, the patients were scheduled for telephone interviews every 3 months to assess potential side effects and to emphasize the importance of compliance. For patients undergoing aortic valve replacement (AVR) during the study period, the findings from the last transthoracic echocardiogram, laboratory tests, and electrocardiogram before AVR were used in the present analysis. The medical ethics committee of each participating center approved the PROCAS study, and all patients gave written informed consent. The clinical trial registration number was ISRCTN56552248 (available at: *www.controlled-trials.com/*).

Eligible patients were selected from the CONgenital CORvitia (CONCOR) database,[1] the Dutch registry for adult patients with congenital heart disease, and from the Leuven local congenital heart disease database. We included men and women 18 to 45 years old with native valvular congenital AS, with a peak aortic valve velocity >2.5 m/s. The patients who already used statins or had contraindications for the use of statins, such as known muscle disease, active liver disease, creatine kinase >600 U/L, or severe kidney dysfunction (creatinine >200 µmol/L) were excluded. Other exclusion criteria were previous AVR, a history of acute rheumatic fever, mitral valve stenosis or regurgitation, and severe aortic regurgitation. For young women, the wish to become pregnant within the next 5 years was also a contraindication. Eligible patients were randomized in a 1:1 fashion in blocks of 4 to receive either rosuvastatin 10 mg daily or a matching placebo. The randomization schedule was centralized and generated by a computer program at the Erasmus Medical University Center pharmacology department, which had no access to the rest of the data. When a center was ready to randomize a patient, the pharmacology department sent a randomization number to the site coordinator and the study medication to the patient. The patients, treating physicians, and investigators were all unaware of the treatment assignment.

Annually, a complete Doppler transthoracic echocardiogram was performed by trained echocardiographers. Randomly selected studies were reviewed to ensure that the studies and measurements were performed in accordance with the protocol. The recommended parameters for the clinical evaluation of AS severity are the peak velocity, mean gradient, and aortic valve area.[2]

We used the peak aortic velocity as the primary end point, because it is the most reproducible measurement of the severity of AS and left ventricular (LV) function was normal in all patients.[2] The ascending aorta diameter was measured at 4 levels: the annulus, sinus of Valsalva, sinotubular junction, and proximal ascending aorta. We considered the aorta dilated if the value was 2 standard deviations greater than the normal value, according to gender, in the guidelines.[3] The LV mass was calculated using the Devereux-modified formula.[4] LV hypertrophy was defined by a body surface area-indexed threshold of >134 g/m^2 for men and >110 g/m^2 for women.[5] We defined the aortic valve as calcified if thickening was present combined with increased echogenicity of the leaflets in the parasternal long- or short-axis views. Annual laboratory tests included high-sensitivity C-reactive protein, N-terminal pro-brain natriuretic peptide (NT-proBNP), lipid profile, creatine kinase, and creatinine. After a patient had rested for 30 minutes, venous blood samples were collected and stored at −80°C until the end of the study. Kits to determine the NT-proBNP levels were offered by Roche Diagnostics (Basel, Switzerland), with a cutoff value for elevation of 125 pg/ml.[6] Creatine kinase was considered elevated at >200 U/L in men and 170 U/L in women.

For the statistical analyses, the Statistical Package for Social Sciences, version 15.0 (SPSS, Chicago, Illinois) and R (version 2.11.1, available at: *www.r-project.org*) were used. All statistical tests were 2-sided; p <0.05 was considered statistically significant. The primary end point was the annual peak aortic valve velocity progression. The secondary end points were progression of the LV mass, ascending aorta diameter, and NT-proBNP. The data were analyzed according to an intention-to-treat analysis. To account for different follow-up durations, the annualized changes were calculated by dividing the change by the follow-up duration. On the basis of a standard deviation of 0.15 m/s annually, we calculated that a sample size of 90 patients in each treatment group would give the study 80% power at a 5% significance level to detect a difference in the primary end point of 0.06 m/s annually in the peak velocity. Group differences were assessed using the 2-sample *t* test, chi-square test, or Mann-Whitney *U* test. Normally distributed continuous variables were summarized using the mean ± SD. Non-normally distributed continuous variables were summarized using the median and interquantile range. The categorical variables were summarized using the frequency and percentage. The treatment groups were compared through the use of the 2-sample *t* test or Mann-Whitney *U* test. A subgroup analysis was performed in patients with less severe AS (peak aortic velocity <3.0 m/s) and in patients without aortic valve calcifications. To compare the changes in cholesterol and high-sensitivity C-reactive protein levels within the groups over time, the repeated measurements analysis of variance test and Friedman test were used for comparison. Intervention-free survival analysis to detect differences between the treatment groups was performed using the Kaplan-Meier survival analysis. Cox regression analysis was used to evaluate the prognostic significance of variables that potentially could predict intervention-free survival. A correlation analysis of the NT-proBNP level with age and AS severity parameters was performed using the Pearson correlation test or Spearman correlation test.

Results

From December 2005 to December 2007, 242 patients were assessed for eligibility to participate in the PROCAS trial (Figure 1). The main reason for refusal was the burden of taking medication for 3 years. The main reasons for not meeting the inclusion criteria were young women considering pregnancy, previous AVR, and severe aortic regurgitation. The median follow-up was 2.4 years (interquartile range 1.9 to 3.0). The baseline characteristics of the 2 treatment groups were well balanced (Table 1), without significant differences between the treatment groups at baseline.

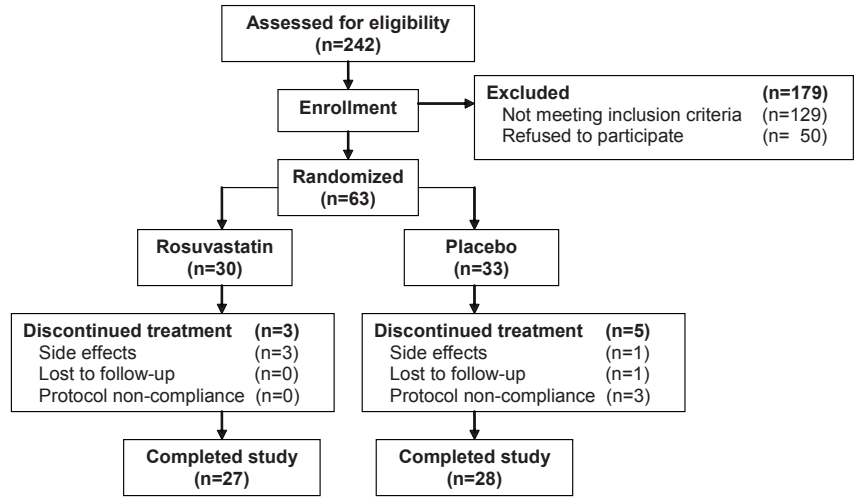

Figure 1. *Enrollment and randomization of patients in PROCAS trial.*

No significant differences were found between the rosuvastatin and placebo group in the annual change in the primary and secondary end points (Table 2). The subgroup analyses did not show interaction effects for the annual progression of peak aortic velocity in patients with less severe AS (p = 0.864) or in patients without baseline aortic valve calcification (p = 0.316). Figure 2 shows the comparison data for AS progression at 0, 1, 2, and 3 years of treatment. The numerical values for the echocardiographic parameters at baseline and at the end of the study are listed in Table 3. The median NT-proBNP in the rosuvastatin group at baseline was 50 pg/ml (interquartile range 19 to 98) and 21 pg/ml (interquartile range 12 to 65) at the end of the follow-up period (p = 0.638). The median NT-proBNP in the placebo group at baseline was 40 pg/ml (interquartile range 20 to 92) and increased with time to 56 pg/ml (interquartile range 26 to 153; p = 0.008). The NT-proBNP level showed weak correlations with the peak velocity (r = 0.311; p = 0.020), peak gradient (r = 0.291; p = 0.029), mean gradient (r = 0.297; p = 0.026), aortic valve area (r = −0.338; p = 0.011), and age (r = 0.320; p = 0.016). The prevalence of aortic root dilation was high: 33% at the annulus level, 27% at the sinus of Valsalva level, 79% at the sinotubular junction level, and 78% at the proximal ascending aorta level. Dilation of the ascending aorta at any of the 4 levels occurred in 84% of the patients.

Table 1. *Baseline characteristics of PROCAS trial.*

Variable	Rosuvastatin (n=30)	Placebo (n=33)
Age (years)	33 ± 9	32 ± 10
Male	21 (70%)	24 (73%)
Body mass index (kg/m²)	25 ± 3	25 ± 4
Blood pressure (mmHg)		
Systolic	129 ± 16	131 ± 16
Diastolic	76 ± 10	78 ± 9
Smoker		
Current	7 (23%)	10 (30%)
Former	1 (3%)	1 (3%)
Never	22 (73%)	22 (67%)
Prior intervention (surgical valvulotomy or balloon valvuloplasty)	22 (73%)	26 (79%)
Bicuspid valve	28 (93%)	29 (88%)
Aortic regurgitation		
Non / grade 1	21 (70%)	18 (55%)
Grade 2	6 (20%)	10 (30%)
Grade 3	3 (10%)	5 (15%)
Aortic valve calcium	12 (40%)	12 (36%)
Measurements of aortic stenosis		
Peak aortic valve velocity (m/s)	3.4 ± 0.7	3.6 ± 0.9
Peak aortic gradient (mmHg)	48 ± 18	56 ± 28
Mean aortic gradient (mmHg)	27 ± 10	32 ± 17
Aortic valve area (cm²)	1.3 ± 0.4	1.3 ± 0.5
Aortic diameter at 4 levels (mm)		
Annulus	24 ± 5	25 ± 5
Sinus of Valsalva	32 ± 6	32 ± 6
Sinotubular junction	27 ± 6	28 ± 6
Proximal ascending aorta	36 ± 6	37 ± 8
Fractional shortening (%)	39 ± 8	39 ± 7
Left ventricular mass (gram)	214 ± 59	212 ± 77
Left ventricular hypertrophy	6 (20.0%)	11 (33.3%)
Lipids		
Total cholesterol (mg/dl)	177 ± 36	176 ± 39
Total cholesterol (mmol/l)	4.6 ± 0.9	4.6 ± 1.0
Low-density lipoprotein cholesterol (mg/dl)	106 ± 31	104 ± 35
Low-density lipoprotein cholesterol (mmol/l)	2.8 ± 0.8	2.7 ± 0.9
High-density lipoprotein cholesterol (mg/dl)	46 ± 13	48 ± 15
High-density lipoprotein cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.4
Triglycerides (mg/dl)	49 ± 28	52 ± 29
Triglycerides (mmol/l)	1.3 ± 0.7	1.3 ± 0.7
High sensitivity C-reactive protein (mg/l)	1.4 (0.8 - 5.3)	1.3 (0.5 - 2.9)
N-terminal Pro Brain Natriuretic Peptide (pg/ml)	50 (19 - 98)	40 (20 - 92)
Creatinine (µmol/l)	69 ± 15	73 ± 11
Creatine kinase (U/l)	96 (65 - 110)	92 (68 - 124)

Data are presented as mean ± SD when normally distributed, as median (interquantile range) when non-Gaussian distributed, and as n (%) when frequencies.

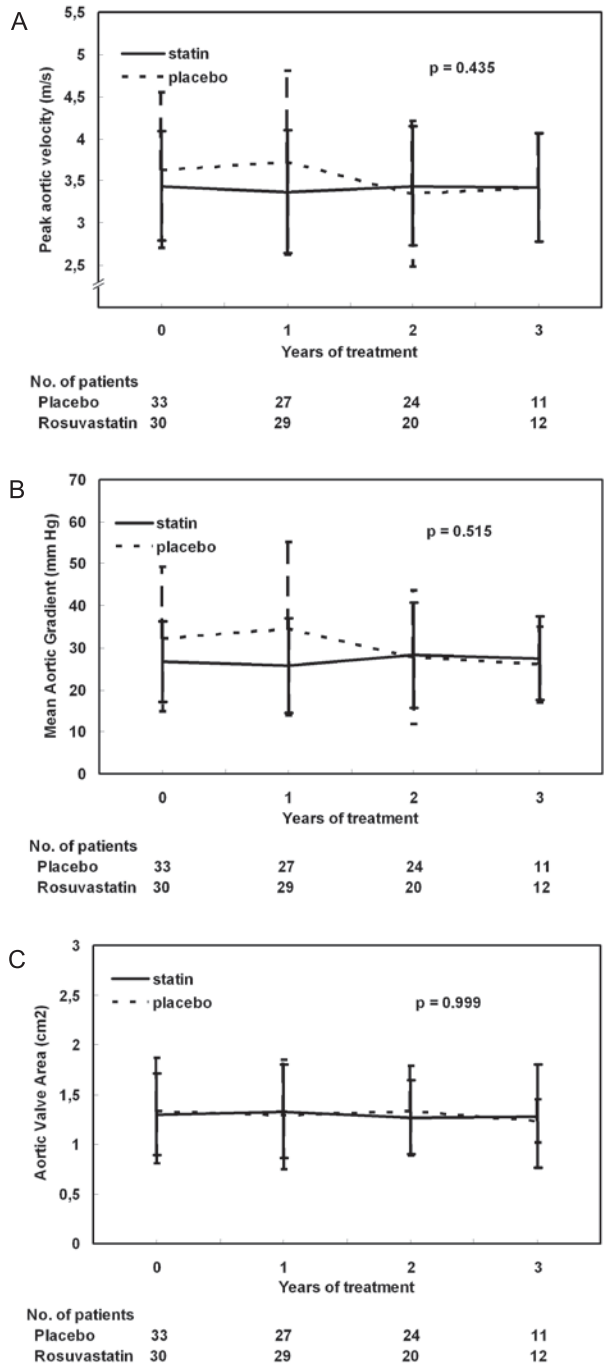

Figure 2. *Progression of congenital aortic stenosis in rosuvastatin and placebo group in peak aortic velocity (A), mean aortic gradient (B) and aortic valve area (C).*

Table 2. *Annualized changes in primary and secondary end points.*

Variable	All patients (n=59)	Rosuvastatin (n=27)	Placebo (n=32)	p-value
Aortic stenosis progression				
Peak aortic velocity (m/s)	0.07 ± 0.23	0.05 ± 0.21	0.09 ± 0.24	0.435
Peak aortic gradient (mmHg)	3.0 ± 7.7	2.5 ± 5.7	3.5 ± 9.2	0.638
Mean aortic gradient (mmHg	1.6 ± 4.2	1.2 ± 3.3	1.9 ± 4.8	0.515
Aortic valve area (cm^2)	-0.03 ± 0.15	-0.03 ± 0.11	-0.03 ± 0.18	0.999
Aortic diameter progression				
Annulus (mm)	0.4 ± 2.2	0.1 ± 1.9	0.7 ± 2.5	0.330
Sinus of Valsalva (mm)	0.2 ± 1.6	0.2 ± 1.2	0.1 ± 1.7	0.802
Sinotubular junction (mm) *	0.2 ± 2.1	-0.1 ± 1.4	0.5 ± 2.5	0.332
Proximal ascending aorta (mm) *	0.4 ± 1.6	0.4 ± 1.7	0.5 ± 1.6	0.826
Left ventricular mass (gram)	-1.6 ± 25.2	1.1 ± 15.8	-3.7 ± 30.9	0.476
N-terminal Pro Brain Natriuretic Peptide (pg/ml) †	0.4 (-8.0 - 8.7)	-0.9 (-8.0 - 6.3)	4.1 (-6.9 - 13.4)	0.187

Data are presented as mean ± SD when normally distributed and as median (interquantile range) when non-Gaussian distributed.
** Rosuvastatin group n=26, placebo group n=31, total n=57.*
† Rosuvastatin group n=24, placebo group n=24, total n=48.

Table 3. *Changes echocardiographic characteristics.*

	Rosuvastatin (n=30)			Placebo (n=32)		
Characteristics	**Baseline**	**Follow-up**	**p-value**	**Baseline**	**Follow-up**	**p-value**
Peak aortic valve velocity (m/s)	3.4 ± 0.6	3.5 ± 0.7	0.410	3.6 ± 0.9	3.7 ± 1.1	0.046
Peak aortic gradient (mmHg)	46 ± 16	51 ± 18	0.042	55 ± 28	60 ± 35	0.034
Mean aortic gradient (mmHg)	26 ± 8	29 ± 11	0.082	31 ± 17	35 ± 22	0.038
Aortic valve area (cm^2)	1.3 ± 0.4	1.3 ± 0.5	0.251	1.3 ± 0.5	1.3 ± 0.5	0.260
Annulus (mm)	24 ± 5	24 ± 4	0.904	25 ± 5	26 ± 6	0.294
Sinus of Valsalva (mm)	31 ± 5	32 ± 5	0.441	32 ± 6	32 ± 6	0.948
Sinotubular junction (mm) *	27 ± 6	27 ± 5	0.665	28 ± 5	29 ± 6	0.508
Proximal ascending aorta (mm) *	35 ± 6	36 ± 6	0.229	37 ± 8	38 ± 8	0.110
Left ventricular mass (gram)	212 ± 56	212 ± 75	0.947	209 ± 77	203 ± 77	0.456

Values are shown as mean ± standard deviation when normally distributed and as median (interquantile range) when non-Gaussian distributed.
** Rosuvastatin group n=26, placebo group n=31, total n=57.*

During the trial, 9 patients (14%) underwent surgical AVR after a median follow-up of 1.7 years (range 0.8 to 2.0). No significant difference was found in the occurrence of AVR between the rosuvastatin and placebo groups (log-rank, 0.978; p = 0.323; Figure 3). No deaths or other aortic valve-related complications (i.e., endocarditis, aortic dissection) occurred during the follow-up period. Two factors associated with a shorter interval to AVR were identified: a greater peak aortic velocity at baseline (hazard ratio 1.8, 95% confidence interval 1.2 to 2.6) and aortic valve calcification (hazard ratio 1.7, 95% confidence interval 1.0 to 2.9).

The peak aortic velocity at baseline in patients who underwent AVR was greater than that in patients who did not undergo AVR (4.5 ± 0.7 vs 3.4 ± 0.7 m/s; p <0.001). The AVR patients more often had valve calcifications at baseline (78% vs 32%; p = 0.021). The annual AS progression rate (0.41 ± 0.28 vs 0.02 ± 0.17 m/s; p <0.001) and LV mass at baseline (266 ± 32 vs 203 ± 69 g; p = 0.010) were greater in those requiring AVR, as was the median NT-proBNP (108 pg/ml, interquartile range 27 to 446, vs 42 pg/ml, interquartile range 18 to 74; p = 0.061).

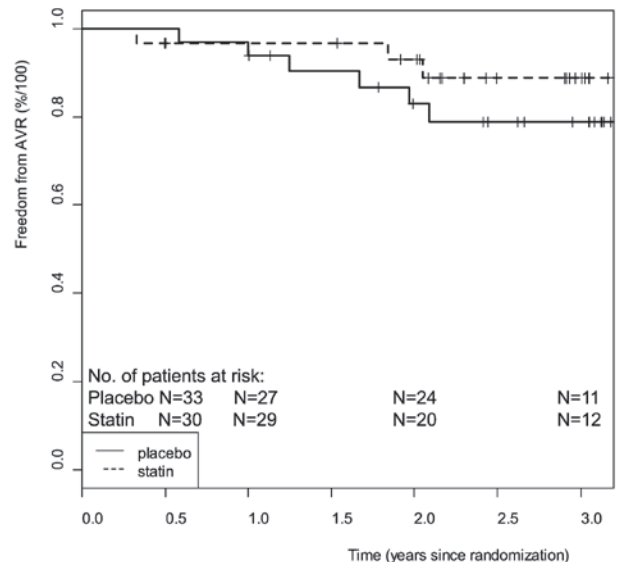

Figure 3. *Kaplan-Meier curves for freedom from AVR for rosuvastatin and placebo group (log-rank: 0.978; p=0.323).*

Table 4. *Changes in cholesterol and high-sensitivity C-reactive protein levels.*

	Rosuvastatin (n=27)			Placebo (n=32)		
Characteristic	**Baseline**	**Follow-up**	**p-value**	**Baseline**	**Follow-up**	**p-value**
Total cholesterol (mg/dl)	177 ± 36	120 ± 30	<0.001	176 ± 39	178 ± 36	0.362
Total cholesterol (mmol/l)	4.6 ± 0.9	3.1 ± 0.8	<0.001	4.6 ± 1.0	4.6 ± 0.9	0.362
Low-density lipoprotein cholesterol (mg/dl)	106 ± 30	61 ± 22	<0.001	104 ± 35	97 ± 32	0.170
Low-density lipoprotein cholesterol (mmol/l)	2.8 ± 0.8	1.6 ± 0.6	<0.001	2.7 ± 0.9	2.5 ± 0.8	0.170
High-density lipoprotein cholesterol (mg/dl)	46 ± 13	46 ± 13	0.273	48 ± 16	47 ± 24	0.713
High-density lipoprotein cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	0.273	1.3 ± 0.4	1.2 ± 0.6	0.713
High sensitivity C-reactive protein (mg/l)	1.4 (0.8 - 5.3)	1.2 (0.6 - 3.0)	0.019	1.3 (0.5 - 2.9)	1.6 (0.8 - 2.5)	0.158

Values are shown as mean ± standard deviation when normally distributed and as median (interquantile range) when non-Gaussian distributed.

Compliance with the study medication was judged satisfactory, according to the cholesterol and high-sensitivity C-reactive protein levels (Table 4). No difference was seen in the frequency of adverse events between the 2 groups. The incidence of muscular pain, leading to discontinuation of the study drug, was similar in the rosuvastatin and placebo group (10% vs 3%, p = 0.340). Furthermore, the incidence of elevated creatine kinase levels was comparable between the rosuvastatin and placebo group (17% vs 12%, respectively, p = 0.725). No cases of rhabdomyolysis, kidney failure, severe creatine kinase elevation, or cancer were observed.

Discussion

The present small, prospective, double-blind, randomized, placebo-controlled multicenter PROCAS trial could not detect a significant effect of rosuvastatin on the progression of congenital AS in asymptomatic adult patients aged 18 to 45 years. Also, rosuvastatin did not have a significant effect on the progression of ascending aorta diameter, LV mass, or AVR-free survival. The results of the PROCAS trial have confirmed and extended the findings of the Scottisch Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE), Tyrolean Aortic Stenosis Study (TASS), Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) and Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trials.[7-10] The largest difference between these trials and the PROCAS trial was the approximately 30-year younger average age of the PROCAS patients. The PROCAS trial only included patients with congenital AS, and the other trials included populations with predominantly degenerative, calcified AS in elderly patients. The PROCAS trial confirmed the findings of the subgroup analysis in the patients with a bicuspid valve in the ASTRONOMER trial.[10] The PROCAS trial showed that 38% of included young adults already had aortic valve calcification. The subgroup analysis of patients with less severe AS or without valve calcifications showed the same nonsignificant results.

In the PROCAS study, the mean age of the patients was 33 years. The vast majority of these young patients with congenital AS (84%) already had dilation of the ascending aorta, especially at the level of the sinotubular junction and the proximal ascending aorta. Statins did not have an effect on the progression of aortic dilation, which, on average, was 0.3 mm/year. In patients with Marfan syndrome, promising evidence has shown that angiotensin II blockade slows the rate of progressive aortic root dilation.[11] Because aortic dilation in bicuspid valve disease shows similarities with Marfan syndrome with regard to abnormalities in fibrillin-1 and matrix metalloproteinases, the effect of angiotensin II blockade on the progression of aortic dilation should be further investigated.[12]

The PROCAS trial showed that NT-proBNP increased over time in patients with congenital AS, and statins were able to halt this increase. It is possible that lipid-lowering therapy improves cardiac function in patients with congenital AS. A recent study of patients with heart failure showed that statin therapy reduced the NT-proBNP levels and improved cardiac function.[13] Statins also decreased the NT-proBNP levels and improved cardiac function in patients with dilated cardiomyopathy.[14] The exact mechanism and clinical implications for patients with congenital AS remain to be elucidated, and additional research of larger study populations of those with congenital AS is necessary to confirm these findings.

Although many studies have been reported about the diagnostic and prognostic value of NT-proBNP in degenerative AS, no data are available on this matter in young adult patients with congenital AS. Therefore, we did not only focus on the effect of rosuvastatin on NT-proBNP, but also explored the correlation among the congenital AS severity, AVR, and NT-proBNP. The PROCAS trial prospectively showed that the NT-proBNP levels correlated positively with congenital AS severity. This is in line with degenerative AS studies of elderly patients, which also showed a similar NT-proBNP correlation with AS severity.[15] It has also been shown that the level of NT-proBNP predicts symptom development and the postoperative outcome after AVR.[16] The NT-proBNP level decreases after successful surgical therapy but increases in conservatively treated patients.[17] In our study, the NT-proBNP levels at baseline were much greater in the subgroup of patients who underwent AVR during follow-up, suggesting a correlation between a high NT-proBNP level and the need for AVR. Future research is needed to determine and confirm the diagnostic and prognostic value of NT-proBNP in congenital AS.

Observer variability and suboptimal imaging windows in transthoracic echocardiography can affect reproducibility. We limited this by trained echocardiographers using standardized protocols. Transthoracic echocardiography might not be precise enough to detect small changes, especially in the LV mass and aortic diameters. Cardiac magnetic resonance might be more suitable for those measurements in future trials.

Although a total of 242 patients were assessed for eligibility to enter the PROCAS trial, the inclusion proved very difficult. At the time of inclusion, many negative publications regarding statins had appeared in the Dutch press; consequently, young asymptomatic patients were reluctant to take statin medication. This resulted in inclusion of only 63 patients, although 180 had been anticipated. However, even if the desired number of enrolled patients had been achieved in the PROCAS trial, the follow-up time might not have been sufficient to detect an effect. According to the low-density lipoprotein density-radius theory, a longer period is required to reduce AS progression.[18] Because of the size of the radius, vascular occlusion will respond more quickly to statin therapy than will valve stenosis.[18] However, our institutions' ethical committee limited the follow-up duration to only 3 years. Statin therapy might be more beneficial in patients with mild AS and hypercholesterolemia, as was previously showed in an open-label, prospective study of calcific AS.[19] We were not able to check this hypothesis, because only 5 patients in the PROCAS trial had elevated low-density lipoprotein levels >130 mg/dl. A larger prospective, randomized, controlled trial, including more patients with hypercholesterolemia and mild AS, is necessary to draw firm conclusions about the effect of statin therapy on AS progression in young adult patients with asymptomatic congenital AS. Currently, no evidence is available to support the prescription of statins to prevent the progression of congenital AS.

Acknowledgments

We thank Elini R. Andrinopoulou, BSc, for her support in data analysis.

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Ascending aorta dilatation in patients with bicuspid aortic valve stenosis: a prospective CMR study

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Eur Radiol. E-pub 26 Sep 2012.

Abstract

Background

The aim of this study was to evaluate the natural progression of aortic dilatation and its association with aortic valve stenosis (AoS) in patients with bicuspid aortic valve (BAV).

Methods

Prospective study of aorta dilatation in patients with BAV and AoS using cardiac magnetic resonance (CMR). Aortic root, ascending aorta, aortic peak velocity, left ventricular systolic and diastolic function and mass were assessed at baseline and at 3-years follow-up.

Results

Of the 33 enrolled patients, 5 needed surgery, while 28 patients (17 male; mean age: 31±8 years) completed the study. Aortic diameters significantly increased at aortic annulus, sinus of Valsalva and tubular ascending aorta levels (P<0.050). The number of patients with dilated ascending aortas increased from 32% to 42%. No significant increase in sino-tubular-junction diameter was observed. Aortic peak velocity, ejection fraction and myocardial mass significantly increased while the early/late filling ratio significantly decreased at follow-up (P<0.050). The progression rate of the ascending aorta diameter correlated weakly with the aortic peak velocity at baseline (R^2=0.16, P=0.04).

Conclusion

BAV patients with AoS showed a progressive increase of aortic diameters with maximal expression at the level of the tubular ascending aorta. The progression of aortic dilatation correlated weakly with the severity of AoS.

Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect with an estimated prevalence of 0.5% - 2% [1]. Patients with BAV show an increased risk of developing aortic valve dysfunction and dilatation of the thoracic aorta [2,3]. There is still controversy whether the pathogenesis of the dilatation of the ascending aorta in BAV patients is caused by a genetic predisposition or by the aortic valvular stenosis causing post-stenotic dilatation due to blood flow turbulences (haemodynamic theory). In addition, despite the high prevalence of BAV disease in the general population, longitudinal data investigating the natural history of the disease process are scarce.

Therefore the aims of this study were to prospectively evaluate the natural progression of ascending aorta dilatation in asymptomatic BAV patients with aortic stenosis (AoS) and its association with the haemodynamic progression of valvular stenosis using cardiovascular magnetic resonance (CMR) as reference standard.

Methods

Study design and population

This prospective study included asymptomatic patients with BAV and AoS. Consecutive patients visiting the out-patient clinic of our hospital were invited to participate. Inclusion criteria were age between 18 and 50 years, a bicuspid aortic valve and a peak flow velocity over the valve above 250 cm/s based on echocardiographic measurements. Exclusion criteria were subvalvular or supravalvular aortic stenosis, severe aortic regurgitation, symptoms, previous aortic valve replacement or a concomitant significant mitral valve lesion. Patients underwent CMR at baseline and after 3 years of follow-up. Patients who did not complete the follow-up were excluded from further analysis. The study protocol was approved by the institutional review board of our university hospital. All patients gave written informed consent.

Cardiac magnetic resonance

CMR imaging was performed at 1.5T (Signa CV/I, GE Medical Systems at baseline upgraded to Signa Discovery 450, GE Healthcare, Milwaukee, Wisconsin at follow-up). Patients were placed in supine position and entered feet first into the magnet. A dedicated cardiac coil (4-channel coil at baseline and 8-channel coil at follow-up) was placed on the thorax of each patient and used for the acquisition of the images. All the studies were analysed on a remote workstation. CAAS- MRV (version 3.1; Pie Medical Imaging, Maastricht, The Netherlands) was used for the left ventricular (LV) function evaluation. Quantitative flow measurements were performed using CINE software (version 3.4, GE Medical System, Milwaukee, Wisconsin, USA).

Left ventricular function

Cine MR images were obtained using a breath-holding ECG triggered balanced steady state free precession (SSFP) pulse sequence. Imaging parameters included the following: FOV 36-40 x 28-32 cm; matrix 224 x 196; TR: 3.4 ms; TE: 1.5 ms; flip angle 45°; 12 views per segment.

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Slice thickness was 8 mm with a gap of 2 mm. These parameters resulted in a temporal resolution per image of 41 ms with a heart rate of 60 bpm. First, three rapid surveys were obtained for the determination of the cardiac position and orientation; two- and four-chamber cine MR images were then obtained. The series of short axis images were obtained from the reference images provided by the two- and four-chamber end-diastolic images at the end of expiration. Approximately 10 to 12 slices were acquired to cover the entire length of the heart. For all patients LV function was analysed using both a combination of the short axis view and the long axis views [4]. Endocardial and epicardial contours were automatically detected by dedicated software and manually corrected on each cardiac phase [4,5]. The papillary muscles were considered as being part of the blood pool. End-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), stroke volume (SV) and cardiac output (CO) were calculated for each patient at both baseline and follow-up times and presented either as absolute numbers or indexed to body surface area (BSA).

Time-volumes curves of the left ventricle were plotted as volume versus time during the diastolic phase for the determination of LV diastolic function. The volumetric filling curves were also transformed to the first derivative to obtain early and late profiles [6]. Peak early filling rate (PEFR), time to PEFR, peak late filling rate (PLFR) and early/late ratio were calculated. Heart rate (HR) was recorded during CMR acquisition.

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Aortic diameters

Cine SSFP images for the measurements of the aortic diameters were acquired in the coronal oblique and double oblique sagittal plane of the left ventricular outflow tract (LVOT). The diameter of the ascending aorta was measured at four different levels: aortic annulus, defined as the hinge points of the atrioventricular valve (level 1), sinus of Valsava, defined as the mid point of the aortic sinus of Valsalva (level 2), sino-tubular junction (level 3) and tubular portion of the ascending aorta, at the level of the pulmonary trunk (level 4) (Figure 1). At each level the external diameter was measured perpendicular to the axis of blood flow during peak systole [7]. Aortic measurements were presented either as absolute numbers or indexed to BSA.

Images were assessed by two independent observers (AR and TL). One observer who was blinded to the previous results measured the datasets twice, at least 12 weeks after the first measurement.

Aortic valve function

A retrospective gated velocity-encoded sequence during expiratory breath-holds was used (FOV: 36-40 x 16-20 cm; TR: 6.5ms; TE: 3.1ms; flip angle: 30°; matrix: 256x128). The three-chamber view was used to plan three velocity-mapping planes parallel to the aortic valve as described previously [8]. Regions of interest (ROI) were drawn on each of the 30 frames of the velocity-encoded sequence to include the aortic valve and the aorta depending on slice position. Peak velocities were extracted for the greatest velocity recorded in any pixel within the ROI. Aortic valve area (AVA) was calculated using the continuity equation as previously described [8].

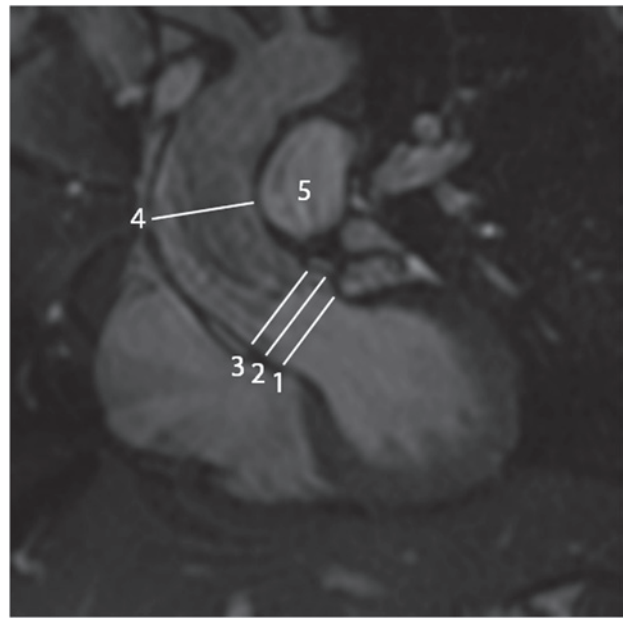

Figure 1. *Measurements of the aortic diameters.*

The oblique coronal sagittal SSFP view of the aorta shows the measurements of the aortic root: at the level of the aortic annulus (1), the sinus of Valsalva (2), the sinotubular junction (3) and the tubular portion of ascending aorta (4) at the level of the pulmonary trunk (5).

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Statistical analysis

Statistical analysis was performed using SPSS software (version 17.0, SPSS Inc., Chicago, Illinois, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Continuous data are expressed as mean ± standard deviation (SD) and qualitative variables as count and percentage. Differences of baseline characteristics between the group of patients who completed the study and the group of patients who interrupted the study were tested using the Mann-Whitney U test. Continuous variables between the two different time points were compared by the paired samples t-test if the data were normally distributed, or the Wilcoxon signed ranks test for non-normal data. Annual rates of progression of aortic diameters were calculated and expressed as mean±SD. Linear regression models were performed between the progression rate of ascending aorta diameter and aortic peak velocity at baseline and diameter of ascending aorta at baseline. Intra- and inter-observer variability of each aortic diameter were assessed in 25 randomly selected patients and presented as mean difference (measure of precision) with SD (measure of accuracy) and the corresponding correlation coefficient (r). A *P*-value <0.05 was considered significant.

Results

Demographic characteristics

Thirty-three asymptomatic patients were enrolled in the study and underwent baseline CMR. During follow-up five patients needed surgical correction of their aortic stenosis. Two of them underwent a Bentall procedure and three isolated aortic valve replacement. The mean time±SD between study inclusion and aortic valve replacement was 21±11 months. These 5 patients were excluded from further analysis.

Twenty-eight patients completed the study and underwent follow-up CMR. Mean follow-up was 34±6 months. Seventeen patients (61%) were male. The age ranged from 21 to 49 years (31±8 years). Mean BSA was 1.9±0.2 m^2. Twenty-three/28 (82%) patients showed no or mild aortic regurgitation at echocardiography while 5/28 (18%) showed moderate aortic regurgitation.

Baseline characteristics of all patients are reported in Table 1. Myocardial mass, diameter of tubular ascending aorta and aortic peak velocity were significantly higher in the group of patients who underwent surgery.

Table 1. *Baseline characteristics of the overall BAV population and grouped according to the completion of the study*

Population variable	Total population (n=33)	Population with baseline and follow-up CMR (n=28)	Population who underwent aortic surgery (n=5)	P-value
Age (years)	32±8	32±8	38±9	0.108
Men	22 (67%)	17 (61%)	5 (100%)	0.068
Systolic blood pressure (mmHg)	132±15	132±15	130±17	0.706
Diastolic blood pressure (mmHg)	76±10	75±9	83±10	0.138
EF (%)	56±8	57±7	54±12	0.209
SV (ml)	115±36	112±38	131±17	0.098
CO (L/min)	7.7±2.4	7.5±2.6	8.6±1.6	0.192
Mass (g)	133±42	124±38	184±27	0.009
Aortic annulus (mm)	27±6	26±7	30±3	0.119
Sinus of Valsalva (mm)	33±5	33±6	34±4	0.615
Sino-tubular junction (mm)	29±5	28±5	31±5	0.340
Tubular ascending aorta (mm)	38±7	37±6	44±5	0.022
Aortic peak velocity (cm/sec)	335±80	319±74	423±53	0.009

Data are reported as mean±SD or n(%).
SV = stroke volume; EF= ejection fraction; CO= cardiac output

LV parameters and mass

Changes in LV haemodynamic parameters and mass are described in Table 2. Ejection fraction and LV mass significantly increased from baseline to follow-up (P<0.001 and P=0.006, respectively). End-systolic volume significantly decreased (p=0.010). No significant changes over time were observed for EDV, SV and CO. The early/late ratio was significantly lower at follow-up compared to baseline (P=0.032).

Table 2. *Comparison of LV haemodynamic parameters and mass at baseline and follow-up (n=28).*

	Baseline	Follow-up	P-value
EDV (ml)			
Absolute (ml)	197±65	198±61	0.929
Indexed (ml/m^2)	103±31	103±29	0.716
ESV (ml)			
Absolute (ml)	86±32	81±32	0.010
Indexed (ml/m^2)	45±17	43±16	0.009
EF (%)	57±7	59±7	<0.001
SV (ml)			
Absolute	112±38	116±35	0.104
Indexed	59±17	61±17	0.078
CO (L/min)	7.5±2.6	7.9±2.1	0.246
Mass (g)			
Absolute	124±38	128±39	0.006
Indexed	65±18	67±18	0.011
Heart rate (bpm)	68±10	69±10	0.649
PEFR (ml/s)	509±187	571±148	0.601
PLFR (ml/s)	281±210	362±164	0.067
TPEFR (s)	140±39	153±33	0.226
Early/late ratio	2.4±1.1	1.8±0.7	0.032

Data are reported as mean±SD.
EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; SV = stroke volume; CO = cardiac output; PEFR = peak early filling rate; PLFR = peak late filling rate; TPEFR = time to peak filling rate.

Aortic diameters and valvular stenosis

The largest diameter was found at the level of the tubular ascending aorta. Of the 28 patients, 9 (32%) showed dilatation of the tubular portion of the ascending aorta (> 4 cm) at baseline. The number of patients with dilated aorta increased to 12/28 at follow up (43%). Absolute aortic diameters significantly increased during follow-up at the levels of aortic annulus, sinus of Valsava and tubular portion of ascending aorta. No significant changes were observed at the level of sino-tubular junction (Table 3, Figure 2). Aortic diameters at all levels were significantly larger in the subgroup of patients with moderate aortic regurgitation compared with the group of patients with no or mild aortic regurgitation (P<0.050).

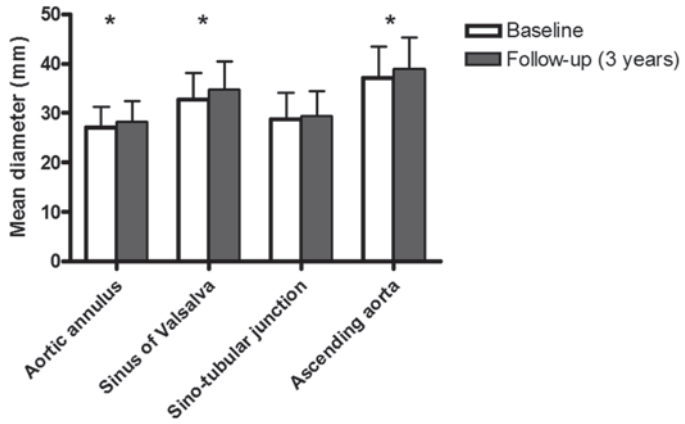

Figure 2. *Comparison of aortic diameters and valvular stenosis at baseline and follow-up.*
** P-value<0.050.*

The mean progression rate of the tubular portion of the ascending aorta diameter was 0.7±0.6 mm/year (Table 3). In the overall population, the mean aortic peak velocity increased significantly at follow-up (P=0.010) with a mean increase of 11±21 cm/s/year (Table 3). The aortic valve area significantly decreased from 1.4 cm^2 at baseline to 1.2 cm^2 at follow-up (P=0.004).

The patients were classified in three different groups based on the mean progression rate of the tubular portion of ascending aorta diameter. Fourteen patients (50%) showed a progression rate between 0 and 0.5 mm/year ("slow progression group", mean progression rate: 0.2±0.2 mm/year), 8 patients (28.6%) had a progression rate between 0.5 and 1.0 mm/year ("moderate progression group", mean progression rate: 0.7±0.1 mm/year), while 6 patients (21.4%) had a progression rate>1.0 mm/year ("fast progression group", mean progression rate: 1.7±0.4 mm/year). Baseline characteristics and aortic diameters did not differ within the different subgroups (P>0.050). The peak velocity over the aortic valve at baseline was 300±71 cm/s in the "slow progression group", 325±63 cm/s in the "moderate progression group" and 354±93 cm/s in the "fast progression group"; P=0.443.

The progression rate of the tubular portion of the ascending aorta diameter calculated in the overall population correlated weakly with the aortic peak velocity at baseline: R^2=0.16, P=0.04, Figure 3. No significant correlation was found between the progression rate of the tubular portion of the ascending aorta diameter and the diameter of the tubular portion of the ascending aorta at baseline: R^2=0.01; P=0.631.

The results of inter-observer and intra-observer variability of aortic diameters are reported in Table 4.

Table 3. *Comparison of aortic diameters and valvular stenosis at baseline and follow-up (n=28).*

	Baseline	Follow-up	P-value	Progression rates
Aortic Annulus				
Absolute (mm)	26±7	28±4	0.011	0.6±1.1 mm/year
Indexed (mm/m^2)	14±2	15±2	0.010	
Sinus of Valsalva				
Absolute (mm)	33±6	35±6	0.001	0.8±1.1 mm/year
Indexed (mm/m^2)	17±3	18±3	<0.001	
Sino-tubular junction				
Absolute (mm)	28±5	29±5	0.168	0.2±1.2 mm/year
Indexed (mm/m^2)	15±3	16±3	0.229	
Tubular ascending aorta				
Absolute (mm)	37±6	39±6	<0.001	0.7±0.6 mm/year
Indexed (mm/m^2)	20±3	21±4	<0.001	
Aortic peak velocity (cm/s)	319±74	348±94	0.010	11±21 cm/s/year

Data are reported as mean±SD.

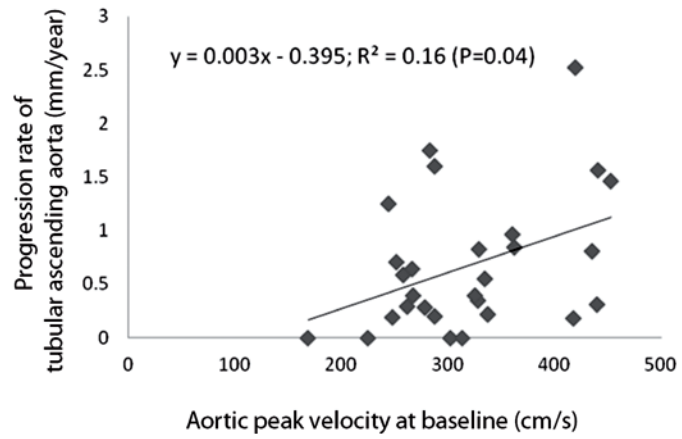

Figure 3. *Regression line between the progression rate of tubular ascending aorta diameter and the aortic peak velocity at baseline.*

Table 4. *Intra- and inter-observer variability of aortic diameters by CMR*

	Intra-observer variability		***Inter-observer variability***	
Variable	Absolute mean difference	r	Absolute mean difference	r
Aortic annulus (mm)	0.8±5.5	0.6	0.1±6.1	0.5
Sinus of Valsalva (mm)	0.4±4.2	0.7	1.4±3.1	0.8
Sino-tubular junction (mm)	1.0±2.9	0.8	0.4±3.1	0.8
Tubular ascending aorta (mm)	0.2±0.8	0.9	0.2±2.2	0.9

Data are reported as mean±SD.

Discussion

To our knowledge the present study is the first investigating the natural progression of aortic dimensions and aortic valve function in adult BAV patients with AoS using a prospective design and CMR as reference standard. This study showed that patients with BAV experienced a progressive increase in thoracic aortic dilatation and severity of aortic stenosis over time and that the rate of aortic dilatation was weakly correlated with aortic peak velocity at baseline.

Natural history of BAV patients

The natural history of patients with BAV and AoS differs from that of patients with stenotic tricuspid aortic valve in two aspects. Firstly, BAV patients show an earlier onset of significant aortic valve stenosis and regurgitation already during the third or fourth decade of life. In our study population the annual change of aortic jet velocity was 11 cm/s/year, which is in concordance with previous echocardiographic studies [9-11]. We found a concomitant increase in LV mass. As previously shown, hypertrophy is an initial adaptive response to pressure overload, which may lead to adverse consequences in the long run [12]. In our population, we observed a reduced ESV over time with a consequent increased ejection fraction. This has not been described before. An early decrease in diastolic function was also observed. This may be related to the stiffer ventricle due to the significant increase in LV mass. As shown in previous clinical studies LV diastolic dysfunction may precede LV systolic dysfunction [13]. In the 5 patients who underwent surgery during the study the mean ejection fraction at baseline was slightly lower. The exact point at which to intervene in asymptomatic patients with severe AoS is still disputed, but perhaps more detailed longitudinal studies will reveal that the development of LV diastolic and systolic dysfunction in association with LV mass thickness can be used as indicators of the need for intervention.

The second difference is the dilatation of the ascending aorta which is a common finding in BAV patients [14]. Indeed, up to 50% of BAV patients with normally functioning aortic valves show aortic dilatation [15,16]. The prevalence of aortic dilatation in our cohort, composed by BAV patients with aortic stenosis, was 32% at baseline and increased to 42% at follow-up. Only a few echocardiographic studies have estimated the rate of progression of aortic dilatation over time [17-19]. Similarly to the findings of Ferencik and Pape [18], we observed a significant progressive increase of aortic dimensions at all levels with the exception of the sino-tubular junction where the mean diameter remained unchanged over time. A possible explanation may be a different expression at this level of matrix protein and tissue inhibitor of metalloproteinases compared with the other sites of the aortic root and the tubular portion of the ascending aorta [20]. In agreement with previous echocardiographic studies, in our study the largest diameter was measured at the level of the tubular portion of the ascending aorta. It has been reported previously that dilatation at this level occurs more rapidly than in other segments [21]. In our study, the mean progression rate was 0.7 mm per year, which is slightly slower than the progression rate of 0.9 mm per year reported by Ferencik and Pape [18]. The younger age of our patients may explain the slower progression rate of aortic dilatation observed in our study.

Association between AoS and aortic dilatation

Currently, there are two theories explaining the aortopathy observed in BAV patients [22]. The first theory suggests that the association of aortic dilatation with BAV may be secondary to an intrinsic aortic wall pathology, resulting in weakness of the aortic wall and consequent dilatation. Indeed, marked degenerative changes of the aortic wall, including cystic medial necrosis [23] and loss of elastic elements [24], have been described in the aorta of BAV patients. The second theory suggests that there may also be some haemodynamic factors that contribute to the aortic dilatation, although dilatation has been described in the absence of AoS and regurgitation. The haemodynamic theory is based on the idea that the orientation and the morphology of a BAV cause turbulent blood flow in the ascending aorta and an increase in aortic wall shear stress. Hope et al [25,26] demonstrated recently an abnormal systolic helical flow in BAV patients which was not found in any of the healthy volunteers or patients with a tricuspid aortic valve. We found a significant correlation, although weak, between aortic peak velocity at baseline and progression of aortic dilatation. The high aortic peak velocity with concomitant turbulence in the aortic root and in the tubular portion of the ascending aorta may be one of the mechanisms in the development of aortic dilatation [27]. Although we indeed expect this to be a cause-effect relation, we cannot exclude a genetic origin based on these findings, as both severity of aortic stenosis and aortic dilatation may be just an effect of time. Our study is the first to identify a relationship between the severity of the aortic stenosis and the rate of progression of the dilatation of the tubular portion of the thoracic aorta. This is still not overwhelming evidence, and more studies on long-term outcome in native BAV patients and patients after isolated aortic valve replacement are needed to understand better the underlying mechanism of aortic dilatation. This is clinically relevant as it will influence the surgical techniques employed and the frequency of aortic screening [28,29].

Diagnostic management of BAV patients

In BAV patients diameters of aortic root and tubular ascending aorta should be monitored periodically due to the increased risk of developing concurrent ascending aortic aneurysm that may require surgical repair [30]. Transthoracic echocardiography (TTE) is a widely used, non-invasive imaging investigation, but the mid ascending aorta can be difficult to examine with ultrasound. In recent guidelines of the European Society of Cardiology the use of CMR is suggested as the first line investigation for the assessment of aortic diameters as a guide for the therapy of the patient [31]. It has been proven that measurements of the diameters of the entire thoracic aorta can be performed accurately with SSFP technique with high contrast between vessels and surrounding tissues with good intra- and inter-observer variability [32]. In addition CMR can provide other information such as reliable judgment of systolic and diastolic LV function, valve assessment, aortic distensibility and pulse wave velocity.

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Limitations

This study has some limitations that are either related to our study design or are more general limitations of CMR technology.

Study design. Firstly, the number of patients enrolled in the study was small and 3-year follow-up was relatively short. Secondly, we decided to include only BAV patients with AoS, so our findings cannot be translated to BAV patients without stenosis. In addition, the exclusion of patients who underwent surgery may have led to an underestimation of the incidence and rate of progression of aortic dilatation. Finally, we did not look at the different BAV morphologies or at the specific dilatation pattern, which may play a role in the haemodynamic theory of BAV-aortopathy [33,34].

CMR technology. Although several validation studies have shown that anterograde velocity as measured by CMR correlates well with TTE, CMR has a trend to underestimate the aortic peak velocity and the mean pressure gradient [35,36]. Moreover, differently from cardiac CT, CMR does not provide information of valvular and aortic calcifications [33].

Conclusion

Our study demonstrates that in adult asymptomatic patients with BAV and AoS there is a progressive increase of aortic diameters over time, which is maximal at the level of the tubular portion of the ascending aorta. The weak correlation between the progression of aortic dilatation and AoS severity partially supports the hemodynamic theory of causation of the aortopathy associated with BAV.

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Ascending aortic diameters in congenital aortic stenosis: cardiac magnetic resonance versus transthoracic echocardiography

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Echocardiography. E-pub 11 Jan 2013.

Abstract

Objectives/background

Congenital aortic stenosis (AS) is the most common obstructive left heart lesion in the young adult population and often complicated by aortic dilatation. Our objective was to evaluate accuracy of aortic imaging with transthoracic echocardiography (TTE) compared to cardiac magnetic resonance (CMR).

Methods

Aortic diameters were measured at 4 levels by CMR and TTE. Agreement and concordance were assessed by Pearson's correlation and Bland-Altman analysis.

Results

Fifty-nine patients (age 33±8 years; 66% male) with congenital AS and a bicuspid aortic valve (BAV) were included. Aortic diameters were generally smaller with TTE than with CMR. The best correlation was found at the level of the sinotubular junction (R^2 = 0.78) with a bias of 1.46 mm (limits of agreement: -5.47 to +8.39 mm). In patients with an aortic aneurysm >40 mm (n=29) the correlation and agreement between TTE and CMR were found to be less good when compared to patients with normal aortic diameters, especially at the level of the proximal ascending aorta. The correlation and agreement between both imaging modalities was better in patients with type 1 BAV compared to type 2 BAV. Intra- and interobserver variability was smaller with CMR (1.8-5.9%) compared to TTE (6.9-15.0%).

Conclusions

CMR was found to be superior to TTE for imaging of the aorta in patients with congenital AS, especially at the level of the proximal ascending aorta when an aortic aneurysm is present. Therefore, ideally CMR should be performed at least once to ensure an ascending aortic aneurysm is not missed.

Background

Congenital valvular aortic stenosis (AS) is responsible for approximately 4% of all congenital heart defects [1]. The underlying cause for congenital AS is usually a bicuspid aortic valve (BAV), which is strongly associated with aortic dilatation [2,3]. Since both the valve and the aorta can be affected, active surveillance of both structures is indicated. Stringent follow-up is necessary to determine the optimal timing of surgical replacement of the aortic valve and/or ascending aorta [4]. Two-dimensional transthoracic echocardiography (TTE) has become the clinical standard for evaluation of AS severity [5]. Recent ESC guidelines consider cardiac magnetic resonance (CMR) superior to TTE for imaging of the ascending aorta [6]. However, no study has ever focused on agreement between both imaging techniques at the various aortic levels in this patient group.

The purpose of the present study was to evaluate correlation and agreement between CMR and TTE measurements of aortic diameters in young adult patients with congenital AS.

Methods

We prospectively included asymptomatic adult patients with congenital valvular AS who visited the outpatient clinic for Adult Congenital Heart Disease of the Erasmus Medical Center Rotterdam and Radboud University Nijmegen Medical Center. Inclusion criteria were: age 18-50 years, BAV and peak aortic velocity >2.5 m/s based on echocardiographic measurements. Patients with general contraindications for CMR (pacemaker, metallic implants or claustrophobia), previous aortic valve replacement, or concomitant severe mitral or aortic regurgitation were excluded. Patients underwent TTE and CMR on the same day. The study protocol was approved by the Medical Ethics Committee, and all patients gave written informed consent.

Cardiac magnetic resonance

CMR imaging was performed using a 1.5T scanner (Signa Discovery 450, GE Healthcare, Milwaukee, Wisconsin). The patient was placed in supine position and a dedicated cardiac coil was placed on the thorax of the patient. CMR image acquisitions and analyses were performed by an experienced investigator blinded to TTE results.

Cine magnetic resonance long axis 3-chamber view images were obtained using a breath-holding electrocardiogram triggered balanced steady state free precession (SSFP) pulse sequence for a standard ventricular function examination. The parameters of the SSFP sequence were: field of view 360-400 x 280-320 mm^2; matrix 224 x 196; repetition time: 3.4 ms; echo time: 1.5 ms; flip angle: 45 degrees; 12 views per segment; slice thickness 8 mm; gap of 2 mm; temporal resolution 41 ms. CAAS-MRV (version 3.1; Pie Medical Imaging, Maastricht, The Netherlands) was used for the left ventricular function evaluation.

End-diastolic tubular ascending aortic diameters were measured in the oblique sagittal view (Figure 1A). End-diastolic internal aortic diameters were measured at three levels in the 3-chamber view images: aortic annulus, sinus of Valsalva and sinotubular junction (Figure 1B). At each level the measurement was taken perpendicular to the long axis of the aorta.

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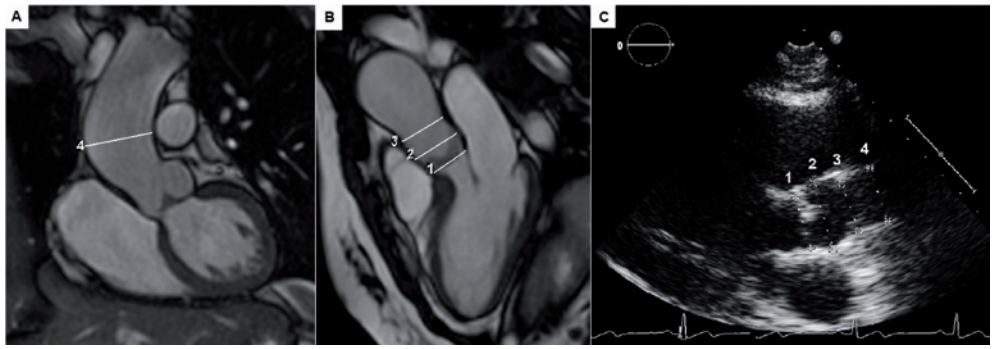

Figure 1. *Aortic measurements.*

Multimodality imaging of the aorta showing measurements of the aortic diameters at the level of the aortic annulus (1), sinus of Valsalva (2), sinotubular junction (3) and ascending aorta (4) by (A, B) cardiac magnetic resonance (the oblique sagittal and 3-chamber view) and (C) two-dimensional transthoracic echocardiography (parasternal long-axis view).

Transthoracic echocardiography

TTE examinations were performed and analyzed by experienced sonographers (blinded to CMR data) using commercially ultrasound systems (Sonos 7500, iE33 and iE33 xMATRIX X5-1, Philips Medical Systems, Best, The Netherlands). According to EAE/ASE guidelines, AS severity was evaluated by peak aortic velocity, mean transaortic gradient and continuity equation aortic valve area [5]. The end-diastolic diameter of the aortic valve annulus, sinus of Valsalva, sinotubular junction and proximal ascending aorta were measured from leading edge to leading edge in the parasternal long-axis view (Figure 1C). An aortic aneurysm was defined as a diameter of >40 mm in one or more aortic diameter measurements. BAV morphology was determined in the parasternal short-axis view according to the orientation of the commissures [7,8]. Type 1 BAV is a fusion of the right and left coronary cusps. In type 2 BAV the non-coronary and right coronary cusps are fused. Type 3 BAV involves a fusion of the non-coronary and left coronary cusps.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences, version 19.0 (SPSS, Chicago, Illinois) and GraphPad, version 5.0 (GraphPad Software, Inc, La Jolla, California). Significance was defined as $p<0.05$. Continuous data are expressed as mean ± standard deviation (SD). Categorical variables are summarized by the use of frequency and percentage. The normality of the data was verified with a Shapiro-Wilk test and histograms. Correlations between CMR and TTE measurements were assessed by linear regression analysis and Pearson's correlations. Bland-Altman analysis was used to determine bias (mean of the difference) with 95% limits of agreement (± 1.96 SD) [9]. To compare aortic diameters measured with both imaging modalities, a paired Student's t-test was performed. The reproducibility of the TTE and CMR measurements was evaluated in 25 randomly selected patients. We expressed the intra-observer and inter-observer variability by the coefficient of variation (CV), which is defined as the SD of the difference between the two readings (or readers) divided by their mean value, times 100.

Results

Fifty-nine patients with congenital AS were included in this study and completed the imaging protocols without difficulty. All patients were in sinus rhythm and New York Heart Association Class I. Patient characteristics are reported in Table 1.

Table 1. *Patient characteristics*

	Patients (n=59)
Age (years)	33 ± 8
Male gender, n(%)	39 (66)
Systolic blood pressure (mmHg)	132 ± 15
Diastolic blood pressure (mmHg)	76 ± 9
Body surface area (m^2)	1.94 ± 0.25
Peak aortic valve velocity (m/s)	3.6 ± 0.8
Ejection fraction (%) *	58 ± 7
Left ventricular mass (g) *	133 ± 40
Aortic aneurysm (>40 mm), n (%)	29 (49.2)
Bicuspid aortic valve morphology, n (%) †	
Type 1 (fusion right and left coronary cusp)	28 (47.5)
Type 2 (fusion non-coronary and right coronary cusp)	26 (44.1)
Aortic valve calcification, n(%) ‡	20 (34)
Aortic regurgitation, n(%) ‡	
None	38 (64)
Mild	11 (19)
Moderate	10 (17)
Severe	0 (0)

Data are presented as mean ± SD, or as n(%) when frequencies.
** Derived from cardiac magnetic resonance measurements.*
† In 5 patients the bicuspid aortic valve morphology could not be determined.
‡ Derived from transthoracic echocardiography measurements.

Figure 2 shows correlation and agreement for aortic diameter measurements by TTE and CMR. Aortic diameters measured by TTE were generally smaller than aortic diameters measured by CMR (Table 2). The best agreement was found at the aortic annulus level (bias 0.23 mm, limits of agreement: -6.47 to +6.94 mm; correlation $R^2 = 0.63$; Figure 2A,E). The best correlation was found at the level of the sinotubular junction ($R^2 = 0.78$) with a bias of 1.46 mm (limits of agreement: -5.47 to +8.39 mm) (Figure 2C,G). At the level of the sinus of Valsalva, the correlation and agreement were good ($R^2 = 0.73$; bias 1.02 mm, limits of agreement: -6.22 to +8.25 mm; Figure 2B,F). The agreement was least at the level of the proximal ascending aorta ($R^2 = 0.75$; bias 1.36 mm, limits of agreement: -8.70 to +11.42 mm; Figure 2D,H).

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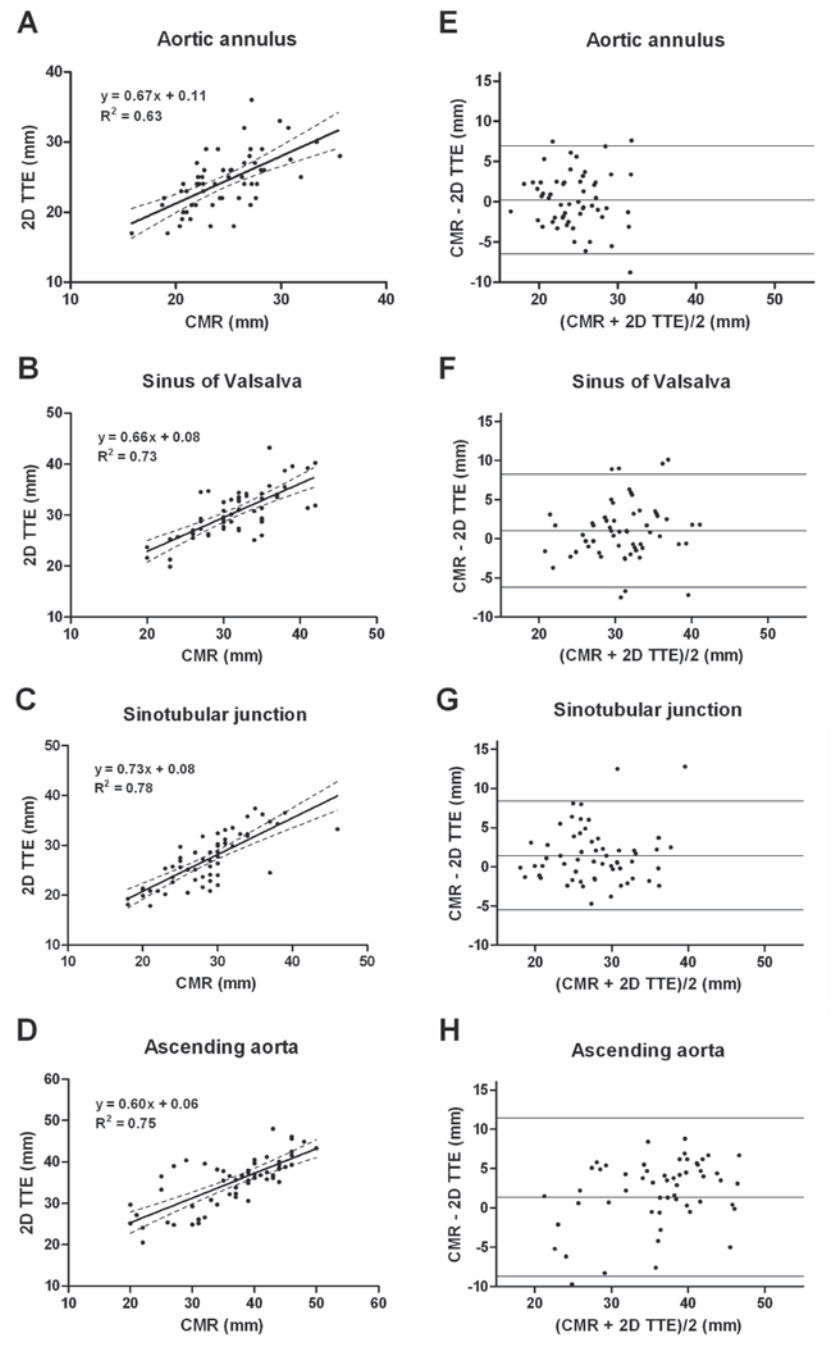

Figure 2. *Aortic diameters: comparison between CMR and TTE*

Comparison between cardiac magnetic resonance and two-dimensional transthoracic echocardiography measurements of aortic diameters at the level of the (A, E) aortic annulus, (B, F) sinus of Valsalva, (C, G) sinotubular junction and (D, H) ascending aorta, as shown by regression lines (left) and Bland-Altman plots (right).

Table 2. *Aortic diameters.*

	TTE	CMR	p-value
Aortic annulus (mm)	24.3 ± 4.1	24.5 ± 3.9	0.606
Sinus of Valsalva (mm)	30.6 ± 4.7	31.6 ± 5.2	0.041
Sinotubular junction (mm)	27.1 ± 5.2	28.5 ± 5.5	0.003
Ascending aorta (mm)	35.2 ± 6.2	36.6 ± 7.8	0.048

Data are presented as mean ± SD.
CMR = cardiac magnetic resonance; TTE = transthoracic echocardiography.

Patients with and without aortic aneurysm

Twenty-nine patients (49%) were found to have an aortic aneurysm (>40 mm in at least 1 of the measurement levels). Table 3 shows the results of the correlation and agreement between CMR and TTE in patients with and without an aortic aneurysm. Especially at the level of the proximal ascending aorta the correlation between both imaging techniques was lower in patients with an aortic aneurysms compared to patients with normal aortic diameters (respectively R^2=0.40 versus R^2=0.59;Table 3). Bland-Altman analysis shows that the bias and limits of agreement were also worse in patients with an aortic aneurysm as compared to patients without an aortic aneurysm (Table 3, Figure 3).

Table 3. *Correlation and agreement in patients with and without an aortic aneurysm.*

	No aneurysm n=30	Aneurysm (>40 mm) n=29
Annulus		
Diameter TTE versus CMR (mm)	22.7 ± 3.5 vs. 22.8 ± 2.7	25.9 ± 4.1 vs. 26.3 ± 4.1
P-value Diameter TTE versus CMR	p = 0.854	p = 0.619
Correlation	R^2 = 0.58	R^2 = 0.55
Bias (95% limits of agreement)	0.10 (-5.59 to 5.79)	0.37 (-7.31 to 8.04)
Sinus of Valsalva		
Diameter TTE versus CMR (mm)	28.7 ± 4.2 vs. 28.8 ± 4.5	32.5 ± 4.6 vs. 34.5 ± 4.3
P-value Diameter TTE versus CMR	p = 0.920	p = 0.008
Correlation	R^2 = 0.68	R^2 = 0.65
Bias (95% limits of agreement)	0.07 (-6.73 to 6.86)	1.97 (-5.34 to 9.27)
Sinotubular junction		
Diameter TTE versus CMR (mm)	24.4 ± 4.4 vs. 26.0 ± 4.2	29.8 ± 4.4 vs. 31.0 ± 5.5
P-value Diameter TTE versus CMR	p = 0.006	p= 0.110
Correlation	R^2 = 0.75	R^2 = 0.69
Bias (95% limits of agreement)	1.69 (-4.24 to 7.61)	1.23 (-6.67 to 9.13)
Ascending aorta		
Diameter TTE versus CMR (mm)	31.0 ± 5.5 vs. 31.2 ± 6.4	39.5 ± 3.5 vs. 42.0 ± 4.8
P-value Diameter TTE versus CMR	p = 0.808	p = 0.009
Correlation	R^2 = 0.59	R^2 = 0.40
Bias (95% limits of agreement)	0.24 (-10.27 to 10.76)	2.48 (-6.77 to 11.73)

Reported data are expressed as mean ± SD.
CMR = cardiac magnetic resonance, TTE= transthoracic echocardiography.

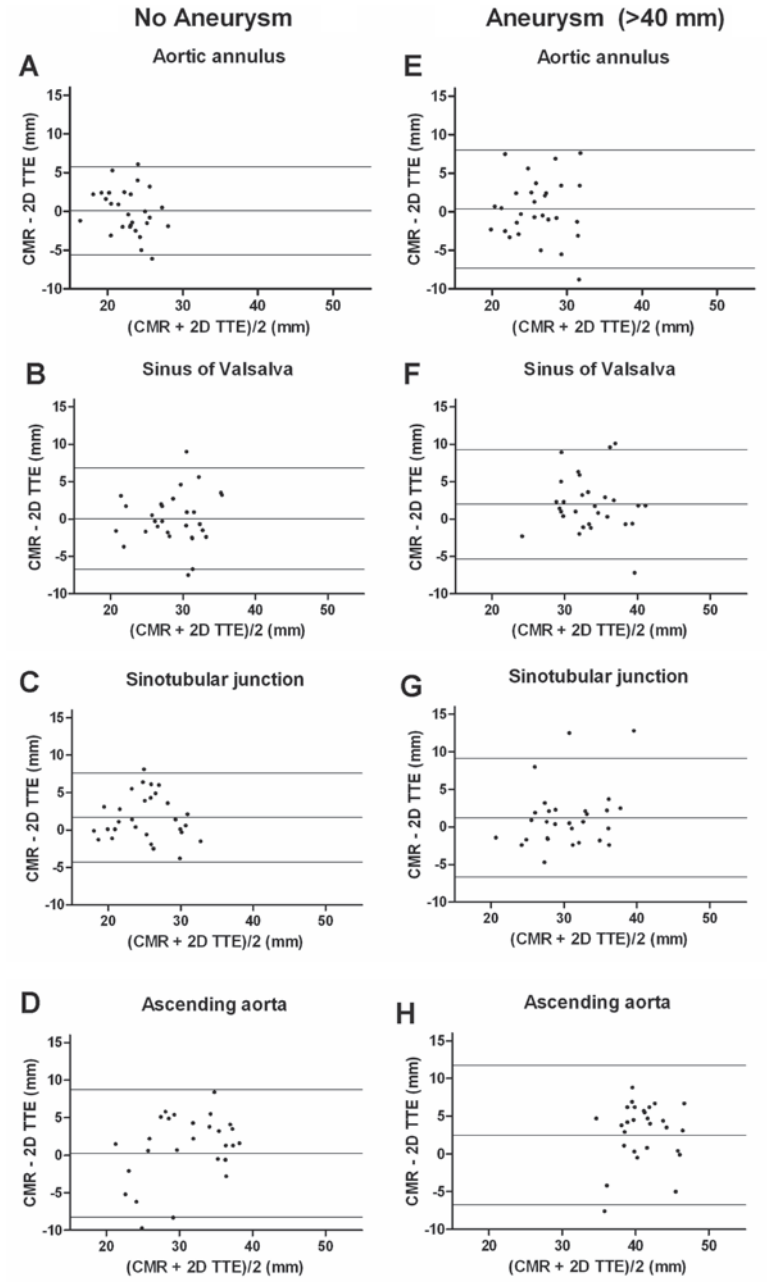

Figure 3. *Agreement between CMR and TTE in patients with normal aortic diameters and aneurysms.*

Bland-Altman plots demonstrating the comparison between cardiac magnetic resonance and two-dimensional transthoracic echocardiography measurements of aortic diameters at the level of the (A, E) aortic annulus, (B, F) sinus of Valsalva, (C, G) sinotubular junction and (D, H) ascending aorta, in patients with (right) and without (left) an aortic aneurysm.

Bicuspid aortic valve morphology

Twenty-eight patients were found to have a fusion of the right and left coronary cusp (Type 1 BAV) and 26 patients were found have a fusion of the non-coronary and right coronary cusp (Type 2 BAV). No patients exhibited a type 3 BAV. In 5 patients the BAV morphology could not be determined with certainty. In six patients with a type 2 BAV the aortic root showed marked asymmetry on the TTE short-axis view.

Table 4 and Figure 4 show the results of the correlation and agreement analyses between CMR and TTE comparing patients with type 1 and 2 BAV. The correlation and agreement between both imaging techniques was better in patients with type 1 BAV at all aortic levels.

Table 4. *Correlation and agreement according to bicuspid aortic valve morphology.*

	Type 1 BAV (fusion right and left coronary cusp) n=28	**Type 2 BAV (fusion non-coronary and right coronary cusp) n=26**
Annulus		
Diameter TTE versus CMR (mm)	22.4 ± 3.4 vs. 22.7 ± 3.1	26.2 ± 3.9 vs. 26.5 ± 3.7
P-value Diameter TTE versus CMR	p = 0.606	p = 0.718
Correlation	R^2 = 0.57	R^2 = 0.44
Bias (95% limits of agreement)	0.30 (-5.63 to 6.23)	0.28 (-7.61 to 8.19)
Sinus of Valsalva		
Diameter TTE versus CMR (mm)	29.6 ± 5.0 vs. 29.1 ± 4.3	33.5 ± 4.7 vs. 32.3 ± 4.8
P-value Diameter TTE versus CMR	p = 0.348	p = 0.169
Correlation	R^2 = 0.81	R^2 = 0.58
Bias (95% limits of agreement)	-0.54 (-6.26 to 5.18)	-1.20 (-9.68 to 7.28)
Sinotubular junction		
Diameter TTE versus CMR (mm)	26.5 ± 4.9 vs. 25.7 ± 5.1	30.7 ± 5.4 vs. 28.8 ± 4.6
P-value Diameter TTE versus CMR	p = 0.108	p= 0.034
Correlation	R^2 = 0.87	R^2 = 0.67
Bias (95% limits of agreement)	-0.82 (-5.86 to 4.21)	-1.82 (-9.94 to 6.30)
Ascending aorta		
Diameter TTE versus CMR (mm)	34.0 ± 8.7 vs. 32.8 ± 7.4	37.9 ± 6.1 vs. 36.8 ± 3.6
P-value Diameter TTE versus CMR	p = 0.181	p = 0.363
Correlation	R^2 = 0.85	R^2 = 0.33
Bias (95% limits of agreement)	-1.22 (-10.25 to 7.81)	-1.08 (-12.79 to 10.62)

Reported data are expressed as mean ± SD.
BAV = bicuspid aortic valve, CMR = cardiac magnetic resonance, TTE= transthoracic echocardiography.

Intra- and interobserver variability

The intra- and interobserver variability data are displayed in Table 5. Intra-observer variability was between 2.4 and 11.2%. Interobserver agreement demonstrated more variation and was between 1.8 and 15.0%. The highest variation was found at the level of the annulus (5.4-15%) and the smallest variation at the level of the proximal ascending aorta (1.8-8.2%). Variability was generally smaller with CMR (1.8-5.9%) compared to TTE (6.9-15.0%).

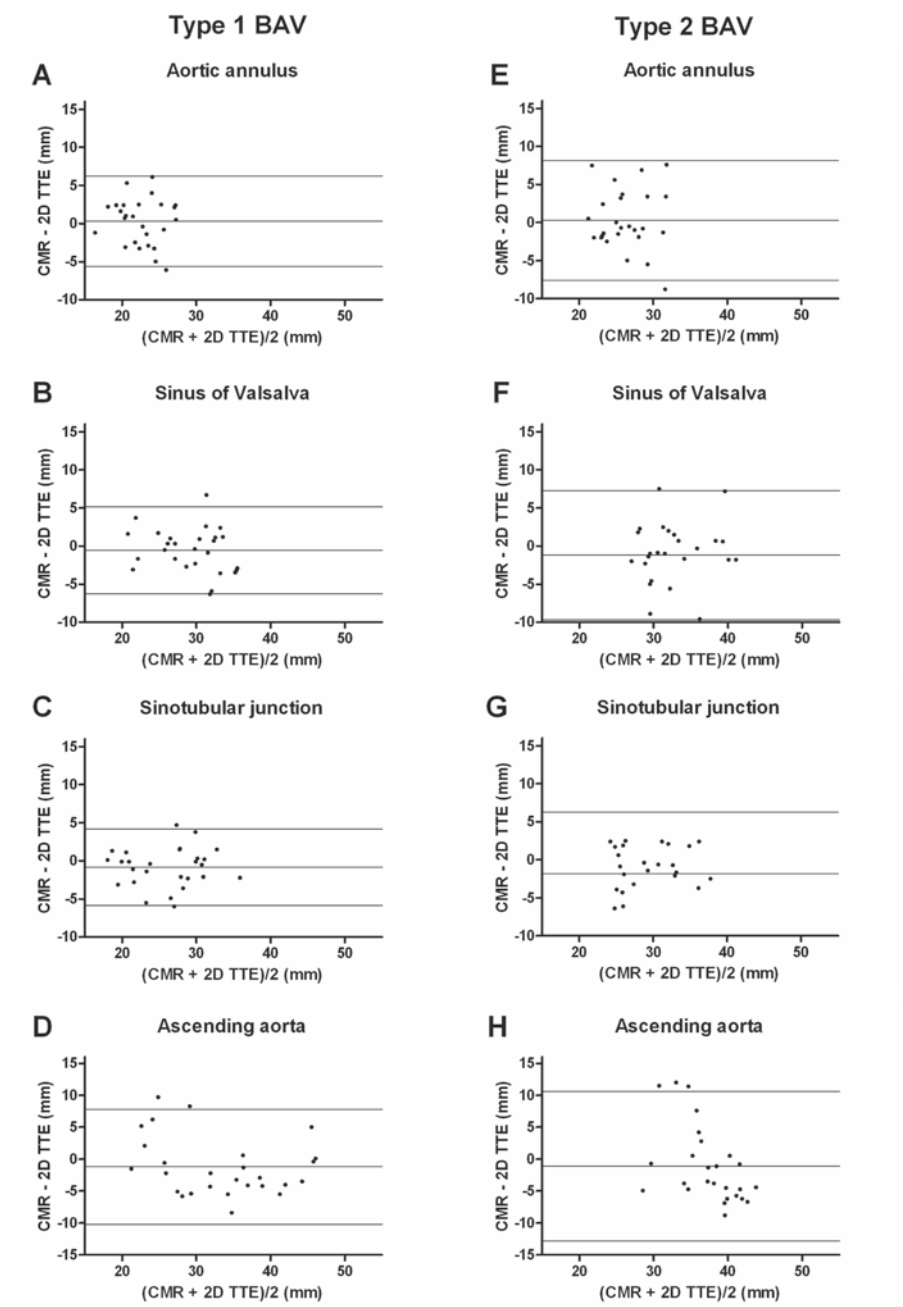

Figure 4. *Agreement between CMR and TTE according to bicuspid aortic valve morphology.*

Bland-Altman plots demonstrating the comparison between cardiac magnetic resonance and two-dimensional transthoracic echocardiography measurements of aortic diameters at the level of the (A, E) aortic annulus, (B, F) sinus of Valsalva, (C, G) sinotubular junction and (D, H) ascending aorta, in patients with type 1 (left) and type 2 (right) bicuspid aortic valve morphology.

Table 5. *Intra- and interobserver variability.*

	Intra-observer variability			Inter-observer variability		
	Mean difference ± SD	Mean value ± SD	CV	Mean difference ± SD	Mean value ± SD	CV
TTE						
Annulus	0.5 ± 2.4	24.5 ± 3.8	10.0%	1.6 ± 3.8	25.0 ± 4.1	15.0%
Sinus of Valsalva	0.1 ± 2.2	31.9 ± 5.4	6.9%	0.8 ± 2.8	32.3 ± 5.2	8.7%
Sinotubular junction	1.5 ± 3.2	28.2 ± 4.8	11.2%	1.7 ± 3.9	28.2 ± 5.1	13.8%
Ascending aorta	1.1 ± 3.0	37.2 ± 6.3	7.9%	0.1 ± 3.0	36.6 ± 6.6	8.2%
CMR						
Annulus	0.3 ± 1.4	24.2 ± 2.8	5.9%	0.1 ± 1.3	23.9 ± 3.1	5.4%
Sinus of Valsalva	0.1 ± 0.8	30.1± 4.0	2.7%	0.1 ± 1.4	26.5 ± 4.8	5.3%
Sinotubular junction	0.2 ± 0.7	26.8 ± 4.8	2.6%	0.4 ± 1.0	29.9 ± 4.3	3.5%
Ascending aorta	0.1 ± 0.9	36.8 ± 5.2	2.4%	0.1 ± 0.7	36.9 ± 5.3	1.8%

Reported data are expressed as mean ± SD. Coefficient of variability (CV): expressed as a percentage of the SD of the difference divided by the mean of the two measurements. Aortic diameters are measured in mm.
CMR = cardiac magnetic resonance; CV = coefficient of variability; SD = standard deviation; TTE = transthoracic echocardiography.

Discussion

The present study systematically investigated correlation and concordance of aortic diameters at different levels using CMR and TTE as imaging modalities in patients with congenital AS due to BAV disease. The results demonstrated that although there seems to be good concordance between both imaging modalities, aortic diameter measurements are slightly smaller (approximately 1 mm) with TTE compared to CMR. In general, the agreement between both imaging techniques was quite good, but least at the level of the proximal ascending aorta, especially in patients with an aortic aneurysm. Measurement reproducibility was better with CMR than with TTE.

Aortic diameter assessment in BAV: which method to use?

Aortic dilatation in BAV disease is especially present at the level of the ascending aorta [10-13]. Therefore, it is of uttermost importance to correctly visualize and measure this part of the aorta. This study clearly showed that the correlation and agreement between CMR and TTE were quite good in patients with normal aortic diameters. Intra- and inter observer variability were better with CMR. These findings confirm several studies in other patient populations [14-19]. However, in patients with an aortic aneurysm >40 mm, the correlation and agreement between both imaging modalities were worse, especially at the level of the proximal ascending aorta. This phenomenon might be explained by the fact that in patients with an ascending aortic aneurysm, TTE acoustic windows might be suboptimal and transection planes incorrect.

In addition, BAV morphology seemed to influence the accuracy of aortic diameters. The correlation and agreement between CMR and TTE were better at all levels in patients with a type 1 BAV as compared to patients with a type 2 BAV. An explanation for this finding might be that the aortic diameters tended to be larger in patients with type 2 BAV as compared to type 1 BAV. Furthermore, we hypothesize that the difference in accuracy according to BAV morphology could be due to the fact that 6 patients in the type 2 BAV group exhibited marked aortic root asymmetry, while none of the patients with a type 1 BAV exhibited marked aortic root asymmetry. The noncircular geometry could be a problem for the aortic measurements in the parasternal long-axis view, because 2D TTE cannot guarantee crossing in the center or prevent oblique transections. Unfortunately our group of 6 patients with aortic root asymmetry was too small to accurately test our hypothesis or draw firm conclusions. Further studies focusing on comparing CMR and TTE in patients with and without aortic root asymmetry are warranted.

Study limitations

The limited sample size is an evident limitation of this study. Furthermore, we did not assess a true gold standard for aortic measurement, which is considered to be direct perioperative measurement. Acoustic shadowing artifact created by aortic valve calcification was not controlled for and could have limited the accuracy and available acoustic windows of TTE. Furthermore, we have to acknowledge that the proximal ascending aorta was measured in the left-right dimension by CMR and in the anterior-posterior dimension by TTE. Since the ascending aorta is typically symmetric, this probably did not affect our results to a large extent. Finally, the results of this study specifically address adult patients with congenital AS and BAV disease, and may not be generalizable to degenerative, calcific AS.

Clinical recommendations

Correct imaging of the aorta is crucial in clinical decision making process regarding surgical interventions in BAV and associated aortic aneurysms [4]. Elective aortic surgery is advised when the aortic diameter reaches 50 mm to avoid acute dissection or rupture [4]. Our study confirms recent ESC guidelines for grown-up congenital heart disease stating that CMR is mainly required to assess aortic dilatation when occurring distal to the sinotubular junction [6]. Thus, when available, CMR should be used at least once in all BAV patients to exclude presence of an ascending aortic aneurysm and might also be the preferred method for follow-up when an aortic aneurysm is suspected and/or confirmed.

For this young asymptomatic patient population computed tomography or transesophageal echocardiography are generally not considered first choice because of the disadvantage of respectively radiation exposure and invasiveness, but there might be a role for three-dimensional TTE [20,21].

Because of certain disadvantages of CMR (contraindicated use in patients with claustrophobia and metallic implants, prolonged duration of imaging acquisition, higher costs and often limited availability), echocardiography is often the most pragmatic choice in routine clinical practice. When availability of CMR is limited, we advise to perform both TTE and CMR at baseline and assess agreement between both techniques in respect to aortic diameter measurements at all 4 levels in the individual patient.

When both imaging techniques agree well and aortic diameter is <40 mm, TTE can be used for regular follow-up. In case of good agreement and an aortic diameter >40 mm, we suggest to repeat CMR at least every 4 years. In case TTE and CMR show poor agreement in that individual patient (>5 mm difference), TTE cannot be used as a reliable tool to assess aortic diameter. In these patients, CMR should be the preferred method for follow-up of aortic diameters; once every 3 to 4 years when aortic diameter is <40 mm, every 1 to 2 years when aortic diameter is >40 mm, and even more frequently when the diameter approaches 50 mm.

Conclusions

In patients with congenital AS, aortic diameter measurements are slightly smaller with TTE compared to CMR and the reproducibility of CMR is better. Agreement between both imaging modalities is good in patients with normal aortic diameters, however poor in patients with an aortic aneurysm. In addition, the agreement between CMR and TTE seems to be lower in patients with a type 2 BAV morphology.

Since BAV associated aortic dilatation mainly occurs at the ascending aortic level, CMR should be performed at least once to ensure that an aortic aneurysm at this level is not missed and might be the preferred method for aortic aneurysm follow-up.

Acknowledgements

We thank the patients and technician assistants from participating centers.

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PART V

Familial thoracic aortic aneurysms and dissections; a new syndrome

“Dit is de laatste foto van ons vieren”

“Deze foto is gemaakt in de bossen bij Ibbenbüren, Duitsland, op 4 april 1982, de dag waarop ons gezin vierde dat mijn moeder precies 70 jaar eerder in Ibbenbüren geboren was. Omdat wij weinig foto’s van de vier broers samen hadden, leek het wel leuk om deze foto toen goed te maken. Niet wetende dat deze foto de laatste van ons vieren zou zijn: mijn broer Ed (2e van links) overleed drie jaar later plotseling op 34-jarige leeftijd, Huub (rechts) nog geen twee maanden later op 40-jarige leeftijd, en Paul (2e van rechts) in 1993 op 44-jarige leeftijd. Voor mij (links met sigaar in de hand, en dat terwijl ik als enige van de vier nog nooit gerookt heb!), onlangs 60 jaar geworden, is daarom deze foto zeer dierbaar: als herinnering aan die bijzondere dag én als herinnering aan mijn drie te jong overleden broers. Pas onlangs hebben artsen ontdekt dat een deel van onze familie aan het Aneurysma-Osteoarthritis Syndroom lijdt.”

André Schröder, Rotterdam 2012

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Aggressive cardiovascular phenotype of Aneurysms-Osteoarthritis syndrome caused by pathogenic *SMAD3* variants

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J Am Coll Cardiol. 2012;60:397-403.

Abstract

Objectives

The purpose of this study was to describe the cardiovascular phenotype of the aneurysms-osteoarthritis syndrome (AOS) and to provide clinical recommendations.

Background

AOS, caused by pathogenic *SMAD3* variants, is a recently described autosomal dominant syndrome characterized by aneurysms and arterial tortuosity in combination with osteoarthritis.

Methods

AOS patients in participating centers underwent extensive cardiovascular evaluation, including imaging, arterial stiffness measurements, and biochemical studies.

Results

We included 44 AOS patients from 7 families with pathogenic *SMAD3* variants (mean age: 42 ± 17 years). In 71%, an aortic root aneurysm was found. In 33%, aneurysms in other arteries in the thorax and abdomen were diagnosed, and in 48%, arterial tortuosity was diagnosed. In 16 patients, cerebrovascular imaging was performed, and cerebrovascular abnormalities were detected in 56% of them. Fifteen deaths occurred at a mean age of 54 ± 15 years. The main cause of death was aortic dissection (9 of 15; 60%), which occurred at mildly increased aortic diameters (range: 40 to 63 mm). Furthermore, cardiac abnormalities were diagnosed, such as congenital heart defects (6%), mitral valve abnormalities (51%), left ventricular hypertrophy (19%), and atrial fibrillation (22%). N-terminal brain natriuretic peptide (NT-proBNP) was significantly higher in AOS patients compared with matched controls ($p < 0.001$). Aortic pulse wave velocity was high-normal (9.2 ± 2.2 m/s), indicating increased aortic stiffness, which strongly correlated with NT-proBNP ($r = 0.731$, $p = 0.005$).

Conclusions

AOS predisposes patients to aggressive and widespread cardiovascular disease and is associated with high mortality. Dissections can occur at relatively mildly increased aortic diameters; therefore, early elective repair of the ascending aorta should be considered. Moreover, cerebrovascular abnormalities were encountered in most patients.

Introduction

Aortic aneurysms and dissections were ranked as the nineteenth most common cause of death in the United States in 2007 (1). The true incidence is probably much higher, because many aortic aneurysms are silent. Thoracic aortic aneurysms and dissections (TAADs) often are found in the context of genetic syndromes, such as Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS), but also are associated with bicuspid aortic valves (2-4). MFS is one of the most common hereditable connective tissue disorders, with abnormalities predominantly in the skeletal, ocular, pulmonary, and cardiovascular systems (2). LDS shows some similarities with MFS, but exhibits widespread arterial aneurysms and tortuosity (3).

Recently, our group found that pathogenic *SMAD3* variants cause aneurysms-osteoarthritis syndrome (AOS) (5). AOS is inherited as an autosomal dominant disorder and is found to be responsible for 2% of familial TAADs (5,6). Aneurysms, dissections, and tortuosity throughout the arterial tree are the main cardiovascular features (5). In addition, early-onset osteoarthritis is present in almost all patients and often is the first reason to seek medical advice (5). Mild craniofacial abnormalities, such as hypertelorism and bifid uvula, also are associated with AOS (5). Furthermore, umbilical or inguinal hernias, or both; varices; velvety skin; and striae are common findings (5). The purpose of this study was to describe the cardiovascular consequences of AOS and to provide clinical recommendations.

Methods

From 2009 onward, all AOS patients with a pathogenic *SMAD3* variant in participating centers were included in this ongoing cohort study. Genetic identification methods have been described previously (5). Patients underwent comprehensive clinical evaluation, including risk factor assessment, physical examination, biochemical measurements, 12-lead electrocardiography, transthoracic echocardiography (TTE), and computed tomography angiography (CTA) of the thorax and abdomen. For logistical reasons, not all examinations could be performed in every patient. In a subset of patients, CTA of the cerebral vessels and arterial stiffness measurements also were performed. These methods are described extensively in the Online Appendix. Patients were monitored for occurrence of cardiovascular events, especially dissection or mortality. Autopsy was requested in case of death and was performed when possible. Biochemical and arterial stiffness measurements were compared 1-to-1 with age-, sex-, and smoking status-matched controls. Apparently healthy controls were recruited among hospital personnel and their acquaintances and underwent only biochemical and arterial stiffness measurements and smoking status assessment. The study was approved by the Institutional Review Board and Ethical Committee of the Erasmus Medical Center in Rotterdam. Written informed consent was obtained from each patient.

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Data analysis

SPSS software version 15.0 (SPSS, Inc., Chicago, Illinois) was used for the statistical analyses. A p value of <0.05 was considered statistically significant. The 1-sample Kolmogorov-Smirnov test and histograms were used to check normality. Normally distributed continuous data are presented as mean ± SD, and categorical variables are presented as frequency (n) and percentages. Non-normal distributed data are presented as median with interquartile range (25th and 75th percentiles). For comparison between the control and patient groups, a Student *t* test taking into account the 1-to-1 pairing or the signed-rank Wilcoxon test was used. Biochemical measurements also were compared with reference values from the clinical chemical laboratory of the Erasmus Medical Center in Rotterdam. For correlation analysis, the Pearson r correlation coefficient and Spearman correlation test were used.

Results

We here describe the cardiovascular features of 44 AOS patients from 7 families. Genetic mutations are specified in Online Table 1. Twenty-seven patients from 3 families were described previously in brief in the first report on AOS (5). Table 1 presents the baseline characteristics of the study population. Two patients (62 and 64 years of age) had hypertension and used antihypertensive drugs.

Table 1. *Baseline characteristics.*

Covariates	AOS patients (n=44)
Age, years	42 ± 17
Male, n (%)	24 (55)
Height, cm	181 ± 13
Weight, kg	78 ± 15
Body mass index, kg/m^2	24 ± 4
Blood pressure, mmHg	
Systolic blood pressure	124 ± 14
Diastolic blood pressure	74 ± 8
Mean arterial pressure	92 ± 11
Oxygen saturation, %	98 ± 1
Smoking, n (%) *	
Never	24 (73)
Current	6 (18)
Former	3 (9)
Creatinine, µmol/l *	72 ± 11

Values are mean ± SD or n(%). AOS indicates Aneurysms-Osteoarthritis Syndrome.
** Smoking status and creatinine measurements could only be obtained from 33 patients.*

Survival

Fifteen deaths in AOS patients with confirmed pathogenic *SMAD3* variants occurred at a mean age of 54 ± 15 years. Autopsy confirmed an aortic dissection as cause of death in 6 patients. In the 9 other patients, no autopsy was performed, but 3 patients were known previously to have aortic aneurysms or dissections. Causes of death with age at time of death are specified in Online Table 1. No intracranial hemorrhage as the cause of death has been reported.

Aneurysms, dissections, and arterial tortuosity in the thorax and abdomen

In 27 (71%) of 38 patients, an aortic root aneurysm was found (range: 36 to 63 mm, z-score: 2.9 to 13.2) (Figure 1A, Online Video 1, Online Figures 1 and 2). For 6 patients, we did not have aortic dimension data because they died before TTE or CTA could be performed. In 8 (33%) of 24 patients, aneurysms in other arteries in the thorax and abdomen were diagnosed: descending thoracic and abdominal aorta (100 mm), pulmonary trunk (50 mm), superior mesenteric, splenic (40 mm), celiac, hepatic, and common, external and internal iliac arteries (80 mm) (Figure 1B, detailed information in Online Table 1, Online Figures 3 and 4). Arterial tortuosity throughout the great vessels of the abdomen and thorax was present in 48% (11 of 23) (Online Video 2).

Mean aortic diameters measured by CTA and TTE are shown in Table 2. The aorta was dilated most often at the level of the sinus of Valsalva. CTA aortic diameter measurements correlated well with TTE (sinus of Valsalva: $r = 0.939$, $p < 0.001$). Two (33%) of 6 evaluated children had aortic diameter *z*-scores that were higher than the normal range according to age (*z* + 2.9 in a 16-year-old boy and *z* + 3.3 in a 15-year-old girl).

Thirteen patients with a mean age of 46 ± 10 years were diagnosed with 1 or more aortic dissections. Stanford type A aortic dissection was diagnosed in 11 patients (Figure 1A, Online Figure 2). In 8 patients, this was the first manifestation of the disease. Range of sinus of Valsalva diameter measured before aortic root dissection occurred was 40 to 63 mm (reliable aortic measurements before dissection were available only for 5 patients). Stanford type B aortic dissection was diagnosed in 2 patients (Figure 1B, Online Video 3, Online Figure 3). In addition, 2 patients were diagnosed with both a type A and B dissection at different time points. None of these aortic dissections occurred during the 23 pregnancies and deliveries in our AOS cohort. In 1 patient, a dissection in a nondilated proximal left anterior descending coronary artery was found.

Elective cardiovascular operations and interventions

Fifteen patients underwent 1 or more elective cardiovascular interventions at a mean age of 41 ± 11 years: 12 valve-sparing aortic root replacements, 1 Bentall procedure, 2 splenic artery coiling procedures, and 1 abdominal aneurysm repair; 1 patient underwent aortic repair surgeries in thorax and abdomen and mitral valve repair. In 2 patients, postoperative complications occurred: 1 patient had painful splenic ischemia for which reoperation was necessary and another patient had a total atrioventricular block after valve-sparing aortic root replacement, for which pacemaker implantation was necessary.

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Table 2. *Outcome measurements.*

Covariates	AOS patients
Electrocardiography (n=31)	
Heart rate, bpm	67 ± 12 (50 – 90)
PR-interval, msec	159 ± 24 (136 – 204)
QRS-duration, msec	101 ± 10 (90 – 118)
Echocardiography (n=31)	
Left atrial diameter, mm	37 ± 5 (26 – 49)
Interventricular septal thickness, mm	10 ± 2 (9 – 15)
Left ventricular posterior wall thickness, mm	10 ± 2 (8 – 14)
Left ventricular wall mass, gram	204 ± 75 (135 – 342)
Left ventricular end-diastolic diameter, mm	52 ± 8 (40 – 64)
Left ventricular end-systolic diameter, mm	33 ± 5 (25 – 42)
Fractional shortening, %	36 ± 7 (28 – 48)
Peak E velocity, m/s	0.6 ± 0.2 (0.3 – 0.9)
Peak A velocity, m/s	0.5 ± 0.1 (0.3 – 0.7)
Transmitral E/A ratio	1.5 ± 0.5 (0.5 – 2.2)
E wave decelaration time, msec	233 ± 82 (134 – 420)
Aortic diameters, mm	
Annulus	26.8 ± 3.1 (20 – 31)
Sinus of Valsalva	40.1 ± 8.2 (30 – 50)
Sinotubular junction	31.9 ± 4.8 (27 – 38)
Proximal ascending aorta	32.8 ± 4.5 (27 – 46)
Computed tomography angiography (n = 38)	
Aortic diameters, mm	
Annulus	29.8 ± 5.9 (23 – 38)
Sinus of Valsalva	41.4 ± 8.2 (30 – 63)
Sinotubular junction	32.0 ± 4.9 (27 – 38)
Ascending thoracic aorta	32.4 ± 5.2 (28 – 39)
Aortic arch	25.6 ± 5.4 (19 – 34)
Descending thoracic aorta	24.9 ± 4.5 (20 – 32)
Diaphragmatic level aorta	22.2 ± 5.0 (16 – 28)
Abdominal aorta	22.3 ± 5.3 (15 – 100)

Values are mean ± SD (absolute range). E/A = early/late atrial velocity. Other abbreviations as in Table 1.

Aneurysms and tortuosity of brachiocephalic and intracranial vasculature

CTA of the brachiocephalic and intracranial vasculature was performed in 16 patients with a mean age of 37 ± 14 years. In 56% (9 of 16), we found cerebrovascular abnormalities (detailed information in Online Table 2). Six patients (38%) were diagnosed with 1 or more intracranial aneurysms (Figure 1C, Online Figures. 5 and 6). Tortuosity of brachiocephalic and intracranial vessels was found in 50% (8 of 16) of the patients (Figure 1C, Online Video 4, Online Figure 7). Thirty-one percent of patients (5 of 16) had a combination of aneurysms and tortuosity. In addition, 1 patient showed multiple caliber changes of both intracranial and extracranial vessels.

In 7 patients, no cerebrovascular abnormalities were found. Two patients were reported to have had a nonfatal stroke at 56 and 76 years of age, respectively, but it is unclear from their medical histories whether these were ischemic or hemorrhagic strokes.

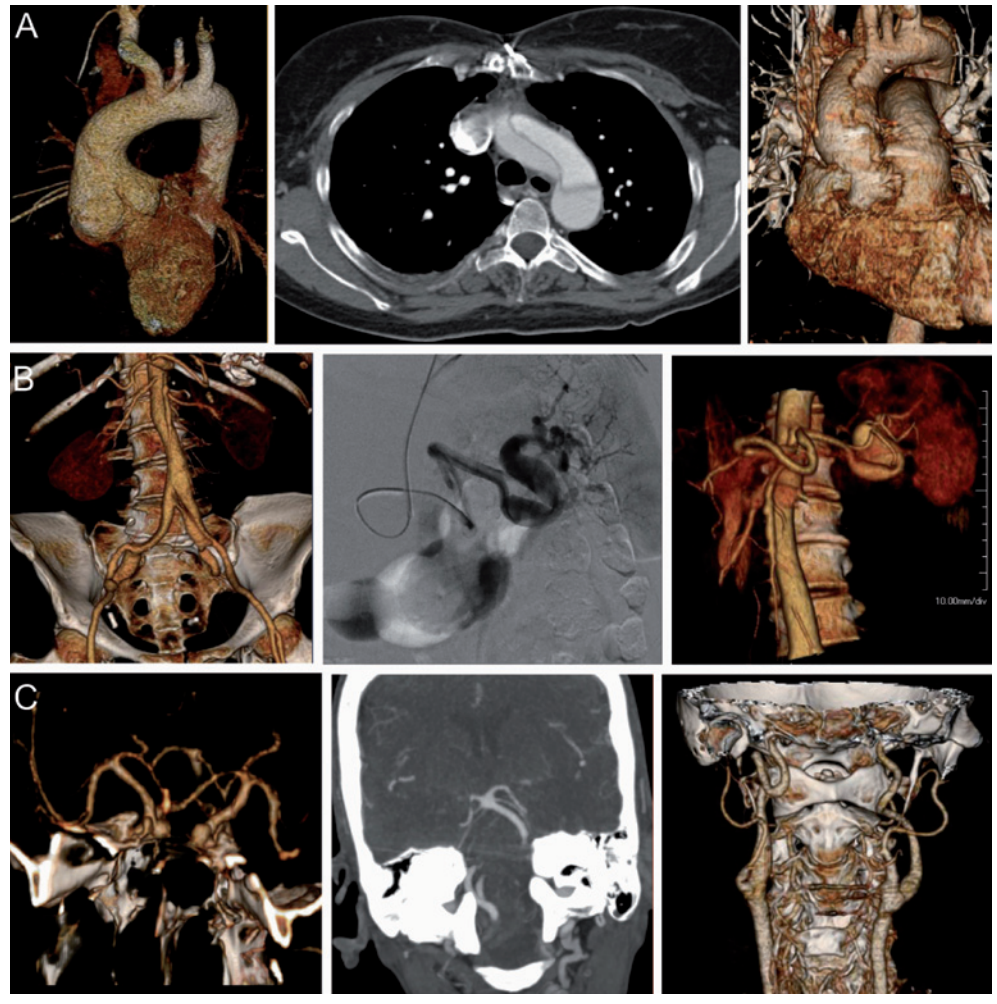

Figure 1. *Cardiovascular Abnormalities throughout the Body in Patients with Aneurysms-Osteoarthritis Syndrome*

***(A)** Thorax: **(left)** aneurysm of the aortic root (54 mm) in 31-year-old man, and **(middle and right)** Stanford type A aortic dissection at a maximal aortic diameter of 40 mm in a 50-year-old woman.*
***(B)** Abdomen: **(left)** aortic dissection at a maximal abdominal aortic diameter of 24 mm with dissection flap extending into the left common iliac artery (true lumen in internal iliac artery and false lumen in external iliac artery) and aneurysm in the right common iliac artery (27 mm) and right external iliac artery (16 mm) in 45-year-old woman; **(middle and right)** tortuosity and aneurysm in left splenic artery (21 mm) in the same 45-year-old woman.*
***(C)** Head and neck: **(left)** 2 saccular aneurysms in the left and right carotid siphon in a 31-year-old man; **(middle)** fusiform aneurysm of the top of the basilar artery in a 26-year-old man; and **(right)** tortuosity of the internal carotid artery in a 34-year-old man.*
Also see Online Videos 1, 2, 3, and 4.

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Cardiac abnormalities

In 18 (51%) of 35 patients, 1 or more mitral valve abnormalities were diagnosed (5 prolapse; 5 billowing; and 5 mild, 2 moderate, and 3 severe cases of mitral valve regurgitation). In 2 patients, structural congenital heart defects were found: 1 patient had an atrial septal defect and persistent ductus arteriosus and another patient had mild congenital pulmonary valve stenosis (peak velocity: 1.82 m/s) and persistent ductus arteriosus. A remarkable finding in this patient was a saccular aneurysm within the persistent ductus arteriosus (7). In addition, 1 patient was found to have a bicuspid aortic valve during surgery.

Left ventricular systolic function and mitral inflow patterns were normal in all patients (Table 2). Left ventricular hypertrophy was present in 19% (6 of 31), with a mean interventricular septal thickness of 12 ± 2 mm, a mean left ventricular posterior wall thickness of 12 ± 2 mm, a mean left ventricular mass of 296 ± 84 g, and mean body surface area-indexed left ventricular mass of 146 ± 34 g/m^2. None of these patients had hypertension, aortic coarctation, or aortic stenosis.

Rhythm disturbances

Electrocardiography revealed sinus rhythm in all patients (Table 2). In 5 patients, premature ventricular contractions (≥3) were found. Seven (22%) of 31 patients had a history of at least 1 episode of documented atrial fibrillation (AF).

Aortic stiffness and biochemical measurements

Online Table 3 shows aortic stiffness and biochemical measurements for healthy controls and AOS patients. The aortic pulse wave velocity (aPWV) tended to be higher in AOS patients compared with controls (9.2 ± 2.2 m/s vs. 7.8 ± 1.8 m/s, p = 0.076). Compared with reference values controlled for age and blood pressure, 6 (33%) of 18 patients had an aPWV value of more than 2 SDs (8). Aortic diameter and aPWV were not correlated (r = −0.278, p = 0.357). N-terminal brain natriuretic peptide (NT-proBNP) was higher in AOS patients than in matched controls (94.1 pg/ml, range: 52.5 to 172.9 pg/ml vs. 12.7 pg/ml, range: 8.5 to 55.1 pg/ml, p < 0.001) and correlated with aPWV (r = 0.731, p = 0.005).

Associated findings of AOS

Osteoarthritis was confirmed by x-rays in 25 (96%) of 26 patients who underwent orthopedic evaluation, whereas 85% exhibited painful joints. Mean age at osteoarthritis diagnosis was 42 years, whereas the youngest patient was 12 years of age. Spine, hands or wrists, and knees most often were affected (detailed information in Online Table 1). Pes planus was present in 91% of patients and scoliosis was present in 61%. Other associated anomalies included hypertelorism (31%); abnormal palate (54%); abnormal uvula (52%); hernia inguinalis or umbilicalis (43%); and uterus, bladder, or bowel prolapse (41%). More detailed information about these associated findings will be reported separately (9).

Discussion

AOS is a recently described autosomal dominant connective tissue disorder characterized by aneurysms, dissections, and tortuosity throughout the arterial tree in combination with osteoarthritis and mild craniofacial features. The AOS phenotype may resemble that of other connective tissue disorders such as MFS and LDS (Online Table 4). The main site of aortic aneurysms in AOS is the sinus of Valsalva. Similar to LDS, AOS is an aggressive disease with substantial mortality and a high risk of aortic rupture and dissection in mildly dilated aortas (10). AOS and LDS both are associated with widespread arterial tortuosity and aneurysms in the thorax and abdomen (10). In contrast to MFS, cerebrovascular abnormalities frequently occur in AOS and LDS (11). Identification of the underlying genetic defect in TAAD patients is crucial, considering the variability in prognosis, treatment strategy, and risk assessment in family members.

Cardiac abnormalities in AOS

In addition to the aneurysms and tortuosity of the arterial tree, we also found cardiac abnormalities. A remarkable finding in approximately one fifth of the patients was left ventricular hypertrophy in the absence of hypertension or aortic stenosis. Primary cardiomyopathy is reported in one quarter of MFS patients showing mainly a reduced left ventricular ejection fraction, but only in a minority (2.9%) was LV mass increased (12). Mice studies have determined that TGF-β induces proliferation of cardiac fibroblasts and hypertrophic growth of cardiomyocytes (13). Furthermore, TGF-β neutralizing antibodies were able to attenuate LV hypertrophy, and losartan reduced nonmyocyte proliferation, implying possible therapeutic implications in humans as well (14).

Similar to MFS, mitral valve abnormalities were common in AOS patients, and 22% of AOS patients had a history of AF. Mice studies have shown that TGF-β1–induced myocardial fibrosis in the atria plays an important role in predisposing individuals to AF (15). Atrial fibrogenesis in patients with AF occurs in 2 phases: an early increase, but later loss of responsiveness to TGF-β1, while the fibrosis progresses (16).

Furthermore, evidence from mouse studies suggests that TGF-β signaling is essential in the embryogenesis of the heart, valvular pathogenesis, and organization of the aortic wall (17,18). In many mouse models with disrupted TGF-β signaling activities, congenital heart defects are present (17). In the future, *SMAD3* knockdown mice will help to explore the mechanism behind the cardiac abnormalities in AOS.

Aortic stiffness and NT-proBNP in AOS

NT-proBNP in AOS patients was elevated compared with that in controls, although none of the patients had extremely high NT-proBNP levels of more than 250 pg/ml. In vivo and in vitro studies have shown that treatment with brain natriuretic peptide can attenuate cardiac hypertrophy via the TGF-β1 pathway (19). One may hypothesize that the elevated NT-proBNP levels in AOS patients in fact are a protective mechanism against the emergence of LV hypertrophy.

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Because (mildly to moderately) elevated NT-proBNP levels in other patient groups are reported to predict cardiovascular outcome and AF recurrence, evaluation of the prognostic value of NT-proBNP in AOS patients with respect to clinical outcome may be important (20,21).

The aPWV as a measure of aortic stiffness was high-normal in AOS patients, as was described previously in, for instance, patients with MFS and bicuspid aortic valve (22,23). Ascending aortic diameter and aPWV were not correlated, suggesting that arterial stiffness occurs independently of aneurysm formation. In MFS patients, an augmentation index of more than 11% has been reported to predict progression of aortic diameters, so further research is warranted to test whether this also holds true for AOS patients (24).

Clinical suggestions for cardiologists treating AOS patients

Although AOS is a recently discovered aneurysm syndrome and the full spectrum of the disease and its progression need to be clarified, some preliminary suggestions may be derived from the current findings. Because multisystem involvement frequently is observed, cooperation in a multidisciplinary team with clinical geneticists, cardiologists, orthopedic surgeons, radiologists, neurologists, and, when necessary, (vascular or cardiothoracic) surgeons is important.

Monitoring and screening

Cardiologists should suspect AOS in every TAAD patient without molecular diagnosis or known cause and should test these patients for *SMAD3* mutations. Furthermore, we suggest that clinicians treating patients with arterial aneurysmal disease in any large artery (intracranial, iliac, splenic artery, and so on) should at least ask whether these patients report joint symptoms. In the physical examination, one must pay special attention to presence of AOS-associated findings, such as joint anomalies and abnormal uvula.

Extensive cardiovascular evaluation using echocardiography and CTA or magnetic resonance imaging (head to pelvis) is recommended in every adult AOS patient. Initially, these diagnostic investigations should be performed annually to determine rate of progression. Thereafter, frequency of imaging should be guided by the findings, for instance, annually if the aortic diameter is more than 35 mm or if the aortic diameter shows significant growth (>5 mm/year).

The phenotype seems to be age-dependent, because aneurysms mainly and dissections only occurred in adulthood; however, our series included only 6 children with AOS. Concerning screening in childhood, clear suggestions are difficult to formulate at this time. We suggest that frequency of cardiologic evaluation with TTE, magnetic resonance imaging, or both must be guided by the aortic root *z*-score and presence of other cardiac abnormalities.

Although in our cohort no dissections occurred during pregnancy or delivery, pregnancy should be considered high risk in AOS patients with aneurysms, as in those with MFS and LDS (25).

Treatment

The implication of TGF-β signaling in the pathogenesis of aortic aneurysm syndromes suggests a TGF-β antagonist as a specific pharmaceutical target (26). Although losartan showed promising results in MFS mouse models, we have to await the results of randomized clinical trials in MFS, *SMAD3* knockdown mice, and consequently AOS clinical trials (26). At the moment, attention should be focused on genetic counseling, screening of relatives, and interventional or surgical treatment. Medical treatment with losartan, beta-blockade, or both may be beneficial. Stringent control of hypertension to limit aortic wall stress is recommended (27).

Because dissections in AOS patients can occur at relatively small aortic diameters, early elective surgical intervention is indicated to reduce the risk of mortality. Because data are limited and the rate of progression is unknown, we suggest applying the surgical recommendations for LDS (27). Valve-sparing aortic root replacement using the reimplantation technique is the intervention of choice (28). For peripheral aneurysms, individual size or rate of growth and location must determine the treatment strategy.

Currently, the risk of rupture of intracranial aneurysms associated with AOS is unknown. No deaths resulting from intracranial hemorrhage occurred in our series. Life expectancy and size, location, and rate of growth of the aneurysm are the most important determinants to decide whether intervention is needed.

Study limitations

First, the number of subjects included in the present study is relatively small, because AOS has been discovered only recently. Second, the population is quite heterogeneous, particularly in disease severity and age, and because of logistical reasons and mortality, it was not possible to perform every examination in all 44 patients. Further research is necessary to confirm our findings and to gain more insight in the disease mechanism and progression.

Conclusions

AOS is an aggressive, inherited, connective tissue disorder characterized by arterial tortuosity, aneurysms, and osteoarthritis. Aortic root enlargement is the most common cardiovascular finding in our series, but cerebrovascular abnormalities were also present in more than 50% of patients. Aortic dissections occur at smaller diameters than observed in, for instance, MFS, and as such need early elective surgical treatment. Larger prospective follow-up studies are warranted to determine progression over time and clinical relevancy of the cardiac and intracranial abnormalities.

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Acknowledgments

The authors thank the participating patients, their families, and their referring physicians. The authors also thank all control subjects and technician assistants from the participating centers.

@ **For an expanded Methods section, and supplementary figures, videos, and tables, please see the online version of this article available at:** *http://www.sciencedirect.com/science/article/pii/S0735109712012387.*

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Phenotypic spectrum of the *SMAD3*-related Aneurysms-Osteoarthritis Syndrome (AOS)

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J Med Genet. 2012;49:47-57.

Abstract

Background

Aneurysms–osteoarthritis syndrome (AOS) is a new autosomal dominant syndromic form of thoracic aortic aneurysms and dissections characterised by the presence of arterial aneurysms and tortuosity, mild craniofacial, skeletal and cutaneous anomalies, and early-onset osteoarthritis. AOS is caused by mutations in the *SMAD3* gene.

Methods

A cohort of 393 patients with aneurysms without mutation in *FBN1*, *TGFBR1* and *TGFBR2* was screened for mutations in *SMAD3*. The patients originated from The Netherlands, Belgium, Switzerland and USA. The clinical phenotype in a total of 45 patients from eight different AOS families with eight different *SMAD3* mutations is described. In all patients with a *SMAD3* mutation, clinical records were reviewed and extensive genetic, cardiovascular and orthopaedic examinations were performed.

Results

Five novel *SMAD3* mutations (one nonsense, two missense and two frame-shift mutations) were identified in five new AOS families. A follow-up description of the three families with a *SMAD3* mutation previously described by the authors was included. In the majority of patients, early-onset joint abnormalities, including osteoarthritis and osteochondritis dissecans, were the initial symptom for which medical advice was sought. Cardiovascular abnormalities were present in almost 90% of patients, and involved mainly aortic aneurysms and dissections. Aneurysms and tortuosity were found in the aorta and other arteries throughout the body, including intracranial arteries. Of the patients who first presented with joint abnormalities, 20% died suddenly from aortic dissection. The presence of mild craniofacial abnormalities including hypertelorism and abnormal uvula may aid the recognition of this syndrome.

Conclusion

The authors provide further insight into the phenotype of AOS with *SMAD3* mutations, and present recommendations for a clinical work-up.

Introduction

Aortic aneurysm is a common condition, with high mortality from dissections and ruptures.[1] Whereas abdominal aortic aneurysms usually occur sporadically, thoracic aortic aneurysms and dissections (TAAD) can be inherited in an autosomal dominant manner with decreased penetrance and variable expression.[2] Familial TAAD is subdivided into non-syndromic forms, sometimes associated with bicuspid aortic valve and/or persistent ductus arteriosus,[3–5] and syndromic forms with features of a systemic connective tissue disorder. Non-syndromic familial TAAD can be caused by mutations in genes encoding proteins of the contractile unit of the vascular smooth muscle cell such as the *ACTA2, MYH11* and *MYLK* genes.[3–5] However, in the majority of patients, the genetic cause is still unknown.

Syndromic familial TAAD includes several systemic connective tissue disorders such as: Marfan syndrome (MFS), caused by mutations in the *FBN1* gene; Loeys–Dietz syndrome (LDS), caused by mutations in the *TGFBR1* or *TGFBR2* gene; arterial tortuosity syndrome (ATS), caused by mutations in the *SLC2A10* gene; and autosomal recessive cutis laxa type I (AR-CL), caused by mutations in the *FBLN4* gene.[6–11] As all these syndromes are characterised by increased transforming growth factor (TGF)-β signalling in the arterial wall, it has become evident that TGFβ signalling plays a central role in the pathogenesis of arterial aneurysms.[6–11]

Recently, we described a new syndromic form of autosomal dominant TAAD characterised by the presence of arterial aneurysms and tortuosity, mild craniofacial features, skeletal and cutaneous anomalies, and osteoarthritis at a young age.[12] As arterial aneurysms and early-onset osteoarthritis are the cardinal features of this new disorder, the term aneurysms–osteoarthritis syndrome (AOS) was coined. Patients with AOS show aneurysms throughout the arterial tree and a high risk of early dissection/rupture, resembling patients with LDS. Interestingly, early-onset joint abnormalities, including osteoarthritis, intervertebral disc degeneration, osteochondritis dissecans (OCD) and meniscal anomalies, are present in almost all patients with AOS, whereas they are uncommon in LDS, MFS and ATS. This establishes early-onset joint abnormalities as a key feature of this new syndrome.

We previously showed that AOS in three different families is caused by heterozygous mutations in the *SMAD3* gene encoding SMAD3, which is a key protein in the TGFβ pathway.[12] Here we identified five novel *SMAD3* mutations and present an extensive clinical description of 45 patients from eight families with SMAD3-related AOS.

Methods

Patient collection

DNA from 393 patients (95 Dutch, 158 Belgian, 133 Swiss and seven North American) with TAAD but without mutation in the coding region of the *FBN1*, *TGFBR1* and *TGFBR2* genes was analysed for mutations in the coding region of the *SMAD3* gene. When a *SMAD3* mutation was found, clinical data on the patient were collected, clinical investigations were performed, and a family tree was constructed or extended through family histories, whereby possibly affected relatives were studied and screened for the *SMAD3* mutation found in the index.[12]

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A total of 34 patients with a mutation in *SMAD3* were interviewed and examined by a clinical geneticist, six of whom have subsequently died. All had extensive clinical investigations, with scoring of five major systems implicated in connective tissue disorders, including the cardiovascular, joint, skeletal, craniofacial and cutaneous systems. Medical records from 11 deceased patients were reviewed. This study was approved by the medical ethics committee of the Erasmus Medical Center Rotterdam (Erasmus MC), and all patients gave written informed consent for this study.

Cardiovascular studies

Extensive cardiovascular studies were performed in 29 patients with AOS with a *SMAD3* mutation, and included physical examination, ECG, transthoracic echocardiography and imaging of the thorax and abdomen by CT angiography (CTA) or magnetic resonance angiography (MRA) as described previously.[12] Aortic root dilatation was defined as a Z-score ≥2 at any level. Z-scores were calculated on the basis of body surface area-corrected normal values published by Roman *et al*.[13] For the other arteries, aneurysm is defined as a 50% or greater increase in diameter compared with the expected normal diameter of the vessel. CTA of the cervical and intracranial arteries was performed in 17 AOS patients with a *SMAD3* mutation. Tortuosity of the thoracic, abdominal and cerebral arteries was scored by a radiologist.

Joint studies

Twenty-five patients were evaluated by an orthopaedic surgeon. An extensive physical examination for signs of osteoarthritis, intervertebral disc degeneration, spondylolysis or spondylolisthesis, OCD, meniscal lesions and joint laxity was performed.

Nineteen patients filled out a questionnaire about joint complaints. A radiographic skeletal survey of the total spine, hips, knees, hands and feet was performed in 26 patients. Osteoarthritis in the extremities is characterised by the degradation of articular cartilage and subchondral bone of joints and was scored as described previously.[12] In addition, the presence of spondylolysis or spondylolisthesis was scored. OCD, defined as separation of an articular cartilage subchondral bone segment from the remaining articular surface, was scored in all patients who were radiologically evaluated. MRI of the joint was performed when abnormalities were seen on radiography or if patients had symptoms. Every patient who had surgery for meniscal pathology, OCD or joint replacement because of osteoarthritis was considered to be affected for the respective feature.

Phenotypic studies

Physical examination was performed by a clinical geneticist. Hypertelorism was defined as an inner canthal distance ≥+2 SD without lateral displacement of the inner canthi.[14] Dolichostenomelia was defined as an arm span/height ratio of ≥1.05. Arachnodactyly was scored when the middle finger length exceeded the palm length, as described by Hall.[14] Scoliosis was radiographically defined as a lateral curvature of the spine greater than 20 degrees in the coronal plane accompanied by vertebral rotation in the axial plane measured on standing x-rays.

Hypermobility was scored when the Beighton score was ≥5. Acetabular protrusion was scored on pelvic radiographs or CT scans when the acetabular line crossed the normal oval shape formed by the two iliopectineal lines.

Molecular studies

Genomic DNA was isolated from peripheral blood using standard procedures (Gentra Systems, Minneapolis-USA). DNA samples from deceased patients were obtained from stored autopsy tissue (frozen or paraffin-embedded tissue). Bidirectional sequencing of all coding exons and exon–intron boundaries of the *SMAD3* gene was undertaken as previously described.[12] For annotation of cDNA and protein changes, the Mutation Nomenclature Guidelines from the Human Genome Variation Society were followed (the A from the ATG start codon and Met of the reference sequence NM_005902.3 and NP_005893.1, respectively, were numbered 1).

If *SMAD3* missense mutations were identified in patients with AOS, the possible presence in controls was investigated by direct sequencing in at least 342 ethnically matched control chromosomes. The putative pathogenicity of missense variants was investigated in silico using the prediction programs PolyPhen-2, HOPE and SIFT.

Results

Identification of eight families with SMAD3 mutations

SMAD3 sequence analysis in 393 patients with TAAD (without mutations in the *FBN1*, *TGFBR1* and *TGFBR2* genes) revealed five novel heterozygous *SMAD3* mutations: c.313delG (p.Ala105ProfsX11), c.539_540insC (p.Pro180ThrfsX7), c.788C→T (p.Pro263Leu), c.1045G→C (p.Ala349Pro), c.1080dupT (p.Glu361X) (figure 1A). Three other mutations have previously been reported by our group: c.741_742delAT (p.Thr247fsX61), c.782C→T (p.Thr261Ile) and c.859C→T (p.Arg287Trp) (figure 1A).[12] The eight families with *SMAD3* mutations are unrelated and originate from the Netherlands (four families), Belgium (two families), Spain (one family) and the USA (one family). After molecular screening, 45 patients with a *SMAD3* mutation were identified. The genealogical trees of these AOS families are shown in figure 1B. In four families, multiple patients were reported (figure 1B, families 1, 2, 4 and 5). In three families, the parents were unavailable for testing and no medical records were available.

The mutations were located in exons 2, 4, 6 or 8 of the *SMAD3* gene (figure 1A). Four mutations introduced a frame shift (p.Ala105ProfsX11, p.Pro180ThrfsX7 and p.Thr247fsX61) or stop codon (p.Glu361X), and were considered to be pathogenic. Four missense mutations (p.Thr261Ile, p.Pro263Leu, p.Arg287Trp and p.Ala349Pro) were probably pathogenic, based on the following observations: (1) all involved residues that are highly conserved throughout evolution (from primates to zebrafish, data not shown); (2) in silico analysis predicts that these missense variants are likely to be pathogenic; (3) in two familial cases the *SMAD3* mutation co-segregated with AOS; (4) these four mutations were absent in at least 342 ethnically matched control chromosomes. All variants are absent in the 1094 individuals from the 1000Genomes project.

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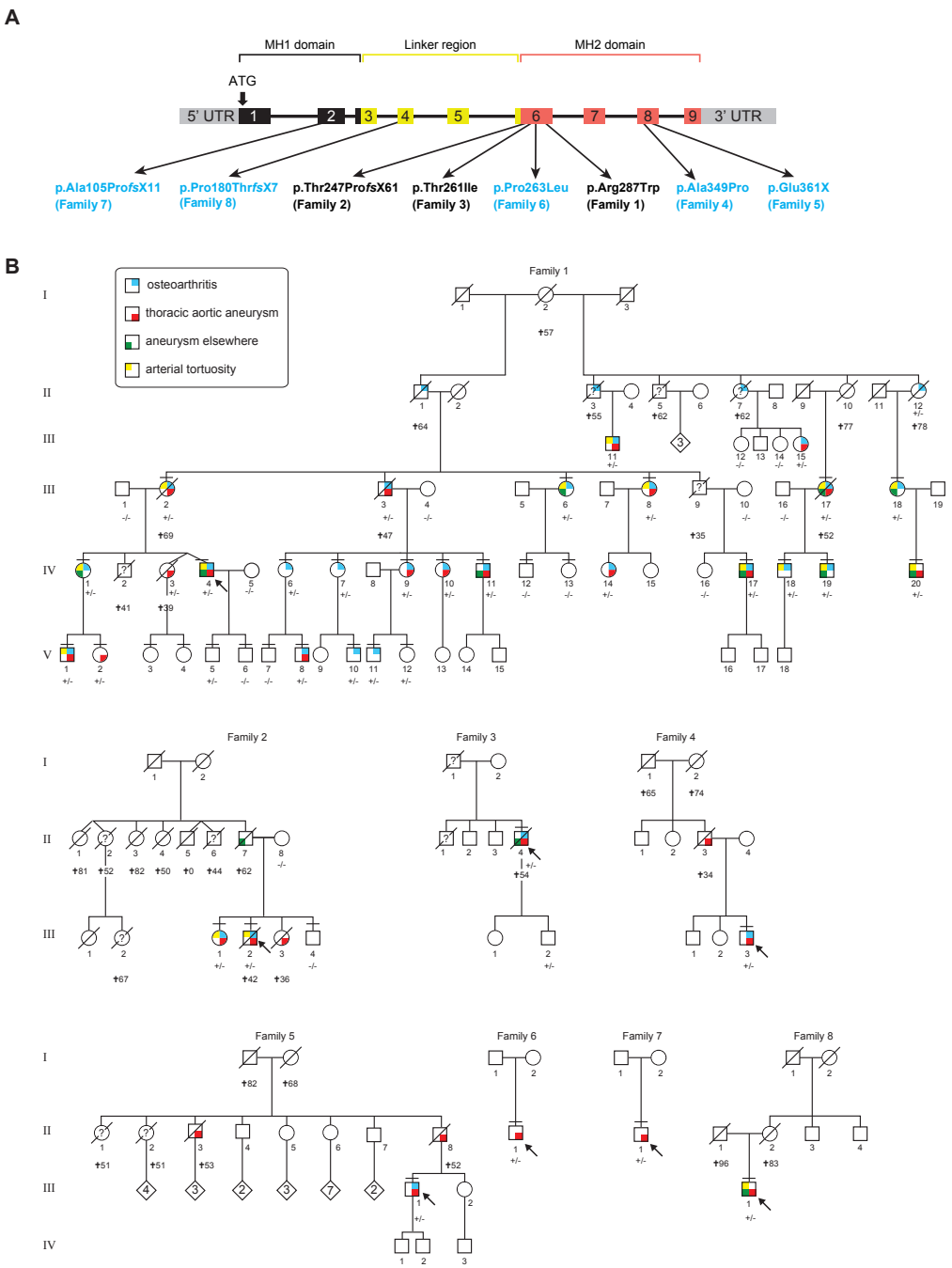

Figure 1. *SMAD3 mutations in eight families with Aneurysms-Osteoarthritis Syndrome (AOS)*

(A) *Schematic representation of the* SMAD3 *gene. Boxes represent exons 1–9 with the untranslated regions (UTRs). The three main functional domains MH1, MH2 and the linker region are indicated. Mutations previously identified in the AOS syndrome[12] are depicted in black font, and mutations identified in this study are depicted in blue.* ***(B)*** *Simplified family trees of eight unrelated families with AOS. Squares indicate males, circles represent females. A horizontal line above the symbol indicates medical examination by one of us. Owing to lack of space, generation III from family 1 is split into two levels. An arrow points to the index patient. The upper right blue square indicates the presence of osteoarthritis, the lower right red square the presence of a thoracic aortic aneurysm, the lower left green square the presence of an aneurysm in any other artery, and the upper left yellow square the presence of arterial tortuosity. Open symbols are individuals with a normal or unknown phenotype. Four individuals with open symbols (family 1, patient II-10, V-5, V-12 and family 3, patient III-2) had other signs of AOS, not indicated in the legend. A question mark (?) indicates sudden cardiovascular death possibly from an arterial rupture or dissection without autopsy. Age of death is displayed below the symbol. The presence (+/–) or absence (–/–) of a* SMAD3 *mutation is indicated underneath.*

Initial clinical features

Clinical data for 45 patients with a *SMAD3* mutation were collected. The mean age of these patients with AOS was 45 years, including six children aged 17 (n=3), 15, 13 and 9 years. The main clinical characteristics of all 45 individuals from the eight families are summarised in table 1. All patients with a *SMAD3* mutation had one or more signs of AOS.

Table 1. *Clinical findings in 45 individuals with aneurysms-osteoarthritis syndrome*

Features	No	Percentage
Cardiovascular anomalies	40/45	89%
Arterial anomalies	33/40	83%
Thoracic aortic aneurysm	28/39	72%
Abdominal aortic aneurysm	4/33	12%
Aortic dissection/rupture	13/39	33%
Aneurysm(s) of thoracic/abdominal arteries	9/25	36%
Aneurysm(s) of cerebral arteries	6/16	38%
Aortic tortuosity	10/26	38%
Arterial tortuosity of thoracic/abdominal arteries	8/21	38%
Arterial tortuosity of cerebral arteries	8/16	50%
Ventricular hypertrophy	6/33	18%
Atrial fibrillation	8/33	24%
Mitral valve anomalies	18/36	50%
Congenital heart malformation*	3/33	9%

** Congenital heart malformations included atrial septal defect (ASD), persistent ductus arteriosus (PDA), pulmonary valve stenosis (PS) and bicuspid aortic valve (BAV)*

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Table 1. *Clinical findings in 45 individuals with aneurysms-osteoarthritis syndrome (Continued)*

Features	No.	Percentage
Joint anomalies		
Osteoarthritis of ≥1 joint	25/26	96%
Osteoarthritis feet/ankle	8/26	31%
Osteoarthritis hand/wrist	14/26	54%
Osteoarthritis knee	13/26	50%
Osteoarthritis hip	4/26	15%
Osteoarthritis facet- and/or uncovertebral joints (spine)	20/26	77%
Intervertebral disc degeneration	34/37	92%
Spondylysis/spondylolisthesis	10/26	38%
Meniscal lesions	7/25	28%
Osteochondritis dissecans	14/25	56%
Painful joints	23/27	85%
Joint laxity	3/31	10%
Skeletal anomalies		
Dolichostenomelia	7/33	21%
Long slender fingers	13/33	39%
Camptodactyly	4/30	13%
Pectus deformity	12/33	36%
Scoliosis	22/36	61%
Protrusio acetabulae	7/20	35%
Pes planus	30/33	91%
Other phenotypic anomalies		
Hypertelorism	10/32	31%
Abnormal palate	15/28	54%
Abnormal uvula	13/25	52%
Velvety skin	18/29	62%
Striae	17/32	53%
Easy bruising	10/28	36%
Hernia inguinalis/umbilicalis	17/40	43%
Prolapse of bladder/uterus/bowel	7/17	41%
Migraine/severe headache	15/30	50%
Varices	18/31	58%
Chronic fatigue	11/28	39%

Adults

All but three adult patients had consulted different physicians because of AOS symptoms before this study. In 19/35 (54%) of the adult patients, joint complaints were the initial symptom for which medical advice was sought (age range 18–61 years). In none of them was a (aneurysm) syndrome suspected. In these patients with AOS, joint abnormalities mainly consisted of OCD, osteoarthritis and meniscal lesions.

Cardiovascular abnormalities were the presenting feature in 46% (16/35) of the adult patients (age range 20–66 years). Sudden death from aortic dissections, aortic aneurysms and severe mitral valve insufficiency was the most common presentation. In three patients, the diagnosis of MFS was made at the time of presentation on the basis of the revised Ghent criteria.[15]

One patient (figure 1, family 1, patient II-1) died suddenly at the age of 64 years from an unknown cause.

Children

All six children (aged 9–17 years) were referred for initial check-up after AOS was diagnosed in the family. Radiological studies were performed in three patients (family 1, patients V-8, V-10 and V-11). A 12-year-old patient presented with knee and lower back pain. Radiography and MRI showed agenesis of the anterior cruciate ligaments, OCD of the knee and severe intervertebral disc degeneration. A 17-year-old boy with mild back pain had severe intervertebral disc degeneration at multiple levels. One 16-year-old boy had a tenodesis of the first metacarpophalangeal joint.

All six children had cardiovascular examinations, which revealed an aortic aneurysm at the level of the sinus of Valsalva in two patients. These aneurysms were first diagnosed at the age of 14 and 16 years. Two children had mitral valve prolapse.

Cardiovascular abnormalities

Cardiovascular abnormalities were documented in 89% (40/45) of our patients with AOS. These included thoracic aortic aneurysm and/or dissection, aneurysm of other arteries, tortuosity of the arterial tree, left ventricular hypertrophy, atrial fibrillation and congenital heart malformation. Arterial anomalies were present in 83% of patients.

Thoracic aortic aneurysms were present in 28 of 39 patients who had aortic root measurements. They were mainly present at the level of the sinus of Valsalva and ranged from 36 mm (Z-score 2.9) to 63 mm (Z-score 13.2) with a mean age at diagnosis of 39 years (range 14–65 years) (figure 2A). Eleven patients had been successfully operated on by elective aortic root replacement at maximum aortic diameters between 40 and 63 mm. Mean age at surgery was 41 years (range 20–64). In four patients, an abdominal aortic aneurysm was reported, at ages 49, 50, 61 and 62 years (figure 2E).

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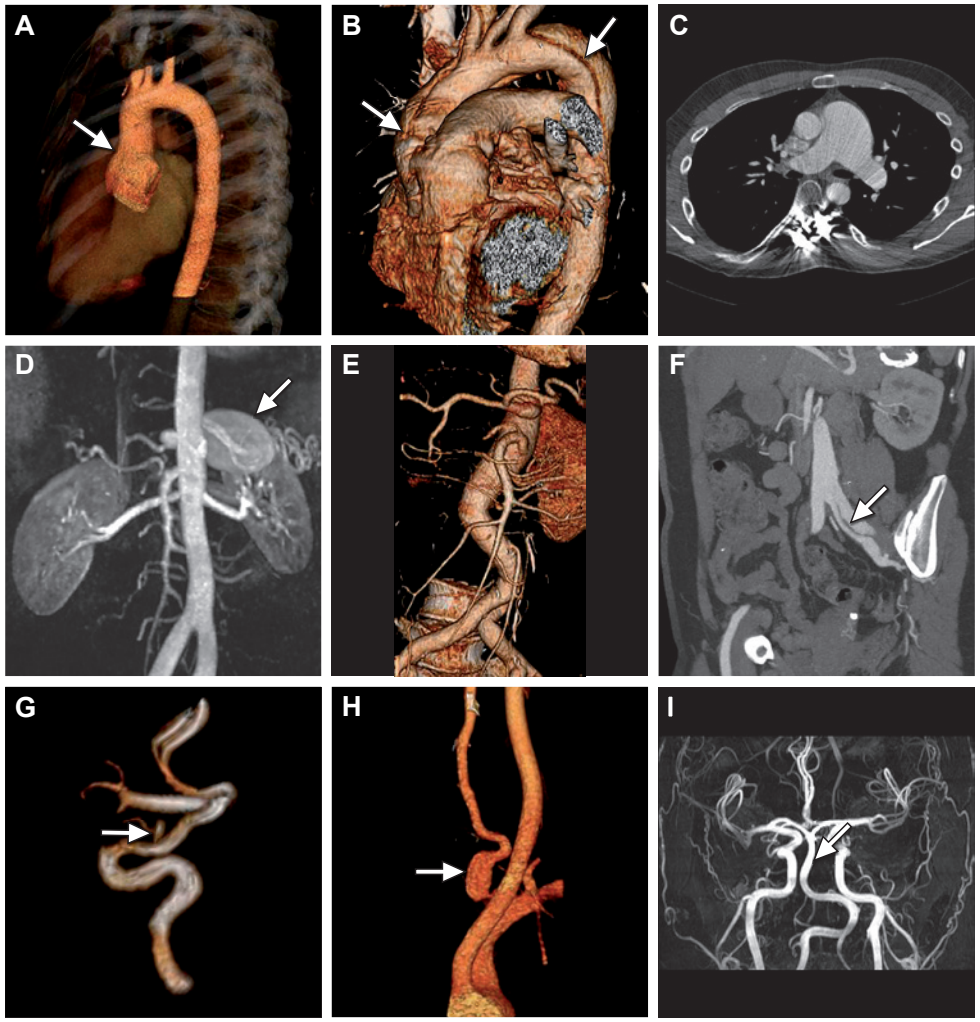

Figure 2. *Arterial anomalies, including aneurysms, dissections and tortuosity*

(A) *Three-dimensional (3D) reconstructed CT angiography (CTA) of a 20-year-old man (family 1, patient V-1) shows an aneurysm at the level of the sinus of Valsalva of 45 mm (arrow).* ***(B)*** *3D reconstructed CTA of a 50-year-old woman (family 1, patient III-17) showing a Stanford type A aortic dissection (arrows) extending into the brachiochephalic trunk at a maximal aortic diameter of 40 mm.* ***(C)*** *CTA of a 29-year-old man (family 1, patient IV-19) shows an aneurysm of the truncus pulmonalis of 50 mm.* ***(D)*** *Magnetic resonance angiography (MRA) of a 38-year-old man (family 1, patient IV-4) shows an aneurysm of the splenic artery of 40 mm (arrow) and marked arterial tortuosity of the splenic artery.* ***(E)*** *3D reconstructed CTA of a 50-year-old woman (family 1, patient III-17) showing tortuosity of the abdominal aorta, suprarenal aneurysm of the abdominal aorta of 30 mm, and aneurysms of the coeliac trunk, and left common iliac artery.* ***(F)*** *CTA of a 45-year-old woman (family 1, patient IV-1) shows a Stanford type B aortic dissection at a maximal abdominal aortic diameter of 24 mm with dissection flap extending into the left common iliac artery (arrow).* ***(G)*** *MRA of a 34-year-old man (family 1, patient IV-17) shows a saccular aneurysm of the right ophthalmic artery of 3.5 mm (arrow).* ***(H)*** *3D reconstructed CTA of a 29-year-old man (family 1, patient IV-19) shows a fusiform aneurysm of the left vertebral artery of 11 mm (arrow).* ***(I)*** *MRA of a 41-year-old man (family 4, patient III-3) showing the cerebral arteries. The calibre of the basilar artery is similar to that of the internal carotid arteries, indicating fusiform dilatation.*

In total, 13 patients had an aortic dissection. A Stanford type A dissection was present in 11 patients; in five of them, the aortic root diameters could be determined before dissection occurred and ranged between 40 and 63 mm (mean 51 mm). In two patients, aortic dissections occurred while the aorta was only mildly dilated (figure 1B, family 1, patients III-2 and III-17), with maximal ascending aortic diameters of 45 mm and 40 mm, respectively (figure 2B). Five patients with a Stanford type A dissection had a successful aortic root replacement at a mean age of 46 years (38–52 years). Four patients had a Stanford type B dissection, and in two of them the dissection occurred in only mildly or non-dilated abdominal aortas (figure 2F). Two patients had both a Stanford type A and B dissection. Three patients had dissections in other non-dilated arteries, namely the coronary, common and internal iliac, and superior mesenteric artery.

Fifteen patients with AOS died suddenly between 34 and 69 years of age. Autopsy was performed in six patients and confirmed a Stanford type A dissection in five patients and a Stanford type B dissection in one patient. In seven patients, no autopsy was performed, but three of them were previously known to have aortic aneurysms/dissections. Other arterial aneurysms were detected in nine of 25 (36%) patients studied, mainly involving the vertebral, pulmonary, splenic, iliac and mesenteric arteries (figure 2C–E). One patient (figure 1B, family 1, patient IV-4) had an aneurysm of the splenic artery of 40 mm (figure 2D), and another patient (figure 1B, family 2, patient II-7) showed bilateral internal iliac aneurysms of 80 mm, as well as an abdominal aortic aneurysm of 100 mm. Imaging of the cerebral arteries revealed both intra- and extra-cranial aneurysms in 38% of patients involving the vertebral, carotid, basilar and ophthalmic arteries (figure 2G–I). In two patients (figure 1B, family 1, patient II-10 and II-12), a stroke was reported, at 56 and 76 years. The family history of family 2 revealed two 50% risk carriers with a stroke at 52 and 67 years (figure 1B, family 2, patients II-2 and III-2).

Tortuosity of the large- or medium-sized arteries was present in the majority of patients. Aortic tortuosity was found in 38% (figure 2E), tortuosity of other thoracic and abdominal arteries (mainly the subclavian and splenic arteries) in 38% (figure 2D), and tortuosity of the cerebral arteries (including the vertebral, internal carotid, cerebral and pericallosal arteries) in 50% of our patients with AOS.

Left ventricular hypertrophy was diagnosed in 18% of patients. It was mild to moderate, mainly concentric, and was not the consequence of hypertension, as most patients were normotensive without treatment. Atrial fibrillation was a common finding, with 24% (8/33) of patients having at least one episode. The age at onset ranged between 23 and 76 years. Three of eight patients had a single episode of atrial fibrillation after surgery. Mitral valve abnormalities were reported in half of the patients, the youngest being 14 years old. These anomalies ranged from mild prolapse to severe regurgitation requiring valve replacement. Congenital heart malformations were found in 9% (3/33) of our patients with AOS, and included bicuspid aortic valve, pulmonary valve stenosis, persistent ductus arteriosus and atrial septal defect. Of 13 women having a total of 23 pregnancies, one had a severe postpartum haemorrhage, but no other vascular complications or uterine ruptures were reported. In more than 30% of patients who initially presented with cardiovascular anomalies, joint abnormalities were reported later in life.

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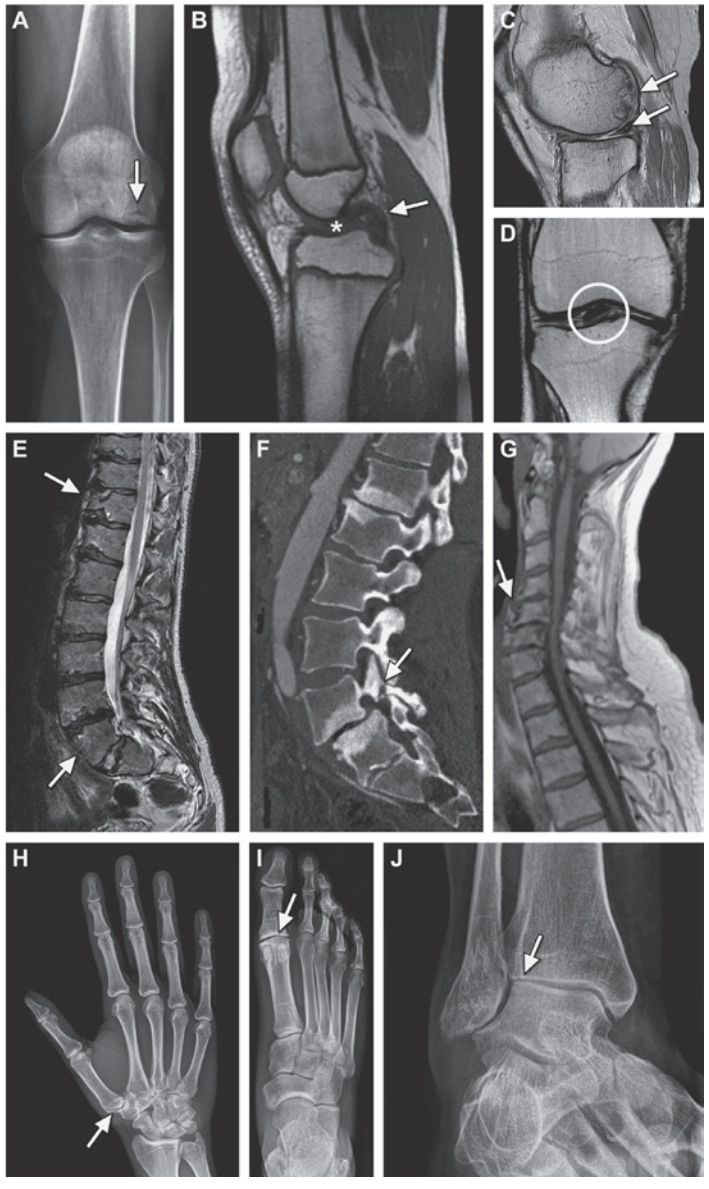

Figure 3. *Osteoarthritis and osteochondritis*

(A) *X-ray of the left knee of a 41-year-old patient (family 4, patient III-3) shows a large osteochondral lesion without separation in the lateral femoral condyle (arrow).* ***(B)*** *MRI of the right knee of a 12-year-old patient (family 1, patient V-10) shows congenital absence of the anterior cruciate ligament (ACL). Asterisk: no ACL is seen in its expected location. The arrow points to the normal posterior cruciate ligament.* ***(C)*** *MRI of the knee of a 48-year-old woman (family 2, patient III-1) shows a large osteochondral lesion without separation in the medial femoral condyle (upper arrow). There is also a horizontal tear of the medial meniscus (lower arrow).* ***(D)*** *MRI of the right knee of a 17-year-old man (family 1, patient V-1) with a loose intra-articular body (encircled) due to a large osteochondral lesion of the medial femoral condyle (not shown).* ***(E)*** *MRI of the thoracic and lumbar spine of a 17-year-old man (family 1, patient V-8) with marked irregularity and impression of the anteroinferior endplates at multiple levels (see arrows for examples).* ***(F)*** *CT scan of a 44-year-old woman (family 1, patient IV-6) with severe multilevel degenerative disc disease and a spondylolisthesis at the L4–L5 level due to a bilateral spondylolysis (arrow).* ***(G)*** *MRI scan of a 50-year-old man (family 3, patient II-4) with marked degenerative abnormalities of the lower cervical spine (arrow) with narrowing of the spinal cord.* ***(H)*** *X-ray of the right hand and wrist of a 31-year-old man (family 1, patient IV-18) with moderate osteoarthritis of the first carpometacarpal joint (arrow).* ***(I)*** *X-ray of the right foot of a 31-year-old man (family 1, patient IV-18) with moderate osteoarthritis of the first metatarsophalangeal joint (arrow).* ***(J)*** *X-ray of the ankle of a 40-year-old woman (family 1, patient IV-9) with marked degenerative changes of the talocrural joint with severe lateral joint space narrowing (arrow).*

Joint anomalies

Almost all (96%) patients studied had radiologically proven osteoarthritis, with 75% of these in two or more joint types. Eighty-five per cent of these patients had painful joints. The mean age at osteoarthritis diagnosis was 42 years, and the youngest patient with osteoarthritis was detected at 12 years of age. The joints that were mostly affected were spine, hands and/or wrists, and knees, but osteoarthritis was also reported in all other joints including feet and/or ankle, hip and shoulder (figure 3H–J). Hand/wrist osteoarthritis was present in 14 patients, and in half of them the first carpometacarpal joint was involved (figure 3H). Other affected joints were the scaphotrapeziotrapezoidal, distal interphalangeal, proximal interphalangeal and occasionally metacarpophalangeal I joints. Furthermore, intervertebral disc degeneration mainly involving the cervical and lumbar discs was present in 92% (34/37) of patients (figure 3E–G) on retrospective evaluation of x-rays and CT scans. In addition, vertebral bodies showed shape irregularities located in the region of the anterior growth plates. In some documented cases, these abnormalities were already present at a young age (youngest 12 years).[12] Spondylolysis and/or spondylolisthesis (figure 3F) were common (38%).

More than half of the patients (56%) had non-traumatic OCD even at a young age (figure 3A,C,D). OCD occurred mainly in the knee and occasionally in the ankle or hip. Patients with OCD were operated on before the age of 40 years—the youngest at the age of 10 years. OCD was asymptomatic in some cases (figure 3A). Seven patients with AOS (28%) had meniscal lesions, one of whom had bilateral meniscectomy at the age of 13 years. In one patient, a congenital absence/agenesis of the anterior cruciate ligament was seen on MRI of the knee at the age of 12 years (figure 3B). Three patients had an arthroplasty of the knee at an average age of 64 (range 61–68 years), and one patient had an arthroplasty of the thumb base at the age of 58 years. Joint laxity defined as a Beighton score of ≥5, was seen in a minority (10%) of patients.

In the 19 patients who initially presented with joint abnormalities, extensive cardiovascular work-up was performed in the following years because of their family history or cardiovascular symptoms. In 64%, cardiovascular abnormalities were reported. More importantly, four of the 19 died suddenly from an aortic dissection.

Skeletal anomalies

Approximately 40% of the patients had long and slender fingers and toes, but overt arachnodactyly (as defined above) was not present. A positive thumb sign was seen in seven patients, and a positive wrist sign in one patient. Dolichostenomelia was present in 21% of patients.

Twelve patients (36%) had pectus carinatum, pectus excavatum or asymmetry of the costosternal junction. Scoliosis was present in 61% of our patients, and three of them were operated on for severe scoliosis. One patient had foraminal stenosis requiring foraminotomy of L5–S1 with spondylodesis of L4–S1. Protrusio acetabulae was present in one-third (35%) of patients and was usually mild. Over 90% of patients had pes planus. Camptodactyly was present in four out of 30 (13%) patients.

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Craniofacial abnormalities

Figure 4 illustrates the facial features of 20 patients with AOS. Facial characteristics included high forehead, hypertelorism, long face, flat supraorbital ridges and malar hypoplasia, but were generally mild. Uvular anomalies (raphe, broad or bifid) were common in our series (52%). Of the 13 patients with uvular abnormalities, 62% had a broad uvula with or without a raphe and 38% had a bifid uvula. Uvular abnormalities may be an easy diagnostic clue, as they only occur in LDS but not in other syndromic or non-syndromic forms of TAAD. High-arched palate was common, and one patient was operated for a cleft palate. Dental malocclusion and retrognathia were occasionally seen. No craniosynostosis was observed or reported. There was a marked inter- and intra-familial variability in facial features (figure 4).

Figure 4. *Facial features of 20 AOS patients from four different families.*

Facial features of 20 patients with aneurysms–osteoarthritis syndrome from four different families. Photographs are boxed in red (family 1), green (family 2), blue (family 4) and yellow (family 5). Facial features include hypertelorism, a long face, flat orbital ridges, a high forehead and malar flattening. Overall, the most prominent facial feature is hypertelorism. Written consent was obtained for publication of these images.

Additional features

Some features that are common in connective tissue disorders are also common in AOS. Umbilical and/or inguinal hernias were present in 17/40 (43%) of patients (age range 1–50 years). Pelvic floor prolapse occurred in seven of 17 adult women and mainly involved the uterus (6/7) and occasionally the bladder (2/7) and bowel (1/7). The mean age at operation for pelvic floor prolapse was 50 years (range 43–64). Varices or thread veins were reported or observed in 18 of 31 patients, usually already present at a young age (youngest patient 17 years) and were therapy (surgery)-resistant. Velvety skin and striae were present in the majority (62% and 53%, respectively) of the patients.

Other recurrent findings included easy bruising and atrophic scars. Recurrent severe headaches or migraine was present in half (15/30) of the patients and did not co-occur with the cerebrovascular abnormalities.

Some additional features occurred sporadically in the eight families, but were not systematically evaluated in all patients. Diverticulosis was reported in four patients, and dural ectasia in seven patients. Two patients had unexplained severe lung emphysema, at the age of 63 and 54 years; one patient did not smoke, but no details on smoking or other risk factors for emphysema were available for the other patient. In three patients, xanthelasmata around the eye were reported, although no dyslipidaemia was found. Almost 40% (11/28) of patients complained of chronic or intermittent increased fatigue. Ophthalmological examination in 29 patients revealed no lens luxation. One patient had cataract surgery and multiple procedures for retinal detachment; one patient had mild cataract at the age of 54 years, and amblyopia was present in two patients. Hydrocephaly was not found. No moderate or severe developmental delay was reported in any patient, although no IQ tests were performed.

Discussion

SMAD3 mutations

We have identified here five new and private heterozygous *SMAD3* mutations in five unrelated AOS families. As we screened 393 patients with TAAD (negative for *FBN1*, *TGFBR1* and *TGFBR2* mutations), *SMAD3*-associated TAAD represents a small fraction of TAAD. Because patients in our cohort were initially analysed for syndromic TAAD genes, this cohort may be enriched for patients with MFS and LDS features.

In total, we have identified eight *SMAD3* mutations, six of which were located in the MH2 domain, which mediates oligomerisation of SMAD3/SMAD4 and Smad-dependent transcriptional activation. Two frame-shift mutations were located upstream within the MH1 or proline-rich linker region. They led to truncated transcripts, which were probably subjected to nonsense-mediated mRNA decay, as shown before for the p.Thr277ProfsX61 mutation.[12] The most likely effect of these mutations is loss of function, with TGFβ signals not being propagated via SMAD3. Notably, we have previously shown that this leads to a paradoxical increase in TGFβ signalling in the aortic wall,[12] which has also been found in other syndromes characterised by arterial wall anomalies, such as MFS, LDS, ATS and FBLN4-related AR-CL.[7, 10, 11, 16]

Regalado *et al*[17] recently described four different *SMAD3* mutations (p.Ala112Val, p.Asn218fs, p.Glu239Lys and p.Arg279Lys) in patients with TAAD and aneurysms affecting other vessels, including cerebral arteries, and osteoarthritis. The frequency of *SMAD3* mutations in their cohort of non-syndromic familial TAAD patients was 2%, which is comparable to that in our cohort of (not necessarily familial) TAAD patients.

In addition, a p.Asn197Ile missense variant was found in a patient with osteoarthritis who was not evaluated for other AOS anomalies.[18]

Patients with AOS

We present the clinical and molecular data for 45 patients with *SMAD3* mutations from eight unrelated families with AOS. The patients come from families of Dutch, Belgian, Spanish and American ancestry. All patients with a *SMAD3* mutation exhibited symptoms or signs of AOS, with the youngest patient being 9 years old. Although not all families could be completely evaluated, the penetrance of the mutations is nearly 100%. The expression varied from very mild (isolated bifid uvula in a 9-year-old girl, family 1, patient V-12) to severe (multiple aneurysms and dissections in a 50-year-old woman, family 1, patient III-17) disease. Age-dependent progression of the phenotype is evident, as aneurysms and osteoarthritis were encountered mainly during adulthood, although this study only included six children. The cardiovascular abnormalities at a young age were generally mild and mainly included mitral valve prolapse or congenital heart malformations. The youngest patient diagnosed with an aortic aneurysm was 14 years old. All dissections occurred in adulthood—the youngest patient was 34 years of age.

AOS is mainly characterised by a combination of arterial anomalies with early-onset osteoarthritis, but mild craniofacial anomalies and other features reminiscent of connective tissue disorders are also present. The AOS phenotype with typical cardiovascular and orthopaedic anomalies was present in at least five of the eight families. Two families were not screened for joint abnormalities, and in only one family joint problems were not reported. Similarly, Regalado *et al* reported osteoarthritis or joint disease in four of their five families (37% of their cases) with *SMAD3* mutations, although radiological investigations to assess osteoarthritis were not performed.[17]

Intrafamilial variability, as illustrated by the clinical findings in a large family of 33 patients with AOS, was significant: while some patients presented mainly with arterial aneurysms and dissections, others only had joint abnormalities. Therefore the genotype–phenotype correlation, if present, will be difficult to establish.

Cardiovascular anomalies

The vast majority (89%) of patients with AOS had cardiovascular abnormalities. Aneurysms and tortuosity were found throughout the complete arterial tree studied, in both large and medium-size vessels, including the cerebral arteries. Despite the presence of intracranial aneurysms, stroke has rarely been reported in AOS. Dissections occurred in the aorta and in medium-/small-sized arteries, including a coronary artery. Arterial dissection and rupture occurred occasionally in aortas that were only mildly dilated; therefore early preventive surgery with resection of the aneurysms is advised.

Apart from arterial aneurysms and tortuosity, there were also other cardiovascular anomalies present in many patients with AOS, including mitral valve anomalies, congenital heart malformations, ventricular hypertrophy and atrial fibrillation. The congenital heart malformations were significantly more common than expected in the general population ($p<0.0001$). It is very likely that *SMAD3* mutations also lead to cardiac hypertrophy and atrial fibrillation via TGFβ upregulation. It is currently unclear how loss-of-function mutations in *SMAD3* lead to a paradoxical increase in TGFβ signalling[12] and the congenital and age-related cardiovascular anomalies described above.[19]

Joint anomalies

Most of the patients developed joint abnormalities, including OCD, meniscal lesions, intervertebral disc degeneration and osteoarthritis. These abnormalities were already present at a young age. Interestingly, joint complaints were the first symptom for which clinical advice was sought in the majority of patients.

OCD was present in more than half of patients, mainly in the medial, but also in the lateral, femoral condyle of the knee. Interestingly, mutations in the *ACAN* gene encoding the proteoglycan aggrecan have been described in families with autosomal dominant inheritance of OCD.[20] Aggrecan is a downstream effector of the TGFβ signalling pathway, and may mediate *SMAD3*-associated OCD in AOS.

Intervertebral disc degeneration was present in most (92%) patients and mainly involved the cervical and lumbar spine. Mice studies have shown that TGFβ is essential for promoting and/or maintaining the intervertebral disc during development.[21]

Osteoarthritis was present in almost all patients with AOS, and primarily involved the joints of the knee, spine, hand and foot. In SMAD3-related disease, osteoarthritis could be secondary to OCD, joint laxity or disc degeneration, which are present in many patients with AOS. However, OCD of the medial femoral condyle (most commonly observed in patients with AOS) rarely results in osteoarthritis. This area is non-weight-bearing and therefore less prone to osteoarthritis.[22] In addition, osteoarthritis is also present in joints not affected by OCD or meniscal lesions. Joint laxity may also play a role in development of osteoarthritis: pes planus, scoliosis and joint hypermobility may indicate ligamental insufficiencies. Therefore, in addition to intrinsic abnormalities of the hyaline cartilage of the joints, early-onset osteoarthritis in these families may be enhanced by overload based on abnormal menisci, intervertebral discs and/or ligaments. Spinal osteoarthritis at the intervertebral and uncovertebral joints may be the result of the early disc degeneration.

It is likely that osteoarthritis in AOS is due to secondary changes and abnormal development of the cartilage directly caused by the *SMAD3* mutation. TGFβ has a dual role in chondrocytes, primarily acting as a stimulator in chondrocyte differentiation and, in later stages of development, blocking chondrocyte terminal differentiation.[23–25] SMAD3 has an important function in this TGFβ-mediated growth inhibition and maintenance of the articular cartilage.[25,26] This is corroborated in *Smad3* knock-out mice, which show premature chondrocyte maturation and subsequent premature osteoarthritis.[25,27] A direct role for SMAD3 in osteoarthritis is further supported by the identification of a *SMAD3* mutation in a patient with knee osteoarthritis,[18] the recent association between a single-nucleotide polymorphism in intron 1 of *SMAD3* and the risk of both hip and knee osteoarthritis,[28] and several in vitro studies.[29]

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Other phenotypic anomalies

A MFS habitus with dolichostenomelia, long slender fingers, pectus deformity and scoliosis was present in a minority of patients. Aspecific cutaneous anomalies commonly seen in connective tissue disorders, including velvety skin with striae and easy bruising, were present in the majority of patients with AOS. Craniofacial features were often mild or absent and mainly included hypertelorism (figure 4) and a broad or bifid uvula. Overall, the phenotypic anomalies in many patients with AOS were discrete, and missed on consultation for cardiovascular anomalies, whereby the patients were classified as non-syndromic TAAD.

Comparison with other TGFβ-related syndromes

Although many cases of AOS were classified as non-syndromic TAAD, the phenotype overlaps with that of aneurysm syndromes such as MFS and LDS. Some patients had a MFS habitus, whereas others had craniofacial anomalies with features such as hypertelorism and broad/bifid uvula reminiscent of LDS. The cardiovascular features in patients with AOS are similar to those of LDS, including thoracic aortic aneurysms at the level of the sinus of Valsalva and aneurysms and tortuosity throughout the arterial tree. However, involvement of the entire arterial tree, including the intracranial arteries, is rare in patients with MFS. Similarly to LDS, the aortic aneurysms of patients with AOS tend to rupture at smaller aortic diameters than in MFS. Aneurysms are less common in ATS than in AOS, although a similar tortuosity of the entire arterial tree is found.

Atrial fibrillation and ventricular hypertrophy (24% and 18%, respectively) have not yet been reported in LDS and are both uncommon in MFS,[30] whereas some patients with ATS show ventricular hypertrophy.[31] Mitral valve anomalies, mainly prolapse, are equally common in patients with AOS (50%) and MFS (54%)[32] and less common in LDS (35%).[33]

Congenital heart malformations are found in only 9% of patients with AOS, in contrast with 22–35% in LDS.[8] The nature of these defects—that is, persistent ductus arteriosus and atrial septal defect—are similar in both disorders.[8] In only 1% of patients with MFS have congenital heart malformations been reported.[33]

Joint anomalies with osteoarthritis, OCD and meniscal lesions are key features of AOS, being present in almost all patients. Such anomalies are rarely described in LDS, MFS or ATS. None of the 90 patients with LDS type I or II described by Loeys *et al* were reported to have osteoarthritis, OCD or meniscal abnormalities, although cervical dislocation or instability, spondylolisthesis and intervertebral disc degeneration have been occasionally described.[8,34] Interestingly, arthralgia, osteoarthritis of the hand, hip and/or spine was reported in several patients from a large family with LDS due to a *TGFBR2* mutation.[35] Also in MFS, osteoarthritis, OCD and meniscal abnormalities have only sporadically been described,[36] although spondylolisthesis is present in 6% of patients with MFS.[37] Further joint studies in patients with MFS and LDS are warranted to establish the frequency of osteoarthritis and OCD in these related syndromes.

Conclusions

In conclusion, joint anomalies such as osteoarthritis, OCD and meniscal abnormalities may be a useful discriminating feature from other forms of TAAD. Therefore the syndrome is named AOS.

X-ray examinations of knees, total spine and hands, particularly in TAAD patients with a medical or family history of joint complaints or abnormalities, is recommended. Furthermore, as these typical joint anomalies may be the presenting feature of AOS before symptoms or signs of the cardiovascular features become obvious, we recommend imaging of the heart and complete arterial tree, including cerebral arteries, to exclude arterial anomalies in patients with early-onset osteoarthritis in combination with OCD or a family history of aortic aneurysm or sudden death.

Acknowledgments

We thank all patients and family members for their enthusiastic participation in the study. We thank the referring physicians for sharing the data on the patients. We acknowledge T. de Vries-Lentsch and R. Koppenol (Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, The Netherlands) for the photographic work.

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Progression rate and early surgical experience in the new aggressive Aneurysms-Osteoarthritis Syndrome

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Ann Thorac Surg. 2013;95:563-9.

Abstract

Background

Aneurysms-osteoarthritis syndrome (AOS), caused by *SMAD3* mutations, is a recently described autosomal dominant condition characterized by aneurysms throughout the arterial tree in combination with osteoarthritis. The objective of the present study was to evaluate progression rate of aortic dilatation and surgical outcome in AOS patients.

Methods

All AOS patients are regularly monitored according to our clinical AOS protocol. Patients with at least two follow-up visits or who underwent aortic root surgery during follow-up were included in this cohort study. Clinical and surgical data were obtained from chart abstraction.

Results

We included 22 patients (age 38±15 years; 41% male) with the molecular diagnosis of AOS. Follow-up duration was 3.3 years (interquartile range, 1.6-5.1). In the 17 patients, who were managed conservatively, aortic root diameter increased from 37.5±5.1 at baseline to 40.3±6.2 mm at follow-up (p=0.008). Progression rate of aortic dilatation was highest at the level of the sinus of Valsalva (2.5±5.8 mm per year) and significantly correlated with the initial diameter (r=0.603, p=0.017). Ten patients successfully underwent valve sparing aortic root replacement, 5 patients after previous watchful waiting. Mean pre-operative aortic diameter was 46.6±4.0 mm. The operations were not complicated by fragility of tissue. After a post-operative period of 2.8 years (interquartile range, 0.7-5.4), no mortality or reoperations had occurred, and all patients remained asymptomatic.

Conclusions

Aneurysm growth in AOS patients can be fast and unpredictable, warranting extensive and frequent cardiovascular monitoring. Valve sparing aortic root replacement is a safe and effective procedure for the management of aortic root aneurysms in AOS patients.

Introduction

Aortic aneurysms and dissections are common conditions, ranking as the 19th most common cause of death in the US in 2007 (1). The predilection for thoracic aortic aneurysms and dissections (TAAD) can be inherited in an autosomal dominant manner (2). Familial TAAD is subdivided into nonsyndromic and syndromic forms. Nonsyndromic familial TAAD can be associated with bicuspid aortic valve or patent ductus arteriosus, or both (3,4). Syndromic familial TAAD includes several systemic connective tissue disorders, such as Marfan syndrome and Loeys-Dietz syndrome (5,6).

Recently, our group described a new syndromic familial TAAD form: aneurysms-osteoarthritis syndrome (AOS), caused by mutations in the *SMAD3* gene (7–11). Its key features are arterial aneurysms and tortuosity, early-onset joint abnormalities, and mild cutaneous and craniofacial features (7–9). This syndrome is an autosomal dominant disorder and is found to be responsible for approximately 2% of familial TAAD (7,12). Aneurysms most commonly occur at the level of the sinus of Valsalva, but can be present throughout the entire arterial tree (7–11). Aortic dissections can occur in relatively mildly dilated aortas and are associated with a high mortality rate (7–9). Moreover, cerebrovascular abnormalities are encountered in the majority of patients (8,9). The best discriminating feature between AOS and other connective tissue disorders is the presence of early onset osteoarthritis, which is often the first reason to seek medical advice (7–9).

The cardiovascular phenotype of *SMAD3*-related AOS has extensively been described (7–9); however, knowledge about the progression of the aneurysms over time and outcome after surgery in this patient group is lacking. In other disorders affecting the aorta, for example, vascular type Ehlers-Danlos syndrome, fragility of aortic tissue may complicate surgical intervention (13). When considering prophylactic surgery to prevent aneurysms from rupturing, it is important to know whether friable vascular tissue is also present in AOS patients. Therefore, the purpose of this study was to evaluate the progression rate of aortic dilatation and surgical outcome of valve-sparing aortic root replacement in AOS patients.

Patients and Methods

All previously identified AOS patients (9) are intensively monitored at regular intervals according to our clinical AOS protocol (8). Only living patients with at least two follow-up visits with radiologic evaluation and those who underwent aortic root surgery were included in this cohort study. The AOS patients without follow-up visits at our centers or who had already died, were excluded. The diagnosis of AOS was confirmed by molecular and clinical genetic analysis (7). The study was approved by the Institutional Review Board and Ethical Committee of the Erasmus Medical Center in Rotterdam. Written informed consent was obtained from each patient.

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Data collection

Data were abstracted from electronic patient records. Collected variables included demographics, medical history, family history, cardiovascular imaging, operative details, and complications. Electrocardiography-gated computed tomography angiography or magnetic resonance angiography from head to pelvis was used to evaluate presence, size, and location of arterial aneurysms, dissections, and tortuosity. Aortic dimensions were repeatedly measured at eight standardized levels, and the annualized growth rate was calculated. The follow-up period of this study was defined as the time between first and last radiographic evaluation. Transthoracic echocardiography was used to evaluate presence of valvular or congenital pathology and left ventricular hypertrophy and function. The N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured by radio-immunoassay (Phoenix Pharmaceuticals, Burlingame, CA). Arterial stiffness was assessed by aortic pulse wave velocity (SphygmoCor system; ArtCor, Sydney, Australia) and carotid distensibility (Wall Track System; Pie-Medical/Esaote, Maastricht, Netherlands).

Operative technique

In patients requiring surgical intervention, valve-sparing root replacement (VSRR) with the David procedure is our technique of choice (14). The native aortic valve is resuspended within a Dacron tube graft with prefashioned pseudosinuses (Gelweave Valsalva graft; Vascutek, Renfrewshire, Scotland).

Data analysis

For the statistical analyses, the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, IL) was used. All statistical tests were two-sided; p less than 0.05 was considered statistically significant. The one-sample Kolmogorov-Smirnov Test and histograms were used to check normality. Normally distributed continuous data are presented as mean ± SD, and categorical variables as frequency (n) and percentages. Nonnormal distributed data are presented as median with interquartile range. For comparison within subjects over time, the paired t test and signed-ranks Wilcoxon test was used. For correlation analysis, the Pearson r correlation coefficient and Spearman correlation test were used.

Results

A total of 22 patients (age 39±15 years; 41% male) from three families with the diagnosis of AOS were included in this study. Longitudinal natural history data were available for 17 patients. Five patients underwent surgery immediately after initial screening, and another 5 patients underwent surgery after previous watchful waiting (Figure 1). Median follow-up period was 3.3 years (interquartile range, 1.6-5.1). Baseline characteristics are shown in Table 1. All patients were in New York Heart Association functional class I and in sinus rhythm at baseline. No deaths or aortic dissections occurred during follow-up. No aortic valve pathology was found.

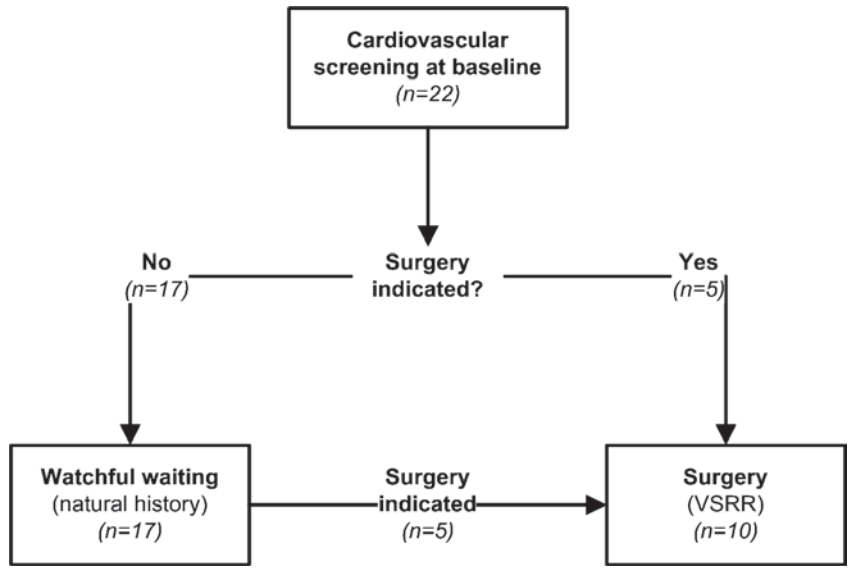

Figure 1. *Flowchart demonstrating the number of Aneurysms-Osteoarthritis Syndrome patients included in this study.*

VSRR = valve-sparing aortic root replacement.

Table 1. *Baseline characteristics.*

	AOS patients (n=22)
Age, years	39±15
Gender (male)	9 (41)
Body mass index, kg/m^2	24±4
Arterial tortuosity thorax/abdomen	8 (18)
Mitral valve abnormalities	
Billowing	5 (23)
Prolapse	1 (5)
Mild mitral valve regurgitation	5 (23)
Moderate mitral valve regurgitation	2 (9)
Severe mitral valve regurgitation	0 (0)
Congenital heart defects	
Persistent ductus arteriosus	2 (9)
Pulmonary valve stenosis (mild)	1 (5)
Atrial septal defect	1 (5)
Left ventricular hypertrophy	3 (14)
Fractional shortening, %	36±7

Values are expressed as n(%) or mean±SD.
AOS = Aneurysms-Osteoarthritis Syndrome

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Progression rate of aortic dilatation

Table 2 shows the progression rate of aortic dilatation in the 17 conservatively managed patients. Statistically significant progression occurred at the level of the sinus of Valsalva and in the ascending thoracic aorta (respectively, p=0.008 and p=0.004). The highest progression rate was found at the level of the sinus of Valsalva (2.5±5.8 mm/year; interquartile range, -1.4-20.9 mm/year), which significantly correlated with the initial sinus of Valsalva diameter (r=0.603, p=0.017).

No correlations were found between aortic progression rate and baseline age (r=0.261; p=0.368), low-density lipoprotein cholesterol (r=-0.214; p=0.463), systolic blood pressure (r=-0.280; p=0.332) or left ventricular mass (r=0.264; p=0.383). Furthermore, sex did not influence aortic progression rate (p=0.240).

Table 2. *Progression rate of aortic dilatation measured by computed tomography angiography (n=17).*

	Baseline aortic diameter (mm)	Follow-up aortic diameter (mm) [a]	p-value	Progression rate (mm/year)
Annulus	27.9±5.2	28.2±5.0	0.842	+0.9±3.7
Sinus of Valsalva	37.5±5.1	40.3±6.2	0.008	+2.5±5.8
Sinotubular junction	30.7±3.5	30.9±4.6	0.659	+0.2±1.7
Ascending thoracic aorta	29.9±4.3	31.2±4.0	0.004	+0.6±0.7
Aortic arch	24.7±4.7	26.4±4.0	0.164	+1.4±5.3
Descending thoracic aorta	24.4±3.4	25.6±4.3	0.095	+0.9±2.9
Diaphragmatic level aorta	21.9±3.9	22.5±3.3	0.542	+0.4±1.7
Abdominal aorta	18.6±3.2	20.6±3.3	0.063	+0.8±3.7

Values are expressed as mean±SD.
[a] Follow-up period: 3.*3 years (interquartile range, 1.6-5.1)* .

Arterial stiffness and NT-proBNP measurements

No statistically significant changes in aortic pulse wave velocity, NT-proBNP, or blood pressure were observed within a time interval of 11.2 months (interquartile range, 6.1-15.3; Table 3). Carotid stroke change and distensibility coefficient significantly decreased over time (respectively, p=0.035 and p=0.004). No correlations were found between progression rate at the level of the sinus of Valsalva and NT-proBNP (r=0.243; p=0.423), carotid distensibility coefficient (r=0.191; p=0.533), aortic pulse wave velocity (r=0.110; p=0.748), or augmentation index (r=0.050; p=0.871).

Elective valve-sparing aortic root replacements

Ten patients underwent elective VSRR in our centers (age 38.4±14.7 years; 60% male; Table 4 provides details for each patient). Preoperative aortic root diameter at the level of the sinus of Valsalva was 46.6±4.0 mm (range, 39 to 57 mm). Mean cardiopulmonary bypass and cross-clamp times were 168±12 and 141±17 minutes, respectively.

During surgery aortic fragments from 7 patients were obtained (unfortunately not from the first 3 patients who underwent operation). Histopathology examination showed characteristic loss and fragmentation of elastic fibers, and mucoid medial degeneration in five fragments (71%). No abnormalities were observed in the aortic tissue specimens from the other 2 patients.

The operation was uncomplicated in all patients, apart from 1 patient who had a complete atrioventricular block perioperatively, requiring a permanent pacemaker implantation. In none of the patients was a rethoracotomy necessary. One patient had two episodes of paroxysmal atrial flutter 3 weeks postoperatively, treated successfully with beta blockade. No patients had postoperative infections, thromboembolism, or endocarditis.

After a post-operative period of 2.8 (interquartile range, 0.7-5.4) years, no mortality or reoperations had occurred, and all patients remained in New York Heart Association functional class I.

Table 3. *Arterial stiffness and N-terminal pro-brain natriuretic peptide at baseline and during follow-up (n=17).*

	Baseline	Follow-up	p-value
Heart rate, beats/min	65.8±12.3	62.9±15.4	0.347
Pulse wave velocity, m/s	9.7±3.0	9.5±3.1	0.782
Transit time, ms	166.1±65.5	173.1±66.0	0.566
Augmentation index at HR75, %	24.2±17.3	18.6±21.9	0.145
Systolic blood pressure, mmHg			
Brachial	127.1±15.0	125.8±10.4	0.680
Central	117.1±12.9	113.5±10.1	0.252
Diastolic blood pressure, mmHg			
Brachial	73.5±8.6	73.5±8.2	0.970
Central	75.0±8.8	74.6±7.9	0.816
Mean arterial pressure, mmHg			
Brachial	93.2±8.9	90.9±8.4	0.353
Central	93.2±8.9	90.9±8.4	0.353
Pulse pressure, mmHg			
Brachial	53.5±7.9	52.3±7.0	0.640
Central	42.1±8.0	38.9±6.3	0.182
Carotid intima-media thickness, µm	609.8±183.6	593.4±107.4	0.764
Carotid end-diastolic diameter, mm	6.8±1.4	6.5±1.2	0.546
Carotid stroke change, µm	403.1±140.3	303.4±137.5	0.035
Distensibility coefficient, 10^{-3}/kPa	27.5±10.1	16.9±5.4	0.004
NT-proBNP, pg/ml	101.7 (55.1-169.5)	102.5 (44.9-184.8)	0.778

Values are expressed median (interquartile range) or mean±SD.
HR75 = heart rate of 75 beats per minute; NT-proBNP = N-terminal Pro Brain Natriuretic Peptide.

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Table 4. *Surgical details per patient.*

Age at time of surgery (years)	Sex	Time since surgery (years)	Preop aortic root diameter (mm)	Preop degree of AR	Type of operation	Additional surgical procedures	Prosthetic diameter (mm)	Postop degree of AR	CPB time (minutes)	Cross-clamp time (minutes)	Length of hospital (ICU) stay (days)	Postop complications
57.9	female	7.2	48	mild	VSRR	none	24	mild	…	…	…	none
32.0	male	1.0	57	trace	VSRR	none	30	trace	178	159	6 (1)	none
20.3	male	1.5	46	none	VSRR	none	28	none	158	137	15 (1)	Complete AV-block
39.9	male	4.4	47	none	VSRR	none	26	none	158	124	6 (1)	none
41.1	female	1.7	39	trace	VSRR	none	26	mild	165	123	5 (1)	none
34.0	female	6.5	45	none	VSRR	none	24	none	…	…	…	none
31.2	male	3.9	46	none	VSRR	none	28	none	172	131	6 (1)	AF
45.3	female	5.5	49	none	VSRR	none	26	mild	…	…	…	none
64.2	male	1.0	45	none	VSRR	none	30	trace	158	144	7 (1)	none
18.3	male	0.1	46	none	VSRR	none	28	none	189	168	7 (1)	none

Elipsis (…) indicates information could not be retrieved.
AF = atrial flutter; AR = aortic regurgitation; AV = atrioventricular; CPB = cardiopulmonary bypass; ICU = intensive care unit; Postop = postoperative; Preop = preoperative; VSRR = valve-sparing aortic root replacement.

Comment

The present study provides data on the progression of aortic dilatation and early surgical experience in patients with AOS.

Key clinical features of AOS

Aneurysms-osteoarthritis syndrome is a recently described autosomal dominant disorder that predisposes patients to widespread arterial aneurysms, dissections and tortuosity (7-9). It is caused by mutations in the *SMAD3* gene, which likely causes loss of function and a paradoxical increase in TGF-β signaling in the aortic wall (7). On histology of aortic wall specimens, disorganization of the tunica media with fragmentation and loss of elastic fibers, as well as characteristic mucoid medial degeneration and accumulation of collagen in media can be encountered (7).

While aneurysms are most frequently localized in the aortic root, they can be found throughout the arterial tree, including the iliac, visceral, and intracranial arteries (8-11). Because dissections can occur at relatively mildly dilated aortic diameters, early elective surgical repair should be considered (8). Extensive cardiovascular evaluation using computed tomography or magnetic resonance angiography from head to pelvis and echocardiography is recommended in every AOS patient at baseline and after 1 year (8). Thereafter, progression rate, location and size of aneurysms, and presence cardiac abnormalities should guide individualized frequency of imaging (8).

Although AOS might resemble other TAAD syndromes such as Marfan and Loeys-Dietz syndrome (5,6), it can be discriminated by the presence of early onset joint anomalies such as osteoarthritis, osteochondritis dissecans, and meniscal abnormalities (9). Other features that are frequently related to AOS include hypertelorism (widely-spaced eyes), uvula abnormalities (broad or bifid), umbilical and inguinal hernias, pelvic floor prolapse, varices, scoliosis, and velvety skin (7-9).

Aortic aneurysm progression in AOS patients

Annualized progression of aortic dilatation in AOS patients was found to be highest in the sinus of Valsalva with approximately 2.5 mm per year. Although this estimate is based on a small number of AOS patients and should be confirmed in the future by larger studies with longer follow-up intervals, it has become clear that aortic growth in AOS patients can be fast and unpredictable. The annual progression rate seems comparable to or even higher than in Marfan patients with progression ranging from 0.4 to 2.1 mm per year (15–19). In patients with a bicuspid aortic valve the progression of ascending aortic dilatation seems to be lower, with a large variety ranging from 0.2 to 1.9 mm/year (20–23). Unfortunately, we could not find any longitudinal studies involving Loeys-Dietz or vascular type Ehlers-Danlos syndrome patients with which to compare our results to. Similar to Marfan patients, the baseline aortic diameter was also correlated to progressive aortic dilatation in AOS patients (24).

Interestingly, we noted that carotid distensibility significantly decreased, indicating increased arterial stiffness. However, the aortic pulse wave velocity did not change over time. Arterial stiffness depends on structural and functional properties of the arterial wall. The measure of carotid distensibility is a local measure of stiffness that provides information on elastic arteries, whereas aortic pulse wave velocity reflects the arterial wall stiffness of a larger part of the arterial tree, providing information on both elastic and muscular arteries (25).

Although these findings need to be confirmed in a larger patient sample after a longer follow-up period, we speculate that early signs of degeneration in AOS patients might be more prominent in elastic arteries. For future research directions, it would be interesting to evaluate whether this might significantly impact which type of arteries develop aneurysms and whether there is a difference in aneurysm growth between elastic and muscular arteries.

Early surgical experience in AOS patients

The AOS patients tolerated VSRR well and excellent early results were achieved. No mortality occurred, and 2.8 years post-operatively, all patients remained in New York Heart Association functional class I. No significant aortic regurgitation developed, and no reoperations were required. Furthermore, all aortic valves could be saved. These favorable preliminary results seem comparable to the excellent results of VSRR in other patients with aortic aneurysms, including Marfan and Loeys Dietz syndrome patients, but need to be confirmed in larger series (26–31). Unlike patients with vascular type Ehlers-Danlos syndrome who have a high incidence of intraoperative and early postoperative vascular events due to fragile arterial tissue (13), that was not encountered in AOS patients. The aortic tissue of AOS patients did not feel extremely thin or fragile, as is the case in Ehlers-Danlos syndrome.

Because growth of aortic root aneurysms in AOS patients can be fast and unpredictable, aortic dissections have been reported to occur in relatively mildly dilated aortas (7–9), and elective VSRR shows favorable results, early prophylactic surgical intervention should be considered to avoid vascular catastrophes. As AOS highly resembles Loeys-Dietz syndrome with regard to aortic aneurysms and dissections, we suggest applying the current surgical recommendations for Loeys-Dietz Syndrome (32). Individualized assessment of risk versus benefit, based on family history and patient characteristics, should always be taken into account. For postoperative surveillance, we recommend transthoracic echocardiography at 6 months post-operatively and annually thereafter to monitor aortic root diameter and valve competence. Given the widespread involvement of the arterial tree in AOS patients, repeated head-to-pelvis imaging in patients after VSRR remains crucial to evaluate other large and medium-sized arteries.

Study limitations

The main limitations of this study are the small number of patients with AOS and the relatively short follow-up period. This was inevitable, as this syndrome is only recently discovered and relatively unknown. To control for differences in follow-up length, the annual rate of progression was calculated. Owing to the limited number of patients, we were not able to check whether progression is correctly described in a linear way and which factors could influence progression rate. Despite our efforts to measure aortic diameters repeatedly in a standardized way with optimal imaging, we have to acknowledge the limitations of the imaging techniques to accurately detect small changes in diameters. Selection bias certainly plays a role in this study, because this is a highly selected population of alive AOS patients with follow-up visits.

Despite these limitations, this study adds important clinical information for the management of this patient group. Definitive recommendations regarding management of AOS patients will require longer follow-up studies in a larger sample of patients.

Conclusions

AOS is known to predispose patients to aggressive and widespread cardiovascular disease. Progression rate of aortic dilatation in AOS patients is highest at the level of the sinus of Valsalva with approximately 2.5 mm per year and is correlated with the initial aortic diameter. A VSRR is a safe and effective surgical option for the management of aortic root aneurysms in AOS patients. Certainly, as more patients with AOS will be identified in the future, a better understanding of the natural history and surgical outcome will become evident. For now, cardiologists and (cardio)vascular surgeons should be aware of this new syndrome and its aggressive behavior.

Acknowledgements

We thank the participating patients, their families, and their referring physicians. We also thank the technician assistants from the participating centers.

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Saccular aneurysm within a persistent ductus arteriosus

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Lancet. 2012;379:e33

Clinical picture

A 26-year old man with a proven *SMAD3* mutation underwent cardiovascular evaluation, because his 52-year old mother died of an aortic dissection and his 28-year-old brother has an aortic root aneurysm of 41 mm. CT angiography showed a dilated pulmonary trunk (50 mm) and a saccular aneurysm of a persistent ductus arteriosus (figure A; see also webvideo 1). During catheterisation the pressure in the aneurysm was 75% of systemic arterial pressure. To prevent further enlargement and possible rupture, the aneurysm (18x14 mm) was filled with an Amplatzer Vascular Plug II (AGA Medical, Plymouth, USA) (figure B and C; see also webvideo 2). A recently discovered syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis, caused by pathogenic *SMAD3* mutations, is characterized by aneurysms, dissections and tortuosity throughout the arterial tree, predominantly in the aortic root.[1] In our case, CT angiography was a useful screening method.

Reference

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@ **For the supplementary videos, please see the online version of this article available at:**
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)61352-4/fulltext

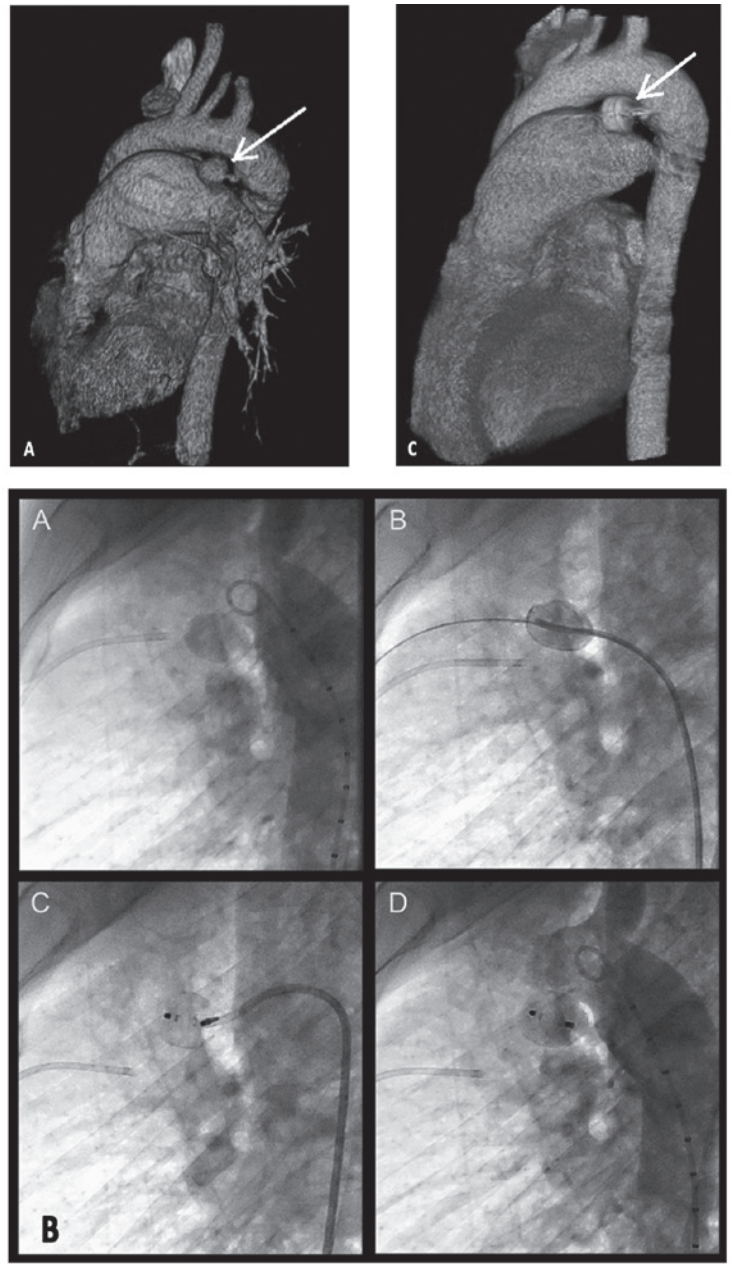

Figure 1. *Saccular aneurysm within a persistent ductus arteriosus and placement of a vascular plug.*

(A) 3D reconstruction of CT angiography showing a dilated pulmonary trunk (50 mm) and a saccular aneurysm of a persistent ductus arteriosus (arrow). (B) Angiography images showing different stages of the catheterization procedure: (a) aneurysm of the persistent ductus arteriosus (14x18 mm); (b) catheter positioned within the aneurysm; (c) delivery of the vascular plug (size 16x12 mm); (d) closure of the persistent ductus arteriosus with the vascular plug in place. (C) 3D reconstruction of CT angiography showing the result after interventional closure of the aneurysm with a vascular plug (arrow).

Aneurysms-Osteoarthritis Syndrome with visceral and iliac artery aneurysms

13

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J Vasc Surg. 2013;57:96-102.

Abstract

Objective

Aneurysms-Osteoarthritis Syndrome (AOS), caused by *SMAD3* mutations, is a recently described autosomal dominant syndrome characterized by arterial aneurysms, tortuosity and aortic dissections in combination with osteoarthritis. Our objective was to evaluate the AOS-related vascular consequences in the visceral and iliac arteries and raise awareness for this aggressive syndrome among vascular specialists.

Subjects

All AOS patients were monitored regularly according to our clinical AOS protocol. The study included those with one or more visceral aneurysms or tortuosity, or both. Clinical and surgical data were obtained from record abstraction.

Results

The study included 17 AOS patients (47% male) aged 47±13 years. A total of 73 aneurysms were encountered, of which 46 were located in the abdomen. The common iliac artery was most commonly affected (37%), followed by the superior mesenteric artery (15%), celiac trunk (11%) and splenic artery (9%). Rapid aneurysm growth ≤1 year was found in three arteries (gastric, hepatic and vertebral artery). Furthermore, arterial tortuosity was noted in 94% of patients. Four patients underwent six elective (endo)vascular interventions for aneurysms in the iliac, hepatic, gastric, or splenic artery, without major perioperative or postoperative complications.

Conclusions

AOS predisposes patients to widespread visceral and iliac artery aneurysms and extreme arterial tortuosity. Early elective aneurysm repair should be considered because the risk of aneurysm rupture is estimated to be very high and elective (endo)vascular interventions were not complicated by fragility of arterial tissue. Given the aggressive behavior of AOS, it is of utmost importance that vascular specialists are aware of this new syndrome.

Introduction

Visceral and iliac aneurysms are relatively rare, yet potentially catastrophic when rupturing.[1-4] Although most visceral and iliac aneurysms are degenerative, they can also be encountered in the setting of connective tissue disorders, such as Loeys-Dietz and vascular type Ehlers-Danlos syndrome.[5-7] Recently, our group discovered a new syndrome: the Aneurysms-Osteoarthritis Syndrome (AOS).[8] This autosomal-dominant connective tissue disorder is caused by heterozygous mutations in the *SMAD3* gene, located on chromosome 15q22.33 (OMIM #613795).[8] The syndrome is typically characterized by widespread arterial aneurysms and tortuosity, early-onset joint abnormalities and mild craniofacial and cutaneous features.[8-11] Penetrance is nearly 100%, and so far, AOS has only been identified in families originating from North America and Europe.[10,12] The expression seems to be age-dependent and may vary from very mild (isolated bifid uvula) to severe (multiple aneurysms, dissections, or death at young age).[10]

AOS is estimated to be responsible for approximately 2% of familial thoracic aortic aneurysms and dissections, as well as intracranial, aortic and bilateral iliac aneurysms segregating in an autosomal dominant manner.[8,12] The incidence of AOS in patients with primary visceral and iliac artery aneurysms is currently unknown and remains to be determined.

The major source of early death in AOS is aortic root dilatation, potentially leading to aortic dissection and rupture.[9] In some individuals, aortic dissection occurred at relatively mildly enlarged aortic diameters.[8-10] However, arterial involvement is not limited to the aorta, but can be widespread, with peripheral and intracranial aneurysms and arterial tortuosity, thereby resembling Loeys-Dietz syndrome.[9,13,14] Furthermore, early-onset osteoarthritis is present in nearly all patients and useful to discriminate AOS from other connective tissue disorders.[8-10] The osteoarthritis is often the first reason the individual seeks medical advice, with a mean age at diagnosis of 42 years (youngest, 12 years old).[8-10] Although the genetic background and thoracic aortic pathology of *SMAD3*-related AOS have been described before, so far the vascular consequences of AOS beyond the aortic root have not been highlighted. Therefore, the purpose of this study was to evaluate the AOS-related vascular abnormalities in the visceral and iliac arteries and raise awareness for this aggressive syndrome among vascular specialists.

Methods

The study was approved by the Institutional Review Board and Ethical Committee of the Erasmus MC in Rotterdam. Written informed consent was obtained from each patient.

Patients

The medical records of the 45 identified AOS patients[10] were reviewed to evaluate visceral and iliac vascular abnormalities. As previously described, aneurysmal findings included thoracic aortic aneurysms (72%), abdominal aortic aneurysms (12%), aneurysms in other thoracic or abdominal arteries (36%) and intracranial aneurysms (38%).[9,10]

Aortic dissection/rupture was present in 33% of patients.[9,10] AOS diagnosis was confirmed by genetic analysis and clinical phenotype.[10] All AOS patients were intensively monitored at regular intervals according to our clinical AOS protocol.[9] Only AOS patients with one or more visceral or iliac aneurysms or tortuosity, or both, were included in this report.

Data collection

Clinical data were collected from chart abstraction and electronic patient records. Collected variables included demographics, medical history, family history, cardiovascular imaging, and (endo)vascular interventions. Computed tomography angiography (CTA) or magnetic resonance angiography (MRA) from head-to-pelvis was used to evaluate presence of vascular abnormalities. An experienced cardiovascular radiologist evaluated presence, location, and size of aneurysms, dissections and tortuosity. An aneurysm was defined as a dilatation of an artery by > 1.5 times the expected arterial diameter. Visceral arterial tortuosity was defined as a severe (pigtail-like) curve or multiple curves in an artery. Aortic and iliac tortuosity was defined as described by Chaikof et al.[15]

Results

The study included 17 AOS patients with visceral and iliac aneurysms (n=15) or tortuosity (n=9), or both. The primary reason for presentation in one patient was a symptomatic visceral or iliac artery aneurysm. This 32-year old male presented with pain and a pulsating mass in the lower abdomen, which was caused by bilateral aneurysms in the common iliac arteries (69 and 42 mm; patient 1). In the remaining 16 patients, the visceral or iliac artery aneurysms were found when extensive imaging was performed at the time of identification of AOS because of an aortic dissection (n=5), aortic root aneurysm (n=6) or screening of asymptomatic family members (n=5). Baseline characteristics are summarized in Table 1.

Overall, these 17 AOS patients exhibited 73 aneurysms, of which 46 aneurysms were located in the abdomen (Figure 1). Detailed information about each individual patient is provided in the Supplementary Table (online only). Aneurysms were most frequently found at the common iliac artery (17 aneurysms in 10 patients), followed by the superior mesenteric artery (seven aneurysms), celiac trunk (five aneurysms) and splenic artery (four aneurysms). Additional aneurysms were found in the external iliac, internal iliac, hepatic, renal, gastric, gastroduodenal, and femoral artery. The majority of patients (59%) also had an aortic root aneurysm. In six patients the abdominal aorta was dilated (range, 23 to 100 mm) and four patients exhibited a Type B aortic dissection. Chronic bilateral common iliac artery dissections were present in one patient at a diameter of 9 and 17 mm (none to mild dilatation). Extensive arterial tortuosity was noted throughout the arterial tree, most frequently located in the vertebral, iliac, splenic, carotid and intracranial arteries (Figure 2, Video 1, online only).

Table 1. *Baseline characteristics of patients with Aneurysms-Osteoarthritis syndrome.*

	Mean ± SD or No. (%)
Patients	17
Age, y	47±13
Gender (male)	8 (47)
Body mass index, kg/m^2	24±4
Blood pressure, mmHg	
Systolic	131±17
Diastolic	95±8
Cholesterol, mmol/L	
Total	5.0±1.1
High-density lipoprotein	1.5±0.4
Low-density lipoprotein	3.1±0.9
β-blockade medication	3 (18)
Smoking	
Never	15 (88)
Current	2 (12)

SD, Standard deviation

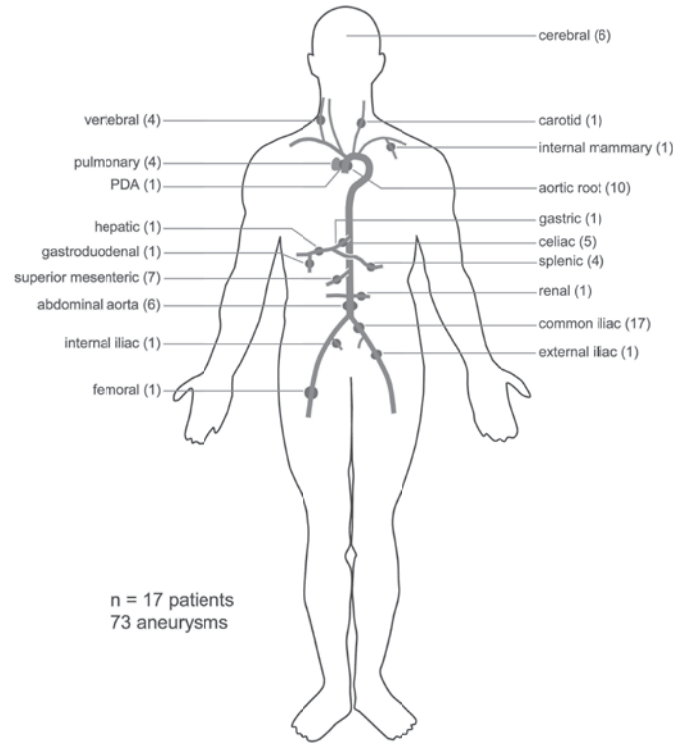

Figure 1. *Distribution of 73 aneurysms within 17 patients with Aneurysms-Osteoarthritis Syndrome. PDA, Patent ductus arteriosus.*

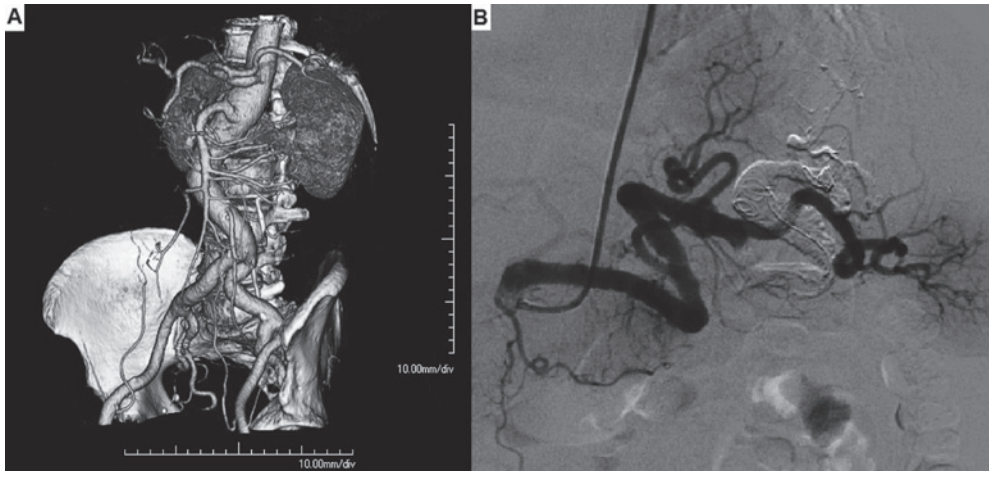

Figure 2. *Arterial tortuosity in (A) aorta, visceral and iliac arteries, and (B) in the splenic artery.*

Aneurysm growth

Repeated CTA or MRA scans were available in six patients, and rapid growth of an aneurysm was noted in two patients. A 30-year-old man (patient 8) had a 6-mm fusiform aneurysm in the left proximal vertebral artery, which increased to 11 mm within 10 months. An aneurysm in the right hepatic artery in a 43-year-old man (patient 7) increased in size from 11 to 18 mm in 9 months' time. Furthermore, a completely new fusiform aneurysm (15x11 mm) in the left gastric artery (normal diameter, 7 mm) developed in patient 7 within 11 months' time. The scans in the patients 3, 4, 11, and 15 did not show aneurysmal growth in a time period of 1 to 3 years.

Elective vascular interventions

Four patients underwent six elective open or endovascular interventions for aneurysms in the iliac, hepatic, gastric, or splenic artery. Patient 1, a 32-year-old man with bilateral large iliac artery aneurysms, underwent aortobiiliac graft implantation (Gelsoft prosthesis, Vascutek, Renfrewshire, United Kingdom). No peri-operative complications occurred. A follow-up MRA at 1 month showed relative stenoses of the distal anastomoses due to progressive tortuosity and elongation of the native common and external iliac arteries that were reimplanted on the prosthetic limbs (Figure 3). At 3 months, he required a mesh repair of an incisional hernia, which was likely to be related to the abnormal collagen composition due to AOS.

Patients 4 and 10 underwent coil embolization with occlusion of the splenic artery both proximal and distal to the aneurysm (Figure 4, Video 2, online only). Both patients exhibited abdominal pain for some days postprocedurally, which was most likely due to splenic ischemia and adequately managed with analgesics.

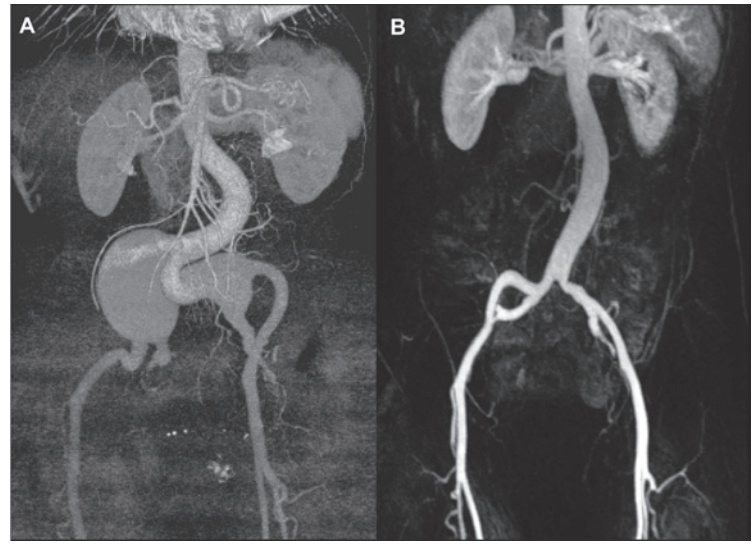

Figure 3. *Iliac artery aneurysm surgery.*

(A) A three-dimensional magnetic resonance angiography (MRA) shows bilateral large iliac artery aneurysms (69 and 42 mm). (B) A postoperative MRA shows relative stenoses of the distal anastomoses due to progressive tortuosity and elongation of the native iliac arteries.

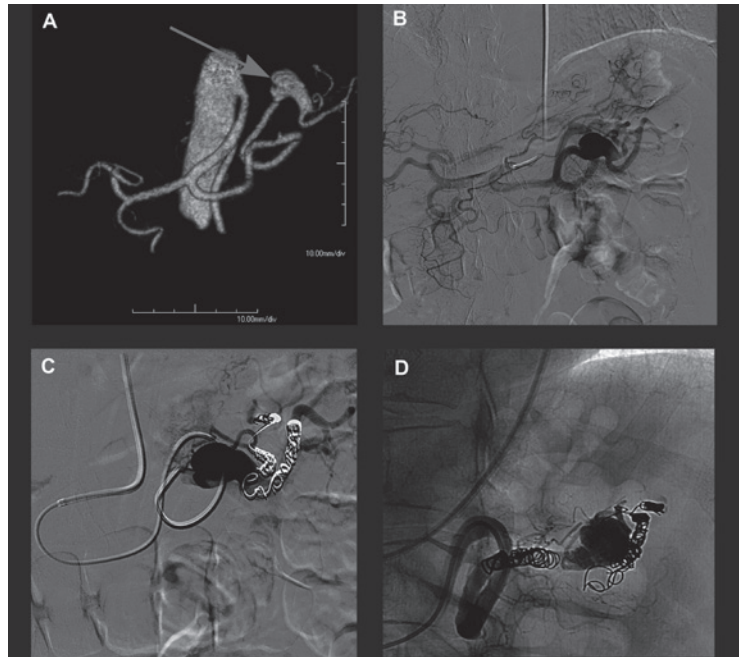

Figure 4. *Coil embolization of a splenic artery aneurysm.*

(A) A three-dimensional computed tomography angiography and (B) angiography showing a splenic artery aneurysm (21 mm) and tortuosity. Coil embolization procedure to occlude of the splenic artery (C) distal and (D) proximal to the aneurysm.

Patient 7, a 35-year-old man, underwent surgical resection with end-to-end anastomosis of a splenic artery aneurysm. He presented 5 years later with abdominal pain. CTA revealed an expanding hepatic artery aneurysm for which a covered self-expandable stent graft (Viabahn; W.L. Gore, Flagstaff, Arizona, USA) was implanted in the extrahepatic part of this aneurysm, thereby closing of a second small saccular intrahepatic artery aneurysm (Supplementary Figure 1, online only). This patients successfully underwent coil embolization of a fusiform aneurysm in the left gastric artery 6 months later. After a postprocedural period of 1 month to 8 years, all four patients who underwent elective interventions were alive and asymptomatic.

Discussion

To our knowledge, this is the first report describing the implications of *SMAD3*-related AOS in the visceral and iliac arteries. Although previous studies mainly focused on the genetic background and thoracic aortic involvement[8-10]; it is important to raise awareness for the vascular consequences of AOS beyond the aortic root.

General features of AOS

AOS is a recently described autosomal-dominant disorder that can predispose patients to widespread arterial aneurysms, dissections, and tortuosity.[8-10] Although AOS may resemble other connective tissue disorders such as Loeys-Dietz syndrome, it can be discriminated by the presence of early onset joint anomalies such as osteoarthritis, osteochondritis dissecans and meniscal abnormalities.[10]

Mutations in the *SMAD3* gene have been identified as the underlying cause for AOS.[8] The most likely effect of these mutations is loss of function and a paradoxic increase in transforming growth factor-β signalling in the aortic wall.[10] On histology of aortic wall fragments, evident disorganization of the tunica media with fragmentation and loss of elastic fibers was observed, as well as characteristic mucoid medial degeneration and accumulation of collagen in media.[8]

AOS seems to be responsible for approximately 2% of familial poly-aneurysm disease.[8,12] Because AOS has only been identified recently, data regarding the natural history of the disease are scarce, although it has become evident that aneurysmal growth can be fast and unpredictable and dissections may occur in only mildly dilated arteries.[9] In addition, AOS is also associated with additional features that are common in connective tissue disorders, such as umbilical and inguinal hernias, pelvis floor prolapse, varices, scoliosis and velvety skin.[8-10] Furthermore, mild craniofacial features including hypertelorism (widely-spaced eyes) and uvula abnormalities (broad or bifid) might be present.[8-10]

Involvement of the visceral and iliac arteries in AOS

The visceral and iliac arteries in our patient group displayed widespread abnormalities, such as aneurysms and extreme tortuosity. Although aneurysms were encountered in many arteries, splenic and iliac artery aneurysms were often the largest aneurysms and therefore most frequently required treatment. Moreover, arterial tortuosity was also most prominent in the splenic and iliac arteries.

Although widespread arterial tortuosity and aneurysms can also be found in Loeys-Dietz and arterial tortuosity syndrome, this is rare in patients with Marfan syndrome.[13-17] Therefore this feature can be helpful to discriminate AOS patients from Marfan patients.

It would be interesting to elucidate why the arteries of AOS patients become tortuous. Mechanical stability of arteries highly depends on elastin, which provides arterial elasticity and stiffness.[18] Elastin degradation weakens the arterial wall, thereby compromising mechanical stability of arteries.[18] Studies in fibulin-4- and fibulin-5-deficient mice and humans have demonstrated the association between arterial tortuosity and profound failure of elastogenesis.[19] Aortic wall specimens of AOS patients also demonstrated elastin degradation.[8] Therefore, we hypothesize that failure of elastogenesis is the probable cause of arterial tortuosity in AOS patients.

(Endo)vascular treatment in AOS patients

Because AOS can be complicated by dissections at relatively small diameters, early elective aneurysm repair seems to be appropriate to avoid vascular catastrophes. Nevertheless, potential benefits should always be weighed against the risks of an intervention. Knowledge of aneurysmal growth, procedural complication rates and late postoperative outcomes is crucial. Although rate of aneurismal growth is not entirely elucidated yet, it has become clear that growth can be fast and unpredictable. The current general consensus in atherosclerotic aneurysmal disease is that (endo)vascular treatment is indicated in asymptomatic visceral artery aneurysms >2.0 cm and iliac artery aneurysms >3.0 cm.[20-25] However, due to the sometimes rapid aneurysmal growth and occurrence of dissections in only mildly dilated arteries, a more aggressive treatment strategy seems to be necessary in AOS patients.

So far, (endo)vascular treatment experience in AOS patients is limited due to the recent discovery of this syndrome. Although this report only describes six (endo)vascular interventions in four AOS patients, it represents the largest cohort of abdominal (endo)vascular interventions to date. In vascular-type Ehlers-Danlos syndrome, friable vascular tissue leads to high surgical complication rates.[7] In contrast, fragility of arterial tissue was not an issue in the described interventions in AOS patients nor in aortic surgery.[9] Tissue handling felt the same as in patients without a connective tissue disorder; thus, elective interventions seem to be feasible and safe in AOS patients so far.

Although endovascular treatment of aortic aneurysms is generally discouraged in patients with connective disorders, little is known about open vs endovascular repair of visceral aneurysms in patients with connective tissue disorders.[26] In our opinion, the potential harmful impact of persistent radial forces of a stent-graft is less of an issue in visceral arteries than in the aorta and no issue with coil embolization. Furthermore, visceral aneurysms might be difficult to reach and treat through an open surgical procedure, and periprocedural morbidity and mortality will generally be lower in endovascular procedures. Therefore, we usually prefer an endovascular approach in AOS patients, although we strongly encourage an individualized approach weighing all potential benefits and harms, and multi-disciplinary deliberation before deciding on the treatment strategy.

Clinical implications

Vascular specialists should be aware of AOS as potential underlying of visceral and iliac aneurysms or tortuosity, or both, especially in patients with aortic aneurysms or dissections, joint complaints, multiple arterial aneurysms or a strong family history of aortic dissections or sudden death. Patients should be offered genetic testing and counselling for *SMAD3* gene mutations when AOS is suspected. In additon, at least a transthoracic echocardiogram should be performed to look for an aortic root aneurysm. If a mutation is identified, additional counselling of family members is strongly recommended.

Because AOS is notable for unpredictable, sometimes rapid aneurismal growth and occurrence of dissections in mildly dilated arteries, imaging of the entire arterial tree with CTA or MRA should be performed annually in confirmed AOS patients.[9]

To prevent aneurysm rupture or dissection, or both, elective (endo)vascular intervention in AOS patients should be considered in any visceral or iliac artery aneurysm exceeding twice the expected arterial diameter and in those that grow rapidly (>3 mm/year). Open and endovascular approaches can be used safely; however, endovascular procedures may be complicated by extreme tortuosity and should thus be performed by an experienced endovascular specialist. Imaging diagnostics using three-dimensional CTA or MRA reconstructions may be useful in planning treatment. After aneurysm repair, the entire arterial tree should be monitored because it remains at risk for aneurysm development and dissections or ruptures.

Study limitations

The retrospective nature and small sample size of this study are evident limitations. However, this study serves its most important goal, namely to raise awareness for this new, aggressive aneurysm syndrome. When AOS patients are not recognized, vascular complications that might have been prevented may occur. Larger prospective follow-up studies are warranted to elucidate the clinical course of AOS and long-term surgical outcome.

Conclusions

AOS is a recently discovered connective tissue disorder that predisposes patients to arterial aneurysms, dissections and tortuosity and early-onset joint complaints. Extensive CTA or MRA screening frequently identified (multiple) aneurysms and extreme tortuosity within visceral and iliac arteries in these patients. Although surgical experience is limited, fragility of arterial tissue does not seem to complicate (endo)vascular procedures in AOS patients. Owing to the occurrence of dissection in mildly dilated arteries, a more aggressive treatment strategy seems to be necessary. To prevent rupture, elective aneurysm repair should be considered in any visceral or iliac artery aneurysm that exceeds twice the expected arterial diameter or grows rapidly. It is paramount vascular specialists are aware of this new syndrome and its aggressive behavior since many AOS patients are still unrecognized.

Acknowledgements

We thank the participating patients, their families, and their referring physicians. We would also like to thank the technician assistants from the participating centers, especially René Frowijn, for his support in creating illustrations.

@ **For supplementary figures, videos, and tables, please see the online version of this article available at:**
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PART VI

Discussion

14

Summary
General Discussion

Summary

This thesis focuses on congenital disorders affecting the left ventricular outflow tract: specifically subaortic stenosis, valvular aortic stenosis and aortic aneurysms. The goal of this thesis is defined as “to investigate epidemiology, natural history, treatment, prognostic factors and genetic aspects of congenital aortic stenosis and aneurysms”. **Chapter 1** is the introduction to this thesis. First the epidemiology of congenital heart disease and the anatomy of the left ventricular outflow tract and aorta are briefly introduced. Thereafter the clinical features, etiology, diagnostic tools and treatment modalities of congenital aortic stenosis and aneurysms are described.

Epidemiology of congenital heart disease

Birth prevalence of CHD is generally considered to be around 8 per 1000 live births, but varies widely between published reports. In **Chapter 2** we aim to provide a complete worldwide overview of the reported birth prevalence of congenital heart defects and the eight most common subtypes from 1930 and 2010. To achieve this goal, we conducted a systematic literature review and meta-analysis, incorporating all previously published studies that reported birth prevalence of congenital heart disease or subtypes. This study shows that the reported total congenital heart disease birth prevalence increased substantially during the past century, eventually stabilizing around 9 per 1000 live births after 1995. Significant geographical differences were found, with the highest birth prevalence in Asia and the lowest in Africa. Furthermore, pulmonary outflow tract obstructions (pulmonary stenosis and tetralogy of Fallot) were more common in Asia, while left ventricular outflow tract obstructions (aortic stenosis and coarctation) were less common in this part of the world. Surprisingly, the birth prevalence in Europe was significantly higher than in North America. In addition, this study shows large differences in congenital heart disease birth prevalence between high- and low-income countries.

Discrete subaortic stenosis

Chapter 3 describes the natural history of discrete subaortic stenosis (DSS) in 149 adult patients in four participating centers during a median follow-up period of 6.3 years. Survival was excellent and comparable to the general population. This study confirms that conservatively managed DSS progresses slowly in adulthood, though patients with associated congenital lesions are at risk for faster DSS progression. Interestingly, the rate of DSS progression is not related to the baseline peak left ventricular outflow tract (LVOT) gradient, thereby questioning whether it is indicated to recommend surgery in asymptomatic patients based on a certain LVOT gradient cut-off value. Associated mild aortic regurgitation is common, but nonprogressive over time. Thus, prophylactic surgery to prevent further aortic valve damage does not seem justified in adult patients with conservatively managed DSS.

Chapter 4 delineates the long-term outcome of adult patients who previously underwent surgery for fibromuscular DSS in one of the four participating centers. We describe 313 patients who underwent 412 operations during a median follow-up period of 13 years. This study demonstrates that surgery for DSS offers excellent long-term results in adult patients, with a low individual re-operation rate (2% per patient-year) and good survival. Postoperatively, the LVOT gradient progresses slowly, though faster in older and female patients. Mild AR is common in operated DSS patients, but usually non-progressive over time. However, patients with a pre-operative LVOT gradient >80 mmHg are at risk for progression to moderate aortic regurgitation postoperatively. Since myectomy did not reduce the risk of recurrence or re-operation and was associated with an increased risk of a complete heart block, we conclude that myectomy should only be considered in case of marked septal hypertrophy and should otherwise be discouraged.

Congenital valvular aortic stenosis

Chapter 5 presents a large multicenter cohort study in asymptomatic young adult patients with congenital valvular aortic stenosis (AS). A total of 414 patients were included with a median follow-up period of 4 years. We demonstrate that in general, congenital AS does not progress over time; however, patients with left ventricular hypertrophy (LVH) are at risk for faster disease progression. Thereby, this study is the first to demonstrate the unfavorable prognostic implications of LVH in congenital AS, confirming previous findings in degenerative AS. This evidence contributes to the hypothesis that perhaps LVH is not just a consequence of AS, but otherwise involved in the disease mechanism. Furthermore, this makes us wonder whether LVH should influence timing of aortic valve replacement. As expected, proximal ascending aortic dilatation was present in almost half of the patients with congenital AS. The aorta grows steadily over time at a mean rate of 0.7 mm per year, and thus needs to be monitored repeatedly. The rate of progressive aortic dilatation was faster in men compared to women, but further studies are required to investigate the underlying mechanism of this finding. The presence or progression of aortic dilatation was not related to AS severity in this large cohort of adult congenital AS patients, thereby arguing against the theory that aortopathy in bicuspid aortic valves is caused by abnormal hemodynamic stress on the aortic wall. Fortunately aortic dissections were rare (0.06% per patient-year). However, whether this low rate indicates that we really do not have to fear aortic dissections in congenital AS patients, or reflects that prophylactic aortic surgery >50 mm efficiently prevents aortic dissections, remains to be determined.

Chapter 6 reports the results of a prospective, double-blind, randomized, placebo-controlled, multicenter trial that evaluated the effect of rosuvastatin on the progression of congenital AS in 63 asymptomatic young adult patients (PROCAS trial). The most important finding in this study is that we could not detect a significant effect of rosuvastatin on the progression of congenital AS, confirming several larger trials in degenerative AS patients. However, statins are able to halt an increase in NT-proBNP, suggesting a potential positive effect of statins on cardiac function in young patients with congenital AS. Since the PROCAS trial is underpowered, in the future a larger prospective randomized controlled trial, including more patients with hypercholesterolemia and mild AS, is necessary to draw firm conclusions about the effect of statin therapy on AS progression in asymptomatic young adult patients with congenital AS.

In **Chapter 7** the results of a prospective cardiac magnetic resonance (CMR) study in asymptomatic patients with bicuspid aortic valves and congenital AS are presented. Twenty-eight patients underwent serial CMR imaging scans at a mean interval of 34 months. At baseline, 32% of patients showed dilatation of the aorta (>40 mm), predominantly at the level of the proximal ascending aorta. The mean progression rate of ascending aortic diameter was 0.7 mm per year. This weakly correlated with the peak aortic velocity at baseline (R^2=0.16; p=0.04), suggesting at least some hemodynamic influence of AS on aortic dilatation. No significant correlation was found between progression of aortic dilatation and aortic diameter at baseline (R^2=0.01; p=0.631). Furthermore, this study shows that assessment of left ventricular mass, AS severity and left ventricular function in congenital AS patients is feasible with CMR.

Chapter 8 compares transthoracic echocardiography and CMR as imaging techniques for aortic diameter measurements in young adult patients with congenital AS. Correlation and agreement between the imaging modalities are assessed, as well as intra- and interobserver variability. Fifty-nine patients completed both imaging protocols at the same day. This study shows that CMR generally measures larger diameters than transthoracic echocardiography. Furthermore, concordance between CMR and echocardiography differed at the various levels of the aorta: with best concordance at sinotubular junction level and least concordance at the level of the proximal ascending aorta. Measurement reproducibility was generally better with CMR than with transthoracic echocardiography. Since BAV associated aortic dilatation mainly occurs at proximal ascending aortic level, CMR should be performed at least once to ensure that an aortic aneurysm at this level is not missed and might be the preferred method for aortic aneurysm follow-up.

Familial thoracic aortic aneurysms; a new syndrome

Chapter 9 presents the results of extensive cardiovascular evaluation in 44 patients from 7 families with the recently recognized Aneurysms-Osteoarthritis Syndrome (AOS). AOS is inherited as an autosomal dominant disorder and caused by pathogenic mutations in the *SMAD3* gene. Key features of this syndrome include aneurysms, dissections and tortuosity throughout the arterial tree, early-onset osteoarthritis and mild craniofacial features. Aneurysms are most frequently located in the aortic root (71%), but can also be found in other arteries in the thorax and abdomen (33%). Furthermore, cerebral aneurysms are detected in 38% of patients. Arterial tortuosity is encountered in approximately half of the patients. Thirteen patients (29%) are diagnosed with one or more aortic dissections, occasionally occurring in only mildly dilated aortas. AOS is associated with high mortality (mean age at time of death was 54 years), which was mainly caused by aortic dissections (60%).

Arterial stiffness studies showed a higher aortic pulse wave velocity in AOS patients compared to age- and sex matched healthy controls, indicating increased aortic stiffness. Biochemical studies demonstrated elevated NT-proBNP levels. Echocardiography revealed cardiac abnormalities in a subset of patients, such as congenital heart defects (6%), mitral valve abnormalities (51%) and left ventricular hypertrophy (19%). Moreover, 22% of AOS patients had a history of at least 1 episode of documented atrial fibrillation. Larger prospective follow-up studies are warranted to determine disease progression of AOS over time and clinical relevancy of the cardiac and intracranial abnormalities. Basic research in smad3 knockout mice will be useful to unravel the underlying disease mechanisms and explore possible pharmaceutical targets.

In **Chapter 10** the phenotypic spectrum of *SMAD3*-related AOS is explored further. Clinical and molecular data of 45 AOS patients from eight families are presented. Since all investigated patients with a *SMAD3* mutation exhibited signs or symptoms of AOS, the penetrance is found to be nearly 100%. However, the phenotypic expression varies widely, from very mild (isolated bifid uvula or mitral valve prolapse) to very severe (multiple aneurysms, dissections and sudden death at young age). The phenotype seems to be age-dependent, as aneurysms and dissections are predominantly encountered in adulthood, while cardiovascular abnormalities at young age are generally mild and mainly included mitral valve prolapse. The intrafamilial variability is significant: while some patients presented mainly with arterial aneurysms and dissections, others predominantly had joint abnormalities. Therefore, the genotype-phenotype correlation, if present, will be difficult to establish. In the majority of patients joint anomalies such as osteoarthritis, osteochondritis dissecans or meniscal abnormalities are the first reason to seek medical advice, since arterial aneurysms are generally asymptomatic. The early-onset joint anomalies seem to be a useful tool to discriminate AOS from other familial aneurysm syndromes such as Marfan and Loeys-Dietz syndrome.

Chapter 11 describes the first longitudinal follow-up data available for 17 AOS patients to evaluate the aortic dilatation progression rate. Furthermore, it describes the first surgical experience with elective valve sparing aortic root replacement (VSRR) in 10 AOS patients. Despite the fact that the follow-up is short and the number of patients limited, this first evaluation reveals that the aortic growth rate in AOS patients can be fast and unpredictable, warranting frequent imaging. So far, VSRR seems to be a safe and effective procedure for the management of aortic root aneurysms in AOS patients. No mortality occurred, no tissue fragility was encountered and all aortic valves could be saved. After a median postoperative period of almost 3 years, all patients remain asymptomatic. Since progression of aortic root aneurysms in AOS patients can be fast and unpredictable with aortic dissections occurring in relatively mildly dilated aortas, early prophylactic surgical intervention should be considered to avoid vascular catastrophes, especially as elective VSRR shows favorable results.

In **Chapter 12** a case of a 26-year old male with AOS is presented. He was asymptomatic, but underwent cardiovascular evaluation, because his 52-year-old mother had died of an aortic dissection and his 28-year-old brother had an aortic root aneurysm of 41 mm. Computed tomography angiography (CTA) revealed a dilated pulmonary trunk (50 mm) and a saccular aneurysm of a persistent ductus arteriosus (18x14 mm). To prevent further enlargement and possible rupture, the aneurysm was filled with an Amplatzer Vascular Plug II (AGA Medical, Plymouth, USA). This case illustrates the variety of aneurysm locations that can be encountered in AOS patients.

Chapter 13 focuses on the vascular consequences of AOS in the visceral and iliac arteries. This study describes 17 AOS patients, in whom a total of 46 abdominal aneurysms were diagnosed. The common iliac artery was most commonly affected (37%), followed by the superior mesenteric artery (15%), celiac trunk (11%) and splenic artery (9%). Rapid aneurysm growth within a year was found in three arteries. Furthermore, arterial tortuosity was noted in most patients (94%). Four patients underwent 6 elective (endo)vascular interventions for aneurysms in the iliac, hepatic, gastric or splenic artery without major peri- or post-operative complications. Given the aggressive behavior of AOS, we advocate early elective aneurysm repair, since the risk of aneurysm rupture is estimated to be very high and elective (endo)vascular interventions were not complicated by fragility of arterial tissue.

General discussion

This thesis investigated the epidemiology, natural history, treatment, prognostic factors and genetic aspects of congenital aortic stenosis and aneurysms. In this general discussion, we will address our research questions and discuss the outcomes against the background of the published literature. First, the difficulties in determining the "true" birth prevalence of congenital heart disease will be discussed. Secondly, the implications of the knowledge gained about adult patients with discrete subaortic stenosis will be delineated. Thereafter, the potential therapeutic options for young adults with congenital valvular aortic stenosis will be explored. Furthermore, we deliberate why aortopathy evolves in patients with bicuspid aortic valves. Finally, we review what we have learned, and perhaps more importantly, what is still unknown, about the cardiovascular phenotype of the new Aneurysms-Osteoarthritis Syndrome. As is often the case, research generates more questions than answers. Therefore, future directions and perspectives in the field of congenital aortic stenosis and aneurysms will be suggested as well.

How to identify the "true" birth prevalence of congenital heart disease?

Birth prevalence of congenital heart disease (CHD) is generally considered to be around 8 per 1000 live births.[1-2] However, this number is an estimate and does not take variability between studies, changes throughout time and geographical differences into account.[1] In Chapter 2 we aimed to provide reliable estimates of birth prevalence worldwide in the past century by compiling data from 114 reports in a systematic review and meta-analysis.[3] This study revealed that the overall worldwide birth prevalence of CHD is stable around 9 per 1000 live births since 1995. Geographical differences are certainly present.[3]

By pooling data from different sources in an objective and systematic way, a meta-analysis aims to increase the power and reduce the confidence limits. Although this method is likely to produce a more precise estimate than an individual study, it is important to realize that this method does not guarantee to provide the "true" birth prevalence estimate and is subjective to certain limitations.[4] First of all, it is important to acknowledge that confounding and selection bias often distort the findings of observational studies. Larger is not necessarily better, especially not in the context of biased or confounded results. Consequently, this implies the danger that meta-analyses of observational data produce very precise, though spurious results.[5] Heterogeneity is one of the most important potential sources of bias that might have impacted our results. By pooling data from different studies, and thus different centers, continents, detection methods, income groups and time periods, substantial heterogeneity was encountered. One of the main issues was the lack of a universal definition for birth prevalence of congenital heart disease. Therefore inclusion criteria varied with regard to CHD subtypes, age limits and the way patients were screened.

Before the era of echocardiography, detection of CHD was dependent on autopsy reports, death certificates, physical examination, X-rays, catheterization and surgical reports. Therefore, only severely affected subjects or autopsy cases could be detected.

In the 1970s, echocardiography was widely introduced into clinical practice, allowing diagnosis of asymptomatic patients as well as patients with mild lesions.[6] The impact of these changes over time is clearly demonstrated in Chapter 2 by the enormous increase of reported CHD birth prevalence over time, especially in the VSD, ASD and PDA prevalence, probably due to the use of echocardiography. In the upcoming decades we expect to see the impact of increased use of fetal echocardiography and pregnancy termination on CHD birth prevalence, which will most likely cause a decrease in liveborns with complex CHD types.[7]

Societal factors, such as differences in healthcare and referral systems, can vary considerably between countries and continents and thereby strongly influence research findings. Chapter 2 shows a clear positive correlation between income status and CHD birth prevalence, implying that cases are missed in low income countries.[3] If access to healthcare is limited or there is a lack of resources, medical insurance or screening programs, the reported birth prevalence is likely to underestimate the true birth prevalence. In addition, information from the lowest income countries in the world is scarce, as only the minority of children with CHD are detected in infancy.[8] As hospital-based data from Africa indicate that CHD remains an important cause of heart failure in Africa, the true prevalence is probably not less than in other parts of the world.[9]

Given all these limitations, it is probably fair to admit that while Chapter 2 approaches the "true" prevalence as well as possible, it does not give us a definitive estimation of the "true" prevalence of CHD.[3] It turned out to be particularly challenging to determine whether reported differences are real or merely methodological.[2] However, this study contributed to insight in changes over time and may guide the planning of CHD care. Furthermore, the interesting finding of geographical differences in CHD subtypes hopefully gives rise to basic research studies unraveling the etiology of CHD and more studies in developing countries. For the future, a major step forward would be to clearly define one universal definition of CHD and diagnostic method of choice.

Discrete subaortic stenosis: what about prognosis in adult patients?

While the literature about discrete subaortic stenosis (DSS) in childhood is comprehensive, data regarding DSS in adulthood are scarce.[10] In this thesis a multicenter retrospective cohort study including 427 DSS patients (Chapter 3 and 4) aimed to shed light on this relatively unexplored area of medicine. The goal was to identify changes over time and prognostic markers in conservatively managed as well as operated DSS patients.

In order to establish this goal, collecting as much data as possible is not enough. Advanced and appropriate statistical analyses are essential. In the past decades, the computational power of computers has increased tremendously, causing a giant leap in the field of biostatistics. To avoid the use of outdated and/or incorrectly employed statistical methods, collaboration between clinicians and biostatisticians is crucial. This allows for the powerful combination of the use of advanced statistics with a correct translation back to clinical practice; from complexity to simplicity. *"Everything should be made as simple as possible, but not one bit simpler" (Albert Einstein)*. So which statistical tools did we use for the analyses of the long-term outcome of DSS?

First of all, it is important to realize that in longitudinal data (repeated measurements over time within a patient) two observations are not independent, but inevitably correlated by sharing the same characteristics. To allow for these within-subject correlations, mixed-effects models were employed.[11-16] In contrast to standard regression methods, mixed-effects models are able to include more than one source of random variation, and therefore provide a flexible tool for modeling.[16] Furthermore, mixed-effects models have the ability to accommodate irregular and missing observations, which are often encountered in retrospective cohort studies.[11-13] The second important realization is that longitudinal data can be important predictors or surrogates of a time to event. Classical models do not consider dependencies between these two different data types (longitudinal and time-to-event data). Joint models for longitudinal and time-to-event data are models that bring the two data types together (simultaneously) into a single model to allow for the dependency and association between, in our case, longitudinal echocardiographic data and survival data.[17-19] This method aims to reduce bias in estimates and improve efficiency in the assessment of prognostic factors.[17] The goal of these complex statistical methods is to allow modeling to be as realistic and unbiased as possible, aiming to reflect the closest approximation of the truth. Of course we always have to keep in mind the famous saying of George E.P. Box: *"Essentially, all models are wrong, but some are useful"*.[20]

In contrast to reports about DSS in childhood,[10,21-27] we showed that DSS in adulthood progresses slowly and linearly along several decades, in conservatively managed as well as operated patients. The rate of progression was not influenced by the baseline DSS severity. Furthermore, while aortic regurgitation is common, it is generally mild and typically does not progress over time. These results confirm the findings of Oliver et al. who described a series of 134 DSS patients in 2001.[10] Combining this evidence, it has become less clear that there is an indication to send asymptomatic patients to surgery at a peak left ventricular outflow tract gradient of 50 mmHg, as is currently recommended in the American guidelines.[28] In line with the valvular aortic stenosis guidelines, our data support DSS surgery is only indicated in the presence of symptoms, impaired systolic left ventricular function, or an abnormal exercise test.[29-30] Furthermore, our data suggest that prophylactic surgery to prevent aortic valve damage is not justified in adult patients, since aortic valve damage generally does not progress over time. These findings will have important implications for the clinical management of adult DSS patients.

In conservatively managed patients, the only independent predictor for faster DSS progression over time was the presence of an associated congenital lesion, particularly a VSD. This finding is not only relevant for the follow-up frequency of these patients in clinical practice, but also asks for further research to comprehend the poorly understood etiology of DSS. Nowadays, the general agreement is that DSS develops as a consequence of genetic predisposition in combination with abnormal geometrical arrangements, increasing mechanical stresses and eventually triggering cellular proliferation.[31] We hypothesize that in DSS patients with associated congenital lesions, the hemodynamic forces are altered more extensively, thereby evoking a more intensive cellular proliferation response and faster progression of the left outflow tract obstruction.

Since these are all just speculations, future rheological studies in adult DSS patients are certainly warranted to test this hypothesis. Various case reports and breeding experiments in dogs suggest genetic predisposition and familial occurrence of DSS, but the inheritance pattern and risk are not well known.[32-40] Furthermore, it is speculated that DSS belongs to a spectrum of left ventricular outflow tract obstructions, ranging from a short-segment membranous obstruction to long-segment obstructions and hypertrophic cardiomyopathy.[23] Larger studies in siblings and offspring of DSS patients in large pedigrees might help in revealing the underlying inheritance pattern and phenotypic spectrum.

Surgery for DSS is known to be associated with a high recurrence risk and need for re-operation.[41-47] In our population the overall percentage of re-operations was 26%, which translates to an annualized individual risk of re-operation of 1.8% per patient year. A major factor in DSS recurrence is believed to be inadequate relief of the obstruction.[48] Therefore some groups advocate concomitant selective myectomy to achieve complete relief of the LVOT obstruction,[47-50] whereas others have reported that this does influence the recurrence rate.[26,45-46,51-55] We clearly showed that an additional myectomy does not reduce the number of re-operations, whereas it is associated with a higher risk of a complete atrioventricular block. Therefore, myectomy should be discouraged in the majority of adult patients, and only be performed in case of marked left ventricular hypertrophy. Despite the fact that our models took a lot of possible confounding factors into account, residual bias might be present. Ideally, one would like to design a randomized controlled trial assigning patients to either isolated enucleation or enucleation with additional myectomy and evaluate the outcome of recurrence over decades of follow-up. Unfortunately, the feasibility of such a trial is low. Another way to statistically assess this controversial issue might be to perform a propensity score analysis, although this probably leaves us with the same residual bias issues. For future research, complete registration of patient data in electronic databases, such as the CONCOR database, from childhood on and collaboration between centers is important to expand our knowledge about DSS.

Congenital valvular aortic stenosis: a role for pharmacological therapy?

Since congenital AS mainly affects patients at young adult age in the prime of their lives, ideally one would like to avoid or postpone the need for an (surgical) intervention by prescribing some kind of medical therapy. In Chapter 6 we investigated whether statins would be able to reduce the progression of congenital AS.[56] Recent insights showed that the calcification of the aortic valve is an active inflammatory and potentially modifiable process.[57-59] Despite promising animal experiments and nonrandomized human trials,[60-66] the prospective randomized trials SALTIRE, TASS, SEAS and ASTRONOMER did not confirm the expected benefit in degenerative AS patients.[67-70] We hypothesized that earlier treatment, thus before extensive calcification of the valve, might be more beneficial. Unfortunately, the PROCAS trial (Chapter 6) did not show any effect of rosuvastatin on the progression of congenital AS or aortic dilatation.[56] Since the PROCAS trial was underpowered, a larger prospective randomized controlled trial, including more patients with hypercholesterolemia and mild AS, is necessary to draw firm conclusions about the effect of statin therapy on AS progression in asymptomatic young adult patients with congenital AS. For now, there is no evidence to support the prescription of statins to prevent the progression of congenital AS.

So are there any other potential targets for medical therapy to reduce AS progression? Various studies have demonstrated increased angiotensin-converting enzyme (ACE) and angiotensin II activity and expression in AS, providing a rationale for ACE-inhibitor or angiotensin receptor blocker (ARB) therapy in AS.[71-72] However, so far two retrospective studies have provided conflicting data.[62,73] Since ACE-inhibitors and ARB's have also been proposed as target to slow down aortic dilatation progression,[74-75] this clearly remains a worthwhile topic of future prospective studies in congenital AS patients. In addition, bisphosphonates might be suitable candidates to reduce the AS progression rate due to their ability to inhibit bone resorption and indirect actions via inhibition of inflammation and fibrosis.[76-77] Two small retrospective human studies have shown promising results, but these findings need to be confirmed in larger prospective trials.[78-79]

Congenital valvular aortic stenosis: the future of surgical treatment

Congenital valvular aortic stenosis (AS) is the most frequent indication for aortic valve replacement (AVR) in adults under the age of 60 years.[80] Survival of these patients progressively falls below that of the age-matched normal population.[81] In this thesis, a substantial proportion (14-17%) of young adults with congenital AS within the longitudinal studies (Chapter 5 and 6) required AVR around the age of 35 years. Surgery has a major impact on young adults in this dynamic period of their lives, as most of them have an active lifestyle, endure in competitive sports, women may wish to become pregnant and careers are being achieved. Balloon valvuloplasty may be considered in adolescents and young adults with non-calcified valves, however since re-intervention rate is high, this is mainly suitable to postpone the need for AVR.[82-83]

When it comes to AVR in young adults with congenital AS, patients roughly have to choose between a tissue valve (likely requiring re-operation in the future) or a mechanical valve with anticoagulation (hazards of thrombosis and bleeding). Besides the technical possibilities, patient characteristics and surgeons' preference, the patients' preference should be a valuable component in this decision.[84] The upcoming trend in health care is the recognition of the importance of shared decision making: really putting patients at the centre of their own care.[85] In the end it is the patient who is at stake, not the doctor; thus the patient should be involved in the decision making process. As we are moving toward shared models of decision making, it would be helpful if clinical practice guidelines could promote shared decision making by highlighting decision points, suggesting what information should be communicated and how to involve patients.[85-86] Nowadays various tools are available to assist patients in this decision. For example, online at www.healthwise.net, patients can find the patient decision aid "Heart Valve Problems: Should I choose a mechanical valve or tissue valve to replace my heart valve?" In six elements this tool helps patients to understand what their choices are and formulate a well informed decision. Firstly, it educates patients about their disease and the (dis)advantages of the available valves. Secondly, it makes patients think about their opinion regarding various aspects of the long-term consequences of both valves. Thirdly, it examines whether the patient actually understood all provided information. Last of all, it creates a summary of the patients' input.

In this way, patients are much better informed and prepared before they talk to their surgeon, so the outpatient consult can be more focused and shorter. Another helpful tool to assist in the decision making process is microsimulation. This complex statistical method allows for the estimation of the lifetime event occurrence and outcome of an individual patient by simulating the postoperative remaining lives of ten-thousands of virtual patients with similar predefined characteristics, based on primary datasets or meta-analyses of outcome after a particular intervention.[87-88] An example of a microsimulation model that was built to predict age- and gender-specific patient outcome after AVR with different valve prostheses is available at www.cardiothoracicresearch.nl.

So what new surgical developments might the future hold for young adults with congenital AS? One of the promising breakthroughs is transcatheter aortic valve implantation (TAVI).[89-93] Currently, TAVI is the treatment of choice for patients considered not to be candidates for surgical AVR and is a proven alternative for high surgical risk patients.[94-97] However, TAVI is associated with important downsides, such as residual paravalvular aortic regurgitation and risk of peri-procedural complications such as stroke, major vascular complications and conduction disturbances requiring pacemaker implantation.[90] Nevertheless, promising preliminary data exist for "valve-in-valve" TAVI for failed bioprosthetic heart valves and the treatment of lower-risk patients.[98-107] "Valve-in-valve" TAVI opens up a new avenue for the management of young patients who require reoperation after surgical AVR at some point in their lives, such as our congenital AS patients. This might cause a shift towards the preference to use tissue valves for AVR in young patients, as it is expected that by the time a re-operation is required, this might be done less invasively through a TAVI procedure (multistep approach). Improvements in transcatheter valve technology, long-term results of the durability, and confirmation of feasibility of TAVI for "valve-in-valve" procedures and lower-risk patients, will determine the expansion of TAVI towards the treatment of a broader spectrum of patients.[90]

Another new, emerging alternative for current mechanical and biological prostheses is tissue engineering.[108-109] The main concept of tissue engineering is to create a viable valve resembling the native valve with the capability of growth, repair and remodeling.[110] This is the only technology with the potential for the creation of tissues analogous to a native human heart valve, with longer sustainability and fewer side-effects.[108,111] A clinically attractive approach would be to implant a cell-free scaffold into a patient that will recruit cells to colonize and generate new tissue in situ.[112] Despite promising preliminary results, further progress in scaffold technology and insights in the complex interplay between cells, material and hemodynamics are required before this technique can be introduced in clinical practice.[112] Although there is still a long way to go, tissue-engineered heart valves might have the capability to revolutionize cardiac surgery in the future.[108-110] The combination of TAVI with a tissue-engineered valve that is able to remodel and grow would theoretically be an attractive solution for young patients with congenital AS.

Aortic dilatation in bicuspid aortic valve disease: hemodynamics or genetics?

The strong association between bicuspid aortic valve (BAV) disease and ascending aortic aneurysms is well known,[113] and was once again confirmed in our studies (Chapter 5-8). The immediate question that arises from this is: why does the aorta dilate in patients with BAV? Two theories have been proposed:

- The genetic theory assumes that the aortic wall fragility is secondary to a common developmental defect involving both the aortic valve and the aortic wall.[114] Many studies have identified several structural abnormalities, such as fragmentation and loss of elastic fibers, at the cellular level in the aorta of BAV patients.[115-125]
- According to the hemodynamic theory, turbulent flow due to abnormal valve morphology, cusp orientation and stenosis, induces abnormal hemodynamic stress on the aortic wall, thereby causing aortopathy.[114,126-130]

In the literature, conflicting evidence exists as to whether aneurysm formation and progression is related to the hemodynamic valvular function or not. Some studies state that aortic dilatation occurs independently of valvular hemodynamic abnormalities,[131-132] whereas others report the opposite.[133] Even within this thesis, conflicting evidence exists. In a large retrospective cohort study in congenital aortic stenosis patients (Chapter 5), the aortic dilatation rate was not associated with aortic stenosis severity or the presence of aortic regurgitation. However, in a small prospective cardiac magnetic resonance cohort study (Chapter 7), the progression of aortic dilatation was correlated with the severity of aortic stenosis and presence of aortic regurgitation.

All together, in my view, the most plausible explanation for the aortic dilatation in BAV disease is a genetically determined intrinsic aortic wall weakness. On top of that, concomitant hemodynamic valvular dysfunction causing turbulent flow can contribute to aortic dilatation once an underlying structural abnormality is present. Further research should be focused on finding what distinguishes BAV patients with aortic dilatation from BAV patients without aortic dilatation. Promising areas of ongoing research include molecular studies in excised aortas after surgery, and identification of new biomarkers and genetic polymorphisms. Unraveling the mechanism behind aortic dilatation in BAV patients will contribute to the search for a pharmacological therapy that would be able to halt progression of aortic dilatation. Currently, one trial investigates the effects of angiotensin II type 1 receptor blocker telmisartan and/or beta blockade on aortic dilatation in BAV patients, based on promising results in Marfan patients and similarities in histopathological studies of the aortas of BAV and Marfan patients (www.clinicaltrials.gov, Canadian BAV study).

Aneurysms-Osteoarthritis Syndrome: where do we go from here?

Aneurysms-Osteoarthritis Syndrome (AOS), caused by *SMAD3* gene mutations, is recently recognized as a new form of inherited thoracic aortic aneurysms and dissections.[134] Extensive cardiovascular evaluations (Chapter 9-13) have established that this syndrome predisposes patients to aggressive and widespread cardiovascular disease.[135-137] In addition, key features of the syndrome include early-onset osteoarthritis and mild craniofacial and cutaneous anomalies.[134] Whereas the discovery of the cause of this aggressive disease and its associated cardiovascular consequences has certainly been a useful and important accomplishment, this has opened up an entire new set of research questions that needs to be addressed in the future.

First of all, it will be important to completely unravel the underlying etiology and biological processes that cause the various AOS-related anomalies. Currently, it is not completely understood how the underlying genetic mutations, which most likely cause loss of function, lead to a paradoxical increase in TGF-β signals in the aortic wall.[134,137] Furthermore, what role does the TGF-β pathway play in the presence of more than expected left ventricular hypertrophy, congenital heart defects and atrial fibrillation? And, how can we explain the variety of phenotypic expression, ranging from only osteoarthritis or mitral valve prolapse to several aneurysms, dissections and death at young age, in patients with the same underlying mutation? Studies in the smad3 knockout mouse model might help us to unravel these mysteries. By simulating the disease in genetically identical mice, these studies can provide us with valuable information about the response processes of other genes, proteins, RNA and microRNA expression to the down regulation of the *SMAD3* gene activity. Fluorescent imaging studies in mice can show us differences between wildtype and knockout mice in for example the activity of matrix metalloproteinases (MMP's) throughout the aorta. Echocardiographic studies might help to evaluate the presence of described cardiac abnormalities in knockout mice.

Since AOS has only been discovered recently and the full spectrum of the disease is not entirely elucidated yet, inevitably current clinical recommendations are mainly based on intuition and multidisciplinary expert consensus. In the future, close follow-up of identified patients is crucial for both clinical as well as research purposes. Serial full body imaging scans will provide us with information regarding the extent of vascular abnormalities and the aneurysmal growth rate. Biomarkers, such as NT-proBNP, MMP's and circulating TGF-β, and arterial stiffness measurements might be useful to distinguish a high risk, fast progressing subgroup within the full spectrum of AOS. Effort should be made to create evidence-based algorithms to define the optimal timing of surgical interventions.

Furthermore, we should ask ourselves if we should actively start searching for more AOS patients. Is AOS really rare or are there many unrecognized patients out there? And if so, how can we identify them? Since the vascular consequences of AOS are generally asymptomatic, the first reason for AOS patients to seek medical advice is usually joint complaints.[134] However, many people have joint complaints every once in a while. Given the a priori chance of this rare disease, screening should be targeted to a higher risk population. A possible target population for cardiovascular imaging might be:

patients with early-onset osteoarthritis in combination with a positive family history for sudden death at young age or aortic aneurysms/dissections and presence of other AOS-related features, such as pes planus, hypertelorism or bifid uvula. Furthermore, we suggest that clinicians treating young patients with arterial aneurysmal disease in any large artery (intracranial, iliac, splenic artery etcetera) should evaluate whether these patients exhibit joint complaints and screen them for AOS.[135]

An important goal for the future is to provide patient-centered care, addressing AOS patients in an integral manner, rather than to focus on specific organs. AOS commonly affects several organ systems and therefore a multidisciplinary approach is applicable. This multidisciplinary team should consist of dedicated clinical geneticists, cardiologists, orthopedic surgeons, (interventional) radiologists, neurologists, vascular and cardiothoracic surgeons, and internists. Consultation between members of this team should be easy and fast, to avoid keeping patients waiting in unbearable uncertainty. Over the past year, we have made some important steps in this direction by the initiation of a special outpatient clinic for aortic disease in the Erasmus Medical Center Rotterdam. One specialized nurse practitioner (under supervision of cardiologists) is the central, easily approachable contact for the patients. This nurse practitioner also pays attention to the psychosocial wellbeing of the patients and regulates the multidisciplinary consults. If necessary, she can organize more intensive psychological support. Furthermore, we have implemented a special clinical protocol for AOS patients, providing general guidelines about follow-up frequency and when consultation of other specialists and/or surgery is required. To ensure safe emergency care, we gave all AOS patients an "SOS-letter" that briefly explains this rare syndrome to doctors that are not familiar with AOS, informs and warns them for the associated risks of vascular complications and contains personal information about the known AOS-related abnormalities of that specific patient.

Finally, an unresolved challenge remains in the quest for an effective medical treatment that can halt progression of aneurysms in AOS patients. Probably the most extensively studied, although also debatable, area is that of medical therapy in Marfan syndrome-related aortic pathology.[138] On a cellular level, aortic specimens from AOS and Marfan patients show similarities, such as fragmentation and loss of elastic fibers and mucoid medial degeneration.[134] For a long time beta blockade has been the treatment of choice in Marfan syndrome, based on a theoretical decrease in aortic wall stress and positive results from one small trial in 1994.[139] However, a recent meta-analysis of six studies showed no clinical benefit from beta blockade in Marfan syndrome.[140] The role of TGF-β signaling in the pathogenesis of aortic aneurysms suggests TGF-β antagonists as another promising specific pharmaceutical target.[74] Losartan, angiotensin II type 1 receptor blocker and TGF-β antagonist, has shown promising effects in a Marfan mouse model and small pediatric cohort of Marfan patients.[141-142] These promising results gave rise to several large randomized clinical trials with losartan versus placebo or beta blockade in Marfan patients.[75,143-146] The results of these trials will be expected in the upcoming years. Meanwhile, further studies regarding the understanding of the physiological functioning of the TGF-β signaling pathway and the paradoxical increase of TGF-β are warranted before clinical trials with losartan can commence in AOS patients.[134]

Conclusions and prospects

Congenital heart disease is the most common birth defect, affecting approximately 9 per 1000 newborns. Breakthroughs in cardiovascular diagnostics and cardiothoracic surgery in the past century, lead to an improved survival and thus a steadily growing population of adults with congenital heart disease. Furthermore, every day new genes and syndromes are identified. Gradually gaps in knowledge regarding the long-term outcome and prognostic markers in these adult patient populations will become defined.

Large multicenter cohort studies have enhanced our knowledge about the progression of various forms of aortic stenosis over time and provided us with new clinical recommendations, but there is still a lot to learn. We start to realize more and more that we do not fully understand the underlying pathological mechanisms. In addition, we should become aware of the possibilities of emerging new statistical tools to answer our research questions. Basic training in epidemiology and statistics is essential for clinicians in order to translate results of advanced statistical analyses back to clinical practice.

Finally, the evolving field of improving therapeutic options may not only benefit us, but also leaves us with new challenges. Patients can easily access information through the internet, but the key is to provide them with reliable information and get them to fully understand their own disease and treatment options. Current clinical practice will have to adapt to the concepts of shared decision making and patient-centered care.

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Nederlandse samenvatting

Curriculum Vitae

PhD portfolio

List of publications

Dankwoord

Nederlandse samenvatting

In dit proefschrift ligt de nadruk op aangeboren afwijkingen van de linker ventrikel uitstroombaan: met name discrete subvalvulaire aorta stenose (vernauwing vlak onder de aortaklep), valvulaire aorta stenose (vernauwing van de aortaklep zelf) en aorta aneurysmata (verwijdingen van de grote lichaamsslagader). Het doel van dit proefschrift is als volgt geformuleerd “het onderzoeken van de epidemiologie, het natuurlijk beloop, de behandeling, prognostische factoren en genetische aspecten van congenitale aorta stenose en aneurysmata”. **Hoofdstuk 1** is de inleiding van dit proefschrift. Allereerst wordt toegelicht hoe vaak congenitale (aangeboren) hartafwijkingen voorkomen. Vervolgens wordt de anatomie van de linker ventrikel uitstroombaan en aorta kort geïntroduceerd. Tot slot worden de klinische presentatie, etiologie, diagnostiek and behandelingsopties van congenitale aorta stenose en aneurysmata beschreven.

Epidemiologie van congenitale hartafwijkingen

Naar schatting worden ongeveer 8 op de 1000 baby’s geboren met een aangeboren hartafwijking. Echter, dit getal varieert aanzienlijk in verschillende rapportages. In **Hoofdstuk 2** proberen wij een compleet overzicht te geven van het wereldwijd voorkomen van aangeboren hartafwijkingen en de diverse subtypen in de periode van 1930 tot 2010. Om dit doel te bereiken, hebben wij een systematisch literatuuronderzoek en meta-analyse uitgevoerd, waarin alle gepubliceerde artikelen over de geboorte prevalentie van aangeboren hartafwijkingen geïncludeerd zijn. De uitkomst van onze studie is dat de gerapporteerde geboorte prevalentie van aangeboren hartafwijkingen stijgt gedurende de afgelopen eeuw, en uiteindelijk vanaf 1995 stabiliseert rond 9 per 1000 levendgeborenen. Significante geografische verschillen werden geconstateerd, met de hoogste geboorte prevalentie in Azië en de laagste in Afrika. Daarnaast kwamen bepaalde subtypen vaker voor in het ene gebied dan in een ander gebied. Zo kwamen obstructieve afwijkingen van de rechter ventrikel uitstroombaan (zoals pulmonalis stenose en tetralogie van Fallot) vaker voor in Azië dan elders in de wereld, terwijl obstructieve afwijkingen van de linker ventrikel uitstroombaan (zoals aorta stenose en coarctatie van de aorta) hier juist minder vaak voorkwamen. Een verrassende bevinding was ook dat de geboorte prevalentie van aangeboren hartafwijkingen hoger was in Europa dan in Noord-Amerika. Tenslotte toonde onze studie dat er grote verschillen in geboorte prevalentie van aangeboren hartafwijkingen zijn tussen welvarende landen en ontwikkelingslanden.

Discrete subvalvulaire aorta stenose

Hoofdstuk 3 beschrijft het natuurlijk verloop van discrete subvalvulaire aorta stenose (DSAS) in 149 volwassen patiënten uit vier participerende centra met een mediane follow-up duur van 6.3 jaar. De overleving was uitstekend en vergelijkbaar met de algemene populatie. Onze studie laat zien dat de progressie van DSAS in volwassen patiënten over het algemeen traag is, alhoewel patiënten met geassocieerde andere aangeboren hartafwijkingen het risico lopen op snellere progressie van DSAS.

Een interessante bevinding is het feit dat de progressie snelheid van DSAS niet gerelateerd was aan de ernst van DSAS aan het begin van de studie. Hierdoor ontstaat er twijfel of het wel legitiem is om chirurgie te adviseren bij asymptomatische patiënten op basis van een bepaalde afkapwaarde van de linker ventrikel uitstroom baan gradiënt. Daarnaast bleek uit onze studie dat milde aorta insufficiëntie weliswaar vaak voorkomt bij DSAS, maar deze niet achteruitgaat door de tijd heen. Daarom lijkt preventieve DSAS chirurgie niet gerechtvaardigd bij volwassen patiënten om verdere achteruitgang van de aorta insufficiëntie te voorkomen.

In **Hoofdstuk 4** worden de lange termijn uitkomsten na chirurgie voor DSAS in volwassenen patiënten beschreven. In deze studie zijn 313 patiënten, die in totaal 412 operaties ondergingen, geïncludeerd uit vier participerende centra. Postoperatief werden deze patiënten gemiddeld 13 jaar gevolgd. Deze studie demonstreert dat chirurgie voor DSAS uitstekende lange termijn uitkomsten heeft, met een laag individueel heroperatie risico (2% per patiëntjaar) en een goede overleving. Postoperatief zien we een langzame toename in de linker ventrikel uitstroombaan gradiënt, hoewel deze toename sneller is bij vrouwelijke en oudere patiënten. Milde aorta insufficiëntie komt vaak voor bij geopereerde DSAS patiënten, maar neemt doorgaans niet toe over de tijd heen. Echter, patiënten met een preoperatieve linker ventrikel uitstroombaan gradiënt >80 mmHg hebben een verhoogd risico op progressie van milde tot matige aorta insufficiëntie. Het verrichten van een additionele myectomie (het wegsnijden van spier) tijdens de operatie reduceerde het risico op terugkeer van DSAS of re-operatie niet, maar was wel geassocieerd met een verhoogd risico op een compleet hartblok. Daarom concluderen wij dat een additionele myectomie alleen overwogen moet worden in het geval van duidelijke septale hypertrofie en in andere gevallen ontraden dient te worden.

Congenitale valvulaire aorta stenose

In **Hoofdstuk 5** worden de resultaten van een grote multicenter cohort studie in asymptomatische jongvolwassen patiënten met congenitale valvulaire aorta stenose (AS) gepresenteerd. In totaal werden 414 patiënten gevolgd gedurende 4 jaar. Wij demonstreren dat in het algemeen congenitale AS niet progressief is over de tijd heen; echter, patiënten met linker ventrikel hypertrofie (verdikking van de hartspierwand) lopen wel een verhoogd risico op snellere progressie. Hierdoor is deze studie de eerste studie die de ongunstige prognostische implicaties van linker ventrikel hypertrofie in congenitale AS demonstreert. Hiermee bevestigen wij eerdere bevindingen in oudere patiënten met degeneratieve AS. Dit bewijs draagt bij aan de hypothese dat linker ventrikel hypertrofie misschien niet simpelweg een gevolg is van AS, maar op een andere manier betrokken is in het ziektemechanisme. Bovendien, zet het ons tot nadenken of linker ventrikel hypertrofie niet meegenomen moet worden als factor in de beslissing en timing van chirurgische aortaklepvervanging.

Zoals verwacht, was dilatatie (verwijding) van de proximale aorta ascendens aanwezig in bijna de helft van de patiënten met congenitale AS. De aorta groeide gemiddeld 0.7 mm per jaar, wat frequente controle noodzakelijk maakt.

Opvallend was het feit dat de aorta harder groeide bij mannen dan bij vrouwen, maar verdere studies zijn noodzakelijk om de onderliggende verklaring voor dit fenomeen te vinden. De aanwezigheid of progressie van de aorta dilatatie was niet gerelateerd aan de ernst van de stenose in dit grote cohort van volwassen congenitale AS patiënten. Dit pleit tegen de hypothese dat de aorta dilatatie bij bicuspide aorta kleppen veroorzaakt zou worden door abnormale hemodynamische stress op de aortawand. Gelukkig waren aorta dissecties (scheur in de aortawand) in ons cohort zeldzaam (0.06% per patiëntjaar). Echter, of dit lage getal aangeeft dat we niet zo bang hoeven te zijn voor aorta dissecties bij congenitale AS patiënten, of reflecteert dat preventieve aorta chirurgie >50 mm succesvol aorta dissecties voorkomt, blijft een onbeantwoorde vraag.

Hoofdstuk 6 rapporteert de resultaten van een prospectieve, dubbelblinde, gerandomiseerde, placebo-gecontroleerde, multicenter trial welke het effect van rosuvastatine op de progressie van congenitale AS in 63 asymptomatische jongvolwassen patiënten evalueert (PROCAS trial). De belangrijkste bevinding van deze trial was dat we geen significant effect van rosuvastatine op de progressie van congenitale AS konden detecteren. Hiermee bevestigen we de resultaten van diverse grote trials met statines in oudere patiënten met degeneratieve AS. Echter, statines waren in onze studie wel in staat om een stijging in NT-proBNP tegen te gaan. Dit suggereert een potentieel positief effect van statines op de cardiale functie in jongvolwassen patiënten met congenitale AS. Omdat de PROCAS trial helaas te klein was om voldoende statistische power te bereiken, zal een grotere prospectieve gerandomiseerde trial (inclusief meer patiënten met hypercholesterolemie en milde AS) noodzakelijk zijn om definitieve conclusies over het effect van statines op AS progressie in asymptomatische jongvolwassen patiënten met congenitale AS te trekken.

In **Hoofdstuk 7** worden de resultaten van een prospectieve magnetic resonance imaging (MRI) studie in asymptomatische patiënten met een bicuspide aorta klep en congenitale AS gepresenteerd. Met een gemiddelde periode van 34 maanden ertussen, ondergingen 28 patiënten herhaaldelijke MRI scans. Aan het begin van de studie werd bij 32% van de patiënten een dilatatie van de aorta (>40 mm) geconstateerd. De dilatatie van de aorta was vooral gelokaliseerd aan het begin van de aorta ascendens. Gemiddeld groeide de aorta 0.7 mm per jaar. Er werd een zwakke correlatie geconstateerd tussen de groeisnelheid van de aorta en de ernst van de stenose (R^2=0.16; p=0.04). Dit suggereert een kleine invloed van de hemodynamiek van AS op de aorta dilatatie. Er werd geen significante correlatie gevonden tussen de groeisnelheid van de aorta en de aorta diameter aan het begin van de studie (R^2=0.01; p=0.631). Tot slot toont deze studie dat MRI geschikt is voor de beoordeling van de linker ventrikel massa, ernst van de stenose en linker ventrikel functie in congenitale AS patiënten.

In **Hoofdstuk 8** worden transthoracale echocardiografie en MRI met elkaar vergeleken als afbeeldingtechnieken om de aortadiameter te meten in jongvolwassen patiënten met congenitale AS. De accuraatheid en reproduceerbaarheid van beide afbeeldingtechnieken werd beoordeeld. Negenenvijftig patiënten ondergingen beide onderzoeken op dezelfde dag. Deze studie toonde dat met MRI over het algemeen de aorta diameter groter wordt gemeten dan met echo. Daarnaast was er een verschil in overeenstemming tussen beide afbeeldingtechnieken op verschillende niveaus van de diameter metingen: met de beste overeenstemming op het niveau van de sinotubulaire junctie en de slechtste overeenstemming op het niveau van de proximale aorta ascendens. De reproduceerbaarheid van de MRI metingen was meestal hoger dan van de echo metingen. Omdat aorta dilatatie in deze patiëntengroep vooral voorkomt ter hoogte van de proximale aorta ascendens, is ons advies om in ieder geval eenmalig een MRI te verrichten om er zeker van te zijn dat een aorta ascendens aneurysma niet gemist wordt met echo. MRI zou mogelijk ook de voorkeursmethode zijn om aorta dilatatie bij congenitale AS patiënten te vervolgen, echter vanwege bepaalde praktische bezwaren (contra-indicaties, wachttijden) is dit niet altijd mogelijk in de klinische praktijk.

Familiaire thoracale aorta aneurysmata; een nieuw syndroom

Hoofdstuk 9 beschrijft de resultaten van uitgebreide cardiovasculaire evaluatie van 44 patiënten uit 7 families met het recent erkende Aneurysma-Osteoarthritis Syndroom (AOS). AOS is een autosomaal dominant overervende aandoening, die veroorzaakt wordt door pathogene mutaties in het *SMAD3* gen. Dit syndroom wordt gekenmerkt door aneurysmata (verwijdingen), dissecties (scheuren in de vaatwand) en tortuositeit (kronkeling) van arteriën door het gehele lichaam, artrose op jonge leeftijd en milde craniofaciale afwijkingen. Aneurysmata zijn het meest gelokaliseerd in de aortawortel (71%), maar kunnen ook voorkomen in andere arteriën in de buik en borstkas (33%). Daarnaast, werden ook cerebrale aneurysmata (hoofd/hals) gedetecteerd in 38% van de patiënten. Arteriële tortuositeit werd gevonden in ongeveer de helft van de patiënten. Dertien patiënten (29%) werden gediagnosticeerd met één of meer aorta dissecties in soms mild gedilateerde aorta's. AOS is geassocieerd met een hoge mortaliteit (gemiddelde leeftijd van overlijden was 54 jaar oud), wat vooral veroorzaakt wordt door aorta dissecties.

Arteriële stijfheidmetingen toonden een verhoogde drukgolf snelheid over de aorta in AOS patiënten vergeleken met leeftijd en geslacht gematchte gezonde controles. Dit betekent dat de aorta van AOS patiënten stijver is dan normaal. Biochemische studies demonstreerde verhoogde NT-proBNP levels in AOS patiënten. Echocardiografie onthulde cardiale afwijkingen in een gedeelte van de AOS patiënten, zoals congenitale hartafwijkingen (6%), mitralisklep prolaps (51%) en linker ventrikel hypertrofie (19%). Bovendien had 22% van de AOS patiënten ooit een episode van atrium fibrilleren doorgemaakt. Grotere prospectieve follow-up studies zijn noodzakelijk om de ziekte progressie van AOS op lange termijn te analyseren en de klinische relevantie van gevonden cardiale en cerebrale afwijkingen te bepalen. Onderzoek in smad3 knockout muizen zal mogelijk helpen om het onderliggende ziekte mechanisme te doorgronden en te zoeken naar medicijnen die het ontstaan van aneurysmata kunnen afremmen.

In **Hoofdstuk 10** wordt het fenotypische spectrum van het *SMAD3*-gerelateerde AOS nader geëxploreerd. Klinische en moleculaire data van 45 AOS patiënten uit 8 families worden gepresenteerd. Omdat alle patiënten met een *SMAD3* mutatie tekenen of symptomen van AOS vertonen, is de penetrantie van dit ziektebeeld zo goed als 100%. Echter, de fenotypische expressie toont een brede variatie, van zeer mild (geïsoleerde bifide uvula of mitralisklep prolaps) tot zeer ernstig (meerdere aneurysmata, dissecties en plotse dood op jonge leeftijd). Het fenotype lijkt leeftijdsafhankelijk te zijn, omdat aneurysmata en dissecties vooral bij volwassenen worden aangetroffen, terwijl de cardiovasculaire afwijkingen op kinderleeftijd over het algemeen nog mild zijn en vooral een mitralisklep prolaps betreffen. Ook de intrafamiliale variabiliteit is groot: terwijl sommige familieleden zich presenteren met aneurysmata en dissecties, hebben andere patiënten van dezelfde familie alleen gewrichtsafwijkingen. Daarom is het lastig om de genotype-fenotype correlatie vast te stellen, als deze überhaupt aanwezig is. Voor de meerderheid van de patiënten waren de gewrichtsafwijkingen, zoals artrose, osteochondritis dissecans of meniscus afwijkingen, de eerste reden om naar een dokter te gaan, omdat aneurysmata over het algemeen asymptomatisch zijn. Het optreden van gewrichtsklachten op jonge leeftijd kan een nuttig hulpmiddel zijn om AOS te onderscheiden van andere familiaire aneurysmata syndromen, zoals Marfan en Loeys-Dietz syndroom.

Hoofdstuk 11 beschrijft de eerst beschikbare longitudinale follow-up data van 17 AOS patiënten om de aorta groeisnelheid te bepalen. Bovendien wordt de eerste chirurgische ervaring met electieve klepsparende aortawortel vervanging beschreven in 10 AOS patiënten. Ondanks het feit dat de follow-up duur kort is en het een klein aantal patiënten betreft, onthult deze eerste evaluatie dat de aorta van AOS patiënten snel en onvoorspelbaar kan groeien. Om deze reden adviseren wij zeer frequente controle van de aorta in AOS patiënten. Tot nu toe lijkt klepsparende aortawortel vervanging een veilige en effectieve procedure voor aortawortel aneurysmata in AOS patiënten. Er was geen mortaliteit tijdens de operaties, de weefsels voelden niet kwetsbaar aan en alle aortakleppen konden gespaard worden. Na een mediane postoperatieve periode van bijna 3 jaar zijn alle patiënten nog steeds asymptomatisch. Omdat de progressie van aortawortel aneurysmata in AOS patiënten snel en onvoorspelbaar kan zijn, aorta dissecties al kunnen optreden in mild gedilateerde aorta's en electieve klepsparende aortawortel vervanging gunstige resultaten toont, adviseren wij om vroegtijdige preventieve chirurgische interventie te overwegen bij AOS patiënten om vasculaire catastrofes te voorkomen.

In **Hoofdstuk 12** wordt een casus gepresenteerd van een 26-jarige man met AOS. Hij had geen klachten, maar onderging cardiovasculaire evaluatie omdat zijn moeder op 52-jarige leeftijd overleden was aan een aorta dissectie en een aortawortel aneurysma van 41 mm geconstateerd was bij zijn 28-jarige broer. Computer tomografie (CT) angiografie toonde een gedilateerde truncus pulmonalis (50 mm) en een sacculair aneurysma in een open ductus van Botalli (18x14 mm). Om verdere toename en mogelijk scheuren te voorkomen, werd het aneurysma gevuld met een Amplatzer Vasculaire Plug II (AGA Medical, Plymouth, USA). Deze casus is een goede illustratie van de variëteit van aneurysma locaties die men kan tegenkomen in AOS patiënten.

Hoofdstuk 13 focust zich op de vasculaire consequenties van AOS in de viscerale en iliacale arteriën (buik/liezen). Deze studie beschrijft 17 AOS patiënten, bij wie in totaal 46 aneurysmata in de buikregio werden gediagnosticeerd. De arteria iliaca communis was het meest aangedaan (37%), gevolgd door de arteria mesenterica superior (15%), truncus coeliacus (11%) en arteria lienalis (9%). Drie aneurysmata toonden zeer snelle groei binnen een jaar. Bovendien, werden arteriële tortuositeit (kronkeling) vastgesteld in de meeste patiënten (94%). Vier patiënten ondergingen 6 electieve (endo)vasculaire interventies voor aneurysmata in de lies-, lever-, buik- of miltarterie. Er waren geen belangrijke peri- of postoperatieve complicaties. Gezien het agressieve karakter van AOS, pleiten wij voor vroegtijdige electieve aneurysma interventies, omdat het risico op het scheuren van aneurysmata zeer hoog wordt ingeschat en electieve (endo)vasculaire interventies niet gecompliceerd worden door de kwetsbaarheid van vasculaire weefsels.

Curriculum vitae

Denise van der Linde was born on October 12th, 1988 in Rotterdam, The Netherlands. After graduating cum laude from secondary school in 2006 (Gymnasium, Nature & Health, Veurs Lyceum, Leidschendam-Voorburg), she started medical school at the Erasmus University Rotterdam. During her second year, she commenced with the Master of Science program in Clinical Research (Netherlands Institute of Health Sciences, Rotterdam; and summer session at Harvard School of Public Health, Boston, USA). In 2008 she successfully participated in the Erasmus University Honours Program, an interdisciplinary academic training program to explore the boundaries of science together with students from other disciplines. Furthermore, she was one of the founding editors of the Erasmus Journal of Medicine (EJM), a journal that aims to stimulate scientific development of medical students.

In 2010 she graduated cum laude from the preclinical years of medical school and initiated her MSc research at the department of Cardiology in the Erasmus Medical Center (supervisor: Prof. dr. J.W. Roos-Hesselink). For this research project concerning patients with congenital aortic stenosis she won a Royal Netherlands Academy of Arts and Sciences (KNAW) fellowship and travel grant. In 2011 she graduated cum laude from the MSc in Clinical Research and received the Professor Bruins Prize for best research master student at the Erasmus University Rotterdam.

In February 2011 she started her PhD project entitled “Congenital aortic stenosis and aneurysms” at the Department of Cardiology and Cardio-Thoracic Surgery of the Erasmus Medical Center, under supervision of prof.dr. J.W. Roos-Hesselink, prof.dr. A.J.J.C. Bogers and prof.dr. J.J.M. Takkenberg. During this time she spent a research period abroad at the Peter Munk Cardiac Center in Toronto, Ontario, Canada, under supervision of prof. E.N. Oechslin.

Currently, she is doing her medical internships, which she expects to complete in May 2014.

PhD Portfolio

Name PhD student:	Denise van der Linde
Erasmus MC Departments:	Cardiology and Cardio-Thoracic Surgery
Research school:	Cardiovascular Research School (COEUR), Erasmus MC
Title thesis:	Congenital aortic stenosis and aneurysms
Promotors:	Prof.dr. J.W. Roos-Hesselink
	Prof.dr. J.J.M. Takkenberg
Date of defense thesis:	April 19th, 2013

Academic education

2008-2011	MSc in Clinical Research, NIHES, Rotterdam, The Netherlands
2008	Erasmus Honours Program, EUR, Rotterdam, The Netherlands
2006-2010	Doctorate in Medicine, Erasmus MC, Rotterdam, The Netherlands

PhD training (50.2 ECTS)

In-depth courses (19.8 ECTS)

2010-2012	COEUR research seminars and lectures, Erasmus MC, Rotterdam, The Netherlands
2012	Bayesian statistics, NIHES, Rotterdam, The Netherlands
2012	ICIN Masterclass for PhD students, Heart Institute, Utrecht, The Netherlands
2012	Arrhythmia Research Methodology, COEUR, Rotterdam, The Netherlands
2012	Intensive Care Research, COEUR, Rotterdam, The Netherlands
2011	Academic Teaching Rounds, Peter Munk Cardiac Center, Toronto, Canada
2011	Congenital Heart Disease, COEUR, Rotterdam, The Netherlands
2011	Heart Failure Research, COEUR, Rotterdam, The Netherlands
2011	NWO Talentday “Negotiating”, NWO, Zeist, The Netherlands
2011	NWO Talentday “How to network”, NWO, Zeist, The Netherlands
2010	Boerhaave Congenital Heart Disease course, LUMC, Leiden, The Netherlands
2010	Cardiovascular Imaging and Diagnostics, COEUR, Rotterdam, The Netherlands
2010	Clinical Cardiovascular Epidemiology, COEUR, Rotterdam, The Netherlands
2010	Society and Health, Harvard School of Public Health, Boston, USA
2010	Vector-born and zoonotic diseases, Harvard School of Public Health, Boston, USA

Teaching (7.0 ECTS)

2013 Lecture "Cardiovascular consequences of *SMAD3* mutations", at the Patient Information Evening, Erasmus MC, Rotterdam, The Netherlands

2011-2012 Supervising a nurse practitioner in training for the clinical management of patients with Aneurysms-Osteoarthritis Syndrome, Erasmus MC, Rotterdam, The Netherlands

2012 Lecture "*SMAD3* mutations and aneurysmatic disease", at the COEUR Course Atherosclerotic and Aneurysmal Disease, Erasmus MC, Rotterdam, The Netherlands

2012 Lectures at research meetings at the departments of Pediatric Cardiology, Adult Congenital Cardiology and Surgery, Erasmus MC, Rotterdam, The Netherlands

2012 Supervising 2nd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands

2011 Lecture "Birth prevalence of congenital heart disease" for 3rd year medical students, Erasmus MC, Rotterdam, The Netherlands

2011 Supervising 2nd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands

2010 Supervising 3rd year medical students in writing a systematic review, Erasmus MC, Rotterdam, The Netherlands

Symposia and conferences (23.4 ECTS)

Oral presentations

2012 Dutch Society of Cardiology (NVVC) Autumn Congress
Arnhem, The Netherlands

2012 European Society of Cardiology (ESC) Congress
Munich, Germany

2012 22nd International Symposium on Adult Congenital Heart Disease
Toronto, Canada

2012 Dutch Workgroup of Epidemiology Research (WEON) Congress
Rotterdam, The Netherlands

2012 Association for European Pediatric Cardiology (AEPC) Annual Meeting
Istanbul, Turkey

2012 Valves in the Heart of the Big Apple (HVSA/SHVD) Conference
New York City, USA

2012 Dutch Society of Cardiology (NVVC) Spring Congress
Noordwijkerhout, The Netherlands

2012 Winter Meeting General Cardiology
Davos, Switzerland

2012 COEUR Annual PhD-day
Rotterdam, The Netherlands

2011 American Heart Association (AHA) Scientific Sessions
Orlando, USA

2011 Dutch Society of Cardiology (NVVC) Autumn Congress
Arnhem, The Netherlands

2011 Society for Heart Valve Disease (SHVD) Biennial Meeting
Barcelona, Spain

2011 COEUR Annual PhD-day
Oestgeest, The Netherlands

2010 Dutch Society of Cardiology (NVVC) Spring Congress
Arnhem, The Netherlands

Poster presentations

2012 European Society of Cardiology (ESC) Congress
Munich, Germany

2012 22nd International Symposium on Adult Congenital Heart Disease
Toronto, Canada

2011 EuroEcho and other Imaging Modalities
Budapest, Hungary

2011 American Heart Association (AHA) Scientific Sessions
Orlando, USA

2011 European Society of Cardiology (ESC) Congress
Paris, France

Attended

2013 Coarcation and other aortic pathologies
Utrecht, The Netherlands

2012 Transposition of the Great Arteries
Utrecht, The Netherlands

2011 Thoracic aortic pathology: new insights and treatment modalities
Rotterdam, The Netherlands

2011 Cardio-thoracic surgery and interventions for congenital heart disease
Utrecht, The Netherlands

2011 Hypertrophic Cardiomyopathy
Rotterdam, The Netherlands

2010 EuroEcho Congress
Copenhagen, Denmark

2010 Cardiology and Vascular Medicine update and perspective
Rotterdam, The Netherlands

2010 Acute Myocardial Infarction: the next decade
Rotterdam, The Netherlands

Invited lectures

2013 *"Aneurysms-Osteoarthritis Syndrome: where do we go from here?"*
Aortic symposium, Rotterdam, The Netherlands
Invited by prof.dr. Jolien W. Roos-Hesselink.

2012 *"Aortic aneurysm, is it always Marfan?"*
Cardiology, Erasmus MC, Rotterdam, The Netherlands
Invited by prof.dr. Jolien W. Roos-Hesselink

2012 *"Congenital aortic stenosis and aneurysms"*
Philips High Tech Campus, Eindhoven, The Netherlands
Invited by the Philips Research Lab Team

2011 *"Aortic root aneurysms, is it always Marfan?"*
Cardiology, Peter Munk Cardiac Center, Toronto, Canada
Invited by prof.dr. Erwin N. Oechslin

2011 *"A new aggressive aneurysm syndrome"*
Cardio-Thoracic Surgery, Peter Munk Cardiac Center, Toronto, Canada
Invited by dr. Tirone E. David

Awards and grants

2012 2nd Abstract Prize, 22nd International Symposium on Adult Congenital Heart Disease, Toronto, Canada

2011 Professor G.W.J. Bruins Prize for best Research Master's student for the purpose of research abroad, Erasmus University Rotterdam, The Netherlands

2011 High Score Abstract Poster Prize, EuroEcho and other Imaging Modalities Congress, Budapest, Hungary

2010 Royal Netherlands Academy of Arts and Sciences (KNAW) travel grant to attend the EuroEcho Congress, Copenhagen, Denmark

2010 Royal Netherlands Academy of Arts and Sciences (KNAW) fellowship for MSc research at the Department of Cardiology, Erasmus MC, Rotterdam, The Netherlands

List of publications

Full papers

1. **Van der Linde D**, Roos-Hesselink JW, Rizopoulos D, Heuvelman HJ, Budts W, Van Dijk APJ, Witsenburg M, Yap SC, Oxenius A, Silversides CK, Oechslin EN, Bogers AJJC, Takkenberg JJM. Surgical outcome of discrete subaortic stenosis in adults: a multicenter study. *Circulation. 2013; In press.*

2. **Van der Linde D**, Takkenberg JJM, Rizopoulos D, Heuvelman HJ, Budts W, Van Dijk APJ, Witsenburg M, Yap SC, Bogers AJJC, Silversides CK, Oechslin EN, Roos-Hesselink JW. Natural history of discrete subaortic stenosis in adults: a multicenter study. *Eur Heart J. E-pub 13 Dec 2012.*

3. **Van der Linde D**, Andrinopoulou ER, Oechslin EN, Budts W, Van Dijk APJ, Pieper PG, Wajon EMCJ, Post MC, Witsenburg M, Silversides CK, Oxenius A, Bogers AJJC, Takkenberg JJM, Roos-Hesselink JW. Congenital aortic stenosis in adults: predictors for rate of progression and aortic dilatation. *Int J Cardiol. E-pub 16 Nov 2012.*

4. **Van der Linde D**, Verhagen HJ, Moelker A, Van de Laar IMBH, Van Herzeele I, De Backer J, Dietz HC, Roos-Hesselink JW. Aneurysms-Osteoarthritis syndrome with visceral and iliac artery aneurysms. *J Vasc Surg. 2013;57:96-102.*

5. **Van der Linde D**, Bekkers JA, Mattace-Raso FUS, Van de Laar IMBH, Moelker A, Van den Bosch AE, Van Dalen BM, Timmermans J, Bertoli-Avella AM, Wessels MW, Bogers AJJC, Roos-Hesselink JW. Progression rate and early surgical experience in the new aggressive Aneurysms-Osteoarthritis Syndrome. *Ann Thorac Surg. 2013;95:563-9.*

6. **Van der Linde D**, Rossi A, Yap SC, McGhie JS, Van den Bosch AE, Kirschbaum SWM, Russo B, Van Dijk APJ, Moelker A, Krestin GP, Van Geuns RJ, Roos-Hesselink JW. Ascending aortic diameters in congenital aortic stenosis: cardiac magnetic resonance versus transthoracic echocardiography. *Echocardiography. E-pub 11 Jan 2013.*

7. Rossi A, **Van der Linde D**, Yap SC, Lapinskas T, Kirschbaum S, Springeling T, Witsenburg M, Cuypers JAAE, Moelker A, Krestin GP, Van Dijk A, Johnson M, Van Geuns RJ, Roos-Hesselink JW. Ascending aorta dilatation in patients with bicuspid aortic valve stenosis: a prospective CMR study. *Eur Radiol. E-pub 26 Sep 2012.*

8. Cuypers JAAE, Witsenburg M, **Van der Linde D**, Roos-Hesselink JW. Pulmonary stenosis: update on diagnosis and therapeutic options. *Heart. E-pub 8 Jan 2013.*

9. **Van der Linde D**, Van de Laar IMBH, Bertoli-Avella AM, Oldenburg RA, Bekkers JA, Mattace-Raso FUS, Van den Meiracker AH, Moelker A, Van Kooten F, Frohn-Mulder IME, Timmermans J, Moltzer E, Cobben JM, Van Laer L, Loeys B, De Backer J, Coucke PJ, De Paepe A, Hilhorst-Hofstee Y, Wessels MW, Roos-Hesselink JW. Aggressive cardiovascular phenotype of Aneurysms-Osteoarthritis syndrome caused by pathogenic SMAD3 variants. *J Am Coll Cardiol 2012;60:397-403.*

10. **Van der Linde D**, Witsenburg M, van de Laar I, Moelker A, Roos-Hesselink J. Saccular aneurysm within a persistent ductus arteriosus. *Lancet 2012;379:e33.*

11. Van de Laar IM, **Van der Linde D**, Oei EH, Bos PK, Bessems JH, Bierma-Zeinstra SM, van Meer BL, Pals G, Oldenburg RA, Bekkers JA, Moelker A, de Graaf BM, Matyas G, Frohn-Mulder IM, Timmermans J, Hilhorst-Hofstee Y, Cobben JM, Bruggenwirth HT, van Laer L, Loeys B, De Backer J, Coucke PJ, Dietz HC, Willems PJ, Oostra BA, De Paepe A, Roos-Hesselink JW, Bertoli-Avella AM, Wessels MW. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. *J Med Genet 2012;49:47-57.*

12. **Van der Linde D**, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: A systematic review and meta-analysis. *J Am Coll Cardiol 2011;58:2241-2247.*

13. **Van der Linde D**, Yap SC, Van Dijk AP, Budts W, Pieper PG, Van der Burgh PH, Mulder BJM, Witsenburg M, Cuypers JAAE, Lindemans J, Takkenberg JJM, Roos-Hesselink JW. Effects of Rosuvastatin on Progression of Stenosis in Adult Patients with Congenital Aortic Stenosis (PROCAS trial). *Am J Cardiol 2011;108:265-271.*

14. **Van der Linde D.** Marfan syndrome: wait for aortic dissection or not? Editorial comment. *Erasmus Journal of Medicine 2011;2:6.*

15. **Van der Linde D**, Van de Laar IMBH, Moelker A, Wessels MW, Bertoli-Avella AM, Roos-Hesselink JW. Geen syndroom van Marfan, maar wat dan? *Ned Tijdschr Geneeskd. 2013; In press.*

16. **Van der Linde D**. Hoofdstuk 15 "Congenitale hartziekten" in *"ABC van de Cardiologie"* van Deckers JW et al. 2010 Uitgevers, Rotterdam 2012.

Abstracts

1. **Van der Linde D**, Takkenberg JJM, Rizopoulos D, Heuvelman HJ, Witsenburg M, Budts W, Van Dijk APJ, Yap SC, Oechslin EN, Roos-Hesselink JW. Natural history of discrete subaortic stenosis in adults: A multicentre study. *Eur Heart J 2012;33:S268-S269.*

2. **Van der Linde D**, Takkenberg JJM, Rizopoulos D, Heuvelman HJ, Witsenburg M, Budts W, Van Dijk APJ, Yap SC, Oechslin EN, Roos-Hesselink JW. Long-term surgical outcome of discrete subaortic stenosis in adults. *Eur Heart J 2012;33:S13-S14.*

3. **Van der Linde D**, Takkenberg JJM, Rizopoulos D, Heuvelman HJ, Witsenburg M, Budts W, Van Dijk AJP, Bogers AJJC, Yap SC, Silversides CK, Oechslin EN, Roos-Hesselink JW. Long-term outcome of discrete subaortic stenosis in adults: A multicenter study. *Cardiol Young 2012;22:S34-S35.*

4. **Van der Linde D**, Andrinopoulou ER, Oechslin EN, Budts W, Van Dijk APJ, Pieper PG, Wajon EMCJ, Post MC, Witsenburg M, Bogers AJJC, Takkenberg JJM, Roos-Hesselink JW. Factors influencing natural course of congenital aortic stenosis in young adults: A multicenter study. *Cardiology 2012;121:142.*

5. **Van der Linde D**, Rossi A, Yap SC, McGhie JS, Van den Bosch AE, Kirschbaum SWM, Van Dijk APJ, Moelker A, Krestin GP, Van Geuns RJM, Roos-Hesselink JW. Ascending aortic dimensions: comparison between cardiac magnetic resonance and transthoracic echocardiography in congenital aortic stenosis patients. *Cardiology 2012;121:142.*

6. **Van der Linde D**, Van de Laar IMBH, Wessels MW, Bekkers JA, Moelker A, Tanghe HL, Van Kooten F, Oldenburg RA, Bertoli-Avella AM, Roos-Hesselink JW. Cardiovascular phenotype of the recently discovered aggressive aneurysms-osteoarthritis syndrome caused by smad3 mutations. *Eur J Echocardiography 2011;12:S2ii107.*

7. **Van der Linde D**, Van de Laar IM, Wessels MW, Oldenburg RA, Bekkers JA, Mattace-Raso FU, Van den Meiracker AH, Moelker A, Tanghe HL, Van Kooten F, Bertoli-Avella AM, Roos-Hesselink JW. Cardiovascular phenotype of the recently discovered aggressive Aneurysms-Osteoarthritis Syndrome (AOS) caused by SMAD3 mutations. *Circulation 2011;124:S1.*

8. **Van der Linde D**, Van de Laar IM, Mattace-Raso FU, Van den Meiracker AH, Oldenburg RA, Wessels MW, Moltzer E, Bertoli-Avella AM, Roos-Hesselink JW. Increased Aortic Stiffness in Patients with Aneurysms-Osteoarthritis Syndrome. *Circulation 2011;124:S1.*

9. Rossi A, **Van der Linde D**, Springeling T, Moelker A, Krestin GP, Van Geuns RJ, Roos-Hesselink JW. Changes in ascending aorta dimensions, aortic valve function and systolic ventricular function over time in patients with congenital aortic stenosis. *J Cardiovasc Magn Reson 2011;13:S1.*

10. **Van der Linde D**, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselink JW. Birth prevalence of congenital heart disease; Meta-analysis on changes during the last 80 years. *Eur Heart J 2011;32:S121-S122.*

11. **Van der Linde D**, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, Roos-Hesselink JW. Birth prevalence of congenital heart disease; Meta-analysis on geographical differences. *Eur Heart J 2011;32:S121-S122.*

Dankwoord

"Life is a journey, not a destination"

Het is af! Wat een geweldig gevoel! Het resultaat van een ontdekkingsreis door de wondere wereld van het onderzoek! Een reis vol plotse wendingen, teleurstellingen, maar bovenal ook veel persoonlijke groei en successen. Natuurlijk heb ik deze reis niet alleen gemaakt, en ben ik de vele mensen die mij geïnspireerd, uitgedaagd en geholpen hebben zeer dankbaar.

Mijn promotoren, prof.dr. Roos-Hesselink en prof.dr. Takkenberg, ik voelde mij gezegend met zulke krachtige vrouwen als begeleiders. Jullie vormen een inspiratiebron voor velen.

Prof.dr. Roos-Hesselink, beste Jolien, allereerst wil ik jou bedanken voor de jarenlange fijne begeleiding en steun. Mijn bewondering is groot voor jouw persoonlijke manier van begeleiding, waarbij niet alleen gefocust wordt op de wetenschappelijke activiteiten, maar ook gevraagd wordt hoe het daadwerkelijk met mijzelf gaat. Ongelofelijk hoe je het scala aan werkzaamheden combineert met je gezin, alle congressen en patiëntenzorg. Ik herinner me nog goed hoe ik, als "jonkie", 3 jaar geleden vol ongeduld aan mijn eerste onderzoek bij jou begon. Eén van de belangrijkste ontwikkelingen tijdens mijn promotietraject lag misschien niet zozeer op wetenschappelijk gebied: voor mij is het vooral een periode van persoonlijke ontwikkeling en volwassen worden geweest. Jij leerde mij mijn ongeduld (iets) te temperen, stimuleerde mij om op ontdekkingstocht te gaan en om een netwerk op te bouwen. Gesteund door jouw motto "Nee heb je, ja kun je krijgen" hebben we grotere successen bereikt dan ik voorafgaand ooit had durven hopen. Ik hoop dat we deze mooie samenwerking ook in de toekomst mogen voortzetten.

Prof.dr. Takkenberg, beste Hanneke, sinds mijn eerste onderzoeksproject motiveerde jij mij om mijzelf verder te ontwikkelen in de soms wat angstaanjagende wereld van de epidemiologie en statistiek. Doorzetten om je iets onbekends eigen te maken. De meta-analyse was de eerste (letterlijk) grote hindernis, maar ook die werd overwonnen en het is een prachtig artikel geworden. Daarna volgden de mixed-effects en joint models, die na een tocht door een soms onherbergzame jungle, uiteindelijk ook tot een klinisch toepasbaar resultaat hebben geleid. Ik bewonder jouw grote kracht om, door middel van complexe statistische methoden, patiëntgerichte tools te ontwikkelen. Ook jij hebt een gave om ongelofelijke hoeveelheden werk te combineren met een gezin en persoonlijke begeleiding van ons als promovendi. Bedankt voor alles en ik hoop dat hiermee onze samenwerking nog niet voorbij is.

Prof.dr. Bogers, hartelijk dank voor de begeleiding op chirurgisch vlak gedurende de afgelopen jaren en het zitting nemen in de grote commissie. U leerde mij de kracht van "Less is more".

Prof.dr. Oechslin, dear Erwin, it was an honor to work with you and your staff in Toronto. You are so enthusiastic, generous and joyful. When I arrived in Toronto, I immediately felt welcome. You gave me so many opportunities to learn at the outpatient clinics, collect my data and present my work at various occasions. Even though you did not know me, from the beginning you believed in me. When I had to leave Toronto, you and Doris even organized a special Swiss goodbye dinner for me. It is a major compliment for me that you are willing to take place in the reading committee and fly to the Netherlands for my defense. Thank you for everything. I hope we will continue to collaborate in the future.

Graag wil ik prof.dr. Hunink en prof.dr. Lesaffre hartelijk danken voor het plaatsnemen in de leescommissie en voor de deskundige beoordeling van mijn proefschrift. Tevens wil ik prof.dr. Klautz en prof.dr. Budts vriendelijk bedanken voor het zitting nemen in de grote commissie.

Alle co-auteurs wil ik danken voor hun bijdrage en waardevolle commentaar. Sing Yap, bedankt voor de interessante discussies, je aanstekende enthousiasme en de kritische evaluatie van mijn manuscripten. Eleni-Rosalina Andrinopoulou, thank you for helping me out and providing me insight in the wondering world of mixed-effects and joint models. Dimitris Rizopoulos, bedankt voor je hulp met de complexe statistische modellen en vooral ook jouw geduld bij mijn vele vragen en verzoeken tot extra analyses. Helena Heuvelman, lady, mijn dank voor jouw inzet bij SUBVAS studie en de gezelligheid in New York en Barcelona. Lisanne Konings en Maarten Slager, zonder jullie was de mooie meta-analyse er nooit gekomen, bedankt voor het spitten door de (oneindige) stapel artikelen. Alexia Rossi, you are such a cheerful person, thanks for your help with our joint echo/MRI projects.

Sommige mensen zeggen dat ik gedurende mijn promotietraject zo'n beetje overal en nergens door Nederland en België rondzwierf. Soms met koelbox en al in de trein: Nijmegen, Groningen, Enschede, Nieuwegein, Amsterdam, Leuven, niets was te ver. Ik ben alle cardiologen die mij de mogelijkheid boden om mijn studies naar congenitale aorta stenose uit te breiden tot grote multicenter studies zeer dankbaar: Arie van Dijk, Els Pieper, Elly Wajon, Marco Post, Barbara Mulder en Werner Budts. Dank voor jullie enthousiasme en inzet. Tevens dank aan al het ondersteunde personeel van de diverse ziekenhuizen. Ook wil ik mijn mede-promovendi in Leuven en Groningen bedanken: Alexander van de Bruane en Ali Balci, jullie zorgden dat ik mij thuis voelde en fleurden mijn lange dataverzamelingsdagen op.

"We've been expecting you", the slogan of the city of Toronto. And it seemed like everyone I met actually lived up to that motto. Candice Silversides, crazy busy, yet you always made time to ask me whether I was all right or needed help. Jack Colman, I learned a lot from you at the outpatient clinics, and even though you have so many great papers, somehow you were always complementing me on mine. Tirone David, it was such an honor for me to be in the OR with you, discussing the Dutch cows and tulips while you were operating on an aorta, amazing! Carole Ryan, thank you helping me out in finding my way. Angela Oxenius, thanks for explaining me all about the electronic system.

Francisca Arancibia Galilea, always happy, I will never forget our dinosaur experience. Kyle Pasternac, Radhika Nair and Akasha Atwell, your presence made it bearable to go through the endless number of patient files and echocardiograms. Lizzie McNeely, thank you for your hospitality and showing me around in Toronto.

Mijn promotietraject nam een onverwachte wending toen ik betrokken raakte bij het recent ontdekte Aneurysma-Osteoarthritis Syndroom. Dit bijzondere, veelomvattende project heeft veel indruk op mij gemaakt. Allereerst wil ik de patiënten en hun familieleden bedanken voor hun deelname aan de studies en hun enthousiaste medewerking. Ondanks de enorme impact die de onderzoeken op jullie gehad moeten hebben, deden jullie er alles aan om familieleden op te sporen en te motiveren om mee te werken aan onze onderzoeken. De diverse publicaties en het klinische protocol konden alleen maar tot stand komen dankzij het teamwork binnen dit enorme multidisciplinaire project, waarvoor dank aan alle betrokken collega's. Ingrid van de Laar, mijn bewondering voor jouw eindeloze doorzettingsvermogen tussen de stapels statussen, en dat naast je patiëntenzorg en gezin. Marja Wessels en Aida Bertoli-Avella, bedankt voor jullie inzet en uitleg van de soms voor mij onbegrijpelijke genetische begrippen. Francesco Mattace-Raso, il mio favorito e vivace italiano, het was altijd prettig om met jou samen te werken. Jos Bekkers, bedankt voor jouw hulp en vooral ook de vruchtvolle discussies aangaande de timing van aorta chirurgie. Adriaan Moelker, mijn bewondering voor jouw precisie wat betreft 3D CT-reconstructies tussen alle drukte door en het zeer behulpzame commentaar op mijn manuscripten. Hence Verhagen, met veel plezier kijk ik terug op onze samenwerking en interessante discussies leidend tot het vaatchirurgische AOS artikel. Fop van Kooten, dank voor jouw expertise en inzet op neurologisch gebied. Els Moltzer, jij was mijn voorbeeld in vele opzichten, dank voor je hulp. Jeroen Essers, bedankt voor het begrijpelijk uitleggen van diverse muizenstudies. Wilma de Vries, dank voor jouw ondersteuning en de toewijding waarmee jij alle personen uit de AOS families begeleidt.

Kamer Ba-308, ook wel "het kippenhok" genoemd, onze thuishaven: de congenitale werkkamer vol met kakelende dames (en een enkele verdwaalde heer). Een kamer met een mysterieuze aantrekkingskracht tot bepaalde personen die er eigenlijk niets te zoeken hebben. Annemien van den Bosch, hoe druk het ook is, uiterlijk altijd de rust en efficiëntie zelve, en altijd tijd voor vragen van iedereen. Jannet Eindhoven, de koningin van de kamer, en soms ook wel een klein beetje mijn "mama". Judith Cuypers, altijd chaos op je bureau, maar dat geeft niet want jijzelf bent altijd één en al stralende vrolijkheid. John Younge, onze man als stabiliserende factor, hoe houd je het uit tussen zoveel vrouwen?! Maarten Witsenburg, snel de chaos ontvlucht naar boven, bedankt voor al jouw waardevolle hulp bij mijn manuscripten. Petra Opić, mijn MSc buddy, met plezier kijk ik terug op onze mooie epidemiologische en statistische discussies. Titia Ruys, altijd vrolijk en vol energie, je staat altijd voor alles en iedereen klaar. Samen deelden we veel onderzoeksfrustraties en –successen. Bedankt voor de gezelligheid, goede sfeer en bovenal de onderlinge steun door dik en dun! Veel succes en sterkte met de afronding van jullie promotietrajecten; ik kijk uit naar het resultaat!

Tineke van der Kolk en Celeste Manley: jullie zijn onmisbaar! Tineke, je bent zo'n warm persoon, ik kon altijd bij je terecht. Bedankt voor alles wat je voor me regelde en uitzocht. Celeste, hoeveel dingen kan één mens op één dag regelen? Niet te geloven hoe jij altijd alles wel even regelde, verstuurde, inplande en noem het allemaal maar op, bedankt daarvoor.

Jackie, thank you for helping me struggle through the most exhausting paper in this thesis and your indispensible echocardiographic knowledge. Natuurlijk wil ik ook Ellen, Marianne, Linda, Lourus, Mariëtte, Karina, Anja, Debbie, Beata en Wim hartelijk bedanken voor alle echo's die jullie voor mijn studies gemaakt hebben. Tevens dank aan alle hartfunctie laboranten voor jullie inzet. René Frowijn, mijn onuitspreekbare dank voor het creëren van de illustraties in mijn diverse artikelen en dit proefschrift, en tevens jouw geduld als ik voor de zoveelste keer weer eens met een ICT-probleempje kampte.

Erna Egelie, jij regelde alle portfolio's, cursussen, en bovenal kon ik bij jou terecht om even gezellig bij te kletsen. Liesbeth Duinink en Cecile Sweers, bedankt voor jullie hulp bij mijn METC aanvragen. Ron van Domburg, bij jou kon ik altijd even binnenlopen voor een snelle statistische vraag. Dr. Deckers, bedankt voor de kans die u mij gaf om een hoofdstuk uit het *ABC van de Cardiologie* boek te schrijven. Dr. Klootwijk, met de colleges in jaar 1 en de ECG-cursus wakkerde u bij mij het enthousiasme voor het vak Cardiologie aan.

Hardlopen en cardiologie: een onafscheidelijk duo? Als het aan Tineke van den Berg en Jonathan Lipton ligt wel. Hoewel het met de nodige pijn gepaard ging, de estafette run naar het ESC in Parijs was voor mij een fantastische ervaring die ik nooit meer zal vergeten! Alle hardlopers, bedankt voor de sportiviteit en gezelligheid. Borrelen en cardiologie: nog zo'n onafscheidelijk duo! Alle arts-assistenten en onderzoekers: bedankt voor alle lol en gezelligheid tijdens de vele borrels, diners, feesten en congressen! Davos-gangers, bedankt voor de fantastische tijd op de ski's in het zonnige Davos.

Ik wil graag de Koninklijke Nederlandse Akademie van Wetenschappen, het Erasmus Trustfonds, de familie Bruins en alle sponsoren bedanken voor het financieel mogelijk maken van mijn onderzoek en dit proefschrift.

Geloof het of niet, gelukkig bestaat er ook nog een leven buiten het ziekenhuis… en ja, ook zij kregen regelmatig te kampen met de nodige onderzoeksfrustraties en het bijbehorende gezeur.

Daarom wil ik al mijn vrienden en vriendinnen bedanken voor hun luisterende oor en steun, maar vooral ook voor de gezelligheid en ontspanning! Romy en Myrthe, bedankt dat jullie mijn paranimfen wilden zijn. Romy, mijn maatje gedurende de MSc en tijdens onze mooie rondreizen in Australië en Amerika. Myrthe, partner in crime, we wisselen mooi de wacht. Ik wens jullie veel succes met jullie promotietrajecten en kijk uit naar de dag dat het voor jullie zover is!

Liselotte en Leonora, chica's, wij zijn alle drie totaal verschillend, maar daarom misschien juist zo'n krachtige en gezellige combinatie? Nathalie, gul liefde gevend, als we vallen, vangen we elkaar altijd weer op. Anne, vol kracht en uithoudingsvermogen. Marjolein, al die jaren mijn trouwe collegemaatje. Maryse, mijn Honours buddy, mooie tijden samen in Parijs en New York. Robin, altijd in voor een knuffel en goed diner. Colin, Patrick, Willem en Maarten, voor de nodige stapavonden om even alle stress te vergeten en eruit te dansen!

Tot slot wil ik mijn familie bedanken, die mij van jongs af aan gestimuleerd heeft om al het mogelijke uit mijn leven te halen. Lieve mama en papa, ook al werd het geen economie, dank voor jullie onuitputtelijke interesse en steun voor mijn studie, promotietraject en al het andere in het leven. Jullie leerden mij dat ik alles kon bereiken wat ik wilde en vingen mij altijd op als het even wat minder goed ging. Lieve oma en opa, jullie gaven mij zoveel liefde en steun, jullie trots vormde voor mij een belangrijke drijfveer. Lieve tante Edith, met jouw opbeurende persoonlijkheid kon ik af en toe even aan alles ontsnappen.

Helaas komt deze reis hier tot een einde. Met veel plezier en trots kijk ik terug op deze mooie periode! Slechts één vraag resteert: waar zal de toekomst mij brengen?

Denise van der Linde

“...en je reis gaat verder. Waar die ook heen zal gaan, wij staan achter je.”
Je trotse ouders

“Wij zijn enorm trots op je en wensen je verder heel veel succes.”
Ir. D. de Bruijn en mw. M.W. de Bruijn-Lafeber, grootouders

“Voor mijn slimste en liefste nichtje Denise!”
Trotse tante Edith