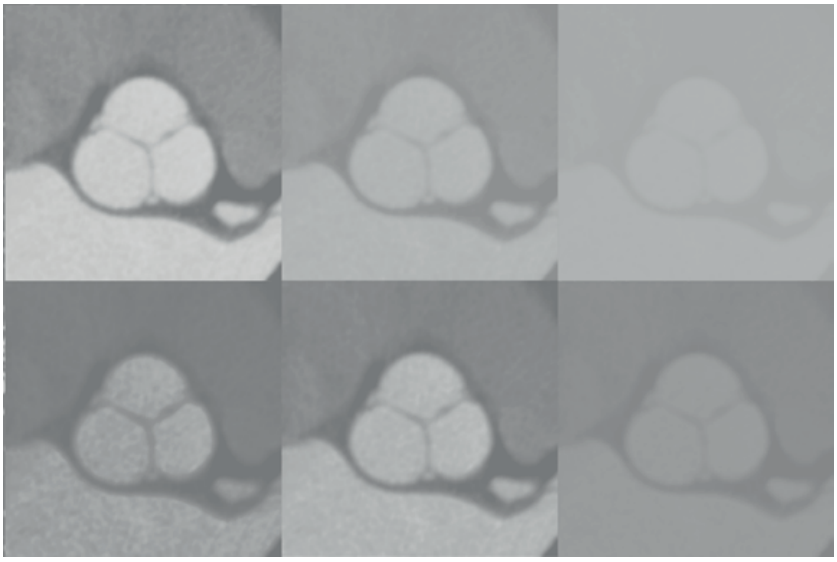
VASILEIOS KAMPERIDIS

Diagnosis and management of left valvular heart disease with advanced echocardiography and cardiac computed tomography



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POTONTA

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To my precious
Vasiliki, Nikoleta & Olga

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CHAPTER 1

General Introduction and Outline of the Thesis

TYPES OF LEFT VALVULAR HEART DISEASE

Prevalence and spectrum of the disease

Left-sided significant valvular heart disease is a fast growing worldwide problem that expands proportionally to the increment of the life expectancy of the population and its prevalence is expected to double by 2050.[1] In a large-scale community screening cohort study that enrolled 2500 participants aged ≥65 years, the prevalence of moderate or severe valvular heart disease was 11.3%.[1] According to the Euro-Heart survey II on valvular heart disease, aortic stenosis (AS) and mitral regurgitation (MR) are the two most common types of valvular heart disease in adults.[2] Among those who suffer from moderate or severe valvular disease, AS is the most common cause with a prevalence of 41.2% followed by MR with a prevalence of 21.3%.[2] The aetiology of the native valve disease is mainly degenerative in AS for about 90% of cases and in primary MR for about 60% of cases based on the recently reported Euro-Heart survey II.[2] However, 33% of the MR is categorized as secondary and 51.6% of the secondary, as ischemic in origin.[2] Degeneration as a cause of valvular heart disease is highly indicative of its association with the ageing of the population; as age increases from 55 to 75 year-old, the prevalence of AS and MR rises from 2% to 6% and 9% respectively.[3] In a cohort with significant AS, patients older than70 years were 56% and the nonagenarians were 38%, whereas among patients with MR the prevalences were 44% and 17%, respectively.[4] Furthermore, in patients with multiple left-sided valvular heart disease, 33% were older than 80 years.

Challenges in diagnosis

Although it has been well established that left-sided valvular heart disease is a problem increasing with age, it is still underdiagnosed in about 10% of patients 75-84 year-old and 20% of patients aged ≥85 years.[1] Thus there is an unmet need for accurate and timely diagnosis of the disease, so that appropriate treatment can be applied.

Aortic stenosis

AS is associated with adverse outcomes when there is imbalance between left ventricular hemodynamic load – mainly due to aortic valve obstruction and secondary due to increased arterial pressure- and left ventricular capacity to overcome the increased load.[5] This pathophysiological imbalance in AS leads to left ventricular hypertrophy, concentric remodeling, myocardial fibrosis and heart failure.[6] Hence, in a comprehensive approach of AS, apart from the aortic valve assessment (which is the cornerstone of the assessment), the afterload and the left ventricle have to be evaluated to define the disease severity and prognosis (Figure 1).

AS is considered severe when the peak aortic jet velocity (Vmax) is ≥4m/s, mean pressure gradient (MPG) ≥40mmHg, aortic valve area (AVA) <1cm2 and AVA index <0.6cm2/m2 assessed on echocardiography.7, 8 However the AVA and AVA index have to be evaluated because Vmax and MPG are flow dependent and in case of a high-flow condition such as anaemia, infection, hyperthyroidism, arteriovenous shunt they may overestimate severity.8

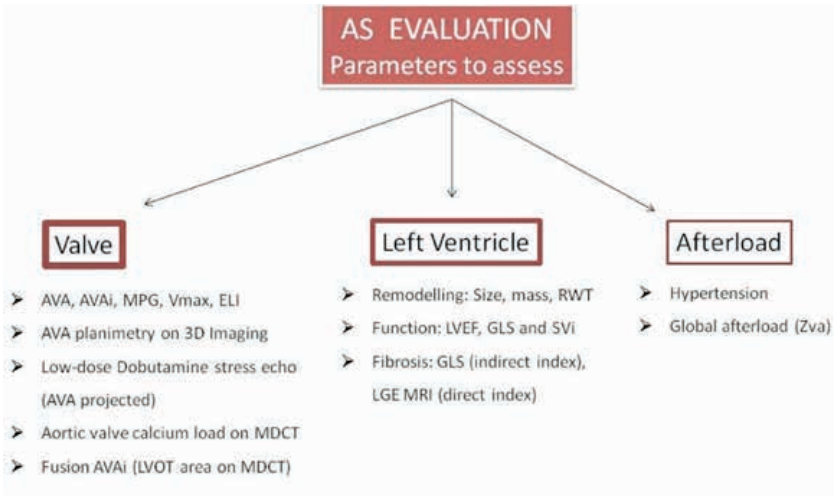

Figure 1. Severe aortic stenosis is a disease of the valve that affects the myocardium and the symptoms begin when left ventricular capacity fails to overcome the imposed afterload by the valve and the aorta. Thus for a comprehensive evaluation of AS all three parts involved have to be evaluated: 1. The Valve: by aortic valve area (AVA), AVA index to body surface area (AVAi), mean pressure gradient (MPG), maximum velocity through the valve (Vmax), energy loss index (ELI), AVA planimetry on 3-dimentional (3D) imaging such as 3D echo and cardiac computed tomography, AVA and MPG on low-dose dobutamine stress echo in classical low-gradient AS and AVA projected at normal flow in paradoxical low-gradient AS, aortic valve calcium load in Agatston units on cardiac multidetector computed tomography (MDCT), fusion AVA by combining in the continuity equation Doppler haemodynamics with left ventricular outflow tract (LVOT) planimetry area on MDCT. 2. The Left Ventricle: remodeling by evaluating the size, the relative wall thickness (RWT) and the mass, function by evaluating the left ventricular ejection fraction (LVEF), the global longitudinal strain (GLS) as an estimation of intrinsic myocardial function and the forward stroke volume index (SVi), myocardiac fibrosis evaluated directly by late gadolinium enhancement (LGE) in cardiac magnetic resonance imaging (MRI) and indirectly by GLS with the echocardiographic method of speckle tracking. 3. The Afterload: by measuring the blood pressure (systolic arterial pressure (SAP)/ diastolic arterial pressure) and estimating the global afterload with the valvuloarterial impedance (Zva) by the equation Zva = (SAP+MPG)/SVi.

About 40% of patients with severe AS have low-gradient stenosis which has been recently endorsed by the guidelines as severe under specific circumstances.9 This type of AS, also called "discordant grading" (having Vmax<4m/s, MPG<40mmHg and concomitantly AVA <1cm2 and AVA index<0.6cm2/m2), is divided into three subgroups based on the forward flow and the left ventricular ejection fraction (LVEF): 1. Low-flow, low-gradient with low ejection fraction <50% (classical low-flow low gradient), 2. Low-flow, low-gradient with preserved ejection fraction (paradoxical low-gradient) and 3. Normal-flow, low-gradient.9-11 Flow is defined as low when the forward stroke volume index assessed by Doppler echocardiography is <35ml/m2.8 The classical low-gradient type is pathophysiologically attributed to low forward flow due to reduced LVEF.12 The paradoxical low-gradient type is attributed to low-flow due to pronounced concentric remodeling and small left ventricular cavity, to diastolic dysfunction, to atrial fibrillation, to increased afterload, to MR or mitral stenosis and to tricuspid regurgitation.13, 14 Among these low-gradient cases, about 30-70% are proven to be true severe stenosis after double-checking for possible Doppler echocardiography pitfalls underestimating the gradients or undersizing the left ventricular outflow tract area, after using stress echocardiography,

advanced echo techniques or multidetector computed tomography (MDCT) cardiac analysis.[10, 11]

Patients with high-gradient severe AS or with low-gradient AS proved to be severe, if (i) symptomatic with clinically relevant symptoms and (ii) really asymptomatic but with reduced LVEF <50% or aortic Vmax >5.5m/s or Vmax increase rate ≥0.3m/s/year, benefit from surgical or transcatheter aortic valve replacement (AVR).[8, 10, 15, 16] Recently a study of 1678 asymptomatic patients with severe AS and preserved LVEF suggested that even patients with LVEF <55% benefit from AVR.[17] The treatment modality, (transcatheter or surgical) is defined by the Heart Team taking into consideration the surgical risk (Euroscore II >4% or log Euroscore >10%), patient's frailty, the type of stenosis (low-flow, low-gradient), left ventricular flow and systolic reserve (absence of reserve on dobutamine stress echocardiography) and other anatomical aspects (porcelain aorta on MDCT).[8, 10] For the low-flow, low-gradient severe AS patients the preferred treatment option is the transcatheter approach, taking under consideration that these patients have small LV cavity and small annulus and many co-morbidities; in the case of low LVEF the preferred access site is the transfemoral.[10]

Defining the time and type of treatment in AS is mainly designated by the accurate diagnosis of AS type and severity, thus multimodality imaging is the cornerstone for the diagnosis and treatment.

Challenges in diagnosis

Mitral regurgitation

MR is the second most common valvular heart disease according to EuroHeart Survey II leading to impaired quality of life and increased mortality.[2] The mitral valve has a complex anatomy that includes the mitral annulus, the leaflets, the chorda (primary and secondary), the papillary muscles and the left ventricle.[18] The proper diagnosis of regurgitation involves thorough assessment of all parts of the valvular apparatus. The quantification of the disease severity and the clarification of the regurgitant mechanism are mandatory to guide personalised patient care.[19]

MR moderate or severe (the trivial or mild is not further assessed) is classified as primary, secondary and mixed: 1. In primary type, the aetiology is the abnormal leaflet morphology (also called organic) associated with (i) normal leaflet motion (like in leaflet perforation, in endocarditis, in cleft), (ii) increased leaflet motion (leaflet prolapse or flail) or (iii) decreased leaflet motion in systole and diastole (restriction due to calcification or rheumatic valve). 2. In secondary type (also called functional), the leaflet morphology is normal (trivial leaflet thickening age-related is accepted) and the MR is attributed to pathology of the other parts of the apparatus, (i) with normal leaflet motion due to left atrial remodeling leading to mitral annulus dilatation (e.g. in atrial fibrillation) and (ii) with restricted leaflet motion only in systole due to left ventricular remodeling, ischemic or not, leading to papillary muscle apical dislocation and leaflet tethering (e.g. after myocardial infarction, dilated cardiomyopathy). 3. In mixed type, there is abnormal leaflet morphology, combined with left atrial or ventricular remodeling (e.g. hypertrophic obstructive cardiomyopathy, MR secondary to myocardial infarction and flail leaflet due to chorda rupture).[18-20]

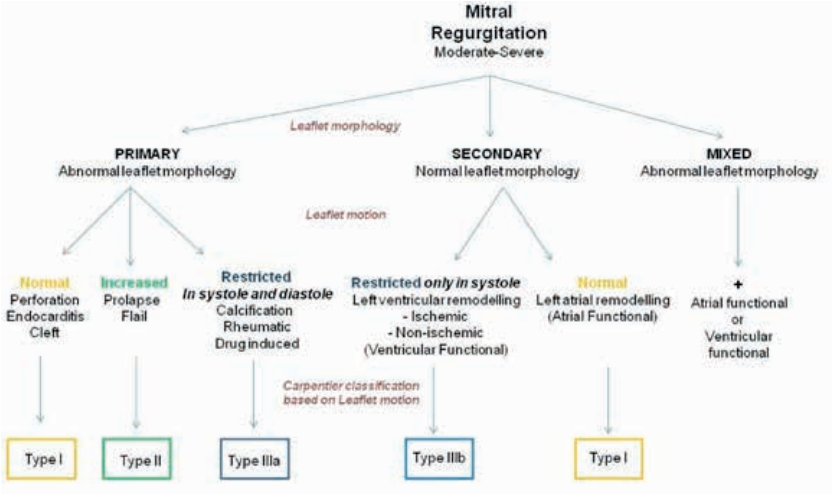

Figure 2. Mitral valve regurgitation classification based primarily on leaflet morphology (normal / abnormal) and secondary on leaflet motion (normal / increased / restricted) and their matching with Carpentier classification for surgical use.

Apart from the three types of MR described above, there is another classification proposed by Carpentier based merely on the leaflet motion that allows better communication between cardiologists and surgeons: Type I with normal leaflet motion, Type II with increased leaflet motion (prolapse or flail), Type IIIa with restricted leaflet motion in systole and diastole and Type IIIb with restricted leaflet motion only in systole.[18] The three types of MR endorsing the Carpentier classification are presented in Figure 2.

The impact of severe MR on survival is detrimental for all the disease types.[20] The treatment applied depends on the type of the MR.[8] In the case of primary MR if the patient is symptomatic the best treatment option is surgical mitral valve repair. If the patient is asymptomatic the decision for mitral valve repair relies on the left ventricular function (LVEF ≤60%), size (LVESD ≥45mm), the presence of new onset atrial fibrillation, elevated pulmonary pressures (>50mmHg), flail leaflet or severely dilated left atrium (≥60ml/m^2) in the presence of dilated left ventricle (LVESD >40mm).[8] The patients with secondary MR have worse survival than those with primary MR. However, the patients with secondary MR due to left atrial remodeling have better survival and lower incidence of heart failure compared to secondary MR due to left ventricular remodeling.[20] For the former, the optimal treatment is usually surgical restrictive annuloplasty.[21] Patients with secondary MR due to left ventricular remodeling have usually significantly dilated left ventricle and impaired LVEF, and if they are on optimal medical treatment for heart failure including cardiac resynchronisation, if indicated, the decision to operate is ambiguous, considering the lack of robust data demonstrating a survival benefit for surgery compared to medical management.[22, 23] Losartan has been recommended as an option for secondary MR after myocardial infarction because it allows the adaptive leaflet growth and modulates their profibrotic changes.[24] Cardiac resynchronization therapy is indicated not only for left ventricular functional improvement but it has been suggested to reduce functional ventricular MR by at least 1 grade.[25] If the patient remains

symptomatic under medical treatment and resynchronisation, surgical repair has an indication IIb unless concomitant revascularization can be offered upgrading the indication to IIa, according to guidelines.[8]

A community cohort study demonstrated that the patients with severe MR treated surgically are only few; 37% of those with primary MR and 7% of those with secondary MR.[20] Thus there is an unmet need for new treatments of MR. The percutaneous mitral valve edge-to-edge repair with the MitraClip implantation has arisen as an alternative option. For the primary MR patients, MitraClip has been proven in a randomised trial (EVEREST II) to be a safe and effective alternative to surgical repair, with comparable outcomes.[26] Real world studies that followed the initial randomised trial, suggested in line that the short and long term clinical events and survival post MitraClip or surgery are comparable in-between and better than optimal medical treatment alone (including resynchronization).[27, 28] However, these studies included mainly secondary MR population.[27, 28] Randomised trials for patients with secondary MR and reduced systolic function have been performed with conflicting conclusions. MITRA-FR trial suggested no survival benefit and no reduction in heart failure related hospitalisations between MitraClip and medical treatment alone at 1-year follow-up.[29] On the contrary, the COAPT trial demonstrated lower mortality and heart failure related hospitalizations at 2-years follow-up for the MitraClip group.[30] Although the two trials included patients with secondary MR, the COAPT included patients with more severe MR and MITRA-FR with more diseased left ventricle with reference to its dilation and function which could be a reasonable explanation for the opposing results.[31] Thus, is reasonable to perform MitraClip in symptomatic patients on optimal medical treatment who have severe MR (EROA >30mm^2 and/or regurgitant volume >45ml) and LVEF 20-50% with left ventricular systolic diameter <70mm.[31]

Concomitant aortic stenosis and mitral regurgitation

AS and MR are the 2 most common left heart valvulopathies and they may co-exist in about 20% of patients with severe AS.[32] The two valvulopathies are interrelated to a different extent according to their type. From the cardiac pathophysiology perspective, severe AS is leading to left ventricular remodeling that may cause papillary muscles traction and displacement and leaflet tethering leading to secondary MR. Additionally, it increases left ventricular systolic pressure, leading to increased ventricular-atrial gradient, worsening all types of MR and dilates the left atrium, through diastolic dysfunction, leading to secondary MR (left atrial remodeling).[33, 34] On the contrary, MR reduces the forward flow, by driving blood backwards to low-pressure left atrium and by increasing the prevalence of atrial fibrillation, modifying AS to low-flow, low-gradient.[33, 34] Thus, coinciding MR may be the reason of underestimation of AS and AS may be the reason of worsening MR especially if secondary. Hence, the type of each valvular disease is indicative of their interdependence, which is of paramount importance for the decision making of their treatment. It has been demonstrated that the double operation on both valves is high risk with 5-12.5% in-hospital mortality.[35] To avoid this, the guidelines suggest that surgical intervention on mitral valve is in general not necessary and that secondary MR usually improves post AVR.[8] If the MR is secondary, after AVR the effective regurgitant orifice area and the regurgitant volume are reduced significantly more than in primary MR and

at the same time left ventricular reverse remodeling with greater volume reduction occurs.[36] Apart from the secondary type of MR, other parameters associated with MR reduction post AVR alone are: absence of mitral annular calcification, high gradient AS, dilated left ventricle (left ventricular end-diastolic diameter ≥50mm, left ventricular end-systolic diameter ≥36mm), absence of atrial fibrillation, absence of pulmonary hypertension and successful AVR without aortic regurgitation and with left ventricular pressure reduction, especially if a balloon expandable transcatheter valve is implanted without prosthesis-patient mismatch.[36-38] The reduced MR post-isolated TAVR, but not after surgical AVR, has a positive impact on survival compared with the stable or increased MR.[39, 40] However, the decision of operating on mitral valve has to be taken without the a priori knowledge of the possible MR reduction. Although there are plenty of survival data regarding the impact of untreated significant MR on patients' survival post AVR, they are controversial. Whereas isolated surgical AVR or TAVR is performed some studies support that untreated MR impacts on the survival and others not.[37, 38, 41] It is of note that in low-gradient AS the prevalence of MR is higher compared to high-gradient AS, the presence of significant MR has deleterious impact on survival and TAVR treatment improves survival compared with medical treatment alone.[42] The final treatment decision, keeping in mind the interrelation of the valvular diseases and after a comprehensive evaluation of the AS and MR severity, depends on the type of the mitral valve disease: In primary MR with major anatomic lesions it is highly unlikely to experience MR reduction post AVR. Thus in low/intermediate risk patients, surgical replacement is proposed and in intermediate/high risk patients TAVR followed by transcatheter or minimally invasive surgical mitral repair. In secondary MR, isolated AVR is suggested, surgical AVR or TAVR according to Heart team, trying to avoid prosthesis-patient mismatch which is usually achieved in TAVR.[37, 38]

MULTIMODALITY IMAGING for the DIAGNOSIS of AORTIC and MITRAL VALVE PATHOLOGY

Role of advanced echocardiography

Aortic Stenosis

AS diagnosis is based mainly on echocardiography. Classically, 2-dimensional echocardiography and Doppler are used in every-day clinical practice to assess the severity of AS. Nowadays, with the endorsement of low-gradient stenosis in the spectrum of severe the classical measurements of aortic Vmax, MPG and AVA have to be done even more accurately and have been fortified by new parameters applying cutting-edge echocardiography techniques.

The Vmax and the MPG measured with continuous wave Doppler have to be estimated from the cardiac apex and additionally from the right parasternal side with a stand-alone probe and from subcostal and suprasternal site, wherever the Doppler beam is in line with the blood flow, to ensure that the highest possible Vmax and MPG is obtained, avoiding underestimation of the stenosis or pseudo-low-gradient stenosis.[43] The acceleration time of

this signal is then measured AT>110msec and its ratio over ejection time AT/ET >0.36 are indicative of severe AS.[9] The pulsed wave Doppler signal at the left ventricular outflow tract has to be representative of laminar flow and should be traced after reducing the gain and increasing the reject of the echocardiography device. Afterwards the Doppler velocity index can be estimated from the equation DVI=VTI LVOT / VTI aortic, <0.25 is indicative of severe stenosis.[9] All the aforementioned measurements of transvalvular gradient have to be performed after normalization of the blood pressure, because arterial hypertension may lead to underestimation of the gradient, thus in a pseudo-low-gradient.[44] The left ventricular outflow tract diameter has to be measured at the parasternal long axis at the hinge points or just below in mid-systole avoiding the presence of valve calcium. The area is then estimated from the equation 0.785xdiameter^2 assuming that it is circular. However, it has been well demonstrated that LVOT is oval in shape. Thus it is more accurate to evaluate it by direct planimetry at 3-dimentional echo where the real short axis of the LVOT can be seen en-face and measured.[45] This measurement is more accurate when transoesophageal echo is performed. The stroke volume is then estimated from the equation LVOT area x VTI LVOT. After indexing to BSA the flow state can be defined based on the SVi. AVA is estimated from the continuity equation (the flow that goes through LVOT in 1 beat is the same with the flow through aortic valve in 1 beat, preferably measured at stable heart rate) using all the measurements described above. This area corresponds to the effective orifice area, which is the area of the vena contracta of the forward flow jet, i.e. the narrowest area of the jet. However, AVA can be measured with direct planimetry of the valve opening in a short axis view or more accurately at a 3D transoesophgeal short axis view tracing at the tips of the cusps, evaluating the anatomic valve area which is usually bigger, estimating the area at the tips of the cusps and not downstream at the narrowest point of the forward flow.[46] In the case of a small aorta with diameter <3cm the AVA with continuity may overestimate the severity of the stenosis because it doesn't account for the pressure recovery.[47] For such patients the energy loss index = [(AVAxAortaArea)/(AortaArea-AVA)]/BSA is a better measure of the stenosis severity as it estimates the net pressure imposed to left ventricle after the kinetic energy partly convers to static. This pressure is comparable to the pressure measured with the wire in the catheterization laboratory and for this reason energy loss index improved the prediction of events due to AS compared to AVA.[48]

Stress echocardiography is a modality applied in AS for severity assessment in low-gradient patients and for risk stratification in asymptomatic patients.[49] Low dose (till 20mg/Kg/min) dobutamine stress echo is performed in low-gradient patients with reduced ejection fraction for the assessment of severity and risk stratification.[8] If during the test the MPG increases >40mmHg and AVA remains <1cm^2 the test is indicative of severe stenosis, if the MPG remains <40mmHg and AVA increases >1cm^2 the stenosis is moderate (pseudo-severe) and if MPG remains <40mmHg and AVA remains <1cm^2 the test is inconclusive so far, due to lack of flow reserve and the next step is to calculate the AVA projected at normal flow conditions (250ml/min), if the flow increases by 20%, and if AVA projects <1cm^2 the stenosis is severe.[50-52] A recent study suggests that AVA projected is the best parameter to clarify severity in dobutamine stress echo.[53] The presence of flow reserve during the test, i.e. increase of the stroke volume >20%, is considered a sign

of good prognosis.[52] However, even patients without flow reserve are doing better after surgical replacement compared to medical treatment and more recently after transcatheter replacement the survival was comparable in between the 2 groups of flow reserve.[54-56] It is of note that after TAVR the LVEF improves independently of the flow reserve.[54, 55] In low-flow, low-gradient patients with preserved ejection fraction, the low-dose stress echo has restricted application. It has been proposed to be used for the evaluation of the AVA projected at normal flow, indicating severe stenosis if AVA <1cm^2, or AVA index < 0.55cm^2/m^2.[57] In asymptomatic patients exercise stress echocardiography may reveal symptoms neglected by the patient or blood pressure fall below baseline indicative of bad prognosis urging to AVR besides the echocardiography findings.[52, 58] An increase of the transaortic MPG by >18mmHg, a systolic pulmonary artery pressure >60mmHg or absence of contractile reserve during exercise defined as drop or increase less than 4-5% of the LVEF are indicative of AS related events and valve replacement should be considered.[52, 58]

Mitral Regurgitation

Echocardiography is the cornerstone diagnostic method to assess all the parts of the mitral valve apparatus (left ventricle, papillary muscles, chorda, leaflets and annulus) and to evaluate MR severity and type in order to do a comprehensive assessment of MR. Transthoracic echocardiography is the first step in this approach for assessing mitral valve pathology on grey scale, left ventricular and atrial size and function and then perform qualitative and quantitative MR evaluation.[59] Normal sized left ventricle and left atrium exclude chronic severe MR.[59] MR is a dynamic phenomenon and as such before echo the heart rate, rhythm and blood pressure have to be monitored. In the qualitative assessment the type of MR has to be evaluated as described above (Figure 2) and MR jets have to be described by number, direction and duration in systole. The quantitative assessment is based on the Colour Doppler, continuous wave Doppler and pulsed wave Doppler. An area of the regurgitant jet >50% of the left atrium and a vena contracta width >7mm are indicative of severe MR.[8, 18] Proximal isovelocity surface area (PISA) is used for evaluating the effective regurgitant orifice era >0.4cm2, the regurgitant volume >60ml, the regurgitant fraction >50% and radius >1cm at Nyquist limit 30-40cm/s. These cut-offs are endorsed by the European society of Cardiology for primary MR. For secondary MR the lower cut-offs of effective regurgitant orifice area >0.2cm^2 and regurgitant volume >30ml are proposed.[8] However, the American Heart Association/ American College of Cardiology approve the former cut-offs only for both primary and secondary MR.[7] Vena contracta and PISA method may overestimate severity based on EROA in case of non-holosystolic MR, thus regurgitant volume has to be estimated. On the contrary PISA may underestimate severity in case of small size patient with small left ventricular cavity.[18] The continuous wave Doppler used in PISA inform us about the duration of MR in systole and about the peak velocity, considering that the beam is aligned with the blood flow, which is indicative of the left atrial pressure (the lower the velocity the higher the atrial pressure).[18] Pulsed wave Doppler should be used for the mitral inflow with E wave >1.2m/sec indicative of severe MR and for pulmonary vein signal with systolic flow reversal indicative of severe MR.[59]

Transoesophageal echocardiography with the use of 3D imaging is necessary for better visualization of the complex mitral valve apparatus in case the findings on transthoracic are indeterminate or discordant and before any intervention, surgical or transcatheter repair. The 3D imaging enables the operator to specify the type of valve disease, to identify a leaflet cleft or perforation, to name the prolapsing scallop, to check the commissures, to apply PISA method more accurately.[59] It has been demonstrated that 3D echocardiography assesses the effective regurgitant orifice area more accurately than 2D and is comparable to MRI, by planimetry of the vena contracta area, perpendicular to the flow direction at the narrowest position.[60] Subsequently the regurgitant volume is more accurate too.[60] Before the transcatheter repair with MitraClip, 3D transoesophageal echocardiography has to be performed to predict the feasibility of the method. If the segment 2 prolapses, there is no calcification, the flail gap on 4 or 5 chamber view is <10mm, the flail width on short axis is <15mm, the mitral valve area is >4cm^2 and the transmitral gradient is <4mmHg there is a high chance of a successful MitraClip implantation.[59]

Exercise stress echocardiography may be applied in primary MR. In asymptomatic patients it may reveal symptoms or systolic pulmonary pressure ≥60mmHg for risk stratification. In symptomatic primary MR that is at least moderate, an increase of MR severity by ≥1 grade, or systolic pulmonary pressure ≥60mmHg are indicative of worse prognosis. Moreover, absence of contractile reserve of left ventricle (LVEF increase <5%) or right ventricle (TAPSE <18mm) are associated with poor outcome.[52,61] In secondary MR, exercise stress echocardiography may predict worse prognosis if an increase of the effective regurgitant area by ≥13mm^2 is demonstrated or if dynamic pulmonary systolic pressure ≥60mmHg is measured.[52]

Role of multidetector computed tomography

Aortic Stenosis

Cardiac computed tomography angiography, including a non-contrast acquisition as the first step of an exam, can be used to calculate the coronary artery calcium with the Agatston method. This technique has been extrapolated to aortic valve calcium. Thus, with a simple acquisition the aortic valve calcium can be estimated in arbitrary units.[62] The more the calcium detected on the valve the more severe the stenosis grade is. This has been endorsed by the guidelines with a cut-off >3000AU for men and >1600AU for women indicating a high likelihood of severe stenosis.[8] Aortic valve calcium evaluation is of paramount importance in the discordant low-gradient group of patients because it can discriminate severe from moderate stenosis after adjustment for the aortic annulus area and for the body surface area in a reproducible and personalized way.[63] The clinical significance of the aortic valve calcium load has been well recognized because it has been associated with the mortality of AS patients beyond clinical parameters and Doppler echocardiographic criteria.[64]

The contrast MDCT has the best spatial resolution among all other imaging modalities. Thus its role in evaluating the aortic valve is gradually evolving. The aortic valve can be seen "en-face" at a double oblique transverse view (the real short axis of the valve) and a complete anatomical analysis can be easily done.[65] The type of valve, tricuspid or bicuspid, the extent of valve

calcification and its exact location (which cusp and where), the length of each leaflet, the left, right and non-coronary sinuses diameter and the AVA with planimetry can be estimated (of note this is the anatomical area not the hemodynamic) in diastole at 75% of the cardiac cycle and in systole at phase 35%.[65, 66] The aortic annulus area and perimeter can be accurately measured by planimetry at the real short axis, allowing accurate sizing of the prosthetic valve in severe AS patients in order to avoid prosthesis patient mismatch and paravalvular regurgitation after the implantation of a transcatheter valve.[67] Then the aortic root can be evaluated, the diameter of sinotubular junction and the distance of the coronaries origin from the annulus in the pre-TAVR assessment to avoid obstruction of the coronaries.[65, 66] An area that always has to be accurately measured for the diagnosis of severe AS is the left ventricular outflow tract. It has been demonstrated that this area is not circular but oval in shape and thus calculating it by one diameter as a circle instead of measuring the area by planimetry on 3-dimentional echocardiography imaging leads to overestimation of AS.[68] The next step evolution is the introduction of the planimetered area on MDCT (Figure 3) in the continuity equation.

Mitral Regurgitation

MDCT has been recently applied to illustrate based on its best spatial resolution the complex mitral valve. The quantification of MR by PISA method has been described above and the value of 3D imaging for the more accurate measurement of effective regurgitant area has been annotated. A study including primary and secondary MR proposed the integration of real cross-sectional mitral effective regurgitant area measured on the 3D volume dataset taken by MDCT in the PISA equation and proved that the fusion regurgitant volume estimated significantly reclassified 7/73 patients from severe MR according to echocardiography to non-severe MR and 10/73 from non-severe to severe MR grade.[69] Secondary MR due to atrial remodeling - type I Carpentier – has been studied and confirmed that mitral annulus area and perimeter measured by planimetry on short axis were independently associated with significant MR, shading light to the pathophysiology of atrial functional MR.[70] In primary MR, MDCT can reliably detect the prolapsing scallop by cross-referencing long-axis views with short-axis views of the various scallops and can evaluate left ventricular and left atrial size.[71] Moreover, the use of MDCT has been explored for annulus evaluation of size and calcifications (extent, location) which is important in planning percutaneous mitral prosthesis implantation.[72] Another important role of MDCT is to predict the left ventricular outflow tract obstruction after the implantation of transcatheter prosthesis achieved by 2 means: 1. By evaluating the aorto-mitral angle created by the left ventricular outflow tract long-axis and the mitral annular trajectory line; the risk of obstruction is high at 90° and lowest when the two valves are almost parallel and the angle almost 0°. 2. By using the dedicated software created for evaluating the neo-outflow tract.[73]

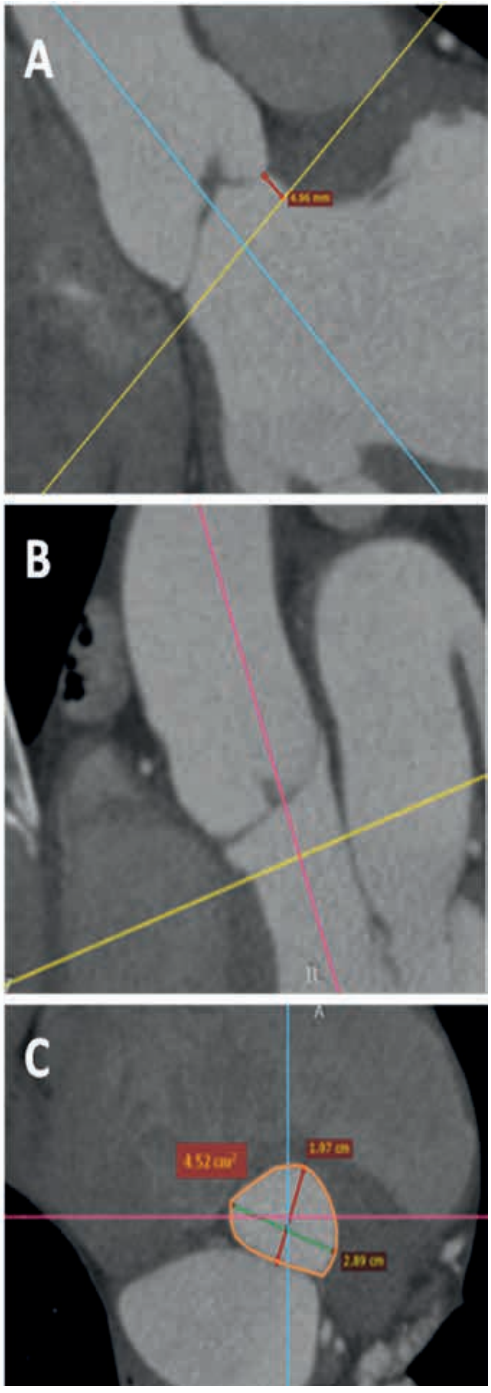

Figure 3. Cardiac multidetector computed tomography provides a 3-dimentional cardiac volume and by applying the tri-planar orthogonal system in the coronal (A) and saggital (B) view at the level of left ventricular outflow tract (LVOT) ie 5mm below aortic annulus, the double-oblique view is created (C) where the real LVOT short axis can be seen. Then, the LVOT area can be accurately measured by planimetry of the area.

LEFT VENTRICULAR SYSTOLIC FUNCTION ASSESSMENT IN LEFT-SIDED VALVULAR HEART DISEASE

Clinical value of global longitudinal strain

Global longitudinal strain (GLS) derived by speckle tracking echocardiography has emerged as an alternative way to assess LVEF. This technique is based on detecting and following the movement of myocardial speckles in the longitudinal way. Its advantage is that it is relatively independent of preload and afterload changes compared to LVEF and that it evaluates the intrinsic myocardial function and not on the volumetric changes of left ventricle which is the case in LVEF.[74, 75] Moreover, the changes in pressure and volume loading conditions of the left ventricle may cause myocardial diffuse interstitial fibrosis and focal mid-wall fibrosis starting from the basal parts of the ventricle in AS or subendocardial interstitial fibrosis in MR, which can be indirectly detected by GLS.[76, 77] In this regard, the clinical value of GLS in valvular heart disease should be appreciated.

Aortic stenosis

AS is a disease of the valve and myocardium. The increased pressure overload causes left ventricular hypertrophy with excess mass, relative wall thickness increase and concentric hypertrophy. When the left ventricle cannot further compensate for the imbalance with the afterload, LVEF deteriorates, the haemodynamic consequences of the disease become obvious and symptoms become clinically apparent.[78] It has been demonstrated that GLS worsens as the severity of the valve disease progresses, although LVEF remains stable.[79] GLS has been suggested as a more sensitive marker of subtle myocardial dysfunction before the LVEF is reduced and the symptoms appear.[79, 80] This is of paramount importance as it could lead to AVR before any ischemic, systolic and diastolic damage is done to the myocardium and in advance of irreversible structural and functional myocardial changes.[78, 80] Figure 4 demonstrates such a case. The guidelines propose for the asymptomatic severe AS the cut-off 50% for LVEF as an indication to AVR. However, there are studies challenging this cut-off as too low by demonstrating that when LVEF is lower than 60% there is a decline to outcome.[81, 82] Maybe it is time to incorporate in the formal assessment of asymptomatic AS the GLS as an expression of early endomyocardial dysfunction irrespective of left ventricular remodeling that may preserve the LVEF.[78, 80] For such patients the GLS >-18% has been suggested for an integrate approach of stenosis severity, timely treatment decision and better clinical outcome.[78, 83]

AS has been categorised according to forward flow and gradient and the groups of low-flow low-gradient with reduced (classical) or preserved (paradoxical) LVEF have been recognised as severe AS. GLS has a prominent role in enlightening the pathophysiology of low-gradient severe AS with preserved LVEF. Left ventricular remodeling with thick walls and small cavity has a compensatory effect to intrinsic myocardial dysfunction and creates a supernormal LVEF, while the GLS is impaired.[84] This impaired GLS is an

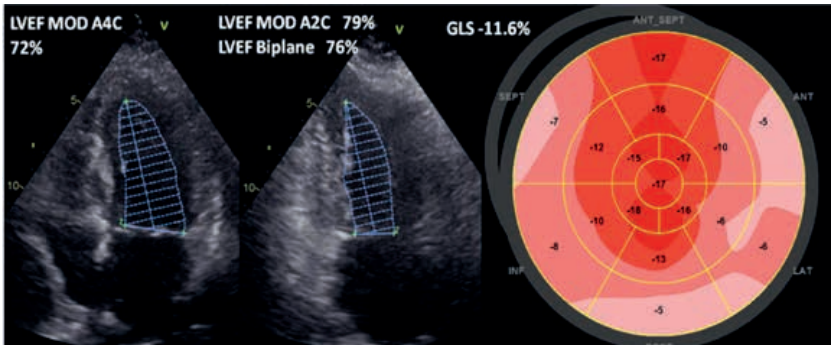

Figure 4. In an asymptomatic patient with severe aortic stenosis and preserved left ventricular ejection fraction (LVEF 76%), the global longitudinal strain GLS evaluated by speckle tracking echocardiography is impaired -11.6%, and worse in the basal segments of the left ventricular myocardium, indicating endomyocardial dysfunction.

explanation of the low-flow and thus low-gradient condition although LVEF remains preserved.[14] However, the prognostic value of GLS in these patients is not well elucidated. On the contrary for the patients with low-flow, low-gradient with reduced LVEF, GLS prognostic value has been proven by studies from the TOPAS cohort.[85] GLS is impaired alongside with LVEF but has independent prognostic value measured at rest and stress during the low-dose dobutamine stress echo that the TOPAS patients undergone.[86] Recently, the GLS cut-off of >-12% has been suggested to identify patients with lack of reverse remodeling after TAVR.[87]

GLS not only detects the subtle myocardial changes and defines the prognosis in severe AS with high or low gradient; it has also the ability to elicit subtle changes in myocardial function post AVR when the pressure overload is retracted. After 1.5 years of surgical AVR, GLS improves although LVEF is still stable and this is due to afterload reduction rather than mass reduction or reverse remodeling.[88] After TAVR in AS patients the GLS improved at 1-year follow-up and the greatest the improvement the lower the mortality rate.[89] However, there are scarce data about the left ventricular functional recovery after TAVR in low-gradient AS.

Mitral regurgitation

In order to avoid the poor outcome of primary MR it has to be repaired at the proper time, which is defined by symptoms or by LVEF and left ventricular dilation in asymotomatic patients.[8] In severe MR volume overload and emptying of the ventricle partly to a low pressure cavity, left atrium, leads to increased LVEF, because this is merely volume dependent. Thus LVEF may not accurately reflect myocardial performance or may mask myocardial dysfunction. Left ventricular GLS in such patients has been independently associated with survival after mitral valve repair and GLS <-20% has been proposed to define the appropriate timing of surgical repair (Figure 5).[90] Pre-operative GLS has increased prognostic value when added on top of the classical proposed by guidelines factors such as age, left atrial size, LVEF, atrial fibrillation.[91] Thus in primary MR GLS enables early detection of subtle myocardial dysfunction designating the optimal surgical timing for better outcome.

The clinical and prognostic value of GLS has been scarcely investigated in secondary MR. A study of 41 patients with secondary MR, treated with MitraClip demonstrated that GLS was the only independent predictor of cardiac events at 2-years follow-up.

Clinical value of forward stroke volume

Aortic Stenosis

The forward flow is a parameter of paramount importance in the assessment of AS severity. The low-flow defined as stroke volume index ≤35ml/m^2 may be the reason for low-gradient although the AS is severe. Thus, the forward stroke volume has been implemented in the guidelines for the assessment and categorization of AS.[7, 8] The low-flow may be attributed to the low LVEF called "classical low-flow" or to the small left ventricular cavity due to remodeling or diastolic or intrinsic systolic dysfunction, despite the preserved LVEF called "paradoxical low-flow". If the low-flow is associated with high gradient AS, this is indicative of super severe AS, implying that the aortic valve opening is so small that the pressure gradient is elevated even though the forward flow through the valve is low.[14]

The forward stroke volume, having such a prominent role in diagnosis and classification of severe AS, has been inevitably studied for its clinical consequences. The patients with preserved LVEF and low-flow, low-gradient severe AS had worse survival compared with the high-gradient AS patients after AVR and when they followed conservative treatment their survival was as poor as or even worse than the high-gradient AS patients treated medically.[92, 93] The normal-flow, low-gradient, preserved LVEF AS patients had survival comparable to the moderate AS and better that the low-flow, low-gradient.[94] However, in another study, the normal-flow low-gradient AS patients who were treated medically had comparable outcome with the low-flow low-gradient AS patients, creating a controversy.[15] When all AS patients were treated with AVR the 10-year survival was worse for those with low-flow (low-flow, low-gradient 37±10% and low-flow, high gradient 51±8%) and better for those with normal flow (normal-flow low-gradient 61±7% and normal-flow, high-gradient 68±4%).[16]

Patients with low LVEF that leads to low-flow (classical low-flow low-gradient AS) are at very high surgical risk. However, these patients if left untreated (under medical care without AVR), have poor prognosis and very high

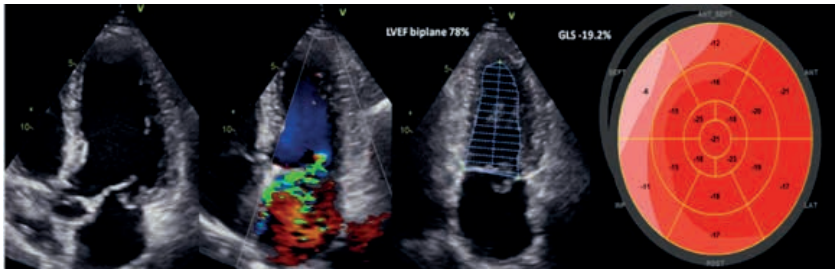

Figure 5. A case of an asymptomatic patient with primary organic mitral regurgitation due to posterior leaflet prolapse and preserved left ventricular ejection fraction (LVEF 78%) who has impaired global longitudinal strain by speckle tracking echocardiography (GLS -19.2%). According to the impaired GLS that was worse than -20% the patient was considered for surgical mitral valve repair.

mortality rate.[11, 56] On the other hand their survival is significantly improved with surgical AVR especially if there is flow-reserve, i.e. stroke volume increase by >20%, during the low-dose dobutamine stress echocardiography. Otherwise, there is high operative mortality.[56] This obstacle of the peri-operative mortality for those patients has been surpassed nowadays by treating them with TAVR; the presence or absence of forward flow reserve had no impact on the survival post-TAVR and furthermore, LVEF improved in both patient groups.[54]

When all AS patients were treated with TAVR the low-flow was an independent predictor of poor survival.[95, 96] However, the outcome was significantly better for the low-flow patients if treated with TAVR, which is the preferred method of treatment, compared to medical care alone.[95] Even the patients with heart failure and low-flow with moderate AS may be considered for TAVR, to unload the left ventricle and increase the forward flow, but the answer to these triggering thoughts will be given after the completion of the UNLOAD trial.[97]

In case this low-flow state is not improving after TAVR and remains low at discharge, it is indicative of poor outcome.[98]

Mitral Regurgitation

In MR patients LVEF may be increased without corresponding to good left ventricular function, because it merely represents a change in total left ventricular volume from diastole to systole without taking into consideration where the blood goes. In MR the left ventricle partially empties into the low-pressure left atrium, instead of the high-pressure aorta. Thus the forward left ventricular flow and the blood supply to the periphery is reduced. Thus, the forward stoke volume and forward ejection fraction (forward stroke volume expressed as a percentage of left ventricular end-diastolic volume) may be better predictors of left ventricular function and more clinically relevant. Comparing with AS, in MR the patients with preserved LVEF and low-flow state can be identified. Although the impact of forward flow on AS prognosis has been extensively studied and the low-flow has been recognized to be deleterious on survival, its role in MR has not been yet elucidated.

OBJECTIVES AND OUTLINE OF THE THESIS

The current thesis explores the most common left-sided valvular heart diseases: AS and MR. By applying novel techniques such as deformation imaging by echocardiography and 3-dimentional imaging with excellent spatial resolution by MDCT the diagnosis of left-sided valvular heart disease and its prognosis after surgical or novel transcatheter treatment, is enlightened through this thesis.

Part I focuses on aortic valve stenosis diagnosis and management. Chapter 2, explores the use of fusion AVA for reclassification of AS severity in patients with low-gradient AS and preserved LVEF, by implementing the planimetered left ventricular outflow tract area on MDCT in the continuity equation. In chapter 3 the diagnosis and management of AS in patients with heart failure and reduced ejection fraction are reviewed. Chapter 4, aims to prove that left ventricular functional recovery and reverse remodeling occurs after TAVR in patients with low-flow and low-gradient AS with reduced or preserved ejection fraction. Chapter 5 refers to the management of severe AS with surgical sutureless or transcatheter aortic valves and aims to compare the hemodynamic performance of the two different valve types and the impact clinical outcomes in propensity score-matched high-risk populations.

Part II focuses on secondary mitral valve regurgitation diagnosis and management. Chapter 6 aims to investigate whether in patients with secondary MR, speckle tracking GLS is an alternative and better, than LVEF, way to assess left ventricular systolic function. Chapter 7 studies patients with non-ischemic dilated cardiomyopathy and secondary MR and evaluates left ventricular reverse remodeling and increase of forward flow after mitral valve repair.

Part III studies the prognosis of AS and MR. Chapter 8, evaluates the calcium of aortic and mitral valve detected on contrast-enhanced MDCT and its association with the outcome in patients with suspected coronary artery disease. Chapter 9 studies the impact of left ventricular forward flow and GLS on outcome post AVR in patients with low-gradient severe AS and preserved LVEF. In chapter 10, patients with severe secondary MR are evaluated with the aim to identify the prognostic implications of left ventricular forward flow after surgical mitral valve repair.

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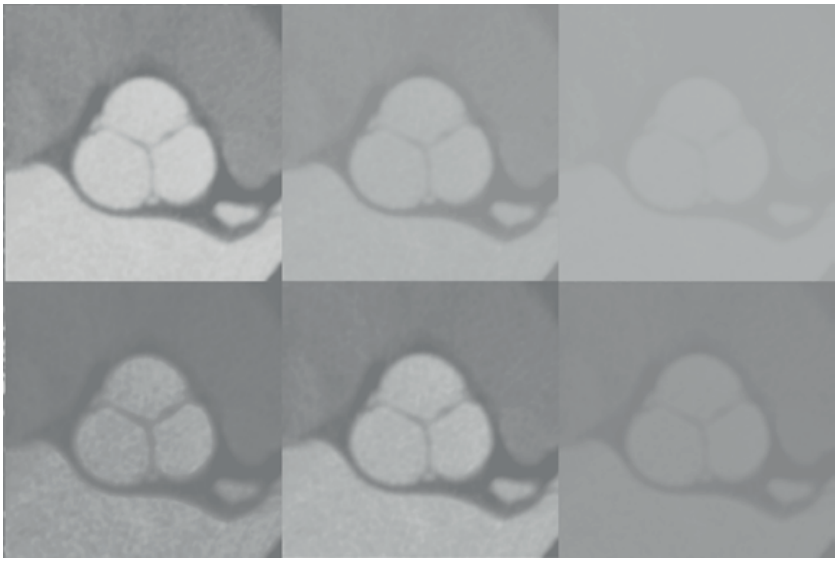
PART I

AORTIC VALVE STENOSIS: DIAGNOSIS AND MANAGEMENT

CHAPTER 2

Low gradient severe aortic stenosis with preserved ejection fraction: reclassification of severity by fusion of Doppler and computed tomographic data



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ABSTRACT

Aims

Low gradient severe aortic stenosis (AS) with preserved left ventricular ejection fraction (LVEF) may be attributed to aortic valve area index (AVAi) underestimation due to the assumption of a circular shape of the left ventricular outflow tract (LVOT) with 2-dimensional echocardiography. The current study evaluated whether fusing Doppler and multi-detector computed tomography (MDCT) data to calculate AVAi results in significant reclassification of inconsistently graded severe AS.

Methods and results

In total, 191 patients with AVAi <0.6cm2/m2 and LVEF ≥50%, (mean age 80±7 years, 48% male) were included in the current analysis. Patients were classified according to flow (stroke volume index <35 or ≥35 ml/m2) and gradient (mean transaortic pressure gradient ≤40 or >40 mmHg) into 4 groups: normal flow - high gradient (n=72), low flow - high gradient (n=31), normal flow - low gradient (n=46) and low flow - low gradient (n=42). LVOT area was measured by planimetry on MDCT and combined with Doppler hemodynamics on continuity equation to obtain the fusion AVAi. The group of patients with normal flow - low gradient had significantly larger AVAi and LVOT area index compared with the other groups. Although MDCT-derived LVOT area index was comparable among the 4 groups, the fusion AVAi was significantly larger in the normal flow - low gradient group. By using the fusion AVAi, 52% (n=24) of patients with normal flow - low gradient and 12% (n=5) of patients with low flow - low gradient would have been reclassified into moderate AS due to AVAi ≥0.6cm2/m2.

Conclusion

The fusion AVAi reclassifies 52% of normal flow - low gradient and 12% of low flow - low gradient severe AS into true moderate AS, by providing true cross-sectional LVOT area.

INTRODUCTION

Patients with inconsistently graded severe aortic stenosis (AS), defined by an aortic valve area index (AVAi) <0.6cm2/m2 and low mean transaortic pressure gradient (≤40mmHg), pose a diagnostic and therapeutic challenge.1 Particularly, in patients with preserved left ventricular (LV) ejection fraction (LVEF), severe AS with discordant gradient may be observed in 30% of patients.2 One of the factors underlying this inconsistent grading of AS severity is the assumption of a circular geometry of the LV outflow tract (LVOT) when using 2-dimensional echocardiography, introducing in the continuity equation a squared error.3 Initial studies in AS patients, using 3-dimensional imaging techniques (3-dimensional echocardiography or multi-detector computed tomography [MDCT]) have shown that the introduction of the planimetered LVOT area in the continuity equation leads to a significantly larger aortic valve area compared with the use of 2-dimensional echocardiography derived LVOT diameter.4, 5 However, the inclusion of patients with low flow due to systolic LV dysfunction may introduce another error in the evaluation of AS severity which can be unmasked by performing dobutamine stress echocardiography. By including patients with low gradient AS and preserved LVEF, this confounding factor is obviated.6 The present evaluation fused MDCT and echocardiography data to derive aortic valve area and assessed the impact of MDCT-derived LVOT area on AS severity grading in patients with low gradient severe AS and preserved LVEF.

METHODS

Patients

Patients with severe AS (AVAi <0.6cm^2/m^2) and preserved LVEF (≥50%) who underwent transcatheter aortic valve replacement were evaluated with transthoracic echocardiography and MDCT prior to the procedure. Patients with more than moderate aortic or mitral regurgitation, or prosthetic aortic valves were excluded.

Clinical, echocardiographic and MDCT data were prospectively collected and stored on a dedicated departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and were retrospectively analyzed. The Institutional Review Board approved this retrospective analysis of clinically acquired data and waived the need for patients' written informed consent.

Echocardiography analysis

Comprehensive 2-dimensional and Doppler transthoracic echocardiography was performed with a commercially available ultrasound system (Vivid-7 and E9, General Electric, Horten, Norway) equipped with 3.5 MHz or M5S transducers. Data were stored digitally and analyzed offline on a dedicated workstation (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). Aortic valve area was estimated by the continuity equation according to current echocardiography guidelines and then indexed to body surface area.[3, 7] From the LV apical long-axis or 5-chamber views, continuous wave Doppler spectral recordings through the aortic valve were obtained and the mean pressure gradient was estimated with the modified Bernoulli equation.[3] The highest aortic valve velocity was obtained systematically in all patients and was found in non-apical locations in 16 (35%) of patients. The LVOT area was derived from the LVOT diameter measured on a zoomed parasternal long-axis view, 5 mm below the aortic annulus. The velocity time integral was measured on the spectral pulsed wave Doppler recordings of the LVOT obtained from the LV apical long-axis or 5-chamber views with the sample volume located 5 mm below the aortic annulus. Stroke volume index (SVi) was then calculated as previously described and indexed to body surface area.[8, 9] From the LV apical 4- and 2-chamber views, the LV volumes and LVEF were assessed using the Simpson's biplane method.[10] From the parasternal long-axis views, using M-mode recordings of the LV, the LV mass was calculated with the Devereux formula and then indexed to body surface area.[10] The global LV afterload was assessed by calculating the valvulo-arterial impedance according to the formula Zva= (systolic arterial pressure + mean pressure gradient) / SVi and the pulsatile arterial load by the systemic arterial compliance from the formula SAC= SVi x (systolic – diastolic arterial pressure).[8, 9, 11]

Based on SVi, patients with low gradient severe AS were classified into 4 groups: 1. Normal flow - high gradient (SVi >35 ml/m^2 and mean pressure gradient >40mmHg), 2. Low flow - high gradient (SVi ≤ 35 ml/m^2 and mean pressure gradient >40mmHg), 3. Normal flow - low gradient (SVi >35 ml/m^2 and mean pressure gradient ≤40mmHg), 4. Low flow - low gradient (SVi ≤ 35 ml/m^2 and mean pressure gradient ≤40mmHg).[12]

Table 1. Clinical characteristics among the four groups of severe aortic stenosis with preserved ejection fraction

Clinical Characteristics	Normal Flow High Gradient (n=72)	Low Flow High Gradient (n=31)	Normal Flow Low Gradient (n=46)	Low Flow Low Gradient (n=42)	p-value*
Age, years	80±7	81±7	81±7	79±7	0.67
Male, n (%)	33 (45.8)	14 (45.2)	20 (43.5)	25 (59.5)	0.42
Body surface area, m^2	1.87±0.21	1.86±0.23	1.83±0.21	1.90±0.20	0.56
Hypertension, n (%)	54 (75.0)	26 (83.9)	39 (84.8)	36 (85.7)	0.41
Diabetes, n (%)	19 (26.4)	10 (32.3)	13 (28.3)	13 (31.0)	0.92
Hyperlipidemia, n (%)	43 (59.7)	18 (58.1)	32 (69.6)	31 (73.8)	0.36
Coronary artery disease, n (%)	42 (58.3) ¥	22 (71.0)	35 (76.1)	36 (85.7) †	0.01
Systolic arterial pressure, mmHg	143±22	142±20	142±24	135±23	0.37
Diastolic arterial pressure, mmHg	69±11	72±12	70±12	71±12	0.54

* ANOVA or Chi-square overall comparison within the four groups.
† vs Normal Flow - High Gradient group.
¥ vs Low Flow - Low Gradient group

MDCT data acquisition and analysis

MDCT scans were performed using a 64- or a 320-detector row computed tomography scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan and Aquilion ONE; Toshiba Medical Systems, Tochigi-ken, Japan, respectively). With the 64-detector row system, the data were acquired with a collimation of 64 x 0.5 mm, a gantry rotation time of 400 ms and a tube current set of 300-400 mA. With the 320-detector row system, the collimation was set at 320 x 0.5mm, the gantry rotation time was 350 ms and the tube current was 400 to 580 mA. The voltage was 100, 120, or 135 kV, depending on body mass index of the patients. A prospectively ECG-triggered coronary calcium computed tomography data set was obtained. Then, a contrast-enhanced scan was performed and the dataset was reconstructed at 75% (diastolic phase) and 30-40% (systolic phase) of the RR interval, according to the local protocol.[13] All the reconstructed datasets were stored to a remote dedicated workstation for off-line analysis (Vitrea 2, Vital Images, Plymouth, Minnesota).

From the coronary calcium computed tomography dataset, the aortic valve calcium burden was evaluated using the Agatston method.[14] In order to adjust for patients' body size the aortic valve calcium density and the aortic valve calcium index were calculated by indexing calcium to MDCT-measured aortic annulus area and body surface area, respectively.[15] From the contrast-enhanced dataset, the 3 multiplanar reformation planes were aligned on the standard orthogonal coronal and sagittal views to obtain the double oblique transverse view of the aortic valve. On systolic phase, the LVOT area was measured by planimetry, 5 mm below the predefined aortic annulus level. LVOT area was then indexed to body surface area.

Fusion of Doppler with MDCT data

By combining hemodynamic echocardiographic data and LVOT area measured on contrast-enhanced MDCT, the fusion AVAi was calculated introducing the MDCT-derived LVOT area in the continuity equation formulae:

$$Fusion\ AVAi = \left(\frac{MDCT\ LVOT\ area \times Echo\ VTI\ PW\ LVOT}{Echo\ VTI\ CW\ Aortic\ Valve} \right) \Big/ Body\ Surface\ Area$$

where VTI is the velocity time integral, PW is pulse wave Doppler and CW is continuous wave Doppler. An example demonstrating the evaluation of echocardiographic and fusion AVAi in a patient with normal flow - low gradient severe AS is shown in Figure 1.

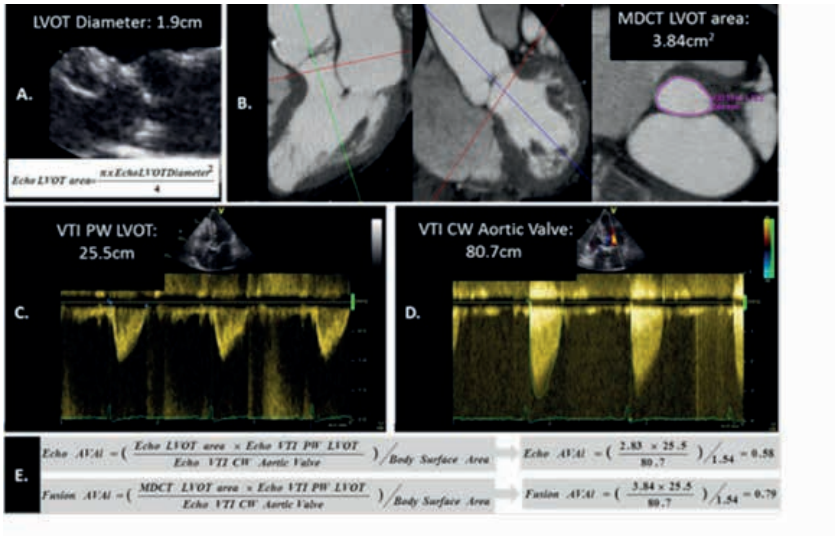

Figure 1. Aortic valve area index (AVAi) evaluated by echocardiography (Echo) and by fusion of multi-detector computed tomography (MDCT) and Doppler-echocardiographic data. By echocardiography, the left ventricular outflow tract (LVOT) diameter was measured 5 mm below the aortic annulus and the LVOT area was estimated (A). Using MDCT, the LVOT area was planimetered at the reconstructed double-oblique transverse view in systole, 5 mm below the annulus (B). The velocity time integral (VTI) of the flow at the LVOT was measured on pulsed wave (PW) Doppler recordings obtained from the apical 5-chamber view with the sample volume located 5 mm below the aortic annulus (C). The VTI of the flow at the aortic valve was measured on continuous wave (CW) Doppler recordings (D). By applying the continuity equation, the echo and the fusion AVAi were evaluated by using the echo-estimated LVOT area and the MDCT-derived LVOT area respectively (the Doppler hemodynamics as described in C & D were consistently used) (E).

Statistical analysis

Categorical variables are expressed as frequencies (percentage) and were compared with the X^2 test. Continuous variables are expressed as mean±-standard deviation, if normally distributed and as median and interquartile range if non-normally distributed. Comparisons between normally distributed continuous variables were performed with the one-way ANOVA test using the Bonferroni's post-hoc analysis. The Kruskal-Wallis test was performed to compare non-normally distributed continuous data. Correlations between continuous variables were performed with the Pearson test. Bland-Altman plots were used to evaluate the agreement between MDCT and echocardiography to measure LVOT and AVA areas. Univariable analysis was performed with binary logistic regression analysis and the variables with a p<0.1 were introduced in the multivariable model. The odds ratio and 95% confidence interval were reported. Aortic valve calcium, aortic valve calcium index and aortic valve calcium density were not-normally distributed and were introduced in the uni- and multivariable analysis after log-transformation. The statistical analysis was performed with the SPSS version 20.0 (SPSS, Chicago, Illinois). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 191 patients (mean age 80±7 years, 48% male) with severe AS (AVAi <0.6cm^2/m^2) and preserved LVEF (≥50%) who had echocardiographic and MDCT evaluation prior to TAVI were included in the current analysis. Echocardiographic AVAi was 0.38±0.10cm^2/m^2, mean pressure gradient 45±16mmHg, SVi 38±10ml/m^2 and LVEF 63±7%. Patients were classified into 4 groups according to flow and transaortic gradient: normal flow - high gradient (n=72, 38%); low flow - high gradient (n=31, 16%); normal flow - low gradient (n=46, 24%); low flow - low gradient (n=42, 22%).

Clinical and echocardiographic characteristics

Table 1 presents the demographic and clinical characteristics of the 4 groups of patients. The 4 groups were comparable in terms of body surface area, cardiovascular risk factors and blood pressure. In the low flow - low gradient group the prevalence of coronary artery disease was higher compared to the normal flow - high gradient.

Table 2 shows the comparison of the hemodynamic and anatomic echocardiographic characteristics among the 4 groups. By definition, SVi and mean gradient were significantly different across the groups. Despite AVAi was less than 0.6cm^2/m^2 in all patients, those with normal flow - low gradient severe AS had significantly larger AVAi, larger LVOT area index and more concentrically hypertrophied LV compared with their counterparts. In addition, the global LV afterload was significantly lower in patients with normal flow - low gradient severe AS compared with the other groups.

Table 2. Hemodynamic and anatomic data evaluated by echocardiography among the four groups of severe aortic stenosis with preserved ejection fraction

Echocardiographic Data	Normal Flow High Gradient (n=72)	Low Flow High Gradient (n=31)	Normal Flow Low Gradient (n=46)	Low Flow Low Gradient (n=42)	p-value*
SVi, ml/m^2	44.91±8.38 ‡‡,¥¥	30.32±3.51 ††,§§	43.17±6.28 ‡‡,¥¥	26.66±4.71 ††,§§	<0.001
MPG, mmHg	56.85±10.87 §§,¥¥	55.83±11.45 §§,¥¥	31.99±5.83 ††,‡‡	29.71±6.28 ††,‡‡	<0.001
Vmax, m/sec	4.79±0.47 §§,¥¥	4.70±0.46 §§,¥¥	3.71±0.37 ††,‡‡	3.51±0.41 ††,‡‡	<0.001
AVA, cm^2	0.70±0.15 ‡‡,§§	0.50±0.12 ††,§§,¥¥	0.89±0.15 ††,‡‡,¥¥	0.64±0.15 ‡‡,§§	<0.001
AVAi, cm^2/m^2	0.37±0.08 ‡‡,§§,¥	0.27±0.05 ††,§§,¥¥	0.49±0.06 ††,‡‡,¥¥	0.34±0.07 †,‡‡,§§	<0.001
LVEF, %	64.76±7.48 ¥	62.16±8.14	62.61±6.94	60.24±6.81 †	0.02
LVEDVi, ml/m^2	48.74±15.96	44.15±15.55	51.26±18.52 ¥	38.22±12.80 †,§	0.001
LVESVi, ml/m^2	18.55±8.89	17.05±8.57	21.05±10.02 ¥	15.47±6.17 §	0.02
LV mass index, gr/m^2	136.58±36.05	127.80±27.42	130.24±38.40	120.61±33.85	0.11
RWT, %	65.04±13.67	62.84±16.06	59.72±14.18	67.56±16.62	0.08
Zva, mmHg/ml/m^2	4.58±1.00 ‡‡,¥¥	6.59±1.11 ††,§§	4.10±0.74 ‡‡,¥¥	6.38±1.47 ††,§§	<0.001
SAC, ml/mmHg/m^2	0.65±0.19 ‡‡,¥¥	0.46±0.11 ††,§§	0.65±0.21 ‡‡,¥¥	0.45±0.15 ††,§§	<0.001
LVOT area, cm^2	3.11±0.63	2.79±0.62 §§	3.37±0.60 ‡‡,¥	2.96±0.65 §	<0.001
LVOT area index, cm^2/m^2	1.67±0.31 ‡,§	1.49±0.27 †,§§	1.84±0.26 †,‡‡,¥¥	1.56±0.31 §§	<0.001

AVAi, aortic valve area index;
LV, left ventricular;
LVEDVi, left ventricular end-diastolic volume index;
LVEF, left ventricular ejection fraction;
LVESVi, left ventricular end-systolic volume index;
LVOT, left ventricular outflow tract;
MPG, mean pressure gradient;
RWT, relative wall thickness;
SAC, systemic arterial compliance;
SVi, stroke volume index;
Vmax, maximum transvalvular velocity;
Zva, valvulo-arterial impedance.

* ANOVA overall comparison within the four groups.
† vs Normal Flow - High Gradient group
‡ vs Low Flow - High Gradient group
§ vs Normal Flow - Low Gradient group
¥ vs Low Flow - Low Gradient group
1 symbol: p<0.05 and 2 symbols: p<0.001

Fusion of MDCT anatomy and Doppler hemodynamics

The MDCT-derived LVOT area and LVOT area index were comparable among the 4 groups, in contrast to the echocardiographic evaluation. However, fusion AVA and AVAi were significantly larger in the normal flow - low gradient group (Table 3). The LVOT area measured on MDCT showed good correlation with the LVOT area measured with echocardiography (Figure 2A) with a mean bias of 1.16±0.92cm^2 (Figure 2B) and the fusion AVA showed a good correlation with echocardiographic AVA (Figure 2C) with a mean bias of 0.23±0.20cm^2 resulting in a larger fusion AVA area (Figure 2D).

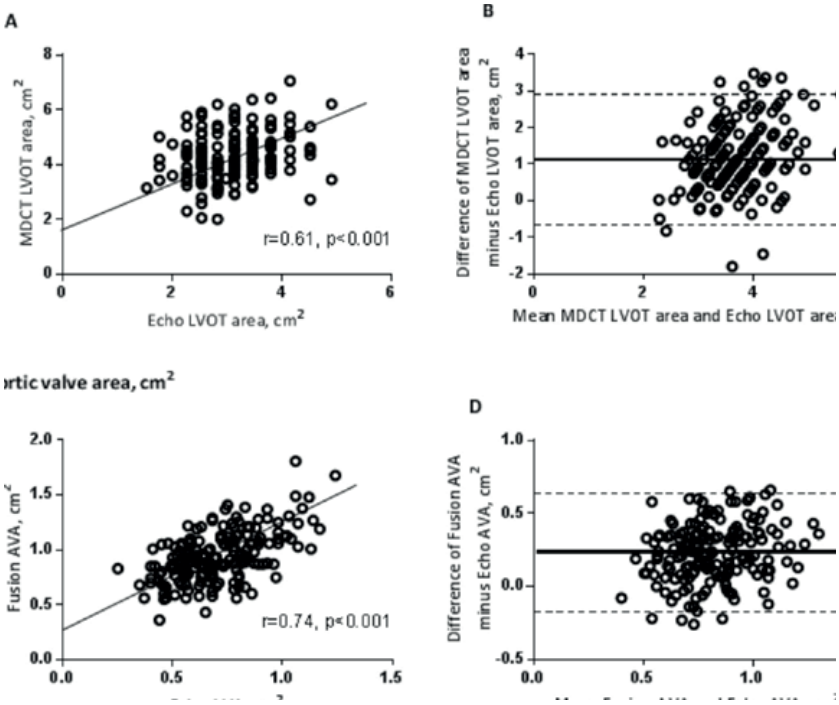

Figure 2. Correlation and Bland-Altman plots comparing echocardiography (Echo), multi-detector computed tomography (MDCT) and fusion measurements of the left ventricular outflow tract (LVOT) area and aortic valve area (AVA). Pearson correlation showed fair agreement between MDCT and Echo measurements of the LVOT area (panel A). The Bland-Altman plot demonstrates that LVOT area is underestimated by Echo compared with MDCT (panel B). On average, Echo underestimated the LVOT area by 25% compared with MDCT. The fusion AVA had good linear correlation with Echo AVA (panel C). However, the Bland-Altman plot shows that Echo underestimates the AVA compared with fusion AVA (panel D). On average, Echo underestimated the AVA by 25% compared to fusion technique.

The aortic valve calcium, calcium density and calcium index were significantly different among the 4 groups, but the calcium load was comparable in-between the 2 low gradient groups and in-between the 2 high gradient groups (Table 3).

The aortic valve calcium load was independently associated to low gradient severe aortic stenosis (odds ratio 0.02, 95% confidence interval 0.003-0.13, p<0.001) (Table 4). However, aortic valve calcium load was not associated with flow (odds ratio 1.01, 95% confidence interval 0.31-3.32, p=0.99) (Table 5), indicating that aortic valve calcium load may not be able to discriminate between normal and low flow severe aortic stenosis patients who have comparable gradient.

By using the fusion AVAi, 52% (n=24) of patients with normal flow - low gradient AS and 12% (n=5) of patients with low flow - low gradient AS would have been reclassified into true moderate AS due to low gradient and AVAi≥0.6cm^2/m^2 (Figure 3). Those patients reclassified to true moderate AS had comparable aortic valve calcium burden to that of patients with low gradient severe AS (2226 [1467-3342] versus 2227 [1543-3098] AU, respectively; p=0.73).

Table 3. Anatomic data evaluated by multi-detector row computed tomography and their fusion with hemodynamic Doppler data among the four groups of severe aortic stenosis with preserved ejection fraction

MDCT and Fusion Data	Normal Flow High Gradient (n=72)	Low Flow High Gradient (n=31)	Normal Flow Low Gradient (n=46)	Low Flow Low Gradient (n=42)	p-value*
MDCT AVC, AU	3412 (2245–4360) §§,¥	3183 (2242–5230) §	2143 (1246–3067) ††,‡	2310 (1586–3352) †	<0.001
MDCT AVC index, AU/m^2	1727 (1183–2399) §§,¥	1740 (1226–2779) §	1128 (653–1597) ††,‡	1243 (811–1696) †	<0.001
MDCT AVC density, AU/cm^2	728 (545–956) §§,¥	757 (587–994) §§,¥	482 (290–663) ††,‡‡	518 (377–718) †,‡	<0.001
MDCT LVOT area, cm^2	4.14±0.98	4.33±0.77	4.40±0.78	4.26±0.79	0.46
MDCT LVOT area index, cm^2/m^2	2.21±0.51	2.33±0.31	2.39±0.40	2.25±0.43	0.16
Fusion AVA, cm^2	0.90±0.18 ‡,§§	0.75±0.17 †,§§,¥	1.14±0.22 ††,‡‡,¥¥	0.93±0.21 ‡,§§	<0.001
Fusion AVA index, cm^2/m^2	0.48±0.09 ‡,§§	0.40±0.08 †,§§,¥	0.62±0.11 ††,‡‡,¥¥	0.49±0.11 ‡,§§	<0.001

AU, arbitrary units; AVC, aortic valve calcium; AVA, aortic valve area; LVOT, left ventricular outflow tract; MDCT, multi-detector computed tomography.

* Kruskal-Wallis or ANOVA overall comparison within the four groups.
† vs Normal Flow - High Gradient group
‡ vs Low Flow - High Gradient group
§ vs Normal Flow - Low Gradient group
¥ vs Low Flow - Low Gradient group
1 symbol: p<0.05 and 2 symbols: p<0.001

Table 4. Uni- and multivariable associates of low gradient (≤40mmHg), severe aortic stenosis with preserved ejection fraction

	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Clinical Parameters						
Age, years	0.98	0.94-1.03	0.49			
Male	1.25	0.70-2.20	0.45			
Body surface area, m^2	1.01	0.26-3.90	0.98			
Coronary artery disease	2.54	1.31-4.94	0.006	5.09	1.80-14.39	0.002
Diabetes	1.07	0.57-2.00	0.83			
Hypertension	1.66	0.78-3.51	0.19			
Hemodynamic Parameters						
ECHO AVAi, mm^2/m^2	1.07	1.03-1.10	<0.001	-	-	-
Fusion AVAi, mm^2/m^2	1.09	1.06-1.13	<0.001	1.09	1.05-1.14	<0.001
LV Ejection fraction, %	0.95	0.92-0.99	0.02	0.96	0.91-1.01	0.15
SVi, ml/m^2	0.99	0.99-1.00	<0.001	-	-	-
Zva, $mmHg/ml/m^2$	1.00	0.82-1.21	0.98			
SAC, $ml/mmHg/m^2$	0.40	0.09-1.72	0.22			
LV mass index, gr/m^2	0.99	0.98-1.00	0.10			
Relative wall thickness, %	0.99	0.98-1.01	0.67			
Anatomical Parameters						
ECHO LVOTa index, cm^2/m^2	2.55	1.00-6.47	0.048	2.89	0.75-11.13	0.12
MDCT LVOTa index, cm^2/m^2	1.52	0.77-3.01	0.23			
Aortic valve calcium	0.04	0.01-0.17	<0.001	-	-	-
Aortic valve calcium index	0.04	0.009-0.16	<0.001	0.02	0.003-0.13	<0.001
Aortic valve calcium density	0.02	0.003-0.09	<0.001	-	-	-

Aortic valve calcium, Aortic valve calcium index and Aortic valve calcium density were introduced in the uni- and multivariable analysis as log transformation

AVAi, aortic valve area index;
ECHO, echocardiography;
LV, left ventricular;
LVOTa, left ventricular outflow tract area;
MDCT, multi-detector computed tomography;
SAC, systemic vascular compliance;
SVi, stroke volume index;
Zva, valvulo-arterial impedance.

Table 5. Uni- and multivariable associates of low flow (stroke volume index ≤35ml/m^2), severe aortic stenosis with preserved ejection fraction

	Univariable			Multivariable		
	OR	95%CI	p-value	OR	95%CI	p-value
Clinical Parameters						
Age, years	1.00	0.96-1.04	0.98			
Male	1.41	0.78-2.53	0.25			
Body surface area, m^2	1.95	0.49-7.78	0.35			
Coronary artery disease	2.06	1.04-4.07	0.04	2.37	0.80 – 6.99	0.12
Diabetes	1.24	0.65-2.34	0.51			
Hypertension	1.51	0.69-3.30	0.29			
Hemodynamic Parameters						
LV ejection fraction, %	0.95	0.91-0.99	0.01	0.94	0.88–1.00	0.07
Zva, mmHg/ml/m^2	6.43	3.77-10.94	<0.001	6.50	2.87–14.70	<0.001
SAC, ml/mmHg/m^2	0.001	0.001-0.007	<0.001	1.87	0.03-106	0.76
LV mass index, gr/m^2	0.99	0.98-1.00	0.04	0.99	0.97-1.00	0.20
Relative wall thickness, %	1.01	0.99-1.03	0.25			
ECHO AVAi, mm^2/m^2	0.84	0.79-0.88	<0.001	-	-	-
Fusion AVAi, mm^2/m^2	0.93	0.90-0.96	<0.001	0.83	0.005-145	0.94
Anatomical Parameters						
ECHO LVOTa index, cm^2/m^2	0.10	0.04-0.30	<0.001	0.53	0.09 – 2.94	0.47
MDCT LVOTa index, cm^2/m^2	1.01	0.50-2.03	0.98			
Aortic valve calcium	1.13	0.35-3.67	0.84			
Aortic valve calcium index	1.01	0.31-3.32	0.99			
Aortic valve calcium density	0.97	0.27-3.54	0.97			

Aortic valve calcium, Aortic valve calcium index and Aortic valve calcium density were introduced in the uni- and multivariable analysis as log transformation
AVAi, aortic valve area index; ECHO, echocardiography;
LV, left ventricular;
LVOTa, left ventricular outflow tract area;
MDCT, multi-detector computed tomography;
SAC, systemic vascular compliance;
Zva, valvulo-arterial impedance.

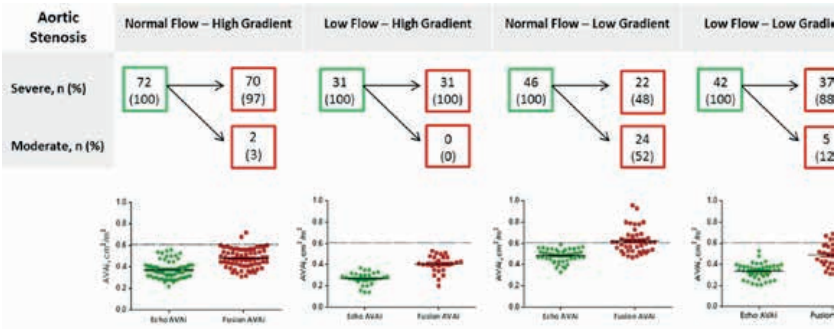

Figure 3. Reclassification of aortic stenosis severity in patients with echocardiographic severe aortic stenosis and preserved ejection fraction. AVAi, aortic valve area index.

DISCUSSION

The present study demonstrated that in patients with low gradient severe AS and preserved LVEF, the evaluation of fusion AVAi, by incorporating the MDCT-derived LVOT area in the continuity equation, reclassified 52% of the normal flow - low gradient and 12% of the low flow - low gradient severe AS patients to true moderate AS.

Prevalence of low gradient severe AS with preserved LVEF

Inconsistently graded severe AS, defined as an AVAi <0.6cm^2/m^2 and low gradient (<40 mmHg) is rather common in clinical practice and poses a diagnostic and therapeutic challenge. Low stroke volume, inaccurate measurements of the LVOT dimensions with 2-dimensional echocardiography and the presence of a small ascending aorta (which enhances the pressure recovery phenomenon) have been identified as the main reasons for the inconsistently graded severe AS. However, Minners et al have shown that 26% of patients undergoing cardiac catheterization to calculate AVAi by applying the Gorlin formulae may also show inconsistently graded severe AS.[2] The Gorlin formulae provides the anatomic aortic valve area, which may be larger than the effective orifice area calculated with echocardiography. In addition, during catheterization the pressure recovery phenomenon may also overestimate the aortic valve area leading to a lower percentage of inconsistently graded severe AS compared with echocardiography (26% vs. 34%, respectively). An important factor that may also cause this discrepant severe AS grading is the presence of low flow despite preserved LVEF. The prevalence of low flow - low gradient severe AS ranges between 13% and 28% whereas the prevalence of normal flow - low gradient severe AS is 23%.[16, 17] The present study observed similar prevalence with 22% and 24% of severe AS patients with preserved LVEF having low flow - low gradient and normal flow - low gradient AS, respectively. Accurate assessment of the cross sectional area of the LVOT is crucial to minimize the inaccurate measurement of AVAi.

Reclassification of low gradient severe AS with preserved LVEF according to fusion AVAi

Incorporation of the true cross sectional area of the LVOT in the calculation of the AVAi may reduce the prevalence of inconsistently graded severe AS by reclassifying patients into moderate AS.[3] The true cross sectional LVOT area can be evaluated by 3-dimensional echocardiography, MDCT and cardiac magnetic resonance imaging.[4, 18, 19] MDCT provides accurate visualization of the elliptical shape of the LVOT. Several studies have demonstrated that the LVOT diameter measured on 2-dimensional echocardiography corresponds to the diameter of the minor axis of the ellipse measured on MDCT, leading to underestimation of the LVOT area and subsequently of the AVAi.[4, 18, 20] A typical example of the oval LVOT true cross-sectional area at a 3-plane reconstructed MDCT view is depicted in Figure 1B. In routine clinical practice, by using the 2-dimensional echocardiography data the short diameter of the oval-shaped LVOT is measured (Figure 1A) and by assuming a circular-shaped LVOT the AVAi is underestimated (Figure 1E). This could be avoided by applying the true LVOT cross-sectional area assessed with 3-dimensional imaging in the continuity equation (Figures 2B and 2E). The LVOT area (independently of the modality used for measuring it) should be evaluated at a level 5mm apical to the aortic

annulus level in correspondence to the Doppler pulse wave sampling that provides hemodynamic information at the specific level.[3, 21]

MDCT permits calculation of AVAi either by direct planimetry of the aortic anatomic orifice area or by fusing the MDCT-derived LVOT area with echocardiographic Doppler data of the aortic valve in the continuity equation, obtaining the aortic effective orifice area.[5, 18, 22] In contrast to the anatomic aortic valve area, the effective orifice area of the aortic valve represents the workload that the LV has to overcome due to AS and therefore provides a more physiological evaluation of AS severity.[23, 24]

The aortic effective orifice area has been previously evaluated by applying the MDCT-derived aortic annulus or LVOT area in the continuity equation.[4,5] In 53 patients with severe AS undergoing transcatheter aortic valve implantation, Ng et al showed that the aortic annulus area was significantly underestimated by 2-dimensional echocardiography compared with 3-dimensional echocardiography and MDCT resulting in reclassification of 25% of patients into moderate AS.[4, 5] Similarly, Clavel et al evaluated the distribution of patients with inconsistently graded AS based on AVA with echocardiography and with MDCT.[25] Among 205 patients with preserved LVEF, 13% had low mean gradient and an echocardiographic AVA ≤1cm^2 while the percentage of patients with low mean gradient and tight AVA based on MDCT (≤1.2 cm^2) was 12%. In contrast to the present study, the authors used a higher cut-off value to define severe AS based on MDCT measurements of AVA explaining the discrepant results. In addition, it is important to note that, previous studies did not take into consideration the LV stroke volume, another important determinant of inconsistently graded severe AS. The impact of MDCT-derived LVOT area in the calculation of the AVAi in patients with low or normal flow may differ significantly. In the present study, 52% of the echocardiographic normal flow - low gradient severe AS patients could be reclassified to true moderate AS whereas only 12% of the low flow - low gradient severe AS patients should be reclassified to true moderate AS. Therefore, the evaluation of SVi should be incorporated in routine clinical practice to improve hemodynamic characterization of low gradient AS severity.

This reclassification may have important therapeutic implications since previous studies have shown that patients with normal flow - low gradient severe AS and preserved LVEF had comparable survival to that of patients with moderate AS whereas patients with low flow - low gradient severe AS and preserved LVEF have worse survival than patients with moderate AS (3-year survival 58% vs. 85%, respectively; p=0.002).[9,26,27] Furthermore, Maes et al showed that patients with low flow - low gradient severe AS and preserved LVEF represent an earlier stage of the disease since almost 40% of those patients developed high gradients on subsequent echocardiography and showed better survival than patients with high gradient severe AS.[28]

Proposed reclassification of low gradient severe AS with preserved LVEF

The present evaluation proposes a novel method to reclassify patients with low gradient severe AS, with normal or low flow, and preserved LVEF. Implementation of fusion AVAi may be the first discriminatory method between true severe and true moderate AS. By applying the fusion AVAi, 52% of the normal flow and 12% of the low flow - low gradient severe AS patients would be reclassified to true moderate AS. Eventually, in the group with low flow - low gradient severe AS,

the projected AVAi on stress echocardiography could be used to correct for the potential error caused by the low flow and discriminate between true severe and pseudo-severe AS.[29] This algorithm, for low gradient severe AS assessment, eliminates the potential errors in AVAi calculation due to anatomical assumptions in 2-dimensional echocardiography or low flow effect.

Additionally, assessment of aortic valve calcium burden using coronary calcium computed tomography data has been recently proposed to identify patients with true severe AS among patients with inconsistently graded severe AS.[14] Operative data have shown that the weight of the excised aortic valve of patients with paradoxical low flow - low gradient severe AS was significantly lower than that of patients with normal flow - high gradient severe AS, despite a significant overlap between the groups (1.9 [1.63-2.50] g versus 2.60 [1.66-3.32] g, respectively; p=0.03).[30] In addition, Clavel et al confirmed that patients with low gradient severe AS had significantly lower aortic valve calcium on coronary calcium computed tomography (1926 [1214-2695] AU for men and 1145 [854-1743] AU for women) compared with patients with high gradient severe AS (2617 [1819-2819] AU for men and 1320 [747-1429] AU for women) but significantly higher compared with patients with moderate AS (1240 [720-1833] AU for men and 487 [251-890] AU for women).[14] However, differences in aortic valve calcium burden between patients with normal flow - low gradient and low flow - low gradient severe AS have not been reported so far. The present study showed no differences in aortic valve calcium load between these two groups, suggesting a relatively homogeneous aortic valve calcium load in these two patient groups, but significantly lower compared with the high gradient groups. Noteworthy, the aortic valve calcium load could differentiate between the different gradient groups but not between the different flow groups. This finding suggests that in patients with low gradient severe AS, accurate assessment of true cross sectional LVOT area (using 3-dimensional imaging techniques) may play a more relevant role on the aortic stenosis grading rather than assessing the aortic valve calcium load.

Limitations

The current retrospective analysis of prospectively collected data is an observational study. The prognostic implications of fusion AVAi need to be demonstrated in prospective studies. In the current analysis the AVA was indexed to body surface area. However, in obese patients, the grade of underestimation of the AVA may be larger.

CONCLUSION

In patients with low gradient severe AS with echocardiographic AVAi $<0.6 cm^2/m^2$ and preserved LVEF, fusion AVAi evaluation (by combining the true cross-sectional LVOT area from 3-dimensional MDCT imaging and Doppler hemodynamics in the continuity equation) permits reclassification to true moderate AS in 52% of the normal flow and 12% of the low flow - low gradient severe AS patients.

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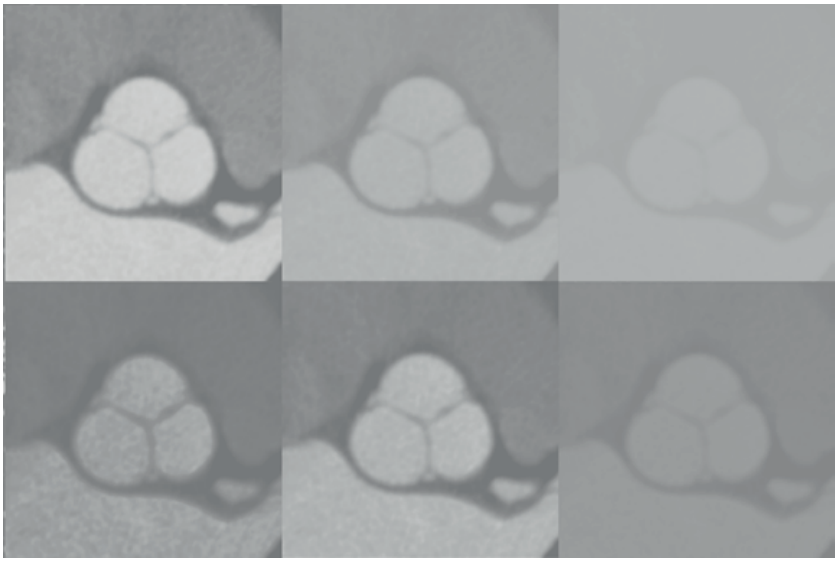
CHAPTER 3

Diagnosis and management of aortic valve stenosis in patients with heart failure



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Abstract

Aortic stenosis (AS) is the most frequent degenerative valvular heart disease in Western countries and its prevalence increases parallel to the ageing process of the population. Heart failure (HF) may be present in up to a quarter of patients with severe AS posing diagnostic and management challenges. The present article reviews the prevalence of HF in severe AS patients, discusses the diagnostic challenges and the advances in multimodality imaging to identify the patients that may benefit from surgical or transcatheter aortic valve replacement and summarizes the current evidence on management for this group of patients.

Keywords

Aortic stenosis;
Heart failure;
Stress echocardiography;
Multi-detector computed tomography;
Transcatheter aortic valve replacement

INTRODUCTION

Aortic stenosis (AS) is the most frequent degenerative valvular heart disease in Western countries and its prevalence increases with the ageing of the population.[1, 2] While the development of symptoms (angina, syncope or dyspnea) demarks an inflexion point in the survival of the patients with AS, the correlation between severity of AS and onset of symptoms is poor and depends largely on the hypertrophic response of the left ventricle (LV) to the pressure overload.[3] LV hypertrophy is a compensatory mechanism to restore wall stress and maintain cardiac output under increasing pressure afterload caused by the stenotic valve. However, progressive cardiomyocyte death and consequent fibrosis that accompany LV hypertrophy may lead to the development of LV dysfunction and heart failure (HF) symptoms. The onset of symptoms is not the only determinant of the timing for intervention in severe AS. Reduction of LV ejection fraction (LVEF) <50% even in asymptomatic patients with severe AS is also considered as class I indication (level of evidence B) for aortic valve replacement.[4, 5] However, the co-existence of severe AS, reduced LVEF and HF is complex and poses diagnostic and clinical decision-making dilemmas.

In HF patients with low LVEF, aortic valve area (AVA) ≤1.0cm^2 and low mean transaortic pressure gradient (<40mmHg) frequently co-exist challenging the diagnosis of severe AS.[6] In this circumstance, differentiation between true severe AS and pseudosevere AS is mandatory. In true severe AS, the compensatory mechanism of LV hypertrophy is exhausted with cardiomyocyte death and myocardial fibrosis that lead to reduced LVEF and low stroke volume and transaortic gradient. This entity is known as "classical" low-flow low-gradient severe AS. In contrast, in pseudosevere AS, reduced LVEF is caused by a primary dysfunction of the myocardium leading to reduced stroke volume, reduced opening forces of the valve and underestimation of AVA.

Besides the "classical" low-flow low-gradient severe AS, another circumstance characterized by inconsistent grading of severe AS is the "paradoxical" low-flow low-gradient severe AS, where LVEF is preserved (≥50%) and the reason of low-flow and consequently low-gradient AS is other than systolic HF. This condition is characterized by a small LV chamber size due to pronounced concentric remodeling in response to increased global afterload and reduced systemic arterial compliance which cause impaired LV mechanics (despite preserved LVEF) and diastolic filling.[6]

The decision making for patients with severe AS, reduced LVEF and HF is an important clinical dilemma. Currently the therapeutic options are conservative medical treatment, surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI).[4, 5] Data from randomized clinical trials and observational registries have provided important evidence on the benefits and risks of SAVR versus TAVI.[7, 8] However, there remain areas of uncertainty in the treatment of patients with severe AS and HF (i.e. patients with LVEF<30%, treatment options for patients with pseudosevere AS and patients with preserved LVEF and inconsistently graded severe AS).

The present review article provides an overview of current literature on the prevalence of HF (defined as reduced LVEF) in patients with severe AS, focusing on the diagnostic challenges and the various therapeutic options.

PREVALENCE OF HF IN SEVERE AS PATIENTS

In AS the left ventricle responds to the increased pressure load with adaptive concentric wall hypertrophy that maintains wall stress and LVEF. However, at this point, LV diastolic filling and LV longitudinal shortening are already impaired.[3, 9] In more advanced stages of AS, the pressure overload cannot be counterbalanced by the LV hypertrophy leading to reduced LVEF and HF symptoms and poor outcomes.[3, 9]

The prevalence of HF among severe AS patients varies largely based on the definition of HF (i.e. LVEF<50%, presence of symptoms) and the characteristics of patients included in the studies (Figure 1).[7, 10-13] In a large retrospective series of 9940 patients with severe AS, the prevalence of symptomatic LV dysfunction (LVEF<50%) was 24% whereas the prevalence of asymptomatic LV dysfunction was 0.4%.[10] In addition, in a retrospective population-level epidemiological study of hospitalized care in Scotland, among 13 200 patients diagnosed with AS (mean age 76±11 years old, 47% male), 25.1% were admitted with concomitant HF and 10.5% had at least one episode of previous HF hospitalization.[14] This prevalence was higher in a retrospective study including 453 patients with severe AS (mean age 75±13 years old, 48% male) who were conservatively treated during 1.5 years of follow-up: 35% of patients had an LVEF<40%.[11]

Reduced LVEF is associated with increased operative mortality risk and up to 30% of the patients with severe AS and reduced LVEF were deemed inoperable according to the EuroHeart Survey.[15] The advent of TAVI has changed the management of patients with severe AS and data from randomized clinical trials and registries on TAVI may provide more information on the prevalence of HF in severe AS patients. For example, among the 971 patients with severe AS included in the Placement of Aortic Transcatheter Valve (PARTNER) trial cohorts A and B, 23% had LVEF<50%.[7] In the US CoreValve trial, which randomized 795 patients with severe AS and high operative risk to TAVI or SAVR, 19% of patients reported NYHA functional class IV HF symptoms while the prevalence of LVEF<50% was not reported.[16] These randomized clinical trials excluded patients with LVEF<20% and, therefore may not represent the real-world patients treated with TAVI. In the the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry, including 7710 patients treated with TAVI, the prevalence of LVEF<30% was 7%.[13] Similar prevalence has been reported across several European registries of patients with severe AS treated with SAVR or TAVI.[12, 17-20] The largest European registry so far is the German Aortic Valve Registry (GARY) including 15 964 patients treated with TAVI;[12] in this registry the prevalence of LVEF<30% was 9.5%.

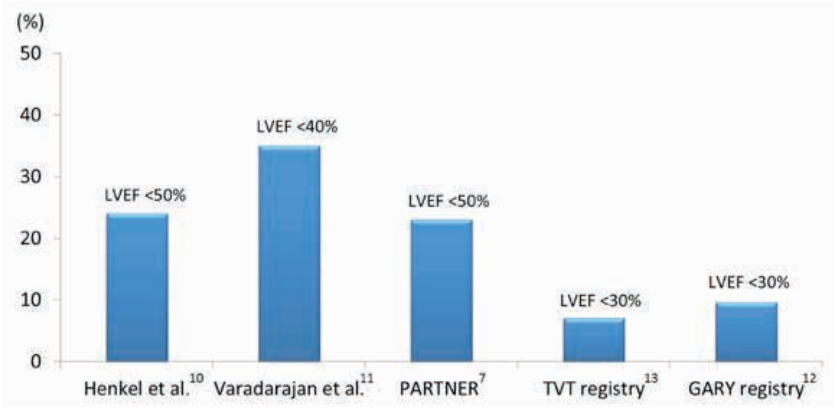

Figure 1. Prevalence of heart failure based on left ventricular ejection fraction (LVEF) in patients with severe aortic stenosis.

Besides failure of LV concentric hypertrophic remodeling to match the increased pressure overload, concomitant underlying coronary artery disease (CAD) is an important cause of HF in AS patients and has important therapeutic and prognostic implications.[21] Calcific AS and CAD share common pathophysiologic mechanisms and therefore frequently coexist.[22] In patients undergoing SAVR, coronary artery bypass grafting was performed in >50% of patients aged over 70 years.[23] In a recent observational analysis comparing 2286 patients with severe AS undergoing SAVR and coronary artery bypass grafting versus 1637 patients undergoing isolated SAVR, the short- and long-term prognosis of the former group was worse (survival rates at respective 30 days and 10 years: 97.6% versus 98.7% and 43% versus 59%).[24] The study showed that the increased mortality of patients undergoing combined SAVR and coronary artery bypass grafting was associated with the effects of pre-existing ischemic myocardial damage and co-morbidities. Therefore, evaluation of the presence of significant coronary artery disease and its consequences on LV performance is relevant for appropriate timing of SAVR.

In the randomized clinical trials on TAVI, the reported prevalence of coronary artery disease ranged between 74-76%[7, 16] whereas this prevalence is lower in the TAVI registries ranging from 31% to 69%.[12, 13, 17, 18, 20] In this specific group of patients, management of concomitant significant coronary artery disease remains controversial. In elderly patients, complete revascularization in patients undergoing TAVI seems less paramount.[25, 26] However, similarly to surgical series, some observational studies have suggested that the presence of myocardial ischemic damage (myocardial scar) is associated with worse outcome after TAVI.[27, 28]

DIAGNOSTIC CHALLENGES IN PATIENTS WITH SEVERE AS AND HF

In patients with reduced LVEF, inconsistently graded severe AS (tight AVA with low transvalvular gradients/velocity) can be observed in 5-10% of patients with severe AS posing a diagnostic dilemma.[29, 30] Differentiation between true severe AS and pseudosevere AS is crucial to decide the most appropriate management (aortic valve replacement or medical treatment, respectively).

True severe AS versus pseudosevere AS

The outcome of patients with low flow low gradient severe AS and reduced LVEF is dismal under medical therapy but the operative mortality is high and therefore accurate assessment of the AS grade and the severity of LV myocardial damage is crucial to select the appropriate treatment.[29, 30] Calculation of AVA in this subgroup of patients is challenging since it is directly proportional to the cardiac output. Therefore, increasing the cardiac output (improving myocardial contractility and increasing stroke volume) with intravenous administration of dobutamine may help to assess the AVA in different flow status and differentiate between fix severe AS and pseudosevere AS.[31, 32] During intravenous administration of dobutamine at 5mcg/kg/min increase every 3-5 minutes until a maximum doses of 20 mcg/kg/min, the mean transvalvular gradient and the stroke volume are measured keeping constant the LV outflow tract diameter. The AVA is then calculated by continuity equation. An increase in ≥20% in wall motion score and in ≥20% in stroke volume relative to baseline define LV contractile[32] and flow reserve,[31] respectively. In true severe AS, LV wall motion score, stroke volume and transvalvular gradients increase (>30 mmHg) at low dose dobutamine whereas AVA remains fixed (≤1.0 cm^2). In contrast, in pseudosevere AS, the improvement in LV contractility and stroke volume leads to an increase in AVA (>1.0 cm^2 or absolute increase >0.3 cm^2) while the transvalvular gradients remain low.

Assessment of AS severity in patients without LV contractile or flow reserve

However, one third of the patients with low flow low gradient severe AS and reduced LVEF may not show LV contractile or flow reserve during dobutamine stress echocardiography.[31, 32] In this situation, definition of the severity of AS remains difficult. Several series have demonstrated that these patients have the highest operative mortality and the worst prognosis if medically treated.[31, 33] The lack of LV contractile or flow reserve can be due to increased afterload that blunts the myocardial response to dobutamine, the presence of significant coronary artery disease that reduces myocardial blood flow or the presence of extensive myocardial scar. To overcome the limitations of dobutamine stress echocardiography, several additional echocardiographic variables and imaging techniques have been proposed to identify patients with true severe AS.[34, 35]

In the multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) study, including 46 patients with low flow low gradient severe AS (AVA≤1.2 cm^2 or indexed AVA≤0.6 cm^2/m^2, mean gradient <40 mmHg and LVEF≤40%), the accuracy of the projected AVA to differentiate between true severe AS

and pseudosevere AS was investigated.[34] Twenty-three patients underwent SAVR and the severity of the AS was assessed by the surgeon. The projected AVA is defined as the AVA calculated at standardized flow rate (250 ml/s which corresponds to the normal flow rate observed in patients with severe AS and normal LVEF) using the formula: $AVA_{proj}=AVA_{rest} + VC \times (250-Q_{rest})$, where the AVA_{rest} is the AVA at baseline, Q_{rest} is the mean transvalvular flow rate and VC is the valve compliance which corresponds to the slope of the relationship between AVA and flow and represents the rate of change in AVA in relation to the flow during stress. A cut-off value of indexed $AVA_{proj} \leq 0.55$ cm^2/m^2 correctly classified true severe AS in 91% of patients who underwent SAVR.[34] In contrast, the percentage of correct classification of patients with true severe AS reduced to 71%, 65% and 61% when an increase in mean transvalvular gradient >30 mmHg, and AVA at peak stress <1.0 cm^2 or an increase in AVA <0.3 cm^2 were applied (Figure 2). With larger number of included patients (n=142, 52 patients undergoing SAVR), the investigators of the TOPAS study could confirm and extend these results.[36] However, this technique remains inaccurate in patients with increase in mean transvalvular flow rate <15%.[36]

Furthermore, simple evaluation of the aortic valve morphology and amount of calcifications causing restriction of the aortic cusps suggest the presence of severe AS. Computed tomography permits accurate evaluation of the aortic valve calcification burden (Figure 3). Using this imaging modality, Cueff et al. demonstrated in 49 patients with severe AS and LVEF≤40% (20 of them with an AVA<1cm^2 and mean transvalvular gradient≤40 mmHg) that an aortic valve calcification burden of 1651 AU or more identified the patients with true severe AS with an sensitivity, specificity, negative and positive predictive value of 95%, 89%, 80% and 97%, respectively.[35]

Imaging modalities for risk stratification.

Despite a significant reduction in operative mortality from 20% to 10% in the last years,[33] accurate risk stratification of patients with severe AS and reduced LVEF remains challenging. Patients with true severe AS, regardless the presence or absence of LV contractile and flow reserve during dobutamine stress echocardiography, have better prognosis when treated surgically rather than medically [31, 37] whereas patients with pseudosevere AS have better prognosis when medically treated.[38] Therefore, the definition of the severity of AS is the first step in risk stratification of patients with low flow low gradient severe AS and reduced LVEF. The presence of LV contractile or flow reserve has been associated with better prognosis in patients undergoing SAVR.[31] In a multicenter study including 136 patients with low flow low gradient severe AS and reduced LVEF, patients with LV flow reserve defined by an increase in LV stroke volume of ≥20% had lower perioperative mortality compared with patients without LV flow reserve (5% versus 32%, p=0.0002).[31] The presence of LV flow reserve was associated with better perioperative survival (odds ratio 0.091, 95% confidence interval 0.023-0.38; p=0.001) and long-term prognosis (hazard ratio 0.4, 95% confidence interval 0.23-0.69; p=0.001).[31] However, a subsequent study showed that in terms of LVEF recovery, patients with LV flow reserve had similar improvement in LVEF after SAVR as compared to patients without flow reserve.[39] Furthermore, data from the French multicenter registry demonstrated that in patients with

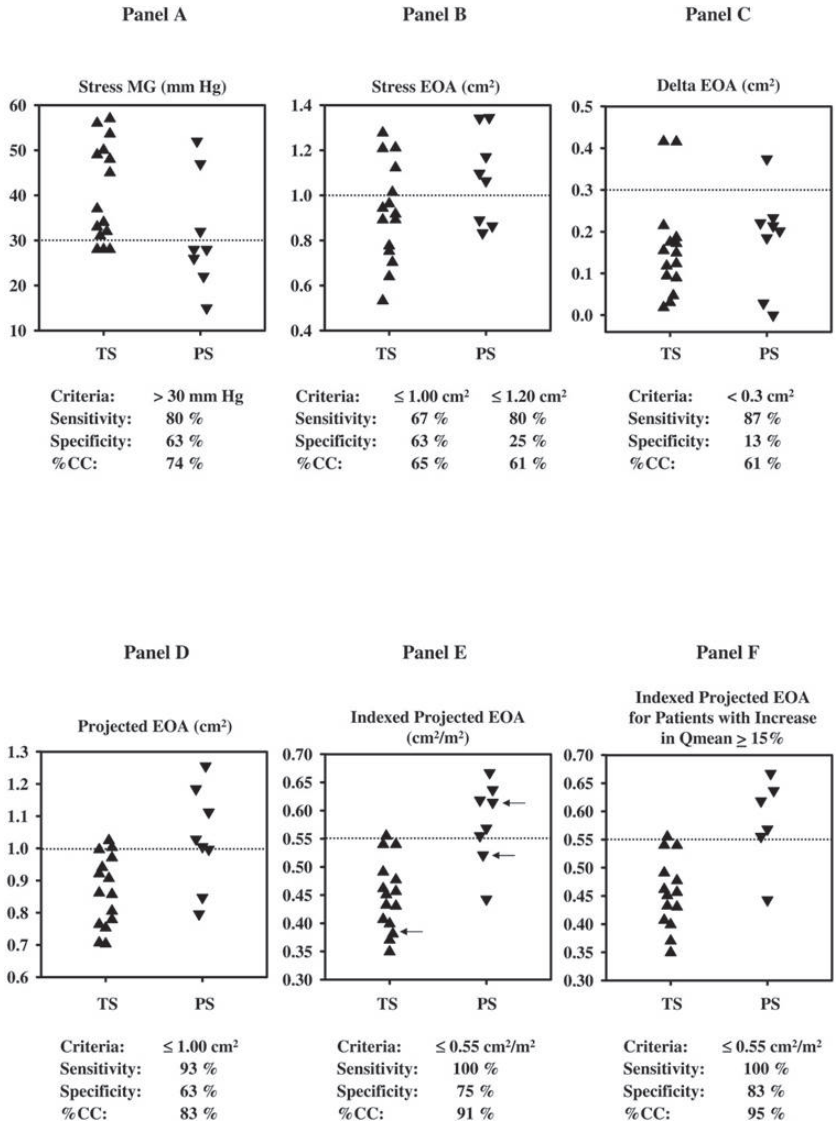

Figure 2. Low dose dobutamine stress echocardiography to differentiate true severe (TS) from pseudosevere (PS) aortic stenosis. The panels indicate the individual data of several echocardiographic parameters across each aortic stenosis category. The percentage of correctly classified true severe or pseudosevere AS was higher using the indexed projected aortic valve area. The arrows in E indicate the 3 patients who had <15% increase in mean flow rate with dobutamine stress. Reproduced with permission from Blais et al.[34]

Abbreviations:
CC: correct classification;
EOA: effective orifice area;
MG: mean gradient;
PS: pseudosevere;
Qmean: mean flow rate;
TS: true severe.

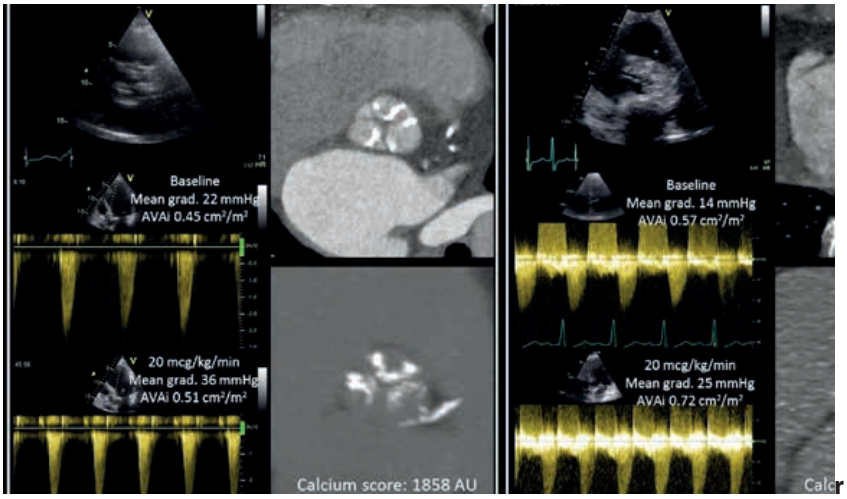

Figure 3. Aortic valve calcification burden assessed with computed tomography to differentiate between true and pseudosevere aortic stenosis. The left panel shows the example of an 85 year old patient with severe aortic stenosis and reduced left ventricular ejection fraction. During low dose dobutamine stress echocardiography, the mean gradient increased to 36 mmHg and the aortic valve area (AVA) remained <0.6 cm^2/m^2. On computed tomography, the calcium score of the valve was 1858 AU (above the cut-off value proposed to define severe AS; see main text). The right panel shows the example of a 79 year old woman with severe aortic stenosis and reduced left ventricular ejection fraction. During low dose dobutamine stress echocardiography, the AVA increased >0.6cm^2/m^2 suggesting the diagnosis of pseudosevere AS. On computed tomography, the calcium score of the aortic valve was below the proposed cut-off value).

low flow low gradient severe AS and reduced LVEF (n=81) and no LV flow reserve on dobutamine stress echocardiography, the long-term prognosis was better after SAVR compared with medical treatment.[37] Therefore, in this specific group of patients other factors should be considered to decide whether SAVR may be a safe and feasible therapeutic option.

Assessment of LV systolic function with conventional echocardiographic parameters such as LVEF or stroke volume in patients with low flow low gradient severe AS and reduced LVEF has several limitations since these parameters are highly influenced by LV geometry and preload conditions. The advent of novel echocardiographic techniques such as speckle tracking echocardiography has permitted detection of early myocardial damage in the left ventricle, and have proven good correlations with extent of myocardial scar assessed with LGE-MRI.[40, 41] By evaluating active myocardial deformation of the LV, speckle tracking echocardiography has shown that patients with aortic stenosis have impaired multidirectional deformation that may improve after SAVR (Figure 4).[42, 43] Particularly in the group of patients with low flow low gradient severe AS, investigators from the TOPAS study demonstrated the prognostic value of LV longitudinal strain in 47 patients (16 of them undergoing SAVR).[44] Peak longitudinal strain (rate) was measured at rest and following peak dose dobutamine infusion. Although peak longitudinal strain did not change (from -7.56±2.34% to -7.41±2.89%, p=0.7), peak longitudinal strain rate improved significantly at peak stress suggesting an improvement in LV contractility (from -0.38±0.12 s^{-1} to -0.53±0.18 s^{-1}, p<0.001). Peak stress longitudinal strain rate had incremental prognostic value over the STS-

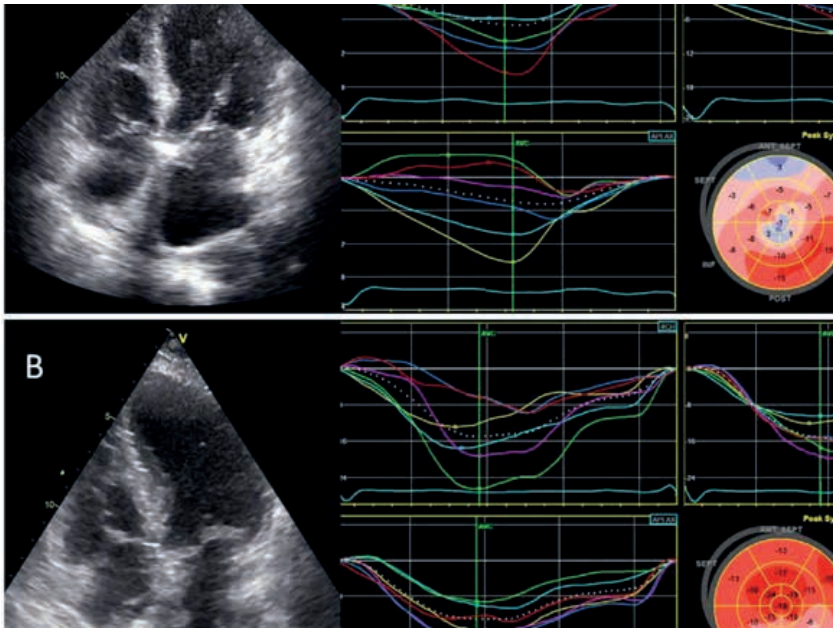

Figure 4. Improvement in left ventricular systolic function after transcatheter aortic valve implantation in an 83 year old female with severe aortic stenosis. Panel A shows the baseline left ventricular systolic function measured with conventional transthoracic echocardiography (LVEF 31%) and speckle tracking echocardiography (global longitudinal strain -5.9%). At 6 months follow-up, LVEF normalized and global longitudinal strain improved to -14.6% (panel B).

PROM (Society of Thoracic Surgeons Predicted Risk of Mortality score) and NT-proBNP (area under the curve 0.89, p=0.034).[44] In a subsequent sub-analysis of the TOPAS trial, including 202 patients with low gradient severe AS and LVEF≤40%, global LV longitudinal strain at rest and at peak stress was independently associated with outcome: a value of global LV longitudinal strain at rest of -9% or higher (indicating more impaired LV shortening) was associated with a two-fold increased mortality risk after correction for age, coronary artery disease, AVA_{proj} and type of treatment (SAVR versus medical treatment).[45] In addition, the lack of LV contractile reserve during dobutamine stress echocardiography (defined by a global LV longitudinal strain value at stress of -10% or higher) had incremental prognostic value over rest global LV longitudinal strain.

The underlying LV substrate is characterized by increasing amounts of myocardial fibrosis, which explains the impaired LV myocardial deformation and lack of LV contractile or flow reserve.[40, 46] The increased afterload imposed by the stenotic valve and associated factors such as hypertension and increased valvulo-arterial impedance lead to development of LV hypertrophy, which may eventually lead to HF if aortic stenosis (and arterial hypertension) is left untreated. This transition is characterized by increased apoptosis and fibrosis (scar) formation. The patterns of replacement fibrosis (scar) in AS patients assessed with late gadolinium contrast-enhanced magnetic resonance imaging (LGE-MRI) can be divided in midwall fibrosis and infarct-like fibrosis (subendocardial or transmural)(Figure 5).[47] In patients with low gradient severe AS, Herrmann et al showed that the amount of replacement

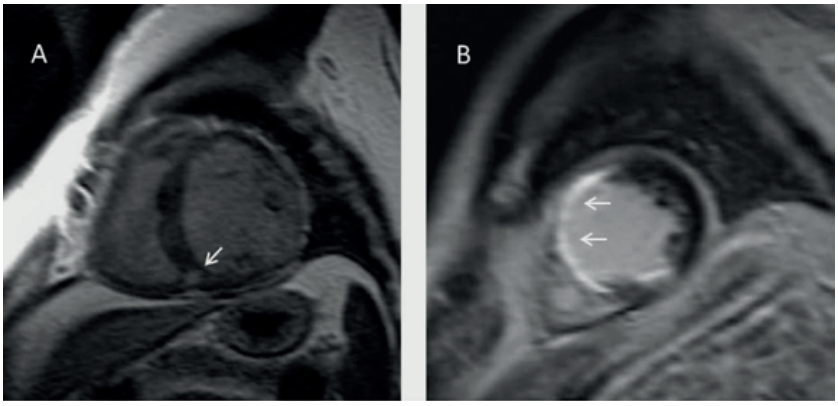

Figure 5. Late gadolinium contrast-enhanced magnetic resonance imaging in aortic stenosis. Panel A shows midwall focal fibrosis at the junction between the right and the left ventricle (arrow). Panel B shows infarct-like myocardial fibrosis with transmural hyperenhacement of the septum (arrows).

fibrosis (scar) was significantly larger compared with patients with high gradient severe AS, and was associated with more impaired LV longitudinal shortening.[46] In 143 patients with at least moderate AS undergoing LG-MRI, the presence of myocardial scar was observed in 64% (38% midwall scar; 28% infarct-like scar).[47] The presence of midwall and infarct-like scar was associated with 8- and 6-fold increase in all-cause mortality, respectively. On multivariate analysis, lower LVEF (HR: 0.96, 95% CI 0.94-0.99; p=0.009) and midwall fibrosis (HR: 5.35, 95% CI 1.16-24.56; p=0.003) were independently associated with all-cause mortality. In patients undergoing SAVR, the presence of LGE was also shown independently associated with worse postoperative mortality (HR:2.8, 95% CI 1.3-6.9; p=0.025).[28]

However, LGE identifies only regional differences in macroscopic replacement fibrosis (scar) and does not detect diffuse interstitial fibrosis, which is the predominant form of fibrosis at earlier stages of AS. MRI T1 mapping techniques have allowed quantifying this interstitial diffuse fibrosis (which can be considered as a precursor of HF). Flett et al applied

T1 mapping in patients with severe AS, and demonstrated that diffuse myocardial fibrosis correlated with clinical symptoms and LV systolic function parameters.[48] Six months after SAVR, LV mass reduced but the amount of diffuse myocardial fibrosis remained unchanged suggesting that regression in LV hypertrophy occurred due to reduction in cell volume rather than regression in diffuse fibrosis.

These studies demonstrate the clinical value of advanced assessment of LV function (beyond LVEF) using strain (rate) imaging or advanced anatomical imaging using MRI T1 mapping to assess myocardial tissue characteristics (fibrosis). These functional and anatomical imaging techniques may help to understand the outcome after SAVR, TAVI and medical treatment of patients with severe AS and reduced LVEF.

Aortic valve replacement is the definitive treatment of severe calcific AS. Recent registries have shown significant declines in 30-day mortality risks after SAVR (from 0.83 in 1992-1994 to 0.64 in 2007-2009).[49] The operative mortality rates for isolated SAVR in patients aged <70 years are 1-3% whereas for older patients the mortality rates range between 4-8%.[4] One of the factors independently associated with increased operative mortality is the presence of HF and reduced LVEF.[11, 50, 51] In a contemporary observational analysis including 114,135 patients aged ≥65 years old who underwent isolated aortic valve replacement, the presence of HF was associated with increased operative mortality and worse long-term survival.[50] In addition, longer duration of HF symptoms before aortic valve replacement was significantly associated with worse outcome.[50] Therefore, management of patients with severe AS and HF requires careful weighing of the operative risks and the clinical benefits.

Medical treatment and percutaneous balloon valvuloplasty may be appropriate therapeutic bridges to definitive aortic valve replacement in specific circumstances such as patients with hemodynamic instability. Indication for SAVR or TAVI relies on Heart Team discussion evaluating the individual's operative risk, frailty and comorbidities as well as the technical suitability for TAVI. Finally, patients with pseudosevere AS represent a specific subgroup with better outcomes under medical therapy than patients with true severe low flow low gradient AS and comparable survival to that of HF patients without AS.[38]

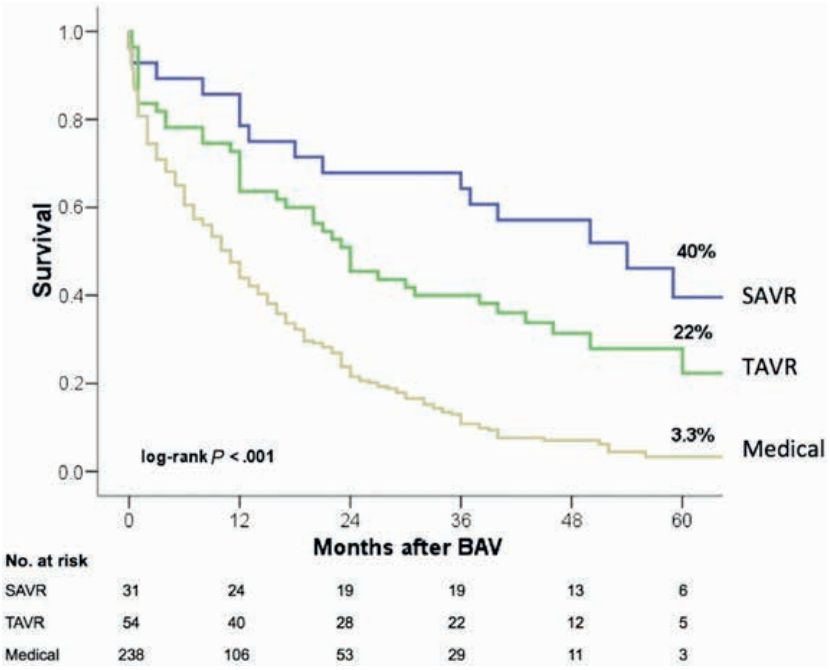

Figure 6. Long-term survival of patients with severe aortic stenosis undergoing balloon aortic valvuloplasty. Reproduced with permission from Eltchaninoff et al. Am Heart J. 2014;167(2):235-40.[54]

Severe AS and decompensated HF.

This high risk situation urges prompt hemodynamic stabilization that cannot be delayed by the screening process to decide suitability for SAVR or TAVI. Few studies have reported on the role of medical treatment in critically ill patients with severe AS and LV systolic dysfunction.[52, 53] Although vasodilators are traditionally contraindicated in this group of patients, small studies have demonstrated that nitroprusside and levosimendan can improve cardiac output and stabilize the hemodynamic condition allowing later referral to SAVR.[52, 53] Of note, patients with hypotension (mean arterial systolic pressure <60 mmHg) or under inotropic treatment were excluded from these trials[52, 53] and therefore, such a therapeutic option would not be indicated in those specific patients. More experience has accumulated with the use of percutaneous balloon aortic valvuloplasty as alternative to inotropic treatment.[54] This technique permits decreases in mean transaortic pressure gradient >50% and improvement in AVA >1.0cm^2 in 80% of the patients. Reductions of the arterial sheaths and development of vascular closure devices have improved the safety of this procedure with significant decreases in vascular complication rates. In 323 patients with severe AS and high operative risk (logistic EuroSCORE 28.7±12.5%) who underwent balloon aortic valvuloplasty, the rate of major inhospital complications was 6.8% and inhospital mortality was 2.5%.[54] After this treatment, 65% of patients continued medical treatment while the remaining patients were bridged to SAVR or TAVI. Single balloon aortic valvuloplasty was associated with worse outcome compared with SAVR and TAVI (Figure 6).

Severe AS and stable compensated HF.

In patients with low flow low gradient severe AS and reduced LVEF and presence of contractile/flow reserve, current guidelines recommend SAVR.[4] Studies comparing the outcomes of SAVR versus medical treatment of patients with classical low flow low gradient severe AS demonstrated that SAVR was associated with better survival at follow-up.[29, 55] Similar results have been reported for patients with classical low flow low gradient severe AS without contractile/flow reserve on dobutamine stress echocardiography.[37] In addition, SAVR was associated with improvement in LVEF at follow-up in patients with classical low flow low gradient severe AS independently of the presence of contractile/flow reserve.[39] The French multicentre study including 66 patients with classical low flow low gradient severe AS (46 with contractile/flow reserve and 20 patients without) showed that after SAVR the increment in LVEF was comparable between patients with and without contractile/flow reserve (19±10% versus 17±11%, p=0.54).[39] The advent of TAVI has altered the management of such high-risk patients. The Placement of Aortic Transcatheter Valves (PARTNER) trial included a large cohort of patients with severe AS who were randomized to TAVI or medical treatment (including balloon aortic valvuloplasty) for patients with contraindications for SAVR (cohort B) and to TAVI or SAVR for patients with increased surgical risk (cohort A).[56, 57] The prevalence of classical low flow low gradient severe AS was 15% (n=147). Low flow status was associated with increased 2-year mortality compared with normal flow status (for both cohorts) (47.1% versus 33.7%; hazard ratio 1.58, 95% confidence interval 1.28-1.95; p<0.001).[7] However, the presence of reduced LVEF (<50%) was not associated with further increase in mortality. Compared with medical treatment, TAVI was associated with significant reductions in 2-year mortality of patients

with classical low flow low gradient severe AS (80% versus 47.1%, p=0.04) whereas there were no differences between SAVR and TAVI (37.1% versus 42.9%, p=0.5).[7] In addition, subanalysis of the PARTNER cohort A showed that SAVR and TAVI lead to comparable improvements in LVEF at follow-up (from 38.0±8.0% to 50.1±10.8% and from 35.7±8.5% to 48.6±11.3%, respectively). Importantly, right ventricular pacing or induction of left bundle branch block (LBBB) after TAVI have been associated with lack of improvement in LV systolic function.[58, 59] Recent series including 3726 patients treated with TAVI showed that, after a mean follow-up of 22 months, 15% and 5.6% of deaths were caused by advanced HF and sudden cardiac, respectively.[60] LVEF≤40% was independently associated with death from advanced HF and sudden cardiac death whereas persistent LBBB following TAVI was associated with increased risk of sudden cardiac death. These findings have important clinical implications and fuel the discussion on the use of cardiac resynchronization therapy with or without defibrillator capabilities in these patients.

Pseudosevere AS.

In this subgroup of patients, optimal medical treatment provides similar survival than that of patients with HF and normal aortic valve function.[38] Cardiac resynchronization therapy, an established HF therapy indicated in patients who remain symptomatic despite optimal medical treatment, reduced LVEF and wide QRS,[61] may be one of the therapies underutilized in this specific group of patients. A recent analysis including 88 patients with classical low flow low gradient severe AS showed that the prevalence of QRS duration ≥130 ms was 56%. [62] In addition, QRS duration was strongly associated with worse outcome (hazard ratio 2.20, 95% confidence interval 1.15-4.24; P = 0.027). Whether treatment with cardiac resynchronization therapy would have resulted in better outcomes remains unknown.

FUTURE DIRECTIONS

Severe AS and HF are common conditions that may coincide having important clinical and prognostic implications. The development of TAVI has shifted the attention to this subgroup of patients who were considered inoperable a decade ago. However, there are still uncertainties regarding the treatment of specific subgroups of patients with severe AS and HF. For example, patients with LVEF<20% have been excluded from recent randomized trials on TAVI.[16, 56, 57] Currently few case reports have shown the safety and feasibility of performing TAVI under extracorporeal membrane oxygenation. Whether patients with such reduced LVEF may benefit from TAVI remains to be elucidated. Probably, accurate assessment of the LV structure and function using late gadolinium contrast enhanced MRI may help to identify the patients with limited amount of scar that can lead to functional recovery after TAVI and better prognosis.[28] Another question is the role of cardiac resynchronization therapy in these patients. Upgrade of right ventricular pacing to cardiac resynchronization therapy or implantation of cardiac resynchronization therapy in patients with LBBB prior or after TAVI may further improve LVEF and improve the prognosis. Finally, afterload reduction with medical therapy is the mainstay of HF therapy. Bearing in mind the increasing prevalence of HF and degenerative AS along with the ageing of the population, additional afterload reduction by TAVI on top of established HF therapy seems an attractive new concept. The Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) is a newly designed international randomized trial to assess whether TAVI on top of optimized HF therapy affects the composite hierarchical endpoint of all-cause death, disabling stroke, hospitalization for HF or aortic valve disease and change in quality of life in patients with HF and proven moderate AS. Additional randomized clinical studies are needed to better define the management of HF patients with aortic stenosis.

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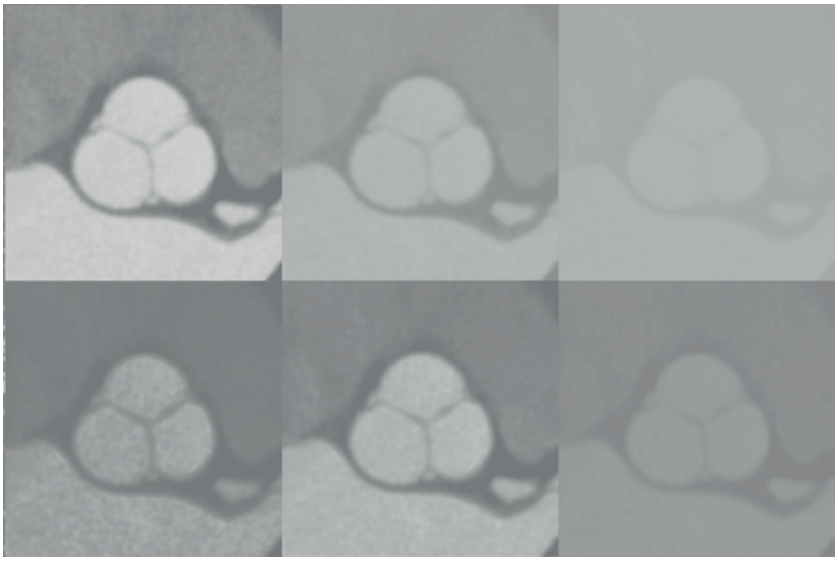
CHAPTER 4

Left Ventricular Functional Recovery and Remodeling in Low-Flow Low-Gradient Severe Aortic Stenosis After Transcatheter Aortic Valve Implantation



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ABSTRACT

Background

Speckle-tracking derived global longitudinal strain (GLS) is a more sensitive method of detecting left ventricular (LV) functional recovery after transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis. However it remains unknown whether LV function improves in low flow, low gradient severe aortic stenosis (LFLGSAS) patients after TAVI. The current study aims to evaluate LV functional recovery and remodeling after TAVI in LFLGSAS patients.

Methods

68 patients (men 57%, mean age 79.1±7.1 years) with LFLGSAS treated with TAVI were evaluated. LV function and remodeling, were investigated pre-TAVI, at 6 and 12 months after TAVI. All echocardiography data were prospectively collected and GLS was retrospectively analyzed.

Results

Among LFLGSAS patients, 35 (52%) had low LV ejection fraction (LVEF<50%) and 33 (48%) had preserved LVEF (≥50%). The low LVEF group had significantly more impaired GLS than the group with preserved LVEF (-8.3±2.6 vs. -13.3±3.5 %; p<0.001). LV systolic function improved after TAVI in both groups. While in the group of patients with low LVEF all functional parameters improved, in the group of patients with preserved LVEF only strain derived parameters significantly improved. There was a significant decrease in absolute LV wall thickness and relative wall thickness and a trend to decrease in LV mass index in both LVEF groups. LV volumes decreased significantly in those with low LVEF but not in those with preserved LVEF. Baseline GLS but not LVEF group was independently associated to GLS improvement at 12 months post-TAVI.

Conclusions

LFLGSAS patients with low and preserved LVEF had a significant improvement in LV function after TAVR, as assessed by GLS. Absolute and relative LV wall thickness decreased in both groups of patients, but only those with low LVEF had a reduction in LV chamber volumes.

Keywords

Aortic valve stenosis,
Low-flow low-gradient,
Speckle tracking, Strain,
Transcatheter aortic valve implantation

INTRODUCTION

The prevalence of low flow low gradient severe aortic stenosis (LFLGSAS) among patients referred for aortic valve replacement is relatively high. Pooled data from the Placement of Aortic Transcatheter Valves (PARTNER) trials (including the inoperable and high-risk cohorts) showed a prevalence of 29% of LFLGSAS.[1] Transcatheter aortic valve implantation (TAVI) in this group of patients leads to a better prognosis than medical treatment.[1-3] The associated factors that may determine an improved outcome remain unknown. Probably, an improvement in LV mechanics and remodeling after relief of pressure overload may influence positively the prognosis of the patients. However, changes in LV function and remodeling after TAVI in this particular group of patients have not been investigated. In addition, it remains unknown when exactly these changes do occur, either early after reducing the pressure overload or later at follow-up.

Left ventricular ejection fraction (LVEF) is the most frequently used parameter to assess LV function although it may not be sensitive enough to detect significant improvement in left ventricular (LV) mechanics after TAVI, particularly in the subgroup of patients with LFLGSAS and preserved LVEF. Recently it has been suggested that speckle tracking global longitudinal strain (GLS) is a more sensitive method than LVEF in detecting LV myocardial recovery after TAVI.[4,5] Therefore, the aim of the present evaluation was to characterize LV functional recovery, estimated by LVEF and GLS, and LV remodeling, estimated by LV mass and volumes, after TAVI in LFLGSAS patients, with special focus on subpopulations with reduced (<50%), known as "classical LFLGSAS", and preserved LVEF (≥50%), known as "paradoxical LFLGSAS", according to ESC/EACTS guidelines.[6] In addition, the time course of these changes was investigated.

METHODS

Patients

From a cohort of 253 patients with symptomatic severe aortic stenosis who underwent TAVI at the Leiden University Medical Center, 68 (27%) patients were identified as having LFLGSAS according the baseline Doppler echocardiography estimation of aortic valve area index (AVAi ≤0.6 cm^2/m^2), mean pressure gradient across the aortic valve (MPG ≤40mmHg) and stroke volume index (SVi ≤35 ml/m^2).[6,7] LV remodeling and functional recovery was evaluated at follow-up after successful TAVI. LV mass index (LVMi) and indexed LV volumes were measured at baseline, 6 and 12 months after TAVI. In addition, LVEF and speckle tracking derived GLS and strain rate were assessed. Further analysis by dividing the population into low LVEF (<50%) and preserved LVEF (≥50%) groups at baseline was performed. Patients who had high gradient aortic stenosis, patients who underwent "valve in valve" procedures or had more than mild aortic regurgitation before TAVI were excluded from the analysis. For this retrospective evaluation the Institutional Review Board waived the need of patient written informed consent.

TAVI procedure

TAVI was performed at the catheterization laboratory under general anesthesia and the 23, 26 or 29-mm Edwards SAPIEN and SAPIEN XT (Edwards Lifesciences, Irvine, California) or the 26, 29, 31-mm Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) were implanted. The preferred approach was transfemoral. The transapical approach was used in patients with unfavourable iliofemoral anatomy or in patients in whom a 29-mm Edwards SAPIEN XT valve was implanted.[8] Successful TAVI procedure was defined as implantation of a well-functioning valve in the aortic annulus, without intraprocedural death.[9]

2D Transthoracic echocardiography

Transthoracic echocardiography was performed before TAVI and at 6 and 12 months after TAVI using commercially available ultrasound system (Vivid-7 and E9, General Electric, Horten, Norway) equipped with 3.5MHz or M5S transducers. Two-dimensional grey-scale images and colour, continuous and pulsed wave Doppler data were acquired from parasternal, apical and subcostal acoustic windows. Data were stored digitally and analyzed offline on a dedicated workstation (EchoPac 112.0.1, GE Medical Systems, Horten, Norway).

The aortic stenosis severity was quantified by measuring the maximum velocity through the aortic valve with the use of continuous wave Doppler. Mean pressure gradient (MPG) was estimated using the modified Bernoulli equation.[10] Left ventricular outflow tract was measured on 2D transthoracic echocardiography and subsequently, aortic valve area (AVA) was calculated with the continuity equation and indexed to body surface area (BSA).[10] Energy loss index (ELI) was calculated according to the formula ELI= [(AVA x A_A)/(A_A-AVA)]/BSA, (A_A: aortic cross sectional area at the level of sino-tubular junction).[10,11] LV dimensions were measured on the parasternal

long-axis view on 2-dimensional grey-scale images. LV mass (LVM) was then estimated according to the formula by Devereux et al (0.8x {1.04 [(LVEDD +PWTd+ SWTd)3 -(LVEDD)3]} +0.6 g; where LVEDD is left ventricular end-diastolic diameter, PWTd is posterior wall thickness in diastole, SWTd is septal wall thickness in diastole and indexed to BSA.[12] Relative wall thickness [RWT=(2xPWTd)/LVEDD][13] and the ratio of LVM to LVEDV were then estimated.[13] LV end-diastolic (LVEDV) and end-systolic volume (LVESV) were calculated from the apical four- and two-chamber views and then indexed to BSA.[12] LVEF was derived with the biplane Simpson method.[12] Stroke volume (SV) was calculated by multiplying the LV outflow tract (LVOT) cross sectional area by the velocity time integral derived from the pulsed wave Doppler recordings acquired at the LVOT. Cardiac output (CO) was estimated by multiplying SV by heart rate (HR) and cardiac index by indexing CO for BSA.[7] Prosthesis-patient mismatch was defined as AVAi ≤0.85 cm^2/m^2.[14]

2D Speckle tracking echocardiography

LV systolic function was assessed with 2D speckle tracking echocardiography (STE) derived global longitudinal strain (GLS) and strain rate (GLSr). In order to estimate GLS, the three-, four- and two-chamber apical views were optimized to achieve a frame rate of at least 40 frames per second, recorded on 2D grey-scale and then analyzed offline at a workstation with commercially available software (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). The aortic valve closure timing was first defined at the apical LV long-axis view and then the LV endocardial border was traced at each apical view at an end-systolic frame. A region of interest was automatically defined and adapted not to extend beyond the epicardial border. Finally, GLS and GLSr were calculated as the average from all 3 apical views. GLS was expressed as % and GLSr as 1/s. Two representative examples of GLS evaluation at the three time points (pre-TAVI, 6 months and 12 months post-TAVI) for a patient with low and a patient with preserved LVEF are presented at Figure 1 and Figure 2 respectively.

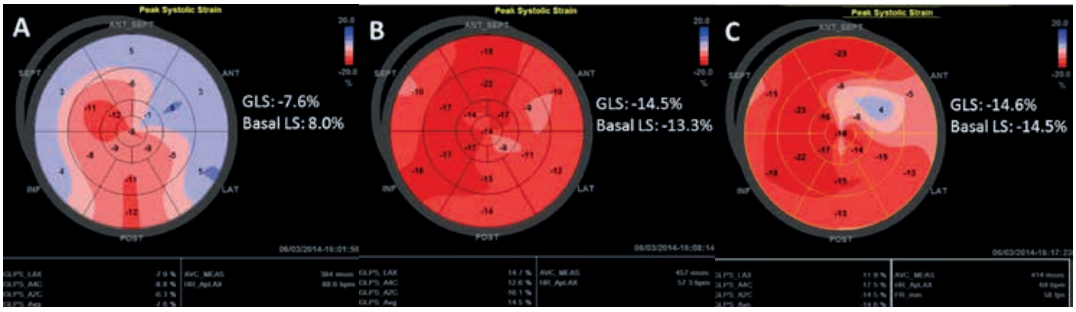

Figure 1.
Illustrative case of left ventricular global longitudinal strain (GLS) evaluation in a patient with low left ventricular ejection fraction and low-flow low-gradient severe aortic stenosis: GLS assessed A. pre-TAVI, B. 6 months post and C. 12 months post-TAVI.

Statistical analysis

Statistical analyses were performed with the SPSS software version 20 (SPSS, Chicago, IL). All categorical values are expressed as frequency (percentage) and continuous variables as mean ± standard deviation. Continuous variables were compared between the 2 groups at baseline with the Student-*t* test or Mann Whitney *U* test, as appropriate, and categorical variables with the x^2 test.

The modeling approach for assessing the overall change of LVEF, GLS, GLSr, LVMi, LVEDVi and LVESVi over the 12-month period after TAVI, was linear mixed modeling with these variables as the dependent variables and time (baseline, 6 and 12 months after TAVI) and LVEF category at baseline (<50% vs. ≥50%) as the main fixed effects. Main effects were compared with Bonferroni confidence interval adjustment. Parameter estimates and tests for covariance estimates were tested with 95% confidence interval. Post hoc testing was done to determine the time points at which the dependent variables differed between the 2 LVEF groups. Clinical and echocardiographic parameters were then tested as covariates to assess their influence on LV function and remodeling over time. Improvement in GLS or GLSr over time was defined by the amplitude of increase in GLS / GLSr regardless of whether these are expressed in positive or negative numbers. In order to identify baseline parameters associated with LV mass regression and GLS improvement, binary logistic regression was performed by defining at 12 months the improvement in GLS as 10% increase of absolute amplitude,[15] and the LV mass regression as 10% reduction.[16]

A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Table 1 summarizes the demographic characteristics of the patients (39 men, mean age 79.1±7.1 years). The mean logistic Euroscore was 26.6±16.3 %. Baseline echocardiographic characteristics are presented in Table 2. The mean AVAi was 0.4±0.1 cm^2/m^2, mean transaortic pressure gradient was 28.1±8.1 mmHg and mean SVi was 26.6±4.6 ml/m^2. Mean LVEF was 45.8±16.2 %.

There were 35 patients with LFLGSAS and low LVEF, whereas the remaining 33 patients had preserved LVEF. Patients with preserved LVEF had significantly smaller LV volumes and more concentrically remodeled LV compared to patients with reduced LVEF. In addition, patients with preserved LVEF had more preserved LV GLS and GLSr (-13.3±3.5 vs. -8.3±2.6 %; p<0.001 and -0.7±0.1 vs. -0.4±0.1 1/s; p<0.001, respectively) compared to patients with reduced LVEF (Tables 1 and 2). Prosthesis-patient mismatch was observed in 14 (20%) patients and paravalvular regurgitation in 32 (47%) of patients.

LV functional recovery and remodeling in LFLGSAS patients after TAVI

LV systolic function significantly improved over 12 months after TAVI in the overall cohort of LFLGSAS patients. Although LVEF had no significant change over time (from 45.8±16.2 % pre-TAVI to 49.7±15.9 % 6 months after TAVI and 49.8±15.2 % at 12 months; p=0.08), LV GLS and GLSr improved

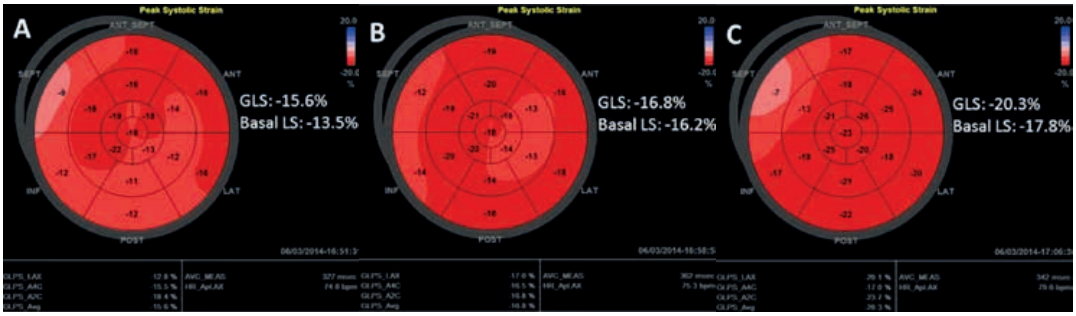

Figure 2. Illustrative case of left ventricular global longitudinal strain (GLS) evaluation in a patient with preserved left ventricular ejection fraction and low-flow low-gradient severe aortic stenosis: GLS assessed A. pre-TAVI, B. 6 months post and C. 12 months post-TAVI.

Table 1. Baseline clinical and TAVI characteristics of the LFLGSAS patients

	Overall (N=68)	LFLG, Low LVEF (N=35)	LFLG, Preserved LVEF (N=33)	p-value*
Demographics				
Age (years)	79.1±7.1	79.2±6.8	78.8±7.5	0.80
Male gender, n (%)	39 (57)	22 (63)	17 (52)	0.34
BSA (m^2)	1.8±0.1	1.8±0.1	1.8±0.1	0.90
Sinus Heart Rhythm, n (%)	40 (59)	18 (51)	22 (67)	0.38
CVD Risk Factors				
Hypertension, n (%)	54 (79)	25 (71)	29 (88)	0.09
Diabetes, n (%)	22 (32)	10 (29)	12 (36)	0.49
Hyperlipidemia, n (%)	43 (63)	21 (60)	22 (67)	0.56
Smoking ever, n (%)	34 (50)	18 (51)	16 (49)	0.80
Medical History				
PVD, n(%)	38 (60)	22 (63)	16 (49)	0.32
Stroke prior to TAVI, n(%)	10 (15)	4 (12)	6 (18)	0.51
CAD, n(%)	52 (77)	26 (74)	26 (79)	0.77
Revascularization, n(%)	45 (67)	22 (65)	23 (70)	0.66
Renal Failure, n(%)	15 (22)	9 (26)	6 (18)	0.56
Symptoms				
Angina, n (%)	24 (35)	9 (26)	15 (46)	0.08
Dyspnea, n (%)	67 (99)	34 (97)	33 (100)	0.32
Syncope, n (%)	9 (13)	3 (90	6 (18)	0.24
Medication				
Beta-blockers, n (%)	50 (74)	24 (69)	26 (79)	0.41
ACEi / ARBs, n (%)	43 (63)	25 (71)	18 (55)	0.20
Surgical Risk				
Logistic EuroSCORE (%)	26.6±16.3	32.7±17.2	20.2±12.8	0.001
TAVI procedure				
Approach-Transfemoral, n(%)	28 (41)	13 (37)	15 (46)	0.4
Valve type-SAPIEN, n(%)	66 (97)	34 (97)	32 (97)	0.9

Values are mean ± standard deviation or n (%)
*p-value for comparison between LFLG, low LVEF and LFLG, preserved LVEF
ACEi, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BSA, Body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STS, society of thoracic surgeons; TAVI, transcatheter aortic valve implantation.

Table 2. Baseline echocardiographic assessment of the LFLGSAS patients

	Overall (N=68)	LFLG, Low LVEF (N=35)	LFLG, Preserved LVEF (N=33)	p-value*
Aortic Stenosis Severity				
Bicuspid valve, n (%)	2 (3)	1 (3)	1 (3)	0.96
Vmax (m/s)	3.4±0.5	3.3±0.5	3.5±0.5	0.07
MPG (mmHg)	28.1±8.1	26.4±8.2	30.0±7.5	0.06
AVAi (cm^2/m^2)	0.38±0.1	0.37±0.1	0.38±0.1	0.64
ELI (cm^2/m^2)	0.44±0.1	0.44±0.1	0.45±0.1	0.73
LV Geometry				
SWTd (cm)	1.4±0.2	1.3±0.2	1.5±0.1	0.002
PWTd (cm)	1.3±0.2	1.2±0.2	1.3±0.1	0.07
LVEDDi (cm/m^2)	2.6±0.5	2.9±0.5	2.3±0.3	<0.001
LVESDi (cm/m^2)	1.9±0.6	2.3±0.5	1.4±0.3	<0.001
LVMi (g/m^2)	138.8±40.3	152.5±46.8	124.2±25.6	0.003
RWT (%)	55.1±16.7	47.6±14.1	63.0±15.8	<0.001
LVEDVi (ml/m^2)	54.1±28.2	68.1±31.1	39.2±14.2	<0.001
LVESVi (ml/m^2)	31.5±23.9	46.8±24.4	15.2±5.7	<0.001
LVM/LVEDV ratio (g/ml)	3.1±1.6	2.64±1.4	3.63±1.5	0.01
LV Systolic Function				
LVEF (%)	45.8±16.2	31.9±8.6	60.6±6.0	<0.001
SVi (ml/m^2)	26.6±4.6	26.2±4.3	27.0±4.9	0.45
CO (l/min)	3.7±0.8	3.7±0.7	3.7±0.9	0.78
CI ($l/min/m^2$)	1.9±0.4	1.9±0.4	2.0±0.4	0.82
LV GLS (%)	-10.7±3.9	-8.3±2.6	-13.3±3.5	<0.001
LV GLSr (%)	-0.5±0.1	-0.4±0.1	-0.7±0.1	<0.001

Values are mean ± standard deviation or n (%)

*p-value for comparison between LFLG, low LVEF and LFLG, preserved LVEF.

AVAi, Aortic valve area indexed;
CI, cardiac index;
CO, cardiac output;
ELI, energy loss index;
LV, left ventricular;
LVEDDi, left ventricular end-diastolic diameter indexed;
LVEDVi, left ventricular end-diastolic volume indexed;
LVEF, left ventricular ejection fraction;
LVESDi, left ventricular end-systolic diameter indexed;
LVESVi, left ventricular end-systolic volume indexed;
LV GLS, left ventricular global longitudinal strain;
LV GLSr, left ventricular global longitudinal strain rate;
LVMi, left ventricular mass indexed;
MPG, mean pressure gradient;
PWTd, posterior wall thickness at end-diastole;
RWT, relative wall thickness;
SVi, stroke volume indexed;
SWTd, septal wall thickness at end-diastole;
Vmax, transaortic valve maximal velocity.

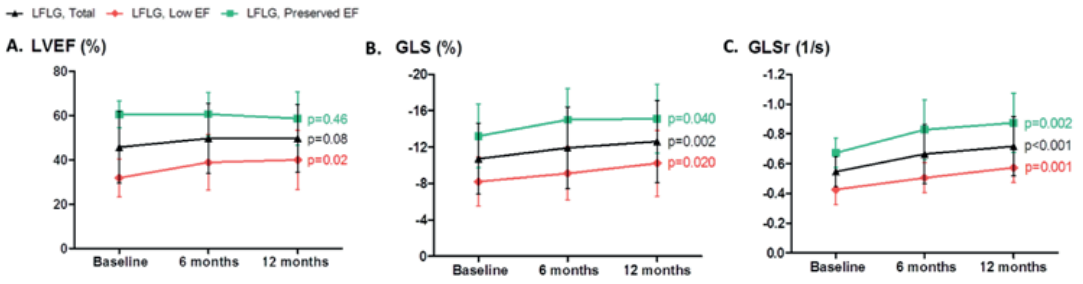

Figure 3. Changes in left ventricular systolic function assessed by (A) left ventricular ejection fraction (LVEF), (B) left ventricular global longitudinal strain (GLS) and (C) left ventricular global longitudinal strain rate (GLSr) in the total low-flow low-gradient severe aortic stenosis population (black line), in the low left ventricular ejection fraction group (red line) and in the preserved left ventricular ejection fraction group (green line) over a 12-month period after transcatheter aortic valve implantation. GLS and GLSr improved over time in the total cohort and in both groups, regarding that GLS and GLSr improvement is expressed by more negative numbers, i.e. the lower the value, the better the systolic function. All parameters are expressed as mean ± standard deviation. P-values for the change of the parameter over the total 12-month follow-up period after TAVI.

significantly during the 12 months of follow-up (-10.7±3.9 vs. -11.9±4.5 vs. -12.6±4.5 %; p=0.002; and -0.5±0.1 vs. -0.6±0.2 vs. -0.7±0.2 1/s; p<0.001; respectively for the same time period) (Figure 3). This improvement in GLS and GLSr occurred mainly during the first 6 months after TAVI. No significant changes were observed in these variables between 6 and 12 months after TAVI. The improvement in GLS over time remained significant after adjusting for age, gender, diabetes, hypertension, coronary artery disease, logistic Euroscore, use of beta-blockers, angiotensin converter enzyme inhibitors / angiotensin receptor blockers, TAVI valve type (self-expandable vs. balloon-expandable), TAVI access (transfemoral vs. transapical), LVMi as well as LVEF category at baseline (adjusted coefficient -1.82, confidence interval -0.51 to -3.13, p=0.007). The extent of improvement in GLS was comparable between patients who underwent transfemoral vs. transapical TAVI (coefficient -1.01, confidence interval 0.81 to -2.84, p=0.27). GLS improvement over time was influenced by the presence of prosthesis-patient mismatch (coefficient 3.29, confidence interval 0.97 – 5.60, p=0.006) but not by the presence of paravalvular regurgitation (coefficient 0.33, confidence interval -2.03 – 2.70, p=0.78) at 6 months post-TAVI. From the baseline variables, GLS was independently associated (OR 1.69, confidence interval 1.18 – 2.42, p=0.004) to a 10% GLS improvement after adjusting for LVEF category at baseline.

Over a 12-month period after TAVI, there were no significant changes in LV volumes. However, relative wall thickness was significantly reduced during the first 6 months after TAVI and remained stable for the next 6 months (from 55.1±16.7 to 48.2±12.8 and 48.7±14.3, p=0.003). Additionally, there was a significant reduction in LVMi during the first 6 months after TAVI that remained stable for the next 6 months (from 138.8±40.3 to 125.5±35.0 and 126.1±32.4 g/m^2; p=0.01) (Figure 4). The reduction in LVMi over time remained significant after adjusting for age, gender, diabetes, hypertension, coronary artery disease, logistic Euroscore, use of beta-blockers, angiotensin converter enzyme inhibitors / angiotensin receptor blockers, TAVI valve type, TAVI access, GLS as well as LVEF category at baseline in the LFLGSAS patients

(adjusted coefficient -12.04, confidence interval -1.28 to -22.79, p=0.02). LV mass regression over time was neither affected by the presence of prosthesis-patient mismatch (coefficient 9.28, confidence interval -10.86 – 29.44, p=0.36) nor by the presence of paravalvular regurgitation (coefficient 9.46, confidence interval -9.51 – 28.44, p=0.32). Any of the baseline parameters was not significantly associated to LV mass regression at follow-up.

Comparison of 1-year LV functional recovery and remodeling between the low LVEF and the preserved LVEF group of LFLGSAS

LVEF improved significantly in the group of patients with low LVEF, but not in the group with preserved LVEF (Table 3). However, in terms of LV GLS and GLSr, both groups of patients significantly improved in LV systolic function over 12 months after TAVI (table 3). Although GLS improvement over time was significant in both groups, it was more prominent in the low LVEF group (coefficient -5.18, 95% confidence interval -3.86 – -6.48, p<0.001). However, LV GLS and GLSr, at each time point, were significantly better in the group of patients with preserved LVEF (coefficient -5.18, confidence interval -3.88 to -6.47, p<0.001 and coefficient -0.27, confidence interval -0.21 to -0.32, p<0.001 respectively) (Figure 3).

LV reverse remodeling in both groups was led by the significant reduction of posterior and septal wall thickness and subsequently reduction of relative wall thickness. LVESVi reduction over time was significant only in the low LVEF group. In the group of patients with preserved LVEF there was no significant change in LV volumes over time. Although LVMi regression over time occurred in both groups, it was more prominent in the low LVEF category (coefficient 25.18, 95% confidence interval 10.20 – 40.17, p=0.001) (Table 3) (Figure 4).

DISCUSSION

The present study demonstrates that TAVI is associated with significant improvement in LV performance and reduction in LV mass in patients with LFLGSAS. LV functional recovery and mass reduction occurred during the first 6 months after TAVI and remained stable for the following 6 months. In contrast to conventional LVEF, LV GLS and GLSr improved significantly in both groups of LFLGSAS patients, with baseline LVEF ≥50% and <50%. Changes in LV GLS and GLSr were independent of LVEF at baseline, LVMi and procedural approach (transfemoral or transapical), among other relevant clinical variables.

In the contemporary era, treatment of patients with LFLGSAS still remains controversial. While medically treated patients with LFLGSAS have a poor prognosis, the operative risk of these patients is also high, with mortality rates significantly higher compared to patients with normal flow and high gradient severe AS.[17,18] TAVI has emerged as a feasible and safe alternative for patients with severe AS and very high operative risk or contraindications for surgery.[19-21] According to the sub analysis of the PARTNER trial, the prevalence of LFLGSAS was 29% (including cohort A, patients with high operative risk, and cohort B, inoperable patients).[1] This subgroup of patients had higher 2-year mortality rates than patients with normal flow AS (47% vs. 34%, hazard ratio 1.5, 95% confidence interval 1.25-1.89, p=0.006). However, the 2-year mortality rates of patients with LFLGSAS who underwent TAVI were significantly lower than the group of patients who was medically treated (46% vs. 76%, p<0.001). Furthermore, in the subgroup of patients with paradoxical LFLGSAS (preserved

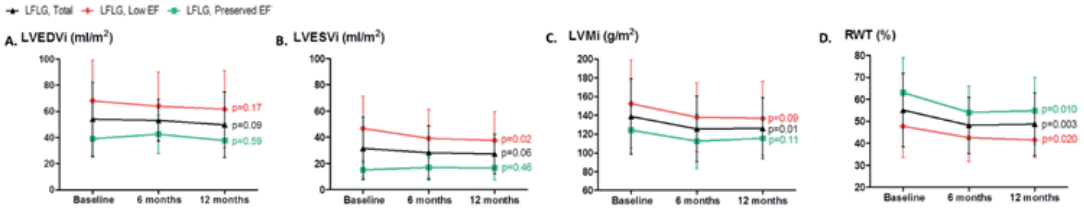

Figure 4. Changes in left ventricular remodeling assessed by (A) left ventricular end-diastolic volume index (LVEDVi), (B) left ventricular end-systolic volume index (LVESVi), (C) left ventricular mass index (LVMi) and (D) relative wall thickness (RWT) in the total low-flow low-gradient severe aortic stenosis population (black line), in the low left ventricular ejection fraction group (red line) and in the preserved left ventricular ejection fraction group (green line) over a 12-month period after transcatheter aortic valve implantation.

All parameters are expressed as mean ± standard deviation. P-values for the change of the parameter over the total 12-month follow-up period after TAVI.

Table 3. Change of the LV systolic function and remodeling in each LFLGSAS group separately, over a 12-month period after TAVI

	LFLGSAS total population (N=68)							
	LFLG, Low LVEF				LFLG, Preserved LVEF			
	Pre- TAVI	6-month FU	12-month FU	p* value	Pre-TAVI	6-month FU	12-month FU	p† value
	N=35	N=23	N=18		N=33	N=26	N=23	
LVEF (%)	31.9±8.6	38.9±12.6	40.0±13.3	0.02	60.6 ±6.0	60.7±9.8	58.7±12.0	0.4
LV GLS (%)	-8.2±2.7	-9.1±2.9	-10.2±3.6	0.02	-13.2±3.5	-15.0±3.4	-15.1±3.8	0.04
LV basal LS (%)	-5.6±3.9	-7.1±4.5	-8.4±4.1	0.02	-8.5±4.7	-9.2±5.7	-12.4±4.9	0.005
LV GLSr (1/s)	-0.4±0.1	-0.5±0.1	-0.5±0.1	0.001	-0.6±0.1	-0.8±0.2	-0.8±0.2	0.002
LVMi (g/m²)	152.5±46.8	138.0±36.8	136.8±39.3	0.09	124.2±25.6	112.5±28.8	115.5±21.8	0.1
LVEDVi ml/m²)	68.1±31.1	64.0±26.3	61.8±29.3	0.1	39.2±14.2	42.6±14.5	37.8±13.2	0.5
LVESVi (ml/m²)	46.8±24.5	39.2±22.2	37.7±21.9	0.02	15.2±5.7	17.0±7.8	16.6±8.9	0.4
RWT (%)	47.7±14.1	42.6±10.9	41.5±7.9	0.02	63.1±15.8	54.1±11.9	54.8±15.2	0.01
SWTd (cm)	1.3±0.2	1.2±0.2	1.1±0.2	0.006	1.5±0.2	1.2±0.1	1.2±0.2	<0.001
PWTd (cm)	1.2±0.2	1.1±0.2	1.1±0.2	0.06	1.3±0.2	1.2±0.1	1.2±0.2	0.02

All values are expressed as mean ± standard deviation.

p* for total change of the parameter over the total FU time in LFLGSAS, low LVEF group

p† for total change of the parameter over the total FU time in LFLGSAS, preserved LVEF group

LVEDVi, left ventricular end-diastolic volume index;
LVEF, left ventricular ejection fraction;
LVESVi, left ventricular end-systolic volume index;
LV GLS, left ventricular global longitudinal strain;
LV GLSr, left ventricular global longitudinal strain rate;
LVMi, left ventricular mass index;
LS, longitudinal strain;
PWTd, posterior wall thickness at end-diastole;
RWT, relative wall thickness;
SWTd, septal wall thickness at end-diastole.

LVEF), TAVI was associated with a significant reduction of the 1-year mortality rates (from 66% to 35%, p=0.02). Changes in LV remodeling and performance after TAVI may be one of the mechanisms underlying the improvement of outcome in these patients. However, data on changes over time in LV dimensions and function after TAVI in this particular subgroup of patients are scarce.

Changes in LV performance and remodeling in patients with LFLGSAS undergoing TAVI.

Several studies have demonstrated LV systolic function improvement and LV hypertrophy regression after TAVI.[4,5,16,22-24] LVEF is the most frequently used method to assess LV systolic function. However, accumulating evidence shows that LVEF may not be the ideal parameter to characterize LV systolic function in patients with severe AS.[7,17,25-27] The compensatory LV hypertrophy that accompanies AS leads to an increase in radial wall thickness which preserves LVEF.[25,28-30] However, LV longitudinal shortening may be impaired at this early stage.[7,25,29] Therefore, assessment of changes in LVEF after TAVI may not be sensitive enough to detect changes in LV function. In contrast, the use of more sensitive parameters such as GLS and strain rate may identify the patients that benefit from TAVI and show significant improvements in LV systolic function. Recently, in 101 consecutive patients undergoing TAVI, Kempny et al showed no significant changes in LVEF at 3 months follow-up whereas GLS and strain rate improved significantly (from -14.0±4.4 to -15.5±4.0% and from -0.68±0.24 to -0.78±0.23 1/s respectively).[4] Similarly, the present study provides more insight into the field by evaluating changes in LV systolic function in patients with LFLGSAS treated with TAVI. While LVEF did not change significantly over time, GLS and strain rate improved significantly at 6 months follow-up. This improvement was sustained at 12 months follow-up.

These changes in LV systolic function are not only related to relief of pressure overload but also associated with LV remodeling. Data from the PARTNER trials showed a significant reduction in LVMi at 2 years follow-up without significant changes in LV volumes.[31] However, data on LV remodeling in LFLGSAS patients after TAVI are very limited. Gotzmann et al demonstrated a significant reduction in LVMi in 10 LFLGSAS with low LVEF patients at 6 months after TAVI.[3] The present study expands those results and also demonstrates that patients with LFLGSAS benefit from TAVI with significant reductions in LV mass and improvement in LV systolic function. These improvements were independent of TAVI access (transfemoral or transapical), baseline LVEF and LVMi and other clinical variables.

Changes in LV performance and remodeling in LFLGSAS with LVEF<50% vs. ≥50%

Among patients with LFLGSAS, two different groups can be identified: patients with low LVEF and patients with preserved LVEF (or so-called paradoxical LFLGSAS).[17,32,33] Patients with LFLGSAS and reduced LVEF show significantly larger LV volumes at baseline and more eccentric hypertrophy than patients with paradoxical LFLGSAS. In addition, based on 2-dimensional speckle tracking analysis, patients with LFLGSAS and reduced LVEF have more impaired GLS and strain rate compared to patients with paradoxical LFLGSAS. However, the time course of LVEF, GLS and strain rate and LVMi and LV volumes after TAVI has not been elucidated in these two groups of patients.

The present study shows that LV systolic function improves after TAVI in both groups of LFLGSAS patients. This improvement was detected by LVEF and GLS in the low LVEF group but only by GLS in the preserved LVEF group. Using 3D transthoracic echocardiography, Schueler et al reported similar findings.[5] In 44 patients treated with TAVI, a significant improvement in LVEF and GLS was observed in patients with baseline LVEF<37%. In contrast, the group of patients with baseline LVEF ≥37% showed a significant improvement in GLS but not in LVEF.[5] However, the study by Schuler et al did not specifically focused on the group of patients with LFLGSAS. In the group of patients with paradoxical LFLGSAS, improvement in GLS may reflect an intrinsic improvement of myocardial contractility.[17,32] In contrast, LVEF may only reflect changes in LV volumes and this particular group of patients did not show any significant change in these parameters. It remains unknown whether this functional improvement is an independent determinant of better prognosis in patients with LFLGSAS.

Limitations

The present evaluation is a single center study and the analysis of the data was retrospective, although prospectively collected. The number of patients included is low, however, this group of patients with LFLG SAS is not common in TAVI studies, representing 15 and 14 % of patients with preserved or low LVEF, respectively.[1] Dobutamine stress echocardiography was not performed systematically before TAVI and therefore data on myocardial contractile reserve were not available. However, all the patients underwent CT scan with an estimated Agatston score of >1650 units from the aortic valve calcification which is suggested to distinguish pseudo- from true- severe AS.[17,34] The loss of patients at follow-up is another limitation. Our results may have been influenced by a survival bias considering that patients who died before 6 or 12 months (perhaps with worse LV function and increased LV hypertrophy) had no echocardiographic measurements included in the 6 and 12 months data analysis.

CONCLUSION

LFLGSAS patients after TAVI significantly improved LV function, regardless of baseline LVEF category. This improvement, which occurred during the first 6 months after TAVI and remained stable for the subsequent 6 months, was detected by LV GLS but not by LVEF change, especially in the preserved LVEF group. In addition, absolute and relative wall thickness decreased in both groups of patients, but only those with low LVEF had a reduction in LV chamber volumes. Overall, TAVI had a positive impact on the LFLGSAS patients, providing LV functional recovery and reverse remodeling.

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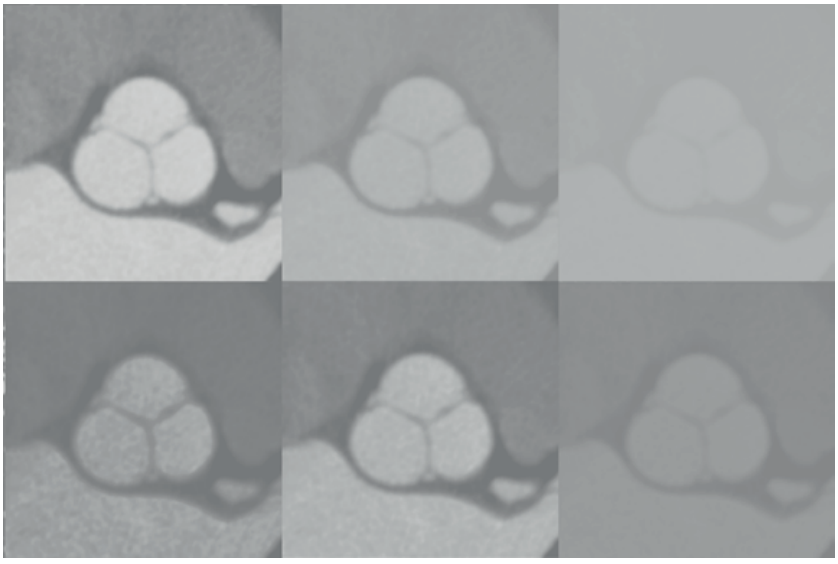
CHAPTER 5

Surgical Sutureless and Transcatheter Aortic Valves: Hemodynamic Performance and Clinical Outcomes in Propensity-Score Matched High-Risk Populations With Severe Aortic Stenosis



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ABSTRACT

Objectives In propensity-score matched patients with severe aortic stenosis treated with surgical aortic valve replacement (AVR) with the 3f Enable sutureless prosthesis (Medtronic) or transcathter aortic valve replacement (TAVR), the hemodynamic performance of both valves and mid-term survival of patients were evaluated.

Background Data on hemodynamic performance of surgical sutureless bioprostheses in high operative risk patients with aortic stenosis are scarce.

Methods Of 258 patients undergoing TAVR or surgical AVR with the 3f Enable valve, 80 (79±5 years old, 100% men) were included in the current analysis based on propensity score 1:1 matching for baseline clinical and hemodynamic characteristics. All patients had hemodynamic echocardiographic evaluation at baseline and discharge. Mid-term survival was analyzed.

Results Compared with the 3f Enable valve, TAVR prostheses (Edwards SAPIEN XT [Edwards Lifesciences, Irvine, CA] and CoreValve [Medtronic, Minneapolis, MN]) had larger effective orifice area index (1.00±0.30 vs 0.76±0.22cm^2/m^2, p<0.001), lower pressure gradient (8.14±4.21 vs 10.72±4.01mmHg, p=0.006), less frequent prosthesis-patient mismatch (PPM) (30.0 vs 67.5%, p=0.001) and low-flow (46.2 vs 72.5%, p=0.02), but more frequent aortic regurgitation (AR) (87.5 vs 20.0%, p<0.001). The presence of PPM was independently associated to low-flow state at discharge (OR 4.70, p=0.004) and independently associated with the use of the sutureless prosthesis (OR 3.90, p=0.02). However, the survival of the two groups was comparable after 1.5 (interquartile range 0.79 to 2.01) years follow-up (log-rank p=0.95).

Conclusions TAVR prostheses showed better hemodynamics than the 3f Enable valve but showed higher incidence of AR. However, these differences did not influence mid-term survival of patients.

Key Words aortic stenosis;
sutureless prosthesis;
transcatheter prosthesis;
prosthesis hemodynamics;
survival

Condensed Abstract The present report highlights the different hemodynamic performance of surgical sutureless and transcatheter aortic valve prostheses, by studying a propensity-score 1:1 matched population who underwent successful surgical sutureless or transcatheter aortic valve replacement (TAVR) for severe aortic stenosis. Compared with sutureless valves, TAVR prostheses had larger effective orifice area index, lower pressure gradient, less frequent prosthesis-patient mismatch (PPM) and low-flow state, but more frequent aortic regurgitation. The presence of PPM was independently associated to low-flow state at discharge and independently determined by sutureless prostheses. However, the mid-term survival of patients treated with TAVR or sutureless valves was comparable.

Abbreviations and Acronyms:

AR: aortic regurgitation
AVR: aortic valve replacement
CI: confidence interval
OR: odds ratio
PARTNER: placement of aortic transcatheter valves
PPM: patient-prosthesis mismatch
SVi: stroke volume index
TAVR: transcatheter aortic valve replacement

INTRODUCTION

In patients with severe aortic stenosis and high operative risk, transcatheter aortic valve replacement (TAVR) has demonstrated to be non-inferior to conventional surgical aortic valve replacement (AVR) when using the balloon-expandable Edwards SAPIEN (Edwards Lifesciences, Inc. Irvine, CA) and superior to surgical AVR when using the self-expandable device CoreValve (Medtronic, Minneapolis, MN) (1-3). Recently, surgical AVR with sutureless prostheses offers minimal surgical access, reduced aortic cross-clamping and cardiopulmonary by-pass times compared to classical surgical replacement and, in contrast to TAVR, the native calcified valve is removed (4-6). In patients with severe aortic stenosis and high operative risk, perioperative complications and in-hospital mortality associated with surgical AVR using sutureless valves are comparable to TAVR (4,6,7). Compared with stentless aortic bioprostheses, TAVR prostheses have demonstrated superior hemodynamics (8). However, little is known about the hemodynamics of sutureless valves in comparison with TAVR prostheses. In propensity-score matched populations, the present evaluation compared the hemodynamic performance of the sutureless 3f Enable valve (Medtronic, Minneapolis, MN) (Figure 1) and transcatheter valves (Edwards SAPIEN XT, Edwards Lifesciences, Inc. Irvine, CA and CoreValve, Medtronic, Minneapolis, MN). In addition, the mid-term survival of patients undergoing surgical sutureless AVR and patients treated with TAVR was evaluated.

Figure 1.
3f Enable® Aortic Root Bioprosthesis. ©Medtronic, Inc. Printed with permission. The valve consists of a self-expanding Nitilol frame and 3 equine pericardial leaflets that form a tube, preserving the aortic sinuses and restoring native stress distribution.

METHODS

Identification of patients

Patients with symptomatic severe aortic stenosis (aortic valve area index <0.6 cm^2/m^2) (9), who were treated according to the Heart Team (10) with surgical AVR using the 3f Enable valve or with TAVR at the Leiden University Medical Centre between November 2007 and February 2013 were evaluated. Only patients with a successful procedure, defined as no immediate procedural mortality within 72h post-procedure (11), were considered eligible for the current analysis. The immediate procedural mortality was 2% for surgical aortic valve replacement using the 3f Enable and 4.5% for TAVR. The Institutional Review Board approved this retrospective analysis of clinically acquired data and waived the need for written patient informed consent.

Prosthesis selection and replacement

TAVR was performed according to current recommendations (12). The type of valve, Edwards SAPIEN XT or CoreValve, the size of valve and the access of implantation (transfemoral or transapical) were selected prior to the procedure based on the multi-detector row computed tomography measurements (13).

Surgical sutureless AVR was performed as recently described (4). The 3f Enable sutureless bioprosthesis was implanted and deployed after medial sternotomy, through transverse aortotomy and after excision of the native valve and decalcification of the aortic annulus (5,14,15). The size of the valve (19, 21, 23, 25 or 27 mm) was selected during the procedure, based on aortic annulus direct observation and measurement with surgical callipers of standard diameter (5).

Hemodynamic assessment with echocardiography

Transthoracic echocardiography was performed at baseline (pre-AVR) and at hospital discharge. Using continuous wave Doppler, the peak velocity through the valve (native and bioprosthesis) and the mean transvalvular pressure gradient were obtained and the aortic valve area of the native valve and the effective orifice area of the bioprosthesis were derived with the continuity equation and indexed to body surface area (9). Moderate and severe prosthesis-patient mismatch (PPM) was defined by an estimated effective orifice area index <0.85cm^2/m^2 and <0.65cm^2/m^2, respectively (16-19). Aortic valve regurgitation (AR) and mitral regurgitation were assessed using colour Doppler data and classified as I-IV (16). The forward flow through the aortic valve, native or bioprosthesis, was evaluated by the stroke volume index (SVi) calculated as the cross sectional area of the left ventricular outflow tract multiplied by the velocity time integral of the left ventricular outflow tract pulsed wave Doppler spectral signal and divided by the body surface area. Subsequently, low-flow state was defined as SVi≤35ml/m^2 (20,21). The ratio of the prosthesis diameter relative to the aortic annulus diameter, measured on the parasternal long-axis view, was estimated to assess the grade of under- or oversizing of the prosthesis (8,22). Left ventricular ejection fraction was evaluated with the Simpson's biplane method (22).

Clinical outcome

The procedural outcome and the periprocedural complications were recorded according to Valve Academic Research Consortium-2 definitions (11). All patients were followed-up after surgical AVR or TAVR and all-cause mortality data were recorded in the Cardiology Department Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) or the Social Security death index and were complete for all patients included in this analysis.

Statistical analysis

To control the selection bias, propensity score matching was performed. The propensity score was created from a multivariate binary logistic regression model, in which the type of procedure (AVR with sutureless valve or TAVR) was the dependent variable. The covariates in this model were clinical parameters that had affected our choice of procedure and the echocardiographic variables that would affect the hemodynamics of the bioprosthesis: age, gender, body surface area, logistic EuroSCORE I, aortic annulus, mean transvalvular pressure gradient, aortic valve area index, SVi and left ventricular ejection fraction at baseline. The Hosmer-Lemeshow goodness-of-fit test was used to check the accuracy of the model (p=0.98). Subsequently, propensity score 1:1 matching was performed without replacement (23).

Continuous variables are expressed as mean ± standard deviation or as median (interquartile range) if not normally distributed and categorical variables as frequencies (percentage %). For comparison of continuous variables, the Student-*t* test, 1-way ANOVA test (with Bonferroni post-hoc analysis) or Mann-Whitney U test were used, as appropriate. For comparison of categorical variables, the Chi-square test or Fisher's exact test were used, as appropriate. Univariate and multivariate binary logistic regression analysis were performed to identify variables that were associated with low-flow state or PPM after surgical AVR or TAVR. Variables with univariate p-value<0.10 were entered in the multivariate models. Odds ratios (OR) and 95% confidence intervals (CI) were reported. The cumulative survival curves were calculated based on Kaplan-Meier method and comparison between surgical AVR and TAVR groups was evaluated by log-rank test.

Statistical analysis was performed using the SPSS software version 20 (SPSS, Chicago, IL). A p-value<0.05 defined statistical significance.

RESULTS

Patients

Of the 258 patients with severe aortic stenosis successfully treated with surgical AVR using the sutureless prosthesis or with TAVR, 80 patients were included in the current analysis after propensity score 1:1 matching. The baseline clinical and echocardiographic data used for propensity score matching of the 2 cohorts are shown in Table 1.

Aortic valve hemodynamics at discharge: TAVR vs. sutureless bioprosthesis

The hemodynamics of the transcatheter and sutureless bioprostheses are shown in Table 2. The TAVR group had significantly lower mean transvalvular pressure gradient (8.14±4.21 vs. 10.72±4.01 mmHg, p=0.006), higher effective orifice area index (1.00±0.30 vs. 0.76±0.22 cm^2, p<0.001), less frequent presence of PPM, higher SVi and less frequent presence of low-flow state, but higher frequency of AR compared with the patients who received a sutureless bioprosthesis (Figure 2).

Table 1. Baseline characteristics included in the propensity score, for the total and 1:1 propensity score matched population

	Total Population, N=258			Propensity Sore Matched, N=80		
	Sutureless AVR, N=47	TAVR, N=211	p-value	Sutureless AVR, N=40	TAVR, N=40	p-value
Age, years	78.5 ± 4.6	80.9 ± 7.1	0.03	79 ± 4.5	79 ± 5.9	0.96
Male, n (%)	47 (100)	105 (50)	<0.001	40 (100)	40 (100)	1
BSA, m^2	1.9 ± 0.36	1.8 ± 0.2	0.17	1.9 ± 0.4	1.9 ± 0.2	0.69
Log EuroScore, %	14.9 ± 10.1	22.8 ± 13.2	<0.001	15.9 ± 10.6	15.5 ± 8.4	0.85
LVEF, %	61.2 ± 10.4	54.8 ± 14.5	0.004	59.9 ± 10.5	59.7 ± 10.7	0.93
MPG, mmHg	43.2 ± 18.1	42.2 ± 17.2	0.74	42.9 ± 18.7	44.7 ± 17.5	0.65
Annulus, cm	2.42 ± 0.2	2.26 ± 0.2	<0.001	2.4 ± 0.2	2.4 ± 0.2	0.68
AVAi, cm^2/m^2	0.37 ± 0.14	0.39 ± 0.10	0.26	0.38 ± 0.14	0.38 ± 0.09	0.72
SVi, ml/m^2	36.3 ± 10.9	37.1 ± 11.5	0.68	35.8 ± 11.0	35.9 ± 10.8	0.96
Low flow, n (%)	24 (51.1)	102 (48.3)	0.74	21 (52.5)	21 (52.5)	1

Values are mean ± SD or n (%).

AVAi=aortic valve area index, A
VR= aortic valve replacement,
BSA=body surface area,
LVEF=left ventricular systolic function,
MPG=mean pressure gradient,
SVi=stroke volume index,
TAVR=transcatheter aortic valve replacement

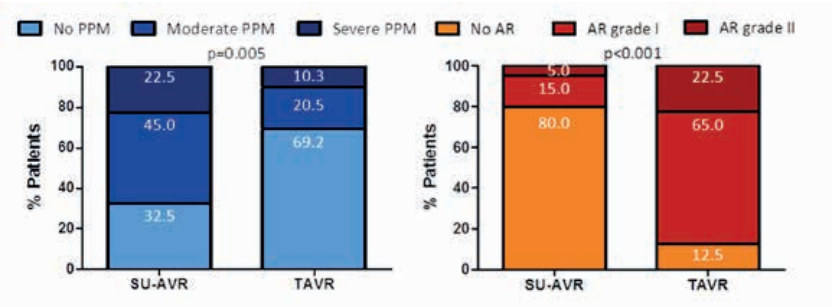

Figure 2. Frequency of prosthesis patient mismatch (PPM) and aortic valve prosthesis regurgitation (AR) after transcatheter (TAVR) or surgical sutureless (SU-AVR) aortic valve replacement. No AR grade III-IV was reported after SU-AVR or TAVR.

Prosthesis patient mismatch, aortic valve prosthesis regurgitation and forward flow at discharge: TAVR vs. sutureless bioprosthesis

The patient population was divided into 4 groups based on the type of prosthesis and the presence of PPM at discharge: surgical sutureless AVR with PPM, surgical sutureless AVR with no-PPM, TAVR with PPM, TAVR with no-PPM. The forward flow was significantly different among the 4 groups (SVi 24.63±7.32 vs. 40.89±6.86 vs. 30.94±9.15 vs. 37.61±13.36 ml/m^2, respectively, ANOVA p<0.001). Patients treated with sutureless AVR who showed PPM had significantly lower SVi than patients without PMM or treated with TAVR (Bonferroni p<0.001 for both). Additionally, PPM patients have significantly lower SVi than the no-PPM patients (38.68±11.66 vs. 26.57±8.35 ml/m^2, p<0.001) (Figure 3A).

Table 2. Comparison of the hemodynamic profile of the sutureless versus transcatheter aortic valve prosthesis at discharge

	Sutureless AVR N=40	TAVR N=40	p-value
Maximum transaortic velocity, m/s	2.32 ± 0.44	1.88 ± 0.41	<0.001
Mean pressure gradient, mmHg	10.72 ± 4.01	8.14 ± 4.21	0.006
Effective orifice area index, cm^2/m^2	0.76 ± 0.22	1.00 ± 0.30	<0.001
Prosthesis patient mismatch, n (%)	27 (67.5)	12 (30.0)	0.001
Doppler Velocity Index	0.46 ± 0.11	0.57 ± 0.15	0.001
Prosthesis size/Annulus diameter	0.97 ± 0.08	1.12 ± 0.11	<0.001
AR grade I, n (%)	6 (15)	26 (65)	<0.001
AR grade II, n (%)	2 (5)	9 (22.5)	
MR grade I-II, n (%)	27 (69.3)	30 (76.9)	0.45
Left ventricular ejection fraction, %	63.50 ± 12.63	59.57 ± 10.46	0.15
Stroke volume index, ml/m^2	29.91 ± 10.47	35.56 ± 12.50	0.03
Low-flow, n (%)	29 (72.5)	18 (46.2)	0.02

Values are mean ± SD or n (%).

AR=aortic valve prosthesis regurgitation,
AVR= aortic valve replacement,
MR=mitral regurgitation,
TAVR=transcatheter aortic valve replacement

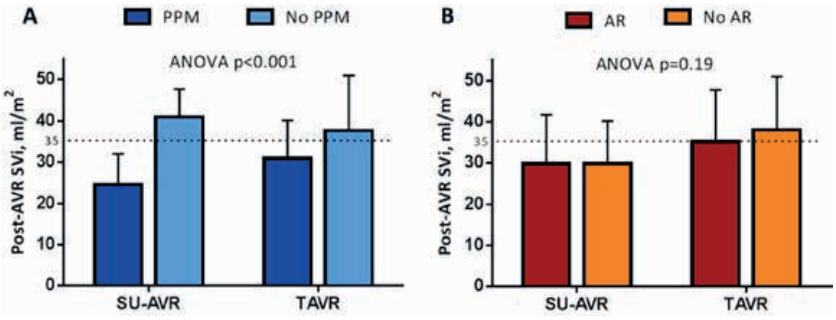

Figure 3. Association between prosthesis patient mismatch (PPM) and aortic regurgitation (AR) and forward flow after surgical sutureless (SU-AVR) and transcatheter (TAVR) aortic valve replacement (AVR). **A.** Patients treated with surgical aortic valve replacement and who showed PPM had significantly lower stroke volume compared with the other groups. **B.** There were no differences in stroke volume between patients with and without significant AR after surgical or transcatheter aortic valve replacement.

Table 3. Uni- and multivariate binary logistic regression analysis to identify factors that define low-flow state post sutureless and transcatheter aortic valve replacement.

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, years	1.06	0.97-1.16	0.18			
Sutureless-AVR	3.08	1.21-7.85	0.02	1.29	0.23-7.26	0.77
PPM	5.81	2.13-15.83	0.001	4.70	1.64-13.48	0.004
AR	0.42	0.17-1.07	0.07	0.70	0.17-2.85	0.62
post LVEF, %	1.04	0.99-1.08	0.12			
AVP size/ Annulus	0.03	0.001-1.55	0.08	0.33	0.002-64.03	0.68
Propensity score	0.69	0.06-8.06	0.77			

AVP size/Annulus=aortic valve prosthesis size/aortic annulus diameter,
AR=aortic valve prosthesis regurgitation,
CI=confidence interval,
LVEF=left ventricular systolic function,
PPM=prosthesis patient mismatch,
OR=odds ratio

Table 4. Uni- and multivariate binary logistic regression analysis to identify factors that define prosthesis patient mismatch post sutureless and transcatheter aortic valve replacement.

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Sutureless-AVR	4.67	1.81-12.07	0.001	3.90	1.22-12.50	0.02
Annulus, cm	1.37	0.19-9.73	0.76			
AVP size/ Annulus	0.01	0.001-0.56	0.03	0.28	0.002-37.61	0.61
Propensity score	0.29	0.03-3.37	0.32			

AVP size/Annulus=aortic valve prosthesis size/aortic annulus diameter,
CI=confidence interval,
OR=odds ratio

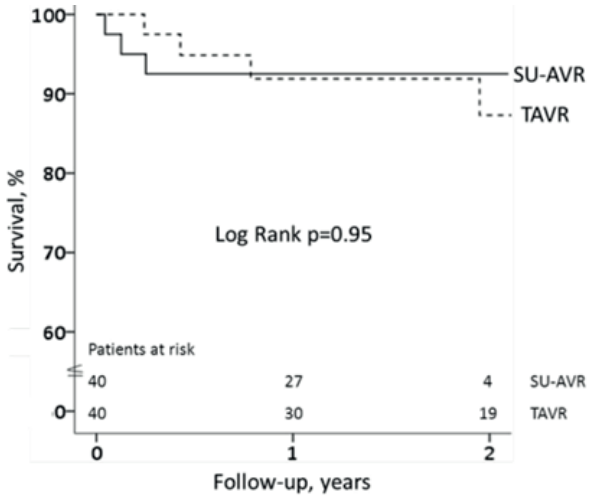

Figure 4. Kaplan-Meier estimates of time to death in patients treated with TAVR and patients treated with surgical aortic valve replacement suing the sutureless 3f Enable valve (SU-AVR).

Table 5. Periprocedural complications based on Valve Academic Research Consortium-2 definitions

	Sutureless AVR N=40	TAVR N=40	p-value
Cerebrovascular accident			
Stroke, n (%)	2 (5)	1 (2.5)	0.31
Transient ischemic attack, n (%)	1 (2.5)	0	
Bleeding			
Minor, n (%)	4 (10)	1 (2.5)	0.07
Major, n (%)	3 (7.5)	0	
Conduction disturbances			
Transient complete AV block, n (%)	3 (7.5)	0	0.69
Pacemaker implantation, n (%)	1 (2.5)	3 (7.5)	
Acute kidney injury			
Stage 1, n (%)	5 (12.5)	6 (15)	0.28
Stage 2, n (%)	0	2 (5)	
Vascular injury			
Major, n (%)	0	0	0.08
Minor, n (%)	0	3 (7.5)	

AV=atrioventricular,
AVR=aortic valve replacement,
TAVR=transcatheter aortic valve replacement

Subsequently, the patient population was divided into 4 groups based on type of prosthesis and the presence of AR at discharge: surgical sutureless AVR with AR, surgical sutureless AVR without AR, TAVR with AR, TAVR without AR. The forward flow was not significantly different among these 4 groups (SVi 29.92±11.83 vs. 29.91±10.32 vs. 35.19±12.60 vs. 38.11±12.85 ml/m^2, respectively, ANOVA p=0.19). Additionally, patients with AR at discharge have not significantly higher SVi than the patients with no-AR (34.18±12.49 vs. 31.02±10.87 ml/m^2, p=0.24) (Figure 3B).

A low-flow state at discharge was present in 79.5% of the patients with PPM vs. 40% of patients without PPM (p<0.001). However, low-flow state was observed in 70% of patients with AR vs. 50% of patients without AR (p=0.07). The presence of PPM was independently associated with low-flow state at discharge (OR 4.70, 95% CI 1.64-13.48, p=0.004) (Table 3). Surgical AVR with sutureless bioprosthesis was independently associated with PPM at discharge (OR 3.90, 95% CI 1.22-12.50, p=0.02) (Table 4).

Clinical outcome

Although the hemodynamic characteristics of the TAVR prosthesis were more favourable compared with the sutureless prosthesis, the survival during a median follow-up of 1.5 years (interquartile range from 0.79 to 2.01) was comparable between the two groups (log rank p=0.95) (Figure 4). The 2-year survival rate for patients treated with a sutureless bioprosthesis was 92.5% compared with 87.3% for patients undergoing TAVR. The periprocedural complications were comparable between the 2 groups, although there was a trend towards more vascular complications in TAVR group and more bleeding complications in the surgical sutureless group (Table 5).

DISCUSSION

The present study demonstrated that transcatheter bioprostheses have better hemodynamic profile than surgical sutureless 3f Enable valve in terms of effective orifice area index, mean transvalvular pressure gradient and PPM. However, AR was more often present after TAVR. The sutureless bioproshtesis was independently associated with PPM at discharge. Although the two types of valves have significant differences in the hemodynamic performance at discharge, the mid-term survival of the patients was comparable.

Hemodynamics of transcatheter and sutureless aortic bioprostheses

The improved hemodynamics of transcatheter aortic bioprostheses compared with stentless or stented surgical aortic bioprostheses have been demonstrated (8,24). Clavel et al. (8) reported larger effective orifice area index (0.90±0.26 cm^2/m^2), lower mean pressure gradient (10±4 mmHg) and less percentage of severe PPM (11%) in transcatheter aortic bioprosthesis compared with stentless (0.80±0.21 cm^2/m^2, 14±6 mmHg and 28%, respectively) and stented (0.76±0.16 cm^2/m^2, 13±5mmHg and 26%, respectively) bioprostheses. However, the presence of AR grade I or more after TAVR was more frequently observed compared with surgical AVR using stentless or stented bioprostheses (50% vs. 12% and 10%, respectively) (8).

Few studies have compared the hemodynamics of transcatheter aortic bioprostheses and surgical sutureless bioprostheses (7,25). In 37 patients, Santarpino et al. (7) reported comparable mean pressure gradients between transcatheter and sutureless bioprostheses (14.2±5.8 versus 13.3±3.9 mmHg, respectively) and higher incidence of AR among patients undergoing TAVR (13.5 versus 0 %, respectively). The present study confirms previous results and provides additional data in terms of incidence of PPM which was lower among patients treated with transcatheter aortic bioprostheses compared with patients receiving a sutureless bioprosthesis. PPM was independently associated with forward low-flow status, which was more prevalent among patients receiving a sutureless bioprosthesis. Additionally, in TAVR the prevalence of low-flow status was low despite having a higher incidence of AR, as compared with sutureless bioprosthesis. These findings are in agreement with the substudy of the Placement of AoRTic TraNscathetER valves (PARTNER) trial showing no association of low-flow status after TAVR with AR (24).

More importantly, current results were reported in a propensity score matched population based on baseline clinical, hemodynamic and anatomic parameters that are known to influence the hemodynamics and the survival. This would have resulted in similar aortic bioprosthesis hemodynamics. However, the observed higher incidence of PPM after sutureless AVR could be explained by relative prosthesis undersizing compared to TAVR bioprostheses (prosthesis size/annulus diameter ratio was 0.97±0.08 versus 1.12±0.11, respectively, $p<0.001$). While cardiac multi-detector row computed tomography was used to select the TAVR bioprosthesis size and generally the selected prosthesis is oversized by 10-15% to minimize paravalvular AR (13,26), sizing of the sutureless bioprosthesis was performed

at the operating theatre by using the pre-sized callipers which may lead to a smaller prosthesis size and effective orifice area (5). On the other hand, AR after surgical AVR with sutureless bioprosthesis was less frequent maybe due to the decalcification of the aortic annulus performed during the procedure (5,14,15), while after TAVR the annular calcium may lead to gaps between the bioprostheses and the native aortic annulus from where the paravalvular AR may arise (2).

Impact of hemodynamic outcome on survival

Presence of residual AR, low-flow state and PPM have been associated with the prognosis of patients undergoing TAVR or surgical AVR for aortic stenosis (24). In several registries and the randomized PARTNER trial, AR grade I or more after TAVR has been associated with poor outcome (2,27-29). However, AR was not a predictor of outcome among patients treated with surgical AVR (24). In contrast, low-flow state at follow-up was associated with poor prognosis after surgical AVR but not after TAVR (24). Furthermore, the association between PPM and survival after TAVR or surgical AVR remains controversial (19,24,30). Ewe et al. (19) and Chacko et al. (30) suggested that PPM was not associated with survival after TAVR or surgical AVR while Hahn et al. (24) concluded that PPM was a predictor of mortality after both TAVR or surgical AVR.

Studies comparing the impact of hemodynamics of transcatheter and sutureless bioprostheses on survival are scarce. Santarpino et al. (7) reported better survival after surgical AVR with sutureless bioprosthesis compared to TAVR and the only difference between patient groups was the higher incidence of AR after TAVR as compared with surgical sutureless AVR. The present analysis showed comparable survival between patients treated with TAVR and patients treated with surgical AVR using sutureless bioprosthesis. The low number of patients and the propensity score matching process may have reduced the power of the study to observe significant differences in survival and has precluded us to investigate independent associates of survival.

Limitations

The main limitation is the limited number of patients included in the analysis. However, the two groups of 40 patients were 1:1 propensity score matched. The inclusion of only men is another limitation since the results of the present study may not be applicable to female patients with smaller body surface areas and aortic annulus. Moreover, systematic echocardiographic follow-up data after discharge were not available for patients treated with a sutureless bioprosthesis. Additionally, the limited number of patients in each group matched for hemodynamic parameters mainly, may bias the survival analysis and a Cox-regression analysis was not performed to explore the independent impact of bioprosthesis hemodynamics on survival, due to the very few events (n=13) during the median follow-up of 1.5 years.

Conclusions

In high operative risk patients with severe aortic stenosis treated with valve replacement, TAVR prostheses have better hemodynamic profile at discharge, in terms of higher effective orifice area index, lower mean transvalvular pressure gradient, lower prevalence of forward low-flow and

PPM, compared to the sutureless 3f Enable valve. However, the incidence of AR is significantly higher among patients treated with TAVR than patients receiving a sutureless bioprosthesis. Nevertheless, these differences did not have prognostic implications since patients treated with sutureless AVR had comparable mid-term survival with those treated with TAVR.

Acknowledgements: None

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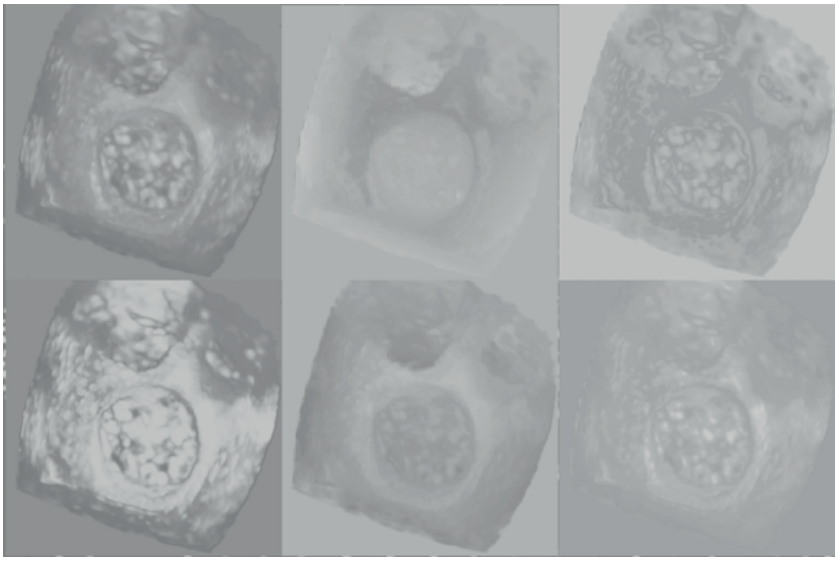
PART II

MITRAL VALVE REGURGITATION: DIAGNOSIS AND MANAGEMENT

CHAPTER 6

Left ventricular systolic function assessment in secondary mitral regurgitation:

left ventricular ejection fraction versus speckle tracking global longitudinal strain



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ABSTRACT

Aims

Left ventricular (LV) ejection fraction (LVEF) is currently considered for the decision making of patients with mitral regurgitation (MR). However, LVEF represents change in LV volume between end-diastole and end-systole but does not characterize the intrinsic function of the myocardium. In contrast, speckle tracking global longitudinal strain (GLS) characterizes myocardial deformation. The present study evaluated whether LV GLS may detect further impairment in LV systolic function in dilated cardiomyopathy patients with and without severe secondary MR matched based on LVEF.

Methods and results

Patients with non-ischemic dilated cardiomyopathy (N=150, 59±12 years old, 58% male) were included: 75 patients with severe secondary MR and 75 patients with none or less than mild MR matched 1:1 according to LVEF. The LV systolic function was evaluated by LVEF (following Simpson s biplane method), forward ejection fraction (forward stroke volume relative to LV end-diastolic volume) and speckle tracking GLS. By definition, LVEF was comparable between the two groups (patients with severe MR 31±10 vs. patients with no/mild MR 31±10%, p=0.93). However, patients with severe MR had significantly lower forward ejection fraction (29±14 vs. 40±18%, p<0.001) and more impaired GLS (-8.08±3.33 vs. -9.78±3.78%, p=0.004) compared to their counterparts. The presence of severe secondary MR was independently associated with worse LV GLS (beta 1.32, 95% confidence interval 0.14 2.49, p=0.03).

Conclusion

In patients with severe secondary MR, speckle tracking GLS shows more deteriorated LV systolic function than LVEF.

Keywords

Severe secondary mitral regurgitation; Left ventricular ejection fraction; Global longitudinal strain

Abbreviations

GLS, global longitudinal strain
LV, left ventricular
LVEF, left ventricular ejection fraction
MR, mitral regurgitation

INTRODUCTION

In routine clinical practice, left ventricular (LV) ejection fraction (LVEF) is currently one of the most requested parameters for the decision making of patients with mitral regurgitation (MR).[1, 2] However, LVEF represents the change in LV volume from end-diastole to end-systole without taking into consideration the direction of the blood flow and the intrinsic properties of the myocardium. In patients with MR, LVEF may not truly represent the LV systolic function since the left ventricle partly empties in the low pressure left atrium and does not reflect the effective stroke volume pumped into the aorta. This may lead to an overestimation of the LV systolic function although the myocardial contraction may be already impaired by the volume overload. Previous studies showed that circumferential myocardial fibre shortening assessed with LV angiography was significantly reduced in patients with chronic MR compared with patients without MR despite comparable LVEF.[3, 4] The American Heart Association/American College of Cardiology guidelines for the management of patients with valvular heart disease have recently introduced the concept of stages of progression of valvular heart disease which takes into account the response of the LV to the volume overload.[2] Characterization of LV structural changes and function using 2-dimensional speckle tracking echocardiography or magnetic resonance imaging techniques may help in refining and personalizing treatment options for patients with MR.[5, 6]

LV global longitudinal strain (GLS), assessed with 2-dimensional speckle tracking echocardiography, has been demonstrated to detect subtle LV systolic dysfunction in patients with organic MR and preserved LVEF.[7] However, in patients with dilated cardiomyopathy and severe secondary MR it has not been demonstrated if LV GLS may show more impaired LV systolic function than LVEF. In this subset of patients, LVEF may overestimate LV systolic function by emptying part of the LV volume into the left atrium, whereas LV GLS may be more impaired than that of patients with dilated cardiomyopathy, similar LVEF and competent mitral valve. Accordingly, the present study evaluated whether LV GLS may detect further impairment in LV systolic function in dilated cardiomyopathy patients with and without severe secondary MR matched based on LVEF.

METHODS

Patients

Patients with non-ischemic dilated cardiomyopathy and chronic severe secondary MR (n=145) were selected from a clinical database (EPD-vision 8.3.3.6; Leiden University Medical Center, Leiden, The Netherlands). Patients with dilated cardiomyopathy due to congenital heart disease, ischemic cardiomyopathy or hypertrophic cardiomyopathy were excluded. In addition, patients with preserved LVEF (≥50%), mitral stenosis, significant aortic valve disease, previous cardiac surgery, or endocarditis were excluded leading to 108 patients with severe MR. Furthermore, patients with non-ischemic dilated cardiomyopathy with less than mild MR (n=220) were selected. After excluding the patients with concomitant other valvular disease or treated with aortic valve replacement / transcatheter aortic valve implantation, 136 patients were eligible for inclusion. Patients with and without significant MR were matched 1:1 based on LVEF. In all patients, invasive coronary angiography was performed and the presence of significant coronary artery stenosis was excluded.

Demographics, clinical characteristics, symptoms and medication of these patients were prospectively collected in the departmental electronic files (EPD-vision 8.3.3.6; Leiden, The Netherlands). All the patients had a complete transthoracic echocardiographic study digitally stored for off-line analysis (EchoPAC 112.0.0, GE Medical Systems, Horten, Norway).

The Institutional Ethics Committee approved this retrospective analysis of clinically acquired data and waived the need for patients' written informed consent.

Echocardiographic analysis

The echocardiograms were performed in hemodynamically stable patients during a scheduled outpatient visit with commercially available ultrasound systems (Vivid-7, and E9, GE-Vingmed, Milwaukee, WI, USA). Two-dimensional grey scale, continuous, pulsed and colour Doppler images were retrospectively analysed for LV function and dimensions as well as grade of MR assessment according to the current recommendations.[8] Various parameters were used for LV systolic function, including LVEF, forward ejection fraction and LV GLS. LVEF was calculated according to the Simpson's biplane method. From the apical 4- and 2-chamber views, the LV end-systolic and end-diastolic volumes were measured and LVEF was derived. In addition, the forward ejection fraction was measured. The LV outflow tract area was derived from the LVOT diameter measured on the parasternal long-axis view of the left ventricle and multiplied by the LV outflow tract velocity-time integral on pulsed wave Doppler recordings obtaining the LV stroke volume. The cardiac output was obtained from the product of stroke volume and heart rate. Finally the forward ejection fraction was calculated by dividing stroke volume by LV end-diastolic volume and expressed as a percentage.[9] Moreover, from the grey scale apical 3-, 4- and 2-chamber views, GLS was measured using 2-dimensional speckle tracking echocardiography.[10] The aortic valve closure was first defined at the apical 3-chamber view. Then the

LV endocardium was traced at each apical view at the end-systolic frame. A region of interest was automatically defined between the endocardial and epicardial borders and manually adjusted to include the LV myocardium. In patients with atrial fibrillation, GLS was repeatedly measured from 3 cardiac cycles and averaged. GLS was then corrected for LV end-diastolic volume and end-systolic volume.

In addition, the wall thickness and the LV end-diastolic diameter were measured at the parasternal long-axis view. LV mass was evaluated by the formula (0.8 x {1.04[(LV end-diastolic diameter + posterior wall thickness in diastole + septal wall thickness in diastole)^3 - (LV end-diastolic diameter)^3]} + 0.6g) and indexed to BSA.[8] In addition, the relative wall thickness ([2 x posterior wall thickness in diastole] / LV end-diastolic diameter) and the ratio of LV mass to LV end-diastolic volume were evaluated.[8] LV volumes and dimensions were indexed to body surface area.

MR grade was assessed using a multiparametric integrated approach as recommended,[11] including vena contracta width and, when feasible, effective regurgitant orifice area and regurgitant volume calculated according to the proximal isovelocity surface area method. Severe functional MR was defined by vena contracta width ≥0.4cm, effective regurgitant orifice area ≥0.2cm^2 and regurgitant volume ≥30ml taking into account the hemodynamic status of the patient and the LV end-diastolic volume as recommended.[11]

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical variables as frequency (percentage). Continuous variables were compared between the groups using the Student's *t* test or the Mann-Whitney *U* test, as appropriate, whereas categorical variables were compared using the x^2 test or Fisher's exact test, as appropriate. Correlations between continuous variables were tested with the Pearson correlation test. Inter- and intra-observer agreements for the measurement of LV GLS were evaluated calculating the intraclass correlation coefficients (ICC) including the lower and upper limits of the 95% confidence interval (CI). Good inter-observer (ICC 0.99, 95% CI 0.98-1.00) and intra-observer (ICC 0.95, 95% CI 0.85-0.98) agreement was found for pre-operative LV GLS strain values. The association between MR and LV GLS was evaluated using the multivariable regression analysis including as independent variables clinical and echocardiographic parameters associated in the univariable analysis with a p-value <0.10. P-values <0.05 were considered statistically significant. Statistical analysis was performed with SPSS version 20 (SPSS, Inc., Chicago, Illinois).

RESULTS

In total, 150 patients with non-ischemic dilated cardiomyopathy were included in the current analysis (59±12 years old, male 58%): 75 with severe secondary MR matched with 75 patients with no/mild MR. Patients with severe MR were older, had higher prevalence of paroxysmal atrial fibrillation, diabetes, worse renal function and New York Heart Association functional class compared to patients with no/mild MR (Table 1).

Patients with severe MR (vena contracta 6.14±1.57 mm, effective regurgitant orifice area 0.28±0.14cm^2, regurgitant volume 32±10ml) had more dilated LV compared with patients with no/mild MR (Table 2). However, both groups showed similar LV mass index, resulting in more eccentric LV hypertrophy in patients with severe MR compared with the no/mild MR group (Table 2). According to the inclusion criteria, there were no differences in LVEF between groups (31±10 vs. 31±10%, p=0.93). However, patients with severe MR had significantly lower forward ejection fraction (29±14 vs. 40±18%, p<0.001) and more impaired GLS (-8.08±3.33 vs. -9.78±3.78%, p=0.004) compared to their counterparts (Table 2). The forward ejection fraction and GLS showed good correlation in the total population (r -0.632, p<0.001), in the severe MR group (r -0.523, p<0.005) and in the no/mild MR group (r -0.648, p<0.001). Figure 1 illustrates the examples of a patient with severe MR and a patient with trivial MR. Despite showing comparable LVEF, GLS was more impaired in the patient with severe MR.

Table 1. Demographic and clinical characteristic of non-ischemic dilated cardiomyopathy patients according to mitral regurgitation

	Total DCM N=150	No/mild MR N=75	Severe MR N=75	p-value
Age, years	59±12	57±10	62±13	0.02
Male gender, n (%)	86 (58)	56 (75)	30 (41)	<0.001
Body surface area, m^2	1.95±0.23	2.00±0.23	1.89±0.22	0.004
Atrial fibrillation, n (%)	43 (31)	11 (17)	32 (43)	0.001
Hypertension, n (%)	70 (47)	33 (44)	37 (51)	0.42
Diabetes, n (%)	21 (14)	6 (8)	15 (20)	0.03
Glomerular filtration rate, ml/min/1.73m^2	66±21	74±19	58±19	<0.001
Systolic blood pressure, mmHg	124±25	125±25	122±24	0.46
Diastolic blood pressure, mmHg	75±12	76±13	73±12	0.13
ACEi/ARBs, n (%)	128 (87)	66 (88)	62 (86)	0.73
Beta-blockers, n (%)	104 (71)	58 (77)	49 (65)	0.10
NYHA class I, n (%) II, n (%) III, n (%) IV, n (%)	24 (17) 60 (42) 48 (33) 12 (8)	24 (32) 42 (57) 7 (10) 1 (1)	0 (0) 18 (26) 41 (59) 11 (16)	<0.001

ACEi/ARBs, angiotensin converting enzyme inhibitor/angiotensin receptor blockers;
DCM, dilated cardiomyopathy;
MR, mitral regurgitation;
NYHA, New-York Heart Association

Independent association between MR grade and LV GLS

Table 3 summarizes the results of the univariable and multivariable analyses. Severe MR was associated with an increase of 1.32% in the mean LV GLS (beta 1.32, 95% confidence interval 0.14 – 2.49, p=0.03) after adjusting for age and diabetes, The association remains significant although the effect of severe MR on LV GLS has been attenuated after the adjustment.

Table 2. Left ventricular systolic function and remodelling in non-ischemic dilated cardiomyopathy patients according to mitral regurgitation

	Total DCM N=150	No/mild MR N=75	Severe MR N=75	p-value
LV ejection fraction, %	31±10	31±10	31±10	0.93
Global longitudinal strain, %	-8.93±3.65	-9.78±3.78	-8.08±3.33	0.004
Corrected global longitudinal strain for LV end-diastolic volume, %/10ml	-0.64±0.44	-0.73±0.50	-0.55±0.36	0.013
Corrected global longitudinal strain for LV end-systolic volume, %/10ml	-1.02±0.82	-1.16±0.92	-0.88±0.69	0.037
Stroke volume index, ml/m^2	27±9	29±8	24±9	<0.001
Cardiac output, L/min	3.77±1.29	4.08±1.29	3.38±1.20	0.002
Cardiac index, L/min/m^2	1.93±0.64	2.03±0.63	1.80±0.64	0.04
Forward ejection fraction, %	35±17	40±18	29±14	<0.001
LV end-diastolic volume index, ml/m^2	90±34	83±30	96±37	0.02
LV end-systolic volume index, ml/m^2	64±31	59±27	69±34	0.04
LV mass index, gr/m^2	137±39	141±38	132±40	0.17
LV relative wall thickness, %	32±11	37±10	27±9	<0.001
LV mass/end-diastolic volume, gr/ml	1.64±0.51	1.81±0.51	1.48±0.46	<0.001

DCM, dilated cardiomyopathy;
LV, left ventricular;
MR, mitral regurgitation

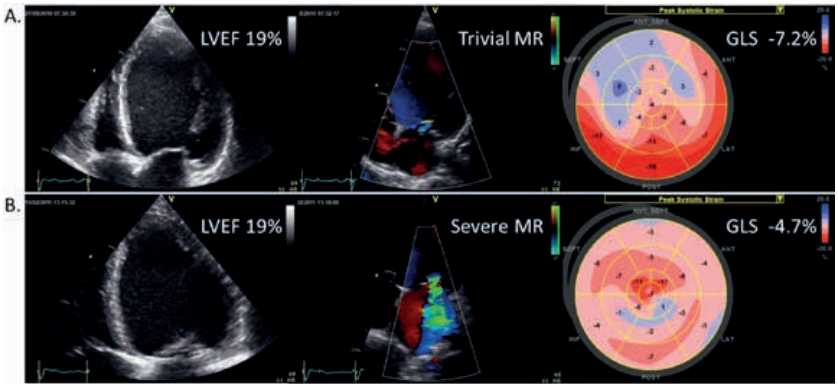

Figure 1. Representative example of two patients with non-ischemic cardiomyopathy. Panel A: patient with trivial mitral regurgitation (MR). Panel B: patient with severe secondary MR. Despite showing comparable left ventricular ejection fraction (LVEF), the patient with severe MR had more impaired left ventricular global longitudinal strain.

Table 3. Parameters associated with global longitudinal strain in non-ischemic dilated cardiomyopathy patients

	Univariable			Multivariable		
	Beta	95% CI	p-value	Beta	95% CI	p-value
Severe MR	1.70	0.55 – 2.85	0.004	1.32	0.14 – 2.49	0.03
Age, years	0.04	-0.006 – 0.09	0.09	0.02	-0.03 – 0.07	0.43
Male gender	-0.08	-1.28 – 1.13	0.90			
Atrial fibrillation	0.13	-1.18 – 1.44	0.85			
Hypertension	-0.01	-1.21 – 1.18	0.98			
Diabetes	2.46	0.80 – 4.12	0.004	1.98	0.28 – 3.67	0.02
GFR, ml/min/1.73m^2	0.001	-0.03 – 0.03	0.97			
ACEi/ARBs	0.04	-1.75 – 1.84	0.96			
Beta-blockers	-1.09	-2.39 – 0.20	0.10			

ACEi/ARBs, angiotensin converting enzyme inhibitor/angiotensin receptor blockers;
CI, confidence interval;
GFR, glomerular filtration rate;
MR, mitral regurgitation

DISCUSSION

The present study demonstrates that LV GLS shows more deteriorated LV performance in patients with dilated cardiomyopathy and chronic severe secondary MR than LVEF.

Assessment of LV inotropic state in chronic MR: GLS versus LVEF

Assessment of LV myocardial performance in patients with chronic MR has been challenging. Initial cardiac catheterization studies demonstrated that the mean velocity of circumferential fibre shortening derived from LV angiograms was significantly reduced in patients with chronic MR compared with patients without MR despite having similar LVEF.[3, 4] These findings suggested that the favourable unloading conditions of the left ventricle into the left atrium through the regurgitant jet may mask reduced LV inotropic state. The measurement of mean velocity of circumferential fibre shortening could be considered the precursor of current echocardiographic derived strain rate imaging since the circumference radius of the left ventricle at each frame is corrected for the end-diastolic circumference.[12] However, this measurement is invasive and time consuming, limitations that have been overcome with current developments in non-invasive imaging enabling the assessment of myocardial velocities and deformation.[8, 13]

Speckle tracking derived LV GLS has been evaluated in patients with primary MR and preserved LVEF to detect the presence of subclinical LV myocardial dysfunction. In 59 patients with chronic severe primary MR and preserved

LVEF, Kim et al.[7] demonstrated that speckle-tracking longitudinal strain was an earlier marker than LVEF of intrinsic LV systolic dysfunction due to MR induced LV remodelling. However, no studies have evaluated to date the use of speckle tracking echocardiography to detect LV systolic dysfunction beyond LVEF in patients with secondary MR.

GLS in severe secondary MR

In contrast to primary MR, secondary MR is caused by LV dilatation and dysfunction which causes tethering of the mitral leaflets and reduced closing forces. In these patients, assessment of LV performance is crucial since the associated operative risks strongly depend on the LV inotropic status. LVEF is the parameter considered in current guidelines to select patients with severe secondary MR for surgical or transcatheter mitral valve repair/replacement.[1,2] However, similarly to patients with primary MR, LVEF may mask the true LV inotropic status. The present study provides further insight into this hypothesis. The two groups of patients with dilated cardiomyopathy had reduced LVEF and impaired LV GLS. Both groups of patients had comparable LVEF which indicates that the ratio of volume change was comparable. However, patients with severe MR had significantly lower forward flow, cardiac output and cardiac index compared with patients without MR. Similarly to the studies using invasive measurements, it could be hypothesized that in patients with severe MR a significant percentage of the regurgitant volume is emptied into the left atrium before the aortic valve opens.[3] In addition, wall stress is lower during early and late systole and the reduced afterload results in increased total LV stroke volume.[14] These pathophysiological mechanisms may mask a further reduced LV performance in patients with severe MR that LVEF cannot reflect. However, with the use of more sensitive measures such as LV GLS, this hypothesis is demonstrated. Indeed, patients with severe secondary MR had more impaired LV GLS than patients without significant MR despite having comparable LVEF.

Limitations

The current analysis is a retrospective observational study of prospectively collected data. The prognostic implications of LV GLS in patients with severe secondary MR have to be demonstrated in future prospective studies. The current study included only non-ischemic dilated cardiomyopathy patients in order to avoid the segmental LV dysfunction and local aneurysmal formation due to ischemic disease. Patients were matched according to LVEF and other factors that may influence LV GLS, such as age, gender, atrial fibrillation, diabetes, chronic kidney disease were not taken into consideration. However, after adjusting for these confounder factors, MR was independently associated with LV GLS. In addition, the presence of LV dyssynchrony, which has been associated with secondary MR, was not evaluated. Furthermore, direct measurement of LV contractility with the use of conductance catheters that quantify simultaneously LV volumes and pressure was not performed. Therefore, the question whether LV GLS represents an accurate measurement of LV contractility in this specific population needs to be elucidated in additional studies.

CONCLUSION

In patients with severe secondary MR and reduced LVEF due to non-ischemic dilated cardiomyopathy, speckle-tracking LV GLS shows more impaired LV performance than LVEF.

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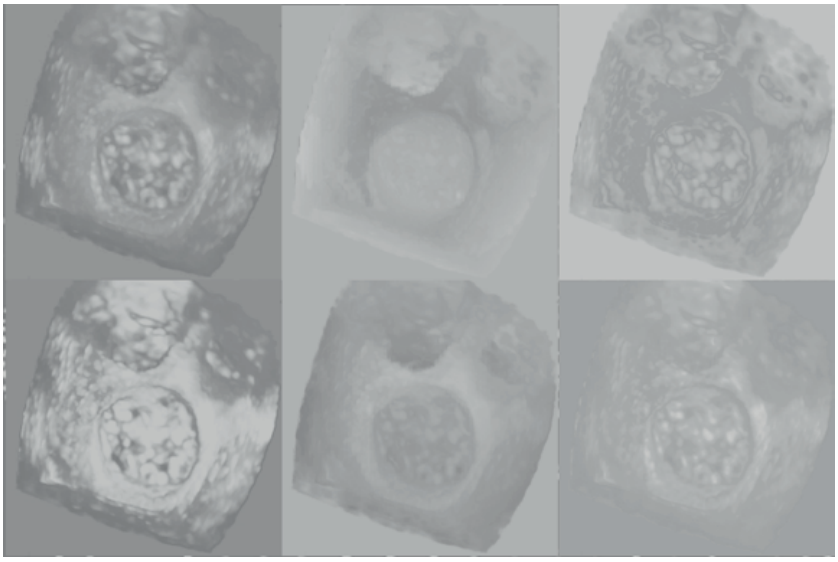
CHAPTER 7

Mitral valve repair for secondary mitral regurgitation in non-ischemic dilated cardiomyopathy is associated with left ventricular reverse remodeling and increase of forward flow



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ABSTRACT

Aims

It remains unclear whether surgical or transcatheter mitral valve repair for secondary mitral regurgitation (MR) in patients with non-ischemic cardiomyopathy reverse the underlying left ventricular (LV) pathophysiology. The present study evaluated the effect of mitral valve repair on LV performance in this group of patients.

Methods and Results

Seventy-six patients (65±14 years old, 43% male) with non-ischemic cardiomyopathy and moderate to severe chronic secondary MR treated successfully with transcatheter or surgical mitral valve repair were evaluated. Transthoracic echocardiography was performed at baseline, discharge and 6 months post-repair. After mitral valve repair, LVEF and LV global longitudinal strain (GLS) corrected for LV end-diastolic volume remained unchanged over time (p=0.90 and p=0.96 respectively). In contrast, LV forward flow increased significantly over time (stroke volume index: from 20±7 to 29±8 and 26±8 ml/m^2, p<0.001; cardiac index: from 1.50±0.44 to 2.36±0.60 and 2.01±0.48 L/min/m^2, p<0.001). In addition, LV end-diastolic and end-systolic volume index significantly reduced over time (from 87±42 to 70±33 and 75±39 ml/ m^2, p<0.001; and from 60±35 to 50±30 and 53±36 ml/ m^2, p=0.004, respectively). These changes were independent of the type of repair.

Conclusion

Surgical and transcatheter mitral valve repair for secondary MR in patients with non-ischemic dilated cardiomyopathy improved LV forward flow and induced LV reverse remodeling but did not change LV systolic function.

Keywords

Secondary mitral regurgitation; Dilated cardiomyopathy; MitraClip; Surgical mitral valve repair; Speckle tracking echocardiography

Abbreviations

GLS, global longitudinal strain
LV, left ventricular
LVEF, left ventricular ejection fraction
MR, mitral regurgitation

INTRODUCTION

Secondary mitral regurgitation (MR) in patients with non-ischemic dilated cardiomyopathy is associated with poor survival.[1] Despite optimal medical therapy and current device therapies, severe secondary MR confers worse prognosis and the outcomes of surgical mitral valve repair remain controversial. Accordingly, current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines consider mitral valve repair in this group of patients as class IIb recommendation.[2, 3] Advances in transcatheter mitral valve repair procedures have provided alternative therapy for patients with increased surgical risk such as patients with non-ischemic cardiomyopathy and depressed left ventricular ejection fraction (LVEF).[4, 5]

It remains unknown whether surgical or transcatheter mitral valve repair techniques may alter the underlying left ventricular (LV) pathophysiology in non-ischemic secondary MR and prevent further LV dilation and dysfunction. In non-ischemic cardiomyopathy, LV remodeling with displacement of the papillary muscles toward more apical positions and tethering of the mitral leaflets causes MR which leads to progressive LV remodeling which begets MR. It is logical to hypothesize that by restoring the mitral valve competence, LV remodeling may be halted and even reversed, improving LV systolic function and clinical prognosis. However, current data reporting on LV remodeling and functional recovery after mitral valve repair for secondary MR concern mainly ischemic cardiomyopathy patients and the results are controversial.[5-7] Accordingly, the current study evaluated patients with non-ischemic dilated cardiomyopathy and secondary MR successfully corrected by transcatheter or surgical repair and analyzed subsequent LV remodeling and functional recovery.

METHODS

Patients

Patients with non-ischemic heart failure and moderate to severe secondary MR who underwent surgical or transcatheter mitral valve repair were retrospectively identified from a clinical database (EPD-vision 8.3.3.6; Leiden University Medical Center, Leiden, The Netherlands). Patients who underwent concomitant aortic valve replacement or LV cardiac support device implantation (CorCap, Acorn Cardiovascular, St. Paul, Minnesota) were excluded. Successful mitral valve repair was defined as residual MR grade ≤2 at discharge.[8] None of the patients included in the current analysis was re-operated for severe MR during the follow-up period.

Demographics, clinical and procedural information and echocardiographic data were retrospectively analyzed from the departmental clinical (EPD-vision 8.3.3.6; Leiden, The Netherlands) and echocardiographic (EchoPAC version 112.0.1; GE Vingmed Ultrasound, Norway) databases.

Mitral valve repair procedures

The type of mitral valve repair (surgical restrictive annuloplasty or transcatheter MitraClip implantation [Abbott Vascular, Venlo, CA, USA]) was decided by the Heart Team, based on patient's characteristics (symptoms, comorbidities, frailty), logistic EuroSCORE and the anatomical suitability for MitraClip implantation.[9] Transcatheter mitral valve repair with the MitraClip device started in 2011 at the Leiden University Medical Center.

Surgical mitral valve repair was performed using restrictive mitral ring annuloplasty.[10] Briefly, through a midline sternotomy approach and under normothermic cardiopulmonary bypass and intermittent antegrade warm blood cardioplegia, the mitral valve was exposed through a vertical trans-septal incision of the interatrial septum. The mitral valve annulus was measured and the mitral ring (Carpentier Edwards Physioring, Edwards Lifesciences, Irvine, CA) was inserted, downsizing the ring by 2 sizes.[10]

Transcatheter implantation of the MitraClip system uses a 24-F torqueable sheath which is introduced through the femoral vein into the right atrium passing to the left atrium through a trans-septal puncture.[11,12] The MitraClip is advanced through the mitral valve into the LV and after aligning the arms of the clip perpendicular to the line of coaptation of the mitral leaflets, the device is pulled back to grasp the leaflets between the grippers and the arms of the clip at the level where the maximum regurgitation occurs. The procedure is performed under the guidance of 2- and 3- dimensional transesophageal echocardiography and the immediate reduction in MR is evaluated.[9] More than one clip can be implanted in order to achieve adequate correction of MR without significant increase in diastolic transmitral gradient.[13]

Echocardiography

Transthoracic echocardiography was performed at baseline, before discharge and at mid-term follow-up (6 month), using a commercially available ultrasound system (Vivid 7 and Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Two-dimensional grey scale images and colour, continuous-wave and pulse-wave Doppler data were digitally stored and were analyzed offline (EchoPAC version 112.0.1; GE Vingmed Ultrasound, Norway).

Mitral regurgitation severity was assessed by an integrated approach as recommended, including measurement of the vena contracta and quantification of the effective regurgitant orifice area and regurgitant volume with the proximal isovelocity surface area method.[14] Severe secondary MR was defined by a vena contracta width of ≥0.4 cm, an effective regurgitant orifice of ≥0.2 cm^2 and a regurgitant volume of ≥30 ml/beat.[14, 15] The residual MR post-repair was quantified in a semi-quantitative method as previously reported.[8, 12]

LV remodeling was evaluated according to current recommendations.[16] LV end-diastolic and end-systolic volumes were evaluated by Simpsons' biplane method and then indexed to body surface area. LV dimensions were measured on the parasternal long-axis view and the LV mass was calculated and indexed to body surface area, as previously described.[16] In addition, the relative wall thickness ([2 x posterior wall thickness in diastole] / LV end-diastolic diameter) and the ratio of LV mass to LV end-diastolic volume were

also assessed.[16]

LVEF was measured using the Simpsons' biplane method.[16] Additionally, LV systolic function was assessed by 2-dimensional speckle tracking systolic global longitudinal strain (GLS).[17] GLS was evaluated at the apical 3-, 4- and 2-chamber views after defining the aortic valve closure timing on the 3-chamber view.[17] Subsequently, GLS was corrected for LV end-diastolic volume (every 100ml) as previously reported.[18] LV pressure and strain are affected by the LV myocardial fibers' length, according to the Frank-Starling law,[19] and as a result when the LV size changes due to MR reduction post-repair, the GLS should be corrected for the LV size.[18, 20] Furthermore, LV forward stroke volume was estimated by multiplying the LV outflow tract cross-sectional area by the velocity time integral derived from the pulse-wave Doppler signal of the LV outflow tract and indexed to body surface area. The cardiac output was calculated from the stroke volume multiplied by the heart rate and the cardiac index by the cardiac output indexed to body surface area. The LV forward ejection fraction was estimated by dividing the stroke volume by the LV end-diastolic volume and expressed as a percentage.[18]

Statistical analysis

The continuous variables are presented as mean ± standard deviation and the categorical variables as frequencies and percentages. The continuous variables were compared with unpaired Students *t*-test or Mann-Whitney *U* test as appropriate. The categorical variables were compared with the chi-square test.

Changes over time in LV function variables (LVEF, GLS, corrected GLS), forward flow variables (stroke volume, stroke volume index, cardiac output, cardiac index, LV forward ejection fraction) and LV remodeling variables (LV end-diastolic volume, end-systolic volume, mass, relative wall thickness, ratio mass/end-diastolic volume) were assessed using linear mixed modelling analysis with all these variables as dependent variables. Time (baseline, pre-discharge and 6 months) and type of repair (MitraClip or surgical repair) were introduced as main fixed effects. Main effects were compared and their interaction was tested using the Bonferroni confidence interval adjustment. Post-hoc analysis was performed with the Bonferroni test to determine the time points at which the dependent variables significantly differed. All statistical analyses were performed with the SPSS version 20 (SPSS, Inc, Chicago, IL) and p values <0.05 were considered statistically significant.

Table 1. Baseline demographic variables

	Secondary MR n=76	Surgical repair n=54	MitraClip repair n=22	p-value
Age, years	65±14	62±14	72±10	0.002
Male, n (%)	33 (43)	22 (41)	11 (50)	0.46
Body surface area, m^2	1.89±0.20	1.92±0.20	1.82±0.19	0.07
Hypertension, n (%)	46 (62)	38 (72)	8 (38)	0.007
Diabetes, n (%)	16 (22)	7 (14)	9 (43)	0.006
Atrial fibrillation, n (%)	39 (53)	29 (53)	10 (48)	0.64
eGFR, mL/min per 1.73 m^2	60±25	65±22	50±30	0.02
NYHA class III-IV, n (%)	47 (63)	30 (56)	17 (77)	0.003
B-blockers, n (%)	52 (69)	37 (69)	15 (68)	0.59
ACEi/ARBs, n (%)	62 (82)	45 (83)	17 (77)	0.38
Diuretics, n (%)	61 (80)	45 (83)	16 (73)	0.23
Calcium antagonists, n (%)	8 (11)	4 (8)	4 (18)	0.16
Digoxin, n (%)	29 (38)	21 (39)	8 (36)	0.53

ACE-I, angiotensin-converting enzyme inhibitor;
ARB, angiotensin-II receptor blocker;
eGFR, estimated glomerular filtration rate;
MR, mitral regurgitation;
NYHA, New-York Heart Association

Table 2. Baseline echocardiographic left ventricular parameters

	Secondary MR n=76	Surgical repair n=54	MitraClip repair n=22	p-value
LV ejection fraction, %	34±10	35±10	32±11	0.20
Global longitudinal strain, %	-9.63±4.11	-10.29±3.87	-8.09±4.32	0.04
Corrected global longitudinal strain, %/100ml	-8.26±7.03	-9.10±7.38	-6.31±5.84	0.12
Stroke volume index, ml/m^2	20±7	21±6	20±8	0.80
Cardiac index, $L/min/m^2$	1.50±0.44	1.48±0.41	1.53±0.51	0.70
Forward ejection fraction, %	29±14	33±13	25±16	0.03
LVEDV index, ml/m^2	87±42	81±36	105±56	0.03
LVESV index, ml/m^2	60±35	55±31	75±46	0.04
LV mass index, gr/m^2	128±42	121±41	148±41	0.01
	29±10	29±10	30±9	0.94
LV mass/LVEDV, gr/ml	1.64±0.59	1.62±0.57	1.65±0.67	0.87

LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation

RESULTS

Baseline characteristics

In total, 76 patients (65±14 years old, 43% male) with severe secondary MR and non-ischemic dilated cardiomyopathy with LVEF <50% who were successfully treated with mitral valve repair were evaluated. Baseline vena contracta, effective regurgitant orifice area and regurgitant volume were 0.63±0.16 cm, 0.21±0.10 cm^2 and 32±12 ml, respectively. Surgical mitral valve repair was performed in 54 (71%) patients whereas 22 (29%) were treated with transcatheter MitraClip implantation (Table 1). Patients treated with the MitraClip device were older and showed more advanced heart failure symptoms compared with patients treated surgically. The parameters characterizing LV function, LV forward flow and remodeling are presented in Table 2. Patients treated with the MitraClip device had more dilated and eccentrically hypertrophied LV but comparable systolic function and LV forward flow than patients treated with surgical repair.

MR change post-repair

Repeated echocardiography was performed pre-discharge (median of 5 days; interquartile range 1-7) and at mid-term follow-up (median of 6 months; interquartile range 4-9). The MR grade at discharge was by definition ≤2, and although it increased at mid-term follow-up, it was still significantly less severe compared with baseline (p<0.001) (Figure 1). Specifically, at mid-term follow-up, in the surgical repair group 38% had no MR, 45% MR grade 1, and 17% MR grade 2 and in the MitraClip group 5% had no MR, 47% MR grade 1, 26% MR grade 2 and 21% MR grade 3. MR at follow-up was significantly less severe than pre-repair in both groups (p<0.001 in both groups).

LV functional recovery, forward flow and remodeling post-repair

Over time after successful repair, LVEF and corrected GLS remained

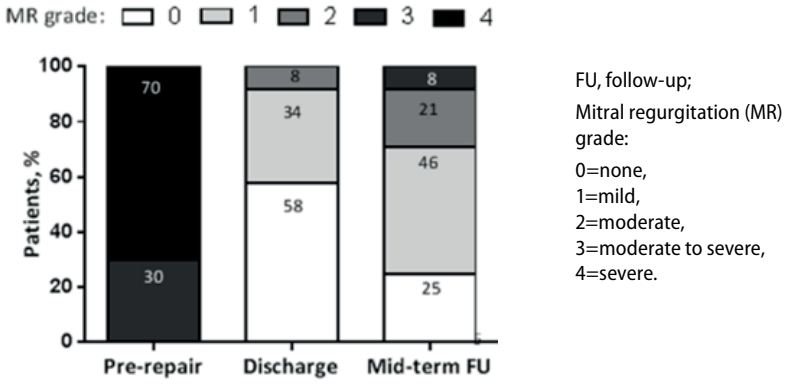


Figure 1. Mitral regurgitation evolution post mitral valve repair in patients with non-ischemic secondary mitral regurgitation.

unchanged (p=0.90 and p=0.96 respectively) (Table 3). However, LV forward flow assessed by stroke volume index, cardiac output, cardiac index and LV forward ejection fraction increased over time (p<0.001 for all parameters). This increase was detected at discharge and although at mid-term follow-up all these parameters were significantly reduced compared with discharge values, they still remained significantly better compared with baseline (follow-up versus baseline Bonferroni p<0.001 for all the forward flow parameters) (Table 3).

There were significant reductions in LV end-diastolic and end-systolic volumes over time after mitral valve repair (p<0.001 and p=0.005 respectively). This reduction occurred immediately after the MV repair at discharge and was sustained at mid-term follow-up (follow-up versus baseline Bonferroni p=0.001 and p=0.004 respectively) (Table 3).

Impact of the type of repair on LV functional recovery, forward flow and remodeling

Over time, the type of repair (MitraClip or surgical) had no impact on LVEF change (coefficient -3.50, 95% CI -8.61 – 1.54, p=0.17) and corrected GLS change (coefficient -1.48, 95% CI -4.64 – 1.67, p=0.35). Moreover, the type of

Table 3. Left ventricular functional recovery and remodeling over time after mitral valve repair (n=76)

	Baseline	Discharge	Mid-term FU	p-value*
Left ventricular functional recovery				
LV ejection fraction, %	34±10	35±12	34±12	0.94
Corrected global longitudinal strain, %/100ml	-8.26±7.03	-8.76±6.20	-8.33±6.50	0.96
Left ventricular forward flow				
Stroke volume, ml	39±12	55±18 †	50±17 ¥,§	<0.001
Stroke volume index, ml/m^2	20±7	29±8 †	26±8 ¥,§	<0.001
Cardiac output, L/min	2.84±0.82	4.44±1.28 †	3.76±0.95 ¥,§	<0.001
Cardiac index, L/min/m^2	1.51±0.44	2.36±0.60 †	2.01±0.48 ¥,§	<0.001
Forward ejection fraction, %	29±14	54±25 †	45±20 ¥,§	<0.001
Left ventricular remodeling				
LVEDV, ml	165±82	133±62 †	142±77 ¥	<0.001
LVEDV index, ml/m^2	87±42	70±33 †	75±39 ¥	<0.001
LVESV, ml	114±69	93±56 †	100±60 ¥	0.005
LVESV index, ml/m^2	60±35	50±30 †	53±36 ¥	0.004
Relative wall thickness,%	29±10	34±9 †	33±10	0.03
LV mass, gr	243±80	249±90	254±105	0.32
LV mass index, gr/m^2	128±42	132±46	134±53	0.39
LV mass/LVEDV, gr/ml	1.64±0.59	2.07±0.76 †	1.90±0.63 ¥	0.004

LV, left ventricular;
LVEDV, left ventricular end-diastolic volume;
LVESV, left ventricular end-systolic volume;
FU, follow-up

*p-value for total change of the parameter over the total follow-up time period
†p<0.05 for comparison of discharge vs. pre-repair with Bonferroni adjustment
¥p<0.05 for comparison of mid-term follow-up vs. pre-repair with Bonferroni adjustment
§p<0.05 for comparison of discharge vs. mid-term follow-up with Bonferroni adjustment

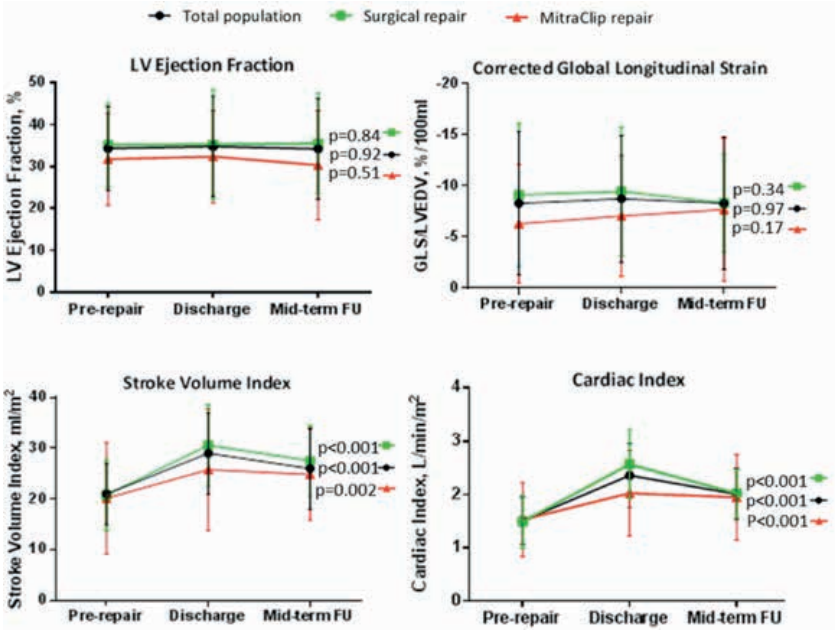
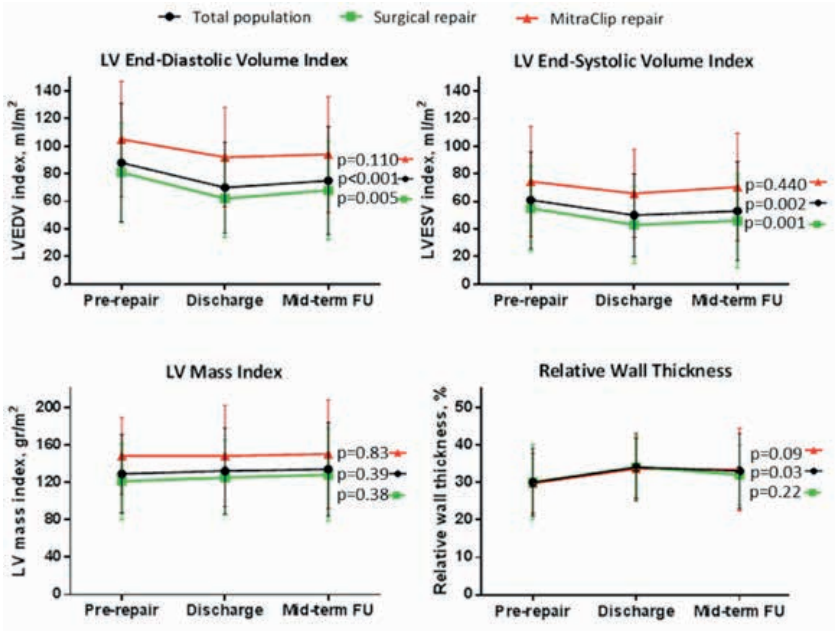


Figure 2. Left ventricular functional recovery post mitral valve repair in patients with non-ischemic secondary mitral regurgitation.



FU, follow-up;
LV, left ventricular;
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FU, follow-up;
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Figure 3. Left ventricular remodeling post mitral valve repair in patients with non-ischemic secondary mitral regurgitation.

repair had no impact on stroke volume index change (coefficient -1.97, 95% CI -4.81 – 0.87, p=0.17) and cardiac index change over time (coefficient -0.13, 95% CI -0.33 – 0.08, p=0.21). As a result the type of repair had no impact on LV functional recovery and forward flow change over time (Figure 2).

Furthermore, patients treated with the MitraClip device had larger LV end-diastolic and end-systolic volume index (coefficient 29.38, 95% CI 11.17 – 47.59, p=0.002 and coefficient 22.17, 95% CI 5.15 – 39.20, p=0.01, respectively) and LV mass index (coefficient 25.40, 95% CI 5.50 – 45.30, p=0.01) compared with the surgical repair group. However, LV reverse remodeling was comparable in both treatment groups (p for interaction 0.46 and 0.65 respectively). In addition, the type of repair had no impact on the relative wall thickness change (coefficient 0.05, 95% CI -0.03 – 0.04, p=0.96) or reduction in LV mass (p for interaction 0.88) (Figure 3). This indicates that both therapies exerted similar LV reverse remodeling over time (Figure 3).

DISCUSSION

The current study shows that successful correction of chronic moderate to severe secondary MR in non-ischemic dilated cardiomyopathy patients partly reverses the underlying LV pathophysiology, with significant increase of LV forward flow and LV reverse remodeling but without changes in LVEF and corrected GLS over time. The type of correction, MitraClip or surgical repair, had no significant impact on changes in LV forward flow over time or the extent of LV reverse remodeling at mid-term follow-up.

LV functional recovery after mitral valve repair

Despite the heterogeneous patient populations (ischemic versus non-ischemic) and the different surgical repair techniques used (isolated mitral valve repair versus associated with coronary artery bypass grafting or LV reconstruction or passive containment with cardiac support devices), the majority of the studies showed modest but statistically significant improvements in LVEF after surgical mitral valve repair for secondary MR.[21] Among the studies including patients with non-ischemic secondary MR, the Acorn trial, where almost 78% of patients had non-ischemic cardiomyopathy, showed significant and sustained improvements in LVEF at 12 months after restrictive mitral valve annnuloplasty.[22] In contrast, a study including 69 patients with non-ischemic cardiomyopathy undergoing restrictive mitral valve annuloplasty showed no significant improvement in LVEF (from 26±8 to 29±11% at 2-year follow-up).[23] Using MitraClip device several series have reported conflicting results in terms of LVEF improvement during follow-up.[5, 24] The Real World Expanded Multicenter Study of the MitraClip System (REALISM) study including 379 patients with secondary MR (12.2% non-ischemic aetiology) showed stable LVEF at 12 months follow-up after MitraClip (44±11 vs. 44±11%).[5] In contrast, the sub-analysis of the Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) registry, including 78 patients (about 62% non-ischemic) with secondary MR, reported significant improvement of the LVEF 12-months post-MitraClip

(from 40.72±11.62 to 46.23±9.03%).[24] In these studies, disparities in patient populations may explain in part the controversial results in terms of LVEF improvement.

However, LVEF may not be the best reflector of improvement in LV systolic function after mitral valve repair. In 24 patients with secondary MR (54% non-ischemic cardiomyopathy) who underwent cine multi-detector row computed tomography prior to and 2 months after restrictive mitral annuloplasty, Takeda et al showed an 11% decrease in global LV end-systolic wall stress along with significant improvement in LVEF (from 27±8% to 33±13%; p=0.0007) and LV reverse remodeling (21% and 13% reductions in LV end-systolic and end-diastolic volumes, respectively).[25] This reduction in LV end-systolic volume would lead to a reduction in LV end-systolic wall stress favoring further reduction in LV systolic volume and exceeding the reduction in LV end-diastolic volume which eventually results in increase in LVEF. In addition, a modest improvement in LV end-systolic wall stress corrected for LV end-systolic volume (a relatively load-independent measure of myocardial contractility) was observed but was weakly correlated with the increase in LVEF suggesting that the improvement in LV ejection performance is most probably related to afterload reduction rather than intrinsic improvement in LV contractility. Similarly, the present study showed no changes in LV GLS corrected for end-diastolic volume. In contrast, improvement in LV forward ejection fraction was observed suggesting that restrictive mitral annuloplasty is not associated with improvements in LV contractility but with significant reductions in afterload.

LV reverse remodeling after mitral valve repair

The prevalence of LV reverse remodeling, defined as 15% reduction in LV end-systolic volume, after surgical mitral valve repair for secondary MR ranges between 50% and 73%.[23, 26, 27] In studies including patients in whom passive restraint devices were used (i.e. CorCap Acorn CV, St Paul, Minn), the magnitude of LV volumes reduction was higher compared with series where these devices were not used.[22, 23] The Acorn trial showed significant and sustained reductions in LV end-systolic and end-diastolic volumes at 5 years after restrictive mitral annuloplasty.[22] Using the MitraClip device, Glower et al reported the 12-month echocardiographic outcomes of 351 patients enrolled in the EVEREST-II (Endovascular Valve Edge-to-Edge REpair Study) High-Risk registry and the REALISM Continued Access Study High-Risk Arm:[4] the LV end-diastolic volume reduced from 161±56 ml to 143±53 ml (p<0.001) and end-systolic volume from 87±47 ml to 79±44 ml (p<0.001). In the present study, both LV end-diastolic and end-systolic volume decreased significantly at follow-up. Interestingly, patients treated with the MitraClip device showed larger LV volumes during follow-up as compared with patients who underwent surgical mitral valve repair. It has been described that the presence of significant residual MR or recurrent MR is associated with less LV reverse remodeling.[5] In line with previous studies,[28, 29] the present study also showed that the prevalence of moderate MR in this study was significantly higher in the MitraClip group at discharge (MR grade 2: 27% vs. 0%, p<0.001) and at follow-up (MR grade 2-3: 47% vs. 17%, p=0.02) compared with the surgical repair group. However, the type of treatment was not associated with the occurrence of LV reverse remodeling. Probably other confounding parameters, apart from the gradual MR increase, may influence this finding.[5]

Clinical implications: does mitral valve repair reverse the underlying pathophysiology of non-ischemic secondary MR

The current analysis demonstrated that LV reverse remodeling and LV forward flow increased after mitral valve repair in patients with non-ischemic secondary MR and these improvements were independent of the type of repair (surgical or transcatheter). Current guidelines indicate that mitral valve repair/replacement may be considered in non-ischemic heart failure patients with symptomatic severe secondary MR despite optimal medical treatment (including cardiac resynchronization therapy) (Class IIbC) due to the limited evidence and the inconsistent results in terms of clinical and echocardiographic outcomes across the various studies.[2, 3] The present study provides further insights into the question on the effects of mitral valve repair on the underlying pathophysiology of non-ischemic secondary MR by showing that, despite no changes in LVEF or GLS corrected for LV end-diastolic volume, LV reverse remodeling occurs and LV forward ejection fraction improves. The fact that these findings were independent of type of repair emphasizes the relevance of role of the Heart team which is able to personalize the treatment according to the surgical risk.

Limitations

The current analysis included a relatively small number of patients which precluded us to perform survival analyses. However the cohort was very homogeneous including only patients with non-ischemic secondary MR. Longer follow-up would have strengthened the results by showing whether changes in LV structure and function were sustained.

CONCLUSIONS

Successful correction of chronic moderate to severe secondary MR in non-ischemic dilated cardiomyopathy patients partly reverses the underlying LV pathophysiology, with significant increase of LV forward flow and LV reverse remodeling but without changes in LVEF and corrected-GLS over time.

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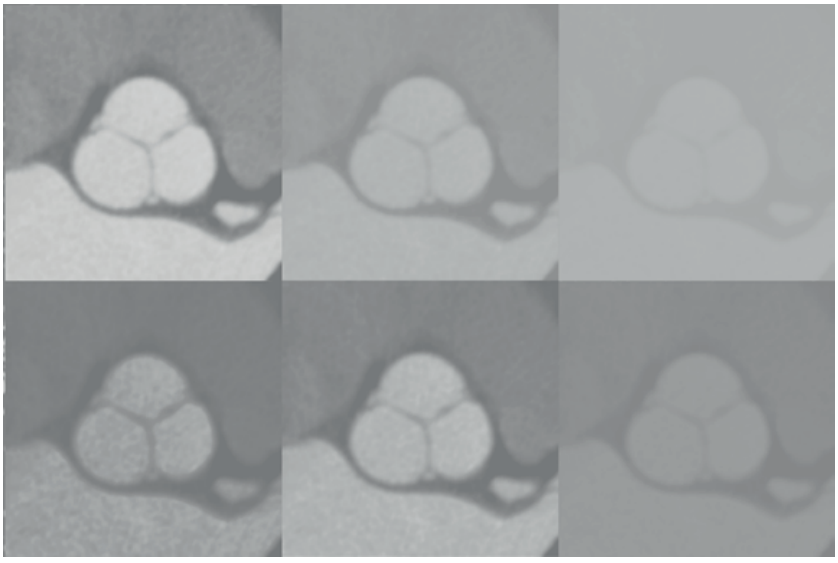
PART III

AORTIC STENOSIS AND MITRAL REGURGITATION: PROGNOSIS

CHAPTER 8

Prognostic Value of Aortic and Mitral Valve Calcium Detected by Contrast Cardiac Computed Tomography Angiography in Patients with Suspicion of Coronary Artery Disease



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ABSTRACT

Aortic valve calcium (VC) detected on non-contrast cardiac computed tomography angiography (CCTA) is known to be associated with all-cause mortality in asymptomatic and primary prevention population. However, the clinical significance of aortic and mitral VC remains unknown in symptomatic patients with suspected coronary artery disease (CAD). The aim of the present study was to assess whether aortic and mitral VC is independently associated with cardiac events and all-cause mortality in symptomatic patients with suspected CAD. A total of 369 symptomatic patients (mean age 55 ± 11 years, 60% male) who were referred for CCTA because of suspected CAD were included in the study. Aortic and mitral VC was detected and quantified by volume on contrast CCTA. Median follow-up (FU) for events (coronary-events and all-cause mortality) was 2.8 (interquartile range: 1.6 to 4.0) with a maximum of 5.5 years. A total of 39 (11%) patients had VC. Increased age, hypertension and increased Agatston coronary artery calcium (CAC) score were associated with VC. During the FU, patients with VC had higher risk for a coronary event (38.8 vs. 11%, log-rank $p<0.001$) and worse survival (92.3 vs. 99.1%, log-rank $p=0.002$) compared to those without VC. Volume of VC was independently associated with outcome, after adjusting for clinical variables (hazard ratio 1.88, $p<0.001$), Agatston CAC score (hazard ratio 1.47, $p=0.03$) and significant CAD (hazard ratio 1.81, $p=0.001$). In conclusion, aortic and mitral VC volume quantified on contrast CCTA was independently associated with coronary events and all-cause mortality in patients with suspected CAD.

INTRODUCTION

Contrast enhanced cardiac computed tomography angiography (CCTA) is nowadays used for the anatomic evaluation of coronary artery disease (CAD) in symptomatic patients with chest pain and low to intermediate probability of CAD.[1,2] Besides CAD, valve calcium (VC) can be detected by contrast enhanced CCTA.[3,4] Aortic and mitral VC detected by CCTA has been associated with increased prevalence of CAD, cardiovascular events and all-cause mortality in asymptomatic patients.[5-8] However, little is known about the prognostic value of aortic and mitral VC detected by CCTA in symptomatic patients. Moreover, the value of VC quantification on contrast enhanced CCTA has never been explored. Therefore, the aim of the current study was to assess the independent association between VC, detected and quantified on contrast CCTA, and prognosis in symptomatic patients with suspected CAD.

METHODS

We included all symptomatic patients who underwent a clinically indicated contrast enhanced CCTA for the evaluation of CAD from November 2007 till April 2010. Patients with previous diagnosis of CAD, congenital heart disease, mechanical valve prosthesis and poor CCTA diagnostic image quality were excluded.

All scans were performed using a 64-detector row computed tomography scanner or a 320-row scanner according established guidelines and local protocol.[9,10] Scan parameters were: 120kV, 300mA (depending on BMI and thoracic anatomy) and collimation of 64x0.5mm; and 120kV, 400-580mA (depending on BMI and thoracic anatomy) and collimation of 320x0.5mm for 64- and 320-row scanners, respectively. Contrast-enhanced CCTAs were reconstructed at 75% of the R-R interval with a slice thickness of 0.3mm for the 64- and 0.5mm, increment 0.25mm for the 320-detector scanner. Non-enhanced CCTAs were also reconstructed at the 75% of the R-R interval but with a slice thickness of 3mm non-overlapping. Reconstructed images were transferred to a remote workstation (Vital Images, Plymouth, Minnesota) for post-processing with dedicated software.

The non-contrast scans were used to evaluate the total coronary artery calcium (CAC) score as described by Agatston et al. applying a threshold of ≥130 Hounsfield units (HU)[11] with commercially available software (Vitrea 2, Vital Images, Plymouth, Minnesota).

To quantify VC on contrast-enhanced CCTA, novel automated data post-processing software (customized research version of CalcScore V11.1 by Medis specials b.v.) was used. Since both calcium and contrast medium have a radio density of >130 HU, a cut-off value of >130 HU as used for non-contrast scans, is not suitable to quantify calcium on contrast enhanced CCTA images.[12] Therefore, in the present study we applied a predefined threshold of 800

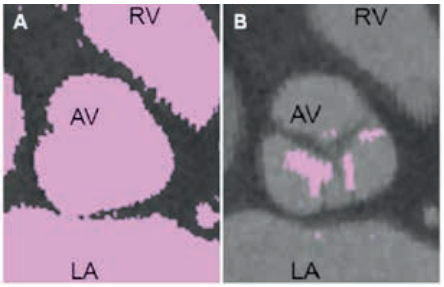

Figure 1. Aortic valve calcium assessed on contrast cardiac computed tomography angiography at the double oblique transverse view. A. Using a threshold of 130 HU detects all contrast, B. Using a threshold of 800 HU detects calcium on the aortic valve. AV=Aortic Valve, HU=Hounsfield Units, LA=Left Atrium, RV=Right Ventricle

HU to quantify calcium on the aortic and mitral valve.[3] An example of both

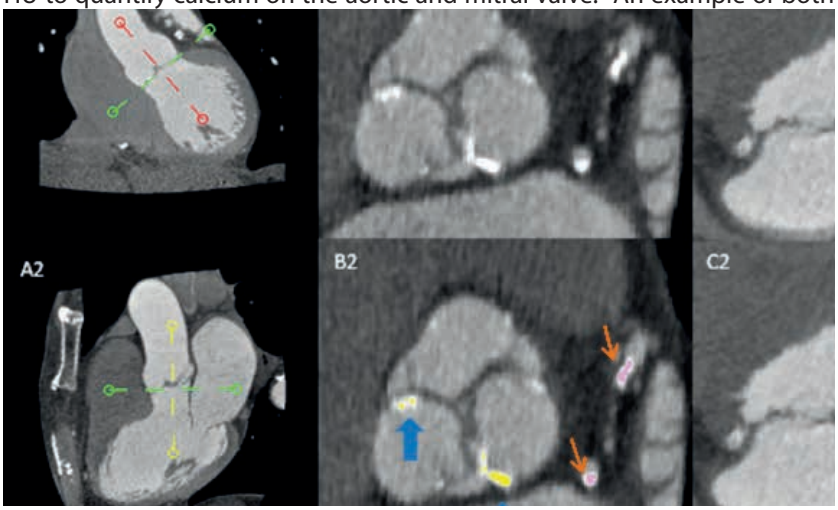

Figure 2. Aortic and mitral valve calcium assessed on contrast cardiac computed tomography angiography with the threshold of ≥800HU. By adjusting the 3 orthogonal multi-planar reformation planes (red, yellow and green dotted lines), based on aortic valve orientation, in the coronal (A1) and single oblique sagittal (A2) views, the double oblique transverse view depicting the real aortic valve short axis (B1) was created. By using the sequential axial images below the aortic annulus, the mitral valve could also be visualized in this view (C1). B2 demonstrates the calcium detected on the aortic valve. Blue arrows point the aortic valve calcium colored yellow after selecting it. Orange arrows point the coronary artery calcium colored pink (not selected). C2 demonstrates the calcium detected on the mitral valve. Red arrow points mitral valve calcium colored green after selecting it.

thresholds is depicted in Figure 1. Because the Agatston score is only suitable for assessing coronary artery calcium,[11] VC was quantified by assessing the volume (mm^3) of calcium on contrast-enhanced CCTA.[3,4]

To quantify VC we performed the following steps: because the aortic valve is depicted obliquely on the standard axial view,[3] the first step was to reorient the image based on the aortic valve. By using three multi-planar reformation planes (Figure 2.A1&A2), a double oblique transverse view was created. In this plane the aortic cusps were equally bisected allowing concomitant visualization of the insertion point of the aortic cusps (Figure 2.B1). Secondly, scrolling through sequential axial images below the aortic annulus, the mitral valve can be visualized in this view (Figure 2.C1). Next, 3mm slabs were created to facilitate accurate VC quantification. Subsequently, the aortic (Fig-

ure 2.B2) and mitral VC (Figure 2.C2) were manually selected. The aortic VC included all calcium within the level of the aortic annulus till the level of the coronary ostia. Mitral VC was defined as calcium of the mitral annulus and leaflets. Finally, the volume of the selected aortic and mitral VC was calculated automatically by the software.

Presence of significant CAD was evaluated from the contrast CCTA as previously described.[13] Significant CAD was defined as ≥50% stenosis.

Cardiovascular risk factors evaluated for this study were: hypertension, defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication; hypercholesterolemia, defined as serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl and/or treatment with lipid lowering drugs; diabetes, defined as fasting glucose ≥ 126mg/dl and/or on blood glucose lowering treatment; smoking, as current; obesity, as BMI ≥ 30 Kg/m^2 and family history: defined as the presence of CAD in first-degree family members diagnosed at the age of <55 years in men and <65 years in women.

Clinical information were recorded prospectively into the departmental Cardiology Information System (EPD, Vision, version 8.3.3.6, Leiden, The Netherlands) and analyzed retrospectively. Follow up was completed till January 2013. Patient follow-up data were gathered using clinical visits or standardized telephone interviews. The primary outcome was all-cause mortality. The secondary end-point was coronary events, including a composite of myocardial infarction (MI) and revascularization (percutaneous coronary intervention (PCI) and coronary artery by-pass grafting (CABG)). The combined (primary and secondary) end-point is described as events.

Statistical analysis was performed with the SPSS software version 20 (SPSS, Chicago, IL). Categorical variables are presented as number and percentages and continuous variables as mean ± standard deviation. Based on the distribution, continuous variables were compared with the Student t-test or the Mann-Whitney U-test. Categorical variables were compared with the x^2 test. Logistic regression analysis was used to evaluate the association between each cardiovascular risk factor and valve calcium as a categorical variable. In the multivariate adjusted analysis only the covariates with a p <0.10 in the univariate analysis were included. CAC Agatston score was introduced in the regression analysis as log(CAC Agatston score + 1). Cumulative event rates from the time of CCTA scanning were calculated using the Kaplan-Meier method. The log-rank test for time to event data with respect to the primary (all-cause mortality) and secondary end point (composite endpoint of MI and revascularization) were used for statistical comparison between the patient groups (VC group vs. the no-VC group). In addition, the Kaplan-Meier estimates of the primary and the secondary endpoints were calculated for patients included in the VC group divided according to the median value of calcium volume. Cox regression analysis was conducted for the evaluation of univariate and multivariate hazard ratios (HRs) for the occurrence of events. CAC Agatston score and valve calcium volume were both introduced in the Cox regression analysis as log(CAC Agatston score + 1) and log(valve calcium volume + 1). HRs were reported with 95% confidence interval (CI). Statistical significance was considered for p value < 0.05.

RESULTS

Of the 384 consecutive symptomatic patients referred for CCTA to detect and evaluate CAD, 369 patients (mean age 55 ± 11 years, 60% men) were finally included in the current analysis. Fifteen patients were excluded because of: mechanical aortic valve prosthesis (N=3, 0.8%) and adult congenital heart disease (N=12, 3%). VC was observed in 39 (10.7%) patients; 34 (9.3%) had aortic VC, 10 (2.8%) had mitral VC and 5 (1.4%) had calcium on both valves. Baseline characteristics are presented in table 1. Patients with VC were older, were more likely to have hypertension and had a higher CAC score. In addition, patients with hypertension and those with Agatston CAC score >100[6,14] had higher VC volumes compared to patients without hypertension and those with Agatston of ≤100, respectively (Table 2).

Table 3 demonstrates the univariate and multivariate analysis for the association of classical cardiovascular risk factors with the presence of VC. Increasing age and Agatston CAC score were the only factors independently associated with the presence of VC.

The median follow-up after the CCTA was 2.8 years (interquartile range 1.6 to 4.0) with a maximum of 5.5 years. During this follow-up period, the combined end-point was observed in 56 (15%) patients; 6 (1%) patients died, 11 (3%) suffered acute coronary syndrome, 32 (9%) underwent PCI, 4 (1%) underwent CABG and 3 (1%) suffered a myocardial infarction during the follow-up period after CCTA. Event-free survival was significantly worse for patients with VC in comparison to those without VC (event rate: 44% vs. 12% respectively, log-rank p<0.001) (Figure 3.A). Patients with higher VC volume had worse event-free survival (event rate: 12% for no VC patients vs. 33% for subgroup of patients with VC volume below the median value of 14 mm^3 [interquartile range 5 to 49] vs. 56% for subgroup of patients with VC volume above this median, log-rank p<0.001) (Figure 3.B). Focusing on the coronary-event-free survival, patients with VC had statistically significant more coronary events than those without VC (coronary-event rate: 39% vs. 11% respectively, log-rank p<0.001) (Figure 3.C). Focusing on all-cause mortality, the survival was significantly worse for those with versus those without VC (survival rate: 92% vs. 99% respectively, log-rank p=0.002) (Figure 3.D).

Table 4 presents the HRs of the univariate analysis for the association of cardiovascular risk factors and VC volume with events. Increasing age, significant CAD, Agatston CAC score and VC volume were significantly associated with events in the univariate cox-regression analysis. VC volume remained independently associated with the endpoint, after adjusting for age, hypertension, smoking and Agatston CAC score or significant CAD (Table 5).

Table 1. Baseline Demographics and Risk Factors According to the Presence of Valve Calcium.

Variable	All subjects	Valve Calcium		p* value
	N=369 (100%)	NO (N= 330)	YES (N=39)	
Age (years)	55 ± 11	54 ± 11	66 ± 9	<0.001
Men	221 (60%)	198 (60%)	23 (59%)	0.90
Body Mass Index (Kg/m^2)	26 ± 4.2	26 ± 4.1	26 ± 4.5	0.72
Diabetes Mellitus	103 (30%)	89 (29%)	14 (36%)	0.37
Hypertension	139 (40%)	117 (38%)	22 (56%)	0.02
Hypercholesterolemia	123 (35%)	105 (34%)	18 (46%)	0.13
Smoker	58 (17%)	50 (16%)	8 (21%)	0.50
Family History of CAD	144 (41%)	133 (43%)	11 (28%)	0.07
Obesity	70 (20%)	63 (20%)	7 (18%)	0.74
Agatston CAC Score	175 ± 478	114 ± 291	666 ± 1059	<0.001

Values are mean ± SD or n (%).

*p value for the comparison of Valve Calcium YES to NO.
Hypertension, defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication. Hypercholesterolemia, defined as serum total cholesterol ≥230 mg/dl and/or serum triglycerldes ≥200 mg/dl and/or treatment with lipid lowering drugs. Obesity, defined as BMI ≥30Kg/m^2. CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease

Table 2. Risk Factors according to Quantified Valve Calcium.

Variable		Valve Calcium Volume	p value
Diabetes Mellitus	+	44.5 ± 394.1	0.18
	0	8.79 ± 78.6	
Hypertension	+	45.6 ± 353.6	0.02
	0	1.8 ± 8.4	
Hypercholesterolemia	+	35.9 ± 360.6	0.18
	0	10.2 ± 82.2	
Smoker	+	21.8 ± 148.4	0.49
	0	18.9 ± 237.4	
Family History of CAD	+	3.6 ± 25.1	0.07
	0	30.4 ± 291.7	
Obesity	+	21.4 ± 137.6	0.65
	0	18.9 ± 242.0	
Agatston CAC Score	>100	74.2 ± 445.4	<0.001
	≤100	1.0 ± 8.1	

All values are mean ± SD in mm^3. +=Yes, 0=No, CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease

Table 3. Univariate and Multivariate Analysis of Risk Factors associated with Valve Calcium.

Variable	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age (years)	1.14	1.09 - 1.20	<0.001	1.11	1.06 - 1.17	<0.001
Diabetes Mellitus	1.37	0.68 - 2.76	0.37			
Hypercholesterolemia	1.66	0.85 - 3.25	0.14			
Hypertension	2.10	1.07 - 4.12	0.03	1.01	0.46 - 2.21	0.98
Family History of CAD	0.52	0.25 - 1.08	0.08	0.68	0.30 – 1.53	0.35
Smoking	1.33	0.58 - 3.06	0.50			
Obesity	0.87	0.37 - 2.05	0.74			
Agatston CAC Score	2.74	1.91 - 3.89	<0.001	1.88	1.28 - 2.76	0.001

Agatston CAC score has been introduced as log(Agatston CAC score + 1)
CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease, CI= Confidence Interval, OR= Odds Ratio

Table 4. Univariate Cox Regression Analyses of factors associated with the Combined End Point.

Variable	Univariate		
	HR	95% CI	p value
Age (years)	1.06	1.03 - 1.08	<0.001
Diabetes Mellitus	1.20	0.69 - 2.09	0.52
Hypercholesterolemia	1.20	0.70 - 2.05	0.51
Hypertension	1.60	0.94 - 2.71	0.08
Family History of CAD	1.45	0.85 - 2.45	0.17
Smoking	1.73	0.93 - 3.23	0.08
Obesity	1.33	0.72 - 2.48	0.36
CA stenosis ≥50%	2.63	1.55 - 4.45	<0.001
Agatston CAC score	2.58	1.98 - 3.38	<0.001
Valve Calcium Volume	2.26	1.71 - 2.99	<0.001

Agatston CAC score has been introduced as log(Agatston CAC score + 1)
Valve Calcium Volume has been introduced as log(Valve Calcium Volume + 1)
CA= Coronary Artery, CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease, CI= Confidence Interval, HR= Hazard Ratio

Table 5. Multivariate Cox-Regression Analyses for Valve Calcium Volume association to Combined End Point.

Variable	Baseline model	Baseline model + Agatston CAC score	Baseline model + CA stenosis ≥50%
	HR (95% CI) p-value	HR (95% CI) p-value	HR (95% CI) p-value
Valve Calcium Volume	1.88 (1.35 - 2.62) <0.001	1.47 (1.04 - 2.08) 0.03	1.81 (1.27 - 2.56) 0.001

Baseline Model: included Age, Hypertension, Smoking and Valve Calcium Volume
Agatston CAC score has been introduced as log(Agatston CAC score + 1)
Valve Calcium Volume has been introduced as log(Valve Calcium Volume + 1)
CA= Coronary Artery, CAC= Coronary Artery Calcium, CAD= Coronary Artery Disease, CI= Confidence Interval, HR= Hazard Ratio

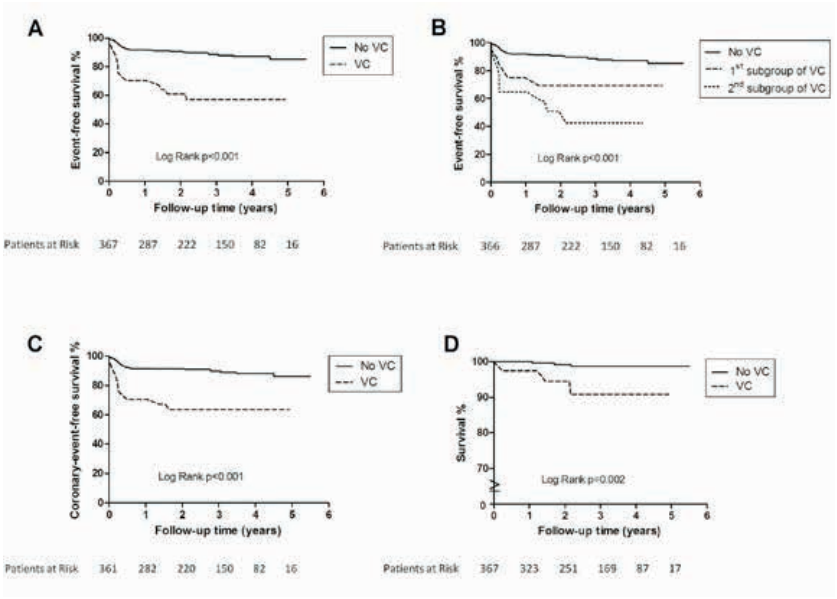

Figure 3. Kaplan-Meier curves for combined end-point (events), coronary-events and all-cause mortality in patients with and without VC. Patients with VC had worse outcome; A. event-free survival was significantly worse for the patients with VC (event rate: 11.8% in no-VC vs. 43.5% in VC, p<0.001). B. event-free survival was significantly worse for the patients with higher VC volume (event rate: 11.8% in no VC vs. 33.3% in 1st subgroup of VC with calcium volume below the median VC volume vs. 55.5% in 2nd subgroup of VC with calcium volume above the median VC volume, p<0.001). C. coronary-event-free survival was significantly worse for the patients with VC (coronary-event rate: 11% in no VC vs. 38.8% in VC, p<0.001). D. survival was significantly worse for the patients with VC (survival rate: 99.1% in no VC vs. 92.3% in VC, p=0.002). VC= valve calcium, vs.=versus

DISCUSSION

The current study sought to investigate the prognostic value of aortic and mitral VC quantified on contrast CCTA in symptomatic patients with suspected CAD. The main findings are: 1) Increased age and CAC score were independently associated with VC. 2) Patients with VC had more events in comparison to those without; and those with higher VC volume, had even more events. 3) VC volume was independently associated with the study endpoint. Furthermore, the current study showed that quantification of VC volume on contrast CCTA was associated with all-cause mortality and cardiovascular events in symptomatic patients with clinical suspicion of CAD.

Non-contrast multi-detector computed tomography (MDCT) is a well-established method for identifying aortic and/or mitral VC.[5-8,15-18] In addition to identifying VC, a few studies focused on quantification of aortic VC.[5,15,19-21] Recently, aortic VC has been identified and quantified on contrast enhanced MDCT in patients with severe aortic valve stenosis undergoing transcatheter aortic valve implantation (TAVI).[3,4] Contrast-enhanced CT allows also accurate discrimination between calcium of the circumflex coronary artery and the mitral annulus, permitting more accurate evaluation of the mitral VC volume.[22]

Echocardiography is an imaging modality that is widely used for identifying aortic and/or mitral VC.[22-27] However, echocardiography can provide semi-quantification of VC and cannot provide absolute quantification of the VC volume.[22] Moreover, with echocardiography the discrimination between calcium and dense fibrosis is difficult, leading to an overestimation of VC in comparison to the reference standard MDCT.[16,19] Cardiac magnetic resonance imaging is an excellent modality for differentiating between mitral annulus VC and caseous calcification, but has not been used for VC assessment in large cohorts of patients.[28]

Aortic and mitral VC are known to be an expression of generalized atherosclerosis as demonstrated by several studies proving strong clinical association of cardiovascular risk factors with the presence of VC on MDCT.[15-17,21,29,30] Advanced age is the risk factor that has been recognized by all studies conducted so far as an independent predictor of VC in the asymptomatic population.[16,17,21,29,30] The other risk factors associated with mitral and/or aortic VC in the asymptomatic population were hypertension, type 2 diabetes, smoking, dyslipidemia and obesity.[16,17,21,29,30] Moreover, quantitative assessment of aortic VC, demonstrated higher VC volumes in hypertensive, diabetic and dyslipidemic patients.[15] The Agatston CAC score, as an expression of the atherosclerotic plaque burden, has been associated with VC, but only recently it was demonstrated to be an independent predictor of mitral VC. [5,17,21,29]

The current study quantified both aortic and mitral VC on contrast CCTA and showed that VC volume was significantly higher in patients with hypertension and in those with Agatston CAC score >100 (table 2). Furthermore, advanced age and Agatston CAC score were independently associated with aortic and mitral VC (table 3) which is in concordance with previous studies,

although the present study focused on symptomatic patients.[16,17,21,29,30]

In addition to the association with clinical risk factors, the prognostic value of VC has been widely studied. Wong et al. studied aortic VC and thoracic aorta calcium on non-contrast cardiac electron beam computed tomography (EBCT) and MDCT in self-referred or physician-referred patients without known CAD and demonstrated the incremental value of VC over the Agatston CAC score for predicting the 10-year risk of CAD estimated by the Framingham risk score.[29] In a similar way, Gondrie et al. studied aortic and mitral VC on chest MDCT in the population of the PROgnostic Value of incidental Information in Diagnostic Imaging (PROVIDI) study and observed that patients with VC had a higher incidence of CAD, heart failure, peripheral artery disease, aortic aneurysm or cerebrovascular disease.[7] The prognostic value of VC on mortality has been studied in the primary prevention Multi-Ethnic Study of Atherosclerosis (MESA) population by Blaha et al.[6] In this study aortic VC on non-contrast cardiac EBCT was an independent predictor of all-cause mortality even after adjusting for the classical cardiovascular risk factors and Agatston CAC score.[6] Analyzing the same MESA study population, Owens et al. concluded that aortic VC detected on non-contrast cardiac MDCT was independently associated with cardiovascular and coronary events and that the risk of cardiac death increased in parallel to increasing VC severity, even after adjusting for the Agatston CAC score.[5]

In contrast to previous studies that assessed the association between aortic VC (assessed with non-contrast MDCT) and mortality, the current study focused on the association of aortic and mitral VC with all-cause mortality quantifying VC on contrast cardiac MDCT. Moreover, our study focused on the quantification of VC in a symptomatic population. Since symptomatic patients are increasingly undergoing contrast CCTA, additional prognostic information can be extracted by quantifying the VC.[1,2,5-7]

Some limitations have to be acknowledged. In the current study, CCTAs were not performed primarily for VC quantification, but for the assessment of CAD. As a result, VC assessment was performed retrospectively. Moreover, CCTA can overestimate coronary artery stenosis leading to referral for invasive coronary angiography and subsequent revascularization. In addition, C-reactive protein was not available for all patients included in the study and its association to VC was not studied. Finally, the cause of death was not systematically available.

Aortic and mitral VC identified on clinically indicated contrast CCTA in symptomatic patients with suspected CAD is associated with worse survival and more coronary events. The volume of VC can be used as an additional and independent predictor of cardiac events.

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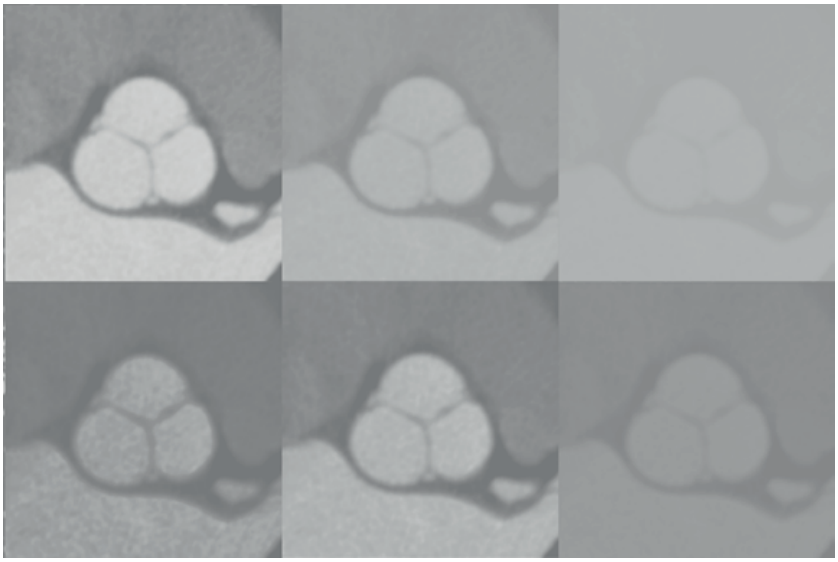
CHAPTER 9

Impact of Flow and Left Ventricular Strain on Outcome of Patients with Preserved Left Ventricular Ejection Fraction and Low Gradient Severe Aortic Stenosis Undergoing Aortic Valve Replacement



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ABSTRACT

The prognostic implications of flow, assessed by stroke volume index (SVi), and left ventricular (LV) global longitudinal strain on survival of patients with low gradient severe aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF) are debated. The aim of this study was to evaluate the impact of flow and LV global longitudinal strain on survival of these patients treated with aortic valve replacement (AVR). Low gradient severe AS patients with preserved LVEF treated with AVR (N=134, age 76±10 years, 50% men) were included in the current study. Aortic valve hemodynamics and LV function were assessed with 2-dimensional, Doppler and speckle-tracking echocardiography pre AVR. Patients were dichotomized based on low (SVi≤35ml/m^2) or normal (SVi>35ml/m^2) flow and impaired (>-15%) or more preserved (≤-15%) global longitudinal strain. The end-point was all-cause mortality. During a median follow-up of 1.8 years (interquartile range 0.5-3 years) after AVR, 26 (19.4%) patients died. Survival was better for patients with SVi>35ml/m^2 or global longitudinal strain ≤-15% as compared with patients with SVi≤35ml/m^2 or global longitudinal strain >-15% (log-rank p=0.01). Atrial fibrillation (hazard ratio 5.40, 95% confidence interval 1.81-16.07, p=0.002) and chronic kidney disease (hazard ratio 3.67, 95% confidence interval 1.49-9.06, p=0.005) were the clinical variables independently associated with all-cause mortality. The addition of global longitudinal strain (X^2 19.87, p=0.029 and C-statistics 0.74) or SVi (X^2 29.62, p<0.001 and C-statistics 0.80) to a baseline model including atrial fibrillation and chronic kidney disease (X^2 14.52, C-statistics 0.68) improved risk stratification of these patients. In conclusion, flow and LV global longitudinal strain are independently associated with survival after AVR in low gradient severe AS patients with preserved LVEF.

Keywords

Low gradient severe aortic stenosis;
Aortic valve replacement;
Survival;
Echocardiography

INTRODUCTION

The decision making of patients with low gradient (mean pressure gradient ≤40mmHg) severe aortic stenosis (AS) (aortic valve area index, AVAi ≤0.6cm^2/m^2) with preserved left ventricular (LV) ejection fraction (EF) (≥50%) has been source of debate.[1, 2] While some studies have reported better survival of these patients after aortic valve replacement (AVR),[3, 4] others have suggested that these patients have comparable prognosis to that of patients with moderate AS.[5] The underlying mechanisms influencing the outcome of these patients remain unclear. Despite having preserved LVEF, these patients have impaired LV mechanics as assessed with LV global longitudinal strain speckle tracking echocardiography and may have normal or low forward flow evaluated by stroke volume index (SVi).[3, 6] The influence of flow and LV global longitudinal strain on the prognosis of patients with preserved LVEF low gradient severe AS remains unexplored. The present evaluation assessed the relative merits of flow and LV global longitudinal strain to predict the outcome of patients with severe AS, low gradient and preserved LVEF who underwent AVR.

METHODS

Patients with symptomatic low gradient severe AS and preserved LVEF who underwent AVR were identified from an ongoing registry and were included in the current analysis (Figure 1).[7]

Patients were clinically evaluated and data were collected on a dedicated departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and analyzed retrospectively. Demographics, clinical symptoms (New York Heart Association (NYHA) functional class), cardiovascular risk factors, medications and presence of atrial fibrillation, chronic kidney disease (defined as moderately to severely decreased creatinine clearance <45ml/min)[8] and chronic pulmonary obstructive disease were collected. The Institutional Review Board approved this retrospective analysis of clinically acquired data and waived the need for written patient informed consent.

All patients underwent a complete transthoracic echocardiogram using commercially available ultrasound systems (Vivid-7 and E9, General Electric, Horten, Norway) equipped with 3.5MHz or M5S transducers. Two-dimensional, colour-, pulsed-wave and continuous-wave Doppler data were acquired in the parasternal and apical views and were stored digitally and analyzed offline on a dedicated workstation (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). LV dimensions and wall thickness were measured from the parasternal long-axis view according to current recommendations.[9] LV mass was estimated according to the formula by Devereux et al.[9] Relative wall thickness and the ratio of LV mass to LV end-diastolic volume were calculated as previously described.[10] LV end-diastolic and end-systolic volumes were measured in the apical 4- and 2-chamber views and indexed to body surface area and LVEF was derived using the Simpson's biplane

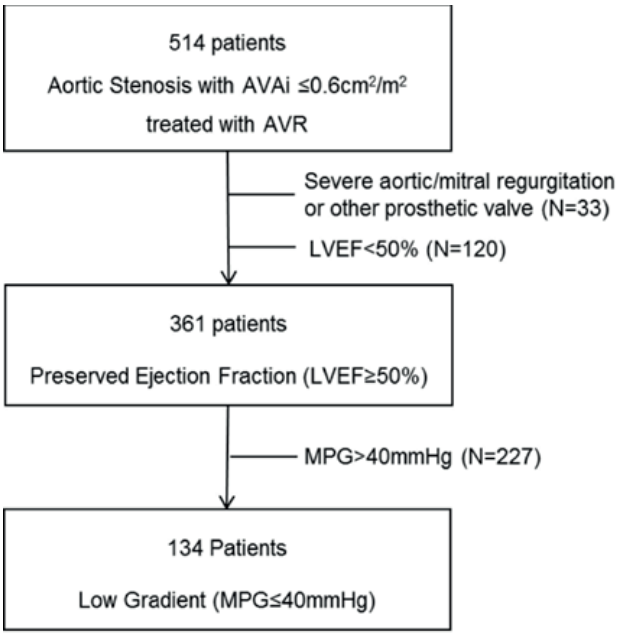

Figure 1. Patient population. AVAi, aortic valve area index;
AVR, aortic valve replacement;
LVEF, left ventricular ejection fraction;
MPG, mean pressure gradient.

method.[9] SVi was estimated by multiplying LV outflow tract area by LV outflow tract velocity time integral on pulse-wave Doppler recordings and then indexed to body surface area. Cardiac output was calculated as the product of stroke volume and heart rate. Stroke work was calculated by the formula (mean arterial pressure + mean peak gradient) x stroke volume x 0.0136 and indexed to LV mass.[11] Peak and mean pressure transaortic gradients were measured in the 3- or 5-chamber apical views according to the simplified Bernoulli equation. AVA was calculated with the continuity equation and then indexed to body surface area. In addition, energy loss index, valvulo-arterial impedance, systemic vascular resistance and systemic arterial compliance were calculated as previously described.[12]

For further evaluation of LV systolic function, offline 2-dimensional speckle tracking longitudinal strain analysis was performed at a workstation with commercially available software (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). From the apical 3-, 4- and 2- chamber views, global longitudinal strain was measured and averaged. Transmitral pulsed-wave Doppler was used for assessment of LV diastolic function. Additionally, left atrial volume was evaluated according to the biplane area-length method and then indexed to body surface area.[9] Co-existing valvular dysfunction was assessed based on the European Association of Echocardiography and the American Society of Echocardiography recommendations.[12]

Based on SVi patients were divided into two categories: low flow was defined as SVi≤35ml/m^2 and normal flow as SVi>35ml/m^2.[2,6,13,14] Patients were also categorized as having an LV global longitudinal strain ≤-15% or >-15%.[7,15-17]

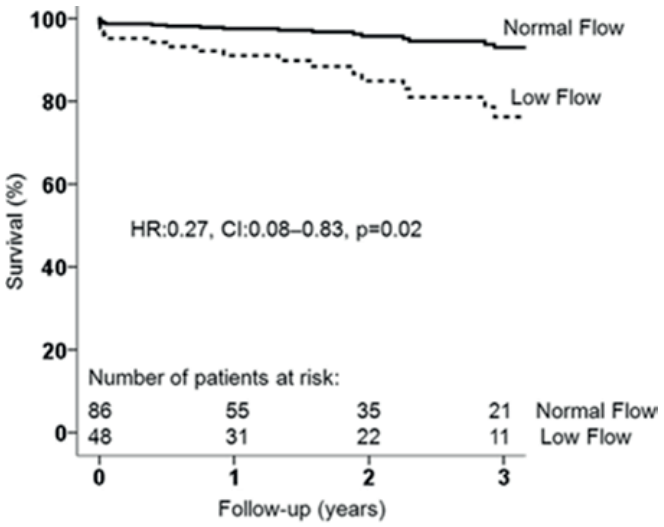

Figure 2. Impact of flow on survival of patients with low gradient severe aortic stenosis and preserved ejection fraction after aortic valve replacement. After adjusting for age, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, New York Heart Association functional class and left ventricular systolic function assessed by global longitudinal strain, normal flow (stroke volume index>35ml/m^2) patients had better outcome than patients with low flow (stroke volume index≤35ml/m^2). CI, confidence interval; HR, hazard ratio.

The end-point of the study was all-cause mortality. All patients were followed-up after AVR. Survival data were collected either from the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands), or by telephone interview or by the Social Security death index and were complete for all subjects included in the study.

Categorical variables are expressed as counts (frequency) and continuous variables as mean ± standard deviation. Continuous variables were compared between the 2 groups (survivors versus non-survivors) with the Student-t test or Mann-Whitney U test, as appropriate and categorical variables with the Chi-square test or Fisher exact test, as appropriate. The intra- and interobserver reproducibility of LV global longitudinal strain and SVi measurements were assessed by the intraclass correlation coefficient. The cumulative event rates were calculated based on Kaplan-Meier method and comparisons between groups were assessed by log-rank test. Cox proportional hazard ratio regression analyses were performed to investigate univariate and multivariate correlates of all-cause mortality. Hazard ratios and 95% confidence intervals were reported. Variables with univariate $p<0.10$ were entered in the multivariate analysis. The incremental value of flow and LV global longitudinal strain category over a baseline clinical model was estimated by the significant change in chi-square of the baseline model. The relative fit of each model was calculated with the −2 log likelihood. Moreover, C-statistics was used for model comparison. Statistical significance was considered for p value <0.05. Statistical analysis was performed with the SPSS software version 20 (SPSS, Chicago, IL).

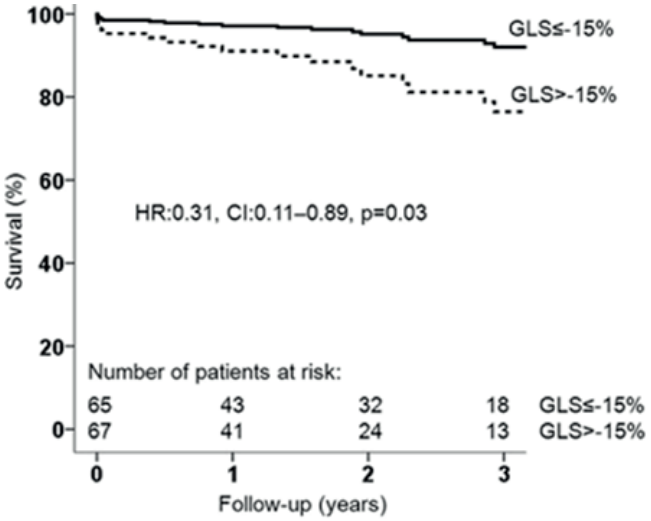

Figure 3. Impact of left ventricular global longitudinal strain (GLS) on survival of patients with low gradient severe aortic stenosis and preserved ejection fraction after aortic valve replacement. After adjusting for age, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, New York Heart Association functional class and flow expressed as stroke volume index, patients with better GLS (≤-15%) had better outcome than patients with GLS >-15%. CI, confidence interval; HR, hazard ratio.

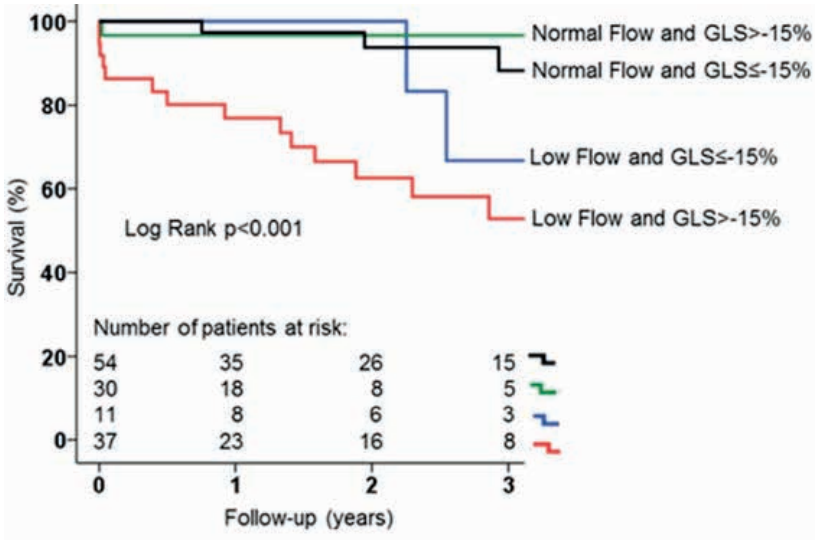

Figure 4. Impact of flow and left ventricular global longitudinal strain (GLS) on survival of patients with low gradient severe aortic stenosis and preserved ejection fraction after aortic valve replacement. Patients with low flow and more impaired GLS (>-15%) had significantly worse outcome compared with the other groups.

RESULTS

The baseline characteristics of 134 patients (75.5±9.9 years old, 50% male) are summarized in Table 1. Surgical AVR was performed in 71 (53%) patients and transcatheter AVR in the remaining 63 (47%). Echocardiographic data are summarized in Table 2. Low flow was identified in 48 (36%) patients and normal flow in 86 (64%) whereas an LV global longitudinal strain >-15% was observed in 67 (51%) patients and ≤-15% in 65 (49%). LV global longitudinal strain measurement was feasible in 132 (98%) patients. The intraclass correlation coefficients for intra and interobserver reprodcubility were 0.95 (95% confidence interval 0.69–0.99) and 0.87 (95% confidence interval 0.50-0.97) for LV global longitudinal strain, respectively, and 0.90 (95% confidence interval 0.60-0.97) and 0.88 (95% confidence interval 0.55-0.97) for SVi, respectively.

During a median follow-up of 1.8 years (interquartile range 0.5-3 years) after AVR, 26 (19.4%) patients died. There were no patients lost at follow-up. At baseline, patients who died exhibited more frequently associated co-morbidities (atrial fibrillation, chronic kidney disease, chronic pulmonary obstructive disease), previous cardiac surgery and worse NYHA functional class as compared with survivors (Table 1). Aortic valve hemodynamics were comparable between non-survivors and survivors. However, non-survivors had a higher LV global afterload, more concentrically remodelled LV, lower flow and more impaired LV global longitudinal strain than survivors (Table 2).

When dichotomizing the population based on low flow and normal flow, patients with low flow had higher mortality rates at 1, 2 and 3 years follow-up after AVR than patients with normal flow (16.7%, 25.0% and 33.3% vs. 2.3%, 3.5% and 4.6%, respectively, log-rank p<0.001). This difference remained significant after adjusting for age, atrial fibrillation, chronic pulmonary obstructive disease, chronic kidney disease, NYHA functional class and LV global longitudinal strain; patients with normal flow had significantly better outcome than low flow patients (Figure 2). When dividing the population according to the pre-specified LV global longitudinal strain cut-off value, patients with more impaired global longitudinal strain (>-15%) had significantly increased mortality at 1, 2 and 3 years after AVR in comparison with patients with more preserved global longitudinal strain (≤-15%) (mortality rate 13.4%, 19.4% and 22.4% vs. 1.5%, 3.1% and 7.7%, respectively, log-rank p=0.01). Survival remained significantly higher in the cohort of patients with global longitudinal strain ≤-15% after adjusting for age, atrial fibrillation, chronic pulmonary obstructive disease, chronic kidney disease, NYHA functional class and SVi (Figure 3). Figure 4 shows the cumulative survival for patients grouped according to global longitudinal strain and flow. Patients with a global longitudinal strain >-15% and SVi≤35ml/m^2 had the worse prognosis. There were 6 patients who died within 30 days post AVR (50% had TAVR). All of them (100%) had impaired global longitudinal strain (>-15%) and 5 (83%) had low-flow. Perioperative mortality was significantly higher in the group with more impaired global longitudinal strain (>-15%) compared with the group with ≤-15% (log rank p=0.015) and in the low-flow

compared to the normal-flow group (log rank p=0.014).

The univariate Cox-regression analysis demonstrated that the presence of atrial fibrillation, chronic pulmonary obstructive disease, chronic kidney disease, previous myocardial infarction and previous cardiac surgery were associated with increased all-cause mortality risk in this population (Table 3). From the echocardiographic variables, lower valvulo-arterial impedance and LV mass/LV end-diastolic volume ratio were associated with improved survival after AVR. Atrial fibrillation and chronic kidney disease were

Table 1. Baseline clinical characteristics

Variable	Overall (N=134)	Survivors (N=108)	Non-Survivors (N=26)	p-value
Age (years)	76 ± 10	75 ± 11	76 ± 5	0.24
Male	67 (50%)	53 (49%)	14 (54%)	0.66
Body mass index (Kg/m^2)	26 ± 4	26 ± 4	26 ± 4	0.92
Body surface area (m^2)	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.64
Atrial fibrillation	10 (8%)	5 (5%)	5 (21%)	0.008
Chronic kidney disease	28 (21%)	16 (15%)	12 (46%)	0.001
Hypertension	98 (74%)	76 (71%)	22 (85%)	0.16
Diabetes mellitus	34 (25%)	24 (22%)	10 (39%)	0.09
Hyperlipidemia	69 (52%)	59 (56%)	10 (39%)	0.12
Smoker	44 (34%)	35 (33%)	9 (36%)	0.77
Family history of CAD	34 (27%)	28 (27%)	6 (24%)	0.75
Coronary artery disease	83 (69%)	67 (69%)	16 (67%)	0.76
Previous cardiac surgery	33 (25%)	22 (20%)	11 (42%)	0.02
Myocardial infarction	19 (14%)	13 (12%)	6 (23%)	0.15
Stroke	16 (12%)	11 (10%)	5 (20%)	0.17
Chronic obstructive pulmonary disease	35 (26%)	24 (22%)	11 (42%)	0.04
Logistic EuroSCORE (%)	14 ± 12	13 ± 11	18 ± 13	0.08
ACEi / ARB	66 (50%)	49 (46%)	17 (65%)	0.07
Beta-blocker	77 (58%)	64 (60%)	13 (50%)	0.36
Calcium channel blocker	39 (30%)	28 (26%)	11 (42%)	0.12
Statin	79 (59%)	64 (60%)	15 (58%)	0.84
Diuretics	62 (47%)	47 (44%)	15 (58%)	0.21
NYHA class I	40 (30%)	36 (33%)	4 (15%)	0.04
II	46 (34%)	37 (34%)	9 (35%)	
III	38 (28%)	30 (28%)	8 (31%)	
IV	10 (8%)	5 (5%)	5 (19%)	

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; NYHA, New York Heart Association.

Hyperlipidemia, defined as serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl and/or treatment with lipid lowering drugs. Family history of CAD, defined as first degree relatives of <55 years in men and <65 years in women who had a cardiac event. Coronary artery disease, defined as previous coronary artery bypass grafting or percutaneous coronary intervention or more than 50% stenosis at the coronary angiography.

independently associated to mortality after AVR and were selected to build a baseline clinical model to test the independent association between flow and global longitudinal strain with survival (Table 3). Global longitudinal strain >-15% and each 1% impairment in global longitudinal strain were independently associated with all-cause mortality (Table 4). In addition, SVi ≤35ml/m^2 and each 5ml/m^2 decrease in SVi were independently associated with all-cause mortality (Table 4).

Table 2. Baseline echocardiographic characteristics

	Overall (N=134)	Survivors (N=108)	Non-Survivors (N=26)	p-value
Aortic valve area (cm^2)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.13
Aortic valve area index (cm^2/m^2)	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.12
Peak velocity (m/s)	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	0.74
Mean gradient (mmHg)	32 ± 6	32 ± 6	32 ± 7	0.93
Energy loss index (cm^2/m^2)	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.09
Valvulo-arterial impedance (mmHg/ml/m^2)	4.9 ± 1.5	4.7 ± 1.4	5.6 ± 1.5	0.004
Systemic vascular resistance (mmHg.min/l)	1741 ± 504	1695 ± 500	1932 ± 485	0.03
Systemic arterial compliance (ml/mmHg/m^2)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.1	0.16
Septal wall thickness in diastole (cm)	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.3	0.11
Posterior wall thickness in diastole (cm)	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	0.08
LVEDDi (cm/m^2)	2.5 ± 0.3	2.5 ± 0.3	2.5 ± 0.3	0.69
LVESDi (cm/m^2)	1.5 ± 0.4	1.5 ± 0.3	1.5 ± 0.4	0.62
Left ventricular mass index (g/m^2)	121 ± 32	118 ± 32	131 ± 31	0.06
Relative wall thickness (%)	56 ± 13	55 ± 13	58 ± 17	0.31
LVEDVi (ml/m^2)	49 ± 17	49 ± 17	47 ± 19	0.49
LVESVi (ml/m^2)	20 ± 8	20 ± 8	19 ± 8	0.85
Left ventricular mass / LVEDV ratio (g/ml)	2.7 ± 1.2	2.6 ± 1.1	3.2 ± 1.3	0.03
Ejection fraction (%)	61 ± 6	62 ± 6	59 ± 5	0.08
Stroke volume index (ml/m^2)	38 ± 10	39 ± 9	33 ± 10	0.001
Cardiac Output (l/min)	4.8 ± 1.1	4.9 ± 1.1	4.4 ± 0.9	0.03
Cardiac Index (l/min/m^2)	2.6 ± 0.6	2.6 ± 0.6	2.3 ± 0.5	0.02
Stroke Work (g.m)	124 ± 35	127 ± 34	110 ± 16	0.02
Stroke Work /100g (g.m)	60 ± 26	62 ± 25	48 ± 25	0.01
Global longitudinal strain (%)	-15 ± 3	-15 ± 3	-13 ± 3	0.005
E wave velocity (cm/s)	77 ± 28	76 ± 29	81 ± 25	0.39
Deceleration time (msec)	257 ± 100	263 ± 98	232 ± 106	0.15
Left atrial volume index (ml/m^2)	37 ± 15	37 ± 16	37 ± 15	0.95
Aortic regurgitation no/mild/moderate, n	56/66/12	42/54/12	14/12/0	0.13
Mitral regurgitation no/mild/moderate, n	67/53/14	55/41/12	12/12/2	0.71

LVEDDi, left ventricular end-diastolic diameter index;
LVEDVi, left ventricular end-diastolic volume index;
LVESDi, left ventricular end-systolic diameter index;
LVESVi, left ventricular end-systolic volume index.

Table 3 Univariate and multivariate Cox regression analysis to identify determinants of all-cause mortality in patients with low gradient, preserved ejection fraction severe aortic stenosis after aortic valve replacement

		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Clinical Variables							
Age (years)		1.04	0.99-1.09	0.08	1.01	0.93-1.09	0.78
Male gender		1.49	0.68-3.29	0.32			
Body mass index (Kg/m^2)		1.01	0.91-1.13	0.81			
Transcatheter aortic valve replacement		1.69	0.74-3.89	0.21			
Logistic EuroScore (%)		1.03	1.00-1.06	0.03	0.98	0.92-1.06	0.69
Coronary artery disease		0.96	0.40-2.27	0.92			
Chronic kidney disease		2.60	1.18-5.74	0.02	3.20	1.10-9.31	0.03
Atrial fibrillation		3.45	1.26-9.40	0.02	4.63	1.22-17.62	0.02
Hypertension		2.28	0.78-6.69	0.13			
Diabetes		1.64	0.72-3.71	0.24			
Hyperlipidemia		0.63	0.28-1.43	0.23			
Previous cardiac surgery		2.37	1.06-5.29	0.04	0.97	0.20-4.71	0.97
Myocardial infarction		2.96	1.16-7.55	0.02	2.57	0.55-12.04	0.23
Stroke		2.08	0.76-5.65	0.15			
Chronic obstructive pulmonary disease		2.57	1.15-5.77	0.02	1.45	0.49-4.25	0.50
New York Heart Association	class I	Ref		0.08			0.62
	class II	3.20	0.96-10.47	0.06	1.75	0.45-6.80	0.42
	class III	2.72	0.77-9.27	0.10	2.07	0.51-8.33	0.31
	class IV	5.63	1.49-21.15	0.01	2.82	0.55-14.26	0.21
Echocardiographic Variables							
Aortic valve area index (cm^2/m^2)		0.06	0.001-5.18	0.21			
Mean pressure gradient (mmHg)		0.98	0.93-1.05	0.61			
Valvulo-arterial impedance (mmHg/ml/m^2)		1.26	1.02-1.57	0.03	1.08	0.80-1.49	0.66
Left ventricular mass index (g/m^2)		1.01	0.99-1.02	0.23			
Relative wall thickness (%)		1.02	0.99-1.05	0.12			
Left ventricular mass / LVEDV ratio (g/ml)		1.63	1.27-2.10	0.001	1.44	0.95-2.17	0.08
Left ventricular ejection fraction (%)		0.94	0.87-1.00	0.07	0.97	0.89-1.06	0.56
Left atrium volume index (ml/m^2)		0.99	0.97-1.02	0.71			

CI, confidence interval; HR, hazard ratio; LVEDV, left ventricular end-diastolic volume.

Table 4. Multivariate Cox regression analysis and c-statistics to test the value of flow (stroke volume index category > and ≤35ml/m^2 or increase per 5ml/m^2) and left ventricular systolic function (global longitudinal strain category > and ≤-15% or increase per +1%) on baseline model (please look at table 3) predicting mortality in low gradient, preserved ejection fraction severe aortic stenosis after aortic valve replacement

	Multivariate Analysis			Model Comparison			
	HR	95% CI	p-value*	Model -2Log Likelihood	Model x^2	p-value†	C-statistics
Baseline model				173.34	14.52	-	0.68
Atrial fibrillation	5.40	1.81-16.07	0.002				
Chronic kidney disease	3.67	1.49-9.06	0.005				
Baseline model + GLS category				166.80	19.87	0.029	0.74
Atrial fibrillation	4.03	1.33-12.18	0.014				
Chronic kidney disease	3.95	1.61-9.69	0.003				
Global longitudinal strain ≤-15%	0.37	0.14-0.94	0.036				
Baseline model + SVi category				158.06	29.62	<0.001	0.80
Atrial fibrillation	3.18	1.00-10.07	0.050				
Chronic kidney disease	3.59	1.41-9.11	0.007				
Stroke volume index >35ml/m^2	0.16	0.06-0.44	<0.001				
Baseline model + GLS 1% increase				164.09	22.29	0.006	0.78
Atrial fibrillation	3.49	1.11-10.92	0.03				
Chronic kidney disease	3.74	1.50-9.31	0.005				
Global longitudinal strain	1.21	1.05-1.39	0.007				
Baseline model + SVi 5ml/m^2 increase				167.86	19.77	0.019	0.77
Atrial fibrillation	3.16	0.93-10.45	0.07				
Chronic kidney disease	3.57	1.44-8.99	0.006				
Stroke volume index	0.77	0.61-0.97	0.03				

*p-value by multivariate Cox regression analysis

†p-value by likelihood ratio test vs. baseline model

CI, confidence interval; GLS, Global longitudinal strain; HR, hazard ratio; SVi, Stroke volume index.

The present evaluation showed that patients with preserved LVEF, low gradient severe AS and normal flow or LV global longitudinal strain ≤-15% have better survival after AVR compared to their counterparts with low flow or global longitudinal strain >-15%. The addition of flow and LV global longitudinal strain to a clinical model improved the risk stratification of patients with preserved LVEF, low gradient severe AS treated with AVR.

Severe aortic stenosis based on AVAi calculation but with low gradient is observed in almost 35% of patients with preserved LVEF.[4-6, 10, 18, 19] Decision making in this subgroup of patients remains controversial. While several series have shown that surgical AVR in patients with severe AS with low gradient and preserved LVEF portends better prognosis compared with medical treatment,[11, 14, 20-22] other studies have shown that the prognosis of these patients medically treated is similar to that of patients with moderate aortic stenosis.[5, 10] The study by Hachicha et al. including 512 patients with severe AS and preserved LVEF, 62% of them with low gradient, showed that patients undergoing surgical AVR had better survival than patients treated medically.[3] Similarly, Ozkan et al. confirmed that patients with symptomatic severe AS, low gradient and preserved LVEF had better prognosis compared to medically treated patients (26% versus 40% mortality after 28 months of mean follow-up).[11] In contrast, Jander et al. demonstrated that patients with asymptomatic severe AS, low gradient and preserved LVEF had comparable outcome to patients with moderate aortic stenosis (major cardiovascular events 14.8±1.0% versus 14.1±1.5%, respectively; p=0.59).[5] Accordingly, the authors considered that patients with low gradient, preserved LVEF severe AS do not represent a true severe AS group and the progression of the disease is similar to moderate aortic stenosis.[5, 10]

These apparently conflicting results may be explained by differences within the group of patients with low gradient, preserved LVEF severe AS. Based on LV stroke volume, patients with preserved LVEF, low gradient severe AS can be further divided into low flow (≤35 ml/m^2) or normal flow (>35ml/m^2) and these two subgroups of patients have distinct clinical and echocardiographic characteristics: the former are more frequently female and older, have higher systemic vascular resistance, lower systemic compliance and higher LV global afterload than the normal flow patients.[4, 6, 21] In addition, low flow patients show smaller LV outflow tract and LV cavity dimensions, increased concentric remodelling and lower LVEF (although within the normal range) than normal flow patients.[4, 10] The increased concentric LV remodelling may have a significant impact on the LV mechanics that cannot be unmasked by LVEF alone. Two-dimensional speckle tracking longitudinal strain analysis can discriminate between these two groups of patients. Lancellotti et al showed that patients with preserved LVEF, low flow-low gradient severe AS had more impaired global longitudinal strain as compared with patients with normal flow-low gradient severe AS (-13.6±4.3% vs. -16.7±2.6%, p<0.001).[23] Therefore, low flow-low gradient severe AS may represent a more progressed disease status and the assessment of LV remodelling and global longitudinal

strain may help distinguishing these two subgroups.

While the prognostic implications of flow (SVi) in patients with low gradient severe AS and preserved LVEF remains debated, the impact of LV global longitudinal strain on the outcome of these patients has not been evaluated. In the sub-study of the Simvastatin and Ezetimibe in Aortic Stenosis trial (including 435 patients with asymptomatic low gradient severe AS) Jander et al.[5] proposed that patients with low flow and patients with normal flow had comparable outcomes in terms of aortic valve and cardiovascular events and cardiovascular death. However, the outcome after AVR was not evaluated. In contrast, the studies by Hachicha et al.[4] and Ozkan et al.[11] suggested that survival after AVR is comparable between low flow and normal flow severe AS patients. Mehrotra et al.[10] provided further evidence to the association between flow and survival in patients with low gradient severe AS and suggested that patients with low flow severe AS had worse survival than normal flow severe AS and patients with moderate aortic stenosis. However, flow was not independently associated with survival of patients with low gradient severe AS. Similarly, Mohty et al.[21] reported an independent association between flow and survival in patients with severe AS and after correcting for AVR (as time-dependent covariate), low flow-low gradient severe AS was associated with increased all-cause mortality risk (hazard ratio 1.84, p=0.014). The present study is in line with the results by Mohty et al.[21] demonstrating that flow status is independently associated with long-term outcome of patients with low gradient severe AS and preserved LVEF treated with AVR. However, the present study provides also incremental value by demonstrating the independent association between LV global longitudinal strain and outcome in this group of patients. After correcting for SVi, LV global longitudinal strain was associated with all-cause mortality. LV global longitudinal strain may be impaired in patients with low gradient severe AS and preserved LVEF possibly due to subendocardial ischemia, myocardial fibrosis, concentric remodelling or increased afterload.[6, 16, 24] LV global longitudinal strain can detect the subtle intrinsic myocardial systolic dysfunction and its impairment precedes LVEF reduction.[16, 25] However, randomized studies would be preferable to confirm the benefits of AVR in this subgroup of patients and impact on current practice guidelines.[1]

Several limitations should be acknowledged. Outcome and echocardiographic data were retrospectively analysed. In addition, patients underwent surgical or transcatheter AVR, introducing a important prognostic bias. We did not use a propensity score to account for this difference. Finally, we did not include a comparator group who were medically treated. However, the comparison of prognostic implications of medical treatment vs. AVR in this group of patients was beyond the scope of the present evaluation.

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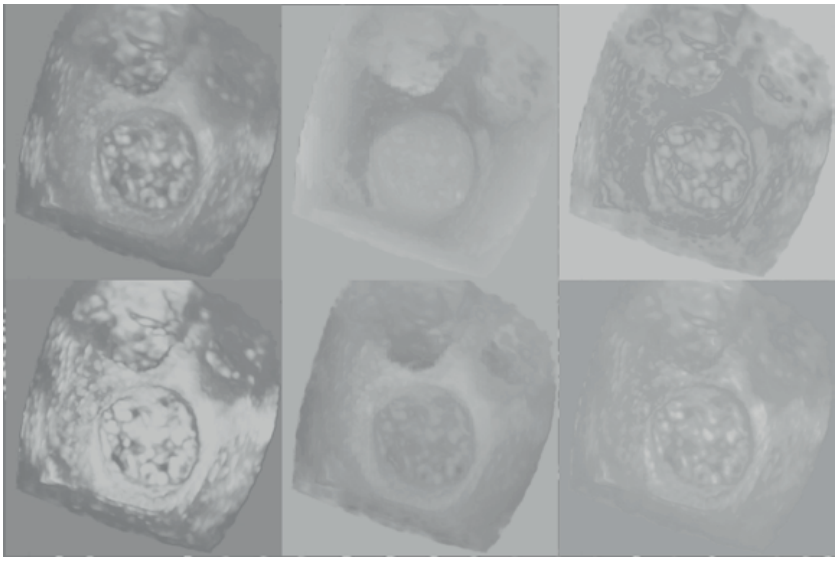
CHAPTER 10

Restrictive Mitral Valve Annuloplasty: Prognostic Implications of Left Ventricular Forward Flow



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ABSTRACT

Background Surgical mitral valve repair for severe secondary mitral regurgitation (MR) remains controversial. The association of MR reduction and changes in left ventricular (LV) hemodynamics with postoperative survival has not been investigated. The aim of the present study was to investigate the independent associates of all-cause mortality in heart failure patients with severe secondary MR who underwent surgical mitral valve repair.

Methods In total, 130 patients (62±12 years old, 55% male) with chronic severe secondary MR and impaired LV ejection fraction (<50%, mean 31±10%) who underwent surgical mitral valve repair were included. Echocardiography was performed at baseline and post-repair at discharge. LV forward flow was assessed by LV forward stroke volume and LV forward ejection fraction. All-cause mortality was the primary endpoint and the secondary endpoint was the combination of major adverse cardiac events and all-cause mortality.

Results At hospital discharge, 77% of patients showed no residual MR and 23% mild MR. LV end-diastolic and end-systolic volumes reduced significantly while LV ejection fraction remained unchanged. In contrast, LV forward stoke volume (53±24 vs. 64±22ml, p<0.001) and LV forward ejection fraction (0.32±0.16 vs. 0.48±0.24, p<0.001) significantly increased at discharge. During a median follow-up of 3.44 years, 33 (29%) patients died and 40 had major adverse cardiac events. On multivariable analysis, LV forward stroke volume post-repair was independently associated with all-cause mortality (hazard ratio 0.98, 95% confidence interval 0.95-1.00; p=0.047) and with the combined endpoint (hazard ratio 0.98, 95% confidence interval 0.96-1.00; p=0.045) after correcting for other baseline, procedural and post-repair characteristics.

Conclusions In patients with severe secondary MR treated with surgical repair, LV forward flow was independently associated with better survival and lower risk of the combined endpoint.

Keywords Secondary mitral regurgitation,
surgical mitral valve repair,
left ventricular forward flow,
prognosis

INTRODUCTION

It has been demonstrated that severe secondary mitral regurgitation (MR) has deleterious influence on survival of patients with ischemic and non-ischemic left ventricular (LV) systolic dysfunction.[1-3] Surgical correction of MR has been associated with reduction in LV volumes and improvement in LV systolic function.[4] However, it has not been demonstrated that surgical mitral valve repair for secondary MR is associated with better prognosis compared with optimal medical treatment (including cardiac resynchronization therapy).[4-6] Current guidelines on management of valvular heart disease consider surgical mitral valve repair in ischemic and non-ischemic secondary MR with a recommendation level IIa and IIb, respectively, due to the lack of robust data on survival benefit.[7, 8]

Surgical mitral valve repair for secondary MR uses frequently undersized annuloplasty rings to improve the coaptation of the mitral leaflets, resulting in reduction of the volume overload. Reduction in LV preload may lead to falsely reduced LV systolic function, based on LV ejection fraction, which merely represents a change in total LV volumes, without taking into account if the direction of the blood flow is regurgitant or forward. After mitral valve repair, the LV volume pumped into the low-pressure left atrium is significantly reduced and as a result the LV ejection fraction may be reduced (less total volume shifted). However, other parameters that more precisely reflect LV forward flow such as LV forward stroke volume, evaluating the blood volume pumped only into the aorta, and LV forward ejection fraction, evaluating the percentage of LV end-diastolic volume pumped into the aorta, may better reflect the remaining LV systolic function after surgical mitral valve repair. The prognostic value of LV forward flow, assessed by LV forward stroke volume and LV forward ejection fraction in patients with secondary MR treated with surgical restrictive mitral annuloplasty has not been evaluated so far. Accordingly, the current analysis evaluated the prognostic implications of LV forward flow on survival after surgical repair in patients with severe secondary MR.

PATIENTS AND METHODS

Patients with severe secondary MR, and LV ejection fraction <50%, treated successfully with surgical repair were included in the current analysis. Successful mitral valve repair was defined as the presence of residual MR less than moderate at discharge. The demographic and clinical characteristics of the population were prospectively collected in the departmental clinical database (EPD-vision 8.3.3.6; Leiden University Medical Center, Leiden, The Netherlands). The institutional ethical committee approved this retrospective analysis of prospectively collected clinical data and waived the need for patient written informed consent.

All patients included in the current analysis were treated with surgical mitral valve repair, consisting of restrictive mitral ring annuloplasty. The mitral ring (Carpentier Edwards Physioring, Edwards Lifesciences, Irvine, CA) implanted was selected downsizing the native annulus by 2 sizes, i.e. if the native ring was estimated 30 the implanted one was 26, as previously described.[9] Whenever necessary, coronary artery bypass grafting, tricuspid valve annuloplasty, cardiac support device implantation (CorCap, Acorn Cardiovascular, St. Paul, Minnesota), LV reconstruction, atrial fibrillation ablation and LV lead implantation for cardiac resynchronization therapy were performed.

Comprehensive transthoracic echocardiography was performed in allpatients at baseline and after surgical mitral valve repair before hospital discharge. Patients were hemodynamically stable during echocardiography which was performed with a commercially available ultrasound system (Vivid 7 and Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway) equipped with 3.5-MHz or M5S transducers. Grey scale images and Doppler data (colour, continuous and pulsed wave) were digitally stored for off-line analysis (EchoPAC version 112.0.1; GE Vingmed Ultrasound, Norway).

Secondary MR severity was assessed with a multiparametric integrated approach.[10] Vena contracta width was measured on a zoomed parasternal long-axis view. Effective regurgitant orifice area and regurgitant volume were evaluated with the proximal isovelocity surface area method. Vena contracta width >4mm, effective regurgitant orifice area ≥0.2cm^2 or regurgitant volume ≥30ml defined severe secondary MR.[10] Residual MR severity at discharge was assessed by colour Doppler as previously described.[11, 12]

LV hemodynamics at baseline and after surgical mitral valve repair were assessed with echocardiography according to current recommendations.[13] Simpson's biplane method was used to measure LV end-diastolic and end-systolic volumes, from which LV ejection fraction was calculated. LV forward stroke volume was estimated on pulsed-wave Doppler spectral recordings obtained at the LV outflow tract, multiplying the velocity time integral of the LV outflow tract by the cross-sectional area of the LV outflow tract. The cardiac output was derived from the product of stroke volume and the heart rate. LV forward ejection fraction was estimated as the ratio of forward stroke volume by the LV end-diastolic volume.[14]

Left atrial volume was assessed by tracing the endocardial borders at end-systole in both four- and two-chamber apical views using the disk summation algorithm.[13] Moreover, right ventricular systolic pressure was evaluated from the summation of the right atrial pressure to the peak pressure gradient between the ventricle and the atrium.[15] Additionally, LV mass and relative wall thickness were estimated according to current recommendations on LV chamber quantification and the ratio of LV mass to LV end-diastolic volume was calculated.[13]

The patients were followed-up after surgical mitral valve repair for the occurrence of major adverse cardiac events (heart failure hospitalization, redo surgery due to repair failure, endocarditis, left ventricular assist device implantation or heart transplant) and all-cause mortality. The primary endpoint of the study was all-cause mortality and the secondary endpoint was the combination of major adverse cardiac events and all-cause mortality. The data were collected from the departmental clinical database (EPD-vision 8.3.3.6; Leiden University Medical Center, Leiden, The Netherlands) or from the Social Security Death Index.

Continuous variables are presented as mean±standard deviation and categorical variables as frequencies and percentages. Continuous variables were compared with paired sample Student s t-test or Mann-Whitney U-test as appropriate.

The cumulative survival rates at 1, 2, and 3 years follow-up were estimated according to the Kaplan-Meier method. Comparison of all-cause mortality and the combined endpoint between two groups of patients divided according to the median value of LV forward stroke volume at discharge was performed by the log-rank test. Univariable Cox proportional-hazards ratio regression analysis was performed to investigate baseline, procedural and post-surgical mitral valve repair parameters associated with all-cause mortality and the combined endpoint. A stepwise multivariable approach was followed to avoid model overfit, by including 4 variables in each multivariable model. Those variables were the most clinically relevant and most significant within the subgroup. In the first model only baseline parameters were introduced. The variables independently associated to the outcome were introduced in the second model which included the procedural parameters. The third model included the variables independently associated with the endpoint and the post-surgical repair parameters. Hazard ratios and 95% confidence intervals were reported. P-values <0.05 were considered statistically significant. All statistical analyses were performed with the SPSS version 20 (SPSS, Inc, Chicago, IL).

The characteristics of the overall population (62±12 years old, 55% male) with chronic secondary MR are summarized in Table 1. Baseline mitral regurgitant jet vena contracta was 6.36±1.73 mm, effective orifice area 0.26±0.13 cm^2 and regurgitant volume 38.10±17.40 ml/beat. All patients underwent surgical mitral valve repair and 23 (18%) had concomitant coronary artery bypasss grafting, 91 (70%) tricuspid valve repair, 5 (4%) LV reconstruction, 55 (42%) CorCap cardiac support device implantation, 48 (37%) LV lead implantation for cardiac resynchronization therapy and 20 (15%) atrial fibrillation ablation.

The hemodynamic changes after surgical mitral valve repair are shown in Table 2. At discharge, 30 (23%) patients had mild MR while the remaining 100 (77%) had no MR. LV end-diastolic and end-systolic volumes were significantly reduced and LV mass was unchanged. Although LV ejection fraction remained stable (31±10 vs. 30±12%, p=0.18), LV forward stoke volume (53±24 vs. 64±22 ml, p<0.001) and LV forward ejection fraction (0.32±0.16 vs. 0.48±0.24, p<0.001) were significantly improved at discharge. Moreover, left atrial volume and right ventricular systolic pressure were significantly reduced at discharge (Table 2).

The study cohort was followed-up for a median period of 3.44 years (interquartile range 1.34 – 8.64 years) after the surgical procedure. The total follow-up time for the entire study population was 662.62 patient-years. The post-surgery survival rates at 1, 2 and 3 years of follow-up were 86%, 79% and 71%, respectively (Figure 1A). The combined endpoint free-survival rates for the combined endpoint were 81%, 72% and 60% at 1, 2 and 3 years, respectively (Figure 1B).

The median value of LV forward stroke volume at discharge was 58.6 ml. Patients with forward stroke volume ≥58.6 ml had better survival and

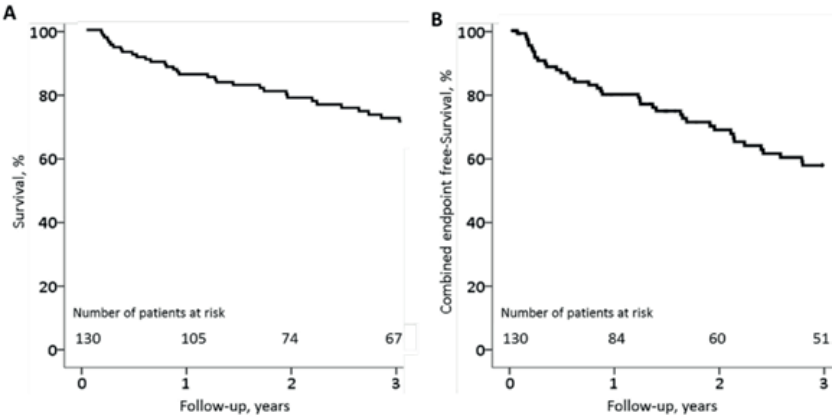

Figure 1. Kaplan-Meier analysis of (A) 3-year survival and (B) combined endpoint free-survival after successful surgical mitral valve repair of patients with chronic severe secondary mitral regurgitation. (A) The survival rate at 1-year was 86% (18 events), at 2-years 79% (26 events) and at 3-years 71% (33 events). (B) The combined endpoint free-survival rate at 1-year was 81% (21 events), at 2-years 72% (31 events) and at 3-years 60% (40 events).

Table 1. Baseline demographic characteristics of patients with chronic severe secondary mitral regurgitation

Variable	n=130
Age, years	62±12
Male, n (%)	72 (55)
Log EuroScore I, %	12±11
Non-ischemic cardiomyopathy, n (%)	102 (78)
Hypertension, n (%)	63 (48)
Diabetes mellitus, n (%)	26 (20)
Chronic kidney disease, n (%)	46 (36)
Atrial fibrillation, n (%)	54 (42)
B-blocker use, n (%)	76 (59)
ACEi/ARB use, n (%)	98 (75)
Previous CRT/D, n (%)	13 (10)
NYHA functional class III-IV, n (%)	78 (61)

ACEi, angiotensin converting enzyme inhibitor;
ARBs, angiotensin receptor blockers;
CRT/D, cardiac resynchronization therapy/defibrillator;
NYHA, New-York heart association

Table 2. Hemodynamic changes post successful surgical mitral valve repair in patients with secondary mitral regurgitation.

	Pre-repair	Post-repair	p-value
LV end-diastolic volume, ml	188±74	155±65	<0.001
LV end-systolic volume, ml	134±65	114±60	<0.001
LV ejection fraction, %	31±10	30±12	0.18
LV forward stroke volume, ml	53±24	64±22	<0.001
Cardiac output, ml/min	3.85±1.60	5.43±1.93	<0.001
LV forward ejection fraction	0.32±0.16	0.48±0.24	<0.001
LV mass, gr	261±83	257±92	0.57
LV mass/LV volume	1.51±0.50	1.82±0.76	<0.001
Relative wall thickness, %	28±9	34±9	<0.001
Left atrial volume, ml	108±55	89±38	<0.001
RV systolic pressure, mmHg	37±12	29±11	<0.001

LV, left ventricular;
RV, right ventricular

Table 3. Univariable Cox-regression analysis to identify baseline, procedural and post-repair determinants of all-cause mortality and the combined endpoint after successful surgical mitral valve repair in patients with secondary mitral regurgitation.

	All-cause mortality			Combined endpoint		
	HR	95% CI	p-value	HR	95% CI	p-value
Baseline Clinical Characteristics						
Age, years	1.04	1.00-1.08	0.03	1.03	1.00-1.07	0.04
Male gender	1.26	0.63-2.52	0.51	1.17	0.63-2.17	0.63
Log EuroScore I, %	1.04	1.02-1.07	<0.001	1.04	1.02-1.06	<0.001
Non-ischemic cardiomyopathy	0.68	0.29-1.59	0.37	0.61	0.28-1.35	0.22
Hypertension	1.09	0.55-2.16	0.80	0.97	0.52-1.82	0.93
Diabetes mellitus	1.50	0.68-3.34	0.32	2.12	1.05-4.25	0.04
Chronic kidney disease	2.93	1.46-5.84	0.002	2.54	1.35-4.79	0.004
Atrial fibrillation	1.71	0.82-3.60	0.16	1.17	0.62-2.22	0.63
B-blocker use	0.82	0.42-1.61	0.56	0.86	0.46-1.60	0.63
ACEi/ARB use	1.06	0.48-2.35	0.89	0.95	0.47-1.89	0.88
Previous CRT/D	1.13	0.39-3.21	0.82	0.83	0.29-2.33	0.72
NYHA functional class III-IV	1.42	0.68-2.99	0.35	1.32	0.37-4.68	0.67
Baseline Hemodynamics						
LV end-diastolic volume, ml	1.00	0.99-1.00	0.22	1.00	0.99-1.01	0.27
LV end-systolic volume, ml	1.00	0.99-1.01	0.24	1.00	0.99-1.01	0.29
LV ejection fraction, %	0.98	0.95-1.02	0.30	0.99	0.96-1.02	0.61
LV forward stroke volume, ml	1.00	0.99-1.02	0.66	0.99	0.98-1.01	0.83
Cardiac output, ml/min	1.07	0.98-1.31	0.53	0.98	0.81-1.19	0.87
LV forward ejection fraction	0.52	0.04-7.34	0.63	0.38	0.04-4.10	0.43
LV mass, gr	1.00	0.99-1.00	0.23	1.00	0.99-1.01	0.13
LV mass/LV volume	1.14	0.57-2.27	0.72	1.23	0.66-2.29	0.50
Relative wall thickness, %	0.99	0.96-1.04	0.83	1.01	0.97-1.04	0.75
Left atrial volume, ml	1.00	0.99-1.01	0.34	1.00	0.99-1.01	0.43
RV systolic pressure, mmHg	1.00	0.97-1.03	0.94	1.01	0.98-1.04	0.64
Procedural Characteristics						
CABG	1.75	0.75-4.06	0.19	2.05	0.94-4.49	0.07
Maze procedure	0.48	0.15-1.56	0.22	0.54	0.19-1.53	0.25
CorCap device	1.65	0.83-3.31	0.16	1.27	0.68-2.37	0.46
CRT/D	1.47	0.74-2.94	0.28	1.71	0.91-3.19	0.09
Post-repair hemodynamics						
LV end-diastolic volume, ml	1.00	0.99-1.01	0.21	1.00	0.99-1.01	0.26
LV end-systolic volume, ml	1.00	0.99-1.01	0.13	1.00	0.99-1.01	0.19
LV ejection fraction, %	0.97	0.94-1.01	0.13	0.99	0.96-1.02	0.40
LV forward stroke volume, ml	0.98	0.96-0.99	0.03	0.98	0.96-0.99	0.04
Cardiac output, ml/min	0.83	0.65-1.07	0.15	0.88	0.70-1.09	0.25
LV forward ejection fraction	0.13	0.02-1.04	0.05	0.15	0.02-1.15	0.07
LV mass, gr	1.00	0.99-1.00	0.64	1.00	0.99-1.00	0.48
LV mass/LV volume	0.69	0.38-1.27	0.24	0.86	0.53-1.42	0.56
Relative wall thickness, %	0.97	0.93-1.01	0.16	0.98	0.95-1.02	0.28
Left atrial volume, ml	0.10	0.98-1.01	0.70	0.99	0.99-1.01	0.45
RV systolic pressure, mmHg	1.00	0.96-1.04	0.96	1.00	0.97-1.04	0.75
Mitral valve MPG, mmHg	0.82	0.64-1.04	0.10	0.97	0.79-1.17	0.73

ACEi/ARBs, angiotensin converting enzyme inhibitor/angiotensin receptor blockers;

CABG, coronary artery bypass grafting;

CI, confidence interval;

CRT/D, cardiac resynchronization therapy/defibrillation

HR, hazard ratio;

LV, left ventricular;

MPG, mean pressure gradient; MR, mitral regurgitation;

NYHA, New-York Heart Association;

RV, right ventricular.

Table 4. Multivariate Cox-regression models to identify baseline, procedural and post-repair determinants of all-cause mortality and combined endpoint after successful surgical mitral valve repair in patients with secondary mitral regurgitation in a stepwise approach.

	All-cause mortality			Combined endpoint		
	HR	95% CI	p-value	HR	95% CI	p-value
Baseline Model						
Age, years	1.04	1.00-1.09	0.04	1.02	0.98-1.05	0.34
Log EuroScore I, %	1.03	0.99-1.05	0.07	1.03	1.00-1.05	0.03
Chronic kidney disease	2.90	1.42-5.91	0.003	2.21	1.16-4.22	0.02
Atrial fibrillation	2.15	0.99-4.67	0.054	-	-	-
Diabetes mellitus	-	-	-	1.65	0.78-3.51	0.19
Baseline + Procedural Model						
Age, years	1.05	1.00-1.09	0.03	-	-	-
Log EuroScore I, %	-	-	-	1.03	1.00-1.06	0.006
Chronic kidney disease	2.95	1.46-5.98	0.003	2.18	1.15-4.15	0.02
CorCap device	1.50	0.74-3.02	0.26	-	-	-
CABG	1.34	0.57-3.18	0.50	1.75	0.79-3.87	0.17
CRT/D	-	-	-	1.24	0.64-2.41	0.52
Baseline + Post-repair Model						
Age, years	1.03	0.99-1.07	0.17	-	-	-
Chronic kidney disease	2.33	1.04-5.24	0.041	1.96	0.95-4.02	0.07
Log EuroScore I, %	-	-	-	1.03	1.00-1.05	0.053
LV forward stroke volume, ml	0.98	0.95-1.00	0.047	0.98	0.96-1.00	0.045
Mitral valve MPG, mmHg	0.86	0.66-1.11	0.24	-	-	-

CABG, coronary artery bypass grafting;
CI, confidence interval;
CRT/D, cardiac resynchronization therapy/defibrillation;
HR, hazard ratio; LV, left ventricular;
MPG, mean pressure gradient.

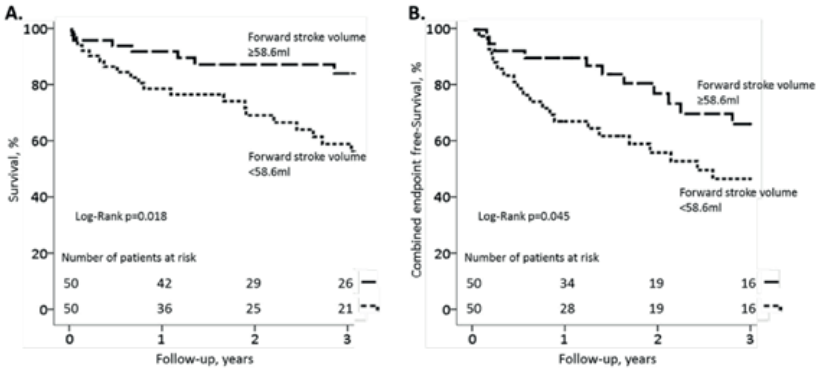

Figure 2. Kaplan-Meier analysis of (A) survival and (B) combined endpoint free-survival according to left ventricular (LV) forward stroke volume at discharge after successful surgical mitral valve repair. Patients with LV forward stroke volume ≥58.6ml (median value) have significantly better 3-year survival (A) and combined endpoint free-survival (B) compared to those with LV forward stroke volume <58.6ml at discharge.

combined endpoint free-survival compared to those with <58.6 ml (log-rank p= 0.018 and 0.045, respectively) (Figure 2). Table 3 summarizes the univariable determinants of mid-term all-cause mortality and the combined endpoint in patients with secondary MR treated successfully with surgical mitral valve repair. In the univariable analysis, age, logistic EuroSCORE I and chronic kidney disease at baseline were associated with worse survival and combined endpoint free-survival along with lower LV forward stroke volume post-repair. In contrast, none of the procedural characteristics were significantly associated with the primary and secondary endpoints. On multivariable analysis, lower LV forward stroke volume post-repair was independently associated with all-cause mortality (hazard ratio 0.98, 95% confidence interval 0.95-1.00, p=0.047) and the combined endpoint (hazard ratio 0.98, 95% confidence interval 0.96-1.00, p=0.045) (Table 4). Each 10 ml increase in LV forward stroke volume was independently associated with 21% decrease in all-cause mortality and 21% decrease in the combined endpoint.

COMMENT

Successful surgical mitral valve repair for secondary MR improves the LV hemodynamics with increased LV forward flow and reduced pulmonary arterial systolic pressure at discharge. LV forward flow, evaluated by LV forward stroke volume, at discharge was the only hemodynamic parameter that was independently associated with overall survival and combined endpoint free-survival.

Successful mitral valve repair eliminates the LV volume overload caused by significant MR and results in acute reductions in LV end-diastolic and end-systolic volumes. Similarly to previous studies in similar groups of patients,[16,17] the present study also showed significant reductions in LV volumes. In contrast, LV ejection fraction remained unchanged. This has been also reported by Acker and coworkers in a study including 155 patients with ischemic and non-ischemic secondary MR treated with surgical mitral valve repair.[11] These findings suggest no significant benefit from surgical mitral valve repair in terms of LV systolic function. However, it may well be that LV ejection fraction does not reflect appropriately the residual LV contractile function. The LV forward flow is a hemodynamic parameter that reflects both the MR reduction post-surgical repair and the LV systolic function. The forward flow improvement after restrictive mitral annuloplasty has been

demonstrated previously using cardiac magnetic resonance in 22 patients with dilated cardiomyopathy and secondary MR treated successfully with mitral valve repair.[18] The current study confirmed the increase in forward flow after successful mitral valve repair in patients with severe secondary MR as an indicator of LV functional recovery although LV ejection fraction remained unchanged.

LV ejection fraction at baseline is a hemodynamic parameter that has not been consistently associated with survival after surgical mitral valve repair. Magne et al. studied 370 patients with ischemic MR treated with surgical mitral valve repair or replacement and reported that baseline LV ejection fraction was independently associated with survival.[19] Moreover, in a study including 54 patients with non-ischemic MR treated with surgical mitral valve repair, LV ejection fraction was independently associated with survival.[4] In contrast, these results were not corroborated in 76 patients with secondary MR of ischemic (34%) and non-ischemic (65%) etiology treated successfully with surgical repair; 93.4% of them had MR grade <2 at discharge and baseline LV ejection fraction was not a predictor of 30-day survival.[20] Similarly, the current study demonstrated that baseline LV ejection fraction was not associated with survival after successful mitral valve repair.

It has been demonstrated that LV ejection fraction does not completely reflect the contractile properties of the left ventricle in patients with secondary MR.[14] By unloading the LV after successful mitral valve repair, the LV volumes reduce acutely and the LV ejection fraction may remain unchanged or even decrease. However, LV forward flow increases resulting in a hemodynamic improvement that may have consequences on the clinical outcome. The present study showed that the improvement in LV forward flow was independently associated with better clinical outcome. Each 10 ml increase in LV forward stroke volume was independently associated with 21% decrease in all-cause mortality and 21% decrease in combined endpoint of major adverse cardiac events and mortality.

The present study has several limitations. The study design is retrospective and may lead to patient selection bias. The study population is relatively small. There was not a comparable group treated medically, to investigate whether surgical mitral valve repair in this group of patients portends better prognosis.

In conclusion, in chronic severe secondary MR, surgical repair is associated with LV hemodynamic improvement at discharge. LV forward flow is independently associated with survival and combined endpoint free-survival whereas conventional parameters of LV systolic function such as LV ejection fraction were not.

Disclosures

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Summary

Chapter 1 of this thesis is the introduction that describes the prevalence of aortic stenosis (AS) and mitral regurgitation (MR) which are the most common valvular heart disease. The types of these diseases are described; AS types are based on flow, gradient and left ventricular ejection fraction (LVEF) categories, making the exact diagnosis of severe AS challenging. MR types are primary, secondary and mixed based on whether they stem from structural valvular disease, left ventricular/atrial disease or a combination of both, respectively. Since several types of the disease exist several types of surgical and transcatheter treatments have been developed. Subsequently, the role of multimodality imaging based on advanced echocardiography and multidetector row computed tomography is discussed for the accurate evaluation of the grade and pathophysiology of the valvular disease, either AS or MR. However, the assessment of the valvular component only is not enough, considering that the left ventricle is one of the main structures affected by the pressure and volume overload, and may impact on the diagnostic accuracy and the prognosis of the disease, especially in low-flow low-gradient AS and in functional MR. Thus, the clinical value of left ventricular global longitudinal strain (GLS) and forward stroke volume are reviewed in the introduction.

PART I AORTIC VALVE STENOSIS: DIAGNOSIS AND MANAGEMENT

Part I of the thesis includes original research on calcified AS which is the most frequent degenerative valvular heart disease in Western countries and its prevalence increases in parallel to the ageing process of the population. The four chapters (Chapters 2 to 5) included in Part I discuss the most appropriate imaging modalities to establish the diagnosis and the proper management of this degenerative disease.

Chapter 2 refers on the accurate AS diagnosis in discordant patients with low-gradient severe AS with aortic valve area index $<0.6 cm^2/m^2$ and LVEF ≥50% who are also called paradoxical low-gradient severe AS. So far, there were no standards to distinguish between true moderate or true severe stenosis in this group of patients. This chapter suggests the use of cardiac multidetector row computed tomography-derived planimetered left ventricular outflow tract area in the continuity equation alongside with the Doppler hemodynamics in order to evaluate the fusion aortic valve area. In patients with low gradient severe AS with echocardiographic aortic valve area index $<0.6 cm^2/m^2$ and preserved LVEF, fusion aortic valve area index evaluation permits reclassification to true moderate AS in 52% of the normal flow and 12% of the low flow patients.

Chapter 3 reviews the diagnosis and treatment of patients with the other type of discordant AS met in heart failure patients, called classical low-flow, low-gradient AS. Heart failure may be present in up to a quarter of patients with severe AS posing significant diagnostic and management challenges. These patients have low-gradient with aortic valve area index $<0.6 cm^2/m^2$ and low LVEF <50% that differentiates them from the paradoxical low-gradient AS discussed in the previous chapter. This chapter reviews the prevalence of HF in severe AS patients, discusses the diagnostic challenges, proposes a diagnostic algorithm for the accurate assessment of the disease severity, describes the advances in multimodality imaging to identify the patients that may benefit from surgical or transcatheter aortic valve replacement and

summarizes the current evidence on management for this group of patients.

Since the accurate diagnosis of severe AS in patients with discordant low-gradient and preserved or reduced LVEF has been studied in chapters 2 and 3, **Chapter 4** focuses on the treatment of these patients. The low-gradient severe AS patients are usually of high surgical risk and frequently referred to transcatheter aortic valve replacement (TAVR). In chapter 4, patients with low-flow low-gradient severe AS treated with TAVR have been proved to have left ventricular functional recovery and reverse remodelling post-TAVR, regardless of baseline LVEF category. This improvement occurred during the first 6 months post – TAVR, remained stable for the subsequent 6 months and was detected by left ventricular (LV) GLS but not by LVEF change, especially in the preserved LVEF group. Changes in LV global longitudinal strain were independent of LVEF at baseline, LV mass index and procedural approach (transfemoral or transapical), among other relevant clinical variables. In addition, absolute and relative wall thickness decreased in both groups of patients, but only those with low LVEF had a reduction in LV chamber volumes. Overall, TAVR had a positive impact on the low-flow low-gradient severe AS patients, providing LV functional recovery and reverse remodeling.

Apart from TAVR that has been evolved as a treatment of high surgical risk patients with severe AS, new minimal invasive surgical replacement options have emerged, such as the surgical sutureless prosthesis. **Chapter 5** studied these two different options of treating severe AS in propensity-score matched high-risk patients and compared their haemodynamic performance and the clinical outcomes. In high operative risk patients with severe AS undergoing aortic valve replacement, TAVR prostheses have better hemodynamic profile at discharge, in terms of higher effective orifice area index, lower mean transvalvular pressure gradient, lower prevalence of forward low-flow and prosthesis-patient-mismatch, compared to the sutureless 3f Enable valve. However, the incidence of aortic regurgitation is significantly higher among patients treated with TAVR than patients submitted to a sutureless bioprosthesis. Nevertheless, these differences did not have prognostic implications since patients treated with sutureless aortic valve replacement had comparable mid-term survival with those treated with TAVR.

PART II MITRAL VALVE REGURGITATION: DIAGNOSIS AND MANAGEMENT

The second part of the thesis consists of two chapters focused on MR, which is the second most common valvular heart disease after AS, and evaluates the role of the LV GLS in the diagnosis and treatment of MR disease. MR can be primary or secondary and Part II focuses on patients with significant MR, secondary to non-ischemic cardiomyopathy.

In patients with MR, LVEF is currently considered for the decision making of the management. However, LVEF does not characterize the intrinsic function of the myocardium, which is merely done by GLS. **Chapter 6** showed that patients with non-ischemic dilated cardiomyopathy and severe MR had significantly worse left ventricular GLS compared to those without MR and comparable LVEF. Additionally, the presence of severe secondary MR was independently associated with worse left ventricular GLS. Thus, in patients with severe secondary MR and reduced LVEF due to non-ischemic dilated cardiomyopathy, speckle-tracking LV GLS is more sensitive to uncover even

more impaired LV performance than LVEF does.

In **Chapter 7** patients with non-ischemic dilated cardiomyopathy and severe secondary MR were successfully treated with surgical or transcatheter mitral valve repair and were studied at medium term follow-up. The study concluded that successful correction of chronic severe secondary MR in non-ischemic dilated cardiomyopathy patients partly reverses the underlying LV pathophysiology at medium-term follow-up; the LV forward flow (stroke volume index and cardiac index) significantly increased and LV reverse remodeling occurred with reduction of LV end-diastolic and end-systolic volume index. However, LV myocardial functional recovery did not ensue, without any changes in LVEF and corrected GLS for LV end-diastolic volume over time. The type of correction, transcatheter MitraClip or surgical mitral valve repair, had no significant impact on changes in LV forward flow or the extent of LV reverse remodeling over time.

PART III AORTIC STENOSIS AND MITRAL REGURGITATION: PROGNOSIS

Part III focuses on the prognosis of AS and MR either as combined valvular heart disease or isolated.

The article in **Chapter 8** studied patients with co-existing aortic and mitral valve disease and focused on the prognostic value of detecting aortic and mitral valve calcification on multidetector row cardiac computed tomography in patients with suspected coronary artery disease. This study demonstrated that increased age and coronary artery calcium score were independently associated with valve calcification. Moreover, patients with valve calcification had more cardiac events in comparison to those without; and those with higher valve calcium volume, had even more cardiac events. The aortic and mitral valve calcium volume were independently associated with all-cause mortality and cardiovascular events in symptomatic patients with clinical suspicion of coronary artery disease. Thus, the volume of valve calcium is indicative of poorer prognosis and is an additional independent predictor of cardiac events.

Chapter 9 refers to the prognosis of patients with severe AS, discordant low-gradient and preserved LVEF treated with surgical or transcatheter aortic valve replacement. This original evaluation showed that patients with preserved LVEF, low gradient severe AS and normal flow or LV GLS ≤-15% have better survival after aortic valve replacement compared to their counterparts with low flow or global longitudinal strain >-15%, respectively. Furthermore, patients with low flow (stroke volume index <35ml/m^2) and concomitantly more impaired intrinsic myocardial function expressed by GLS >-15%, despite the preserved LVEF, had significantly worse survival compared with all the other combinations-groups. The addition of forward flow and LV GLS to a clinical model including atrial fibrillation and chronic kidney disease improved the risk stratification of patients with preserved LVEF, low gradient severe AS treated with aortic valve replacement.

Chapter 10 studied the prognosis of patients with severe secondary MR and heart failure reduced ejection fraction due to non-ischemic dilated cardiomyopathy treated with surgical restrictive mitral valve annuloplasty. The analysis concluded that post surgical repair, the pulmonary arterial systolic

pressure reduced, the LV end-diastolic and end-systolic volumes reduced significantly while LVEF remained unchanged. However, LV forward stroke volume was significantly increased at discharge and was the only hemodynamic parameter independently associated with all-cause mortality at 3.44 years follow-up. Thus, successful surgical mitral valve repair for secondary MR in heart failure patients with reduced LVEF, improves the LV hemodynamics by increasing the LV forward flow that defines their prognosis.

Conclusions and Future Perspectives

This thesis explored the diagnosis, management and prognosis of the most common valvular heart diseases: AS and MR. It enlightened the most challenging conditions of each disease: the discordant low-gradient severe AS and the secondary MR in non-ischemic cardiomyopathy. This thesis provides new insights into the use of fusion aortic valve area index, by incorporating the measurement of left ventricular outflow tract area on cardiac multidetector row computed tomography in the continuity equation, for the diagnosis of low-gradient AS. For the treatment of low-gradient AS, TAVR is shown to result in reverse LV remodeling and functional recovery. In comparison to other minimal invasive surgical methods it results in less prosthesis-patient-mismatch although paravalvular aortic regurgitation is a caveat. Regarding the diagnostic assessment of secondary MR due to LV dysfunction this thesis concluded that LV GLS reflects the real LV dysfunction while LVEF overestimates LV function without accounting for the forward LV flow. Mitral valve repair offers LV reverse remodeling and increase in forward flow when used for the treatment of this challenging condition. Regarding the prognostication of low-gradient AS and secondary MR this thesis advocates for the evaluation of the valvular calcium on cardiac computed tomography and the evaluation of LV GLS and forward flow that are associated with survival.

The current thesis leads the way for further research in low-gradient AS and in secondary MR so as the findings of the research conducted for the purpose of this thesis are further validated and appropriately positioned in the treatment algorithm of these conditions. Testing the fusion aortic valve area index in prospective studies would facilitate the identification of the optimal cut-off value that detects the worst clinical outcomes in low-gradient AS patients and dictates the need for treatment. A prospective study using the GLS in the decision making process of the management of secondary MR with patients randomized based on LVEF or based on GLS to surgical treatment would prove which is the best marker for intervention. Real life longitudinal studies of clinical outcomes such as the changes in NYHA class, renal function, brain function and survival among patients with secondary MR would lead to the better understanding of the value of increased forward stroke volume after mitral valve repair.

Samenvatting

In de introductie van dit proefschrift, **Hoofdstuk 1,** wordt de prevalentie beschreven van de twee meest voorkomende hartklep ziekten, namelijk aortaklep stenose en mitralisklep insufficiëntie**.** Beide klepvitia zijn verder in groepen onder te verdelen. Zo kan voor aortaklepstenose o.b.v. de flow en de druk gradiënt door (en over) de aortaklep en o.b.v. de ejectiefractie van de linker ventrikel (LV) een patiënt verder worden gekarakteriseerd. Mitralisklep insufficiëntie wordt verder gecategoriseerd als primair indien de klepinsufficiëntie door een intrinsieke beschadiging van de klep zelf komt, en als secundair indien de klep niet goed sluit als gevolg van een gedilateerde of disfunctionerende LV. Door specifieker onderscheid te maken in de verschillende categorieën van deze twee hartklepziekten kan beter worden bepaald welke behandeling het meest geschikt voor de patiënt is.

Voor het verkrijgen van een nauwkeuriger inzicht in het specifieke type van klepdysfunctie speelt beeldvorming met o.a. echocardiografie en computed tomografie (CT) een belangrijke rol. Niet alleen visualisatie van de hartklep, maar juist ook van de extra-valvulaire structuren zoals de hartkamers en grote vaten, kan veel pathofysiologisch inzicht geven. Met de beeldvorming van hartkleppen en kamers kan een indruk worden gekregen van wat nu juist de oorzaak danwel gevolg is. Zo wordt bij een aortaklepstenose en bij mitralisklep insufficiëntie het functioneren van de LV sterk beïnvloed door de ernst van het klepprobleem maar wordt daarentegen de hemodynamiek van het klepprobleem dan weer door de functie en het volume van de LV functie bepaald.

Voor een, van het klepprobleem, onafhankelijkere bepaling van de intrinsieke LV functie kan het meten van de contractiele verkorting van het myocard in longitudinale richting door het meten van de globale longitudinale strain een rol spelen. De globale longitudinale myocardiale verkorting (global longitudinal strain [GLS]) kan als maat voor LV functie aanvullende inzichten geven. De klinische toegevoegde waarde van het op deze manier meten van de LV functie, met ook tevens het bepalen van het antegrade slagvolume (in tegenstelling tot de LV ejectiefractie) wordt ook beschreven in de introductie.

DEEL 1 – AORTAKLEP STENOSE : DIAGNOSE EN BEHANDELING

In deel 1 van het proefschrift is er onderzoek gedaan naar gecalcificeerde aortaklep stenose. In Westerse landen is dit de meest voorkomende hartklep afwijking en de incidentie hiervan stijgt in parallel met het verouderen van de populatie. In hoofdstuk 2 tot 5 is onderzocht hoe, en welke, beeldvormingstechnieken gebruikt kunnen worden voor het vast stellen van de diagnose en op wat voor manier beeldvorming de (keuze voor) behandeling verder kan ondersteunen.

In **Hoofdstuk 2** wordt ingegaan op het accuraat vast stellen van de daadwerkelijke ernst van de aortaklep stenose in patiënten bij wie verschillende echografische parameters die de ernst beschrijven discordant met elkaar zijn. Dit hoofdstuk gaat specifiek over patiënten bij wie er een lage gradiënt over de aortaklep wordt gemeten ondanks dat het berekende aortaklep oppervlakte kleiner is dan $<0.6 cm^2/m^2$ maar de LV ejectiefractie wel ≥50% is. Deze patiënten hebben een zo geheten paradoxale low-gradiënt aortaklep stenose. Tot dusver was er in deze patiëntengroep geen goede standaard om onderscheid te maken tussen een matige of een daadwerkelijk ernstige graad van aortaklep stenose. In dit hoofdstuk wordt onderzocht of het met

CT planimetrisch meten van de oppervlakte van de LV uitflow verwerkt kan worden in de (met name in de echocardiografie gebruikte) continuïteitsformule van Bernouilli. Op deze manier kan de nauwkeurig te meten anatomie van CT worden gefuseerd met de echografische schattingen van drukken en snelheden. In dit hoofdstuk bleek met door het gebruik van deze CT-echo fusie parameter 52% van de patiënten met een low gradiënt ernstige aortaklep stenose, een echografisch aortaklep oppervlakte van $<0.6cm^2/m^2$ bij een toch behouden LV ejectiefractie te kunnen worden geclassificeerd tot een matige aortaklep stenose bij een normale flow. Bij een lage flow werd 12% van deze patiënten geclassificeerd.

Hoofdstuk 3 is een review over de diagnose en behandeling van patiënten met hartfalen en een discordante aortaklep stenose. Dit zijn de patiënten met een klassieke lage flow, lage gradiënt, ernstige aortaklepstenose. Hartfalen is aanwezig in tot ruim 25% van de patiënten met een ernstige aortaklep stenose en dit bemoeilijkt de diagnose en ook het besluit voor de optimale behandeling. Deze patiënten hebben een lage gradiënt over de aortaklep, het berekende aortaklep oppervlakte is klein, $<0.6cm^2/m^2$, en de LV ejectiefractie is <50% en dit laatste differentieert deze patiënten van de eerder genoemde patiënten met een paradoxaal lage gradiënt aortaklepstenose. Naast het beschrijven van de prevalentie van hartfalen in patiënten met een ernstige aortaklep stenose beschrijft dit artikel de specifieke diagnostische moeilijkheden in deze groep en wordt er een algoritme voorgesteld voor het bepalen van de ernst van de ziekte en het met beeldvorming bepalen welke patiënten het meest baat zouden hebben bij een chirurgische danwel transcatheter aortaklepvervanging. **Hoofdstuk 4** bediscussieert specifiek de behandeling van deze groep patiënten. Een ernstige aortaklep stenose waarin er een lage gradiënt is, karakteriseert deze patiënten als een groep waarin het chirurgisch risico hoog is. Omdat het risico van langdurende, open hart chirurgie in deze patiënten verhoogd is, worden ze eerder voor minimaal invasievere transcatheter vervanging/implantatie van de aortaklep (TAVI) worden verwezen. In hoofdstuk 4 blijkt dat er herstel/verbetering is van de LV functie in patiënten met een lage flow, lage gradiënt ernstige aortaklep stenose die met TAVI worden behandeld. Dit ongeacht de LV ejectiefractie van de patiënten. Deze verbetering vindt plaats in de eerste 6 maanden na TAVI en bleek de hierop volgende 6 maanden stabiel te zijn. Deze verbetering van LV functie was slechts detecteerbaar met het bepalen van de intrinsieke longitudinale verkortingsfunctie van de LV d.m.v. GLS, en was niet detecteerbaar indien er alleen naar de LV ejectiefractie werd gekeken. Verbeteringen in de longitudinale LV contractiele functie gebeurden onafhankelijk van verschillende baseline karakterisieken, waaronder de LV ejectiefractie, LV massa, en de manier waarop de TAVI verricht was (transfemoraal of transapicaal). Verder bleken ook de absolute en relatieve wanddikten van de patiënten na TAVI te verminderen, maar was er alleen een verkleining van de LV volumina in de patiënten wiens ejectiefractie ook verlaagd was. Al met al bleek het behandelen van patiënten met een lage gradiënt, lage flow ernstige aortaklep stenose een positieve invloed te hebben op het functioneel herstel van de LV functie.

Naast de TAVI zijn er ook andere, minimaal invasievere thorax chirurgische methoden voor het vervangen van de aortaklep ontwikkeld, waaronder de chirurgische "hechtingloze" aortaklep prothese. In **Hoofdstuk 5** werden

deze twee manieren van behandeling, TAVI vs. de chirurgisch "hechtingloze" aortaklep prothese met elkaar vergeleken in een cohort waarin de patiënten van beide behandelingen d.m.v. propensity score aan elkaar werden gematched. Er werd zowel gekeken naar de hemodynamische als klinische uitkomsten van beide behandelingen. In chirurgisch hoog risico patiënten met een ernstige aortaklep stenose bleken de TAVI prothesen qua hemodynamiek op een aantal parameters bij het ontslag gunstigere waarden op te leveren dan de "hechtingloze" chirurgische kleppen. Bij de TAVI prothesen was het geïndexeerde, effectieve openings oppervlakte van de klep groter, was er een lager percentage patient-prothese mismatch en bleek de transvalvulaire drukgradient over de prothese lager te zijn. De incidentie van kunstklep lekkage was echter wel groter in de patiënten die een TAVI hadden gekregen vs. de patiënten die met een "hechtingloze" kunstklep waren behandeld. Op de middellange overleving was er echter geen verschil tussen beide typen van behandeling.

DEEL II – MITRALIS KLEP LEKKAGE – DIAGNOSE EN BEHANDELING

Het tweede deel van het proefschrift bestaat uit 2 hoofdstukken die zich richten op mitralisklep insufficiëntie, de tweede meest voorkomende hartklep ziekte. Er wordt specifiek gekeken naar de rol die de longitudinale contractiele LV functie speelt bij de diagnose en behandeling van patiënten met een mitralisklep insufficiëntie. In tegenstelling tot primaire klepschade, wordt bij secundaire mitralisklep insufficiëntie de lekkage met name veroorzaakt door dysfunctie en remodeling van de LV.

In de huidige besluitvorming in deze patiënten speelt de ejectiefractie van de LV een grote rol in zowel de diagnostiek als behandeling. Echter, met de LV ejectiefractie wordt niet de intrinsieke contractiele functie van het myocard bestudeerd, en dit gebeurt wel met bepalen van de eerder genoemde GLS. In **Hoofdstuk 6** wordt aangetoond dat in patiënten met een non-ischemische, gedilateerde cardiomyopathie en een ernstige miltralisklep insufficiëntie, de GLS verminderd is t.o.v. patiënten met een vergelijkbare ejectiefractie maar zonder ernstige mitralisklep insufficiëntie. Verder was ook omgekeerd de aanwezigheid van een ernstige mitralisklep insufficiëntie onafhankelijk geassocieerd met een verminderde GLS. Speckle tracking van de LV voor het bepalen van de GLS blijkt dus een sensitievere maat voor het detecteren van een verminderde LV performance dan de LV ejectiefractie. In **Hoofdstuk 7** werd de chirurgische en transcatheter behandeling van een ernstige secundaire mitralisklep insufficiëntie in patiënten met een non-ischemische gedilateerde cardiomyopathie bestudeerd. Na een middellange follow-up bleek een succesvolle correctie van de chronische, ernstige secundaire mitralisklep insufficiëntie een deel de LV dysfunctie en geometrische remodeling te kunnen herstellen. Het antegrade LV slagvolume werd groter en de eind-diastolische en eind-systolische LV volumina verminderden. De mitralisklep correctie resulteerde niet in een verbetering van de LV ejectie of van de LV GLS.

Het type van interventie, de transcatheter MitraClip of volledige chirurgie had geen invloed op de veranderingen in antegraad LV slagvolume of de mate van LV reverse remodeling.

DEEL III – AORTAKLEP STENOSE EN MITRALIS KLEP INSUFFICIENTIE: PROGNOSE

In deel III lag de focus op de prognose van patiënten met een aortaklep stenose en mitralisklep insufficiëntie en dit werd nader onderzocht als aparte ziekten en gecombineerd.

In **Hoofdstuk 8** zijn patiënten met verkalking van zowel de aorta- als de mitralisklep onderzocht. Er werd specifiek gekeken naar de prognostische waarde van het met CT detecteren van calcium op beide kleppen in patiënten die gescand zijn met de verdenking op coronairlijden. Calcificatie van beide kleppen bleek geassocieerd te zijn met een toenemende leeftijd en ook met de calciumscore van de coronairen. In patiënten met valvulair calcium ontstond er vaker een cardiaal event dan patiënten die dit niet hadden; verder bleek ook dat hoe hoger het valvulair calcium volume was, hoe meer cardiale events er optraden. In deze patiënten met de verdenking op coronair lijden, was het calcium volume van de aorta- en mitralisklep onafhankelijk geassocieerd met een hogere, algehele mortaliteit en met het optreden van cardiovasculaire events. Hieruit blijkt dat het valvulaire calcium volume een additieve indicator is voor toekomstige cardiale events.

In **Hoofdstuk 9** werd onderzocht wat de prognose is van patiënten met een ernstige aortaklepstenose en een discordant lage gradiënt bij een behouden LV ejectiefractie die behandeld werden met een chirurgische of transcatheter vervanging van de aortaklep. In deze groep van patiënten hadden de patiënten met een normale flow of een behouden GLS van ≤-15% een betere overleving na aortaklepvervanging in vergelijking met de patiënten met een low flow of GLS >-15%. De groep van patiënten met een lage flow en (slag volume index <35ml/m^2) en tevens een matige LV functie (GLS >-15%) had de slechtste prognose t.o.v. de andere groepen. Het toevoegen van de voorwaartse flow en van de GLS aan een klinisch model met atriumfibrilleren en chronisch nierfalen bleek van toegevoegde waarde voor de risico stratificatie van patiënten met een lage gradiënt, ernstige aortaklepstenose en behouden LV ejectiefractie die een aortaklep vervanging ondergaan.

In **Hoofdstuk 10** werd de prognose bestudeerd van patiënten met systolisch hartfalen o.b.v. een non-ischemische gedilateerde cardiomyopathie en hierbij een ernstige secundaire mitralisklep insufficiëntie die chirurgisch werden behandeld met een restrictieve mitralisklep annuloplastiek. Uit de analyse bleek dat na reparatie van de mitralisklep de pulmonaaldrukken waren verlaagd en dat de eind-diastolische en systolische LV volumina waren verminderd. De LV ejectiefractie bleef onveranderd. Het antegrade LV slagvolume steeg significant bij ontslag en dit was de enige hemodynamische parameter die geassocieerd bleek met de algehele mortaliteit na 3.44 jaar follow-up. Een succesvolle, chirurgische reparatie van de mitralisklep in patiënten met een non-ischemische cardiomyopathie, verminderde LV ejectiefractie en een secundaire mitralisklep insufficiëntie leidt tot een betere LV hemodynamiek door het verbeteren van het antegrade slagvolume en dit beïnvloedt de prognose.

Conclusie en Toekomst Perspectieven

In dit proefschrift werd onderzoek gedaan naar de diagnose, behandeling en prognose van de twee meest voorkomende hartklep ziekten: aortaklep stenose en mitralisklep insufficiëntie. Ingewikkelde situaties waarin deze ziekten kunnen voorkomen werden nader onderzocht: ernstige aortaklepstenose met een discordant lage gradiënt en secundaire mitralisklep insufficiëntie in een non-ischemische cardiomyopathie.

Met het gebruiken van een fusie parameter waarin de anatomische oppervlakte van de aortaklep opening werd gemeten op CT en waarbij deze waarde werd geïncorporeerd in de continuïteitsformule met hemodynamische, echocardiografisch parameters kunnen er nieuwe inzichten worden verkregen in de diagnostiek van een aortaklepstenose met een lage gradiënt. Wat betreft de behandeling van een lage gradiënt aortaklepstenose toonde dit proefschrift dat TAVI voor reverse remodeling en functioneel herstel van de LV kan leiden. In vergelijking met andere, minimaal invasieve chirurgische methoden resulteerde TAVI tot minder patiënt-prosthese mismatch maar blijft paravalvulaire lekkage een punt van aandacht.

Voor secundaire mitralisklep insufficiëntie bleek in patiënten met LV dysfunctie o.b.v. een non-ischemische cardiomyopathie dat GLS een betere detectie maat voor LV dysfunctie was dan de LV ejectiefractie welke geen onderscheid kan maken tussen antegrade en retrograde flow. In deze groep blijkt het chirurgisch repareren van de mitralisklep tot reverse remodeling van de LV te leiden met ook een verbetering van de antegrade flow.

Voor prognose bleek verder uit dit proefschrift dat het met CT bepalen van het valvulair calcium volume en het echografisch meten van de LV GLS en antegrade flow van prognostisch belang kan zijn met een impact op de overleving. Na aanleiding van dit proefschrift kan verder onderzoek worden verricht naar de aortaklepstenose met een lage gradiënt, en naar secundaire mitralisklep insufficientie zodat dan de huidige resultaten en voorstellen voor behandelingsalgoritmen kunnen worden gevalideerd. Voor het definiëren van de optimale afkapwaarden voor de CT-echo gefuseerde aortaklep oppervlakte index voor het bepalen of patiënten baat zouden kunnen hebben bij een interventie zijn er prospectieve studies nodig. Ook wat betreft het gebruik van GLS in de besluitvorming voor chirurgie in patiënten met een secundaire mitralisklep insuffiëntie zijn prospectieve studies nodig waarin patiënten worden gerandomiseerd voor chirurgie o.b.v. GLS vs. LV ejectiefractie. Longitudinale uitkomst studies na mitralisklep chirurgie waarin gekeken wordt naar veranderingen in hartfalen-klasse, nierfunctie, hersenfunctie en overleving zijn nodig voor het beter op waarde kunnen schatten van de klinische impact van een toename van antegraad slagvolume post chirurgie.

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CURRICULUM VITAE

Dr Vasileios Kamperidis was born in Kavala, Greece on 5th October 1976. He graduated from the high school in 1994 and after succeeding in the National Greek exam, entered the Medical School of Aristotle University of Thessaloniki, Greece.

In 2000 he was awarded the Medical Degree (MD) from the Aristotle University of Thessaloniki. He holds a Master of Science Degree (MSc) of Echocardiography from the Imperial College London, University of London, with a distinction, since 2007. He was announced Doctor of Philosophy (PhD) from the Medical School, Aristotle University of Thessaloniki, in 2014 on the topic of transcatheter treatment of severe aortic stenosis. In 2017 he was recognized as a Fellow of the European Society of Cardiology (FESC) for his scientific contribution in Cardiology.

Dr Kamperidis specialized in Cardiology at AHEPA University Hospital of Thessaloniki. He sub-specialized in Echocardiography for 2 years in London at the Hammersmith Hospital and Royal Brompton Hospital under the supervision of Prof Petros Nihoyannopoulos and Prof Roxy Senior. During that period he succeeded after exams to be awarded the European Diploma in Transthoracic, Transoesophageal and Congenital Disease Echocardiography. He did a clinical research fellowship (2013-2016) on advanced cardiac imaging by applying new echocardiography and computed tomography techniques, for valvular heart disease in Leiden University Medical Centre (LUMC), at the Heart Lung Centre, under the supervision of Prof Jeroen Bax and Dr Victoria Delgado. For this fellowship he received an ESC training Grant, an EACVI research Grant, a Hellenic Society of Cardiology clinical grant and a Hellenic Foundation of Cardiology research grant.

Dr Kamperidis is the author of 80 cardiology papers (70 indexed in pubmed), has presented his research results (59 abstracts) in international cardiology congresses and (28 abstracts) in Hellenic cardiology congresses, and has been invited as a speaker in 45 Hellenic cardiology congresses. For his research work he has received 1210 citations, h-index 21, i-10 index 39.

Since 2016 he is research associate in Cardiology Department, AHEPA University Hospital, Thessaloniki, runs the outpatient clinic for valvular heart disease and the echo Lab for transoesophageal and stress echo.

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