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Imaging techniques in aortic valve and root surgery

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IMAGING TECHNIQUES

in aortic valve and root surgery

Madelien Veronique Regeer

The research described in this thesis was performed at the Heart Lung Center of the Leiden University Medical Center, Leiden, the Netherlands

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IMAGING TECHNIQUES

in aortic valve and root surgery

Proefschrift

Ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
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Madelien Veronique Regeer
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in 1987

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Table of contents

Chapter 1: General introduction: The role of multimodality imaging in the selection of patients for aortic valve repair
Expert Rev Cardiovasc Ther. 2016;14:75-86 page 9

Part I: preoperative evaluation of patients with aortic regurgitation and/or aortopathy
Progression of disease
Chapter 2: Three-dimensional echocardiography of the aortic valve and root: changes in aortic root dilation and aortic regurgitation
Eur Heart J Cardiovasc Imaging. 2016. In press page 31
Chapter 3: Mitral valve geometry changes in patients with aortic regurgitation
J Am Soc Echocardiogr. 2015;28:455-462. page 47
Chapter 4: Effect of statins on aortic root growth rate in patients with bicuspid aortic valve anatomy
Int J Cardiovasc Imag. 2015;31:1583-1590 page 63

Selection of candidates to valve-sparing aortic root reconstruction
Chapter 5: Aortic valve and aortic root features in CT angiography in patients considered for aortic valve repair
J Cardiovasc Comput Tomogr. 2014;8:299-306. page 79
Chapter 6: Transthoracic echocardiography for selection of tubular graft size in David reimplantation technique
Int J Cardiovasc Thorac Surg. 2015;21:459-464 page 93

Part II: postoperative evaluation of patients after aortic valve and root surgery
Effects of aortic valve and root surgery on left ventricular performance
Chapter 7: Left ventricular reverse remodeling after aortic valve surgery for acute versus chronic aortic regurgitation
Echocardiography. 2016;33:1458-1464 page 109
Chapter 8: Aortic valve repair versus replacement for aortic regurgitation: effects on left ventricular remodeling
J Card Surg. 2015;30:13-19. page 121
Chapter 9: Comparison of left ventricular volume and ejection fraction and frequency and extent of aortic regurgitation after operative repair of type A aortic dissection among three different surgical techniques.
Am J Cardiol. 2016;117:1167-72. page 135

Chapter 10: Left bundle branch block after sutureless, transcatheter, and stented biological aortic valve replacement for aortic stenosis
Eurointervention. 2017. 12:1660-1666. page 149

Effects of aortic valve and root surgery on aortic dilation

Chapter 11: Effect of aortic valve replacement on aortic root dilation rate in patients with bicuspid and tricuspid aortic valves
Ann Thorac Surg. 2016; 102:1981-1987. page 165

Chapter 12: Prognostic implications of descending thoracic aorta dilation after surgery for aortic dissection
J Cardiovasc Comput Tomogr. 2017. 11:1-7. page 179

Summary and future perspectives page 195

Samenvatting en toekomstperspectieven page 201

List of publications page 208

Acknowledgements page 212

Curriculum vitae page 214

Chapter 1:

General introduction
The role of multimodality imaging in the selection of patients for aortic valve repair

M.V. Regeer, M.I.M. Versteegh, N. Ajmone Marsan, J.J. Bax, V. Delgado

Expert Rev Cardiovasc Ther. 2016;14:75-86

Summary

Aortic valve sparing surgery for aortic regurgitation and/or aortopathy serves as an alternative to aortic valve and root replacement. One of the advantages of aortic valve sparing surgery over conventional replacement is that there is no need for life-long anticoagulation, which is particularly attractive in young patients who may receive a mechanical prosthesis otherwise. However, successful aortic valve repair requires high expertise. At present, reparability is determined intraoperatively by direct surgical inspection. Preoperative imaging techniques might improve the patient selection for aortic valve repair. The mechanism of aortic regurgitation, aortic valve morphology and calcification and aortic root dimensions are all of importance when aortic valve repair is considered. The present review focuses on the role of imaging techniques in determining aortic valve reparability.

Introduction

Aortic valve repair for aortic regurgitation and valve-sparing aortic root replacement for aortic root and ascending aorta aneurysm or dissection are feasible and safe alternative techniques to aortic valve replacement and tubular graft implantation. However, successful and durable aortic repair requires high expertise. In contrast to mitral valve repair for mitral valve regurgitation, where the pre-procedural and surgical exploration of the valvular pathology and the surgical techniques are more standardized,[1] aortic valve repair techniques are more heterogeneous. In addition, since the introduction of the remodeling and reimplantation techniques by Drs. Yacoub and David, respectively, several modifications of the techniques have been developed according to the experience of the centers.[2-4] Accurate characterization of the underlying pathology and mechanism of aortic regurgitation is crucial for selection of patients in who aortic valve repair techniques and valve-sparing aortic root replacement will be successful resulting in a durable competent aortic valve.

The present review article focuses on the role of non-invasive imaging to characterize the underlying mechanism of aortic regurgitation and selection of patients who are candidates for surgical aortic valve repair/valve-sparing aortic root replacement techniques

Aortic valve and root anatomy

The aortic root has a complex anatomy consisting of several components as shown in Figure 1. The aortoventricular junction, also called the annulus, is described as a virtual basal ring which separates the left ventricular outflow tract from the aortic root. It is defined by the circumference described by the nadirs of the aortic valve cusp attachments. The sinus of Valsalva consists of three bulges of the aortic wall. The coronary arteries arise from two of the sinuses, the right coronary sinus and the left coronary sinus. The remaining sinus is termed the non-coronary sinus and is spatially related with the interatrial septum. The morphology of the sinuses allows the formation of flow vortices during the left ventricular ejection to reduce the stress on the aortic valve cusps and support coronary flow.[5] The sinotubular junction is the circumference that supports the peripheral attachments of the aortic cusps and separates the aortic root from the ascending aorta.

The aortic valve consists of three semilunar cusps, commissures and intercusps triangles. The aortic cusps are termed according to their corresponding sinus as the left coronary cusp, right coronary cusp and non-coronary cusp. They are attached to the aortic root wall in a semilunar fashion forming the intercusps triangles. The apices of these triangles demark the commissures, defined as the areas where the attachments of the cusps have a parallel course for a short distance. In the general population, 1-2% has a bicuspid aortic valve (BAV) defined by the presence of two commissures and two equally sized cusps without a raphe or, more frequently, three cusps with two of them fused by a raphe.[6,7] Fusion of the left coronary and

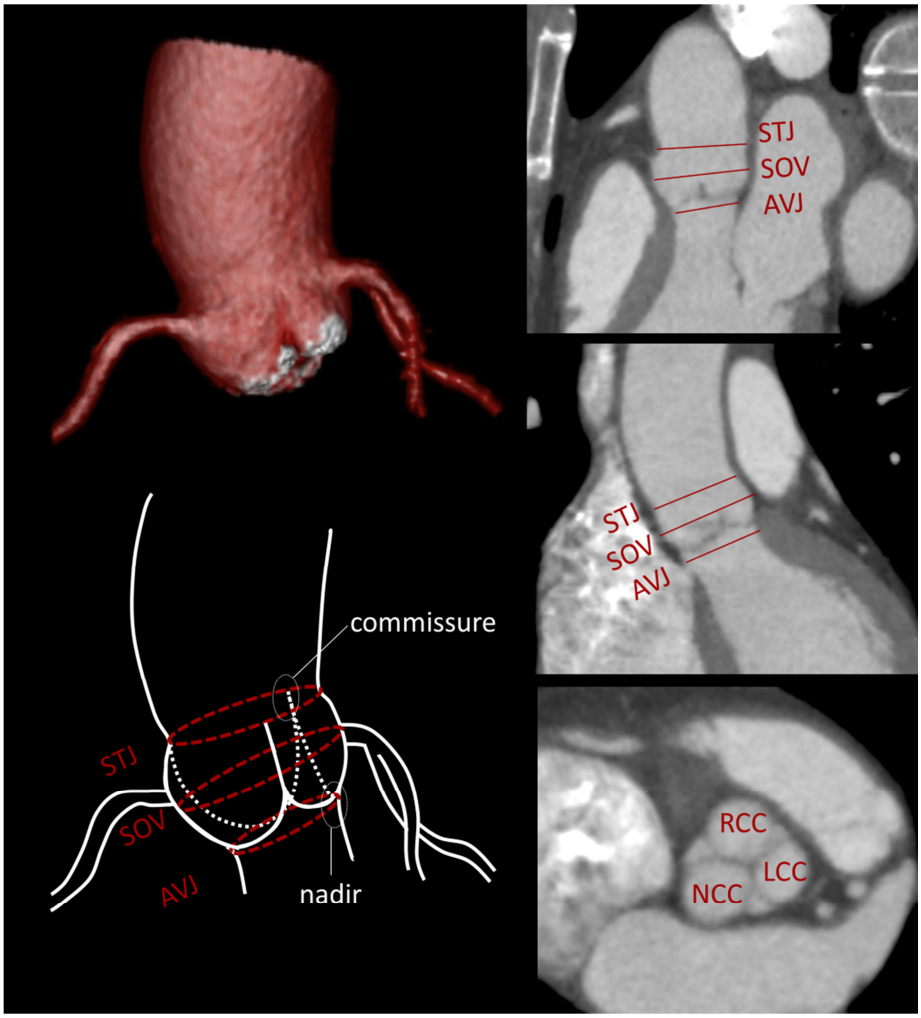

Figure 1. Anatomy of the aortic valve and root.
AVJ: aortoventricular junction, LCC: left coronary cusp, NCC: non-coronary cusp, RCC: right coronary cusp, SOV: sinus of Valsalva, STJ: sinotubular junction

right coronary cusp or right coronary and non-coronary cusp are the most frequent phenotypes.[7] The posterior aspect of the aortic root is supported by fibrous tissue (membranous part of the membranous septum) in its 50% of the circumference, whereas the anterior aspect is surrounded by the left ventricular myocardium.This has important implications for aortic valve repair techniques.

Similarly, successful and durable aortic valve repair requires accurate characterization of the specific geometry of the aortic root. The sinotubular junction is usually 10-15% smaller than the aortoventricular junction or aortic annulus, whereas at the level of the valve commissures, the diameter of the aortic root is comparable to that of the aortic annulus. The height of the

aortic cusps (from the apex of the intercusp triangle to the nadir of the cusp) is 12-18 mm. The non-coronary sinus and its corresponding cusp are larger than the left and right counterparts. These dimensions have been largely studied and formulae to size the tubular graft used in aortic valve repair have been developed to ensure appropriate coaptation of the aortic cusps.[8-12]

Mechanisms of aortic regurgitation

Aortic regurgitation comprises 10% of all moderate to severe valvular heart diseases, being the prevalence of moderate to severe aortic regurgitation in the general population of 0.5%.[13,14] Aortic regurgitation is caused by malcoaptation of the aortic valve cusps, which results either from intrinsic cusp damage or from aortic root dilation.[15] Valvular causes of aortic regurgitation include aortic valve degeneration, congenital malformation of the aortic valve (with BAV being the most common abnormality), rheumatic valvular disease (particularly in developing countries) and infective endocarditis.[14,15] Non-valvular causes of aortic regurgitation include aortic root aneurysm (whether or not in the context of connective tissue disease such as Marfan syndrome), aortic dissection and aortitis.[15]

Similarly to the classification of mitral regurgitation mechanisms, a repair-oriented classification system has been developed to describe the mechanism of aortic regurgitation.[16] Based on the motion of the aortic cusps, the underlying mechanism of aortic regurgitation can be classified as: type 1 characterized by normal motion of the cusps and malcoaptation due to dilatation of the aortic root involving the sinus of Valsalva, type 2 characterized by excessive cusp motion causing prolapse an type 3 characterized by restrictive motion of the cusps (Figure 2). Some of these mechanisms may coexist. Type 1 aortic regurgitation is frequently caused by aortic root aneurysm or aortic dissection, developed due to longstanding hypertension, connective tissue disease or in the context of BAV, whereas the underlying pathology in type 2 and type 3 aortic regurgitation is valvular dysfunction most often due to valve degeneration, congenital malformation and infective endocarditis.[16]

Aortic valve repair techniques

To restore the competence of the aortic valve, the several surgical approaches aim at correcting the underlying mechanism of aortic regurgitation. In type 1 aortic regurgitation, restoration of the normal dimensions of the aortic root is necessary and can be performed with one of the valve-sparing aortic root reconstruction techniques. In patients with aortic root dilation, either the remodeling technique or the reimplantation technique can be performed. In the remodeling technique, the aortic sinuses are resected along the commissures and a Dacron graft with neosinuses is implanted.[17] In the reimplantation technique, the entire aortic root until the aortoventricular junction is resected and replaced by

a Dacron graft and the native aortic valve is reimplanted.[18] In both the remodeling and reimplantation techniques, the coronary arteries are reimplanted in the neo-aortic root. In the last decades, several modifications of these techniques have been proposed. The remodeling technique can be extended with a subvalvular annuloplasty ring in order to stabilize the aortoventricular junction.[3,4] Another modification of remodeling is the sleeve technique in which coronary keyholes are created in the neo-aortic root to prevent reimplantation of the coronary arteries.[19]

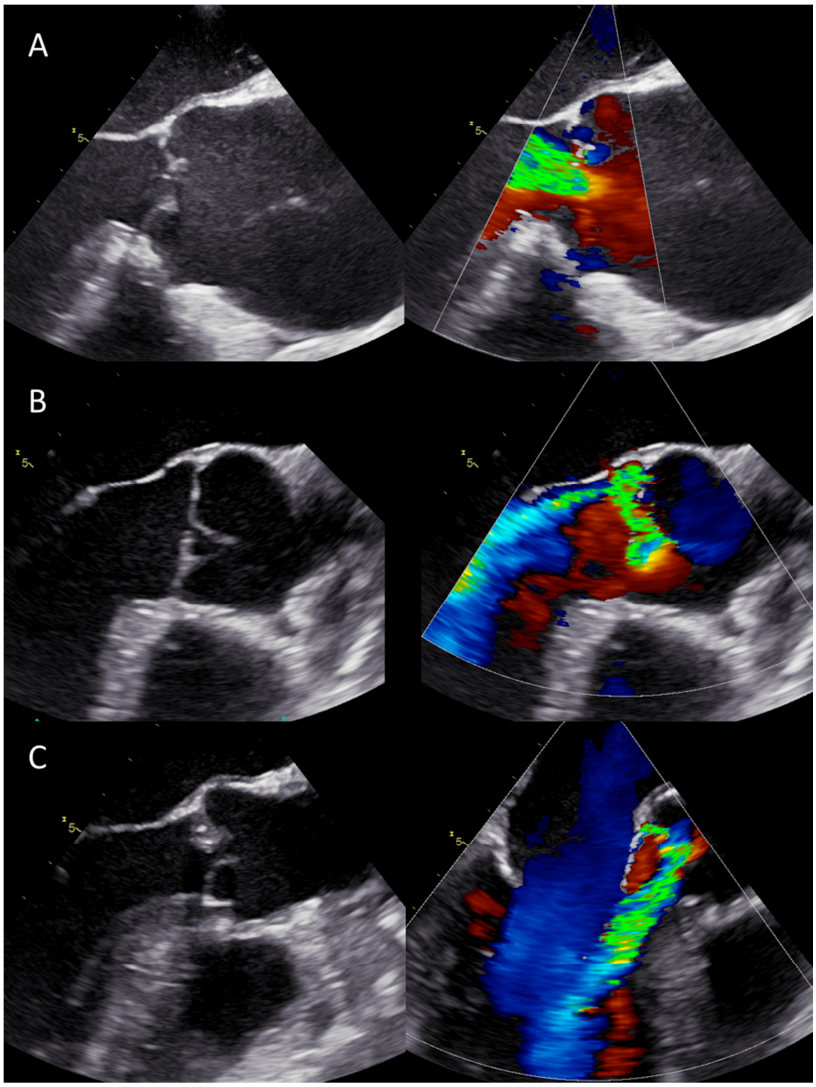

Figure 2. Mechanisms of aortic regurgitation.
A: aortic regurgitation type 1 due to aortic root dilation. B: aortic regurgitation type 2 due to leaflet prolapse. C: aortic regurgitation type 3 due to cusp restriction.

Moreover, the reimplantation technique uses currently a tailored graft with neosinuses or a prefabricated Valsalva-graft (David-V) to provide more physiological hemodyamics.[2] In patients with ascending aorta dilation without aortic root dilation, supracoronary ascending aorta replacement using a Dacron graft and remodeling of the sinotubular junction to prevent residual aortic regurgitation are commonly performed.[18]

Type 2 aortic regurgitation, due to excessive cusp motion, can be repaired using different leaflet repair techniques. When there is prolapse of one of the leaflets, central cusp plication or triangular resection can be performed.[20]. In addition or separately, resuspension of the free edge of the leaflet can be performed. A running suture is passed along the cusp free margin. A cusp defect or large fenestration can be repaired using a pericardial patch sewn into the cusp.[21] In patients with poorly aligned commissures, a subcommissural annuloplasty using three sutures is added.[22]

Type 3 aortic regurgitation results from aortic valve restriction. Frequently, the aortic cusps are thickened and calcified reducing the feasibility of successful and durable repair.[16] Therefore, in patients with this type of regurgitation, aortic valve replacement is the surgical approach of first choice.

In experienced centers, aortic valve repair has shown low early mortality rates (1.1-3.6%) and a 10-year survival rates ranging between 75% and 95%.[16,23-27] Freedom from reoperation and aortic regurgitation recurrence rates at 10 years are 90% and 80%, respectively.[16,23-28] The 5-year survival is better after aortic valve repair (96%) compared to aortic valve replacement with biological prosthesis (89%) and mechanical prosthesis (82%; p=0.02). This may be explained by the lower operative risks of patients who are referred for aortic valve repair compared to that of patients undergoing aortic valve and aortic root replacement.[29]

Several studies have compared the outcomes between different aortic valve repair techniques. David et al. showed that the remodeling technique is marginally associated with a three times higher risk of reoperation than the reimplantation technique (p=0.07).[27] Additionally, in patients with BAV, connective tissue disease or acute type A aortic dissection, freedom from reoperation at follow-up is generally higher after reimplantation approach compared with the remodeling technique.[24,30,31] There is no difference in 8-year freedom from reoperation and 5-year freedom from aortic regurgitation recurrence (92% and 89% and 84% and 90%, respectively)among patients undergoing isolated valve-sparing root replacement or combination of this technique with additional leaflet repair.[32] However, when leaflet repair is applied as an isolated technique, significant worse freedom from reoperation at 10 years follow-up is observed (70%) compared to supracoronary ascending aorta replacement (93%) and remodeling technique (89%; p<0.001).[33] In patients undergoing supracoronary ascending aorta replacement in whom additional subcommissural annuloplasty is performed, the 5-year

freedom survival from aortic regurgitation was better (94%) compared with that of patients in whom this procedure was not performed (58%, p=0.02).[34]

Multimodality imaging in aortic valve repair

Imaging of the aortic valve and root plays an important role in decision-making of patients with aortic regurgitation who may be candidates for aortic valve repair techniques. Different imaging techniques such as 2-dimensional transthoracic and transesophageal echocardiography (2DTTE and 2DTEE), 3-dimensional transesophageal echocardiography (3DTEE), multi-detector row computed tomography (MDCT) and cardiac magnetic resonance (CMR) can be used to assess aortic regurgitation severity, aortic regurgitation mechanism, aortic valve reparability and aortic root dimensions (Table 1).

Table 1. Imaging modalities to assess several aspects of aortic regurgitation.

	2DTTE	**2DTEE**	**3DTEE**	**MDCT**	**CMR**
Aortic regurgitation severity	++	++	++	-	++
Aortic regurgitation mechanism	+	+	+	-	+/-
Aortic root dimensions	+/-	+/-	+	++	++
Aortic valve reparability	+/-	++	+	+	+

2DTEE: two-dimensional transesophageal echocardiography, 2DTTE: two-dimensional transthoracic echocardiography, 3DTEE: three-dimensional transesophageal echocardiography, CMR: cardiac magnetic resonance, MDCT: multidetector row computed tomography.

Quantification of aortic regurgitation.

Echocardiography is the imaging technique of first choice to grade aortic regurgitation. Current guidelines recommend a multiparametric approach using multiple views (parasternal long axis view and apical views) and several qualitative, semi-quantitative and quantitative parameters of regurgitant volume and/or fraction as displayed in table 2.[35,36] Colour Doppler imaging is used to grade aortic regurgitation semi-quantitatively, measuring jet area and jet width ratio (ratio between regurgitant jet width and left ventricular outflow tract width). However, these methods are not recommended when several aortic regurgitation jets are observed.[35] A more quantitative approach can be followed by measuring the vena contracta width, which is defined as the width of the regurgitant jet as it transverses the aortic valve. A vena contracta width of <3mm corresponds with mild aortic regurgitation, 3-6 mm with moderate and >6mm with severe aortic regurgitation. Using continuous wave Doppler of the regurgitant jet, the measurement of a pressure half time <200 ms, indicates the presence of severe aortic regurgitation.[35] In addition, diastolic flow reversal in the descending aorta, measured with pulsed wave Doppler is strongly associated with severe aortic regurgitation. Moreover, quantitative measurement of the effective regurgitant orifice area and regurgitant volume using the proximal isovelocity surface area (PISA) method is highly recommended

when feasible, especially in patients with intermediate vena contracta values (between 3 and 6 mm). Aortic regurgitation is considered severe when the effective regurgitation orifice area is ≥30mm^2 or regurgitant volume is ≥60 ml.[37] However, this method is less feasible when the effective orifice area is not circular (prolapse of one of the cusps) or in very eccentric regurgitant jets.[38]

With the development of 3-dimensional echocardiographic techniques, newer methods to grade aortic regurgitation have been proposed. In particular patients with eccentric jets and multiple jets may benefit from three dimensional assessment of the regurgitant jet. A vena contracta area >0.6cm^2 on 3DTEE indicates the presence severe aortic regurgitation and correlates well with aortic regurgitant fraction on CMR.[39,40] Direct measurement of PISA

Table 2. Echocardiographic parameters to assess severity of aortic regurgitation.

	Mild	Moderate	Severe
Qualitative			
Aortic valve morphology	Normal/abnormal	Normal/abnormal	Abnormal/flail/large coaptation defect
Colour flow aortic regurgitation jet width	Small in central jets	Intermediate	Large in central jets, variable in eccentric jets
Continuous wave signal of aortic regurgitation jet	Incomplete/faint	Dense	Dense
Diastolic flow reversal in descending aorta	Brief, protodiastolic flow reversal	Intermediate	Holodiastolic flow reversal (end-diastolic velocity >20 cm/s)
Semi-quantitative			
Vena contracta width	<3 mm	Intermediate	>6 mm
Pressure half-time	>500 ms	Intermediate	<200 ms
Quantitative			
Effective regurgitant orifice area	<10 mm^2	10-29 mm^2	≥30 mm^2
Regurgitant volume	<30 ml	30-59 ml	≥60 ml

Adopted from Lancellotti et al.[37]

without geometric assumptions is possible with 3DTEE and seems superior to two-dimensional PISA.[41] In patients with inadequate echocardiographic quality, CMR should be used to assess aortic regurgitation severity.[42] Aortic regurgitant fraction >33% on CMR which is defined as the proportion of the regurgitant volume relative to the forward stroke volume identifies patients who progressed to symptoms and surgery.[43] Additionally, effective regurgitant orifice area can be measured on gated MDCT in diastolic phase. An aortic regurgitant orifice area of 0.04-0.25 cm^2 corresponds with mild aortic regurgitation, 0.37-0.44 cm^2 with moderate aortic regurgitation and 0.81-1.05 cm^2 with severe aortic regurgitation.[44,45] Several small studies show good correlation between regurgitant orifice area on MDCT and aortic regurgitation

grade on 2DTTE; however this imaging technique is associated with important radiation dose and low temporal resolution and therefore is not an imaging technique of first choice to grade aortic regurgitation.

Assessment of aortic regurgitation mechanism and factors associated with reparability.
At present, aortic valve reparability is assessed intraoperative by direct surgical inspection. Aortic regurgitation mechanism is an important factor in determining whether the aortic valve is or not reparable.[16] Besides aortic valve calcification, aortic valve morphology and aortic root diameter play an important role in determining reparability. Next to the intraoperative inspection, imaging modalities can be used to assess reparability. In Figure 3, the aortic valve and root on MDCT and 3DTEE are shown in comparison to direct surgical inspection.

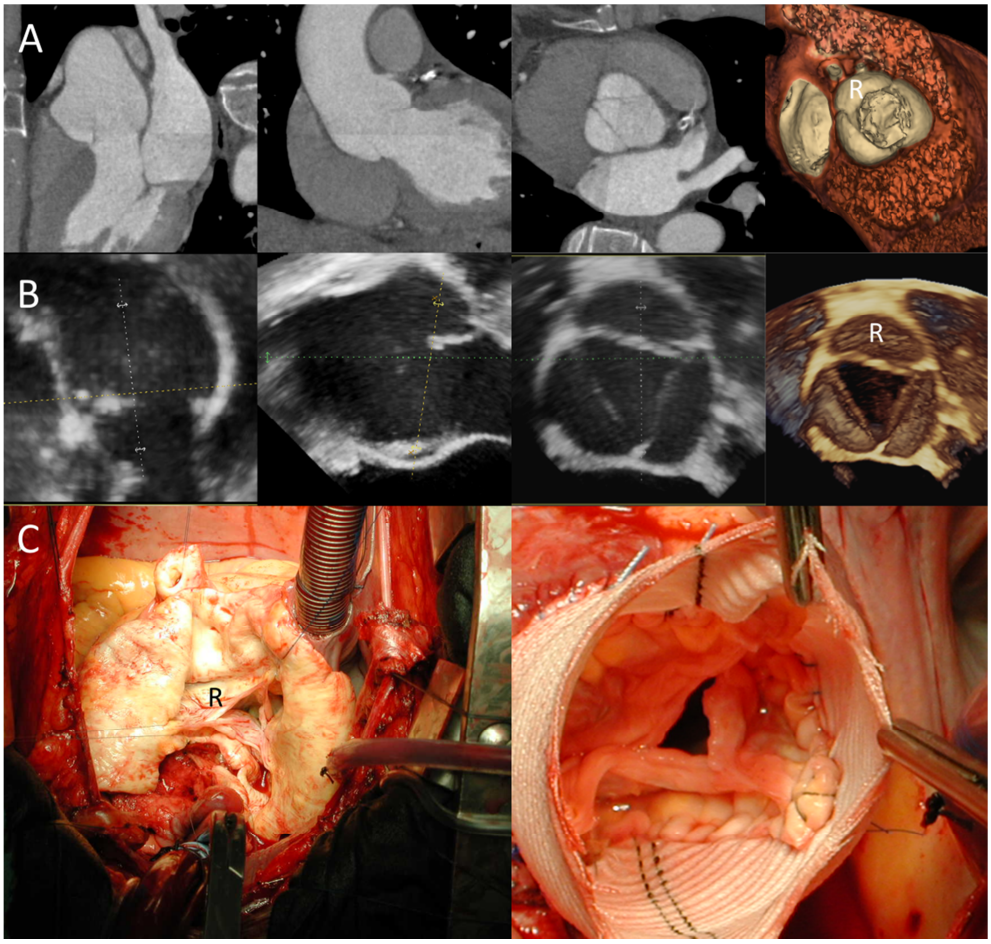

Figure 3 Assessment of the aortic valve and root with multi-detector row computed tomography (A), 3-dimensional transesophageal echocardiography (B) and surgical view (C: before and after reimplantation technique).
The images are rotated to match the surgical view. R indicates right-coronary cusp.

An important advantage of imaging techniques over direct surgical inspection is that the cusp motion can be observed throughout the cardiac cycle. In addition, preoperative imaging can be used at the heart team discussion to decide whether or not aortic valve repair seems feasible and which technique is the most appropriate. Table 3 summarizes factors associated with reparability and the preferred imaging modality to assess these factors.

The mechanism of aortic regurgitation can be assessed with 2DTEE. First, the jet direction is classified as central or eccentric. Central jets are associated with normal cusp mobility and aortic root dilatation whereas eccentric jets are observed in excessive cusp mobility.[46] Moreover, a transverse fibrous band in addition to an eccentric jet characteristically identifies a prolapsing cusp.[16] There is a good agreement between identification of the aortic regurgitation mechanism by 2DTEE and direct surgical inspection with a kappa of 0.90.[47]

In addition, the tissue characteristics of the aortic cusps have an important impact on the durability of the repair. Freedom from recurrent aortic regurgitation grade >2 is significantly impaired after repair in type 3 aortic regurgitation, which is characterized by thickened and restrictive cusps, in comparison with type 1 and type 2 aortic regurgitation (hazard ratio: 2.6, 95% confidence interval: 1.1-11.6, p=0.03).[16] Therefore repair is not recommended in type 3 aortic regurgitation.

Table 3. Factors associated with aortic valve reparability and the preferred imaging modality

Factors associated with aortic valve reparability	Preferred imaging modality
Type 1 and 2 aortic regurgitation	2D/3DTEE
No or only small aortic annular or commissural calcification	2D/3DTEE, MDCT
Bicuspid aortic valve	
with commissural orientation >160°	2D/3DTEE, (gated MDCT)
with eccentric jet without commissural or cusp thickening	2D/3DTEE
with large cusp pliability and small coaptation deficiency index	2D/3DTEE
Aortoventricular junction <28 mm	MDCT, 3DTEE

2DTEE: two-dimensional transesophageal echocardiography, 3DTEE: three-dimensional transesophageal echocardiography, MDCT: multidetector row computed tomography.

In contrast, preoperative severity of aortic regurgitation is not associated with reparability.[32] Patients with aortic regurgitation grade ≥3 need leaflet repair as often as patients with aortic regurgitation grade <3 with comparable freedom from reoperation at 8 years (90±7% vs. 89±11%, respectively; p=0.7).[32] Calcifications of the aortic valve cusps are also important determinants of the success of aortic valve repair. In moderately calcified valves (grade <3), when the calcifications are confined to the free margin, repair is considered feasible.[47] Calcifications in the body of the cusp or interfering with cusp mobility are considered non-reparable.[47] In addition, higher grades of aortic valve commissural and annular calcification, assessed with MDCT, are associated with non-reparability.[48]

In addition, aortic valve morphology has been associated with aortic valve reparability. Echocardiography can demonstrate the presence of BAV with precision.[49,50] The diagnosis of BAV is made when there are two leaflets in systole with two commissures framing an ellipsoid orifice.[37] Moreover, ECG-gated contrast enhanced MDCT is highly accurate to differentiate between tricuspid aortic valves and BAV.[51] CMR can also be used to assess aortic valve morphology.[52] Aortic valve repair techniques provide in general good outcomes in BAV-patients operated by experienced surgeons.[53,54] BAV-patients with an eccentric regurgitant jet, without commissural or cusp thickening on the preoperative 2DTEE are more likely to undergo successful aortic valve repair.[55] Furthermore, greater tissue pliability, defined by tissue normality index on 2DTEE ((diastolic cusp area – systolic cusp area) / diastolic cusp area), and lower coaptation deficiency index, defined on 2DTEE as the sum of conjoint cusp height and reference cusp height relative to diastolic aortic annulus diameter, have been associated with higher rates of successful valve repair in patients with incompetent BAV.[21] On the other hand, BAVs are less often reparable when there is a commissural orientation <160° and preoperative aortic regurgitation grade ≥3.[56]
Aortic root diameter is also of interest in determining reparability. Patients with an aortoventricular junction of >28mm have more often recurrent aortic regurgitation grade >2 and higher risk of reoperation if no additional surgical techniques are employed to restore the dimensions of this aortic root component.[56-58] Figure 4 describes a flowchart which can be used to determine whether or not an incompetent aortic valve is reparable.

Associated aortic root aneurysms.
Due to increased risk of aortic rupture, the presence of associated aortic root aneurysms of >55 mm indicate surgery irrespective of the aortic regurgitation severity.[59] Lower thresholds of 50 mm or 45 mm are applied in BAV or connective tissue disease with additional risk factors such as positive family history of aortic dissection, fast growth of the ascending aorta (>3 mm/year), severe aortic regurgitation or desire for pregnancy.[59]
Aortic root dimensions are evaluated on transthoracic echocardiography as part of routine cardiac evaluation. The aortic root diameter is measured at 3 predefined levels: aortoventricular junction, sinus of Valsalva and sinotubular junction on long axis views during end-diastole.[46,60] Upper normal limits are defined at each level separately for men (aortoventricular junction: 31 cm, sinus of Valsalva: 40 cm and sinotubular junction: 36 cm) and women (aortoventricular junction: 26 cm, sinus of Valsalva: 36 cm and sinotubular junction: 32 cm).[60]

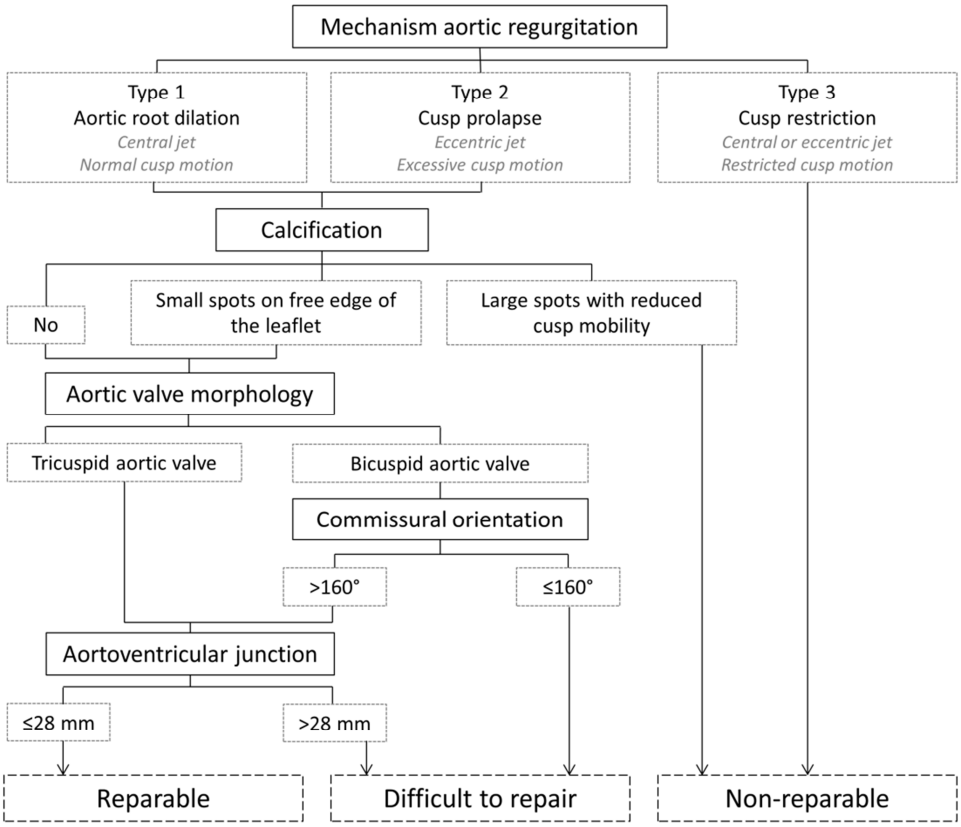

Figure 4 Flowchart to determine aortic valve reparability.

Measurements on 2-dimensional echocardiography significantly underestimate the aortic root diameter in comparison to automated measurements on 3DTEE, CMR and MDCT.[61] Therefore 3-dimensional imaging modalities are preferred over 2-dimensional modalities in the assessment of the aortic root diameter. In 3-dimensional imaging techniques the maximum diameter should be measured perpendicular to the centreline of the vessel using multiplanar reconstruction.[59,62] There is no consensus on whether the aortic wall should be included in the measurement of the aortic diameter and on whether the measurement should be performed in systole or diastole.[59] Echocardiography uses the leading edge-to-leading edge technique whereas MDCT and CMR use the inner edge-to-inner edge technique.[63] In addition, visualization and quantification of dynamic flow patterns with 4-dimensional (4D) flow magnetic resonance imaging (MRI) have shown promising in predicting the development of aortic disease in patients with aortic valve disease (Figure 5). Vectors plots and particle traces (streamlines and pathlines) are the most common approaches to visualize 4D flow data.[64] Vector plots represent the actual velocity data at a given moment in time, streamlines connect

these vectors with imaginary lines that illustrate the instantaneous flow field and pathlines represent blood flow over time and are calculated by releasing imaginary particles intro the flow field and tracking their position across the cardiac cycle.
Quantitative assessment of dynamic flow patterns includes wall shear stress and flow displacement. High wall shear stress states and flow displacement have been associated with aortic dilatation, particularly in patients with BAV.[65,66]

Conclusion

Surgical aortic valve repair demands high experience and surgical skills. In contrast to mitral valve repair where the surgical repair techniques are more standardized, surgical aortic valve repair is more heterogeneous and requires an advanced knowledge on the anatomy, geometry and dynamics of the aortic root. In the evolution of surgical aortic valve repair techniques, cardiac imaging has been an important adjuvant to better select the patient in whom this treatment will be durable and to modify the techniques in order to attain a more physiological function of the replaced aortic root.

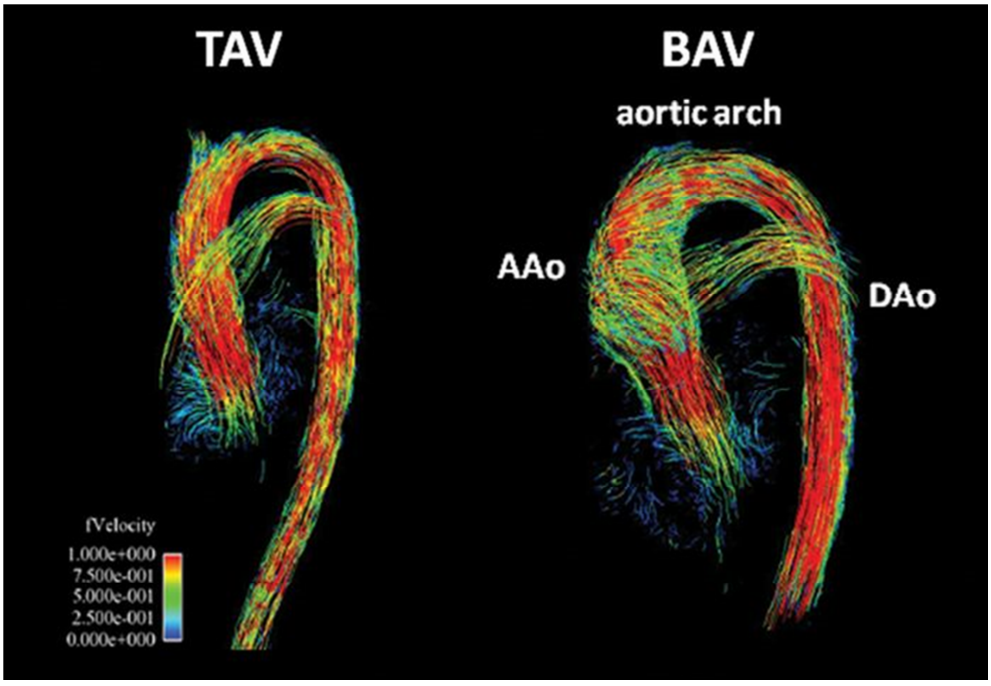

Figure 5. 4D flow MRI of the aortic valve and aorta.
Comparison of 4D flow MRI streamlines of the aortic flow in a patient with tricuspid aortic valve (TAV) and a patient with bicuspid aortic valve (BAV). Reproduced from Meierhofer et al.66 with permission from the Oxford University Press.

Objective and outline of the thesis

The primary objective of this thesis is to improve patient selection for valve-sparing aortic root reconstructive surgery using imaging techniques. This thesis can be divided into two parts. The first part focuses on imaging in patients with aortic regurgitation and/or aortopathy to evaluate disease progression and to determine reparability of the aortic valve in surgical patients. The second part describes the effect of aortic valve and root surgery on left ventricular performance and aortic dilation.

Part I: preoperative evaluation of patients with aortic regurgitation and/or aortopathy
In Part Ia, the progression of disease in patients with aortic regurgitation and/or aortopathy is evaluated. Chapter 2 describes the changes in aortic valve geometry in dilated aortic roots evaluated using three-dimensional transesophageal echocardiography. Chapter 3 focuses on the effect of aortic regurgitation on mitral valve geometry in relation to the presence of mitral regurgitation. Chapter 4 evaluates the effect of statin therapy on aortic root dilation in patients with bicuspid aortic valves. Part Ib consists of two chapters discussing different preoperative imaging techniques in the selection of patients for valve-sparing root replacement techniques. The use of multidetector row computed tomography in determining aortic valve reparability is described in Chapter 5. In Chapter 6, the additional value of echocardiography in selection of the appropriate graft size in valve-sparing root replacement using the reimplantation technique is evaluated.

Part II: postoperative evaluation of patients after aortic valve and root surgery
In Part IIa, the effects of aortic valve and root surgery on the left ventricle are described. The occurrence of postoperative left ventricular reverse remodeling is compared between acute aortic regurgitation and chronic aortic regurgitation in chapter 7. In chapter 8, distinction is made between left ventricular reverse remodeling after repair and replacement of the aortic valve and/or root. Chapter 9 focuses on the changes in left ventricular volumes and function after different surgical techniques for acute type A aortic dissection. In chapter 10, the prevalence of conduction disturbances and its effect on the left ventricle after aortic valve replacement is discussed. Part IIb describes aortic dilation after aortic valve and root surgery. Chapter 11 compares aortic root dilation after replacement of a bicuspid and a tricuspid aortic valve. Lastly, in chapter 12, dilation of the native descending thoracic aorta after surgery for acute type A aortic dissection is evaluated. The final chapters describe a general summary, conclusions and future perspectives.

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PART I

Preoperative evaluation of patients with aortic regurgitation and/or aortopathy

Progression of disease

Chapter 2:

Three-dimensional echocardiography of the aortic valve and root: changes in aortic root dilation and aortic regurgitation

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Abstract

Background: It has been hypothesised that in response to dilation of the aortic root, the aortic valve cusps may remodel to prevent aortic regurgitation (AR). The aim of the present study was to evaluate the association between aortic cusp dimensions and aortic root geometry.
Methods: Three-dimensional transesophageal echocardiography was performed in 40 patients with aortic root dilation (mean age 57±12 years, 75% men, 35% bicuspid aortic valve) and 20 controls with a normal aortic root (mean age 61±13 years, 65% men). Aortic valve geometry was measured and the ratio between closed cusp area and sinotubular junction (STJ) area as a measure of the aortic cusp remodeling relative to the aortic root dilation was assessed.
Results: Patients with aortic root dilation with tricuspid aortic valve (n=26) showed significant increase in aortic cusp size. However, the closed cusp area to STJ area ratio was smaller in dilated aortic roots (0.88 [95% confidence interval: 0.78-0.98]) compared with normal aortic roots (1.22 [95% confidence interval: 1.02-1.41]; p=0.002). In addition, in patients with central AR, there was insufficient cusp tissue, as suggested by a closed cusp area to STJ area ratio of 0.75 (95% confidence interval: 0.67-0.82), compared with relative excess of cusp tissue in eccentric AR with a ratio of 1.14 (95% confidence interval: 1.01-1.27; p<0.001).
Conclusion: Aortic root dilation was associated with significant increase in aortic valve cusp size. However, this increase seemed insufficient to match aortic root size, particularly in central AR, whereas in eccentric AR, there was relative abundance of cusp tissue resulting in relative cusp prolapse.

Introduction

Aortic root dilation involving particularly the aortic annulus can lead to aortic regurgitation (AR) due to malcoaptation of aortic valve cusps.[1] Idiopathic aortic root dilation is the leading cause of valvular insufficiency in about 10-30% of patients with AR.[2,3] However, not all patients with aortic root dilation exhibit AR. It could be hypothesized that in patients with aortic root dilation, the aortic valve cusps may be exposed to increased wall stress that triggers their remodeling and growth to compensate and preserve valvular competence. Indeed, computational models have shown that the aortic valve can adapt in response to aortic root dilation.[4] However, in clinical practice these models are time consuming and require high computational costs. In patients who underwent clinically indicated three-dimensional transesophageal echocardiography (3DTEE), we evaluated whether the aortic valve cusps show remodeling to compensate for the aortic root dilation. The aims of the present study were: 1) to assess whether patients with aortic root dilation show remodeling of the aortic valve cusps to prevent AR and 2) to investigate whether this remodeling is different in patients with central and eccentric regurgitant jets.

Methods

Patients

A total of 40 patients with aortic root dilation (defined as maximum diameter of the sinus of Valsalva (SOV) of ≥40 mm in men and ≥36 mm in women or maximum diameter of the sinotubular junction (STJ) ≥36 mm in men and ≥32 mm in women[5,6]), who underwent clinically indicated 3DTEE, were included. Patients with bicuspid aortic valve were excluded for further geometric analyses. Patients with tricuspid aortic valve were divided into two subgroups according to presence of AR and according to the presence of a central or eccentric AR jet. Patients with more than mild aortic stenosis were excluded. In addition, a control group of 20 patients who underwent clinically indicated 3DTEE (i.e. evaluation of the mechanism of mitral regurgitation, suspected endocarditis, and evaluation of cerebrovascular accident or in the context of left atrial appendage closure) and who had normal dimensions of the aortic root and normal functioning tricuspid aortic valve was included.

Clinical characteristics were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. 3DTEE data of the aortic valve and root geometry were analyzed offline and compared between patients with aortic dilation and controls. In addition, aortic valve and root geometry were compared between patients with central and eccentric AR. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Two-dimensional transthoracic echocardiography

Transthoracic echocardiography was performed using commercially available ultrasound system (Vivid E9, General Electric Healthcare, Vingmed, Horten, Norway) equipped with M5S transducer. Two-dimensional and Doppler data were acquired in the parasternal and apical views according to current recommendations.[7,8] AR grade was assessed using a multiparametric approach including the measurement of the jet width relative to the left ventricular outflow tract width and the vena contracta in parasternal long-axis and apical views. AR was graded as 0 (no), 1 (mild), 2 (mild-moderate), 3 (moderate-severe) or 4 (severe).[7] Left ventricular end-diastolic and end-systolic volumes were measured and left ventricular ejection fraction was calculated in the apical two- and four-chamber views according to the Simpson's biplane method.[8]

Three-dimensional transesophageal echocardiography data acquisition and analysis

3DTEE was performed using commercially available ultrasound system (Vivid E9, General Electric Healthcare, Vingmed, Horten, Norway) equipped with a fully integrated 2D/3D matrix transducer (GE 6VT-D, General Electric Healthcare, Vingmed, Horten, Norway). Mid-esophageal images of the aortic valve and aortic root were obtained in the short-axis at 30-45° and in the long-axis at 120-130°. To acquire 3DTEE images, the aortic root was imaged from the aortoventricular junction (AVJ) to the STJ in two orthogonal planes. Thereafter, single-beat and multi-beat 3DTEE data of the aortic valve and root were acquired to optimize spatial and temporal resolution. Attention was paid to avoid stitching artefacts in the multi-beat data acquisition. The echocardiographic data were digitally stored in cine-loop format and data were retrospectively analyzed using commercially available software (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). For 3DTEE data analysis, three orthogonal multiplanar reformation planes were reconstructed and aligned the centreline of the aortic root to obtain the true short-axis of the aortic valve at the level of cusp coaptation. Figure 1 shows the different aortic valve geometric measurements. An end-systolic 3DTEE frame with the aortic valve closed was used to measure the cusp height, intercommissural distance and closed cusp area. The cusp height was measured from the internal border of the aortic root till the free edge of the cusp for each cusp separately and averaged. The intercommissural distance was measured between each commissure and also averaged. The cusp area was measured per each cusp and then summed to obtain the total closed cusp area. A mid-systolic 3DTEE frame was used to measure each cusp area and then summed to obtain the open cusp area. Two additional measurements were performed during end-systole: the cusp depth was measured per cusp in the cross-sectional image of the middle of the cusp between the deepest point of the belly of the cusp and the cross-sectional plane and thereafter averaged whereas the central coaptation deficit was measured at the central coaptation point between each pair of

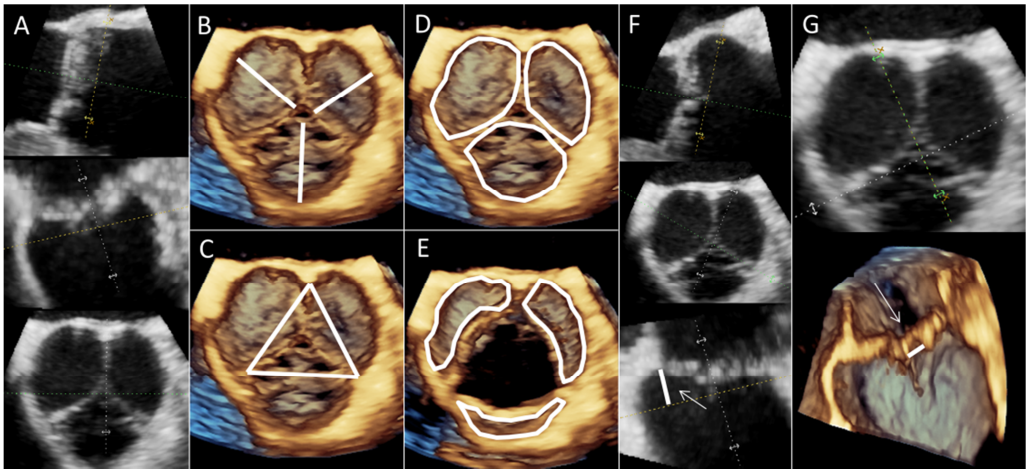

Figure 1. Measurements of aortic valve geometry.
A: Flexi-slice method was used to obtain a true short-axis of the aortic valve at the level of cusp coaptation. B: Cusp height was measured during end-systole from the internal border of the aortic root till the free edge of the cusp. C: Intercommissural distance was measured during end-systole between the commissures. D: Closed cusp area was measured during end-systole for all cusps. E: Open cusp area was measured during mid-systole for all cusps. F: Cusp depth was measured during end-systole per cusp in the cross-sectional image of the middle of the cusp between the deepest point of the belly of the cusp and the cross-sectional plane. G: Central coaptation deficit was measured during end-systole at the central coaptation point between each pair of coapting cusps.

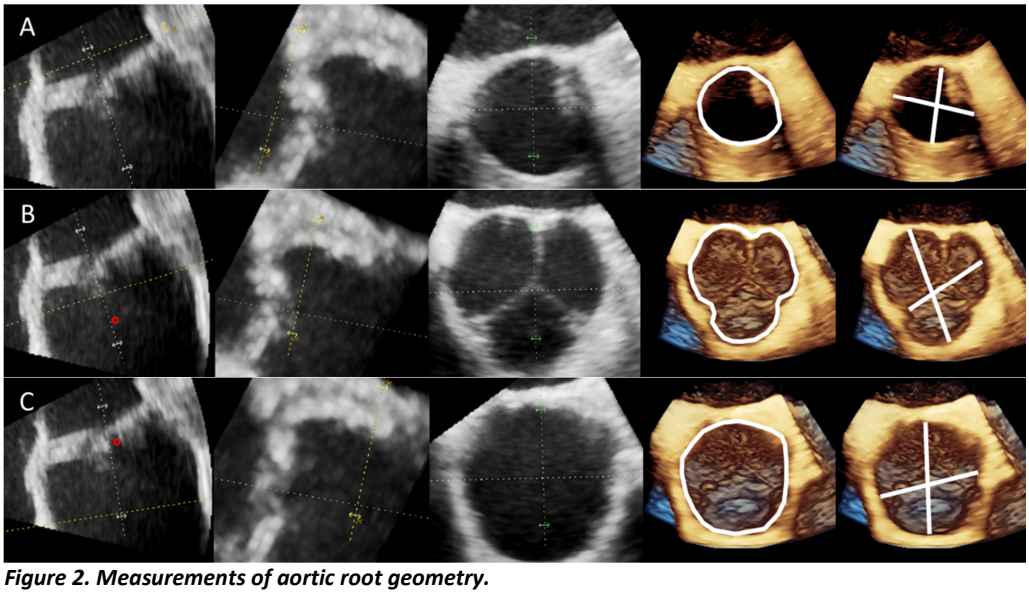

Figure 2. Measurements of aortic root geometry.
Flexi-slice method was used to obtain a true short axis of the aortoventricular junction (A), sinus of Valsalva (B) and sinotubular junction (C). Aortic root area, minimum and maximum diameter were measured during end-systole in 3DTEE images.

coapting cusps and averaged. When there was full coaptation of the cusps in the center, the coaptation deficit was defined as 0 mm.In addition, the aortic root measurements were performed in the true short-axis of the aortic root at three levels as displayed in figure 2. The area, minimum diameter and maximum diameter of the AVJ, SOV and STJ were measured during an end-systolic frame on the 3DTEE image. The eccentricity index was calculated per each level of the aortic root dividing the minimum diameter by the maximum diameter at each particular level.

Statistical analysis

All data analyses were performed using the SPSS software (Version 20.0. IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation and compared with the Student's t-test when normally distributed. Median and interquartile range were reported for non-normally distributed variables and were compared with the Mann-Whitney U-test. Categorical variables were reported as counts and percentages and compared using the chi-square test. Differences between controls, patients with dilated aortic root and bicuspid aortic valve and patients with dilated aortic root and tricuspid aortic valve were reported. Further analyses were performed in subjects with tricuspid aortic valve (patients with aortic root dilation vs. controls), to make sure the morphology of the aortic valve wasn't responsible for the differences between patients with aortic root dilation and controls. Linear regression analysis without including an intercept was used to assess the ratio between the aortic root area at the level of the STJ and the closed cusp area. Subanalysis was performed between aortic dilation patients with tricuspid aortic valve with and without AR and between aortic dilation patients with tricuspid aortic valve with central AR and eccentric AR. The intra-observer and inter-observer variabilities were evaluated in 10 individuals randomly selected. The mean difference and 95% confidence interval between two measurements for all aortic valve and aortic root measurements were calculated. A p-value <0.05 was considered statistically significant.

Results

Table 1 outlines the baseline and echocardiographic characteristics of patients with aortic root dilation (mean age 57±12 years, 75% men) divided by aortic valve morphology and controls (mean age 61±13 years, 65% men). There were no differences in age, gender and body surface area. Per definition, controls showed normal anatomy and dimensions of aortic valve and aortic root. Left ventricular volumes were significantly larger and left ventricular ejection fraction was slightly lower in patients with aortic root dilation compared with controls.

Aortic valve and root geometry in aortic root dilation

Table 1 shows the aortic valve and root geometric measurements in patients with aortic root dilation compared with controls. Per definition, all aortic root measurements were larger in

patients with aortic root dilation in comparison to controls. In patients with dilated aortic roots, the AVJ was slightly more rounded (eccentricity index: 0.80 [interquartile range: 0.75-0.89]) compared with normal oval-shaped aortic roots (eccentricity index 0.76 [interquartile range: 0.71-0.83]; p=0.052). There was no difference in eccentricity index of the SOV and STJ between controls and patients with dilated aortic root. Patients with aortic root dilation showed enlarged aortic cusps as displayed by a larger cusp height, closed cusp area and open cusp area. In patients with normal dimensions of the aortic root, there was no central coaptation deficit, compared with a median central coaptation deficit of 4.0 mm (interquartile range: 2.0-6.4 mm; p<0.001) in patients with dilated aortic root. Furthermore, the cusp depth was larger in patients with dilated aortic root compared with controls.

Table 1: Baseline and echocardiographic characteristics of patients with normal vs. dilated aortic root with tricuspid or bicuspid aortic valve

	Normal aortic root (n=20)	**Dilated aortic root with TAV (n=26)**	**Dilated aortic root with BAV (n=14)**	**p-value**
Age (years)	61±13	59±13	55±11	0.436
Male gender	13 (65%)	21 (81%)	9 (64%)	0.392
Body surface area (m^2)	1.95±0.17	2.04±0.15	1.92±0.22	0.093
Left ventricular end-diastolic volume (ml)	123±24	151±50	158±69	0.080
Left ventricular end-systolic volume (ml)	49±18	64±26	72±44	0.070
Left ventricular ejection fraction (%)	60±10	58±6	57±10	0.364
Cusp height	15.7 (13.8-16.3)	18.2 (16.3-20.2)	19.5 (18.1-22.1)	<0.001
Intercommissural distance	19.3 (17.8-20.6)	25.8 (22.3-28.3)	24.5 (21.8-27.5)	<0.001
Total closed cusp area (cm^2)	6.7 (6.0-7.7)	10.1 (8.5-12.5)	10.0 (7.7-11.4)	<0.001
Total open cusp area (cm^2)	2.5 (2.1-3.4)	5.6 (3.8-6.9)	3.9 (2.6-6.0)	<0.001
Central coaptation deficit	0 (0-0)	2.5 (1.3-4.0)	2.0 (0.8-3.8)	<0.001
Cusp depth	9.0 (7.1-9.3)	10.3 (9.3-12.3)	10.3 (7.4-12.6)	0.003
AVJ area (cm^2)	4.2 (3.7-4.4)	5.2 (4.6-6.2)	5.8 (3.7-6.4)	0.002
AVJ minimum diameter	20 (19-21)	24 (22-26)	24 (21-25)	0.001
AVJ maximum diameter	26 (25-27)	29 (26-31)	29 (25-31)	0.044
AVJ eccentricity index	0.76 (0.71-0.83)	0.80 (0.74-0.89)	0.82 (0.77-0.90)	0.127
SOV area (cm^2)	7.4 (6.7-8.3)	12.1 (10.4-14.8)	11.2 (9.8-14.6)	<0.001
SOV minimum diameter	27 (25-29)	36 (33-38)	33 (29-37)	<0.001
SOV maximum diameter	34 (31-36)	42 (40-47)	42 (39-45)	<0.001
SOV eccentricity index	0.80 (0.76-0.83)	0.83 (0.79-0.87)	0.80 (0.73-0.84)	0.291
STJ area (cm^2)	5.3 (4.9-6.3)	11.4 (8.3-14.4)	9.3 (8.0-13.0)	<0.001
STJ minimum diameter	25 (25-26)	35 (32-40)	34 (29-38)	<0.001
STJ maximum diameter	27 (26-30)	40 (36-44)	38 (33-43)	<0.001
STJ eccentricity index	0.93 (0.85-0.96)	0.91 (0.86-0.95)	0.89 (0.87-0.93)	0.796

Data are presented as number (percentage), mean ± standard deviation or median (interquartile range). Dimensions are displayed in mm unless otherwise specified. AVJ: aortoventricular junction, BAV: bicuspid aortic valve, SOV: sinus of Valsalva, STJ: sinotubular junction, TAV: tricuspid aortic valve.

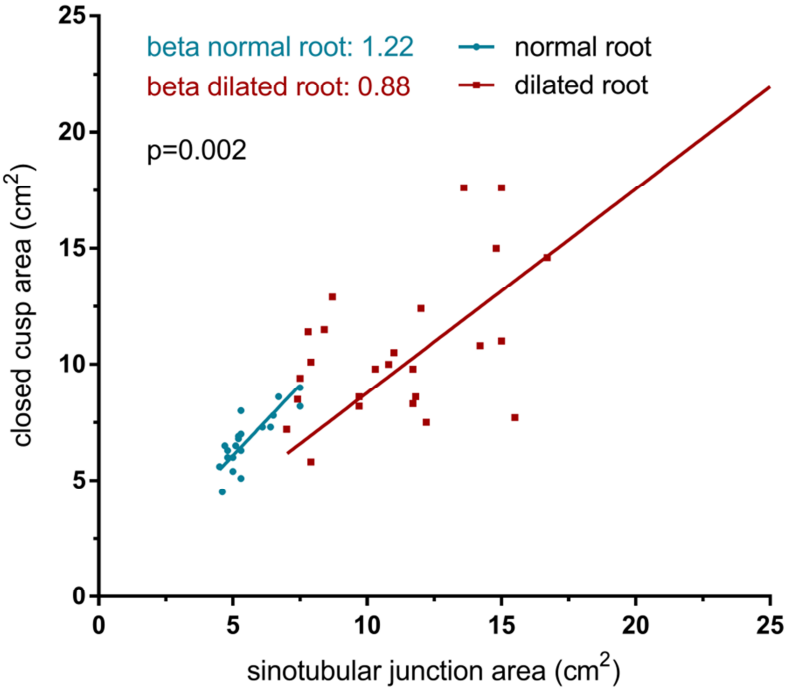

Figure 3. Ratio between sinotubular junction area and closed cusp area in normal vs. dilated aortic roots.
Linear regression analysis through origin was performed to assess the ratio between closed cusp area and sinotubular junction area, which was 0.88 in dilated aortic roots and 1.22 in normal controls.

Table 1 shows the aortic valve geometric measurements for patients with dilated root and tricuspid aortic valve and for patients with dilated root and bicuspid aortic valve.
In controls, the closed cusp area was on average 1.22 times the STJ area (95% confidence interval: 1.02-1.41), whereas in patients with dilated aortic root with tricuspid aortic valve the closed cusp area was only 0.88 times the STJ area (95% confidence interval: 0.78-0.98; p=0.002). This indicates that, although aortic root dilation was associated with cusp enlargement and increase in closed cusp area, this enlargement was not sufficient when compared with normal aortic roots, resulting in more frequent AR (Figure 3).

Aortic valve and root geometry in patients with aortic root dilation and with or without AR
Among the 26 patients with aortic root dilation and tricuspid aortic valve, 15 patients showed AR grade ≥2 (mean age 60±12 years, 87% men) and the remaining 11 patients showed AR grade <2 (mean age 56±14 years, 73% men; Table 2). Patients with AR had significant larger left ventricular volumes and slightly lower left ventricular ejection fraction compared with patients without AR. In terms of aortic dimensions, both groups of patients were comparable.

Table 2: Baseline and echocardiographic characteristics of patients with dilated aortic root with tricuspid aortic valve with and without aortic regurgitation

	AR grade <2 (n=11)	**AR grade ≥2 (n=15)**	**p-value**
Age (years)	56±14	60±12	0.482
Male gender	8 (73%)	13 (87%)	0.698
Body surface area (m^2)	2.02±0.17	2.05±0.14	0.610
Left ventricular end-diastolic volume (ml)	125±34	170±52	0.019
Left ventricular end-systolic volume (ml)	48±15	76±26	0.004
Left ventricular ejection fraction (%)	61±5	55±5	0.004
Cusp height (mm)	17.3 (16.0-20.0)	18.3 (16.7-20.7)	0.467
Intercommissural distance (mm)	24.7 (20.0-28.0)	26.3 (23.0-28.3)	0.125
Total closed cusp area (cm^2)	10.0 (7.7-11.5)	10.5 (8.6-14.6)	0.406
Total open cusp area (cm^2)	4.3 (3.6-6.6)	5.7 (4.1-7.9)	0.392
Central coaptation deficit (mm)	1.7 (0.7-2.7)	3.3 (2.0-5.0)	0.010
Cusp depth (mm)	10.7 (9.7-12.3)	10.3 (9.3-12.3)	0.695
AVJ area (cm^2)	5.6 (4.8-5.8)	4.7 (4.5-6.3)	0.897
AVJ minimum diameter (mm)	24 (21-26)	23 (22-26)	0.793
AVJ maximum diameter (mm)	29 (28-30)	29 (25-31)	0.979
AVJ eccentricity index	0.77 (0.72-0.80)	0.84 (0.75-0.89)	0.287
SOV area (cm^2)	11.5 (9.1-13.4)	12.6 (10.5-16.4)	0.377
SOV minimum diameter (mm)	34 (32-38)	37 (33-42)	0.152
SOV maximum diameter (mm)	41 (38-47)	42 (40-53)	0.251
SOV eccentricity index	0.83 (0.81-0.87)	0.80 (0.78-0.89)	0.795
STJ area (cm^2)	9.7 (7.9-12.2)	11.8 (9.7-15.0)	0.232
STJ minimum diameter (mm)	33 (32-38)	38 (32-41)	0.322
STJ maximum diameter (mm)	36 (33-41)	43 (37-45)	0.138
STJ eccentricity index	0.92 (0.90-0.97)	0.90 (0.85-0.95)	0.311

Data are presented as number (percentage), mean ± standard deviation or median (interquartile range). AR: aortic regurgitation, AVJ: aortoventricular junction, SOV: sinus of Valsalva, STJ: sinotubular junction.

However, there was a difference in the central coaptation deficit, which was only 1.7 mm (interquartile range: 0.7-2.7 mm) in patients with AR grade <2, compared with 3.3 mm (interquartile range: 2.0-5.0 mm; p=0.010) in patients with AR grade ≥2. The ratio between closed cusp area and STJ area was 0.91 (95% confidence interval: 0.73-1.10) in patients without AR and 0.86 (95% confidence interval: 0.74-0.98; p=0.660) in patients with AR.

Aortic valve and root geometry in aortic root dilation patients with central and eccentric AR jet

There were 15 patients with aortic root dilation with tricuspid aortic valve with AR grade ≥2 who were divided into two subgroups: patients with central AR jet (n=8, mean age 64±13 years, 75% men) were compared with patients with eccentric AR jet (n=7, mean age 56±12 years, 100% men).There were no differences in left ventricular volumes and function between these subgroups. Table 3 shows the aortic valve and root geometric measurements in patients with aortic root dilation with central AR jet and patients with eccentric AR jet. Patients with central AR jet were comparable to those with eccentric AR jet regarding aortic cusps size.

Furthermore, there were no significant differences in cusp depth and central coaptation deficit. Patients with central AR jet had slightly larger STJ area compared with patients with eccentric AR jet. Furthermore, the morphology of the aortic root was different between patients with central and eccentric AR jet with more oval AVJ in central AR jet compared to eccentric AR jet (eccentricity index 0.75 vs. 0.89; p=0.005).

Table 3: Baseline and echocardiographic characteristics of patients with dilated aortic root and tricuspid aortic valve with central vs. eccentric aortic regurgitation

	Central AR (n=8)	**Eccentric AR (n=7)**	**p-value**
Age (years)	64±13	56±12	0.284
Male gender	6 (75%)	7 (100%)	0.509
Body surface area (m^2)	2.10±0.16	1.99±0.09	0.123
Left ventricular end-diastolic volume (ml)	160±58	182±47	0.444
Left ventricular end-systolic volume (ml)	73±30	80±22	0.637
Left ventricular ejection fraction (%)	54±4	56±5	0.533
Cusp height (mm)	18.5 (16.5-20.4)	18.0 (16.7-22.3)	0.908
Intercommissural distance (mm)	26.3 (25.2-28.3)	26.3 (22.3-31.0)	0.601
Total closed cusp area (cm^2)	10.7 (8.9-13.7)	9.4 (8.5-17.6)	0.862
Total open cusp area (cm^2)	5.7 (3.6-7.6)	5.7 (4.1-8.7)	0.728
Central coaptation deficit (mm)	3.7 (2.4-5.8)	2.7 (1.3-4.0)	0.201
Cusp depth (mm)	10.3 (8.1-11.9)	9.7 (9.3-14.0)	0.907
AVJ area (cm^2)	4.7 (3.5-6.0)	5.8 (4.6-7.2)	0.245
AVJ minimum diameter (mm)	22 (19-24)	26 (23-29)	0.016
AVJ maximum diameter (mm)	28 (26-31)	30 (25-32)	0.642
AVJ eccentricity index	0.75 (0.70-0.83)	0.89 (0.84-0.96)	0.005
SOV area (cm^2)	12.9 (10.7-15.7)	11.1 (10.0-20.2)	0.602
SOV minimum diameter (mm)	37 (35-41)	34 (32-42)	0.384
SOV maximum diameter (mm)	44 (40-51)	42 (40-54)	0.770
SOV eccentricity index	0.87 (0.80-0.90)	0.80 (0.76-0.85)	0.083
STJ area (cm^2)	13.0 (11.7-16.3)	9.7 (7.4-13.6)	0.093
STJ minimum diameter (mm)	40 (35-41)	32 (29-40)	0.093
STJ maximum diameter (mm)	44 (40-47)	34 (31-45)	0.131
STJ eccentricity index	0.91 (0.85-0.95)	0.89 (0.84-0.87)	0.908

Data are presented as number (percentage), mean ± standard deviation or median (interquartile range). AR: aortic regurgitation, AVJ: aortoventricular junction, SOV: sinus of Valsalva, STJ: sinotubular junction.

The ratio between the closed cusp area and the STJ area was different between groups (Figure 4). Patients with central AR jet had a closed cusp area of 0.75 times the STJ area (95% confidence interval: 0.67-0.82) indicating that there was not enough cusp tissue in relation to the STJ area to cover the aortic orifice. In patients with an eccentric AR jet, the closed cusp area was 1.14 times the STJ area (95% confidence interval: 1.01-1.27) indicating that there was excess cusp tissue in relation to the STJ area to cover the aortic orifice area resulting in a relative prolapse.

Intra-observer and inter-observer variabilities

The variability in measurements within an observer and between observers was evaluated in 10 controls. The mean and 95% confidence interval of the difference between two measurements were displayed in Table 4.

Table 4: Intra-observer and inter-observer variabilities

	Intra-observer variability	Inter-observer variability
Cusp height (mm)	-0.3 (-1.4 to 0.8)	0.4 (-1.0 to 1.8)
Intercommissural distance (mm)	-0.2 (-2.5 to 2.4)	0.6 (-2.7 to 3.8)
Total closed cusp area (cm^2)	-0.2 (-0.9 to 0.6)	0.4 (-0.8 to 1.6)
Total open cusp area (cm^2)	-0.7 (-1.6 to 0.2)	-0.2 (-1.7 to 3.3)
Cusp depth (mm)	-0.3 (-2.6 to 2.0)	-0.7 (-3.3 to 1.9)
AVJ area (cm^2)	0.2 (-0.7 to 1.1)	0.0 (-0.8 to 0.9)
AVJ diameter (mm)	0.7 (-3.5 to 4.8)	0.3 (-5.7 to 6.2)
SOV area (cm^2)	-0.4 (1.5 to 2.6)	0.0 (-1.3 to 1.4)
SOV diameter (mm)	-0.6 (-2.9 to 1.7)	0.3 (-3.8 to 4.8)
STJ area (cm^2)	-0.1 (-1.0 to 0.9)	0.3 (-0.8 to 1.5)
STJ diameter (mm)	-0.1 (-4.1 to 3.9)	0.6 (-2.7 to 3.8)

Data are presented as mean difference between measurements (95% confidence interval). AVJ: aortoventricular junction, SOV: sinus of Valsalva, STJ: sinotubular junction.

Discussion

The present study hypothesized that adaptation of the aortic valve cusps occurs in aortic root dilation. The results can be summarized as follows: patients with aortic root dilation show significant enlargement of the aortic valve cusps, however this remodeling seems insufficient to match the aortic root area resulting in AR. Various types of AR seem to result from different remodeling processes. Central AR was associated with cusp tissue deficiency whereas eccentric AR was associated with relative abundance of cusp tissue resulting in relative prolapse.

The aortic valve and root form a complex structure in which the valvular function is largely dependent on the aortic root dimensions and morphology. In a normal aortic root, the dimensions depend on body size and gender and increase during a life time.[5,6] Computational models have shown that an increase in AVJ diameter was associated with a decrease in coaptation height and coaptation area.[9] Furthermore, in patients with STJ dilation, an increase in the ratio between STJ and AVJ was associated with a decrease in the coaptation height resulting in an incomplete closure of the aortic valve.[10] In addition, in models with aortic root dilation, the aortic cusps are pulled apart resulting in increased stress (defined as force per area) and increased strain (defined as percentage extension of cusp tissue) on the aortic cusps.[4] This may lead to aortic cusp remodeling to bear the higher stress posed on the cusps. Studies on valvular biomechanical properties showed increased cellular stiffness of valvular interstitial cells in left sided heart valves (aortic valve and mitral valve) as opposed to right sided heart valves.[11] This suggests that valvular interstitial cells respond to increased cusp

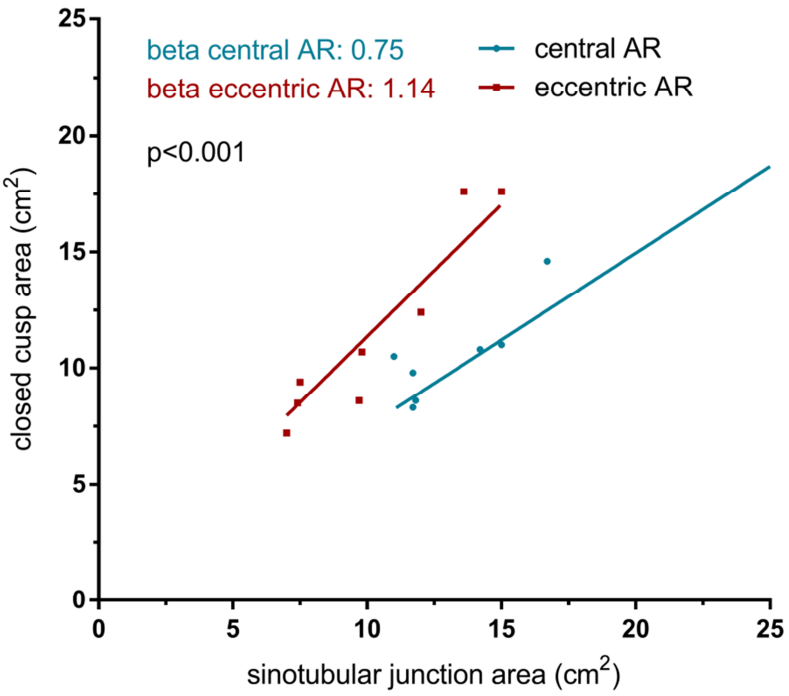

Figure 4: Ratio between closed cusp area and sinotubular junction area in patients with tricuspid aortic valve with dilated aortic root and central vs. eccentric aortic regurgitation.
Linear regression analysis through origin was performed to assess the ratio between closed cusp area and sinotubular junction area, which was 0.75 in patients with central aortic regurgitation and 1.14 in patients with eccentric aortic regurgitation. AR: aortic regurgitation.

stress by altering cellular stiffness.[12] Aortic valvular interstitial cells are phenotypically plastic and can transdifferentiate into myofibroblasts during cusp remodeling.[13] However, exact changes in aortic cusp biomechanics on a microscopic level in aortic root dilation have not been described. Recent studies using advanced noninvasive imaging of the aortic valve suggest the presence of differences in aortic cusp size between dilated and normal aortic roots.[14,15] Measurements of the aortic valve and root geometry with 3DTEE and computed tomography have shown good correlations.[14] Using computed tomography, Kim et al. showed significant changes in aortic cusps sizes in patients with aortic root dilation compared with normal aortic roots.[15] Patients with aortic root dilation had significantly larger aortic cusps compared with patients with normal aortic roots. Furthermore, the ratio between the closed cusp area and aortic root area was reduced in patients with aortic root dilation without AR and even more reduced in patients with AR. In this particular subgroup of patients, AR results from a central coaptation defect due to larger aortic root area.[15] Of note, patients with eccentric AR due to aortic valve prolapse were excluded. To understand whether remodeling of the aortic cusps also occurs in eccentric AR due to prolapse, Sato et al demonstrated that the prolapsing cusp was elongated and expanded in comparison with the other cusps on surgical inspection.[16] The

present study shows that in aortic root dilation patients with eccentric AR, there was a relative abundance of cusp tissue which may result in relative prolapse. However, the underlying mechanism and whether it is indeed an inappropriate adaptation of the cusps to the increased stress due to aortic root dilation remains unclear.

Clinical implications

The present study provides insight into aortic cusp adaptation in patients with aortic root dilation. This might impact on the timing and type of aortic valve reconstructive surgery. Insufficient coaptation of aortic valve cusps in aortic root dilation may result in AR. Current guidelines recommend aortic valve and root surgery in patients with significant aortic root dilation, symptomatic AR or asymptomatic AR with left ventricular dilation or dysfunction.[17] However, long-lasting increased stress on the cusps may result in thickening of the cusps with implications for reparability of the aortic valve. Furthermore, the mechanism of AR is important for the selection of the appropriate technique to reconstruct the aortic valve and root complex. In central AR, purely caused by aortic root dilation, valve-sparing root replacement techniques (remodeling or reimplantation technique) may be sufficient to reduce the aortic root diameter in order to match the aortic valve cusp size.[1] However, in eccentric AR, cusp reconstruction with central cusp plication, triangular resection or cusp resuspension may be needed.[1] In addition to the AR mechanism, the ratio between closed cusp area and STJ area might help in determining which aortic valve reconstructive technique is most appropriate. Further research should elucidate how this ratio can be implemented into clinical practice.

Study limitations

The present study was limited by a small sample size. 3DTEE was performed in all patients and controls with the same vendor. The measurements were performed manually by the same investigator. In future research, automated measurements may be of incremental value for which dedicated software is needed. In addition, although the planes were oriented in order to obtain the true short-axis and long-axis of the aortic valve and root, the measurements were performed in one plane. Therefore, the cusp length over the belly of the cusp could not be determined. In addition, the present software was not able to measure curved lengths such as the free edge cusp length. In the present study, histological samples were not available. Therefore, it cannot be proved that actual cusp remodeling occurred. To obtain more insight into the effects of aortic root dilation on the aortic valve cusps, further research including histological samples of aortic valve cusps in dilated aortic root is needed.

Conclusion

The present study showed an increase in aortic cusp size in patients with aortic root dilation in comparison to patients with normal aortic roots. However, the enlargement seemed insufficient to match the aortic root area as indicated by a decrease in closed cusp area to STJ area ratio in patients with a dilated aortic root. Furthermore, in patients with tricuspid aortic valve and central AR, the cusp area in relation to the aortic root area was small, whereas in patients with tricuspid aortic valve and eccentric AR, there was relative abundance of cusp tissue resulting in relative cusp prolapse. This provides further insight into aortic valve cusp remodeling in patients with aortic root dilation. Additionally, the ratio between closed cusp area and STJ area may be helpful in the future to determine the timing and type of aortic valve reconstructive surgical technique.

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Chapter 3:

Mitral valve geometry changes in patients with aortic regurgitation

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Abstract

Background: Changes in mitral valve geometry in patients with significant aortic regurgitation (AR) have not been evaluated. The aim of the present study was to assess the prevalence of significant secondary mitral regurgitation (MR; grade ≥2) and the geometrical characteristics of the mitral valve in patients with moderate and severe AR (grade ≥2) undergoing aortic valve and root surgery.

Methods: One-hundred twenty patients (mean age, 54±15 years; 65% men) with AR grade ≥2 undergoing aortic valve and root surgery were retrospectively evaluated. The presence of MR grade ≥2 and geometry of the mitral valve were assessed on preoperative transthoracic echocardiography. Left ventricular (LV) dimensions and mitral valve geometry were compared between patients with MR grade ≥2 and patients without.

Results: MR grade ≥2 was present in 28 (23%) patients. Patients with MR grade ≥2 had higher European System for Cardiac Operative Risk Evaluation II scores and more often used β-blockers and diuretics than their counterparts. Patients with MR grade ≥2 had larger tenting areas (mean, 1.59±0.79 vs. 1.25±0.41 cm^2; p=0.003), larger inter-papillary muscle distances (mean, 28.4±9.5 vs. 24.8±5.2 mm; p=0.014), larger left atria (mean, 40.9±13.7 vs. 32.0±12.2 ml/m^2; p=0.002) and lower LV ejection fractions (mean, 47.3±12.2 vs. 54.3±9.3%; p=0.002) as compared to patients with MR grade <2. However, there were no differences in indexed LV volumes. On multivariate logistic regression analysis, LV ejection fraction (odds ratio: 0.94; 95% confidence interval: 0.89-0.99; p=0.018) and indexed left atrial volume (odds ratio: 1.05; 95% confidence interval: 1.01-1.10; p=0.019) remained independently associated with MR grade ≥2 after correcting for tenting area and inter-papillary muscle distance.

Conclusion: Among patients with AR grade ≥2 undergoing aortic valve and root surgery, the prevalence of MR grade ≥2 was 23%. Lower LV ejection fraction and larger left atrial volume were independently associated with MR grade ≥2.

Introduction

The prevalence of secondary mitral regurgitation (MR) in patients with significant aortic regurgitation (AR) ranges between 6 and 45%.[1,2] The left ventricular (LV) pressure and volume overload caused by significant AR leads to LV dilation, with subsequent changes in papillary muscle position and tethering of the mitral leaflets, which may cause coaptation failure and regurgitation. The prognostic implications of concomitant secondary MR in patients with significant AR are not benign and it has been shown that mitral valve surgery in addition to aortic valve surgery is associated with better prognosis.[2] However, it remains unclear why some patients with significant AR have concomitant significant secondary MR while other patients do not show MR.[1]

A pioneer study using three-dimensional transthoracic echocardiography suggested that patients with significant AR show significantly larger total mitral leaflet area compared with patients without AR, which may reflect mitral leaflet remodeling to prevent failure of mitral leaflet coaptation.[1] However, changes in mitral valve geometry, including the subvalvular apparatus in patients with significant AR, have not been evaluated. In addition, the effects of confounding factors such as concomitant ischemic heart disease on LV remodeling and development of secondary MR in this specific subpopulation have not been elucidated. Therefore, the aims of the present study were to investigate the prevalence of significant MR, evaluate changes in mitral valve geometry, and investigate the associates of MR in patients with significant AR.

Methods

Patients

Pre-operative two-dimensional echocardiograms from 166 patients with AR grade ≥2 referred for valve-sparing aortic root reconstruction to the Cardio-Thoracic Surgery department of the Leiden University Medical Center from 2001 to 2014 were evaluated. Patients with acute endocarditis, connective tissue disease, insufficient image quality, organic mitral regurgitation or mitral stenosis were excluded (Figure 1). Clinical characteristics were prospectively collected in the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. Mitral valve geometry, MR grade, AR grade, and LV volumes and function were analyzed. Mitral valve geometry was compared between patients with moderate or severe secondary MR and patients without. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

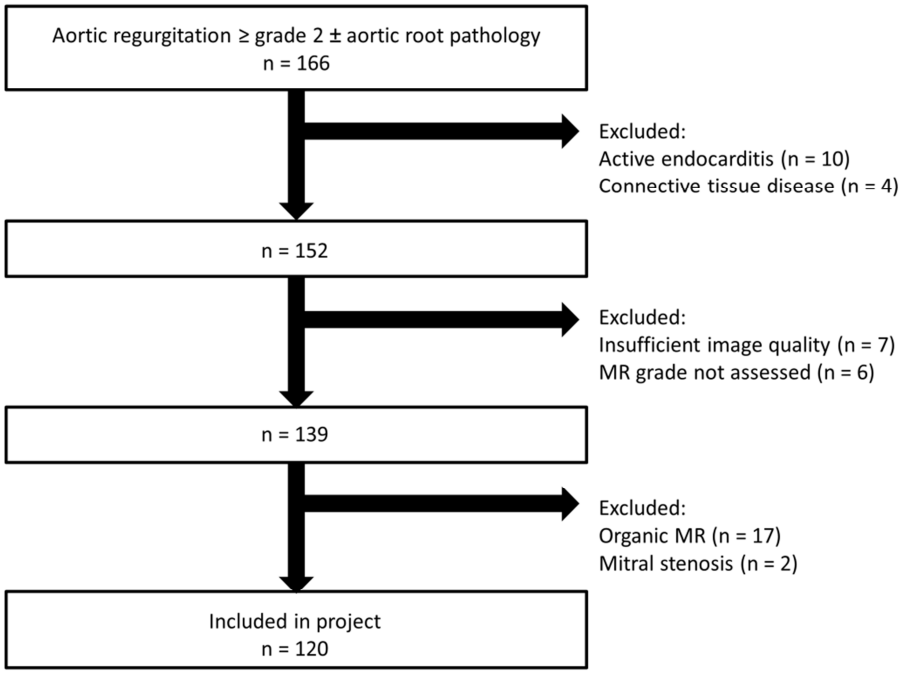

Figure 1. Flowchart of the patient inclusion.

Two-dimensional transthoracic echocardiography

Transthoracic echocardiography was performed preoperatively using commercially available ultrasound systems (System Five, Vivid 7, and Vivid E9, GE Vingmed Ultrasound AS, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Parasternal, apical, subcostal, and suprasternal views were obtained at rest with patients in the left decubitus position. Two-dimensional and Doppler data were acquired according to current recommendations.[3,4] The echocardiographic data were digitally stored in cine-loop format and data were retrospectively analyzed using commercially available software (EchoPAC version 112.0.1, Vingmed Ultrasound AS, Horten, Norway).

AR grade was assessed using a multiparametric approach including the measurement of the jet width relative to the LV outflow tract (LVOT) width and the vena contracta in the parasternal and apical views. AR was graded as grade 2 (mild-moderate; jet width/LVOT width of 0.25-0.45 and/or vena contracta of 3.0-4.5 mm), grade 3 (moderate-severe; jet width/LVOT width of 0.46-0.64 and/or vena contracta of 4.6-5.9 mm) or grade 4 (severe; jet width/LVOT width ≥0.65 and/or vena contracta ≥6.0 mm).[5] The severity of secondary MR was quantitatively determined by proximal isovelocity surface area method or by measuring the vena contracta in the parasternal long-axis view, according to current recommendations.[6] MR was graded as absent when there was no regurgitant jet. Among patients with regurgitant jets,

proximal isovelocity surface area method could be performed in 45 patients. In the remaining 33 patients, vena contracta measurement in parasternal long axis view was used to classify MR. Secondary MR was defined as mild (regurgitant volume <15 ml or vena contracta of 0.1-2.9 mm), moderate (regurgitant volume of 15-29 ml or vena contracta 3-6.9 mm) or severe (regurgitant volume ≥30 ml or vena contracta ≥7 mm).

Mitral valve geometry was assessed in the parasternal long-axis view (Figure 2). Retrospectively, the images were zoomed in on the mitral valve. The measurements were performed by two independent observers, and values were averaged. The length of coaptation between the anterior and posterior mitral leaflets (coaptation length), the distance between the annular plane and the coaptation point (coaptation height), and the area enclosed between the annular line and the mitral leaflets (tenting area) were measured in mid-systole. Anterior and posterior mitral leaflet length was measured in mid-diastole. The parasternal short-axis view was used to measure the end-diastolic inter-papillary muscle distance. The mitral annulus was measured at end-systole in the apical views. The anterior-posterior diameter and intercommissural diameter were obtained from the apical four- and two-chamber views, respectively.

Left atrial volume, LV end-diastolic volume and LV end-systolic volume were measured in the apical two- and four-chamber views and indexed to body surface area (LAVi, LVEDVi and LVESVi). Sphericity index was calculated by dividing the length by the width of the left ventricle in the apical four-chamber view, as previously described.[6] LV ejection fraction (LVEF) was calculated according to the Simpson's biplane method.[3]

Surgery

After median sternotomy, cardiopulmonary bypass was set through cannulation of the distal ascending aorta or the subclavian or femoral artery (in patients with ascending aorta pathology). The aorta was incised at the level of the pulmonary artery and resected until the sinotubular junction.

Intraoperatively, the surgeon decided whether a valve-sparing aortic root reconstruction was feasible. In these patients, either the sinotubular junction was restored using a vascular graft or the native sinuses of Valsalva were resected, a graft was implanted using the reimplantation technique (modified David procedure), or the remodeling technique (Yacoub procedure) and the coronary buttons were reimplanted.[7,8] Otherwise, aortic valve and root replacement using the Medtronic Freestyle stentless bioprosthesis (Medtronic, Minneapolis, MN) was performed. In these patients, the coronary buttons were mobilized, and the aortic root and valve were completely excised. The bioprosthesis was then implanted, usually with a 120° clockwise rotation, with interrupted sutures at one plane at the level of the nadir of the sinus. Thereafter, the coronary buttons were reattached to the bioprosthesis.[9]

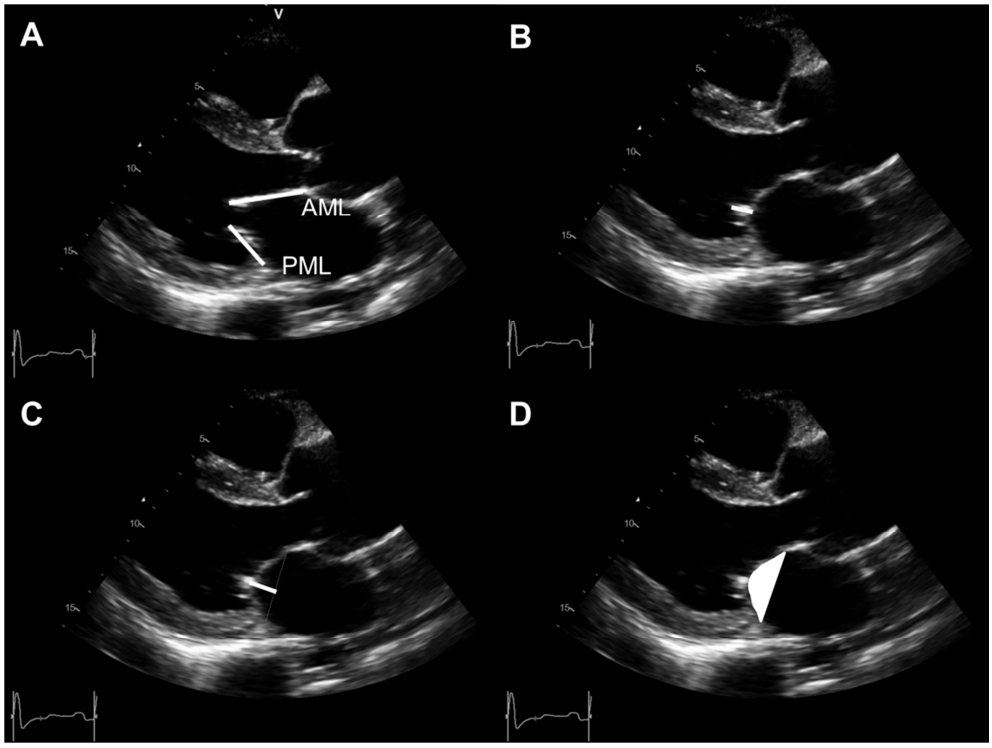

Figure 2. Measurements of mitral valve geometry.
During mid-diastole: mitral valve leaflet length (A) of the anterior mitral leaflet (AML) and the posterior mitral leaflet (PML). At mid-systole: coaptation length (B), coaptation height (C) and tenting area (D).

If secondary MR was present, concomitant mitral valve surgery was performed at the discretion of the surgeon. In all patients in whom concomitant mitral valve surgery was performed, a restrictive ring annuloplasty was used to repair the mitral valve. No mitral valve replacements were performed.

Statistical analysis

All data analyses were performed using SPSS version 20.0 (IBM, Armonk, NY). Continuous variables are reported as mean ± standard deviation or medians and interquartile ranges, as appropriate. Categorical variables are reported as counts and percentages. Patients with no or mild MR (grade <2) were compared with patients with moderate or severe MR (grade ≥2). Continuous and categorical variables were compared by the Student's t-test (or the Mann Whitney U test for variables non-normally distributed) and chi-square test, respectively. Mitral valve geometric changes were compared between patients with normal left ventricles (LVESVi <31 ml/m^2) and patients with dilated left ventricles (LVESVi ≥31 ml/m^2). Multivariate logistic

regression analysis was performed to investigate the independent associates of significant (moderate or severe) secondary MR. All echocardiographic variables with p-values <0.05 on univariate logistic regression analysis were included in the multivariate model. The odds ratio and 95% confidence interval were calculated. All statistical tests were two-sided. A p-value <0.05 was considered statistically significant. Interobserver and intraobserver variability of mitral valve geometric measurements was evaluated using Bland-Altman analysis in 40 randomly selected patients. Furthermore the coefficients of variation were calculated for coaptation length, coaptation height and tenting area.

Results

A total of 120 patients (mean age, 54±15 years; 65% men) were included in the present analysis. AR was grade 2 in 52 patients (43%), grade 3 in 43 patients (36%), and grade 4 in 25 patients (21%). Forty-two patients (35%) did not have MR. Mild, moderate and severe MR were observed in 50 (42%), 25 (21%) and 3 (2%) patients, respectively. The prevalence of significant secondary MR (moderate and severe) was 23%. Patients were divided into two groups according to the presence and severity of the secondary MR: patients without significant secondary MR (n=92) were compared with those with moderate or severe secondary MR (n=28). Table 1 shows the differences in baseline clinical characteristics between groups.

Patients were comparable regarding age, gender, and comorbidities. Patients with significant secondary MR had a higher frequency of prior myocardial infarction than patients without MR; however this difference was not statistically significant. In addition, the presence of cardiovascular risk factors and the need for coronary artery bypass grafting was not different between patients with and without MR. However, β-blockers and diuretics were more frequently used among patients with MR grade ≥2 as compared to their counterparts.

Surgical characteristics

Patients with moderate or severe secondary MR had a higher European System for Cardiac Operative Risk Evaluation II scores (median, 3.6% [interquartile range: 2.5-7.8%] vs. median, 2.4% [interquartile range: 1.6-4.5%]; p=0.003) compared with their counterparts. Seventy-three patients (61%) underwent valve-sparing aortic root reconstruction. The remaining 47 patients (39%) were considered ineligible for repair during surgery and underwent aortic valve and root replacement using the Medtronic Freestyle stentless bioprosthesis. Concomitant coronary artery bypass grafting was performed in 25 patients (21%). Concomitant mitral valve surgery with restrictive ring mitral annuloplasty was performed in 13 patients (11%). Concomitant tricuspid valve surgery (annuloplasty) was performed in 10 patients (8%).

Table 1. Baseline characteristics

	Non-significant secondary MR (n=92)	Significant secondary MR (n=28)	p-value
Age (years)	53.3±15.2	57.7±13.7	0.174
Male	58 (63%)	20 (71%)	0.556
Smoking	25 (27%)	7 (25%)	0.989
Diabetes	3 (3%)	2 (7%)	0.719
Hypertension	45 (49%)	18 (64%)	0.226
Dyslipidaemia	20 (22%)	3 (11%)	0.252
NYHA functional class			1
I – II	70 (76%)	21 (75%)	
III – IV	22 (24%)	7 (25%)	
Creatinine clearance (ml/min)	103±37	85±29	0.023
Coronary artery disease	16 (17%)	6 (21%)	0.838
Previous myocardial infarction			0.435
Anterior	1 (1%)	1 (4%)	
Non-anterior	3 (3%)	2 (7%)	
ACE-inhibitor or Angiotensin Receptor Blocker	45 (49%)	19 (68%)	0.123
Beta-blocker	31 (34%)	18 (64%)	0.008
Calcium channel antagonist	17 (19%)	2 (7%)	0.253
Diuretics	25 (27%)	15 (54%)	0.018
Aortic regurgitation			0.312
Grade 2	39 (42%)	13 (46%)	
Grade 3	36 (39%)	7 (25%)	
Grade 4	17 (19%)	8 (29%)	
EuroSCORE II (%)	2.4 (1.6-4.5)	3.6 (2.5-7.8)	0.003
Aortic valve/root technique			0.048
repair	51 (55%)	22 (79%)	
replacement	41 (45%)	6 (21%)	
CABG	19 (21%)	6 (21%)	1
Mitral valve repair	2 (2%)	11 (39%)	<0.001
Tricuspid valve repair	1 (1%)	9 (32%)	<0.001

Continuous data are presented as mean ± standard deviation or median (interquartile range). Categorical data are presented as number (percentage). ACE = Angiotensin converting enzyme, CABG = Coronary Artery Bypass Grafting, EuroSCORE: European System for Cardiac Operative Risk Evaluation, MR = Mitral Regurgitation, NYHA = New York Heart Association.

Echocardiographic measurements associated with preoperative secondary MR

The preoperative echocardiographic data are presented in Table 2. LV volumes and mitral valve geometric measurements in the parasternal long-axis view were available in all 120 patients, whereas inter-papillary muscle distance and LAVi were available in 108 patients and 119 patients, respectively. Coaptation length, coaptation height and lengths of the anterior and posterior leaflets were comparable in both groups. Patients with moderate or severe secondary MR had larger tenting areas (1.59±0.79 vs. 1.25±0.41 cm^2; p=0.003) and larger inter-papillary muscle distances (28.4±9.5 vs. 24.8±5.2 mm; p=0.014) compared with those without significant secondary MR. There was a tendency toward larger mitral annular

diameters among patients with MR grade ≥2. LVEDVi was comparable between patients with and without secondary MR whereas LVESVi was slightly larger (nonsignificant) in patients with moderate or severe secondary MR. Consequently, the LVEF was significantly lower in patients with moderate or severe secondary MR (47.3±12.2 vs. 54.3±9.3%; p=0.002).

Table 2. Preoperative echocardiographic characteristics

	Non-significant secondary MR (n=92)	**Significant secondary MR (n=28)**	**p-value**
Anterior leaflet length (mm)	24.6±4.1	24.6±4.1	0.970
Posterior leaflet length (mm)	18.3±3.2	18.9±3.6	0.383
Coaptation length (mm)	7.8±1.7	7.3±1.9	0.273
Coaptation height (mm)	8.0±2.3	8.5±2.6	0.287
Tenting area (cm^2)	1.25±0.41	1.59±0.79	0.003
Interpapillary muscle distance (mm)	24.8±5.2	28.4±9.5	0.014
Mitral annulus AP diameter (mm)	31.0±4.9	33.1±6.0	0.068
Mitral annulus intercommissural diameter (mm)	31.4±5.2	33.5±5.6	0.068
LAVi (ml/m^2)	32.0±12.2	40.9±13.7	0.002
LVEDVi (ml/m^2)	77.4±27.9	79.6±28.9	0.715
LVESVi (ml/m^2)	36.1±17.5	42.8±23.9	0.104
Sphericity index	1.59±0.27	1.59±0.25	0.949
LVEF (%)	54.3±9.3	47.3±12.2	0.002

Data are presented as mean ± standard deviation. AP = Anterior-Posterior, LAVi = Left Atrial Volume indexed for body surface area, LVEDVi = Left Ventricular End Diastolic Volume indexed for body surface area, LVEF = Left Ventricular Ejection Fraction, LVESVi = Left Ventricular End Systolic Volume indexed for body surface area, MR = Mitral Regurgitation.

Subgroup analysis was performed to assess the effect of LV dilation on the mitral valve geometry. LVESVi ≥31ml/m^2 was defined as abnormal according to current recommendations.[3] The left ventricle was dilated in 68 patients (57%), with a mean LVESVi of 49.4±17.6 ml. In the remaining 52 patients, the mean LVESVi was 22.2±5.6 ml. In the group of patients with dilated left ventricles, larger inter-papillary muscle distances (26.9±7.5 vs. 24.3±5.3 mm; p=0.047), larger mitral valve annuli (anteroposterior diameter, 32.7±5.4 vs. 30.0±4.6 mm; p=0.005 and intercommissural diameter, 33.6±4.8 vs. 29.7±5.2 mm; p<0.001) and larger left atria (LAVi: 37.0±12.1 vs. 30.2±13.3 ml/m^2; p=0.004) were observed. Furthermore, the sphericity index and LVEF were significantly lower in patients with dilated left ventricles (1.51±0.20 vs. 1.69±0.29; p<0.001 and 48.5±10.0 vs. 58.1±8.5%; p<0.001, respectively). Mitral leaflet tethering was more pronounced in patients with dilated left ventricles as indicated by larger coaptation heights and larger tenting areas (9.0±2.4 vs. 6.9±1.8 mm; p<0.001 and 1.51±0.60 vs. 1.10±0.34 cm^2; p<0.001, respectively). Probably as a compensatory mechanism, patients with a dilated left ventricles had significant larger mitral leaflets compared with those without

dilated left ventricles (anterior leaflet length, 25.9±4.2 vs. 23.0±3.4 mm; p<0.001 and posterior leaflet length, 19.4±3.0 vs. 17.2±3.3 mm; p<0.001). This resulted in slightly larger coaptation length (7.9±1.8 vs. 7.4±1.6 mm; p=0.151).

Correlates of significant secondary MR in patients with significant AR

Table 3 presents the results of the logistic regression analysis to assess correlates of significant secondary MR in patients with AR. Tenting area, inter-papillary muscle distance, LAVi, and LVEF were included as independent variables in the multivariate analysis. However, only LVEF (odds ratio, 0.94; 95% confidence interval: 0.89-0.99; p=0.018) and LAVi (odds ratio, 1.05; 95% confidence interval: 1.01-1.10; p=0.019) remained independently associated with MR grade ≥2 after adjusting for the other echocardiographic parameters in the model.

Table 3. Correlates of significant MR in patients with significant AR

	Univariate analysis			**Multivariate analysis**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Anterior leaflet length (mm)	1.00	0.90-1.11	0.969			
Posterior leaflet length (mm)	1.06	0.93-1.20	0.380			
Coaptation length (mm)	0.87	0.68-1.12	0.272			
Coaptation height (mm)	1.10	0.92-1.31	0.286			
Tenting area (cm^2)	3.26	1.30-8.17	0.012	1.30	0.43-3.98	0.641
Interpapillary muscle distance (mm)	1.08	1.01-1.17	0.028	1.05	0.97-1.15	0.230
Mitral annulus AP diameter (mm)	1.08	0.99-1.17	0.072			
Mitral annulus inter-commissural diameter (mm)	1.08	0.99-1.18	0.071			
LAVi (ml/m^2)	1.05	1.02-1.09	0.003	1.05	1.01-1.10	0.019
LVEDVi (ml/m^2)	1.00	0.99-1.02	0.712			
LVESVi (ml/m^2)	1.02	1.00-1.04	0.111			
Sphericity index	0.95	0.19-4.86	0.948			
LVEF (%)	0.94	0.90-0.98	0.003	0.94	0.89-0.99	0.018

Data are presented from univariate and multivariate logistic regression analysis. AP = Anterior-Posterior, CI = Confidence Interval, LAVi = Left Atrial Volume indexed for body surface area, LVEDVi = Left Ventricular End Diastolic Volume indexed for body surface area, LVEF = Left Ventricular Ejection Fraction, LVESVi = Left Ventricular End Systolic Volume indexed for body surface area, OR = Odds Ratio.

Interobserver and intraobserver variability

Reproducibility of the mitral valve geometric measurements was assessed in 40 randomly selected patients. Figure 3 shows the Bland Altman analysis which indicated fair interobserver and intraobserver agreement for the measurement of the coaptation length, coaptation height, and tenting area. The interobserver and intraobserver coefficients of variation were 11.3% and 11.9% for coaptation length, 28.0% and 11.2% for coaptation height and 9.4% and 11.4% for tenting area, respectively.

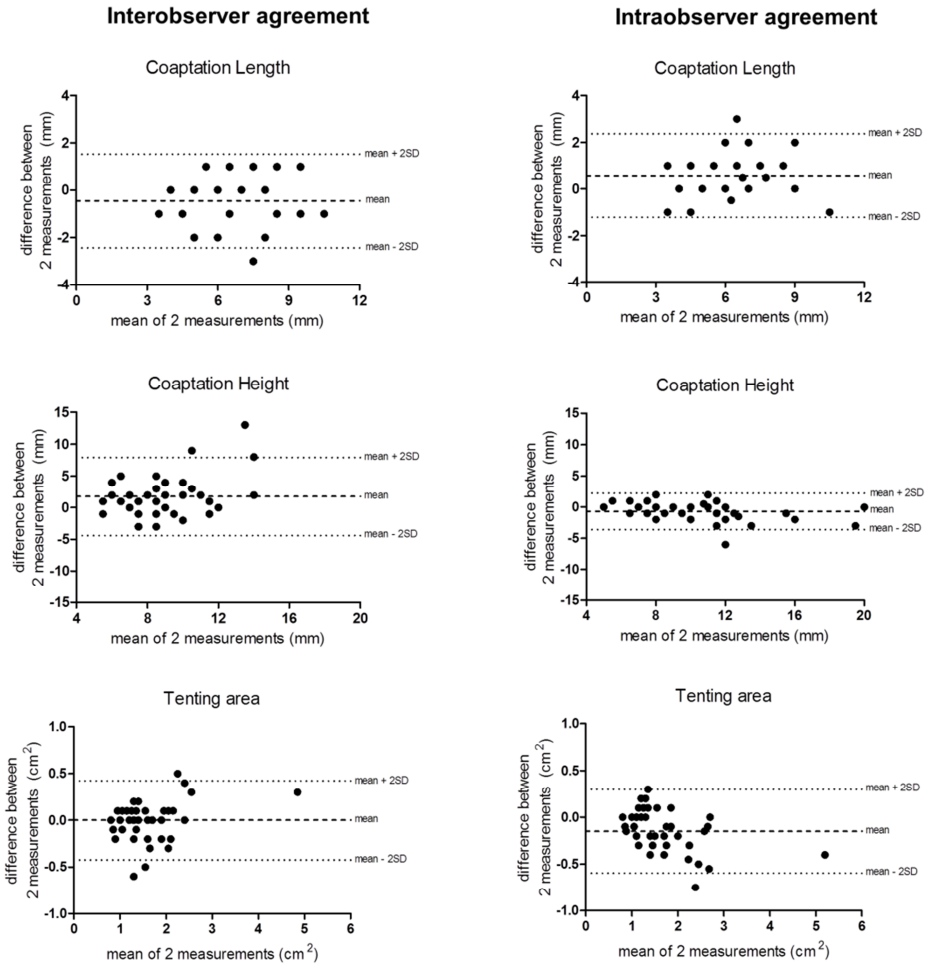

Figure 3. Interobserver and intraobserver agreement.
Bland Altman plots for interobserver and intraobserver agreement of the measurement of the coaptation length, coaptation height and tenting area

Discussion

The present evaluation shows that in selected patients with AR undergoing aortic valve and aortic root surgery, the presence of significant secondary MR was frequent (23%). Lower LVEF and larger LAVi were independently associated with significant secondary MR.

Prevalence of significant secondary MR in patients with significant AR

The previously reported prevalence of significant MR in patients with significant AR differs significantly across the studies (from 6% to 45%).[1,2,10] These differences are probably due to different methodologies to grade MR and different selection of patients. Although some

studies included less load-dependent measures to grade MR, such as vena contracta diameter,[1,2] in other studies, MR was graded on the basis of regurgitant jet area.[10] In terms of patients characteristics, Beaudoin et al.[1] performed a retrospective analysis of an institutional echocardiographic database and included all patients with moderate or severe AR without LV systolic dysfunction (LVEF>40%), associated degenerative mitral valve disease, or connective tissue pathologies (Marfan syndrome), leading to a prevalence of concomitant significant MR of 5.6%. In contrast, Pai and Varadarajan[2] performed a retrospective analysis of patients with severe AR with less strict inclusion and exclusion criteria and reported a prevalence of significant MR of 45%. The present study included a selected cohort of patients undergoing aortic valve and root surgery and further evaluated the differences in mitral valve geometry between patients with concomitant significant secondary MR and patients without. The prevalence of significant MR was 23%. The inclusion of patients undergoing surgical aortic valve replacement may lead to an increased prevalence of significant MR because the presence of combined valvular heart disease prompts the treating physician to refer the patient for surgical repair or replacement. In contrast, the series described by Beaudoin et al. a larger population of patients with moderate or severe AR independently of therapeutic management, which may explain the lower prevalence of concomitant significant MR. The disparate prevalence rates of the present study and the study by Pai and Varadarajan may be attributed to the different methodologies used to grade MR: whereas we used the proximal isovelocity surface area method and vena contracta width to grade MR, Pai and Varadarajan used a more load-dependent measure of MR (regurgitant jet size) which may overestimate the grade of MR.

Mechanisms underlying significant secondary MR in patients with significant AR

In significant AR, LV volume and pressure overload results in an increase in LV dimensions to maintain LVEF. If compensatory LV remodeling fails, LV function deteriorates.[11] Reduced systolic LV function leads to a decrease in closing forces of the mitral valve and MR.[12] Furthermore, LV dilation results in tethering of the mitral leaflets.[13] The imbalance between decreased closing forces and increased tethering forces may lead to secondary MR.[14] The present evaluation confirmed that in LV dilation due to AR, there is a reduction in LV systolic function and more mitral leaflet tethering. Lower LVEF was independently associated with significant MR in patients with AR indicating that the main mechanism of MR in these patients is the reduction in closing forces.

Annular dilation is another contributing factor in developing secondary MR in patients with significant AR.[14] However, MR secondary to isolated annular dilation remains controversial, and a previous surgical study did not show an association between secondary MR and the annular diameter.[15] Also, in our patient population, although annular diameters increased in

patients with dilated left ventricles, there was no significant difference in annular diameters between patients with and without significant secondary MR.
Lastly, it has been shown in both necropsy and echocardiography studies that in patients with AR, compensatory mitral valve enlargement occurs and could prevent MR.[1,16] When this compensatory mechanism fails, MR may appear worsening the LV remodeling process and causing more severe MR. In our cohort of patients with AR and dilated left ventricles, the mitral leaflets were longer, probably in order to increase the coaptation length in an attempt to compensate the leaflet tethering. However, there were no significant differences in mitral leaflet length between patients with and without significant secondary MR.

Clinical implications

The present study shows that secondary MR in patients with AR results mainly from an imbalance in closing forces and tethering forces. Aortic valve surgery in these patients resolves the pressure and volume overload in the left ventricle, which leads to LV reverse remodeling.[17] In theory, this may result in a decrease in tethering of the mitral valve and subsequently a decrease in MR grade. It was recently shown that secondary MR improves after aortic valve surgery for AR in the majority of patients.[10] However, it remains unclear whether this improvement is related to restoration of normal mitral valve geometry postoperatively. Further research is needed to elucidate the mechanisms of decrease in MR grade after aortic valve surgery to determine when additional mitral valve repair is indicated in this specific patient population. Prospective randomized trials comparing aortic valve surgery with and without additional mitral valve repair would provide the evidence to this unmet clinical need.

Limitations

The present study was limited by its retrospective nature. The duration of significant AR before surgery was not recorded. This may have resulted in a more dilated left ventricle and therefore have an effect on the MR grade. Data were acquired over a long period of time and the images were not always zoomed on the mitral valve, which may have hampered the accuracy of the mitral valve geometric measurements. Patients were followed up at the discretion of the treating cardiologist. Changes in MR after aortic valve surgery were not evaluated, because systematic echocardiographic follow-up was not available in all patients. Furthermore, the cohort consisted of patients referred for valve sparing aortic root replacement. The underlying pathology of AR was thus aortic root dilation and/or cusp prolapse, because valve sparing surgery is often feasible in these AR mechanisms. There were no patients with endocarditis or cusp restriction so results cannot be extrapolated to those patients. Also, the present results may not be applicable in a nonsurgical AR cohort. Evaluation of mitral regurgitant volume and fraction using proximal isovelocity surface area method was

feasible in 58% of patients with a regurgitant jet. In the remaining patients, vena contracta was used to grade MR. Measurements of the mitral valve geometry using three-dimensional echocardiography may have been more accurate; however three-dimensional echocardiography was not available in this cohort.

Conclusion

Significant secondary MR was present in 23% of patients with significant AR undergoing aortic valve and aortic root surgery. Multivariate logistic regression analysis identified lower LVEF and larger LAVi as independent associates of significant MR.

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Chapter 4:

Effect of statins on aortic root growth rate in patients with bicuspid aortic valve anatomy

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Abstract

Background: Bicuspid aortic valve (BAV) anatomy is associated with increased growth rate of the aortic root compared to tricuspid aortic valves. Statins decrease the growth rate of abdominal aneurysms; however their effect on the aortic root growth rate has not been elucidated. The present study evaluated the association between use of statins and aortic root growth in patients with BAV.

Methods: A total of 199 patients (43±15 years, 69% male) with BAV who underwent ≥2 echocardiographic measurements of the aortic root ≥1 year apart were included in this retrospective observational study. Median follow-up duration was 4.7 years (interquartile range: 2.7-8.3 years). Growth rate (mm/year) of the aortic root was compared between statin users (n=41) and non-users (n=158).

Results: Statin users were significantly older and had more cardiovascular risk factors than their counterparts. Ascending aorta diameter was significantly smaller at baseline and at follow-up in statin users compared with non-users when adjusted for coronary artery disease, age and medication. The average annual growth rate was 0.08 mm/year (95% confidence interval: 0.03-0.13) for the aortoventricular junction, 0.16 mm/year (0.11-0.21) for the sinus of Valsalva, 0.12 mm/year (0.07-0.17) for the sinotubular junction and 0.45 mm/year (0.37-0.53) for the ascending aorta. The dilation rate of the aortic segments was not different between statin users and non-users.

Conclusion: In patients with bicuspid aortic valve, although the use of statins was associated with smaller ascending aorta, the annual dilation rate of the aortic root was not influenced by the use of statins.

Introduction

Patients with bicuspid aortic valve (BAV) anatomy have shown larger aortic root diameters and faster growth rate of the ascending aorta compared with patients with tricuspid aortic valve (TAV) anatomy leading to an excess risk of dissection and rupture in the former patients.[1] The average growth rate of the ascending aorta in patients with BAV is 0.77 mm/year, 5-fold higher than that of age-matched TAV patients.[2] Pathophysiological factors associated with the increased prevalence of ascending aorta dilation and faster growth rate among BAV patients include abnormal wall stress distribution (particularly in patients with dysfunctional aortic valves), altered aortic wall structure and/or an underlying genetic substrate.[3] Specifically, increased activity and expression of metalloproteinases have been demonstrated in histological samples of ascending aorta aneurysms of patients with BAV.[4] The pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce the expression of metalloproteinases[5,6] and have been demonstrated to limit the growth rate of abdominal aneurysms and to improve the thoracic and abdominal aortic aneurysm rupture and dissection–free survival.[7-11] In patients with BAV, the use of statins has been associated with smaller aortic root and ascending aorta diameters in cross-sectional studies.[12] However, the effect of statins on the aortic root and ascending aorta growth rate of these patients remains unclear. Accordingly, we evaluated the effect of statins on the aortic root and ascending aorta growth rates of patients with BAV in a retrospective study.

Methods

Patients

The present retrospective study included patients aged ≥18 years with BAV who underwent transthoracic echocardiography surveillance from 1995 to 2014 for at least 1 year. If patients underwent aortic valve and/or aortic root surgery during follow-up, the last transthoracic echocardiography before surgery was selected for analysis. Patients with complex congenital heart disease, connective tissue disease and subvalvular aortic stenosis were not included. In total 262 patients were eligible for inclusion. From this group, 48 patients with coarctation of the aorta and 15 patients with an ascending aorta of ≥45mm at baseline were excluded. The final cohort consisted of 199 patients (Figure 1).

Demographic and clinical characteristics were collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. Medication use (statins, angiotensin converting enzyme-inhibitors / angiotensin receptor blockers and beta-blockers) were obtained from chart review. Patients were divided into two groups: patients treated with statins for at least 50% of the follow-up time (statin users) and patients not treated with statins (non-users).

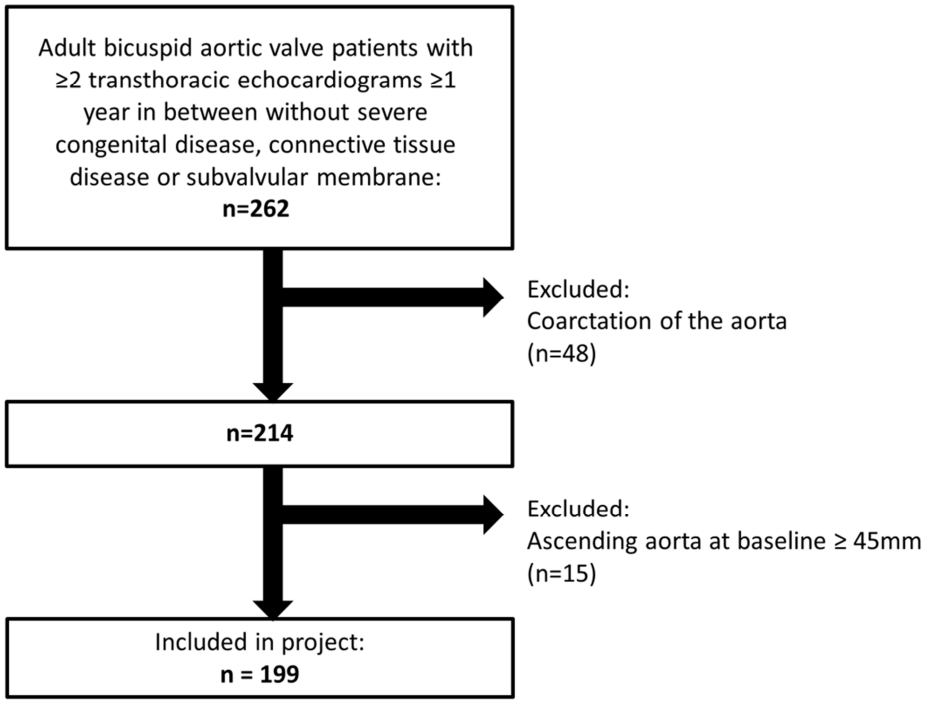

Figure 1. Flowchart of patient inclusion

Aortic root diameters were measured at 4 levels and annual growth rate in mm/year was compared between the two groups. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Two-dimensional transthoracic echocardiography

Transthoracic echocardiography was performed using commercially available ultrasound systems (System Five, Vivid 7, and E9, General Electric Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Parasternal and apical views were obtained at rest with patients in the left decubitus position while subcostal and supra-sternal views were obtained with patients in supine position. Two-dimensional, M-mode and Doppler data were acquired according to current recommendations.[13] The echocardiographic data were digitally stored in cine-loop format and data were retrospectively analysed off-line using commercially available software (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). Left ventricular (LV) end-diastolic and end-systolic diameters were measured in the M-mode parasternal long-axis view recordings. LV end-diastolic and end-systolic volumes were measured in the apical 2- and 4-chamber views and LV ejection fraction was calculated according to the Simpson's biplane method.[13]

BAV was diagnosed on the parasternal short-axis view of the aortic valve by the presence of two commissures in systole.[14] BAV was typical when the commissures were oriented at 4-10, 5-11 or 3-9 o'clock and atypical when the commissures were oriented at 1-7 or 12-6 o'clock. The presence of a raphe was noted.[14] Aortic valve function was evaluated using colour-Doppler, continuous- and pulsed-wave Doppler. Valvular dysfunction was defined as pure aortic regurgitation when ≥ grade 2 and less then mild aortic stenosis, pure aortic stenosis when ≥ moderate and aortic regurgitation ≤ grade 1 or mixed aortic aortic valve disease.[15,16] Aortic root dimensions were measured using the leading edge-to-leading edge technique during end-diastole in the parasternal long-axis view perpendicular to the long-axis of the aorta at 4 predefined levels: (1) the aortoventricular junction (AVJ) defined as the hinge points of the aortic leaflets, (2) the sinuses of Valsalva (SOV), (3) the sinotubular junction (STJ) and (4) the ascending aorta (AAo) (4 cm distal from the aortic valve).[17,18]

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median and interquartile range when appropriate. Categorical variables were reported as numbers and percentages. Continuous and categorical variables were compared with the Student's t-test (or Mann Whitney U test in non-normally distributed variables) and Chi-square test, respectively. Differences in aortic root diameters at baseline and follow-up between groups were assessed with ANOVA test for repeated measures. Statin use was incorporated in the model as factor together with coronary artery disease, use of beta-blockers and the use of angiotensin converting enzyme-inhibitors or angiotensin receptor blockers. Age at baseline was incorporated in the model as covariate. Estimated marginal means ± standard error of the mean for the aortic root diameters were reported for statin users and non-users at baseline and during follow-up. Regression analysis was used to assess the difference in aortic root growth rate in mm/year between statin users and non-users following the previously described instrumental variables approach.[19] Assuming that the aortic root growth is linear, the estimate of the association between aortic root growth and the follow-up was obtained by linear regression analysis without including an intercept. Next statin use multiplied by follow-up duration in years was introduced to assess the additive value of statin use on the growth of the aortic root in mm/year. Intra-observer variability was assessed using Bland-Altman method measuring 20 echocardiograms repeatedly by one observer. Similarly, inter-observer variability was assessed by performing the measurements by two independent observers at least 1 week apart. All statistical tests were two-sided. A p-value<0.05 was considered statistically significant. Data analyses were performed using the SPSS software (Version 20.0. Armonk, NY: IBM Corp).

Results

A total of 199 patients (mean age 43±15 years, 69% men) were included in the present analysis. There were 41 (21%) statin users and 158 (79%) non-users. Baseline characteristics are presented in Table 1. Among statin users, the median duration of the treatment was 3.5 years (interquartile range: 2.4-5.4 years). The types and doses of statins varied over time and were adjusted to patient's tolerance. The majority of patients received simvastatin (usually 20 mg or 40 mg daily) or rosuvastatin (usually 10 mg daily). Other types of statins used were atorvastatin and pravastatin (usually 20 mg or 40 mg daily).

Table 1. Baseline characteristics

	Non-users (n=158)	**Statin users (n=41)**	**p-value**
Age (years)	40±14	55±10	<0.001
Male	106 (67%)	31 (76%)	0.389
Body surface area (m^2)	1.93±0.23	1.98±0.21	0.189
Smoking	29 (18%)	12 (29%)	0.186
Diabetes	4 (3%)	3 (7%)	0.314
Hypertension	26 (16%)	14 (34%)	0.021
NYHA Functional Class			<0.001
I	145 (91%)	27 (66%)	
II	9 (6%)	12 (29%)	
III	4 (3%)	2 (5%)	
IV	0 (0%)	0 (0%)	
Previous cardiac surgery	4 (3%)	4 (10%)	0.098
Coronary artery disease	1 (1%)	15 (37%)	<0.001
ACE-inhibitor or ARB	32 (20%)	25 (61%)	<0.001
Beta-blocker	32 (20%)	24 (59%)	<0.001
Total cholesterol (mg/dl)	195±36	198±47	0.690
LDL cholesterol (mg/dl)	120±32	136±46	0.071
Triglycerides (mg/dl)	128±63	154±85	0.081
HDL cholesterol (mg/dl)	57±17	49±14	0.028
LV end-diastolic diameter (mm)	50±6	49±6	0.160
LV end-systolic diameter (mm)	31±6	31±7	0.994
LV end-diastolic volume (ml)	131±39	120±27	0.089
LV end-systolic volume (ml)	62±24	59±17	0.450
LV ejection fraction (%)	53±7	51±7	0.054
Atypical bicuspid aortic valve	45 (28%)	11 (27%)	0.988
Raphe	135 (85%)	37 (90%)	0.586
Valvular dysfunction			0.274
None	99 (63%)	27 (66%)	
Pure aortic regurgitation	27 (17%)	6 (15%)	
Pure aortic stenosis	21 (13%)	8 (19%)	
Mixed aortic disease	11 (7%)	0 (0%)	

Data are presented as mean ± SD or as number (percentage). ACE: Angiotensin converting enzyme. ARB: Angiotensin Receptor Blocker. HDL: high density lipoprotein. LDL: low density lipoprotein. LV: left ventricular. NYHA: New York Heart Association.

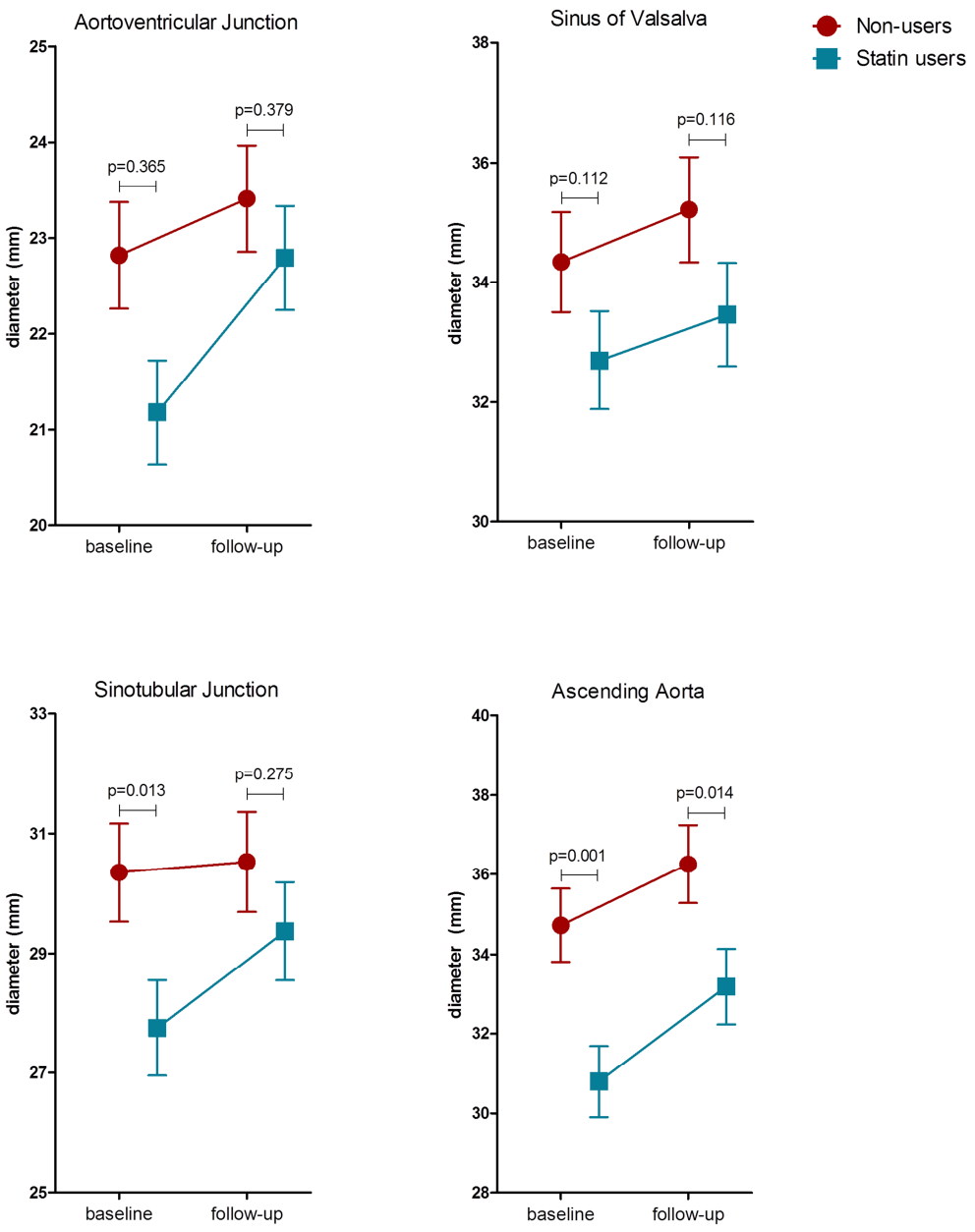

Figure 2. Comparison of aortic diameters at baseline and at follow-up between statin users and non-users.

Data are presented as estimated marginal means ± standard error of the mean calculated for mean age at baseline of 43 years and corrected for the presence of coronary artery disease and the use of angiotensin converting enzyme-inhibitors or angiotensin receptor blockers and beta-blockers.

Statin users were significantly older, with greater incidence of coronary artery disease, hypertension and New York Heart Association II-III functional class heart failure symptoms. Furthermore, statin users received more frequently angiotensin converting enzyme-inhibitors / angiotensin receptor blockers and beta-blockers. There was no significant difference between groups in total cholesterol levels at baseline. However, in statin users there was a tendency towards higher LDL-cholesterol and higher triglycerides. Furthermore the HDL-cholesterol was significantly lower in statin users compared to their counterparts. There was no significant difference in LV end-diastolic and end-systolic dimensions. Statin users had slightly lower LV ejection fraction compared to non-users (51±7% vs. 53±7%; p=0.054). The presence of a raphe, type of bicuspid aortic valve and aortic valvular dysfunction was not significantly different between statin-users and non-users.

Echocardiographic follow-up was complete with a median follow-up duration of 5.1 years (interquartile range: 2.7-8.8 years) in non-users and 3.9 years (interquartile range: 2.6-5.5 years) in statin users (p=0.052).

Figure 2 shows the differences in aortic root diameters at baseline and during follow-up between the groups, using the ANOVA test for repeated measurements adjusted for age at baseline, the presence of coronary artery disease and the use of angiotensin converting enzyme-inhibitors or angiotensin receptor blockers and beta-blockers. The aortic root diameter at the level of the AVJ was not significantly different between statin users and non-users. Aortic root diameter at the level of the SOV was comparable at baseline and at follow-up in statin users (32.7±0.8 mm and 33.5±0.9 mm) compared to non-users (34.3±0.8 mm and 35.2±0.9 mm). At the level of the STJ, the diameter was significantly smaller in statin users compared to non-users at baseline (27.8±0.8 mm vs. 30.3±0.8 mm; p=0.013). However, there was no significant difference in STJ diameter at follow-up. The AAo was significantly smaller in statin users compared to non-users at baseline (30.8±0.9 mm vs. 34.7±0.9 mm; p=0.001) and at follow-up (33.2±1.0 mm vs. 36.3±1.0 mm; p=0.014). The average annual aortic growth rate was 0.08 mm/year (95% confidence interval: 0.03-0.13) for the AVJ, 0.16 mm/year (0.11-0.21) for the SOV, 0.12 mm/year (0.07-0.17) for the STJ and 0.45 mm/year (0.37-0.53) for the AAo. There was no significant additive value of statin use on the annual growth rate of the aortic segments as presented in Table 2.

The intra-observer variability, displayed as 1.96 times the standard deviation of the difference between the two measurements was 1.6 mm for the AVJ, 3.2 mm for the SOV, 4.2 mm for the STJ and 5.1 mm for the AAo. The inter-observer variability was 2.6 mm for the AVJ, 3.9 mm for the SOV, 4.3 mm for the STJ and 4.4 mm for the AAo.

Table 2. Average annual growth rates in mm/year per aortic segment with the additive effect of the use of statins on the annual growth rate

	Annual growth rate		**Additive effect of the use of statins on annual growth rate**	
	B (95% CI)	**p-value**	**B (95% CI)**	**p-value**
Aortoventricular junction	0.08 (0.03 – 0.13)	0.001	-0.03 (-0.16 – 0.11)	0.687
Sinus of Valsalva	0.16 (0.11 – 0.21)	<0.001	-0.06 (-0.20 – 0.08)	0.413
Sinotubular junction	0.12 (0.07 – 0.17)	<0.001	0.13 (-0.02 – 0.28)	0.079
Ascending aorta	0.45 (0.37 – 0.53)	<0.001	-0.05 (-0.27 – 0.17)	0.671

Data are presented as regression coefficient (B) and 95% confidence interval (95% CI) indicating annual growth rates in mm/year.

Discussion

The main results of the present observational study can be summarized as follows: among patients with BAV, those treated with statins had smaller STJ at baseline and smaller AAo at baseline and at follow-up compared with patients non-treated with statins after correcting for age, presence of coronary artery disease and the use of angiotensin converting enzyme-inhibitors or angiotensin receptor blockers and beta-blockers. However, there was no significant effect of statins on the annual aortic growth rate since this was comparable between both subgroups of patients.

Bicuspid aortic valve is the most frequent congenital heart disease with an estimated prevalence of 1.3% in the general population.[20] In addition, BAV anatomy is associated with aortopathy and increased prevalence of aneurysms of the ascending aorta which occur at a younger age than in TAV.[2,21] Specific genotypes, histological and inmunohistochemical factors and changes in hemodynamics with increased shear stress on the aortic wall have been associated with increased risk of ascending aortic dilation in patients with BAV.[21-23] Indeed, in patients with BAV the growth rate of the aortic root and ascending aorta ranges between 0.2 and 0.9 mm/year,[9,24] a growth rate relatively similar to that observed in patients with Marfan syndrome but significantly different from that of patients with TAV and degenerative aortopathy.[24] In a recent study involving 353 patients with BAV who were compared with 51 patients with degenerative aortopathy and 50 patients with Marfan syndrome, Detaint et al. showed that in patients with BAV the maximal dilation rate was 0.42±0.6 mm/year while in patients with Marfan syndrome and in patients with degenerative aortopathy the maximal dilation rate was 0.49±0.5 mm/year and 0.20±0.3 mm/year, respectively (p=0.02).[24] Interestingly, the growth rate was largest at the ascending aorta in patients with BAV (0.42±0.6 mm/year) while in patients with Marfan syndrome, the sinuses of Valsalva showed the largest growth rate (0.49±0.5 mm/year). The present study shows similar growth rates for each level of the aortic root and ascending aorta to those reported by Detaint et al. with the ascending aorta as the segment with the largest growth rate. However, Detaint et al. did not

find an independent association between aortic growth rate and the use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers or beta-blockers.[24] The present study also did not find an association between the use of angiotensin converting enzyme-inhibitors / angiotensin receptor blockers and beta-blockers and the aortic root diameters at baseline and during follow-up. In contrast, the present study provides information on the association between statin use and the aortic growth rate of these patients.

The pathogenesis of ascending aorta dilation in patients with BAV is multifactorial and, in contrast to abdominal aortic aneurysms, ascending aorta aneurysms do not result in atherosclerosis.[25] However, in patients with BAV, there is an increased expression and activity of metalloproteinases that degrade the type IV collagen, elastin and fibrillar collagens.[4] Statins, clinically used as lipid lowering drugs, have various anti-inflammatory and pleiotropic effects.[6] Therefore it has been hypothesized that statins may have an inhibitory effect on aneurysm formation. For example, in experimental models statins have shown to inhibit the progression of abdominal aortic aneurysms independently of the total serum cholesterol levels lowering effect.[5,6] Inhibition of macrophage infiltration into the aorta and preservation of aortic wall elastin and medial smooth muscle cells in the aortic wall are the main underlying mechanisms explaining those findings.[5,6]

Clinical experiences have shown that patients with BAV who receive statin therapy have smaller ascending aorta diameters compared to non-users.[12] In 147 patients with BAV undergoing aortic valve replacement with or without aortic root replacement, Goel et al. showed that patients treated with statins had significantly smaller ascending aorta diameters than patients not receiving statins (3.6±0.7 cm vs. 3.9±0.6 cm, $p<0.001$) and the use of statins was independently associated with a 0.33 cm reduction in aortic size.[12] Furthermore, Jovin et al. showed that in patients with thoracic aneurysms (without specifying the prevalence of BAV), the annual growth rate of the thoracic aortic aneurysm in patients treated with statins (n=46) was comparable to that of patients not treated with statins (n=169) (0.8 mm/year vs. 0.9 mm/year, p=0.7).[9] Angeloni et al. recently published a large propensity score matched cohort study that showed a significantly smaller ascending aorta dilation rate of 0.95 mm/year in statin users compared to 1.27 mm/year in non-users.[11] The reported dilation rates were both larger than those reported in the present study, which might be explained by the inclusion of larger ascending aortic aneurysms at baseline in the study by Angeloni et al.[11] However, it should be emphasized that the anatomy of the aortic valve was not specified and that the age of the population was older than that of the patients included in our study and therefore, the results reported by Angeloni and coworkers may not be extrapolated to a younger BAV patient cohort.

Clinical implications

Ascending aorta dilation is the second most common morbidity in patients with BAV.[1] Due to the associated risk of aneurysm rupture, identification of pathophysiological determinants and potential therapeutic targets to reduce the risk of aortic dilation is a cardiovascular research priority. Besides advances in multimodality imaging that permit accurate diagnosis and characterization of BAV and its hemodynamics; genetic- and biomarker-based risk stratification may help to identify those patients at increased risk of aortic dilation. In addition, prospective studies evaluating the effect of specific therapies such as statins that may reduce the expression and activity of metalloproteinases or angiotensin converting enzymes inhibitors that may favourably affect the shear strain of the aortic wall are needed.

Limitations

The present study, taking into consideration all the limitations of an observational retrospective design, shows that the use of statins is associated with smaller aortic root and ascending aorta dimensions in patients with BAV but does not influence the growth rate. Therefore, it cannot be concluded that BAV patients without an indication for statins, should use a statin as primary prevention for aortic dilation. The relatively small number of patients treated with statins is also another limitation. In addition, patients using statins were different from non-users regarding age, presence of coronary artery disease and the use of angiotensin converting enzyme-inhibitors, angiotensin receptor blockers and beta-blockers. We corrected the statistical analysis for these important confounding factors. However, the influence of potential other unknown confounding factors could not be taken into account. Prospective trials with appropriate sample sizes randomizing patients to statin treatment or placebo are needed to assess the isolated effect of statins on aortic root dilation excluding potential confounding factors (such as cardiovascular risk factors and other drugs used). Other limitations of the present study include the evaluation of a selected cohort of patients with at least 2 echocardiographic studies ≥1 year of follow-up. This may have introduced selection bias, since patients with large or rapid growing aneurysms will be referred immediately for surgery. Furthermore, compared with other imaging techniques that provide higher spatial resolution data, transthoracic echocardiography may provide less accurate measurements of the aortic root and ascending aorta diameters. However, in this study we used linear regression analysis to assess the dilation rate following the previously described instrumental variables approach which mitigates problems associated with random errors such as measurement variability.[19] There was a wide variety in the type and doses of drugs taken by the patients included in the present study. Also within patients, the type and dose of drug could change during follow-up. Therefore a more precise analysis per type and dose of statins

was not feasible. Future studies may provide further insight into the differences between types of statins and their effects on the aortic root dilation rate.

Conclusion

In conclusion, in patients with BAV, the use of statins is associated with smaller STJ and AAo diameters when corrected for confounding factors. However, the annual growth rate of the aortic root and ascending aorta was not influenced by the use of statins.

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PART I

Preoperative evaluation of patients with aortic regurgitation and/or aortopathy

Selection of candidates to valve-sparing aortic root reconstruction

Chapter 5:

Aortic valve and aortic root features in CT angiography in patients considered for aortic valve repair

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Abstract

Background: The underlying mechanism of aortic regurgitation, aortic valve and root characteristics have been associated with the durability of surgical repair. We investigated whether multidetector CT (MDCT) identifies the characteristics of the aortic valve and root that may be associated with the ability to perform successful surgical repair.

Methods: Sixty-one patients with aortic regurgitation and/or aortic root pathology who were evaluated for aortic valve or root repair and underwent clinically indicated gated or non-gated MDCT of the aortic valve and aortic root were included in the present analysis. Patients with endocarditis were excluded. MDCT data of aortic valve anatomy and calcification and thoracic aorta dimensions were analyzed.

Results: The aortic valve and root was successfully repaired in 36 patients (55±13 years; 61% male; median EuroSCORE II, 3.8%) whereas in 25 patients (56±15 years; 52% male; median EuroSCORE II, 2.5%) repair was not attempted (n=20) or valve repair was converted to aortic valve replacement during surgery (n=5). In patients in whom repair was considered not possible or failed, there was a higher percentage of bicuspid aortic valves (48% vs. 17%; p=0.019), more severe commissural calcification, and more severe annular calcification.

Conclusion: The degree of commissural and annular calcification of the aortic valve determined by MDCT is inversely related to the ability to perform surgical valve repair instead of replacement. Similarly, bicuspid valve anatomy predicts failure to perform repair.

Introduction

Valve-sparing aortic root replacement techniques are successfully performed in selected patients with aortic regurgitation (AR) and/or aortic root pathology.[1-4] The underlying mechanism of the AR and several morphological characteristics of the aortic valve and root have been associated with durable aortic valve repair.[5] Based on direct surgical inspection, a classification of AR mechanisms has been developed to guide the decision and feasibility of surgical aortic valve repair.[6] In AR type 1 (functional aortic annulus dilation) and AR type 2 (cusp prolapse), different aortic root and valve repair techniques may be applied unless the valve is heavily calcified. In contrast, in AR type 3 (cusp restriction), repair techniques are not recommended as the risk of failed repair and recurrent significant AR is high.[6] In addition, wide preoperative aortoventricular junction (AVJ) is associated with recurrence of AR after aortic valve repair.[7]

Two-dimensional transesophageal echocardiography (TEE) has been applied: (1) to identify the underlying mechanism of AR, (2) to characterize the anatomy and morphology of the aortic valve, (3) to assess geometry of the aortic root, and (4) to predict surgical reparability.[5] However, 2-dimensional TEE underestimates the diameters of the functional aortic annulus as compared with multidetector CT (MDCT).[8,9] MDCT provides high-spatial resolution data of the aortic valve and root characteristics and permits qualitative (morphology of aortic valve and root, extent of annulus, cusps and commissural calcification) and quantitative (dimensions) evaluation of the aortic valve and root that may be relevant for decision making.[10] The aim of the present study was to investigate whether MDCT provides preoperative insight into characteristics of the aortic valve and root that may be associated with feasible and successful aortic valve repair.

Methods

Patients

The institutional ethical committee approved this retrospective evaluation of clinically acquired data and waived the need for individual written patient consent. A total of 168 patients with AR and/or aortic root pathology were evaluated for surgical valve-sparing aortic root repair at the Leiden University Medical Center between 2003 and 2013. Patients with available preoperative MDCT data of the aortic valve and root were considered eligible for the present study. Patients with endocarditis were excluded. The study population consisted of 61 patients with AR and/or aortic root pathology. MDCT data of aortic valve anatomy and calcification and aortic root dimensions were analyzed and compared between patients who underwent successful valve-sparing aortic root repair (defined as postoperative AR <grade 2) and patients in whom repair was not successful or not feasible and who eventually underwent aortic root replacement using the Freestyle stentless bioprosthesis (Medtronic; Minneapolis,

MN). Clinical and surgical data were collected in the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed.

Multi-detector row computed tomography

MDCT studies were performed to evaluate the presence and extent of aortic root pathology within the Leiden University Medical Center in 40 patients with a 320-slice, 64-slice or 16-slice MDCT scanner (Aquilion; Toshiba Medical Systems, Tokyo, Japan). In the remaining 21 patients, the MDCT studies were performed at the referral hospitals. MDCT angiography data acquisition extended from above the aortic arch to the diaphragm, including the entire thoracic aorta. MDCT data were acquired during breathhold in deep inspiration, with tube potential of 100 or 120 kV and tube current adapted to body habitus, with intravenous contrast enhancement and no electrocardiographic triggering in 77% of patients. In 14 (23%) patients, the scans were electrocardiographically triggered at 45% or 75% of the R-R interval. Data were reconstructed with a slice thickness of 0.5 to 5 mm. All the MDCT datasets were loaded for off-line analysis to a dedicated remote workstation (Vitrea FX 1.0; Vital Images, Minnetonka, MN). MDCT angiography was not performed in patients with chronic kidney disease stage 4 or 5. Chronic kidney disease stage 3 (estimated glomerular filtration rate: 30-59 ml/min) was present in 8 patients. These patients were hydrated orally or intravenously before and after MDCT to prevent contrast-induced nephropathy.

Data analysis was performed by 2 experienced observers blinded to the reparability of the valve. Anatomy of the aortic valve (tricuspid or bicuspid), the degree of calcification of aortic valve, and AVJ[10,11] and the diameter of thoracic aorta at 10 different levels were evaluated.[12,13] Three orthogonal multiplanar reformation (MPR) planes were oriented to obtain the cross sectional plane parallel to the AVJ, just below the hinge points of the coronary cusps.[11]

By orienting the reconstructed single-oblique sagittal and coronal views across the aortic annulus, the true short-axis of the AVJ was displayed on the reconstructed double-oblique transverse view.[11] On this view, the anatomy of aortic valve (tricuspid or bicuspid) was identified, and the grade of commissural calcification was qualitatively assessed based on a scale from 0 to 3 (0= no calcification, 1= small calcium spots <5mm, 2= several calcium lesions >5mm and 3= heavy calcification of all cusps; Figure 1).[10,11] In addition, annular calcification was also visually assessed on a scale from 0 to 3 (0= no calcification, 1= 1 or multiple spots <5mm or one spot >5mm, 2= 2-3 spots >5mm and 3= >3 spots of >5mm diameter; Figure 1).[10] From the double-oblique view the centerline was determined and on the orthogonal coronal and the single-oblique sagittal views, the coronal, and sagittal AVJ diameters were measured[11] (Figure 2) and the average diameter was calculated.

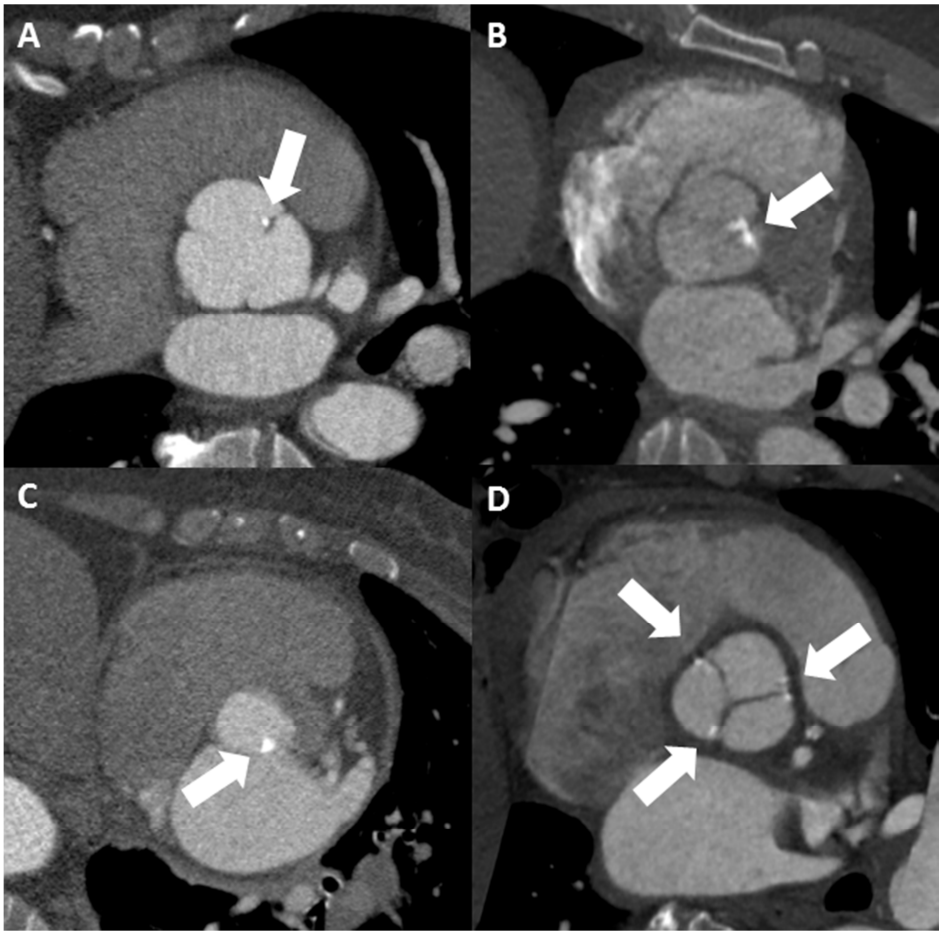

Figure 1. Classification of commissural and annular aortic valve calcification.
Commissural calcification was classified as grade 0 when there was no calcification, grade 1 when there were small calcium spots <5mm (A) or grade 2 when there were several calcium lesions >5mm (B). Annular calcification was considered grade 0 when there was no calcification, grade 1 when there were one or multiple spots <5mm or one spot >5mm (C) or grade 2 when there were 2-3 spots >5mm (D). Scans were acquired at 45 or 75% of R-R interval on 320-slice MDCT-scanner with tube potential of 100 or 120 kV and tube current adapted to body habitus.

The AVJ shape was evaluated by calculating the eccentricity index =1-(sagittal/coronal diameter); when the result of the equation was ≥0.1 the aortic annulus was considered ellipsoid.[14] Next, the diameter of the sinus of Valsalva (SOV) and sinotubular junction (STJ) at the single-oblique sagittal view, orthogonal to the double-oblique transverse view, were measured.[13]

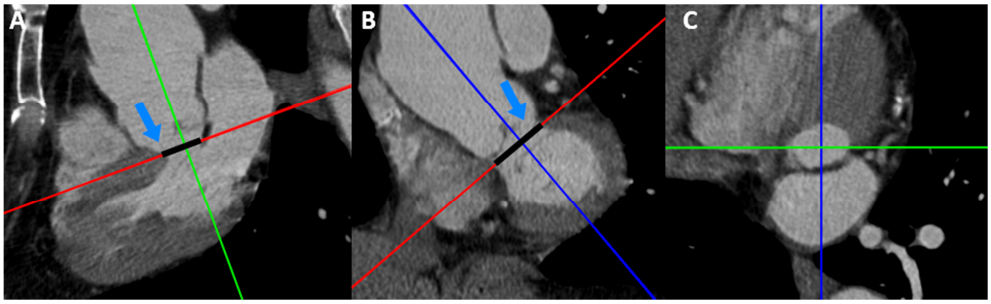

Figure 2. Measurement of aortoventricular junction on MDCT.

The 3 orthogonal multiplanar reformation planes (green, red and blue lines) were oriented on the single oblique sagittal (A) and coronal view (B) to visualize on the reconstructed double oblique transverse view (C) the true cross sectional plane of aortoventricular junction, just below the hinge points of the coronary cusps. The sagittal and coronal aortoventricular junction diameters, pointed by the blue arrows, were measured at the corresponding view (A and B respectively). In this example, the scan was acquired not electrocardiographically triggered on 16-slice MDCT-scanner with tube potential of 100 kV and tube current adapted to body habitus.

The diameters of the different levels of the thoracic aorta (at the level of the tubular ascending aorta, proximal and distal to the innominate trunk, proximal and distal to the left subclavian artery, proximal descending aorta and at the level of the diaphragm) were measured using the standard 3 MPR planes; the single-oblique and the coronal view were adjusted at each level to visualize the true cross-sectional view of each level at the double-oblique transverse view (Figure 3). Then, the aortic diameter at each level was measured at the single-oblique sagittal view.[12,13]

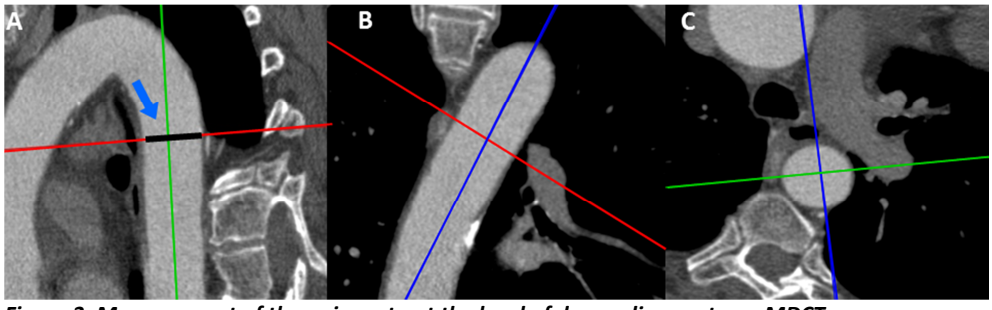

Figure 3. Measurement of thoracic aorta at the level of descending aorta on MDCT.

By using the standard orthogonal 3 multiplanar reconstruction planes (green, red and blue lines); the single oblique sagittal view (A) and the coronal view (B) were adjusted at descending aorta level to visualize the true cross sectional view at the double oblique transverse view (C). Then, the aortic diameter of descending aorta was measured (blue arrow) at the single oblique sagittal view (A). In this example, the scan was acquired not electrocardiographically triggered on 16-slice MDCT-scanner with tube potential of 100 kV and tube current adapted to body habitus.

Surgical repair

After median sternotomy, cardiopulmonary bypass was set through cannulation of the proximal part of the aortic arch or through femoral or preferably subclavian arterial route in patients with ascending aorta dissection or dilation. The aorta was transected at 2 cm above the ostium of the right coronary artery. The aortic root and valve were inspected by the surgeon and based on the AR mechanism, classified as type 1 (AR due to aortic root dilation), type 2 (AR due to cusp prolapse) or type 3 (AR due to cusp restriction).[6] Valve-sparing aortic root reconstruction was considered a feasible option in most type 1 and type 2 ARs unless heavy calcification of the aortic valve. If feasible, a vascular graft was implanted using either the reimplantation technique (modified David procedure) or the remodeling technique (Yacoub procedure) as previously described, with reimplantation of the coronary buttons.[15,16] In some cases, only the STJ was restored using a vascular graft.[17] Concomitant cusp repair techniques such as triangular resection, central cusp plication, resuspension, or shaving of the cusps were performed if needed.[18]

In patients with aortic valve and root considered non-reparable, aortic root replacement was performed using the Freestyle stentless bioprosthesis. The SOV and the aortic valve were excised. The bioprosthesis was then implanted with a 120° clockwise rotation with interrupted sutures, and the coronary buttons were reattached leaving 1 coronary ostium of the prosthesis unused.[19]

Statistical analysis

All data analyses were performed using the SPSS 20.0 (SPSS, Chicago, IL). Categorical variables were reported as frequencies and percentages. Continuous variables were displayed as mean ± standard deviation if normally distributed and as median and interquartile range if non-normally distributed. Differences between patients who underwent surgical valve-sparing aortic root reconstruction and patients who underwent aortic valve replacement were analyzed using the chi-square test, the unpaired Student *t*-test or Mann-Whitney U test as appropriate. All statistical tests were two-sided. A p-value <0.05 was considered statistically significant.

Results

The clinical characteristics of the patient population (mean age 56±14 years; 57% men) are listed in Table 1. Aortic valve and root repair was performed successfully in 36 patients (59%), with postoperative <grade 2 AR. The David reimplantation technique was performed in 24 patients (67%). The Yacoub remodeling technique was performed in 2 patients (6%). In the remaining 10 patients (28%), restoration of the STJ was performed. Additional subcommissural annuloplasty (so called Cosgrove stitches) was executed in 3 patients to diminish the AVJ

dimension. Various cusp repair techniques were performed in 9 patients (25%). Furthermore, in 25 patients (41%) aortic valve repair techniques were considered not feasible or unsuccessful. In 5 of these 25 patients, repair of the aortic valve and root was initially attempted but the residual postoperative AR grade was >2 and were converted to aortic root replacement using the Freestyle stentless bioprosthesis. The clinical characteristics of both groups of patients (aortic valve or root repair group and nonreparable group) were similar (Table 1).

Table 1. Baseline characteristics.

	Nonreparable (n=25)	**Reparable (n=36)**	**p-value**
Age (years)	56.3±14.6	55.4±13.2	0.796
Male	13 (52%)	22 (61%)	0.657
Smoking	7 (28%)	6 (17%)	0.438
Diabetes	2 (8%)	1 (3%)	0.745
Hypertension	9 (36%)	15 (42%)	0.858
Dyslipidemia	5 (20%)	5 (14%)	0.661
NYHA functional class			0.665
I	13 (52%)	17 (47%)	
II	7 (28%)	14 (39%)	
III	3 (12%)	3 (8%)	
IV	2 (8%)	1 (3%)	
Creatinin clearance (ml/min)	108.4±44.3	96.6±33.5	0.238
Chronic Kidney Disease			0.195
Stage 1	16 (64%)	17 (47%)	
Stage 2	5 (20%)	15 (42%)	
Stage 3	4 (16%)	4 (11%)	
EuroSCORE II (%)	3.8 (1.6-6.2)	2.5 (1.8-4.3)	0.747
Setting of surgery			0.754
Emergency	6 (24%)	11 (31%)	
Urgent	5 (20%)	5 (14%)	
Elective	14 (56%)	20 (56%)	
Mitral valve surgery	1 (4%)	4 (11%)	0.602
Tricuspid valve surgery	0 (0%)	4 (11%)	0.231
CABG	5 (20%)	6 (17%)	1.000

Data are presented as number (percentage), as mean ± standard deviation or as median (interquartile range). CABG: Coronary Artery Bypass Grafting; EuroSCORE II: European System for Cardiac Operative Risk Evaluation II; NYHA: New York Heart Association.

MDCT characteristics associated with reparable aortic root and valve

Among the various MDCT variables evaluated, 3 characteristics were more frequently associated with nonreparability: bicuspid anatomy, severe commissural calcification and annular calcification. The prevalence of bicuspid aortic valve (BAV) was significantly higher in the nonreparable group compared with the aortic valve or root repair group (48% vs. 17%; p=0.019). The degree of calcification of the commissures and the aortic annulus is displayed in Figure 4. The valve commissures were more calcified in the nonreparable group than in the

aortic valve or root repair group (grade 1, 14% vs. 14%; grade 2: 29% vs. 0%, respectively; p=0.003). The annulus calcification grade was also higher in the nonreparable group than in the aortic valve or root repair group (grade 1, 5% vs. 14%; grade 2, 14% vs. 0%, respectively; p=0.043).

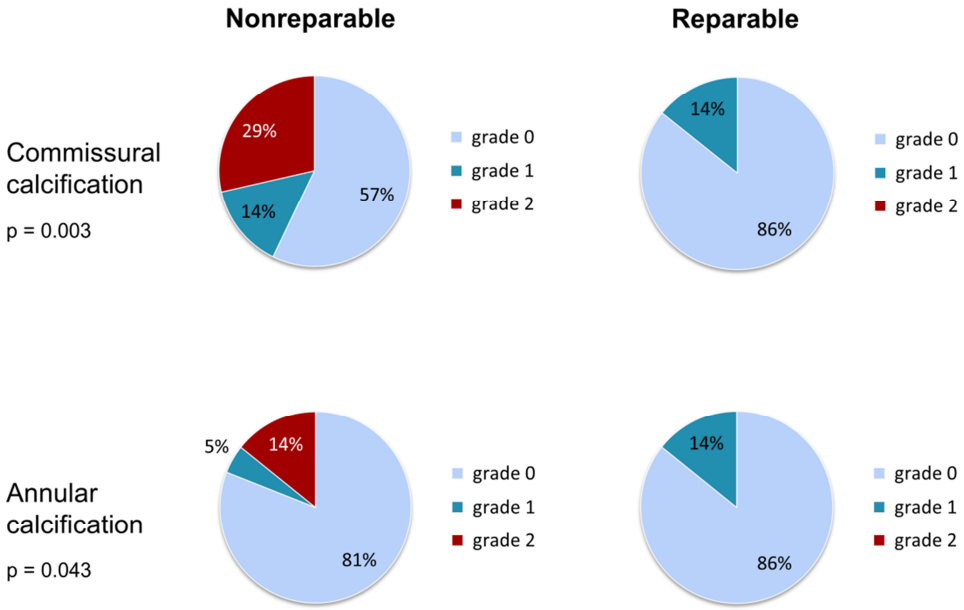

Figure 4. Grade of calcification.
Displayed in percentages per group for commissural calcification and annular calcification.

The eccentricity index of the AVJ was 0.24 in the nonreparable group, compared to 0.26 in the reparable group (p=0.696). The diameters of the aortic root and thoracic aorta were measured at 10 levels (Figure 5). Patients with a reparable valve tended to have a wider SOV compared with the patients in the nonreparable group (48.3±9.3 mm vs. 44.6±7.1 mm, respectively; p=0.103); however, this difference was not statistically significant. All other diameters were comparable between the 2 groups.

Discussion

The present analysis identified anatomic features of the aortic valve and root assessed on preoperative MDCT that may be associated with feasible and successful surgical repair of the aortic valve. Tricuspid anatomy and less commissural and annular calcification were associated with feasible and successful valve repair.

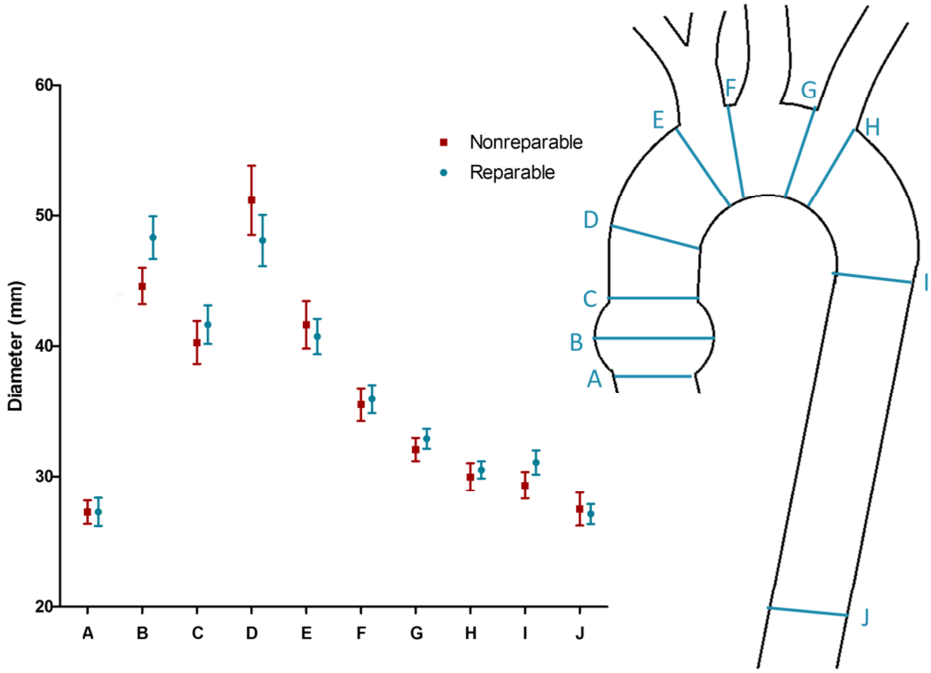

Figure 5. Diameters of the aortic root and thoracic aorta at 10 levels.
Data are displayed as mean and standard error of the mean (SEM).

Aortic valve morphology and geometry and aortic root dimensions are parameters associated with feasibility of surgical aortic valve repair. So far, most studies have evaluated these aspects with TEE.[5] However, MDCT may be frequently requested in AR associated with aortic root pathology. MDCT is highly accurate to differentiate between bicuspid and tricuspid anatomy (particularly in the presence of calcifications) and provides accurate measurements of aortic root and thoracic aorta.[9,20] Valve-sparing aortic root replacement techniques provide good outcomes in patients with BAV who are operated in highly experienced centers. [21,22] However, some valve characteristics have been associated with increased rates of reoperation (up to 20%).[23,24] For example, a commissural orientation of <160º (which indicates asymmetrical size cusps) has been suggested as a risk factor for reoperation in BAV.[1] In contrast, eccentric regurgitant jets and absence of cusp and commissural thickening or calcification have been associated with successful repair in patients with BAV.[25] In the present study, 67% of BAVs were considered nonreparable and importantly 36% had commissural calcification grade ≥2. Calcification extent is also an important characteristic associated with reparability in tricuspid anatomy of the aortic valve.[5] The present analysis demonstrated that higher grades of commissural and annular calcification (grade ≥2) were associated with higher probability of performing eventually an aortic valve replacement rather than aortic valve repair. Using 2-

dimensional TEE, le Polain de Waroux et al. showed that severe calcification of the aortic valve was associated with high recurrence rate of significant AR after surgical repair.[5] MDCT permits accurate assessment, quantification and location of aortic valve calcification and is considered the method of reference.[10]

In addition, several studies have shown less successful repair in patients with a wide annulus, that is, AVJ of >28 mm.[1,7,26] In the present series, the diameter of the AVJ was not different between patients in whom repair was feasible and patients who underwent valve replacement. However, there was a tendency towards a wider SOV in patients who underwent successful aortic valve and root repair. This may be attributed to different pathophysiologic types of aortic regurgitation.[27] Measurement of the aortic root and ascending aorta dimensions is accurately assessed with MDCT since this 3-dimensional imaging technique permits alignment of the MPR across the aortic root and ascending aorta, defining a centerline to avoid off-axis measurements. Therefore, MDCT, frequently requested before valve-sparing aortic root replacement techniques to assess concomitant aortic pathology, provides several important data (morphological and quantitative) that may help to identify the patients in whom AR repair may be successfully performed.

Clinical perspective

MDCT forms a part of the preoperative assessment of patients with AR associated with aortic root pathology. Dimensions of the aortic root and ascending aorta are accurately obtained with MDCT and are paramount to decide the surgical approach.[7,9] However, it is important to note that MDCT data can also provide useful information on the aortic valve anatomy and morphology that can indicate whether aortic valve repair may be successful or not. Furthermore, current advances on computational fluid dynamics have provided insightful data on the pathophysiology of aortic diseases.[28,29] These novel algorithms permit quantification of wall shear stress of the aorta and dynamic pressures of the aortic flow as well as qualitative evaluation of the streamlines that may refine the underling mechanism of AR and predict the feasibility and durability of repair.

However, there are subgroups of patients with contraindications for MDCT in whom these aspects may be analyzed with other imaging techniques. For example, in patients with concomitant stage 4 to 5 chronic kidney disease, MDCT may be contraindicated.[30] In this group of patients, magnetic resonance imaging may be a valuable 3-dimensional imaging technique to assess some of the aforementioned variables. However, calcification of the aortic valve may be difficult to assess with MRI. Currently, TEE is the most frequent technique to assess the grade and mechanism of AR. However, this technique is semi-invasive and does not provide information on the aortic arch at the level of the brachiocephalic and left common carotid arteries. Integration of information obtained with TEE and MDCT may accurately predict which

patients may be suitable for aortic valve-sparing surgical techniques and which type of technique may be the most appropriate. This may result in adequate referral of suitable patients to high-volume centers performing durable aortic valve repair techniques. Additional studies evaluating the impact of a systematic assessment of the aortic valve or root with TEE and MDCT on the outcomes of surgical aortic valve repair techniques would establish the role of these imaging techniques in the clinical management of patients with aortic root pathology associated or not with AR.

Limitations

The present analysis is limited by its retrospective observational nature. Although the surgical repair technique performed by the surgeon was not influenced by the preoperative MDCT data, the relatively small number of patients precluded us to perform statistical analysis to investigate the independent determinants or predictors of successful aortic valve repair. Furthermore, transesophageal echocardiographic assessment to identify the patients in whom aortic valve repair may be feasible was not systematically available. Therefore, the incremental value of MDCT assessment combined with transesophageal echocardiographic evaluation to predict aortic valve reparability could not be investigated. Quantification of aortic valve and root calcification using the Agatston score was not possible because non-contrast enhanced MDCT data were not systematically available. MDCT was performed on a 320-, 64- or 16-slice scanner which may have induced heterogeneity in the MDCT data. MDCT data acquisition was not electrocardiographic triggered in the majority of patients which may have resulted in artifacts particularly in the aortic root and ascending aorta that may hamper the reproducibility of the measurements. However, in our series there were no patients excluded because of non-analyzable MDCT data. Moreover, MDCT data were not consistently acquired in diastole or systole which may introduce an important bias. In 21 patients, MDCT was performed at the referral hospital and information on MDCT data acquisition was not systematically available. Lastly, MDCT angiography is not the imaging technique of first choice in patients with severe chronic kidney disease (stage 4 or 5),[30] and therefore, the results of the present study may not be generalizable to this subgroup of patients.

Conclusion

Tricuspid valve anatomy and less commissural and annular calcification are significantly associated with feasible and successful aortic valve and root repair. The information provided by MDCT regarding valve morphology and calcification might be helpful in determining the surgical strategy in patients with aortic root pathology, associated or not with AR.

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Chapter 6:

Transthoracic echocardiography for selection of tubular graft size in David reimplantation technique

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Abstract

Background: Selection of tubular graft size during David reimplantation technique for aortic root dilation is based on perioperative leaflet height measurements. The present study evaluated whether transthoracic echocardiography (TTE)-based algorithms may help in selecting the graft size preoperatively.

Methods: Thirty patients (52±11 years old, 73% men) who underwent David reimplantation technique were evaluated. The implanted graft size was based on the David's formula. Leaflet height (diameter = 1.1 • ((2 • 2/3 • leaflet height) + 2)), leaflet length (diameter = ((2 • 2/3 • leaflet length) + 2)) and leaflet area (diameter = 0.8 • ((2 • √(total leaflet area / π)) + 2)) TTE-derived formulas were retrospectively developed. The percentage of under- or oversized implanted grafts was calculated and the association between the adequacy of graft sizing using TTE-derived formulas and the incidence of residual aortic regurgitation (AR) was evaluated retrospectively.

Results: The incidence of postoperative mild residual AR was 23%. The actually implanted graft diameter was oversized based on leaflet height in 15 (50%) patients, based on leaflet length in 13 (43%) patients and based on leaflet area TTE-derived formula in 11 (37%) patients. The incidence of mild AR was significantly lower in undersized grafts compared with oversized grafts based on leaflet length TTE-derived formula (6% vs. 46%, p=0.032) and leaflet area TTE-derived formula (5% vs. 55%, p=0.009).

Conclusion: In patients undergoing David reimplantation technique, grafts considered undersized according to the leaflet length or leaflet area TTE-derived formula were associated with less incidence of residual AR than patients with oversized grafts.

Introduction

The David reimplantation technique is a feasible and effective surgical valve-sparing aortic root replacement for patients with aortic regurgitation (AR) due to dilation of the aortic root.[1] The incidence of recurrent significant AR (AR ≥ grade 3) during follow-up ranges between 4 and 22%.[2,3] The presence of residual AR after the surgery has been associated with a 5-fold higher risk of recurrent AR during follow-up.[2] To prevent residual AR, adequate sizing of the tubular graft is pivotal.[4] Leaflet coaptation may be insufficient if the graft is too large (oversized), whereas leaflet prolapse and cusp abrasion may occur if the graft is too small (undersized). In current practice, the tubular graft size is based on intraoperative measurement of the average leaflet height using the David's formula (diameter = $2 \bullet 2/3 \bullet h_{leaflet} + (2 \bullet Ao_{wall})$) where $h_{leaflet}$ is the leaflet height measured with surgical callipers and Ao_{wall} is the thickness of the aortic wall.[5] We hypothesized that preoperative transthoracic echocardiography (TTE) may be helpful in determining the appropriate graft size in David reimplantation technique. Therefore the aims of the present study were first to develop TTE-derived formulas to calculate the recommended graft size and second to assess whether there was an association between graft sizing using the TTE-derived formulas and the presence of residual AR after surgery.

Methods

Patients

Thirty patients with aortic root pathology who underwent surgical valve-sparing aortic root replacement using the David reimplantation technique at the Leiden University Medical Center between 2001 and 2014 with sufficient echocardiographic data were included in the present study. Patients who underwent additional aortic leaflet repair were excluded. Patients who underwent concomitant mitral valve or tricuspid valve surgery were not excluded. Clinical and surgical data were collected at the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, Netherlands) and retrospectively analysed.

AR grade and aortic valve geometry were assessed retrospectively with preoperative two-dimensional (2D) TTE. Three TTE-derived formulas were developed to select the graft size for the David reimplantation technique, based on leaflet height, leaflet length and leaflet area (see below). The implanted graft was sized using the David's formula based on surgically measured leaflet height.[5] Transesophageal echocardiography (TEE) was used to assess residual AR directly after the surgery. The percentage of under- or oversized implanted grafts was reported and the association between the adequacy of graft sizing using the TTE-derived formulas and the incidence of residual AR was evaluated. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Two-dimensional transthoracic echocardiography

Preoperative TTE was performed at rest using commercially available ultrasound systems (System Five, Vivid 7 and E9, General Electric Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. 2D and Doppler echocardiographic data were acquired at the parasternal and apical views according to current recommendations.[6] The echocardiographic data were digitally stored in cine-loop format and were retrospectively analysed using EchoPac (112.0.1, GE Medical Systems, Horten, Norway).

AR grade was assessed using colour, pulsed and continuous wave Doppler recordings and using a multiparametric approach that includes the measurement of the jet width relative to the LV outflow tract diameter, vena contracta and the pressure half time of the regurgitant flow (if feasible) according to current recommendations.[7] AR was graded as 0 (absent), 1 (mild), 2 (mild-moderate), 3 (moderate-severe) or 4 (severe). The AR jet was classified as central or eccentric.

Aortic valve geometry was measured during end-diastole (just before opening of the aortic valve) in the parasternal short-axis and long-axis view. The image was zoomed on the aortic valve. The leaflet height was measured in the parasternal short-axis view from the internal border of the aortic root to the free edge of the leaflet and was averaged per patient (Figure 1). The leaflet depth was measured in the parasternal long-axis view as the distance between the line from the leaflet insertion to the leaflet tip and the most convex point of the leaflet.

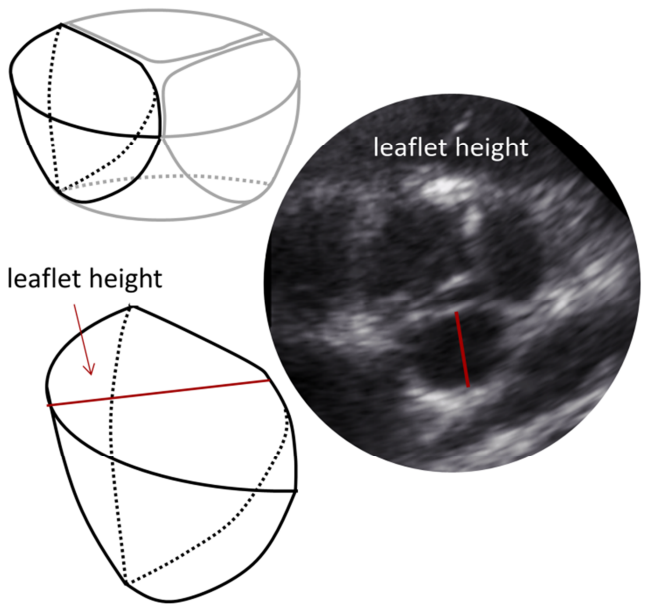

Figure 1. Leaflet height on transthoracic echocardiography. *Leaflet height was measured during end diastole in parasternal short-axis view from the internal aortic root border to the free edge of the leaflet.*

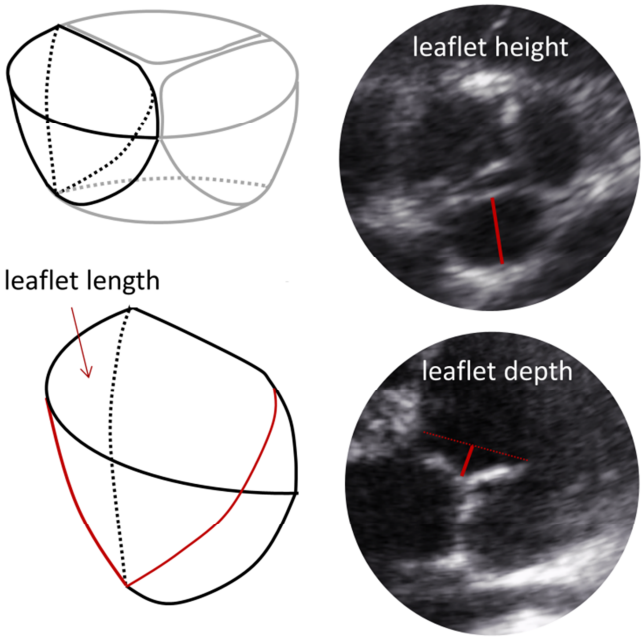

Figure 2. Leaflet length on transthoracic echocardiography. *The leaflet length over the belly of the leaflet was subsequently calculated as the half perimeter of the ellipse described by the average leaflet height as major axis and twice the leaflet depth as minor axis. The leaflet height was measured in the parasternal short-axis view from the internal border of the aortic root to the free edge of the leaflet. The leaflet depth was measured in the parasternal long-axis view as the distance between the line from the leaflet insertion to the leaflet tip and the most convex point of the leaflet.*

The leaflet length over the belly of the leaflet was subsequently calculated as the half perimeter of the ellipse described by the average leaflet height as major axis and twice the leaflet depth as minor axis (Figure 2).The leaflet area was measured in the parasternal short-axis view per leaflet and was then summed per patient to obtain the total leaflet area (Figure 3).

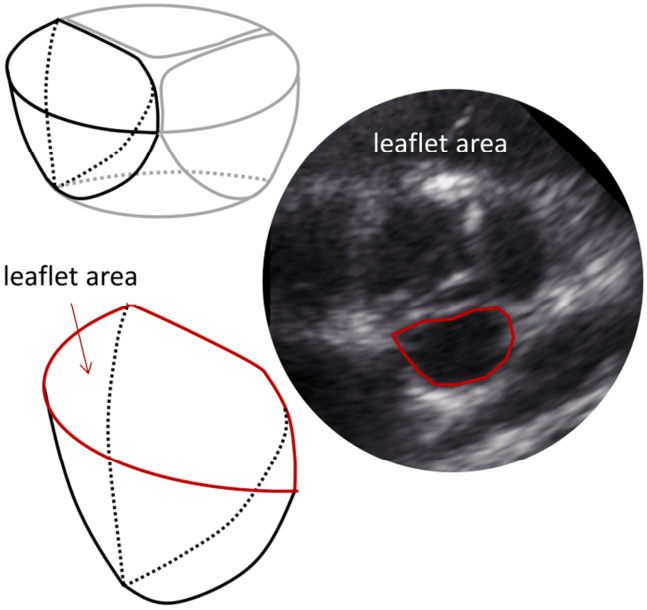

Figure 3. Leaflet area on transthoracic echocardiography. *Leaflet area was measured during end diastole in parasternal short-axis view.*

Surgery

After median sternotomy, cardiopulmonary bypass was set through cannulation of the distal ascending aorta or proximal aortic arch. In patients with aortic dissection or dilation of the distal ascending aorta, cannulation via the sub-clavian or femoral arterial route was performed. The aorta was incised 2 cm above the ostium of the right coronary artery and resected until the aortoventricular junction (AVJ).

The height of all leaflets was measured using surgical callipers from the nadir of the leaflet insertion on the AVJ to the free margin of each leaflet and then averaged. The size of the graft at the level of the AVJ was determined using the David's formula: (diameter = ($h_{leaflet}$ • 2 • 2/3) + (2 • Ao_{wall})), where $h_{leaflet}$ was the average leaflet height measured with surgical calipers.[5] The thickness of the aortic wall (Ao_{wall}) was estimated as 1 mm. David I procedure was performed in 6 patients (20%) as previously described.[5] A modified David V procedure was performed in 24 patients (80%), resizing the ventricular rim of the graft according to the calculated size of the AVJ following the David's formula.[8] In both David I and modified David V techniques, the coronary buttons were reimplanted into the respective neosinuses. Directly after the procedure, the presence of residual AR was assessed using TEE. Residual AR was graded as none, trace or mild based on the TEE report. There was no more than mild AR after the procedures. Furthermore, the coaptation length of the aortic valve was measured on TEE during diastole when the valve was closed.

Statistical analysis

Analyses were performed using the SPSS software version 20 (SPSS, Chicago, IL, USA). Continuous variables were displayed as mean ± standard deviation if normally distributed and as median and interquartile range if non-normally distributed. TTE-derived formulas based on leaflet height, leaflet length and leaflet area were retrospectively developed using linear regression analysis without including an intercept. Per patient, the recommended graft diameter was calculated for each TTE-derived formula and rounded to whole millimetres. Patients with an implanted graft smaller than or equal to that recommended by TTE-derived formulas (undersized) were compared with patients with an implanted graft larger than recommended by TTE-derived formulas (oversized) using the chi-square test. All statistical tests were two-sided. A p-value<0.05 was considered statistically significant.

Results

Development of transthoracic echocardiography-derived formulas

A total of 30 patients (mean age 52 ± 11 years, 73% men) who underwent the David reimplantation technique because of aortic root pathology were evaluated. The clinical, echocardiographic and surgical characteristics are presented in Table 1.

Table 1: Baseline clinical, echocardiographic and surgical characteristics.

	All patients (n=30)
Clinical characteristics:	
Age (years)	52 ± 11
Male	22 (73%)
Body surface area (m^2)	2.02 ± 0.16
Smoking	8 (27%)
Diabetes	0 (0%)
Hypertension	7 (23%)
Dyslipidaemia	5 (17%)
NYHA functional class	
I	17 (57%)
II	6 (20%)
III	7 (23%)
IV	0 (0%)
Echocardiographic characteristics:	
Aortic regurgitation	
Grade 0	5 (17%)
Grade 1	4 (13%)
Grade 2	12 (40%)
Grade 3	5 (17%)
Grade 4	4 (13%)
Aortic regurgitation jet direction	
No jet	5 (17%)
Central jet	15 (50%)
Eccentric jet	10 (33%)
Average leaflet height (cm)	1.9 ± 0.3
Total leaflet area (cm^2)	10.9 ± 3.0
Surgical characteristics:	
Bicuspid aortic valve	3 (10%)
EuroSCORE II (%)	1.9 (1.2 – 2.6)
Reimplantation technique	
David I	6 (20%)
David V	24 (80%)
Graft diameter at level of AVJ (mm)	30 ± 3

Data are presented as number (percentage), as mean ± standard deviation or as median (interquartile range). AVJ = Aortoventricular Junction. EuroSCORE = European System for Cardiac Operative Risk Evaluation. NYHA = New York Heart Association.

The ratio between the surgically measured leaflet height and echocardiographic measured leaflet height was on average 1.1±0.2, indicating that TTE underestimated the leaflet height. This correction factor was taken into account when the TTE-derived formula based on leaflet height was developed similar to the David's formula. Linear regression analysis was performed to compare the calculated diameter based on TTE-measured leaflet height and the diameter based on surgically measured leaflet height (both: diameter = $(2 \bullet 2/3 \bullet h_{leaflet}) + 2$) (Figure 4). The slope was 1.1 (95% confidence interval: 1.0-1.2; $p<0.001$) indicating that the diameter obtained by TTE-derived formula based on the leaflet height had to be multiplied by factor 1.1

to obtain the recommended diameter. Therefore the TTE-derived formula based on leaflet height was: diameter = 1.1 • ((2 • 2/3 • height) + 2).
Secondly, the leaflet length TTE-derived formula was developed. Linear regression analysis was performed to compare the calculated diameter based on leaflet length and the diameter of the actually implanted graft (Figure 4). The slope was 1.0 (95% confidence interval: 0.9-1.0; p<0.001); therefore, no correction factor is needed resulting in the TTE-derived formula based on leaflet length: diameter = ((2 • 2/3 • length) + 2).
Lastly, the TTE-derived formula based on leaflet area was developed. As area equals π times the squared radius, the diameter was calculated as diameter = (2 • √(total leaflet area / π)) + 2. Linear regression analysis was performed to obtain a correction factor for converting the diameter based on TTE measurements to a surgically applicable diameter (Figure 4). The slope was 0.8 (95% confidence interval: 0.7-0.8; p<0.001) indicating that the diameter obtained by TTE-derived formula based on leaflet area had to be multiplied by factor 0.8 for the recommended diameter. The TTE-derived formula based on leaflet area was: diameter = 0.8 • ((2 • √(total leaflet area / π)) + 2).

Relation between oversizing and residual aortic regurgitation
The implanted graft diameter was considered oversized based on leaflet height TTE-derived formula in 15 (50%) patients, based on leaflet length TTE-derived formula in 13 (43%) patients and based on leaflet area TTE-derived formula in 11 (37%) patients. For the overall population, mild residual AR, assessed with intraoperative TEE, was present in 7 (23%) patients whereas the remaining 23 (77%) patients did not have AR.
Chi-square test was performed to assess whether an oversized graft according to TTE-derived formulas was associated with higher rates of residual AR. The results are presented in Figure 5. Residual AR was present in 5 (33%) patients with oversized graft according to the leaflet height TTE-derived formula, and in 2 (13%) patients with an undersized graft (p=0.388). According to the leaflet length TTE-derived formula, residual AR was more often present in patients who received an oversized graft (6 (46%) patients) compared with patients who received an undersized graft (1 (6%) patients; p=0.032). In patients who received an oversized graft according to leaflet area TTE-derived formula, the prevalence of residual AR was 55%. In patients who received an undersized graft, there was only 1 (5%) patient with residual AR (p=0.009). The coaptation length of the aortic valve after surgery was at least 6 mm in all patients and on average 7.6 ± 1.3 mm.

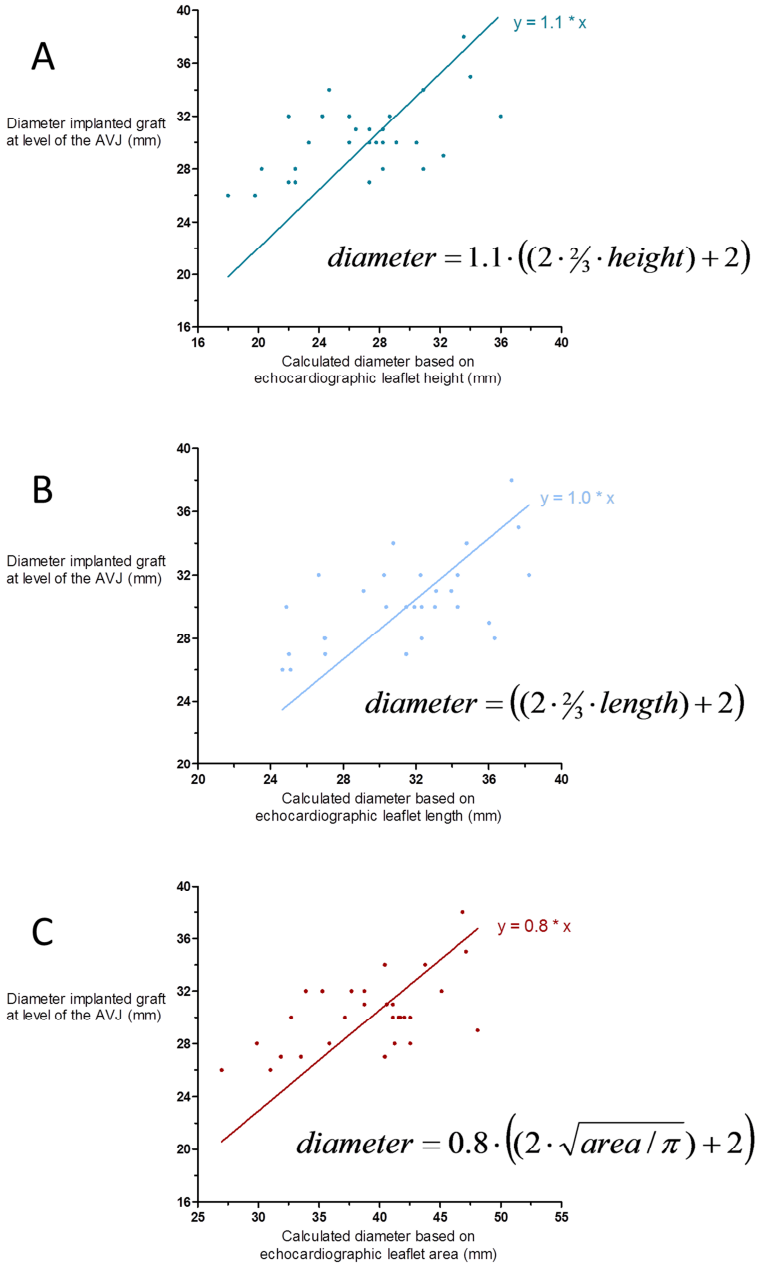

Figure 4. Linear regression analysis for the development of TTE-derived formulas
(A) Linear regression analysis in the development of the leaflet height-based TTE-derived formula. The correction factor of 1.1 should be applied in the general formula.
(B) Linear regression analysis in the development of the leaflet length-based TTE-derived formula. No correction factor is necessary in the general formula.
(C) Linear regression analysis in the development of the leaflet area-based TTE-derived formula. The correction factor of 0.8 should be applied in the general formula. AVJ: aortoventricular junction; TTE: transthoracic echocardiography

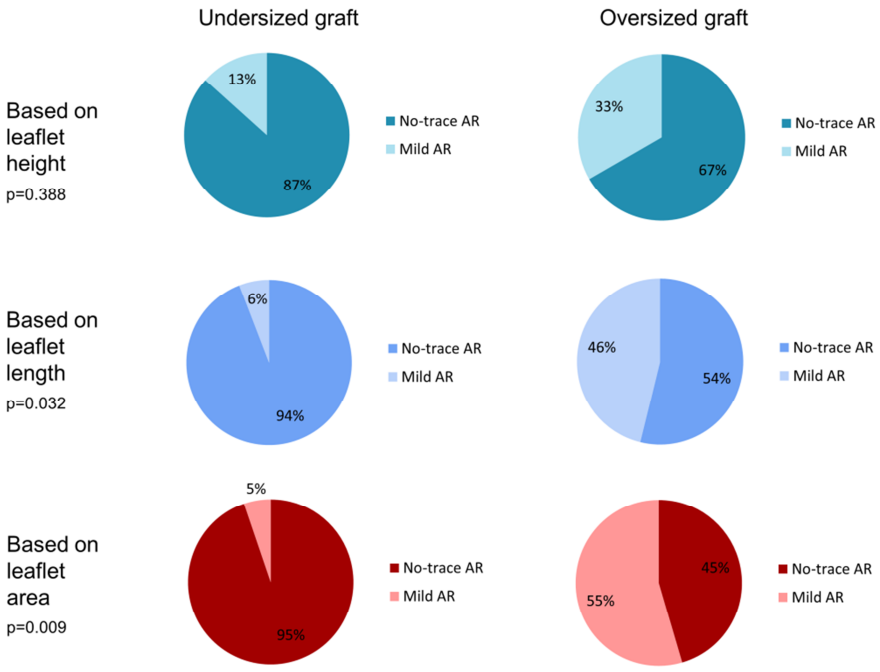

Figure 5. Residual aortic regurgitation in patients with an undersized graft compared to patients with an oversized graft.
AR: aortic regurgitation

Discussion

The David aortic valve reimplantation technique has shown favourable mid- and long-term results in patients with aortic root or ascending aorta aneurysms.[9-11] Accurate sizing of the tubular Dacron graft where the valve is inserted into is pivotal to ensure durable repair. After the first description of the surgical technique by Drs David and Feindel, where the size of the tubular graft was selected upon perioperative measurement of the average leaflet height,[5] several modifications have been developed, including the creation of neosinuses of Valsalva by achieving an area of the Dacron fabric contained within two commissures larger than the anatomical area.[12] However, selection of the appropriate size of the tubular graft remains challenging and several investigational groups have proposed alternative methods for graft sizing. For example, Svensson et al. proposed the implantation of a 28- or 30-mm graft for men and 26- or 28-mm for women and the use of a Hegar's dilator of a size equivalent to the patient's expected normal LV outflow tract size.[13] The proximal end of the graft is sutured and crimped down to the Hegar's dilator size creating neosinuses of Valsalva where the graft is 7-9 mm larger than the LV outflow tract. After sewing the aortic valve in position, the anchoring

sutures at the level of the commissures are placed 4 mm apart narrowing the graft at the level of the neosinotubular junction. One of the advantages of this technique is its reproducibility.[13] Alternatively, de Kerchove et al. proposed a method to select the tubular graft size based on the hypothesis of preserved height of the aortic commissures in aortic root aneurysms.[14,15] Usually measured from the base of the interleaflet triangle to the top of the non-coronary/left-coronary commissure, the height corresponds to the size of the graft and theoretically to the size of the sinotubular junction in normally functioning aortic valves. Eventually, if the height does not correspond to the available labelled graft sizes, the next larger size is selected. This methodology tested in 27 consecutive patients undergoing aortic valve-sparing surgery using the reimplantation technique (59% bicuspid valve, 53% with severe preoperative AR) showed acute favourable results with no (54%) or mild AR (46%) at discharge TTE.[14]

However, all the aforementioned series based the sizing of the graft on surgical inspection and direct intraoperative measurements. Ex-vivo studies have demonstrated that the aortic valve leaflet length is influenced by the pressure on the aortic leaflets[16] and the distensibility of the leaflet tissue may challenge the accurate measurement of the aortic leaflets at the surgical field under cardioplegia.[17] Accordingly, echocardiography could overcome these limitations as measurements are performed in diastole under physiological pressures.

This hypothesis-generating study evaluated the prevalence of under- or oversized tubular graft using a TTE-derived formula and its association with residual mild AR after aortic valve-sparing surgery using the reimplantation technique. The incidence of mild AR was 23% and was significantly higher among patients who received an oversized tubular graft according to the leaflet length and leaflet area TTE-derived formula. The reported incidences of mild AR after aortic valve-sparing surgery using the reimplantation technique range between 24 and 46%.[14,18,19] Leaflet height was easily measured on TTE, however there was a factor 1.1 difference between the TTE-measured and surgically measured leaflet height; therefore a correction factor had to be applied into the leaflet height TTE-derived formula. In addition, there was no significant difference in residual AR in oversized and undersized grafts based on the TTE leaflet height formula. In addition, using the leaflet length formula, oversizing was associated significantly with more residual AR. The leaflet area was easily measured and also resulted in a significant association between oversizing based on the leaflet area formula and more residual AR.

Awaiting prospective evaluation of the performance of these proposed TTE-derived formulas, the present results suggest that the graft size should not be larger than calculated by the leaflet length and leaflet area formula. The leaflet area is easier to measure on TTE in comparison with leaflet length. In our series, the leaflet area TTE-based formula performed best in demonstrating residual AR in relation to oversizing, hence this formula seems to be the

most promising when using TTE in determining the appropriate graft size. Eventually, additional manoeuvres to tailor the size of the graft at the levels of the aortoventricular and sinotubular junctions would be required to achieve good leaflet coaptation while avoiding prolapse or direct contact between cusp and graft that may lead to erosion or retraction of the aortic cusps.[4,20]

Study limitations

The present study was limited by the relatively small number of patients with a heterogeneous cohort including aortic valve reimplantation using the David I technique as well as the David V modified technique. The formulas were retrospectively developed and evaluated. Therefore it remains unknown whether the clinical course of the patients would be different if a graft size based on echocardiography would have been implanted. Nevertheless, the TTE-derived formulas may be helpful to assist the surgeon in decision-making and to prevent oversizing. The present study is a first step in the use of echocardiography to standardize the selection of the graft size in David reimplantation technique. Firstly, retrospective validation of the formulas in a larger cohort and secondly, prospective application of the formulas is needed before introduction into routine clinical practice. In addition, the use of a 2D imaging technique may be limited by the use of off-axis images that may underestimate the leaflet size. The aortic root size probably influences the measurements of the leaflet size on echocardiography since the leaflet height was taken from the internal border of the aortic root to the free edge of the leaflet. The small number of patients hampered subanalysis of performance of the formulas in small and large aortic roots. This topic might be of interest in further clinical research. 3D echocardiography may refine the geometric assessment of the aortic valve and root and should be used in future studies. Automated software for 3D reconstruction of the aortic root might provide more accurate measurements of the leaflet height and area.[21]

The present study shows that undersizing based on the leaflet length and leaflet area TTE-derived formula is better in preventing residual AR compared with oversizing; however, prolapse or direct contact between the leaflet and the graft should be avoided. Therefore, the effect of using a smaller graft on aortic valve degeneration during follow-up should be closely monitored.

Conclusion

In patients undergoing David reimplantation technique, grafts considered undersized according to leaflet length and leaflet area TTE-derived formulas are associated with less AR than patients with oversized grafts. This study provides a proof-of-concept on the use of echocardiography to standardize the selection of the appropriate graft size in David

reimplantation technique. However, future studies are needed to validate the formulas and make them applicable in routine clinical practice.

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PART II

Postoperative evaluation of patients

after aortic valve and root surgery

Effects of aortic valve and root surgery on left ventricular performance

Chapter 7:

Left ventricular reverse remodeling after aortic valve surgery for acute versus chronic aortic regurgitation

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Abstract

Background: Extent of left ventricular (LV) reverse remodeling after aortic valve repair or replacement (AVR) may differ between patients operated for acute aortic regurgitation (AR) and chronic AR. The aim of this study was to compare changes in LV volumes and function between patients with acute and chronic AR who underwent AVR.

Methods: A total of 98 patients (54±15 years, 61% men) with acute (n=21) or chronic AR (n=77) were included in the present retrospective evaluation. LV volumes, LV ejection fraction and global longitudinal strain indexed for LV end-diastolic volume (GLSi) were assessed preoperatively and after a median follow-up of 28 months (interquartile range: 17-66 months).

Results: Patients with acute AR tended to have smaller preoperative LV end-diastolic volume compared to chronic AR (156±15 vs. 183±6 ml; p=0.070). Both in patients with acute and chronic AR, significant LV reverse remodeling with sustained reduction in LV volumes occurred during follow-up with a significant smaller LV end-diastolic volume in acute AR compared to chronic AR (106±8 vs. 128±5 ml; p=0.032). Preoperative and postoperative LV ejection fractions were not significantly different between groups. In contrast, GLSi was better in patients with acute AR compared to chronic AR before AVR (-1.34±0.20 vs. -0.96±0.07 %/10 ml; p=0.042) and during follow-up (-1.65±0.16 vs. -1.29±0.07 %/10 ml; p=0.017).

Conclusion: After AVR, LV reverse remodeling occurs both in patients with acute and chronic AR. However, LV end-diastolic volume was more reduced and GLSi was more preserved during follow-up in acute AR than in chronic AR.

Introduction

The prevalence of aortic regurgitation (AR) in the general population is 10% and is often mild.[1,2] Severe chronic AR results in a combination of left ventricular (LV) volume overload (due to the regurgitant volume) and LV pressure overload (due to systolic hypertension as a result from an increase in total aortic stroke volume).[3] In early stages of the disease, the LV adapts to the volume overload with eccentric LV hypertrophy to preserve LV systolic function.[4] Progressive LV dilation and systolic hypertension increase LV wall stress leading to ultrastructural myocardial changes that may not reverse after aortic valve repair or replacement (AVR).[5-7] In severe acute AR, these changes may not take place and therefore the remodeling process after emergent AVR may be different to that observed in patients with chronic AR.

The studies evaluating the presence and clinical implications of LV reverse remodeling after AVR have focused on patients with severe chronic AR.[8-11] However, little is known about the LV reverse remodeling process in patients with severe acute AR. Accordingly, the aim of the current study was to characterize changes in LV volumes and function after AVR in patients with acute AR and chronic AR.

Methods

Patients

The present retrospective study included adult patients who underwent aortic valve and root surgery for AR or aortic root pathology from 1998 to 2013 at the Leiden University Medical Center, The Netherlands. Patients with moderate to severe and severe AR and no more than mild aortic stenosis were selected from a large echocardiographic database. Patients with available echocardiograms at baseline (before surgery) and at least 6 months after aortic valve replacement were included. If patients underwent reoperation on the aortic valve and/or aortic root during follow-up, the last transthoracic echocardiography before reoperation was considered in the analysis. Concomitant mitral or tricuspid valve disease was not an exclusion criterion.

Baseline clinical characteristics, EuroSCORE II and surgical procedures were recorded. In addition, LV volumes and function and valvular hemodynamics were assessed with 2-dimensional transthoracic echocardiography preoperatively and at 6 months or longer follow-up. All data were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. Patients were divided into two groups: patients with acute AR developed ≤6 weeks before AVR and patients with chronic AR lasting for >6 weeks before AVR.

The institutional ethical committee approved the retrospective analysis of clinical and echocardiographic data and waived the need for patient written informed consent for patients

followed-up at the Leiden University Medical Center, The Netherlands. For retrospective analysis of postoperative echocardiographic data of patients followed-up in referral centers, written informed consent was obtained.

Two-dimensional transthoracic echocardiography

Transthoracic echocardiography was performed at rest with patients in the left decubitus position using commercially available ultrasound systems (System 5, Vivid 7 and E9, General Electric Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Two-dimensional and Doppler data were acquired at the parasternal, apical, subcostal and supra-sternal views according to current recommendations.[12] The echocardiographic data were digitally stored in cine-loop format and data analysis was retrospectively performed using EchoPac (112.0.1, GE Medical Systems, Horten, Norway). LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes were quantified in the apical two- and four-chamber views using the Simpson's biplane method and LV ejection fraction (LVEF) was calculated.[12] Further evaluation of LV systolic function was performed with two-dimensional speckle-tracking longitudinal strain analysis. LV longitudinal strain was measured from apical two-, three- and four-chamber views and averaged to obtain LV global longitudinal strain (GLS). To take into consideration changes in LV volumes over time after AVR, GLS was corrected for LVEDV and expressed as percentage of deformation per 10 ml of LVEDV (GLSi).

Aortic valve function was evaluated using color, continuous- and pulsed-wave Doppler. AR grade was assessed using a multiparametric approach including the measurement of the jet width relative to the LV outflow tract width and the vena contracta width in the parasternal long-axis view and apical three- or five-chamber views and the measurement of the pressure half time (if feasible) with continuous wave Doppler on the apical three- or five-chamber views. AR was graded as 0 (absent), 1 (mild), 2 (mild-moderate), 3 (moderate-severe) or 4 (severe).[13] Aortic stenosis grade was assessed measuring the aortic jet velocity and transaortic mean pressure gradient on continuous-wave Doppler recordings of the valve obtained in the apical three- or five-chamber views. Left ventricular outflow tract velocity was measured using the pulsed-wave Doppler in the apical three- or five-chamber views with the sample volume placed 5 mm below the aortic annulus plane into the left ventricle. Aortic valve area was calculated using the continuity equation. Patients with more than mild aortic stenosis were excluded as per inclusion and exclusion criteria of the study.

Surgery

After median sternotomy, arterial cannulation was performed of the distal ascending aorta (in elective non-dissected aortic pathology and in the absence of dilatation of the distal part of the ascending aorta) or the subclavian or femoral artery (in patients with ascending aorta

dissection or dilatation). Patients underwent aortic valve and root replacement or valve-sparing aortic root reconstruction. In aortic valve and root replacement techniques, the coronary buttons were mobilized and the sinuses of Valsalva and the aortic valve were excised. A mechanical or biological prosthesis was then implanted. Thereafter the coronary buttons were reattached.[14,15] For valve-sparing aortic root reconstruction, either a supracoronary ascending aorta replacement was performed with restoration of the sinotubular junction or the native sinuses of Valsalva were resected and a graft was implanted using the reimplantation technique (modified David procedure) or the remodeling technique (Yacoub technique), as previously described.[16-18] Leaflet repair procedures (leaflet triangular resection, leaflet resuspension and plication of the free edge of the leaflet) were performed if needed. In addition, concomitant aortic arch replacement was performed if the luminal diameter at this level was >45 mm or – in cases of dissection – a (re)entry tear was present in the arch.

Follow-up

Patients underwent two-dimensional transthoracic echocardiography during follow-up at the discretion of the treating cardiologist. The median follow-up duration was 28 months (interquartile range: 17-66 months).

Statistical analysis

All data analyses were performed using the SPSS software version 20 (SPSS, Chicago, IL, USA). Categorical variables are reported as numbers and percentages. Continuous variables are reported as mean ± standard deviation or median and interquartile range. Differences between acute and chronic AR were analysed using the chi-square test (for categorical variables) and the unpaired Student's *t*-test or Mann-Whitney U test (for normally or non-normally distributed continuous variables, respectively). Linear mixed model analysis was used to assess the differences in change in LV dimensions and function over time between the two groups. Onset of AR (acute or chronic) and time of transthoracic echocardiography (preoperative or follow-up) were incorporated in the model as fixed variables. An unstructured covariance matrix was applied. The estimated marginal mean ± standard error of the mean was presented. All statistical tests were two-sided. A p-value<0.05 was considered statistically significant.

Results

A total of 98 patients (mean age 54±15 years, 61% men) were evaluated: acute AR was present in 21 (21%) patients and chronic AR in 77 (79%) patients. Acute AR was classified as moderate-severe in 6 (29%) patients and severe in 15 (71%) patients and the etiology was endocarditis in

14 (66%) patients, acute type A aortic dissection in 5 (24%) and acute pulmonary edema associated with aortic root dilation in the remaining 2 (10%) patients. Chronic AR was classified as moderate-severe in 49 (64%) patients and severe in 28 (36%) patients. The clinical and surgical characteristics of both groups are displayed in Table 1. Cardiovascular risk factors were comparable between groups. However, the creatinine clearance was significantly lower and New York Heart Association class IV heart failure symptoms were more frequently reported in patients with acute AR compared with chronic AR. Patients with acute AR had higher EuroSCORE II compared with patients with chronic AR. Among patients with acute AR, 6 (29%) patients underwent emergent surgery and 15 (71%) patients underwent urgent surgery. In the entire cohort, the aortic valve and root were replaced by a biological prosthesis in 60 (61%) patients and by a mechanical prosthesis in 10 (10%) patients.

Table 1. Baseline and surgical characteristics.

	Acute AR (n=21)	**Chronic AR (n=77)**	**p-value**
Age (years)	56 ± 14	53 ± 15	0.380
Male	10 (48%)	50 (65%)	0.234
Body surface area (m^2)	1.85 ± 0.18	2.03 ± 0.41	0.059
Smoking	5 (24%)	18 (23%)	1
Diabetes mellitus	3 (14%)	2 (3%)	0.110
Hypertension	8 (38%)	29 (38%)	1
Dyslipidaemia	2 (10%)	7 (9%)	1
NYHA functional class			0.002
I	11 (52%)	29 (38%)	
II	3 (14%)	26 (33%)	
III	2 (10%)	20 (26%)	
IV	5 (24%)	2 (3%)	
Creatinine clearance (ml/min)	78 ± 36	104 ± 37	0.008
EuroSCORE II (%)	7.3 (3.3 – 22.4)	2.5 (1.6 – 4.2)	<0.001
Bicuspid aortic valve	2 (10%)	27 (35%)	0.042
Aortic valve and root technique			0.414
Replacement	17 (81%)	53 (69%)	
Valve-sparing restoration	4 (19%)	24 (31%)	
Mitral valve surgery	6 (29%)	15 (19%)	0.549
Tricuspid valve surgery	4 (19%)	10 (13%)	0.725
CABG	2 (10%)	6 (8%)	1

Data are presented as mean ± standard deviation, as median (interquartile range) or as number (percentage). AR: aortic regurgitation. CABG: coronary artery by-pass grafting. EuroSCORE: European System for Cardiac Operative Risk Evaluation. NYHA: New York Heart Association.

In the remaining 28 (29%) patients, a valve sparing procedure was performed with isolated aortic valve repair in 3 patients, supracoronary ascending aorta replacement with restoration of the sinotubular junction in 6 patients, reimplantation technique of David in 17 patients and

the remodeling technique of Yacoub in 2 patients. There were no differences in the number and type of concomitant surgeries performed in both groups.

LV reverse remodeling after AVR for acute versus chronic AR

The median echocardiographic follow-up duration was 34 months (interquartile range: 18-66 months) in patients with acute AR and 26 months (interquartile range: 16-64 months) in patients with chronic AR (p=0.491). Recurrence of moderate-severe or severe AR at follow-up was present in 5 (5%) patients, all in chronic AR patients. At follow-up, the mean aortic valve gradient was similar between patients with acute and patients with chronic AR (9.3±10.3 vs. 7.3±5.3 mmHg; p=0.236).

Figure 1 shows the LV volumes preoperatively and at follow-up. The preoperative LVEDV was slightly smaller in patients with acute AR compared with chronic AR (156±15 vs. 183±6 ml, p=0.070). The preoperative LVESV was comparable between acute and chronic AR (73±10 vs. 85±4 ml; p=0.162). At follow-up, in both groups, LV reverse remodeling occurred with a significant reduction in LVEDV and LVESV. However, the LVEDV was significantly smaller at follow-up in patients with acute AR than in patients with chronic AR (106±8 vs. 128±5 ml; p=0.032).

The change in LV function is displayed in figure 2. The preoperative LVEF was similar in patients with acute AR and chronic AR (55±2 vs. 54±1%; p=0.595) and increased during follow-up with no difference between groups (acute AR: 57±2% vs. chronic AR: 59±1%; p=0.444). In patients with acute AR, GLS was −15.8±1.3% before and −15.5±0.9% after surgery (p=0.874). In patients with chronic AR, GLS was −15.0±0.8% before and −14.3±0.4% after surgery (p=0.373). Because GLS represents shortening of the LV, which is dependent on the size of the LV, GLS was indexed for LVEDV. The GLSi was significantly better in patients with acute AR compared with chronic AR at baseline (−1.34±0.20 vs −0.96±0.07%/10 mL; P=.042) as well as during follow-up (−1.65±0.16 vs −1.29±0.07; p=0.017).

Discussion

The main findings of the present study include the observation that patients with acute AR had slightly smaller pre-operative LVEDV compared with patients with chronic AR suggesting the lack of LV remodeling to compensate the volume and pressure overload in the former group. Despite this observation, significant LV reverse remodeling after AVR was observed in both patients with acute AR and patients with chronic AR, with significantly smaller LVEDV and more preserved LV systolic function (based on speckle tracking echocardiography measurements) at follow-up among patients with acute AR compared with patients with chronic AR.

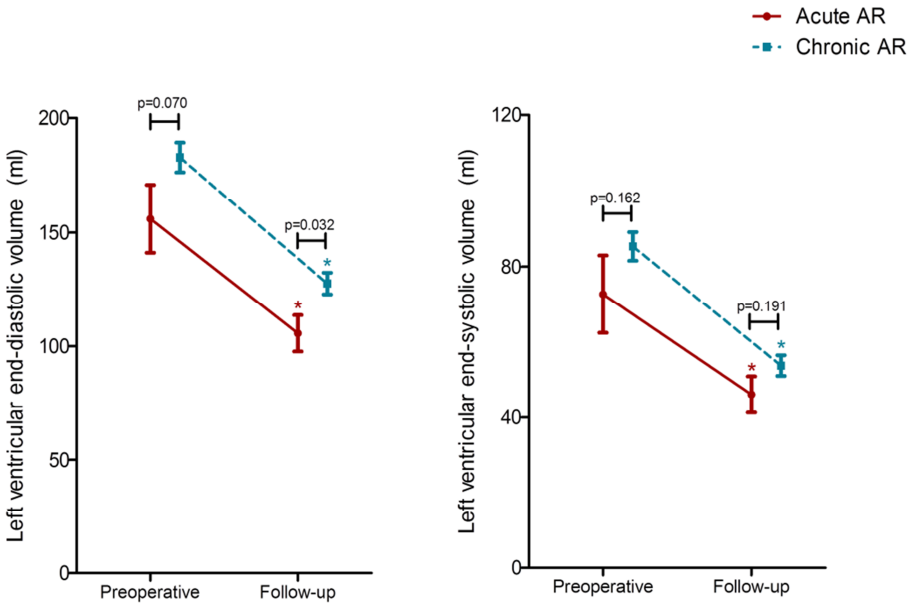

Figure 1. Left ventricular volumes over time in acute and chronic AR.
*Data are displayed as estimated marginal means ± standard error of the mean. *p<0.05 compared with preoperative. AR: aortic regurgitation. LVEDV: left ventricular end-diastolic volume. LVESV: left ventricular end-systolic volume*

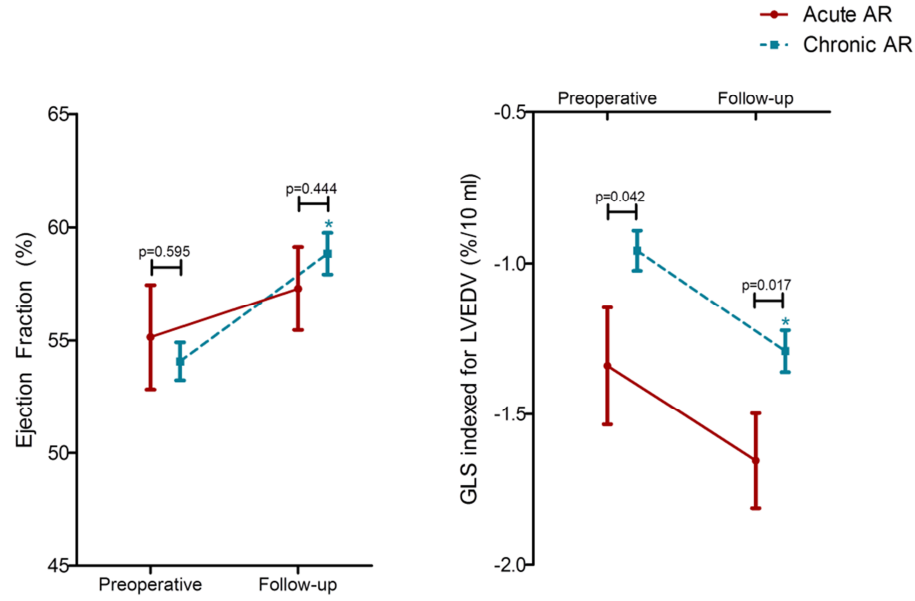

Figure 2. Left ventricular function over time in acute and chronic AR.
*Data are displayed as estimated marginal means ± standard error of the mean. *p<0.05 compared with preoperative. AR: aortic regurgitation. GLSi: global longitudinal strain indexed for left ventricular end-diastolic volume. LVEF: left ventricular ejection fraction.*

Acute versus chronic aortic regurgitation

Timing of aortic valve repair/replacement for AR depends on the presence of symptoms or documentation of LV systolic function impairment or LV dilatation.[19] Acute severe AR is usually associated with abrupt onset of heart failure symptoms, signs of low cardiac output and initial signs of LV remodeling, including LV dilatation and hypertrophy that cannot compensate the abrupt increase in volume and pressure overload.[20] Experimental models have shown changes in extracellular matrix, perivascular fibrosis and increased cardiomyocyte cross-sectional area early after onset of acute severe AR.[20] In contrast, in chronic severe AR, the adaptive changes in LV structure to compensate the gradual increase in volume and pressure overload result in larger LV dilatation and hypertrophy (compared with acute AR) that normalize wall stress and preserve LV systolic function.[4] When the AR progresses and LV wall stress increases, LV systolic dysfunction occurs.[21-23]

In acute AR immediate surgical intervention is usually necessary and can be performed with good outcome,[24,25] whereas in chronic AR patients, surgery is not recommended until symptoms develop or when LVEF<50% or LV end-diastolic diameter >75 mm or LV end-systolic diameter >55mm.[19]

Aortic valve and root surgery restoring the competence of the aortic valve reduces the LV volume and pressure overload inducing LV reverse remodeling. Previous studies have shown that LV reverse remodeling occurs, both after aortic valve and root replacement and after valve-sparing aortic root reconstruction in patients with chronic AR.[8-10] In contrast, comparison of postoperative LV reverse remodeling and change in systolic function between patients operated for acute AR and patients operated for chronic AR have not been described extensively. Kumpuris et al. compared three patient groups with severe AR who underwent aortic valve surgery; chronic AR with postoperative LV reverse remodeling, chronic AR without postoperative LV reverse remodeling and acute AR.[26] Patients operated for acute AR and patients operated for chronic AR who showed postoperative LV reverse remodeling had similar LV end-diastolic and LV end-systolic diameters preoperatively and postoperatively (median 30 days after surgery).[26] The present evaluation also showed LV reverse remodeling in both groups of patients which was more pronounced among patients with acute AR than in patients with chronic AR. Probably, more advanced microscopic remodeling with increased myocardial fibrosis in patients with chronic AR may preclude normalization of LV volumes after AVR.

Furthermore, recovery or normalization of LV systolic function is an important surgical outcome with prognostic implications. In chronic AR patients with preoperative LV systolic dysfunction or severe dilation who underwent aortic valve and root surgery, the LVEF improved significantly.[8,27] Particularly, patients with LV reverse remodeling early after surgery experienced an increase in LVEF from 47±9% to 56±6% during follow up, whereas in patients

without LV reverse remodeling after surgery, the LVEF remained low (from 32±6% to 26±9%).[11] However, LVEF may not be a sensitive marker of LV systolic function in these patients. As previously demonstrated, patients with chronic severe AR may have impaired GLS despite having normal LVEF suggesting the presence of ultrastructural changes of the myocardium.[23] GLS may be also a better reflector of the LV performance after AVR. A previous study including 47 chronic AR patients showed significant postoperative improvement in GLS normalized for LVEDV (from about -0.9 %/10 ml to -1.2 %/10 ml; $p<0.01$).[5] We found similar results in chronic AR patients (from -0.96 %/10 ml to -1.29 %/10 ml; $p<0.001$). In addition, we demonstrated that patients with chronic AR had more impaired GLSi compared to acute AR patients before and after surgery suggesting more myocardial dysfunction in the former patients.

Clinical implications

The present study provides further insight into the effect of AR on LV performance before and after AVR. Chronic AR was associated with less LV reverse remodeling and less improvement in LV function after aortic valve and root surgery compared with acute AR, which might be attributed to increased myocardial fibrosis in patients with chronic AR. Although LVEF was not significantly different between patients with acute and chronic AR before as well as after surgery, GLSi was less affected in patients who underwent surgery for acute severe AR suggesting a lesser degree of microscopic remodeling (myocardial fibrosis and extracellular matrix changes) in these patients.

Current guidelines recommend surgery in asymptomatic patients with chronic severe AR when LV dilation (LV end-diastolic diameter >75mm or LV end-systolic diameter >55mm) or LV dysfunction (LVEF <50%) occurs. The present study indicates that chronicity of AR is associated with diminished postoperative improvement in LV performance and normalization of LV volumes. Therefore, more sensitive parameters of LV dysfunction or early remodeling may be helpful to improve the outcomes of aortic valve surgery for chronic AR. GLSi is able to detect myocardial dysfunction in an earlier stage compared to LVEF.[5,23] Studies including GLSi in surgical decision-making might help in the optimal timing of surgery in patients with chronic AR. Perhaps surgery at an earlier stage can prevent the development of irreversible changes of the myocardium.

Limitations

This was a retrospective study with a limited number of patients. Only patients with preoperative and follow-up echocardiography were included in the present analysis which might have introduced a selection bias. Clinical data for patients who did not meet the inclusion criteria were not collected and therefore comparisons between included and excluded patients are not feasible to investigate the differences and selection bias.

Furthermore, there was no prospective follow-up protocol, thus echocardiographic follow-up was performed at the discretion of the treating cardiologist. The exact duration of AR was unknown in the majority of patients with chronic AR; therefore no further analysis could be performed relating the duration of AR to the extent of LV reverse remodeling and LV function improvement.

Conclusion

LV reverse remodeling occurs after aortic valve surgery both for acute and chronic AR. However, LVEDV was more reduced and GLSi was more preserved during follow-up in patients operated for acute AR than in patients with chronic AR.

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Chapter 8:

Aortic valve repair versus replacement for aortic regurgitation: effects on left ventricular remodeling

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Abstract

Background: Left ventricular (LV) reverse remodeling after aortic valve replacement (AVR) for aortic regurgitation (AR) is associated with superior prognosis. The outcomes of valve-sparing aortic root replacement techniques on LV performance have not been compared with LV reverse remodeling in AVR. The present evaluation compared the extent of long-term LV reverse remodeling in patients with aortic root pathology and/or AR who underwent aortic valve repair (AVr) with patients who underwent AVR.

Methods: A total of 226 patients (54.7±14.3 years, 63% male) with AR or aortic root pathology who underwent AVr (n=135) or AVR with the Freestyle stentless aortic root bioprosthesis [Medtronic, Inc; Minneapolis, Minnesota] (n=91) were included in the present retrospective evaluation. LV volumes and ejection fraction were assessed preoperatively, postoperatively (before hospital discharge) and during follow-up.

Results: Baseline characteristics were comparable between patient groups, except for higher prevalence of bicuspid aortic valve anatomy among AVR patients (38% vs. 16%, $p<0.001$). In addition, patients undergoing AVR had significantly larger LV end-diastolic and end-systolic volumes than their counterparts. After a median follow-up of 46 months (interquartile range: 17-78 months), both groups of patients showed a significant and sustained reduction in LV end-diastolic and end-systolic volumes, with significantly larger reduction in patients undergoing AVR. Ejection fraction decreased significantly postoperatively and improved later during follow-up similarly in both groups. The incidence of significant AR at long-term follow-up was comparable among groups (AVr: 8% vs. AVR: 7%).

Conclusion: LV reverse remodeling occurs after AVR and AVr, reaching comparable LV volumes and function after a median of 4 years of follow-up.

Introduction

Aortic root pathology is present in 11% of patients with aortic regurgitation (AR).[1] Valve-sparing aortic root remodeling/replacement techniques have emerged as safe and effective techniques providing long-term stable aortic valve function in selected patients.[2-5] In patients who are not suitable for valve-sparing aortic root remodeling/replacement, aortic root replacement with concomitant aortic valve replacement (AVR) using bioprostheses has demonstrated excellent results in terms of long-term outcomes, valve function and left ventricular (LV) function.[6-8] In contrast to mitral valve repair and replacement, where the evidence shows that mitral valve repair is associated with superior LV function and remodeling than mitral valve replacement for patients with primary mitral regurgitation,[9] the outcomes of valve-sparing aortic root remodeling/replacement techniques on LV performance have not been compared with AVR. Accordingly, the aim of the present evaluation was to compare changes in LV dimensions and function in patients with aortic root pathology and/or aortic valve regurgitation who underwent valve-sparing aortic root surgery with patients in whom surgical repair techniques were not feasible and were treated with surgical AVR.

Methods

Patients

From July 1993 to June 2013, 247 adult patients with AR and/or aortic root pathology underwent surgical valve-sparing aortic root reconstruction or surgical AVR using the Freestyle stentless aortic root bioprosthesis (Medtronic, Inc; Minneapolis, Minnesota) at the Leiden University Medical Center. Twenty-one patients were excluded due to lack of echocardiographic data. Patients with concomitant significant mitral or tricuspid valve disease (any grade of mitral or tricuspid stenosis and moderate or severe regurgitation) who were treated during the same surgical intervention were not excluded. Patients with more than mild aortic stenosis were excluded from the present analysis.

Baseline clinical characteristics, EuroSCORE II and surgical procedures were recorded. In addition, LV volumes and function and valvular hemodynamics were assessed with two-dimensional transthoracic echocardiography preoperatively, postoperatively and during follow-up when available. Demographic, clinical, surgical, and echocardiographic data were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed. The institutional ethic committee approved this retrospective study and waived the need for individual patient consent.

Patients were divided into two groups: patients undergoing aortic valve repair (AVr) and patients who underwent aortic valve replacement using the Freestyle stentless bioprosthesis (AVR-F). The incidence of recurrent aortic valve regurgitation over time was assessed. In

addition, changes in LV volumes and function over time were assessed and compared between these two groups.

Two-dimensional transthoracic echocardiography

Transthoracic echocardiography was performed at rest with patients in the left decubitus position using commercially available ultrasound systems (Vivid 7, E9 or System 5, General Electric Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Two-dimensional, M-mode and Doppler data were acquired at the parasternal, apical, subcostal and supra-sternal views according to current recommendations.[10] The echocardiographic data were digitally stored in cine-loop format and data analysis was retrospectively performed using EchoPac (112.0.1, GE Medical Systems, Horten, Norway). LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes were quantified in the apical 2- and 4-chamber views using Simpson's biplane method and LV ejection fraction (LVEF) was calculated.[11] AR grade was assessed using colour, pulsed and continuous wave Doppler recordings and using a multiparametric approach that includes the measurement of the jet width relative to the LV outflow tract width, vena contracta, the pressure half time of the regurgitant flow (if feasible) according to current recommendations.[10] AR was graded as 0 (absent), 1 (mild), 2 (mild-moderate), 3 (moderate-severe) or 4 (severe). Peak and mean aortic valve gradient were obtained from continuous wave Doppler recordings on the apical long-axis of 5-chamber views.

Surgery

After median sternotomy, arterial cannulation was performed in the distal ascending aorta (in elective nondissected pathology and in the absence of dilatation of the distal part of the ascending aorta) or the subclavian or femoral artery (in patients with ascending aorta dissection or dilatation).

For valve-sparing aortic root reconstruction, after resecting the native sinuses of Valsalva, a graft was implanted using the reimplantation technique (modified David procedure) or the remodeling technique (Yacoub technique), as previously described.[12-14] Concomitant procedures (leaflet triangular resection, leaflet resuspension and plication of the free edge of the leaflet) were performed if needed. In addition, concomitant aortic arch replacement was performed if the luminal diameter at this level was >45 mm or – in cases of dissection – a (re)entry tear was present in the arch.

For AVR using the Freestyle stentless bioprosthesis, the coronary buttons were mobilized and the sinuses of Valsalva and the aortic valve were excised. The bioprosthesis was then implanted, usually with a 120 degrees clockwise rotation, with interrupted sutures at one

plane at the level of the nadir of the sinus. Thereafter the coronary buttons were reattached to the bioprosthesis.[15]

Follow-up

Patients underwent transthoracic echocardiography postoperatively before discharge and at follow-up (at the discretion of the treating cardiologist).

Statistical analysis

All data analyses were performed using SPSS software version 20 (SPSS, Chicago, IL). Continuous variables were reported as mean ± standard deviation or as median and interquartile range (IQR) and categorical variables were reported as numbers and percentages. Differences between patients who underwent AVr and those who underwent AVR-F were analysed using the unpaired Student's *t*-test, Mann-Whitney U test or a chi-square test. Linear mixed model analysis was used to assess the differences in change in LV dimensions and function over time between the two groups. Type of surgery (AVr or AVR-F) and moment of transthoracic echocardiography (preoperative, postoperative or late follow-up) were incorporated in the model as fixed variables as well as the interaction between type of surgery and moment of transthoracic echocardiography. An unstructured covariance matrix was applied. The estimated marginal means ± standard error of the mean were presented. All statistical tests were two-sided. A p-value<0.05 was considered statistically significant.

Results

A total of 226 patients (mean age 54.7±14.3 years, 63% men) who underwent aortic root and valve surgery because of aortic regurgitation or aortic root pathology were evaluated. AVr was performed in 135 patients. The remaining 91 patients underwent AVR-F. The clinical characteristics of both groups of patients were comparable (Table 1). In the AVR-F group, the number of patients with bicuspid aortic valve was significantly higher than in the AVr group. There were no differences in number of elective surgeries and the surgical risk was comparable between groups. There were no differences in the number and type of concomitant surgeries performed in both groups. The surgical techniques are summarized in Table 1.

Surgical outcome

There were 5 in-hospital deaths, 2 (1%) in the AVr group and 3 (3%) in the AVR-F group (p=0.654). Perioperative complications were comparable between both groups. Postoperative bleeding with cardiac tamponade was treated by pericardiocentesis in 20 (15%) AVr and 9 (10%) AVR-F patients (p=0.377) and/or by resternotomy in 17 (13%) and 8 (9%) patients,

respectively (p=0.498). Thromboembolic complications occurred in 14 (10%) AVr patients and 4 (4%) AVR-F patients (p=0.169). Postoperative atrial fibrillation or flutter was present in 47 (35%) AVr and 32 (35%) AVR-F patients (p=1).

Table 1. Baseline characteristics.

	AVr (n=135)	**AVR-F (n=91)**	**p-value**
Age (years)	54.4 ±13.8	55.2 ±15.0	0.65
Male	83 (61%)	59 (65%)	0.71
Smoking	37 (27%)	18 (20%)	0.30
Diabetes Mellitus	6 (4%)	8 (9%)	0.29
Hypertension	56 (41%)	33 (36%)	0.54
Dyslipidaemia	19 (14%)	20 (22%)	0.09
NYHA functional class			0.47
I	58 (43%)	38 (42%)	
II	45 (33%)	28 (31%)	
III	19 (14%)	14 (15%)	
IV	6 (4%)	9 (10%)	
Creatinine clearance (ml/min)	93.6 ± 34.7	97.2 ± 36.8	0.47
EuroSCORE II (%)	4.3 ± 5.3	5.7 ± 8.9	0.14
Bicuspid aortic valve	22 (16%)	35 (38%)	<0.001
Elective surgery	96 (71%)	64 (70%)	1
Mitral valve surgery	25 (19%)	13 (14%)	0.51
Tricuspid valve surgery	14 (10%)	7 (8%)	0.66
CABG	19 (14%)	12 (13%)	1
Valve-sparing aortic root repair technique			
None	5 (4%)		
Restoration STJ	46 (34%)		
David	68 (50%)		
Yacoub + Hemi-Yacoub	16 (12%)		
Additional aortic cusp repair	21 (16%)		

Data are presented as mean ± standard deviation or as number (percentage). CABG: coronary artery by-pass grafting. EuroSCORE: European System for Cardiac Operative Risk Evaluation. NYHA: New York Heart Association; STJ: sinotubular junction

Valvular hemodynamics after AVr versus AVR-F

In the entire cohort, the median echocardiographic follow-up duration was 46 months (IQR: 17 to 78 months). The median echocardiographic follow-up duration was 49 months (IQR: 18 to 76 months) in the AVr group and 34 months (IQR: 12 to 83 months) in the AVR-F group (p=0.697). The AR grade over time is displayed in Figure 1. In the AVr group, 44% of the patients had preoperatively grade 3 or 4 AR, compared to 47% in the AVR-F group (p=0.81). Immediately after surgery, 99% of the patients in the AVR-F group had grade <2 AR, compared to 83% in AVr group (p = 0.002). During follow-up, the percentage of AR grade 3 and 4 was similar between groups (AVr: 8% vs. AVR-F: 7%, p=1).

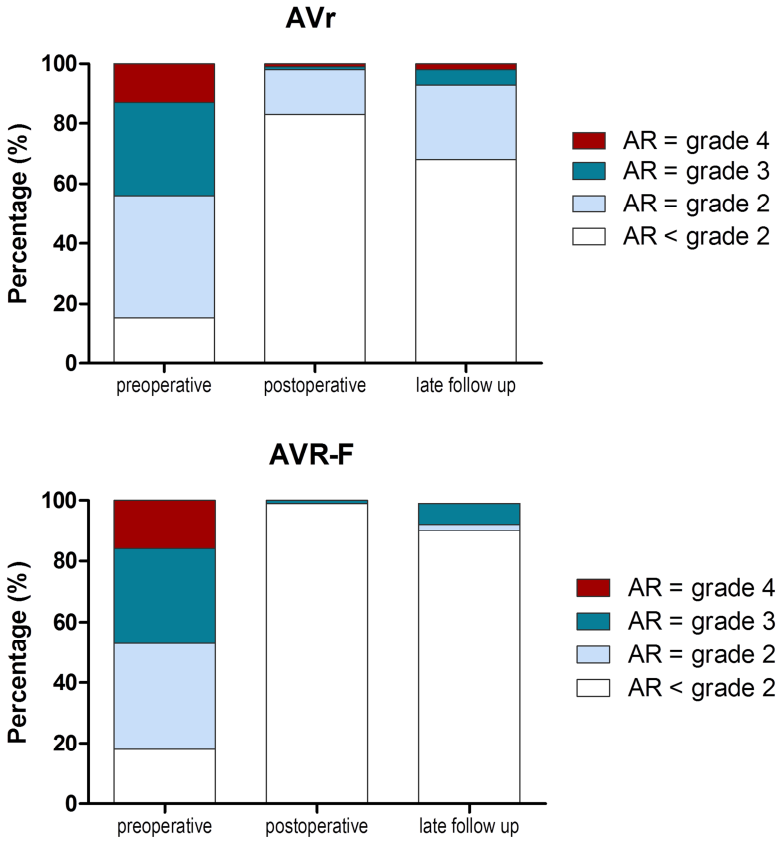

Figure 1. Aortic regurgitation grade over time
Displayed as percentages per group in AVr and AVR-F. AR: aortic regurgitation.

The peak and mean aortic valve gradients over time are displayed in table 2. The peak aortic valve gradient was preoperatively and postoperatively lower in the AVr group compared to the AVR-F group. At late follow-up, there was no significant difference in peak aortic valve gradient between the two groups. The mean aortic valve gradient in the AVr group remained stable over time. In the AVR-F group, the mean aortic valve gradient was slightly higher before surgery as well as after surgery compared to the AVr group. There was a significant difference in peak and mean gradients over time between the groups (p=0.002 and p=0.005, respectively).

LV reverse remodeling after AVr versus AVR-F

Table 2 summarizes echocardiographic characteristics of patients undergoing AVr and AVR-F at baseline, immediately postoperatively and during follow-up. Patients treated with AVR-F showed significantly larger LVEDV and LVESV at baseline compared with patients undergoing

Table 2. Echocardiographic characteristics.

	AVr (n=135)	AVR-F (n=91)	p-value
Peak aortic valve gradient (mmHg)			
Preoperative	11.2 ± 0.7	18.9 ± 1.1	<0.001
Postoperative	11.5 ± 0.6	15.1 ± 1.0 *	0.01
Late follow-up	17.9 ± 7.1	14.1 ± 1.6 *	0.83
Mean aortic valve gradient (mmHg)			
Preoperative	6.4 ± 0.4	10.7 ± 0.6	<0.001
Postoperative	6.6 ± 0.3	8.4 ± 0.6 *	0.04
Late follow-up	5.8 ± 0.3	8.2 ± 1.1	0.002
LVEDD (mm)			
Preoperative	53.4 ± 0.9	56.1 ± 1.2	0.20
Postoperative	47.2 ± 0.7 *	48.5 ± 0.9 *	0.61
Late follow-up	49.2 ± 0.8 *†	48.7 ± 1.2 *	0.91
LVESD (mm)			
Preoperative	36.1 ± 0.9	37.0 ± 1.2	0.75
Postoperative	34.3 ± 0.8	35.9 ± 1.0	0.41
Late follow-up	33.0 ± 0.9 *	32.2 ± 1.2 *†	0.66
LVEDV (ml)			
Preoperative	125.9 ± 4.8	156.5 ± 6.4	0.002
Postoperative	109.9 ± 3.7 *	116.3 ± 4.8 *	0.36
Late follow-up	112.3 ± 4.0 *	117.0 ± 6.6 *	0.65
LVESV (ml)			
Preoperative	59.0 ± 3.4	75.0 ± 4.3	0.045
Postoperative	56.6 ± 3.0	60.1 ± 3.7 *	0.56
Late follow-up	51.0 ± 2.7 *	56.4 ± 4.8 *	0.43
LVEF (%)			
Preoperative	55.1 ± 1.0	54.0 ± 1.0	0.86
Postoperative	50.9 ± 1.0 *	50.9 ± 1.1 *	0.99
Late follow-up	56.5 ± 0.9 †	54.8 ± 1.4 †	0.34

*Data are presented as estimated marginal means ± standard error of the mean. Within groups: * p<0.05 vs preoperative, † p<0.05 vs. postoperative. LVEDD: left ventricular end-diastolic diameter, LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume.*

AVr. However, LVEF was comparable between the two groups. Figure 2 illustrates the changes in LV volumes and function over time. In the AVr-group there was a significant decrease in LVEDV acutely after surgery and remained stable at long-term follow-up. In contrast, LVESV remained unchanged immediately after surgery and reduced significantly at long-term follow-up. LVEF decreased significantly postoperatively but normalized at long-term follow-up. In patients who underwent AVR-F, LVEDV and LVESV showed a significant reduction immediately after surgery and remained stable at long-term follow-up. Similarly to the group of patients undergoing AVr, LVEF decreased significantly after surgery and normalized later during follow-up.

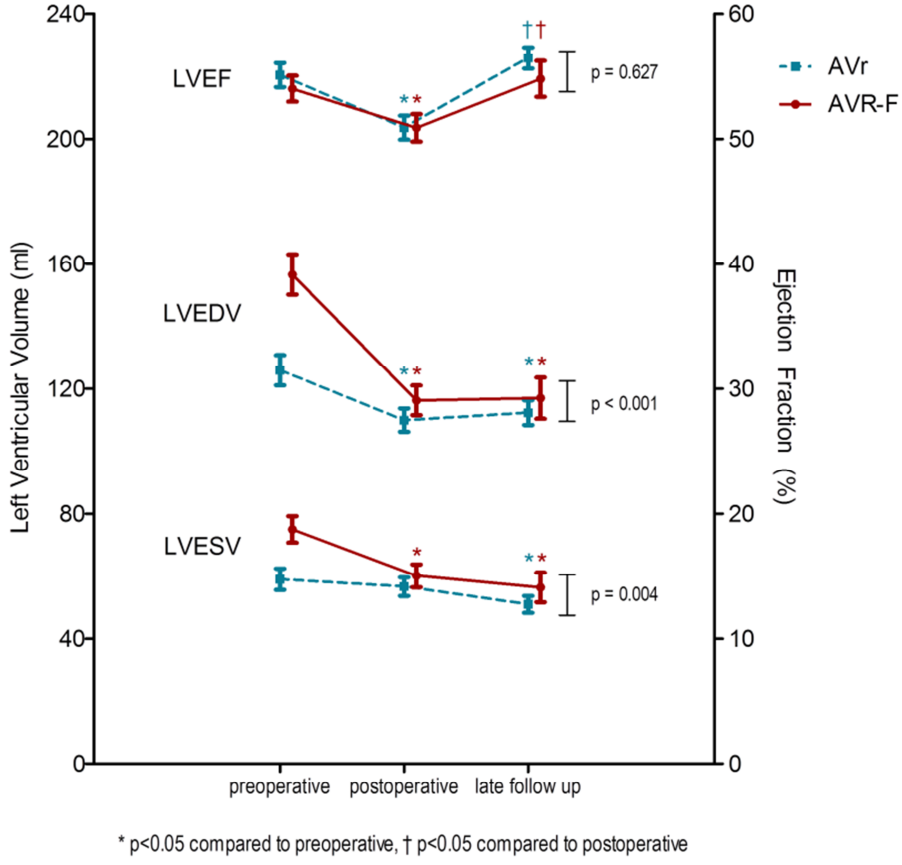

Figure 2. Left ventricular volumes and function over time in AVr compared to AVR-F.
Data are displayed as estimated marginal means ± standard error of the mean. Group-time interaction p-value is given per variable. LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume.

The change in LVEDV and LVESV was significantly different between groups since the group of patients undergoing AVR-F had significantly larger volumes at baseline compared to the group of patients treated with AVr. In contrast, there were no significant differences in LVEF changes between groups (Figure 2).

Discussion

The present study compared the effect of valve-sparing aortic root reconstruction versus AVR on LV remodeling and function at follow-up. Patients with aortic root pathology and/or AR

who undergo these surgical techniques have long-term freedom of recurrence of AR ≥ grade 3 and show favourable LV reverse remodeling with preserved LVEF during follow-up.
Chronic significant AR leads to volume and pressure overload of the LV which responds with an increase in LV dimensions to maintain LVEF.[16] If left untreated, the compensatory LV remodeling eventually fails and LVEF decreases. Patients with severe AR and LV dilation or dysfunction have poor survival if they remain under medical treatment and consequently current guidelines recommend surgical aortic valve replacement in case of symptoms, LVEF<50% or LV end-diastolic diameter >75 mm or end-systolic diameter >55mm.[17] The surgical technique to use depends on the anatomical characteristics of the aortic valve and aortic root and the experience of the surgeon. Aortic valve repair techniques have shown good outcomes in selected patients. A systematic review of the outcomes of aortic valve repair pooling data from 2,891 patients undergoing aortic valve repair procedures showed an early mortality of 2.6% and a 5-year survival free from aortic valve reintervention and >grade 2 AR of 92% and 88%, respectively.[18] The late mortality was 1.3%/patient-year.[18] However, these results are derived from centers with high experience in aortic valve repair techniques which are continuously evolving. In addition, previous series have not compared aortic valve repair and replacement in terms of LV performance outcomes. In contrast to mitral valve repair for primary mitral regurgitation, with an overwhelming evidence showing the superior outcomes in terms of LV function and remodeling over mitral valve replacement (particularly without preserving the subvalvular apparatus),[9] there is a paucity of data on the LV outcomes of aortic valve repair and replacement techniques.
Changes in LV dimensions and function after AVR for significant AR have been reported in several studies.[19,20] In a series of 40 patients with severe AR, Gentles et al. showed significant decreases in LVEDV and LVESV at 7 ± 2 months after AVR while LVEF remained stable.[20] This decrease in LV volumes can be observed acutely after AVR due to an acute correction of the volume overload with the consequent reduction in LVEF. However, at follow-up, this LV reverse remodeling remains with further reduction in LVESV which results in improvement and sometimes normalization of LVEF.[8,21,22] In 93 patients with severe AR undergoing surgical AVR, Tanoue et al. showed that the LVEF changed from 60.2 ± 11.0% preoperatively to 51.9 ± 14.6% directly postoperative and to 57.9 ± 15.2% at 1 year follow-up.[22] This was accompanied by significant reductions in LVEDV and LVESV that were sustained at 1 year follow-up.
A few series have described changes in LV volumes and function after valve sparing aortic root reconstruction.[23,24] In patients undergoing these surgical techniques, the presence of recurrent, significant AR may theoretically halt the LV reverse remodeling process. However, this has not been described. Leshnower et al. evaluated changes in LV volumes and function in 51 patients undergoing David-V reimplantation technique.[23] The authors reported a significant

decrease in LV end-diastolic and end-systolic diameters during follow-up. Furthermore, LVEF improved from 51 ± 7% to 57 ± 6% during a mean follow-up period of 18 months.
The present study provides further insight into this field by comparing changes in LV volumes and function between patients undergoing AVr and patients treated with AVR-F. Both groups of patients showed significant reductions in LVEDV acutely after surgery and remained stable at follow-up. However, LVESV significantly reduced acutely in the group of patients undergoing AVR-F whereas their counterparts showed a further significant LV reverse remodeling at long-term follow-up. This indicates either a different pattern of LV reverse remodeling that may be associated with the surgical technique, or be related to the larger pre-operative volumes in the AVR-F group. Additional studies including larger number of patients are needed to confirm these results. In addition, similarly to previous series, LVEF reduced immediately after surgery but recovered at long-term follow-up.
The results of the present study demonstrate that a durable repair of the aortic valve in patients with AR or aortic root pathology is associated with beneficial LV reverse remodeling and preserved LVEF at follow-up. LV dimensions and function are important prognostic determinants in patients with significant AR and accordingly, current guidelines recommend AVR when significant LV dilatation or reduced LVEF coexist.[17] Similarly to mitral valve repair for primary mitral regurgitation, the possibility of performing a durable aortic valve repair may impact on current guidelines, recommending aortic valve repair in patients with severe AR who do not have yet a significant damage of the left ventricle (LV dilatation or reduced LVEF). Prospective randomized trials comparing a watchful waiting strategy versus aortic valve repair would provide the evidence to this unmet clinical need.
Some limitations should be acknowledged. The present study was retrospective and non-randomized. The surgeon decided intraoperatively whether AVr was feasible. If not, AVR-F was performed, which may have introduced a selection bias. Furthermore systematic preoperative, postoperative and follow-up echocardiography was not available in few patients. In addition, the duration of significant AR before surgery was not recorded. This may have resulted in higher preoperative LV volumes in the AVR-F group which may have the effect of more impressive LV reverse remodeling postoperatively. This study compared the Freestyle stentless aortic root bioprosthesis with a valve sparing technique. Similar results may not occur with stented bioprosthetic or mechanical valves as the replacement technique.

Conclusion

In conclusion, LV reverse remodeling occurs both after aortic valve replacement and repair and comparable LV volumes and function are reached during a median follow-up of 4 years.

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Chapter 9:

Comparison of left ventricular volume and ejection fraction and frequency and extent of aortic regurgitation after operative repair of type A aortic dissection among three different surgical techniques

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Abstract

Background: Differences in recurrence rate of aortic regurgitation (AR) and extent of left ventricular (LV) remodeling across the different surgical options in patients operated for type A aortic dissection remain unknown. The present evaluation compared the AR recurrence rate and changes in LV volumes and systolic function among valve-sparing aortic root replacement (VSAR), supracoronary ascending aorta replacement (SCAR) and aortic valve and root replacement (AVAR).

Methods: A total of 97 patients (58±12 years, 62% men) with acute type A aortic dissection who underwent VSAR (n=24), SCAR (n=43) or AVAR (n=30) were evaluated. Changes in LV volumes and function between postoperative and follow-up were compared using linear mixed models.

Results: Postoperative AR grades were not significantly different between groups. However after median follow-up of 47 months, AR grade ≥2 was significantly more often observed in SCAR (55%) and VSAR (25%) compared to AVAR (0%, p<0.001). LV volumes remained stable in VSAR and AVAR but increased significantly in SCAR (LV end-diastolic volume: from 99±4 to 131±6 ml; p<0.001; LV end-systolic volume: from 49±3 to 66±5 ml; p=0.002). Among patients with recurrent AR grade ≥2 at follow-up, LV volumes increased whereas patients without recurrent AR did not show significant LV dilatation.

Conclusion: Patients with acute type A aortic dissection who underwent SCAR or VSAR showed more frequently AR grade ≥2 recurrence compared to AVAR. However, only patients who underwent SCAR experienced adverse LV remodeling at follow-up. Recurrence of AR grade ≥2 was associated with adverse LV remodeling.

Introduction

Acute type A aortic dissection is a life-threatening condition with 50% mortality within the first 48 hours if left unoperated.[1] Resection of the primary intimal tear, stabilization of the aortic wall and prevention of aortic rupture are the surgical goals and can be achieved by performing a valve-sparing aorta replacement (VSAR), supracoronary ascending aorta replacement (SCAR) or aortic valve and aorta replacement (AVAR).[2] Previous studies showed no difference in perioperative and mid-term survival between these surgical procedures.[3,4] However, SCAR is associated with dilatation of the aortic sinuses and recurrence of aortic regurgitation (AR) at follow-up which may warrant a relatively high risk on reoperation.[1,5] Furthermore, recurrence of AR at follow-up may lead to left ventricular (LV) dilation and systolic dysfunction. However, the effects of the type of surgery for acute type A aortic dissection on LV volumes and function during follow-up have not been evaluated. The aim of the present study was to assess differences in LV remodeling during follow-up for the several surgical procedures in patients with acute type A aortic dissection taking into consideration the differences in AR recurrence rates.

Methods

Patients

Patients with acute type A aortic dissection who underwent surgery at the Leiden University Medical Center between 1 July 1994 and 1 July 2013 and who survived the initial hospitalization were evaluated. Patients were included if postoperative transthoracic echocardiography was available. Ninety-seven patients were divided into three groups according to the surgical procedure performed: VSAR (n=24), SCAR (n=43) or AVAR (n=30). Patients with connective tissue disease were excluded.

Clinical and surgical characteristics were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. LV volumes and function were evaluated with two-dimensional transthoracic echocardiography postoperatively and during follow-up (≥6 months after surgery, available in 53 patients). The institutional ethical committee approved this retrospective study and waived the need for informed consent in patients followed in the Leiden University Medical Center. Written informed consent was obtained when patients were followed in the referral hospital. Changes in LV volumes and function over time were assessed and compared between the three different surgical procedures. In addition, the incidence of recurrent AR over time was assessed.

Two-dimensional transthoracic echocardiography

Transthoracic echocardiography was performed with commercially available ultrasound systems (Vivid 7, E9 or System 5, General Electric Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. The echocardiographic data were digitally stored in cine-loop format and data analysis was retrospectively performed using EchoPac (112.0.1, GE Medical Systems, Horten, Norway). LV volumes were quantified at end-diastole and end-systole in the apical 2- and 4- chamber views using the Simpson's biplane method and LV ejection fraction was calculated.6 AR grade was assessed using a multiparametric approach that included the measurement of the jet width relative to the LV outflow tract width, vena contracta and/or the pressure half time of the regurgitant flow (if feasible) according to current recommendations.[7]

Surgery

The decision to perform VSAR, SCAR or AVAR was left at the discretion of the surgeon on duty. During VSAR, the native sinuses of Valsalva were resected and a graft was implanted using the reimplantation technique (modified David procedure, n=19) or the remodeling technique (Yacoub technique, n=5), as previously described.[8,9] Concomitant procedures (leaflet triangular resection, leaflet resuspension and plication of the free edge of the leaflet) were performed if needed. For SCAR, the ascending aorta was resected until the sinotubular junction and replaced by a Hemashield tubular graft.[10] If necessary, resuspension of the commissures (n=15) and/or restoration of the sinuses of Valsalva using bioglue (n=24) or gelatin-resorcin-formalin glue (n=5) was performed.[11] During AVAR, the native sinuses of Valsalva and valve were excised and replaced by either a biological (n=18) or mechanical prosthesis (n=12).[12,13] In every patient the distal ascending aorta and arch were inspected under deep hypothermic circulatory arrest. If a (re)entry tear was present in the arch, concomitant (hemi-)arch replacement was performed.

Follow-up

All patients underwent transthoracic echocardiography postoperatively before discharge. Transthoracic echocardiography at follow-up was performed at the discretion of the treating cardiologist. Follow-up echocardiography was available in 53 patients and was included in the present study when it was performed at least 6 months after surgery. The median echocardiographic follow-up duration was 47 months (interquartile range: 18-76 months) and comparable between the 3 groups (VSAR: 49 months, interquartile range: 19-74 months. SCAR: 55 months, interquartile range: 31-77 months. AVAR: 24 months, interquartile range: 12-56 months; p=0.150).

Statistical analysis

Data analysis was performed using SPSS software version 20 (SPSS, Chicago, IL). Continuous variables were reported as mean±standard deviation or median and interquartile range (IQR) when appropriate. Categorical variables were reported as numbers and percentages. Differences between the 3 different surgical procedures were analysed using analysis of variance test, Kruskall-Wallis test or Chi-square test. Survival and freedom from reoperation were analyzed using the Kaplan-Meier curves and differences among surgical procedures were assessed with the log-rank test. Linear mixed model analysis was used to assess the differences in change in LV volumes and LV ejection fraction over time among the groups. Type of surgery (VSAR, SCAR or AVAR) and timing of transthoracic echocardiography (postoperative or late follow-up) were incorporated in the model as fixed variables as well as the interaction between type of surgery and timing of transthoracic echocardiography. An unstructured covariance matrix was applied. The estimated marginal mean ± standard error of the mean was presented. Post-hoc analyses were performed using the Bonferroni test to correct for multiple comparisons. Subgroup analysis was performed to compare LV remodeling in patients with and without recurrent AR grade ≥2. All statistical tests were two-sided. A p-value<0.05 was considered statistically significant.

Table 1. Baseline clinical and surgical characteristics.

	VSAR (n=24)	**SCAR (n=43)**	**AVAR (n=30)**	**p-value**
Age (years)	50±7	62±11	58±14	<0.001
Male gender	20 (83%)	22 (51%)	18 (60%)	0.033
Diabetes mellitus	0 (0%)	0 (0%)	2 (7%)	0.087
Hypertension	6 (25%)	26 (60%)	12 (40%)	0.018
Dyslipidemia	0 (0%)	4 (9%)	2 (7%)	0.374
Critical preoperative state	0 (0%)	2 (5%)	2 (7%)	0.460
EuroSCORE II (%)	4.7 (4.1-6.4)	5.3 (3.4-7.2)	6.0 (4.8-8.0)	0.069
Bicuspid aortic valve	1 (4%)	0 (0%)	6 (20%)	0.004
CPB time (min)	267±75	191±48	253±66	<0.001
AoX time (min)	209±66	119±38	178±48	<0.001
Aortic (hemi-)arch replacement	14 (58%)	16 (37%)	15 (50%)	0.299
Mitral valve surgery	0 (0%)	1 (2%)	0 (0%)	0.530
Coronary bypass	0 (0%)	1 (2%)	2 (7%)	0.345

Data are presented as mean ± standard deviation, median (interquartile range) or as number (percentage). AoX time: Aortic cross clamp time. AVAR: Aortic valve and aorta replacement. CPB time: Cardiopulmonary Bypass time. EuroSCORE II: European System for Cardiac Operative Risk Evaluation. SCAR: Supracoronary ascending aorta replacement. VSAR: Valve sparing root replacement.

Results

A total of 97 patients (mean age 58±12 years, 62% men) who underwent emergent surgery for acute type A aortic dissection and survived the index hospitalization were evaluated. Table 1 shows the baseline clinical and surgical characteristics of the patients. Patients who underwent VSAR were significantly younger and more often male than patients who underwent SCAR or AVAR. Hypertension was more often present in patients undergoing SCAR compared to patients treated with VSAR or AVAR. The EuroSCORE II was slightly higher among patients who underwent AVAR compared to VSAR and SCAR. In SCAR, the cardiopulmonary bypass and aortic cross clamp times were significantly shorter compared to VSAR and AVAR.

Survival and reoperation during follow-up

The 5-year survival in this cohort was 91±4% and was not significantly different between the surgical procedures (VSAR: 100%, SCAR: 90±6%, AVAR: 82±10%; log rank p=0.653; Figure 1A). Reoperation at follow-up on the proximal and/or distal thoracic aorta was performed in 2 VSAR, 8 SCAR and 4 AVAR patients. The freedom from reoperation on the proximal and or distal aortic after 5 years follow-up was 86±5% and comparable between the groups (VSAR: 95±5%, SCAR 83±8%, AVAR: 77±13%; log rank p=0.516; Figure 1B).

However, when considering only reoperation on the proximal aorta, aortic valve replacement was performed in 2 and 7 patients treated initially with VSAR and SCAR respectively, while none of the patients treated with AVAR required reoperation of the proximal aorta. Reasons for reoperation were severe recurrent AR in 7 patients, dilatation of the sinuses of Valsalva without AR in 1 patient and aortic valve stenosis in 1 patient. Therefore, the 5-year freedom from proximal reoperation after SCAR (88±7%) was slightly less favorable compared with VSAR and AVAR (95±5% and 100%, log rank p=0.060; Figure 1C).

Aortic regurgitation after surgery

The prevalence of significant AR directly postoperatively and during follow-up is displayed in Figure 2. Postoperative AR grade ≥2 was present in 13% of patients who underwent VSAR compared to 8% in patients who underwent SCAR and 4% of patients who underwent AVAR (p=0.136). In contrast, at long-term follow-up, there was a significant difference in AR grade between the surgical procedures: in patients who underwent VSAR or SCAR, AR grade ≥2 was observed in 25% and 55% of patients, respectively, whereas none of the patients who underwent AVAR showed AR grade ≥2 (p<0.001).

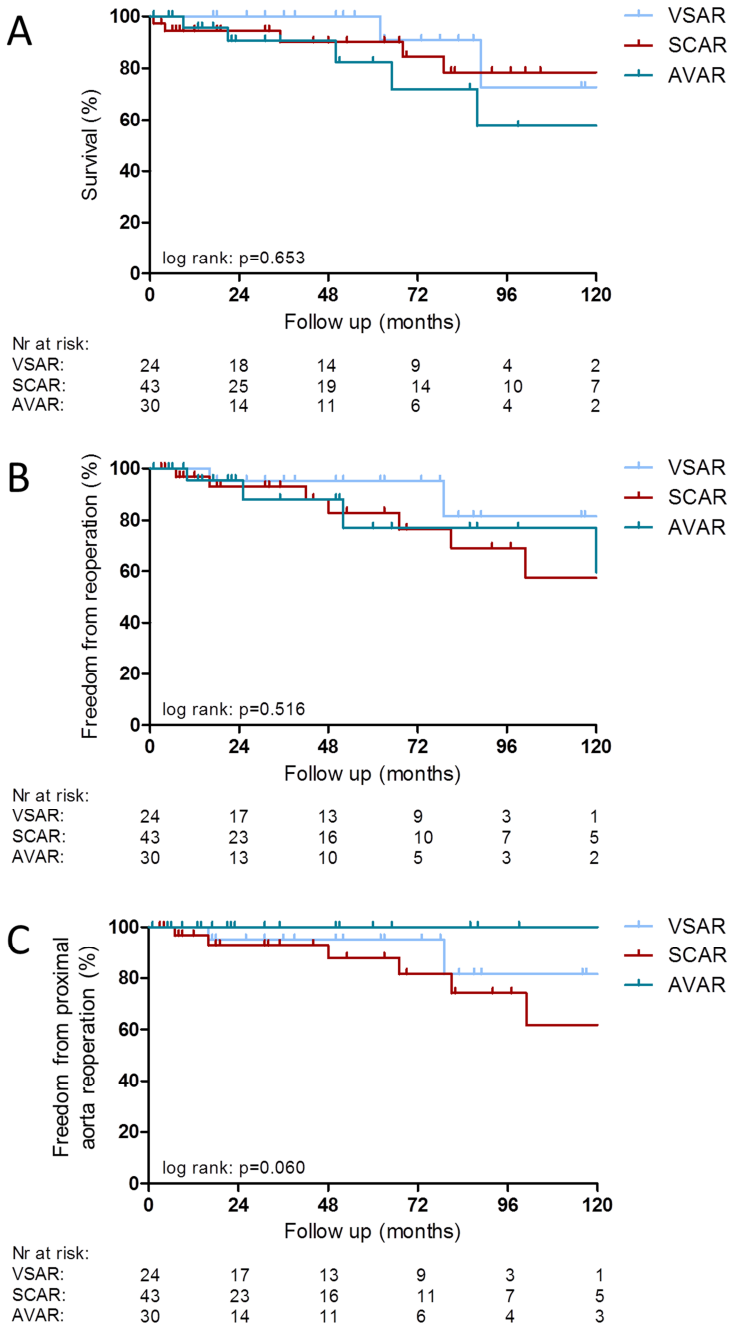

Figure 1. Kaplan-Meier curves for survival, survival-freedom from reoperation and survival-freedom from proximal aorta reoperation.
AVAR: Aortic valve and aorta replacement. SCAR: Supracoronary ascending aorta replacement. VSAR: Valve sparing aorta replacement.

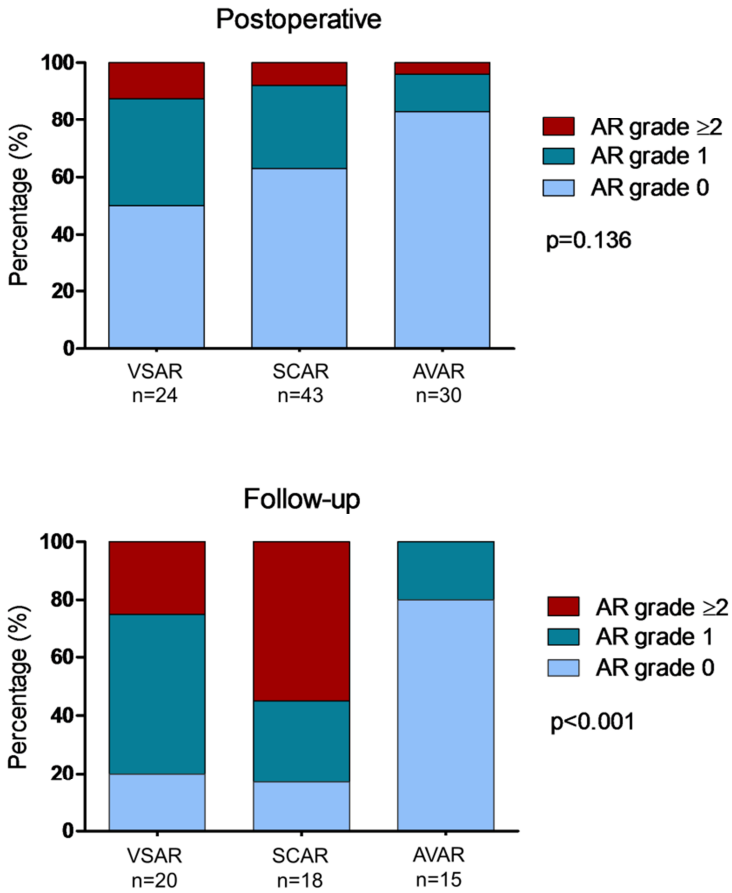

Figure 2. Aortic regurgitation grade postoperatively and during follow-up.
AR: Aortic regurgitation. AVAR: Aortic valve and root replacement. SCAR: Supracoronary ascending aorta replacement. VSAR: Valve sparing root replacement.

LV remodeling after surgery

The immediately postoperative LV end-diastolic volume, LV end-systolic volume and LV ejection fraction were comparable among the 3 groups (Figure 3). However, there was a significant difference in the LV end-diastolic volume and LV end-systolic volume at late follow-up among the surgical procedures. In the VSAR group, the LV end-diastolic volume (108±9 vs. 105±9 ml; p=0.756) and LV end-systolic volume (54±7 ml vs. 47±6 ml; p=0.387) remained stable. In contrast, the LV end-diastolic volume increased during follow-up in SCAR (99±4 vs. 131±6 ml; p<0.001). The LV end-systolic volume also increased significantly in the SCAR group from 49±3 to 66±5 ml (p=0.002). After AVAR, the volumes remained stable.

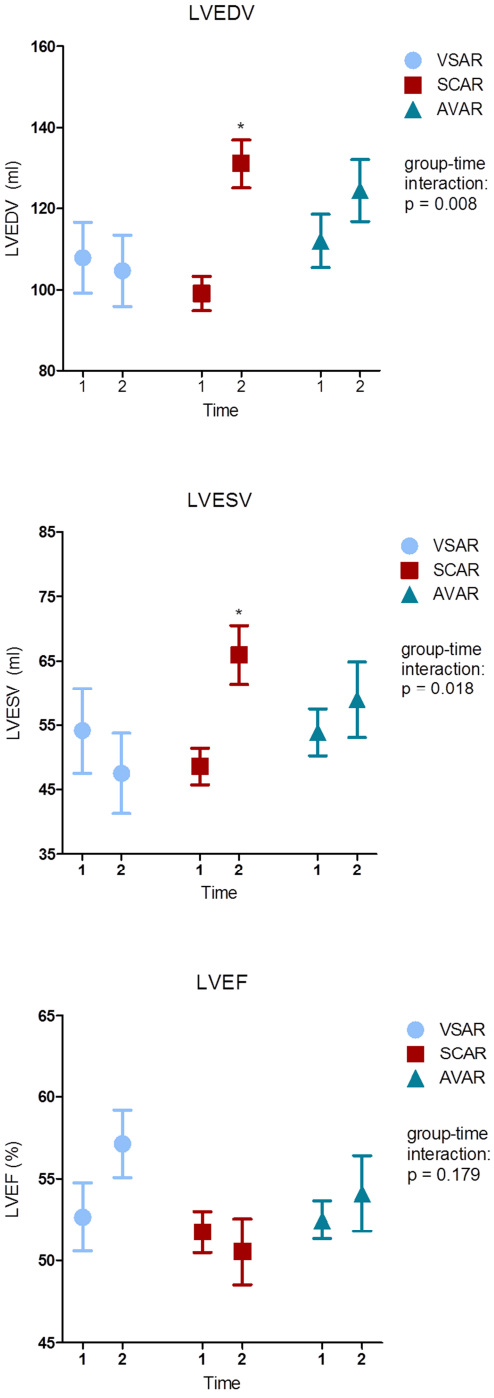

Figure 3. Left ventricular volumes and function over time.

*Left ventricular volumes and function over time in VSAR, SCAR and AVAR. Data are displayed as estimated marginal means ± standard error of the mean. Time 1 represents measurement directly postoperatively and time 2 represents measurement during follow-up. * p<0.05 compared to postoperative. Group-time interaction p-value is given per variable. AVAR: Aortic valve and aorta replacement. LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume. SCAR: Supracoronary ascending aorta replacement. VSAR: Valve sparing aorta replacement.*

The LV ejection fraction tended to improve in VSAR patients (53±2 vs. 57±2%; p=0.074), while it remained stable in both SCAR (52±1 vs. 51±2%; p=0.546) and AVAR (52±1 vs. 54±2%; p=0.489). The group-time interaction effect on LV end-diastolic volume (p=0.008) and LV end-systolic volume (p=0.018) indicated a significant effect of the type of surgery on the change in LV volumes over time.

Effect of recurrent AR on LV remodeling

A subgroup analysis was performed in 53 patients with late follow-up echocardiography available to compare LV remodeling in patients with recurrent AR grade ≥2 versus patients without recurrent AR during follow-up (Table 2). Patients with recurrent AR grade ≥2 experienced significant increase in the LV end-diastolic volume and LV end-systolic volume whereas the LV volumes remained stable in patients without recurrent AR. Furthermore, the LV ejection fraction improved in patients without recurrent AR compared to deterioration in patients with recurrent AR grade ≥2.

Table 2. LV remodeling in patients with and without recurrent aortic regurgitation.

	Recurrent aortic regurgitation		
	No (n=38)	**Yes (n=15)**	**p-value**
LV end-diastolic volume (ml)			0.001
Postoperative	112±6	89±7	
Late follow-up	115±6	132±9*	
LV end-systolic volume (ml)			0.001
Postoperative	55±4	43±5	
Late follow-up	52±4	69±7*	
LV ejection fraction (%)			0.003
Postoperative	53±1	53±3	
Late follow-up	56±1*	49±3*	

*Data are presented as estimated marginal means ± standard error of the mean. Within groups: *p<0.05 vs postoperative, LV: left ventricular.*

Discussion

The main findings of the present evaluation can be summarized as follows: patients who underwent SCAR for acute type A aortic dissection had more adverse LV remodeling and recurrent AR grade ≥2 at follow-up as compared with patients who underwent VSAR or AVAR. Furthermore, recurrent AR grade ≥2 at follow-up was associated with more adverse LV remodeling and deterioration of LV function.

Selection of operative technique in acute type A aortic dissection

Surgical treatment reduces the mortality of acute type A aortic dissection from 90% to 30% and therefore is considered the treatment of choice.[1,14] The optimal operative technique will

depend on the underlying pathophysiology (pre-existing aortopathy associated with connective tissue), extent of the proximal dissection towards the aortic valve, aortic valve competence, aortic annulus dimensions and associated patient's comorbidities. While the SCAR approach is the quickest technique, it is well known that in patients with diseased aortic tissue (i.e. Marfan syndrome), this technique is associated with increased risk of redissection, aneurysm formation and subsequent significant AR because of aortic dilatation (incidence between 25-45%).[15,16] In contrast, AVAR replaces the ascending aorta with a valved tubular graft and has shown excellent results.[3] However, this technique (when performed using a mechanical prosthesis) is associated with the need of lifelong anticoagulation and increased risk of bleeding and thromboembolic complications.[17] Accumulating data have shown the feasibility and safety of the VSAR procedure with excellent results at short- and long-term follow-up.[3,18-20] Although the VSAR procedure is more time-demanding, several registries have shown lower early mortality and similar long-term survival for this technique compared with SCAR and AVAR.[3,18] In addition, VSAR and AVAR resulted in comparable AR recurrence rates.[21] Early mortality is one of the main factors to choose the appropriate surgical technique in patients with acute type A aortic dissection. According to previous series, the 5-year survival of initial hospital survivors is comparable between the 3 surgical procedures ranging between 65%-88% after AVAR, 64%-81% after SCAR and 65%-89% after VSAR.[3,18-20, 22-24] The present study showed comparable 5-year survival rates for each surgical technique. However, the long-term outcomes of the surgical techniques differ significantly among the 3 surgical techniques in terms of reoperation due to aneurysm formation and significant AR recurrence. Similarly to previous series, the present study showed increased risk of reoperation due to significant AR among patients treated with SCAR.[3,5]

However, to date, the effects of recurrent significant AR on LV dimensions and function have not been evaluated. The present study showed significant adverse LV remodeling after SCAR. Furthermore, adverse LV remodeling was present in patient with recurrent AR grade ≥2 compared to stable LV volumes in patients without recurrent AR. Aiming at restoring aortic valve competence and performing a durable repair is an important goal in surgical techniques for acute type A aortic dissection in order to avoid AR recurrence and further deterioration of the left ventricle at follow-up.

Clinical perspective

The present study provides additional information to be taken into consideration when selecting the surgical approach in patients with acute type A aortic dissection. Patients who undergo SCAR benefit from shorter cardiopulmonary bypass and aortic cross clamp times, which is therefore often performed in older patients.[3] However, SCAR is associated with higher rates of AR recurrence, adverse LV remodeling during mid-term follow-up and higher

reoperation rate on the aortic valve and proximal aorta. Therefore, the risk of the initial surgery should be weighed against long-term outcome when selecting the surgical procedure. Whether LV remodeling after surgery for acute type A aortic dissection is associated with worse clinical outcome should be elucidated in future clinical research.

Limitations

Some limitations should be acknowledged. This was a retrospective study with a limited number of patients. Patients who survived the initial hospitalization and who underwent transthoracic echocardiography before discharge were included introducing an important selection bias. The applied surgical technique was not randomly assigned. Preoperative transthoracic echocardiography was not systematically available and therefore preoperative AR grade, LV volumes and LV function, which could be different between the groups, were not included in the analysis. Furthermore, late follow-up echocardiography could only be performed in patients who survived the first 6 months after surgery. The present study was performed in a tertiary care hospital to which patients were referred from other hospitals. Follow-up echocardiograms were performed at the discretion of the treating cardiologist and were retrieved from the referring hospital when possible. Therefore, late follow-up echocardiography was available in only 53 patients of the complete cohort of 97 patients. In addition, computed tomography data of the aorta were not systematically available. The small number of patients limited further multivariate analyses to assess independent predictors of AR recurrence after surgery for acute type A dissection. Furthermore, the impact of changes in LV volumes and function at follow-up on the clinical outcome was not evaluated.

Conclusion

Patients with acute type A aortic dissection who underwent SCAR showed more frequently AR grade ≥2 recurrence which was associated with adverse LV remodeling.

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Chapter 10:

Left bundle branch block after sutureless, transcatheter, and stented biological aortic valve replacement for aortic stenosis

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Abstract

Background: Conventional aortic valve replacement (AVR), sutureless AVR (su-AVR) or transcatheter AVR (TAVI) for severe aortic stenosis (AS) are associated with conduction abnormalities. The aim of the present study was to assess the incidence of left bundle branch block (LBBB) after su-AVR and TAVI, in comparison to conventional AVR.

Methods: A total of 501 patients (mean age 74±8 years, 53% men) without preoperative cardiac conduction disturbances who underwent AVR or TAVI were included.

Results: Su-AVR patients and TAVI patients had a higher incidence of new-onset LBBB at hospital discharge (23% and 16%, respectively) compared to patients treated with conventional AVR (4%; p<0.001). On multivariate logistic regression analyses, type of surgery was independently associated with complete LBBB, taking age, preoperative QRS duration and heart rate into account (su-AVR and TAVI relative to the reference category conventional AVR: odds ratio, 8.5; 95% confidence interval, 3.7-19.5; p<0.001 and odds ratio, 5.8; 95% confidence interval, 2.4 – 14.1; p<0.001, respectively).

Conclusion: Su-AVR and TAVI were associated with higher risk of developing postoperative LBBB compared to conventional AVR, after adjusting for age, preoperative heart rate and QRS duration.

Introduction

Severe aortic stenosis (AS) is the most prevalent valvular heart disease among elderly populations.[1] Selection of type of aortic valve replacement (AVR, surgical versus transcatheter) and type of prosthesis (biological versus mechanical) depends on clinical characteristics and operative risks of the patients.[2] Particularly in the subgroup of elderly patients with symptomatic severe AS, a bioprosthesis is preferred over a mechanical prosthesis in order to minimize the risks of bleeding associated with life-long anticoagulation treatment.[3] The advent of transcatheter aortic valve implantation (TAVI) and the development of sutureless biological prostheses have expanded the therapeutic alternatives in elderly patients with symptomatic severe AS. In high surgical risk patients, several studies have shown comparable mid-term outcomes of transcatheter bioprostheses, sutureless bioprostheses and stented bioprostheses.[4,5] One of the complications that may occur after TAVI and surgical aortic valve replacement (AVR) is new-onset left bundle branch block (LBBB).[6] However, there is a wide range in reported incidences of new-onset LBBB which may be explained by the presence of pre-existing conduction disturbances, position of the prosthesis into the left ventricular (LV) outflow tract and type of prosthesis.[7-10] The aim of the present study was to assess the incidence and factors associated with the development of LBBB after su-AVR and TAVI, in comparison to conventional surgical AVR.

Methods

Patients

Of 682 patients who underwent AVR from 2008 to 2014 at the Leiden University Medical Center (The Netherlands), 501 were considered eligible based on analyzable pre- and postoperative electrocardiograms (ECG) and preoperative transthoracic echocardiography. Patients were divided into three groups, based on the treatment: su-AVR, TAVI or conventional AVR (Figure 1). Clinical characteristics were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Electrocardiography

Standard 12-lead ECG were obtained before and after surgery at the day of hospital discharge. Heart rate, rhythm, heart axis, QRS duration and presence of bundle branch block were assessed. Right bundle branch block (RBBB) was defined as a QRS duration >120 ms in the presence of typical RBBB-morphology (rR' in V1). Left bundle branch block (LBBB) was defined

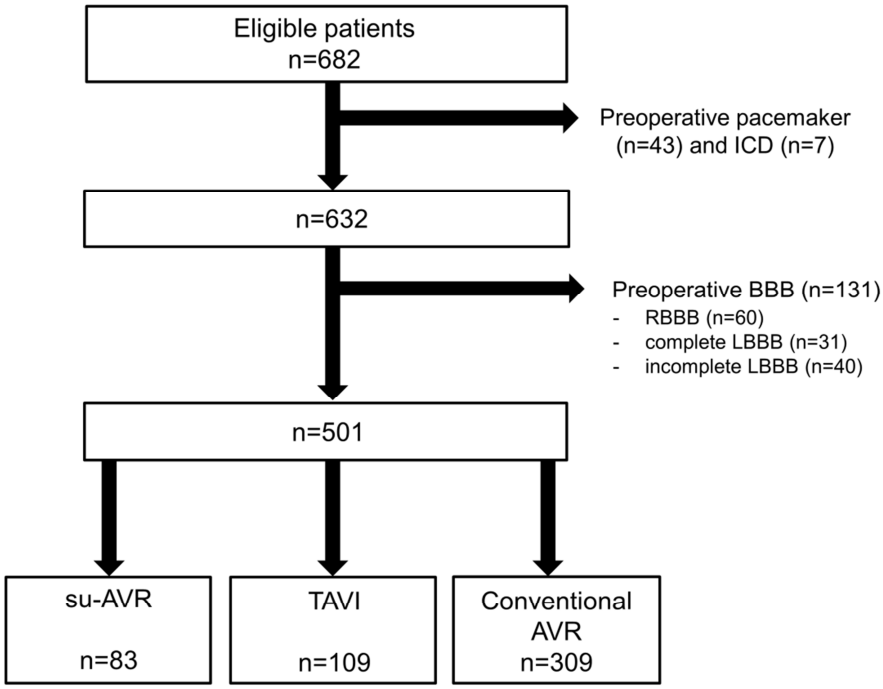

Figure 1. Flowchart of patient inclusion.
AVR: aortic valve replacement; BBB, bundle branch block; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; RBBB, right bundle branch block; su-AVR, sutureless aortic valve replacement; TAVI, transcatheter aortic valve implantation.

as QRS duration >120 ms and QRS complex negative in V1 with a small R or no R. Strict criteria were applied to define complete LBBB (QRS >140 ms in male and >130 ms in female with slurring or notching visible in at least 2 of the following leads: V1, V2, V5, V6, I and aVL).[11]

Two-dimensional transthoracic echocardiography

Preoperative transthoracic echocardiography was performed using commercially available ultrasound systems (System Five, Vivid 7, and E9, General Electric Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Parasternal, apical, subcostal and supra-sternal views were obtained according to current recommendations.[12] The echocardiographic data were digitally stored in cine-loop format and data were retrospectively analyzed using commercially available software (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). Left ventricular (LV) dimensions and ejection fraction (LVEF) were assessed as recommended.[12,13] Preoperative aortic valve function was evaluated using colour Doppler, continuous and pulsed wave Doppler according to current recommendations.[14,15]

Aortic valve replacement and transcatheter aortic valve implantation

Treatment of aortic stenosis (surgical versus transcatheter) was decided based upon heart team discussions. Among patients who underwent surgical AVR, only patients who received a stented bioprostheses were selected in order to minimize heterogeneity and to ensure comparable groups in terms of number of patients. Su-AVR was performed as previously described with Sorin Perceval S valve (Sorin Biomedica Cardio Srl, Sallugia, Italy) or Medtronic 3f Enable valve (Medtronic Inc, Minneapolis, Minnesota).[16]

TAVI was performed according to current recommendations.[17] Only patients who underwent TAVI via the transfemoral approach were included to minimize heterogeneity. Balloon valvuloplasty was performed under rapid right ventricular pacing prior to transfemoral implantation of a balloon-expandable prosthesis (Edwards SAPIEN valve, Edwards Lifescienes Corp, Irvine, California) or self-expandable prosthesis (Medtronic CoreValve, Medtronic Inc, Minneapolis, Minnesota). Figure 2 shows schematically the position of the different implanted prostheses in relation to the conduction system, in particular the left bundle branch.

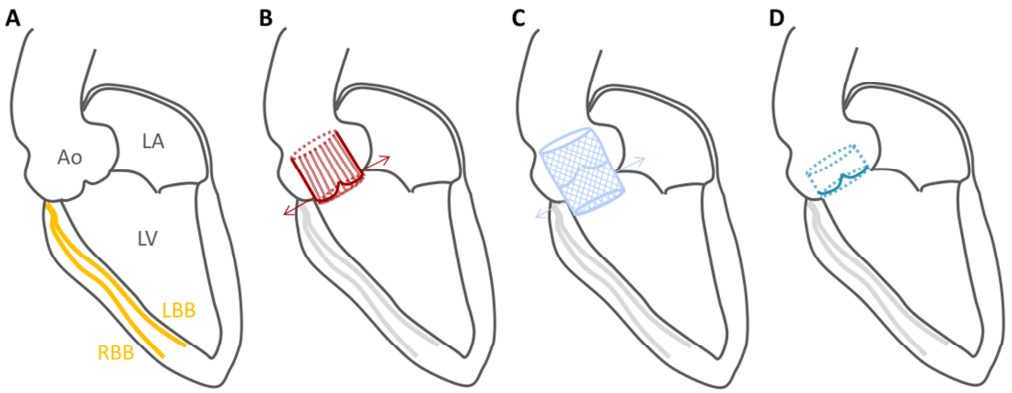

Figure 2. Schematic overview of prosthesis implantation.
A: a 3-chamber view with the bundle branches. The su-AVR prosthesis (B) and TAVI prosthesis (C) were placed intra-annular. The conventional stented AVR prosthesis (D) was placed supra-annular. Ao, aorta; LA, left atrium; LBB, left bundle branch; LV, left ventricle; RBB, right bundle branch

Statistical analyses

All data analyses were performed using the SPSS software (Version 20.0. Armonk, NY: IBM Corp). Continuous variables were reported as mean ± standard deviation or median and interquartile range, as appropriate. Categorical variables were reported as counts and percentages. Differences were analysed using ANOVA or Kruskal Wallis tests and chi-square test. Linear mixed model analysis was performed to compare changes in heart rate and QRS

duration over time between the three groups. Type of surgery and time of ECG were incorporated in the model as fixed variables. An unstructured covariance matrix was applied. The estimated marginal means ± standard error of the mean were presented.
Logistic regression analysis was performed to assess baseline factors associated with postoperative complete LBBB. All variables with p-value <0.1 on univariate logistic regression analysis were included in the multivariate model. The odds ratio and 95% confidence interval were calculated. All statistical tests were two-sided. A p-value <0.05 was considered statistically significant.

Results

A total of 501 patients (mean age 74±8 years, 53% men) were included in the present analysis. Patients who underwent conventional AVR were significantly younger and more often male compared to su-AVR and TAVI groups. Preoperative characteristics are shown in Table 1.

Table 1: Baseline characteristics

	su-AVR (n=83)	**TAVI (n=109)**	**Conventional AVR (n=309)**	**p-value**
Age (years)	77±5	80±7	71±8	<0.001
Male gender	29 (35%)	49 (45%)	189 (61%)	<0.001
Body surface area (m^2)	1.88±0.20	1.87±0.21	1.95±0.21	0.001
Hypertension	58 (70%)	78 (72%)	179 (58%)	0.014
Dyslipidaemia	55 (66%)	59 (54%)	189 (61%)	0.216
Diabetes	25 (30%)	33 (30%)	72 (23%)	0.230
Smoking	4 (5%)	15 (14%)	5 (2%)	0.024
Coronary artery disease	48 (58%)	63 (58%)	160 (52%)	0.420
Creatinine clearance (ml/min)	66±20	61±21	76±26	<0.001
LV end-diastolic diameter (mm)	45±6	45±8	47±8	0.019
LV end-systolic diameter (mm)	28±7	29±9	29±9	0.631
LV ejection fraction (%)	59±11	57±10	58±9	0.302
LV mass indexed (m^2)	118±30	133±41	141±47	<0.001

Continuous variables were reported as mean ± standard deviation. Categorical variables were reported as counts and percentages. AVR: aortic valve replacement; LV: left ventricular; su-AVR: sutureless aortic valve replacement; TAVI: transcatheter aortic valve implantation.

Surgical characteristics

Su-AVR was performed with the Medtronic 3f Enable valve in 68 patients (82%) and with the Perceval S valve in 15 patients (18%). TAVI was performed in 86 patients (79%) with Edwards SAPIEN valve and in 23 patients (21%) with Medtronic CoreValve. Conventional AVR was performed with stented bioprostheses: Carpentier-Edwards Perimount Magna valve (Edwards Lifesciences, Irvine, California) in 111 patients (36%), the Hancock valve (Medtronic Inc, Mineapolis, Minnesota) in 182 patients (59%) and the St Jude Medical Trifecta valve (St Jude Medical, St Paul, Minnesota) in the remaining 16 patients (5%). The size of the prosthesis was

significantly different between the three surgical techniques, the mean size in su-AVR patients was 23.5±2.0, in TAVI patients 25.9±2.2 and in patients undergoing conventional AVR 24.5±1.8 (p<0.001).

ECG changes after AVR

Table 2 shows the ECG parameters pre- and postoperatively at hospital discharge. Postoperative ECG was performed 3 (interquartile range: 2-4) days after TAVI compared to 6 (interquartile range: 5-8) days after su-AVR and 6 (interquartile range: 5-8) days after conventional AVR (p<0.001). The heart rate increased significantly after intervention in all three groups. The majority of the patients were in sinus rhythm (85%) before surgery. After surgery, the percentage of patients with atrial fibrillation increased to 17%, 17 patients showed atrial arrhythmia or junctional rhythm and 11 patients showed paced rhythm.
The QRS duration increased significantly in all three groups after AVR. In addition, at hospital discharge, the QRS duration differed significantly between groups. Postoperatively, complete LBBB was observed significantly more often after su-AVR (23%) and TAVI (16%) compared to conventional AVR (4%; p<0.001). In addition, there were in total 12 patients (2%) with a RBBB and 19 patients (4%) with incomplete LBBB.

Factors associated with complete LBBB

Type of AVR was significantly associated with complete LBBB on univariate logistic regression analysis. Su-AVR (odds ratio: 8.5; 95% confidence interval: 3.7-19.5; p<0.001) and TAVI (odds ratio: 5.8; 95% confidence interval: 2.4 – 14.1; p<0.001) were independently associated with complete LBBB, after adjusting for age, preoperative rhythm and preoperative QRS duration.

Discussion

The main findings of the present study can be summarized as follows: the incidence of LBBB was 23% at discharge after su-AVR and 16% in TAVI patients, compared to 4% in patients undergoing conventional AVR. Su-AVR patients and TAVI patients more often new-onset complete LBBB, in comparison to patients treated with conventional AVR.

Incidence of LBBB after AVR

The incidence of new-onset LBBB after AVR ranged between 4 and 51% in previous studies.[9,10] Differences in incidence of LBBB can be explained by differences in type of procedure, valve type and follow-up duration. In conventional AVR with a stented bioprosthesis, the incidence of LBBB at hospital discharge was low (4-6%).[10,19,20] In contrast, studies reporting the incidence of LBBB after su-AVR or TAVI have shown considerably higher incidences compared with conventional AVR (39% and about 21%, respectively).[7-9,20-23] In TAVI, the type of valve was an

Table 2: Electrocardiographic parameters preoperative and postoperative.

Preoperative		su-AVR (n=83)	TAVI (n=109)	Conventional AVR (n=309)	p-value
Heart rate (bpm)		70±1	74±1	70±1	0.050
Rhythm					0.027
	Sinus rhythm	72 (87%)	85 (78%)	271 (87%)	
	Atrial fibrillation	11 (13%)	20 (18%)	36 (12%)	
	Other atrial rhythm	0 (0%)	4 (4%)	2 (1%)	
QRS axis		0 (0%)	0 (0%)	0 (0%)	
	Normal				0.543
	Left	74 (89%)	99 (91%)	280 (91%)	
	Right	9 (11%)	10 (9%)	25 (8%)	
QRS-duration (ms)		0 (0%)	0 (0%)	4 (1%)	
Bundle branch block		0 (0%)	0 (0%)	0 (0%)	
Postoperative		**su-AVR (n=83)**	**TAVI (n=109)**	**Conventional AVR (n=309)**	**p-value**
Heart rate (bpm)		81±2	80±1	83±1	0.170
Rhythm					0.021
	Sinus rhythm	62 (75%)	78 (72%)	249 (81%)	
	Atrial fibrillation	18 (21%)	20 (18%)	46 (15%)	
	Other atrial rhythm	3 (4%)	4 (4%)	10 (3%)	
QRS axis		0 (0%)	7 (6%)	4 (1%)	
	Normal				<0.001
	Left	73 (88%)	85 (78%)	288 (93%)	
	Right	10 (12%)	20 (18%)	20 (6%)	
QRS-duration (ms)		0 (0%)	3 (3%)	0 (0%)	
Bundle branch block		0 (0%)	1 (1%)	1 (1%)	
	RBBB	113±2	113±2	102±1	<0.001
	iLBBB				<0.001
	cLBBB	3 (4%)	1 (1%)	8 (3%)	

Continuous variables were analysed using linear mixed models and were reported as mean ± standard error of the mean. Categorical variables were reported as counts and percentages. Other atrial rhythm includes atrial rhythm, atrial flutter and atrial tachycardia. AVR: aortic valve replacement; cLBBB: complete left bundle branch block; iLBBB: incomplete left bundle branch block; RBBB: right bundle branch block; su-AVR: sutureless aortic valve replacement; TAVI: transcatheter aortic valve implantation.

important determinant of new-onset LBBB: Medtronic CoreValve was associated with a higher incidence of LBBB (48-51%) compared with Edwards SAPIEN valve (12-27%).[9,21] The present study showed higher incidence of LBBB in TAVI with Medtronic CoreValve (22%) compared to the SAPIEN valve (14%), although not statistically significant (p=0.555). Studies with longer follow-up duration demonstrated that new-onset LBBB present at hospital discharge was transient in some cases and resolved after months of follow-up. Persistent LBBB was present in only 9% of TAVI patients and 2% of patients treated with conventional AVR.[8,10] Local inflammation, oedema and ischemia of the surrounding tissue following aortic valve implantation may explain the transient nature of acute postoperative LBBB.[24]

Mechanism underlying AVR-induced LBBB

New-onset LBBB after AVR can be related to compression by the prosthesis on the conduction system. The bundle branch initiates at the base of the interleaflet triangle between the non-coronary and right-coronary cusps, located at the aortic annulus.[6] Stented biological prostheses are placed supra-annular whereas the su-AVR and TAVI prostheses are placed intra-annular, close to the bundle branch which may lead to increased risk of damage of the conduction system. Previous studies in TAVI patients showed that a lower implantation depth was associated with new-onset LBBB.[25,26]

Besides the position of the valve, the size of the implanted prosthesis relative to the annulus size is important in the pathophysiology of conduction abnormalities. In su-AVR and TAVI, slight oversizing is necessary to prevent severe paravalvular leakage.[27] However, excessive oversizing can result in increased compression of the conduction system and aortic annulus rupture.[28]

Another factor responsible for the occurrence of LBBB after AVR might be related to the expandable property of the su-AVR and TAVI prostheses. The stented biological prostheses are sutured to the annulus and afterwards, the prosthesis does not generate a radial force that compresses the conduction system. In contrast, the su-AVR and TAVI prostheses are anchored into the aortic root and generate a radial force expansion that may compress the conduction system and lead to conduction abnormalities. Previous studies hypothesized that the nitinol frame of the Medtronic CoreValve, with the unique property of shape memory, is responsible for increased ongoing compression on the conduction system, resulting in more frequent LBBB in comparison to the SAPIEN valve.[28] This may additionally explain the higher incidence of LBBB in su-AVR prostheses mounted in a nitinol frame. However, in a direct comparison between Medtronic CoreValve (with nitinol frame) and SAPIEN XT (with cobalt chromium frame), there was no significant difference in the force posed on the annulus.[29]

Clinical implications

The present study showed a significantly higher incidence of new-onset LBBB after su-AVR and TAVI in comparison to conventional AVR. The present results may impact on the selection of the type of surgery, especially in patients with an intermediate surgical risk. Furthermore, attention should be paid to the sizing and positioning of the prostheses in su-AVR and TAVI to improve outcomes with lower incidences of LBBB. Further technical development of both TAVI valves and sutureless valves and careful implantation of the valve (not too deep into the LVOT) may help to reduce the incidence of LBBB. Additionally, further clinical research should elucidate whether the occurrence of LBBB is transient or persistent and whether it impacts on the postoperative LV systolic function. In particular in older patients with preoperative reduced systolic function, this could be of importance when selecting the type of surgery. It

might influence the need for cardiac resynchronization therapy in patients with an impaired LV function who developed LBBB after AVR. Future studies should analyse which patients are more at risk in developing persistent LBBB and what actions can prevent new-onset LBBB.

Study limitations

The present study was retrospective, with all the inherent limitations of such a study design. The ECG parameters were assessed preoperatively and at discharge, with the strict criteria for complete LBBB.[11] However, ECG follow-up was not systematically performed and, therefore, information on whether LBBB was persistent during long-term follow-up was lacking. The LBBB directly postoperative might have been transient and its clinical implications remain unclear. Because patients were discharged earlier after TAVI, the duration between surgery and postoperative ECG at discharge was shortest in this group compared to su-AVR and conventional AVR, which may resulted in an increased number of transient LBBB among TAVI patients. In addition, both Medtronic Corevalve and Edwards Sapien TAVI were used in the TAVI cohort. The Medtronic Corevalve tended to result in more complete LBBB than the Edwards Sapien valve, however this difference was not statistically significant and therefore both types of valves were included in the present analysis. Results cannot be extrapolated to stentless biological and mechanical prostheses and non-transfemoral TAVI. Furthermore, the present study described the first series of su-AVR patients; therefore the learning curve could be a contributing factor to the relatively high incidence of LBBB. The depth of implant of the three types of prostheses was not evaluated and therefore analyses whether depth of implant influenced the prevalence of new-onset LBBB could not be performed.

Conclusion

In conclusion, su-AVR and TAVI patients developed more frequently postoperative LBBB at discharge, in comparison to patients treated with conventional stented AVR bioprostheses. Su-AVR and TAVI were associated with higher risk on developing postoperative LBBB compared to conventional AVR, respectively, after adjusting for age, preoperative heart rate and QRS duration.

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PART II

Postoperative evaluation of patients

after aortic valve and root surgery

Effects of aortic valve and root surgery on aortic dilation

Chapter 11:

Effect of aortic valve replacement on aortic root dilation rate in patients with bicuspid and tricuspid aortic valves

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Abstract

Background: It remains unclear whether aortic valve replacement (AVR) has an effect on the aortic root dilation rate in patients with bicuspid (BAV) and tricuspid aortic valves (TAV). The present study evaluated the pre- and postoperative annual aortic root dilation rate in BAV and TAV.

Methods: A total of 93 patients (67 ± 11 years, 71% male) who underwent AVR between 2003 and 2013 and had at least 2 pre- and post-operative echocardiographic studies 1 year or more apart were included in this retrospective observational study. The sinus of Valsalva (SOV), sinotubular junction (STJ) and ascending aorta (AAo) were measured in the parasternal long-axis view.

Results: Patients with BAV (n=22) were significantly younger and had less coronary artery disease than patients with TAV (n=71). At all points in time, the aortic root diameters were larger in BAV compared with TAV. Preoperatively, the STJ and AAo grew significantly faster in BAV compared with TAV (STJ: 0.27 vs. 0.04 mm/year; p=0.021 and AAo: 0.42 vs. 0.15 mm/year; p=0.019). After surgery, there were no significant differences in aortic root dilation rates between BAV and TAV (SOV: -0.01 vs. 0.15 mm/year; p=0.096, STJ: 0.08 vs. 0.05 mm/year; p=0.676 and AAo 0.28 vs. 0.35 mm/year; p=0.745).

Conclusion: The annual aortic root dilation rates were significantly higher in BAV compared with TAV before AVR. However, after AVR, aortic root dilation rates were similar in BAV and TAV, suggesting an important role of hemodynamics on aortic root dilation in BAV.

Introduction

Bicuspid aortic valve (BAV) anatomy is associated with increased dilation rate of the aortic root compared to tricuspid aortic valve (TAV) anatomy.[1] Although intrinsic differences in the aortic wall structure due to an underlying genetic substrate may explain the differences in aortic root dilatation over time between patients with BAV and those with TAV,[2] abnormal aortic wall stress distribution in patients with BAV is also an important pathophysiologic mechanism explaining faster aortic root dilation compared with patients with TAV.[3]

Surgical aortic valve replacement (AVR) changes valvular hemodynamics and their impact on aortic wall stress distribution, and therefore, we could hypothesize that after AVR, differences in aortic root dilation rate between patients with TAV and those with BAV would be secondary to the underlying genetic substrate. To date, the evidence characterizing aortic root dilation rate after AVR in patients with TAV and those with BAV is controversial.[4-9] The aim of the present study was to assess the differences in patients with TAV and those with BAVundergoing AVR regarding aortic root diameters and dilation rate before and after AVR.

Methods

Patients

Adult patients with symptomatic moderate and severe aortic valve dysfunction and an aortic root and ascending thoracic aorta of less than 45 mm who underwent AVR between 2003 and 2013 at the Leiden University Medical Center, The Netherlands were considered eligible for the present observational study. Patients should have had 2 preoperative and 2 postoperative transthoracic echocardiograms (TTEs) performed with at least 1 year between each. The last TTE was included as the follow-up TTE. In case of repeated aortic root operations during follow-up, the last TTE before the repeated operation was evaluated. Of 656 patients who underwent AVR and who had a preoperative TTE, 123 patients had 4 echocardiograms (2 preoperative and 2 postoperative) meeting the inclusion criteria. Thirty patients were excluded because of aortic coarctation, connective tissue disease, an aortic root diameter of 45 mm or greater at time of AVR and/or concomitant aortic root or ascending aorta replacement during initial surgery. Patients with aortic root or ascending thoracic aorta 45 mm or greater were excluded because contemporary guidelines consider it reasonable to perform aortic root/ascending aorta replacement in patients with dysfunctional bicuspid aortic valves and an indication for AVR (Class IIaC). [9,10] Patients who underwent other concomitant surgical procedures (coronary artery bypass grafting, mitral valve or tricuspid valve surgery) were not excluded. Clinical and echocardiographic characteristics were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and the echocardiographic database (ImageVault General Electric Healthcare) and retrospectively analyzed. The institutional review board approved this

retrospective study of clinically acquired data and waived the need for patient written informed consent.

Two-dimensional transthoracic echocardiography

TTE was performed using commercially available ultrasound systems (System Five, Vivid 7, and E9, General Electric Healthcare, Vingmed, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Two-dimensional, M-mode and Doppler data were acquired according to current recommendations.[11] The echocardiographic data were digitally stored in cine-loop format and data were retrospectively analyzed using commercially available software (EchoPac 112.0.1, GE Medical Systems, Horten, Norway).

Left ventricular (LV) end-diastolic and end-systolic diameters were measured in the M-mode parasternal long-axis view. LV end-diastolic and end-systolic volumes were measured and LV ejection fraction was calculated in the apical 2- and 4-chamber views according to the Simpson's biplane method.[11]

Preoperative aortic valve function was evaluated using color, continuous and pulsed-wave Doppler. Aortic regurgitation (AR) grade was assessed using a multiparametric approach including the measurement of the jet width relative to the LV outflow tract width and the vena contracta in parasternal and apical views and the pressure half time of the regurgitant flow (if feasible). AR was graded as 0 (absent), 1 (mild), 2 (mild-moderate), 3 (moderate-severe) or 4 (severe).[12] Aortic stenosis (AS) grade was assessed measuring the aortic jet velocity and transaortic mean pressure gradient and calculating the aortic valve area using the continuity equation.[13] Pre- and postoperative aortic root dimensions were measured at and end-diastolic frame in the parasternal long-axis view at 3 predefined levels: (1) the sinuses of Valsalva (SOV), (2) the sinotubular junction (STJ) and (3) the ascending aorta (AAo) 4 cm distal from the aortic valve.[14]

Surgery

After median sternotomy, arterial cannulation of the AAo was performed. Blood cardioplegia was delivered antegrade first into the aortic root and later selectively into the coronary ostia. The AAo was incised and the aortic valve was inspected. The presence of BAV or TAV anatomy was noted in the surgical report. The aortic valve was excised and replaced by mechanical or biological aortic valve prosthesis.

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median and interquartile range (IQR) when appropriate. Categorical variables were reported as numbers and percentages. Continuous and categorical variables were compared with the Student's t-test (or

Mann Whitney U test in non-normally distributed variables) and the chi-square test, respectively.
Repeated-measurement analysis of variance was performed to assess the impact of BAV on the aortic root diameters at each point in time. BAV was incorporated in the model as factor. Estimated marginal means ± standard error of the mean for the aortic root diameters were reported.
The aortic root dilation was assumed to be linear and, therefore linear regression analysis without including an intercept was performed separately in BAV and TAV to assess aortic root dilation in millimeters per year in both groups before and after operation. We included BAV multiplied by follow-up duration in years to assess the difference in dilation of the aortic root between BAV and TAV.[15] All statistical tests were two-sided. A p-value <0.05 was considered statistically significant. Data analyses were performed using IBM SPSS Statistics version 20.0 (SPSS Inc, Chicago, IL).

Results

Ninety-three patients (mean age 67 ± 11 years, 71% men) were included. There were 22 (24%) patients with BAV and 71 (76%) patients with TAV. Of the patients with BAV, 19 patients had fusion of the right and left coronary cusps and 3 patients had fusion of the right and noncoronary cusps. Clinical and echocardiographic characteristics at baseline are presented in Table 1.

Preoperative aortic root dilation rate

The estimated mean duration between baseline and preoperative echocardiographic measurements was 5.5 years. The aortic root diameters at baseline and before operation are displayed in Figure 1 and Table 2. The diameters of the aortic root were significantly larger in patients with BAV compared with patients with TAV at baseline and directly preoperatively. In the entire cohort, the average annual dilation rate of the aortic root was 0.13 mm/year at the SOV level, 0.07 mm/year at the STJ and 0.19 mm/year at the AAo. The preoperative aortic root dilation rate for BAV and TAV patients is displayed in Table 3. The dilation of the STJ and AAo was significantly faster in patients with BAV compared with patients with TAV.

Postoperative aortic root dilation rate

The estimated mean duration between postoperative and late follow-up echocardiographic measurements was 4.1 years. The aortic root diameters after surgery are presented in Figure 2 and Table 2. The diameter of the aortic root remained significantly larger in patients with BAV compared with patients with TAV directly postoperatively and during follow-up. In the entire cohort, the average annual dilation rate of the aortic root was 0.11 mm/year at the SOV level,

Table 1. Baseline clinical, echocardiographic and surgical characteristics.

	BAV (n=22)	**TAV (n=71)**	**p-value**
Age (years)	60±10	69±10	0.001
Male	18 (82%)	48 (68%)	0.310
Body surface area (m^2)	2.01±0.20	1.96±0.21	0.287
Smoking	4 (18%)	12 (17%)	1
Diabetes mellitus	1 (5%)	18 (25%)	0.070
Hypertension	9 (41%)	44 (62%)	0.134
Dyslipidemia	9 (41%)	58 (82%)	0.001
NYHA functional class III/IV	6 (27%)	30 (42%)	0.313
Previous cardiac surgery	1 (5%)	11 (15%)	0.330
Coronary artery disease	7 (32%)	46 (65%)	0.013
LV end-diastolic diameter (mm)	52±9	49±8	0.160
LV end-systolic diameter (mm)	34±10	31±8	0.280
LV end-diastolic volume (ml)	149±70	135±48	0.300
LV end-systolic volume (ml)	69±46	63±36	0.522
LV ejection fraction (%)	56±8	55±9	0.637
Aortic regurgitation			0.677
grade 0	7 (32%)	32 (45%)	
grade 1	4 (18%)	13 (18%)	
grade 2	10 (45%)	21 (30%)	
grade 3	1 (5%)	4 (6%)	
grade 4	0 (0%)	1 (1%)	
Aortic stenosis			0.121
mild	3 (14%)	11 (15%)	
moderate	6 (27%)	35 (49%)	
severe	13 (59%)	25 (35%)	
EuroSCORE II (%)	1.0 (0.8-2.0)	2.3 (1.5-5.5)	<0.001
AVR type			0.195
Biological	14 (64%)	55 (77%)	
Mechanical	8 (36%)	16 (23%)	
AVR size	25.3±2.3	23.9±2.1	0.012
Cardio-pulmonary bypass time (min)	140±58	161±62	0.207
Aortic cross clamp time (min)	112±43	117±48	0.638
Mitral valve surgery	3 (14%)	8 (11%)	1
Tricuspid valve surgery	2 (9%)	5 (7%)	1
CABG	6 (27%)	37 (52%)	0.072

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as number (percentage). AVR: aortic valve replacement; CABG: coronary artery bypass grafting; LV: left ventricular; NYHA: New York Heart Association.

0.06 mm/year at the STJ and 0.33 mm/year at the AAo. Table 3 shows the postoperative aortic root dilation rate for patients with BAV and TAV, which was not significantly different at all levels.

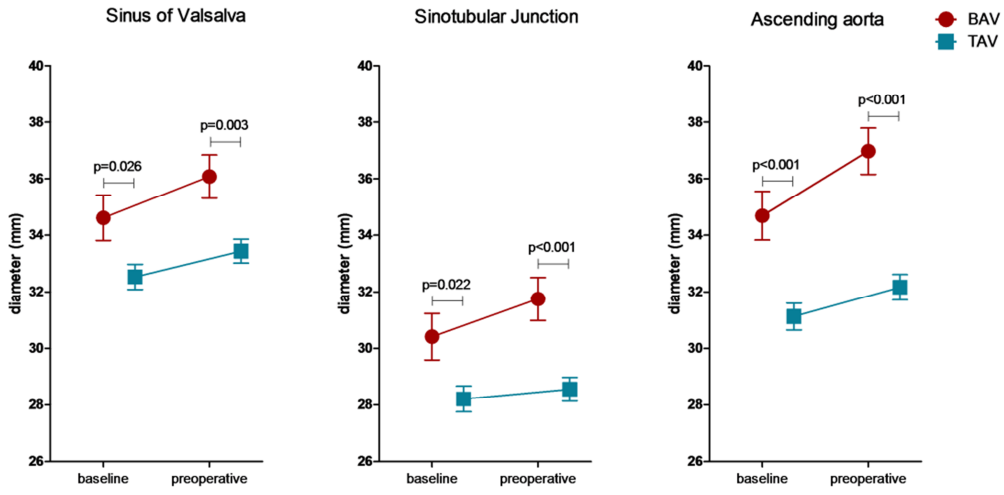

Figure 1. Preoperative change in aortic diameters over time.

Data are presented as estimated marginal mean ± SEM. AAo: ascending aorta, BAV: bicuspid aortic valve, SOV: sinus of Valsalva, STJ: sinotubular junction, TAV: tricuspid aortic valve. Estimation at mean follow-up duration between baseline and preoperative of 5.5 years.

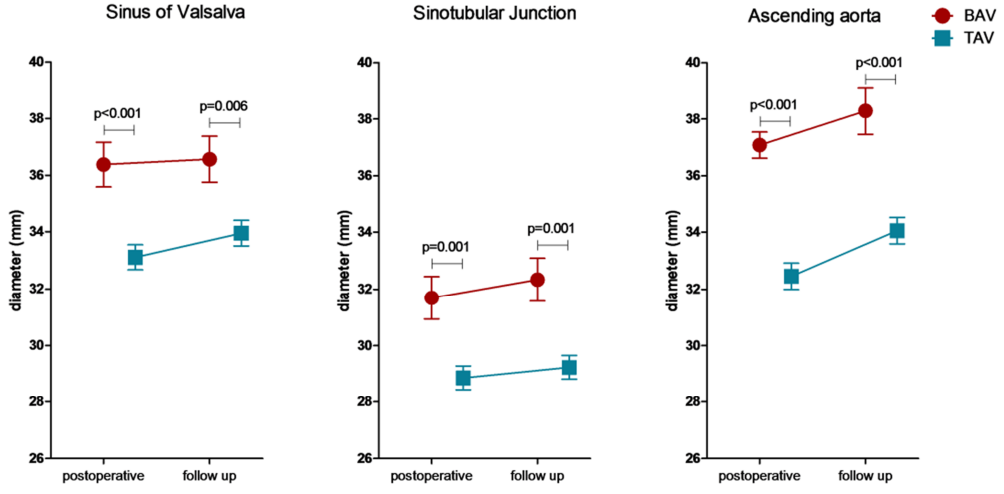

Figure 2. Postoperative change in aortic diameters over time.

Data are presented as estimated marginal mean ± SEM. AAo: ascending aorta, BAV: bicuspid aortic valve, SOV: sinus of Valsalva, STJ: sinotubular junction, TAV: tricuspid aortic valve. Estimation at mean follow-up duration between postoperative and follow-up of 4.1 years.

Table 2. Aortic diameters at baseline, preoperative, postoperative and follow-up.

	BAV (n=22)	TAV (n=71)	p-value
Sinus of Valsalva (mm)			
Baseline	34.6±0.8	32.5±0.4	0.026
Preoperative	36.1±0.8	33.4±0.4	0.003
Postoperative	36.4±0.8	33.1±0.4	<0.001
Follow-up	36.6±0.8	34.0±0.5	0.006
Sinotubular junction (mm)			
Baseline	30.4±0.8	28.2±0.5	0.022
Preoperative	31.7±0.8	28.6±0.4	<0.001
Postoperative	31.7±0.8	28.9±0.4	0.001
Follow-up	32.3±0.8	29.2±0.4	0.001
Ascending aorta (mm)			
Baseline	34.7±0.9	31.1±0.5	<0.001
Preoperative	37.0±0.8	32.2±0.5	<0.001
Postoperative	37.1±0.5	32.5±0.5	<0.001
Follow-up	38.3±0.8	34.1±0.5	<0.001

Data are presented as estimated marginal means and standard error of the mean. BAV: bicuspid aortic valve, TAV: tricuspid aortic valve. Average time between baseline and preoperative TTE is 5.5 years. Average time between postoperative and follow-up TTE is 4.1 years.

Table 3. Average preoperative and postoperative annual dilation rates in mm/year per aortic segment in BAV and TAV.

	BAV		TAV		BAV vs. TAV
	B (95% CI)	p-value	B (95% CI)	p-value	p-value
Preoperative					
SOV	0.24 (0.02-0.46)	0.034	0.11 (0.04-0.19)	0.003	0.207
STJ	0.27 (0.07-0.46)	0.010	0.04 (-0.04-0.11)	0.295	0.021
AAo	0.42 (0.21-0.63)	<0.001	0.15 (0.07-0.24)	0.001	0.019
Postoperative					
SOV	-0.01 (-0.22-0.19)	0.884	0.15 (0.03-0.27)	0.015	0.170
STJ	0.08 (-0.08-0.24)	0.321	0.05 (-0.05-0.15)	0.307	0.790
AAo	0.28 (0.15-0.42)	<0.001	0.35 (0.24-0.46)	<0.001	0.546

Data are presented as regression coefficient (B) and 95% confidence interval (95% CI) indicating annual dilation rates in mm/year. AAo: ascending aorta, BAV: bicuspid aortic valve, SOV: sinus of Valsalva, STJ: sinotubular junction, TAV: tricuspid aortic valve.

Aortic valve hemodynamics

In patients who underwent AVR for severe aortic stenosis, the transaortic mean pressure gradient was 26.7±2.9 mmHg and 22.8±2.0 mmHg at baseline in BAV and TAV, respectively (p=0.273). The transaortic mean pressure gradient was 49.8±3.3 mmHg in patients with BAV and 53.1±2.3 mmHg in patients with TAV at the preoperative TTE (p=0.420). After AVR, in the

overall population, the transaortic mean pressure gradient was comparable immediate after AVR (BAV vs. TAV: 12.5±1.1 vs. 13.0±0.6 mmHg, p=0.702) and during follow-up (BAV vs. TAV: 10.1±1.4 vs. 12.6±0.8 mmHg, p=0.115).

Discussion

The present study shows that patients with BAV had larger aortic roots and significantly faster dilation before surgical AVR compared with patients with TAV. However, in this particular group of patients with BAV, with baseline aortic root diameters <45 mm and who underwent AVR mainly because of severe AS, the aortic root diameters remained relatively stable after AVR and similar to that of patients with TAV.

Aortic root dilation rate before AVR

Before AVR, the dilation rate of the AAo in patients with BAV described in the present study was comparable to previously reported rates. In a study including 353 patients with BAV, Detaint et al showed a dilation rate of the SOV and AAo of 0.21 mm/year and 0.42 mm/year, respectively.[1] In the control group with 51 patients with TAV, these dilation rates were significantly lower (0.09 mm/year and 0.20 mm/year, respectively).[1] In addition, Etz and associates showed an AAo dilation rate of 0.77 mm/year in 116 patients with BAV, which was approximately 5 times higher than age-related AAo dilation for the normal population (0.16 mm/year).[16,17]

Currently there are 2 main hypotheses explaining the relation between BAV and aortic root dilation (aortopathy).[2,3] The first factor which might explain the difference in aortic dilation between BAV and TAV is an underlying genetic substrate. The autosomal dominant inheritance of BAV with reduced penetrance is well documented.[18] In relatives of patients with BAV, 14% had BAV, and of these individuals 67% had associated thoracic aortic aneurysm. Interestingly, 30% of relatives of patients with BAV with normal functioning TAV anatomy also had thoracic aortic aneurysm.[19] Histopathologic studies showed increased smooth muscle cell apoptosis, increased matrix metalloproteinase-9 and lower expression of α smooth muscle actin, smooth muscle 22α, calponin, smoothelin and lamin A/C in aortic wall of patients with BAV.[20,21] Although collagen orientation is almost identical in BAV and TAV, there are some differences in biomechanical properties of the aortic wall that may explain the differences in dilation rate such as decreased wall thickness, lowered aortic distensibility and increased aortic stiffness in patients with BAV.[21-23]

The second hypothesis on the association between BAV and aortic root dilatation is the hemodynamics theory. Recent studies using 4-dimensional flow magnetic resonance imaging have provided more insight into the different hemodynamic burden on the aortic wall caused by flow disturbances.[3,24] In TAV, the flow is directed along the curvature of the aorta. In BAV,

the flow angle is disturbed resulting in different increased wall shear stress, depending on the orientation of the cusps.[3,24] In BAV with fusion of the right and left coronary cusps the flow is directed toward the right anterior, with increased wall shear stress in this region, resulting in aortic root dilation. In BAV, with fusion of the right and noncoronary cusps, the flow is directed higher into the AAo toward the posterior aortic wall resulting in AAo dilation.[3,24]
In addition, these two theories may overlap because increased wall shear stress influences gene expression in the aortic wall.[25] Preliminary clinical data comparing regions with increased and normal wall shear stress in BAV aortas showed increased collagen stiffness and increased transforming growth factor-β_1 and matrix metalloproteinases in regions with increased wall shear stress.[26]

Aortic root dilation rate after AVR
In patients with BAV with an indication for AVR, it is debatable whether concomitant aortic root or AAo replacement, or both, should be performed if the aortic dimensions do not exceed specific cutoff values.[27-29] Current guidelines advise aortic root operations in BAV with aortic root dilation 55 mm or more or 50 mm or more in the presence of additional risk factors (family history, systemic hypertension, coarctation of the aorta or aortic dilation >3mm/year).[30] For patients with an indication for AVR, lower thresholds (>45 mm) can be used for concomitant aortic root and AAo replacement.[30]
If the genetics hypothesis is the only factor determining aortic dilation in BAV, the aortic root dilation rate after AVR would be as high as is was preoperatively. This may result in higher rates of AAo-related complications in operated patients with BAV compared with patients with TAV. However, if the hemodynamics theory were the only factor explaining the different aortic dilation rate between BAV and TAV, once the dysfunctional aortic valve has been replaced, the aortic dilation rate and the risk of adverse aortic events at follow-up would be similar between BAV and TAV. There is conflicting evidence regarding aortic root dilation after AVR. Dayan and colleagues reported that after AVR, the aortic root dimensions remained stable in patients with BAV.[4] Similarly, in a study comparing 143 patients with BAV and 129 patients with TAV undergoing isolated AVR, the aortic dimensions remained stable.[5] Furthermore, Charitos and coworkers compared the aortic dilation rate after AVR in 361 patients with BAV and 87 patients with TAV and observed no significant difference in SOV diameter directly postoperative (difference 0.6±0.5 mm, p=0.2) between BAV and TAV, with comparable postoperative SOV dilation rate (0.13±0.04 mm/year in the entire cohort; difference between BAV and TAV 0.08±0.05 mm/year, p=0.12).[8] Furthermore, the AAo dimensions were slightly larger in patients with BAV compared to those with TAV directly after AVR (difference: 1.2±0.7 mm, p=0.09) whereas the postoperative AAo dilation rate was 0.25±0.05 mm/year in their entire cohort with no significant difference in dilation rate between BAV and TAV.[8] Similar to

the present study, these studies would confirm the role of hemodynamics on the dilation rate of the aortic root and AAo. In contrast, Yasuda and associates showed increased ascending aortic dilation in BAV (0.18 mm/m2/year) compared with regression in aortic size in TAV (-0.08 mm/m2/year; p=0.03) [6], which would confirm the genetics theory.

Study limitations

Several limitations should be acknowledged. This was a small retrospective, single center study in which patients were included when at least 2 preoperative and 2 postoperative TTEs were available. Two-dimensional TTE may underestimate aortic root diameters and is prone for off-axis measurements. In addition, TTE measurements of the aortic diameters, especially at the level of the distal ascending aorta, are challenging and the spatial resolution of TTE is inferior to that of computed tomography or magnetic resonance imaging which may influence on the reproducibility of the measurements.[30] We previously reported the inter-observer and intra-observer variability in aortic root diameter measurements by two-dimensional TTE.[31] Patients with aortic aneurysms 45mm or larger at the time of surgery were excluded; therefore the results of the study cannot be extrapolated to patients with aortic dimensions beyond this cutoff value. Patients with coarctation of the aorta were also excluded since their aortopathy might be of different genesis. Patients with BAV and TAV were different in clinical characteristics such as age and the presence of coronary artery disease which may hamper the comparison between the two groups. The patients included in the BAV group were relatively old (mean age 60 years) and underwent AVR predominantly because of AS. The conclusions drawn from the present study may therefore not be applicable to a younger BAV patient cohort with predominantly AR. Moreover, subanalysis comparing different morphologic types of BAV (fusion of the right and left coronary cusps versus fusion of the right and noncoronary cusps) or different types of valve dysfunction (AR versus AS) was not possible because of the small cohort of patients.

Conclusion

The annual aortic root dilation rates of patients with BAV was significantly higher compared with patients with TAV before AVR. After AVR, there was no significant difference in aortic root dilation rates, indicating that hemodynamics seem to play an important role in aortic dilation. BAV patients who undergo operation in whom the aortic root is not yet dilated should not be treated differently from TAV patients, and regular surveillance after AVR should be similar in both groups of patients.

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Chapter 12:

Prognostic implications of descending thoracic aorta dilation after surgery for aortic dissection

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Abstract

Background: The present study assessed whether descending thoracic aorta growth can be measured reliably on volumetric analysis using multidetector row computed tomography (MDCT) and whether increased growth influences freedom from another aortic intervention in survivors of acute type A aortic dissection.

Methods: A total of 51 patients (58±11 years, 61% male) who underwent surgery for type A aortic dissection DeBakey type 1 with ≥2 postoperative MDCT scans ≥5 months apart were included. Volumetric analysis of the descending thoracic aorta between the left subclavian artery and the level of the apex of the heart was performed with acceptable intraobserver variability. Growth of the complete, false and true lumen was estimated in ml/year and defined as slow growth when it was less than average growth rate and fast growth when it was more than average growth rate.

Results: The complete lumen volume increased from 133±8 ml to 163±9 ml after 3.5 years follow-up ($p<0.001$), with an average growth rate of 6.1 ml/year. The false lumen volume increased from 81±7 ml to 106±12 ml ($p=0.018$) with an average growth rate of 2.8 ml/year. The true lumen changed only slightly from 59±4 ml to 65±8 ml ($p=0.205$). The 5-year freedom from descending thoracic aorta intervention was significantly lower in fast growth of the complete lumen (80±9%) compared to slow growth (100%; $p=0.003$). Similar was true for growth of the false lumen (fast: 74±12% vs. slow: 100%; $p=0.042$).

Conclusion: Increased growth of the false lumen of the descending thoracic aorta after deBakey type 1 aortic dissection was associated with higher risk on secondary intervention on the descending thoracic aorta.

Introduction

Acute type A aortic dissection is a life threatening condition with an incidence of 2.9 per 100 000 patient-years.[1] Emergency surgery is the only option to improve the survival of patients with acute type A aortic dissection.[2] One of the objectives of acute type A aortic dissection surgery is restoration of adequate flow in the true lumen with obliteration, if possible, of the false lumen in the distal aorta.[3] This is particularly important since the presence of a complete patent false lumen (PFL) or only partially thrombosed false lumen (pTFL) is associated with worse outcome, higher reoperation rates and aneurysmal growth.[4-7] Aneurysmal growth has been associated with increased risk of adverse clinical events at follow-up and, accordingly, current guidelines recommend regular surveillance with multi-detector row computed tomography (MDCT) to monitor potential complications and growth of the descending thoracic aorta, especially when the false lumen is not completely thrombosed.[8] Reoperation on the descending thoracic aorta (with open surgery or endovascular stenting procedure) is indicated if aortic rupture or progressive aortic dilation are observed.[4,9] The MDCT data can be used to plan endovascular stenting procedures.[10] In order to reduce the intra- and interobserver variability of manual measurements of serial MDCT of the descending aorta and size of the PFL, automated algorithms to assess these aspects would be the preferred methodology.[11] The present study investigated whether descending thoracic aorta growth can be measured reliably on MDCT data using a semi-automated volumetric method. In addition, descending thoracic aorta growth and patency of false lumen were related to freedom from reoperation on the descending thoracic aorta.

Methods

Patients

Patients with acute type A aortic dissection DeBakey type 1 (dissection progressed distal from ascending aorta) who underwent surgical repair at the Leiden University Medical Center and who survived the initial hospital admission were considered eligible for this study. Fifty-eight patients who underwent postoperative contrast enhanced MDCT surveillance of the thoracic aorta (with ≥5 months elapsed between scans) were included in the present analysis. Clinical and surgical data were collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed. Critical preoperative state was defined as suffering from ventricular tachycardia or ventricular fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before anaesthetic room, preoperative inotropes or intra-arterial balloon pump or preoperative acute renal failure (anuria or oliguria <10ml/hour). The institutional ethical committee approved this retrospective evaluation of clinically acquired data and waived the need for individual written patient consent.

Multi-detector row computed tomography

Contrast-enhanced MDCT studies were performed to evaluate the postoperative status of the thoracic aorta with a 16-, 64-, or 320-slice MDCT scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan). MDCT angiography data acquisition extended from above the aortic arch to the diaphragm, including the entire thoracic aorta. Data analysis was performed by 2 independent observers. First, the false lumen of the descending thoracic aorta was identified and qualified as completely thrombosed (TFL, which was defined as no contrast enhancement of the entire false lumen), partially thrombosed (pTFL, which was defined as part of the false lumen thrombosed and part of the false lumen contrast enhanced) or completely patent (PFL, which was defined as the entire false lumen contrast enhanced).

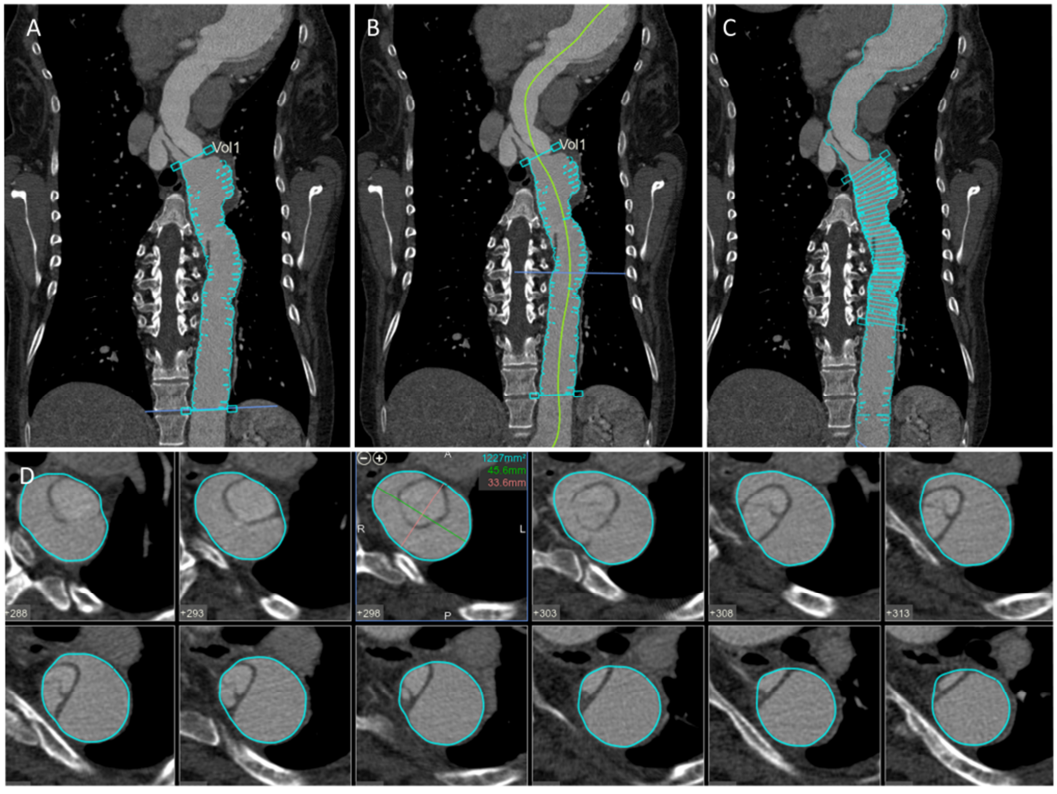

Figure 1. Volumetric measurement of the descending thoracic aorta.
A stretched multiplanar reformation of the aorta is automatically constructed by the software. A: The part of interest (between the left subclavian artery and the aorta at the level of the apex of the heart as assessed on the axial images) is selected for the volumetric analysis. B: The centerline is manually adjusted when necessary. C&D: Along the centerline, cross sections of the aorta every 0.5 mm along the length of the centerline were manually adjusted if the lumen was not correctly defined by the automated software.

The endovascular stent planning module from the post-processing software (Vitrea FX 1.0; Vital Images, Minnetonka, MN) was used to perform the quantitative measurements as displayed in Figure 1. The software was able to recognize the thoracic aorta and reconstruct a stretched multiplanar reformation of the aorta. The descending thoracic aorta was selected for analysis from the left subclavian artery until the level of the apex of the heart (on the axial images). A centerline was drawn automatically through the aorta which could be adjusted manually when necessary. Along the centerline, every 0.5 mm cross sections through the aorta were performed and the contrast-enhanced lumen circumference was defined automatically. When the lumen was not correctly defined by the software, the cross sectional circumferences of the lumen could be manually adjusted. In patients with a PFL, the false and true lumen were both included in the complete lumen volumetric analysis. In patients with pTFL, the true lumen and the contrast-enhanced part of the false lumen were included in the complete lumen volumetric analysis. The volume of the lumen of the descending thoracic aorta was measured distal from the left subclavian artery until the level of the apex of the heart. In addition for patients with a PFL or pTFL, the volume of the true lumen was measured similarly and the (contrast-enhanced) false lumen volume was calculated by subtracting the true lumen volume from the complete lumen volume. Furthermore, the minimum and maximum aortic diameters of the aorta at the level of the left subclavian artery (proximal descending thoracic aorta) and at the level of the apex of the heart (distal descending thoracic aorta) were automatically obtained.

Surgical repair

After median sternotomy, arterial cannulation of the subclavian or femoral artery was performed in the majority of patients. In the remaining cases, cannulation was performed in the distal ascending aorta. Effort was made to identify and resect the primary entry tear. Valve-sparing root replacement, supracoronary ascending aorta replacement or aortic valve and root replacement were performed as previously described. 12-16 In every patient the distal ascending aorta and arch were inspected under deep hypothermic circulatory arrest. If a (re)entry tear was present in the arch, concomitant (hemi-)arch replacement was performed.

Statistical analysis

All data analyses were performed using the SPSS software (Version 20.0. Armonk, NY: IBM Corp). Categorical variables were reported as frequencies and percentages. Continuous variables were displayed as mean ± standard deviation if normally distributed and as median and interquartile range if non-normally distributed. Patients with TFL, PFL and pTFL were compared using chi-square test for categorical variables and ANOVA test or Kruskall Wallis test for normally and non-normally distributed continuous variables, respectively.

Change in descending thoracic aorta volume and diameter over time was assessed with repeated measures analysis of variance. Follow-up duration in years was incorporated in the model as covariate. Estimated marginal means ± standard error of the mean for the aortic root diameters were reported directly postoperatively and during follow-up. Regression analysis was used to assess the descending thoracic aorta growth rate in ml/year following the previously described instrumental variables approach.17 Assuming that descending thoracic aorta growth is linear, the estimate of the association between difference in descending thoracic aorta volume (in ml) and the follow-up duration (in years) was obtained by linear regression analysis without including an intercept. This estimate was used as a cut-off and patients were divided into two groups according to the growth of their aorta; slow growth (growth < estimate) were compared to fast growth (growth ≥ estimate). Kaplan Meier analysis was performed to assess freedom from secondary intervention on the distal descending thoracic aorta. Log-rank test was used to compare groups. In order to assess inter- and intra-observer variability, 23 scans were measured by both observers and repeatedly by one observer, respectively and coefficients of variation were calculated. All statistical tests were two-sided. A p-value <0.05 was considered statistically significant.

Results

The clinical characteristics of the 51 included patients (mean age 58±11 years, 61% male) are presented in Table 1.

Table 1. Baseline characteristics

	TFL (n=20)	**PFL (n=14)**	**pTFL (n=17)**	**p-value**
Age (years)	63±10	52±11	59±11	0.020
Male	8 (40%)	11 (79%)	12 (71%)	0.046
Body surface area (m^2)	1.86±0.21	2.06±0.18	2.00±0.20	0.019
Connective tissue disease	0 (0%)	3 (21%)	2 (12%)	0.112
Hypertension	8 (40%)	4 (29%)	8 (47%)	0.574
Critical preoperative state	3 (15%)	0 (0%)	1 (6%)	0.259
EuroSCORE II (%)	6.1 (4.4-13.6)	4.4 (3.9-6.0)	5.5 (4.1-9.0)	0.124
CPB time (min)	238±55	205±44	246±66	0.211
AoX time (min)	168±44	149±44	194±59	0.123
Aortic arch replacement				0.187
Hemi-arch	7 (35%)	5 (36%)	4 (24%)	
Total arch	6 (30%)	0 (0%)	5 (29%)	

Data are presented as mean ± standard deviation or median (interquartile range) or as number (percentage). AoX time: Aortic cross clamp time. CPB time: Cardiopulmonary Bypass time. EuroSCORE II: European System for Cardiac Operative Risk Evaluation. PFL: Patent false lumen. pTFL: Partially thrombosed false lumen. TFL: Thrombosed false lumen.

The median duration between surgery and the post-operative MDCT was 9 days and in the majority of patients, the post-operative MDCT was performed within the first month after surgery. On the post-operative MDCT, 20 (39%) patients had a TFL, 14 (28%) patients had a PFL and 17 (33%) patients had a pTFL. Patients with PFL were younger compared to patients with TFL and pTFL. Patients with TFL were more often female and had less often connective tissue disease, a smaller body surface area and a higher EuroSCORE II compared with patients with PFL and pTFL.

MDCT measurements of the descending thoracic aorta

Table 2 shows the MDCT measurements of the descending thoracic aorta post-operatively and at follow-up.

Table 2: Change in descending thoracic aorta measurements

	Post-operative	Follow-up	p-value	Growth rate per year
Volume complete descending thoracic aorta (ml)	133±8	163±9	<0.001	6.1±1.6
Volume false lumen descending thoracic aorta (ml) *(n=31)*	81±7	106±12	0.018	2.8±2.4
Volume true lumen descending thoracic aorta (ml) *(n=31)*	59±4	65±8	0.205	2.1±1.1
Minimum diameter proximal descending thoracic aorta (mm)	25.6±0.6	26.6±0.7	0.046	0.24±0.11
Maximum diameter proximal descending thoracic aorta (mm)	30.2±0.6	31.2±0.7	0.052	0.07±0.11
Minimum diameter distal descending thoracic aorta (mm)	26.0±0.7	26.9±0.8	0.205	0.16±0.15
Maximum diameter distal descending thoracic aorta (mm)	29.6±0.7	32.0±0.9	<0.001	0.45±0.13

Data are displayed as estimated marginal means ± standard error of the mean after a mean follow up duration of 3.5 years. In addition, estimated mean growth rates ± standard error of the mean in ml or mm per year are displayed.

The volume of the complete lumen was estimated 133±8 ml directly post-operative and increased to 163±9 ml (p<0.001) at follow-up. In patients with a pTFL and PFL (n=31), the false lumen increased from 81±7ml to 106±12 ml (0.018). The true lumen volume in the patients with pTFL and PFL remained more or less stable (59±4 vs. 65±8 ml, p=0.205). The diameter of the proximal descending thoracic aorta increased significantly during follow-up. A significant increase was also observed in the maximum diameter of the distal descending thoracic aorta.

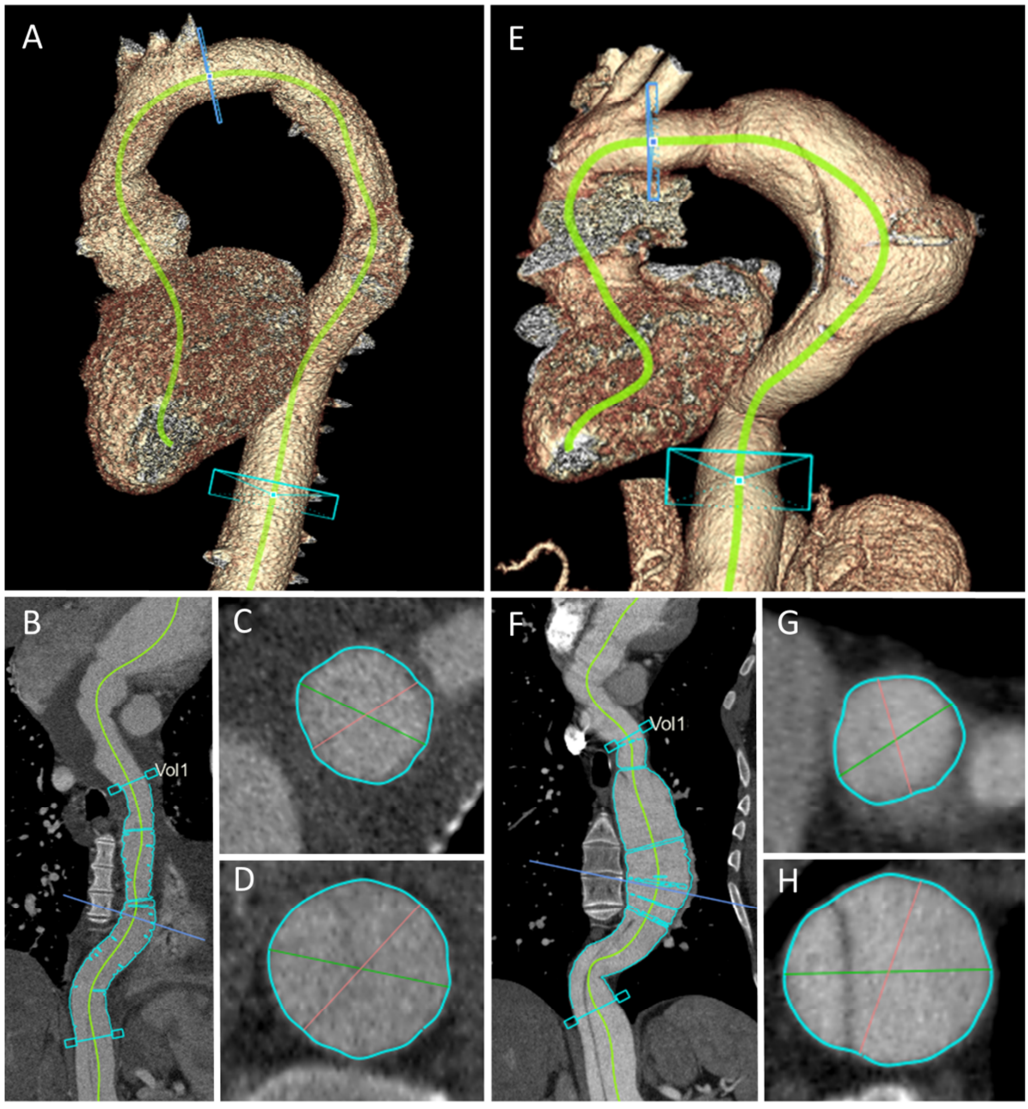

Figure 2. Example of a patient with a fast growing descending thoracic aorta.
A-D: Images of the postoperative MDCT. A: 3 dimensional image of the descending thoracic aorta. B: Volume of the descending thoracic aorta (125 ml). C: minimum and maximum diameter of the proximal descending thoracic aorta (21.3 mm and 23.8 mm). D: minimum and maximum diameter of the distal descending thoracic aorta (29.5 mm and 31.4 mm). E-H: Images of the follow-up MDCT, 33 months after postoperative MDCT. E: 3 dimensional image of the descending thoracic aorta with an aneurysm of the descending thoracic aorta. F: Volume of the descending thoracic aorta (284 ml). G: minimum and maximum diameter of the proximal descending thoracic aorta (20.4 mm and 22.9 mm). H: minimum and maximum diameter of the distal descending thoracic aorta (31.3 mm and 35.1 mm).

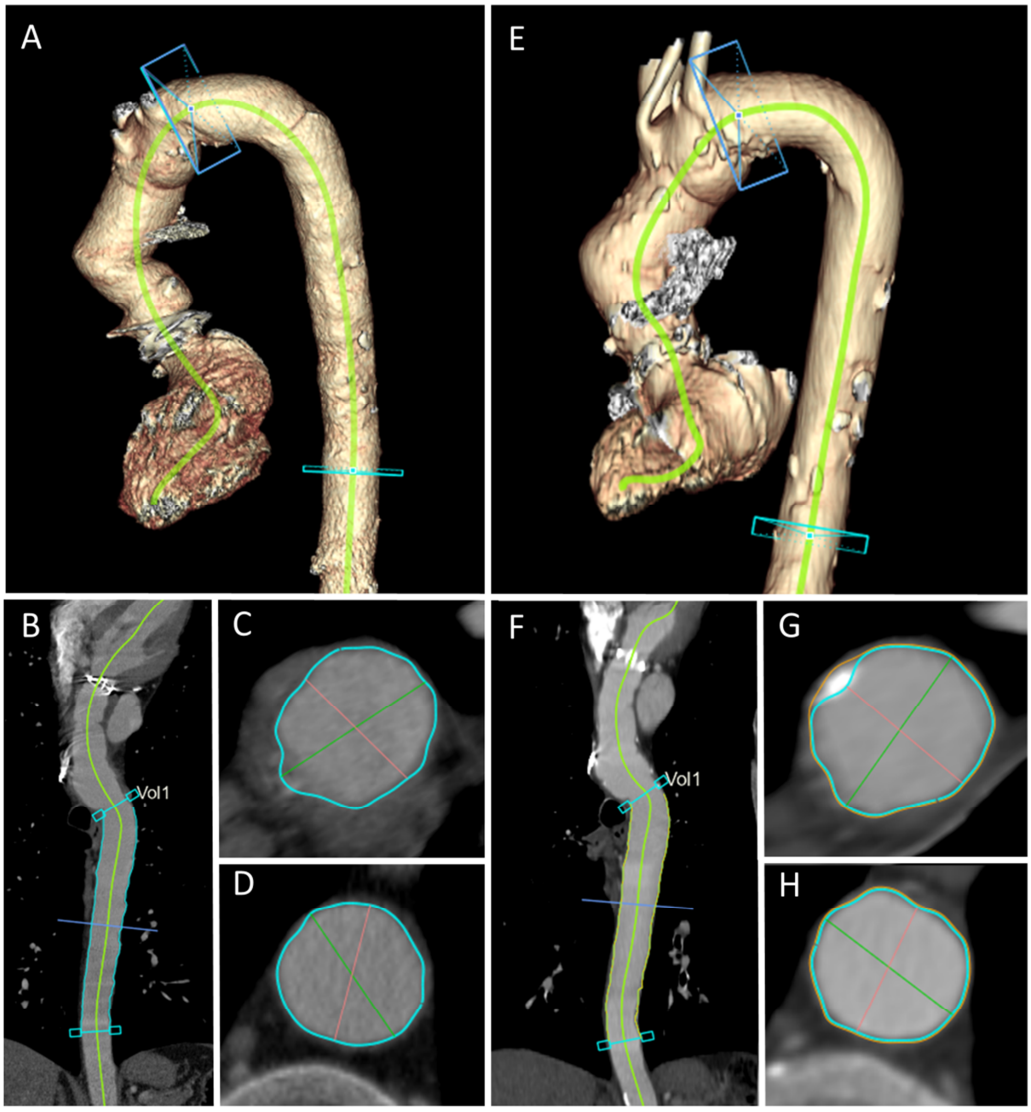

Figure 3. Example of a patient with a stable descending thoracic aorta.
A-D: Images of the postoperative MDCT. A: 3 dimensional image of the descending thoracic aorta. B: Volume of the descending thoracic aorta (105 ml). C: minimum and maximum diameter of the proximal descending thoracic aorta (25.0 mm and 30.3 mm). D: minimum and maximum diameter of the distal descending thoracic aorta (23.5 mm and 24.9 mm). E-H: Images of the follow-up MDCT, 132 months after postoperative MDCT. E: 3 dimensional image of the descending thoracic aorta at follow up. F: Volume of the descending thoracic aorta (111 ml). G: minimum and maximum diameter of the proximal descending thoracic aorta (26.3 mm and 31.8 mm). H: minimum and maximum diameter of the distal descending thoracic aorta (22.7 mm and 25.7 mm).

Descending thoracic aorta growth rate

Linear regression analysis showed significant growth of the descending thoracic aorta in complete lumen volume with an estimated growth rate of 6.1 ml/year. The false lumen volume increased with 2.8 ml/year on average. The true lumen growth was estimated 2.1 ml/year, Patients with fast growth of the complete lumen did not differ from patients with slow growth in terms of gender, age and history of hypertension. The number of patients who used oral anticoagulants after surgery was comparable between the fast and slow growth rate groups.

Figure 2 shows an example of a patient with fast growth rate. The volume of the descending thoracic aorta was 125 ml directly post-operatively. After 33 months of follow-up, the volume increased to 284 ml. This patient underwent distal secondary intervention of the aneurysm of the descending thoracic aorta. Figure 3 shows an example of a patient with slow growth rate. The volume of the descending thoracic aorta was 105 ml post-operatively and 111 ml after 11 years of follow-up.

Freedom from secondary aortic intervention during follow-up

Secondary intervention on the descending thoracic aorta during follow-up was performed in 6 patients. Endovascular repair was performed in 1 patient because of anastomotic leakage. Open repair on the descending thoracic aorta was performed in the other 5 patients because of descending thoracic aorta aneurysm formation >6.0 cm. Fast growth of the descending thoracic aorta was not per se an indication for secondary intervention. The freedom from secondary intervention on the descending thoracic aorta after 5 years follow-up was 80±9% in the group with complete lumen fast growth rate compared to 100% in the complete lumen slow growth rate group (log-rank p=0.003). In particular, patients with pTFL had significantly worse 5 year freedom from secondary intervention (75±11%) compared to patients with TFL and PFL (both 100%; p=0.008). In the patients with pTFL and PFL, the false lumen fast growth was associated with worse freedom from secondary intervention after 5 years (74±12%) compared to false lumen slow growth (100%; p=0.042). On the contrary, the growth rate of the true lumen was not associated with secondary intervention. Kaplan Meier curves are provided in Figure 4. In addition, patients who underwent secondary intervention had a significantly larger complete lumen descending thoracic aorta growth rate with compared to in patients without secondary intervention (25.6 ml/year vs. 5.6 ml/year, respectively; p=0.041).

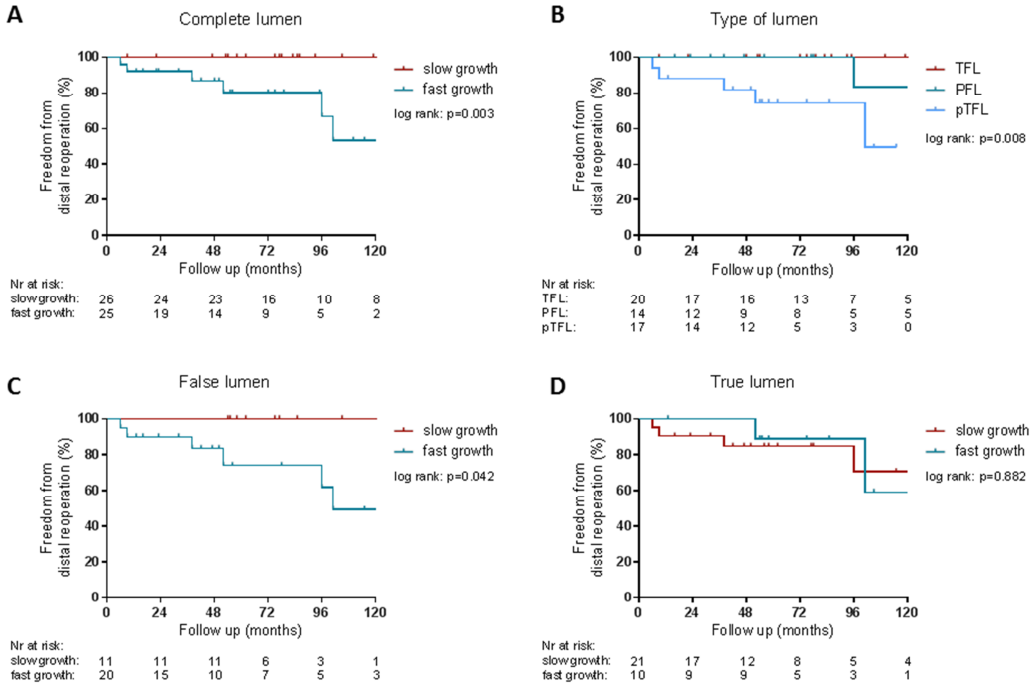

Figure 4: Kaplan Meier freedom from reoperation

A: Freedom from distal reoperation for complete lumen slow growth compared to fast growth. B: Freedom from distal reoperation for type of false lumen. TFL: thrombosed false lumen, PFL: patent false lumen, pTFL: partially thrombosed false lumen.C: Freedom from distal reoperation for false lumen slow growth compared to fast growth. D: Freedom from distal reoperation for true lumen slow growth compared to fast growth.

Inter- and intra-observer variability

The intra-observer variability, calculated as 1.96 standard deviation of the mean difference, was 4.7 ml for the volumetric measurement. The variability for the maximum diameter measurement was 2.7 mm for the proximal descending thoracic aorta and 1.6 mm for the distal descending thoracic aorta. This resulted in a coefficient of variation of 1.1% for the volume and 3.0 and 1.9% for the measurement of the maximum diameter of the proximal and distal descending thoracic aorta, respectively. Inter-observer variability was 27.0 ml for the volumetric measurement with a coefficient of variation of 6.5%. The inter-observer variability of the measurement of the proximal and distal maximum diameter of the descending thoracic aorta was 6.9 and 5.5 mm, respectively, with a coefficient of variation of 7.4 and 6.5%, respectively.

Discussion

The main findings of the present study can be summarized as follows: in survivors of acute type A aortic dissection undergoing emergent surgery, fast growth rate of the descending thoracic aorta, especially of the false lumen when patent or only partially thrombosed, was associated with higher rates of secondary intervention of the descending thoracic aorta. The present MDCT-based software provides an automated and reproducible measure of the growth rate of the descending thoracic aorta with low intra-observer variability. In addition, distinction between the false and true lumen volume can be made and this study shows that in particular increase in false lumen is associated with a higher risk on secondary intervention.
Survivors of an acute type A aortic dissection require regular surveillance with non-invasive imaging techniques of the native descending thoracic aorta to identify potential complications such as further progression of the dissection and aortic rupture or aneurysm formation.[4,5,8] Current guidelines recommend performing this measurement in stretched views along a center line of the descending thoracic aorta to provide the true cross sectional area.[8] The change in diameter of the descending thoracic aorta over time is approximately 1 mm/year.[4-7] Besides the underlying aortopathy (i.e. Marfan syndrome) and cardiovascular risk factors (i.e. hypertension), the status of the false lumen plays an important role in the growth of the descending thoracic aorta.[4,6,7] Kimura et al. showed a significant difference in growth rate of the proximal descending thoracic aorta between PFL (1.9±3.8 mm/year) and TFL (-0.7±2.8 mm/year; p<0.001).[6] Similar results were described by Fattouch et al. with a significant higher growth rate in PFL (2.8±0.4 mm/year) compared to TFL (1.1±0.2 mm/year; p=0.001).[4] However, these studies did not differentiate between complete thrombosis or partial thrombosis of the false lumen. According to Song et al., the descending thoracic aorta growth rate was largest in pTFL (5.5±9.1 mm/year) compared to PFL and TFL (3.8±5.6 mm/year and -0.9±3.9 mm/year, respectively; p=0.005).[7] The present study shows in addition that it is in particular the false lumen that enlarges during follow-up in patients with a PFL of pTFL in contrast to the true lumen volume which remains more or less stable.
Patients with faster growth rate of the descending thoracic aorta are more frequently referred for secondary intervention on the descending thoracic aorta to prevent aortic rupture, as we show in the present study. The status of the false lumen plays an important role in the growth rate of the descending thoracic aorta and therefore affects the need for secondary intervention. Patients with PFL had significantly worse 5-year freedom from secondary intervention on the descending thoracic aorta (72±3%) compared to TFL (97±1%; p<0.001).[4] Secondary interventions on the descending thoracic aorta, whether it was an open or endovascular procedure, were most often performed in pTFL compared to PFL and TFL.[7] In the present study, faster growth of the false lumen was associated with higher need for secondary aortic intervention.

Clinical implications

Current guidelines recommend regular follow-up in patients after acute type A aortic dissection: 1 month after the treatment, after 6 months, 12 months and then yearly.[8] If a stable course has been documented in the first postoperative year, less-strict imaging intervals may be sufficient. However fixed criteria for a stable course have not been proposed in the current guidelines. The present study shows that there is an increased need for secondary intervention on the descending thoracic aorta in patients with fast aortic growth (≥6.1 ml/year). Especially in patients with accelerated growth of the false lumen of ≥ 2.8 ml/year, secondary intervention might be needed in the future. This may be used after the first year of follow-up as a cut off to determine the timing of follow-up and may help physicians to individualize surveillance of patients with a faster growth rate (needing more frequently CT evaluation) and patients with slow growth rate (preventing unnecessary radiation). The effects of this approach should be evaluated in future prospective studies.

Study limitations

The study was limited by its retrospective nature and small sample size. Only patients who survived the initial postoperative period and underwent MDCT at follow-up were included in the study, this might have introduced selection bias. Secondary intervention was performed in 1 patient with anastomotic leakage and in 5 patients with aneurysm formation with a diameter exceeding 6.0 cm. The growth rate itself was not taken into account in decision making whether a secondary intervention was needed. However, MDCT follow-up schemes may already have been adapted in patients with a faster growth rate. To eliminate this potential bias, strict predefined follow-up schemes should be used in future studies. In addition, the present study identified a cut-off of 6.1 ml/year to define fast growth of the complete lumen; this should be validated. The small sample size of the present study hampered multivariable analysis to identify factors associated with faster growth. Furthermore, whether early secondary intervention in patients with fast growth will improve survival should be evaluated in future long term follow-up studies.

The present method did not evaluate aortic arch growth rate; however, there were 2 patients with isolated aortic arch dilation during follow-up who underwent secondary intervention on the aortic arch. These secondary interventions were not included in the present analysis. Lastly, the semi-automated method to measure the descending thoracic aorta volume is more time-consuming compared to measuring aortic diameters. In some patients, only very small adjustments were needed and the volume was obtained in an almost entirely automated fashion. In some patients (particularly the patients with pTFL), it was difficult to define the precise delineation of the aortic lumen and manual adjustments were needed resulting in longer analysis times.

Conclusion

Survivors of acute type A aortic dissection should be closely monitored with MDCT to evaluate complications and annual growth rate of the native descending thoracic aorta. Volumetric measurement of the descending thoracic aorta seems a reliable method with low intra-observer variability. The present study showed that increased growth of the complete lumen and in particular of the false lumen of the descending thoracic aorta after deBakey type 1 aortic dissection was associated with higher risk on secondary intervention on the descending thoracic aorta.

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Summary and future perspectives

Summary

The present thesis described the additional value of cardiac imaging in the selection and evaluation of patients with aortic regurgitation and/or aortopathy undergoing aortic valve and root surgery. In the general introduction (Chapter 1), an overview was provided on aortic valve and root pathology, the indications for surgery, different valve-sparing surgical techniques and the role of multimodality imaging in the selection of patients for valve-sparing aortic root replacement.

Part I: preoperative evaluation of patients with aortic regurgitation and/or aortopathy

Part I focused on imaging performed in the preoperative period to evaluate the progression of disease and to identify patients who may be candidates for valve-sparing procedures. Chapter 2 evaluated the effect of aortic root dilation on the aortic valve geometry using 3-dimensional transesophageal echocardiography. There was an increase in aortic valve leaflet size in patients with aortic root dilation compared to patients with normal aortic roots. However, this adaptive mechanism seemed insufficient to compensate for the increased aortic root area, especially in patients with central aortic regurgitation. In addition, in eccentric aortic regurgitation, there was relative excessive leaflet tissue in relation to the aortic root area resulting in prolapse. In Chapter 3, the effect of aortic regurgitation on the mitral valve geometry was discussed. Aortic regurgitation is associated with left ventricular volume overload and thereby left ventricular dilation and eventually reduction in left ventricular ejection fraction. This may lead to an increased tethering of the mitral leaflets due to papillary muscle displacement on one hand and a decrease in closing forces on the other hand. The mitral valve adapts to the left ventricular dilation by increased leaflet length. However, when compensatory mechanisms fail, significant mitral regurgitation can develop, which occurred in 23% of aortic regurgitation patients. Factors independently associated with significant mitral regurgitation in patients with aortic regurgitation were a larger left atrial volume and a lower left ventricular ejection fraction. Chapter 4 investigated the effect of statin therapy in reducing the progression of aortopathy in bicuspid aortic valve patients. Patients on statin therapy were compared to non-users of this medication. Patients who used statins had smaller aortic root diameters at baseline and after a median follow-up period of 4.7 years even after adjusting for coronary artery disease, age and medication use compared with non-users. The average annual aortic root dilation rates were 0.08 mm/year for aortoventricular junction, 0.16 mm/year for the sinus of Valsalva, 0.12 mm/year for the sinotubular junction, 0.45 mm/year for the ascending aorta. The use of statins had no effect on the aortic root dilation rate. Chapter 5 described the use of multidetector row computed tomography of the aortic valve and thoracic aorta in 61 patients considered for valve-sparing root replacement. The aortic valve was successfully repaired in 36 patients whereas repair was not feasible or not

successful in 25 patients. Patients with a reparable aortic valve had less often bicuspid aortic valve anatomy, less annular calcification and less commissural calcification compared to their non-reparable counterparts. The information provided by multidetector row computed tomography on valve morphology and calcification grade may be helpful in the preoperative assessment of aortic valve reparability. In Chapter 6, the additional value of transthoracic echocardiography in determining the right graft size used during the David reimplantation technique was evaluated. In 30 patients, undergoing valve-sparing root replacement with the reimplantation technique without additional leaflet repair, the average leaflet height, leaflet length and the total leaflet area were measured on echocardiography. Leaflet height (diameter = 1.1 • ((2 • 2/3 • leaflet height) + 2)), length (diameter = (2 • 2/3 • length) + 2) and area (diameter = 0.8 • ((2 • √(total leaflet area / π)) + 2)) were calculated based on transthoracic echocardiography formulas. Patients who received a smaller graft size than calculated with the formulas (undersized), had less often residual mild aortic regurgitation compared to patients who received an oversized graft. However, prospective validation of the formulas is needed before application in daily clinical practice.

Part II: postoperative evaluation of patients after aortic valve and root surgery

Part II focused on the role of imaging after aortic valve and root surgery. In Chapters 7 and 8 the postoperative left ventricular reverse remodeling after aortic valve and root surgery was evaluated. Chapter 7 evaluated the differences in postoperative left ventricular reverse remodeling in patients with acute and chronic aortic regurgitation. Both in patients with acute and chronic aortic regurgitation, there was significant left ventricular reverse remodeling. However, after aortic valve and root surgery for acute aortic regurgitation, the left ventricular end-diastolic volume was more reduced and global longitudinal strain indexed for the left ventricular end-diastolic volume was more preserved in comparison to those observed in patients with chronic aortic regurgitation. Furthermore, patients who underwent a valve-sparing procedure were compared to patients who underwent aortic valve and root replacement with a biological prosthesis in Chapter 8. Patients undergoing aortic valve and root replacement had significant larger left ventricular volumes before surgery as compared with their counterparts. Postoperatively, after a median follow-up of 46 months, both groups of patients showed a significant and sustained reduction in LV volumes, with a larger reduction in patients undergoing aortic valve and root replacement. The recurrence of significant aortic regurgitation during follow up was about 7-8% and not significantly different between repair and replacement techniques. Chapter 9 evaluated the postoperative change in left ventricular volumes and function in 97 patients with acute type A aortic dissection who survived the initial surgery. In this chapter, 3 different procedures were compared; valve-sparing root replacement (with the remodeling or reimplantation technique), supracoronary ascending

aorta replacement, and aortic valve and root replacement (with a biological or mechanical prosthesis). During follow-up, aortic regurgitation grade ≥2 was significantly more often observed in supracoronary ascending aorta replacement and valve-sparing root replacement compared to aortic valve and root replacement. Left ventricular volumes remained stable in valve-sparing root replacement and aortic valve and root replacement whereas in supracoronary ascending aorta replacement, left ventricular volumes significantly increased over time. In addition, among patients with recurrent aortic regurgitation grade ≥2 at follow-up, left ventricular volumes increased significantly over time whereas patients without recurrent aortic regurgitation did not show significant left ventricular dilation. In Chapter 10, the effect of aortic valve replacement on the conduction system was evaluated. Patients who underwent sutureless, transcatheter and conventional stented biological aortic valve replacement were compared. Patients who underwent sutureless and transcatheter aortic valve replacement developed more often new-onset complete left bundle branch block directly after aortic valve replacement in comparison to conventional aortic valve replacement.

Chapters 11 and 12 focused on the postoperative changes in aortic diameter. In bicuspid aortic valves, the aortic root growth rate has been described to be faster compared to that of patients with tricuspid aortic valves due to an underlying genetic substrate and/or altered hemodynamics. In Chapter 11 the aortic root dilation rate in patients with bicuspid aortic valve anatomy was compared to patients with tricuspid aortic valve anatomy before and after aortic valve replacement to obtain better insight in the mechanisms of aortic root dilation in bicuspid aortopathy. The preoperative aortic root dilation rate was significantly faster in patients with bicuspid valve compared to patients with tricuspid valve whereas after surgery, the aortic root dilation rate was comparable between groups, indicating that hemodynamics play an important role in the increased aortic dilation in bicuspid aortopathy.

Chapter 12 investigated the growth rate of the descending thoracic aorta in patients operated for acute type A aortic dissection. The growth rate was assessed using a volumetric measurement of the descending thoracic aorta on multidetector row computed tomography. Increased growth of the complete lumen and in particular of the false lumen of the descending thoracic aorta after aortic dissection was associated with higher risk on secondary intervention on the descending thoracic aorta.

Conclusion and future perspectives

Alongside with increasing life expectancy in the general population, the prevalence of aortic valve disease increases; hence there is a need for aortic valve surgery with long durability and low complication rate. Mechanical and biological (including transcatheter) prosthesis and aortic valve repair are the available approaches for patients with aortic valve disease. The

need for reoperation (aortic valve repair and biological valves) should be balanced against the risk on thromboembolic and bleeding complications (mechanical valves that need lifelong anticoagulation). In addition, patient's preference in this era of shared decision making is an important factor. Aortic valve preservation has shown promising results, however at present there are many different surgical techniques and modifications and the success of these techniques are largely operator-dependent. In the coming years, we may witness standardization of surgical repair techniques and development of durable and less invasive prostheses and these may be possible with the help of developments in 3-dimensional imaging techniques and postprocessing softwares that allow 3-dimensional printing and simulation. Currently, thorough evaluation of the aortic root dimensions and mechanism of aortic regurgitation with echocardiography is mandatory prior to surgery. Transesophageal echocardiography provides better visualization of the aortic root and characteristics of the aortic cusps than transthoracic echocardiography. In addition, 3-dimensional echocardiographic techniques have shown to be more accurate in grading aortic regurgitation than 2-dimensional echocardiography. The ascending aorta is better visualized with multidetector row computed tomography or cardiac magnetic resonance. These 3-dimensional imaging techniques permit reconstruction of the aortic root complex and with specific software, the structure can be printed out in three dimensions allowing the surgeon to tailor the surgical approach. Ongoing research has led to important advances in finite element analyses that provide cardiac models and simulations of the aortic root reproducing the mechanism of aortic regurgitation and evaluating the effects of the surgical technique on the wall stress. This cardiac modelling will permit in the near future personalization of the aortic valve repair, probably resulting in better durability of the repair and competence of the aortic valve. In addition, patients should be discussed at the heart team meeting preparatory to surgery taking into account all information obtained by preoperative cardiac imaging to determine the most appropriate surgical technique for that particular patient. This may require centralization of care with valve-preserving procedures only executed in high volume centers with dedicated surgeons and dedicated cardiologists working together to provide the optimal care. At present, the aortic valve insufficiency and ascending aorta aneurysm international registry (AVIATOR) is ongoing, chaired by Dr. Lansac. The aims of the AVIATOR registry comprise optimized multidisciplinary patient care, uniform scientific reporting and assessment of quality of care. This international multicenter study will play a key role in the coming years to establish the place of repair in aortic valve and root surgery which might impact on guidelines.

Samenvatting en toekomstperspectieven

Samenvatting

Dit proefschrift beschreef de toegevoegde waarde van beeldvormende technieken bij de selectie en evaluatie van patiënten met aortaklepinsufficiëntie en/of aorta-pathologie die aortaklep en –wortelchirurgie ondergaan. De algemene introductie in hoofdstuk 1 gaf een overzicht over aortaklep- en aortawortelpathologie, de operatie-indicatie, de verschillende klepsparende chirurgische technieken en de rol die beeldvorming speelt in de selectie van patiënten voor een klepsparende aortawortelvervanging.

Deel I: preoperatieve evaluatie van patiënten met aortaklepinsufficiëntie en/of aorta-pathologie

Deel I richtte zich op de beeldvorming in de preoperatieve fase om progressie van de ziekte te evalueren en om patiënten die mogelijk geschikt zijn voor een klepsparende operatie te identificeren. In hoofdstuk 2 werd het effect van aortaworteldilatatie op de geometrie van de aortaklep geëvalueerd met behulp van 3-dimensionale echocardiografie. De klepgrootte nam significant toe bij patiënten met een gedilateerde aortawortel in vergelijking tot normale aortawortels. Echter, deze aanpassing leek onvoldoende om te compenseren voor de toegenomen aortawortelgrootte, voornamelijk bij patiënten met centrale aortaklepinsufficiëntie. Bij patiënten met excentrische aortaklepinsufficiëntie was er een relatief overschot aan klepweefsel vergeleken met de aortawortelgrootte wat resulteerde in prolaps. In hoofdstuk 3 werd gekeken naar het effect van aortaklepinsufficiëntie op de mitralisklep. Aortaklepinsufficiëntie is geassocieerd met volume-overbelasting en daarmee dilatatie van de linker ventrikel en uiteindelijk achteruitgang in linker ventrikelfunctie. Dit kan leiden tot een verhoogde spanning op de mitralisklepblaadjes door verplaatsing van de papillairspieren aan de ene kant en een verminderde mitralisklepsluiting aan de andere kant. De mitralisklep past zich aan, aan de linker ventrikeldilatatie, met een verlenging van de klepblaadjes. Als deze compensatoire mechanismen tekort schieten, dan kan er mitralisklepinsufficiëntie ontstaan, wat gebeurde in 23% van de patiënten met aortaklepinsufficiëntie. Een groter linkeratriumvolume en een lagere linker ventrikel ejectiefractie waren onafhankelijk geassocieerd met mitralisklepinsufficiëntie bij patiënten met aortaklepinsufficiëntie. In hoofdstuk 4 werd het effect van statines ter vermindering van progressie van aortadilatatie bij patiënten met een bicuspide aortaklep onderzocht. Patiënten die statines gebruikten werden vergeleken met patiënten die geen statines gebruikten. Statine-gebruikers hadden kleinere aortaworteldiameters bij aanvang van de studie en na een mediane duur van 4.7 jaar, zelfs na correctie voor coronairlijden, leeftijd en gebruik van andere medicatie. De gemiddelde jaarlijkse aortawortelgroeisnelheid was 0.08 mm/jaar voor de aortoventriculaire overgang, 0.16 mm/jaar voor de sinus van Valsalva, 0.12 mm/jaar voor

de sinotubulaire overgang en 0.45 mm/jaar voor de aorta ascendens. Het gebruik van statines had geen effect op de aortawortelgroeisnelheid.
Hoofdstuk 5 ging over het gebruik van computer tomografie van de aortaklep en de thoracale aorta in 61 patiënten bij wie een klepsparende aortawortelreconstructie werd overwogen. De aortaklep was succesvol gerepareerd in 36 patiënten, terwijl in de overige 25 patiënten reparatie niet mogelijk bleek of niet gelukt was. Patiënten met een gerepareerde klep hadden minder vaak een bicuspide aortaklep, minder calcificaties in de annulus en minder calcificaties in de commissuren vergeleken met patiënten bij wie de klep niet te repareren was. De informatie verkregen met behulp van computer tomografie aangaande klepmorfologie en mate van calcificatie kan van toegevoegde waarde zijn in de beslissing of een klep te repareren is. In hoofdstuk 6 werd gekeken of transthoracale echocardiografie kan bijdragen in het bepalen van de juiste maat buisprothese die gebruikt wordt bij de David reimplantatie techniek. In 30 patiënten die een klepsparende aortawortelvervanging middels de reimplantatie techniek ondergingen zonder aanvullende klepreparatie, werd de klephoogte, kleplengte en klepoppervlakte gemeten met behulp van echocardiografie. Er werden formules ontwikkeld op basis van de klephoogte (diameter = 1.1 • ((2 • 2/3 • gemiddelde klephoogte) + 2)), kleplengte (diameter = (2 • 2/3 • kleplengte) + 2) en het klepoppervlakte (diameter = 0.8 • ((2 • √(totale klepoppervlakte / π)) + 2)). Patiënten die een buisprothese kregen die kleiner was dan berekend met de formules, hadden minder vaak residuele milde aortaklepinsufficiëntie vergeleken met patiënten die een grotere buisprothese dan berekend kregen. Er dient nog wel prospectieve validatie van de formules plaats te vinden voordat deze toegepast kunnen worden in de dagelijkse praktijk.

Deel II: postoperatieve evaluatie van patiënten na aortaklep- en aortawortelchirurgie
Deel II richtte zich op de beeldvorming in de postoperatieve fase na aortaklep- en aortawortelchirurgie. In hoofdstuk 7 en 8 werd de postoperatieve remodelering van de linker ventrikel geëvalueerd. In hoofdstuk 7 werd gekeken naar het verschil in postoperatieve linker ventrikelremodelering bij patiënten met acute en chronische aortaklepinsufficiëntie. In beide groepen was er sprake van significante linker ventrikelremodelering. Echter, na aortaklep- en aortawortelchirurgie voor acute aortaklepinsufficiëntie was het linker ventrikel eind-diastolisch volume meer afgenomen en de geïndexeerde globale longitudinale strain beter behouden in vergelijking met chronische aortaklepinsufficiëntie. Vervolgens werden patiënten die een klepsparende operatie ondergingen vergeleken met patiënten bij wie de aortaklep en aortawortel vervangen werd met een biologische prothese in hoofdstuk 8. Patiënten die een aortaklep- en aortawortelvervanging ondergingen hadden significant grotere linker ventrikel volumes voor de operatie. Na de operatie, na een mediane duur van 46 maanden, vond er in beide groepen een significante reductie van linker ventrikelvolumes plaats. De linker ventrikel

ejectie fractie daalde direct na operatie en steeg daarna in beide groepen. De terugkeer van significante aortaklepinsufficiëntie tijdens de studieperiode was ongeveer 7-8% en niet verschillend tussen reparatie en vervanging. Hoofdstuk 9 onderzocht de postoperatieve verandering in linker ventrikelvolumes en -functie bij 97 patiënten met een acute type A aortadissectie die de initiële operatie overleefd hadden. In dit hoofdstuk werden 3 verschillende operaties met elkaar vergeleken: de klepsparende aortawortelvervanging (middels de remodellering techniek of de reimplantatie techniek), de supracoronaire aorta ascendens vervanging en de aortaklep- en aortawortelvervanging (met een biologische of mechanische prothese). Na de supracoronaire aorta ascendens vervanging en de klepsparende aortawortelvervanging werd significant vaker aortaklepinsufficiëntie graad ≥2 gezien dan na aortaklep- en aortawortelvervanging. De linker ventrikelvolumes bleven stabiel na klepsparende aortawortelvervanging en aortaklep- en aortawortelvervanging, terwijl deze significant toenamen na de supracoronaire aorta ascendens vervanging. Bij patiënten met significante aortaklepinsufficiëntie (graad ≥2) na de operatie was er een significante toename in linker ventrikelvolumes, terwijl er geen linker ventrikeldilatatie werd geobserveerd bij patiënten zonder significante aortaklepinsufficiëntie na de operatie.
In hoofdstuk 10 werd het effect van aortaklepvervanging op het geleidingssysteem geëvalueerd. Patiënten die een aortaklepvervanging zonder hechtingen, via een catheter of op de conventionele manier ondergingen werden met elkaar vergeleken. En nieuw linkerbundeltakblok werd vaker geobserveerd na een aortaklepvervanging zonder hechtingen en via een catheter in vergelijking met de conventionele aortaklepvervanging.
Hoofdstuk 11 en 12 legden de nadruk op de postoperatieve veranderingen in aortadiameter. De aortawortelgroeisnelheid is hoger bij patiënten met een bicuspide aortaklep in vergelijking met mensen met een tricuspide aortaklep ten gevolge van een onderliggend genetisch substraat en/of een veranderde hemodynamiek. In hoofdstuk 11 werd de aortawortelgroeisnelheid vergeleken tussen patiënten met een bicuspide aortaklep en patiënten met een tricuspide aortaklep voor en na aortaklepvervanging om beter inzicht te krijgen in de mechanismen van aortaworteldilatatie bij bicuspidie. De preoperatieve aortawortelgroeisnelheid was significant sneller bij bicuspide aortakleppen vergeleken met tricuspide aortakleppen. Terwijl na de operatie, de groeisnelheid hetzelfde was in beide groepen. Dit impliceert dat hemodynamiek een belangrijke rol speelt in de snellere aortadilatatie bij bicuspide aortakleppen.
In hoofdstuk 12 werd gekeken naar de groei van de thoracale aorta descendens bij patiënten die geopereerd waren aan een acute type A aortadissectie. Groei werd bekeken met behulp van metingen van het volume van de thoracale aorta descendens op computer tomografie. Een snellere groei van het complete lumen en in het bijzonder van het false lumen na

aortadissectie was geassocieerd met vaker opnieuw een operatie aan de thoracale aorta descendens.

Conclusies en toekomstperspectieven

De levensverwachting van de algemene populatie neemt nog steeds toe, derhalve is er vraag naar aortaklepoperaties met een lange levensduur en weinig complicaties. Mechanische en biologische (inclusief transcatheter) klepprotheses en aortaklepreparatie zijn de beschikbare opties voor patiënten met aortakleplijden. Het risico op opnieuw een operatie (bij biologische klepprotheses en aortaklepreparatie) moet afgewogen worden tegen het risico op trombo-embolische en bloedingscomplicaties (bij mechanische klepprotheses waarbij levenslang antistolling nodig is). Daarbij komt dat de individuele voorkeur van de patiënt tegenwoordig van groot belang is. Het sparen van de aortaklep heeft al veelbelovende resultaten laten zien, maar op dit moment zijn er veel verschillende chirurgische technieken en modificaties en is het succes grotendeels afhankelijk van de operateur. In de komende jaren zullen chirurgen en cardiologen de praktijk van aortaklepreparatie meer te standaardiseren. Daarnaast kunnen we verwachten dat minder invasieve technieken en protheses met langere levensduur ontwikkeld worden met behulp van 3-dimensionale beeldvormingstechnieken en software welke voorziet in 3-dimensionaal printen.

Tegenwoordig is het noodzakelijk om de aortawortelдimensies en de mechanismen van aortaklepinsufficiëntie te evalueren met behulp van echocardiografie voorafgaand aan de operatie. Slokdarmechocardiografie geeft betere beelden van de aortaklep en -wortel dan transthoracale echocardiografie. Tevens is 3-dimensionale echocardiografie accurater in het beoordelen van de ernst van aortaklepinsufficiëntie dan 2-dimensionale echocardiografie. De aorta ascendens kan daarnaast beter gevisualiseerd worden met computer tomografie of cardiale magnetische resonantie. Door deze 3-dimensionale technieken is het mogelijk om de aortawortel te reconstrueren met behulp van speciale software, zodat de structuur geprint kan worden met behulp van een 3-dimensionale printer. Dit kan de chirurg helpen om de chirurgische techniek te individualiseren. Recent wetenschappelijk onderzoek heeft geleid tot voortgang op het gebied van finite element analyse waardoor cardiale modellen en simulaties van de aortawortel gebruikt kunnen worden om de mechanismen van aortaklepinsufficiëntie te reproduceren en om effecten van chirurgische technieken op de aortawand te evalueren. Cardiaal modelleren kan in de nabije toekomst personaliseren van aortaklepreparatie mogelijk maken wat zou kunnen resulteren in een langere levensduur van de aortaklepreparatie. Daarnaast is het belangrijk dat patiënten besproken worden tijdens een hart team bijeenkomst voorafgaand aan de operatie waarbij alle informatie verkregen middels preoperatieve beeldvorming in acht wordt genomen. De meest geschikte chirurgische techniek kan dan gekozen worden door een multidisciplinair team. Hierbij is het waarschijnlijk

nodig om de zorg met betrekking tot klepsparende operaties te centraliseren in hoog-volume centra met toegewijde chirurgen en cardiologen die samenwerken om de optimale zorg te leveren. Op dit moment is er een lopende registratie van klepsparende aortawortelopera ties waarbij het doel is om de multidisciplinaire patiëntenzorg te optimaliseren, een uniforme manier van rapporteren van resultaten te ontwikkelen en de zorg te beoordelen. Deze internationale multicenterstudie zal een sleutelrol spelen in de komende jaren om de plaats van reparatie in de wereld van aortaklep en -wortelchirurgie te bepalen en daarmee de richtlijnen beïnvloeden.

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Curriculum vitae

Madelien Veronique Regeer was born in Alkmaar (the Netherlands) on the 25th of November 1987. After graduating cum laude from Huygenwaard in 2005, she studied medicine at the Academic Medical Center in Amsterdam. During her studentship, she worked at the Examencursus in Leiden, teaching secondary school students in biology. Furthermore, she provided sailing lessons and trained new instructors at sailing school de Vinkeveense Plassen. In 2011, she obtained her medical degree cum laude and worked as a resident in the cardiology department at the Medical Center Alkmaar. In December 2012, she started her PhD-training at the Leiden University Medical Center under supervision of prof. J.J. Bax, prof. M.J. Schalij and dr. V. Delgado. After nearly three years of research, she started as a resident in training to become a cardiologist in September 2015. At present she works at the internal medicine department of the Alrijne Hospital in Leiderdorp.