Effect of valve replacement for aortic stenosis on ventricular function

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Life is only once

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Abstract

Background：Aortic stenosis (AS) is the commonest valve disease in the West. It results in significant left ventricular (LV) changes, including myocardial hypertrophy, systolic and diastolic dysfunction. Aortic valve replacement (AVR) remains the only available management for AS and results in improved symptoms and recovery of ventricular function however, it carries potential risks. In high-risk AS patients, such as elderly or severe LV dysfunction, the surgical risk could mount up to 3-4 folds that in younger patients or those with maintained ventricular function. The treatment of such patients remains controversial. In addition, it is well known that AVR results in disruption of LV function mainly in the form of reversal of septal motion as well as depression of right ventricular (RV) long-axis function. Trans-catheter aortic valve implantation (TAVI) emerged recently as an alternative to the conventional surgical procedure, particularly for patients with severe LV dysfunction as well as those with other significant comorbidities. Early results are quite promising, carrying satisfactory survival and complication rate. The aim of this thesis was to study, in detail, the early and mid-term response of ventricular function to AVR procedures (surgical and TAVI) as well as post operative patients' exercise capacity.

Methods : We studied LV and RV function by Doppler echocardiography and speckle tracking echocardiography (STE) in the following 4 groups; *(1)* 30 severe AS patients (age 62±11 years, 19 male) with normal LV ejection fraction (EF) and stroke volume (SV) who underwent AVR, *(2)* 20 severe AS patients (age 79±6 years, 14 male) who underwent TAVI, *(3)* 30 healthy controls (age 63±11 years, 16 male), *(4)* 21 healthy controls (age 57±9 years, 14 male) who underwent exercise echocardiography.

The septal radial motion and RV long-axis function presented by tricuspid annulus peak systolic excursion (TAPSE) were measured by M-mode from parasternal long-axis view and apical four-chamber view, respectively. Normally, the septal radial motion at end-systole is towards LV cavity (+), when towards RV cavity it was considered as abnormal (-). From the apical four-chamber view, LV septal and lateral wall peak displacement and time from the onset of QRS to peak displacement, septal and lateral systolic strain were measured using STE as well as global longitudinal systolic and early

diastolic strain rate (GLSRs and GLSRe) during exercise. The LV systolic twist as the net difference between apical rotation and basal rotation was measured from the parasternal apical and basal short-axis views. The conventional echocardiographic measurements were also made according to the guidelines.

Results: After one week of TAVI, the septal radial motion and RV TAPSE were not different from before, while surgical AVR had significantly reversed septal radial motion and TAPSE dropped by 70% compared to before. The extent of the reversed septal radial motion correlated with that of TAPSE (r=0.78, p<0.001) in the patients as a whole after AVR and TAVI. LVEF remained unchanged after one week in the two patient groups, but increased from 46±5.7 to 57±4.5% (p<0.05) in patients with values <50% before TAVI (*Study I*). Compared with controls, the LV twist function was increased in AS patients before and normalized after 6 months of surgical AVR with LVEF remaining normal. In controls, the LV twist correlated with LV fractional shortening (r=0.81, p<0.001), a relationship which became weak in patients before (r=0.52, p<0.01) and after AVR (r=0.34, p=ns) (*Study II*). After 6 months of surgical AVR, the reversed septal radial motion partially recovered compared to 1 week after surgery but was still significantly lower than before. The septal peak displacement also decreased and its time became prolonged. In contrast, the LV lateral wall peak displacement increased and the time to peak displacement was early. The accentuated lateral wall peak displacement correlated with the SV (r=0.39, p<0.05), septal peak displacement time delay (r=0.60, p<0.001) and septal-lateral time delay (r=0.64, p<0.001). Twelve months after AVR, septal radial motion further recovered but remained less than controls, while peak septal and lateral wall displacements were unchanged. Septal time delay regressed but that of lateral wall displacement persisted, resulting in less septal-lateral time delay, despite remaining longer than controls (*Study III*). In our surgical AVR patients, 21 were followed up to 28±12 months (range 12-48 months) and were recalled to participate in the exercise echocardiography study, patients LV function was normal at rest but different from controls with exercise. At peak exercise, oxygen consumption (pVO$_2$) was lower in patients than controls. Although patients could achieve cardiac output (CO) and heart rate (HR) similar to controls at peak exercise, the LV systolic and early diastolic myocardial velocities and global longitudinal strain rate as

well as their delta changes were significantly lower than controls. pVO_2 correlated with peak exercise LV myocardial function in the patients group only, and GLSRs (β=7.18, p=0.03) at peak exercise was the only independent predictor of pVO_2 in multivariate regression analysis (*Study IV*).

Conclusion: Surgical AVR is an effective treatment for AS patients, but results in reversed septal radial motion and reduced TAPSE. The newly developed TAVI procedure improves LV systolic function and maintains RV long-axis function which results in preservation of septal radial motion. In AS, the LV twist function is exaggerated, normalizes after AVR but loses its relationship with basal LV function. While the reversed septal motion results in decreased and delayed septal longitudinal displacement which is compensated for by the accentuated lateral wall displacement and the time early. These changes almost normalize 12 months of AVR, but patients remain suffering from limited exercise capacity years after AVR.

Keywords: Aortic stenosis, aortic valve replacement, echocardiography, speckle tracking, exercise echocardiography, ventricular function, septal radial motion, twist, displacement, strain, strain rate

List of Papers

I. Trans-catheter aortic valve implantation – early recovery of left and preservation of right ventricular function. Zhao Y, Lindqvist P, Nilsson J, Holmgren A, Näslund U, Henein MY. *Interact Cardiovasc Thorac Surg* 2011;12:35-39.

II. Aortic valve replacement normalizes left ventricular twist function. Lindqvist P, Zhao Y, Bajraktari G, Holmgren A, Henein MY. *Interact Cardiovasc Thorac Surg* 2011;12:701-706.

III. Accentuated left ventricular lateral wall function compensates for septal dyssynchrony after valve replacement for aortic stenosis. Zhao Y, Lindqvist P, Holmgren A, Henein MY. *Int J Cardiol* 2011 July 30. [Epub ahead of print] in press.

IV. Residual compromised myocardial contractile reserve after valve replacement for aortic stenosis. Zhao Y, Henein MY, Mörner S, Gustavsson S, Holmgren A, Lindqvist P. *Submitted to European Journal of Echocardiography*.

Abbreviations & Definitions

AS	Aortic stenosis
AVR	Aortic valve replacement
TAVI	Trans-catheter aortic valve implantation
LA	Left atrium
LV	Left ventricle
RA	Right atrium
RV	Right ventricle
IVST	Interventricular septal thickness
PWT	Posterior wall thickness
EF	Ejection fraction
FS	Fractional shortening
SV	Stroke volume
CO	Cardiac output
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
MAPSE	Mitral annulus peak systolic excursion
TAPSE	Tricuspid annulus peak systolic excursion

E	Peak velocity in early diastole
A	Peak velocity during atrial systole
E/A	Ratio of E and A velocity
EDT	E-wave deceleration time
Sm	Myocardial peak systolic velocity
Em	Myocardial peak early diastolic velocity
E/Em	Ratio of E and Em velocity
FT	Filling time
ET	Ejection time
t-IVT	Total isovolumic time
VTI	Velocity time integral
ε	Strain
SR	Strain rate
GLSRs	Global longitudinal strain rate during systole
GLSRe	Global longitudinal strain rate during early diastole
GLSRa	Global longitudinal strain rate during atrial systole
AVA	Aortic valve area
HR	Heart rate
BSA	Body surface area
NYHA	New York Heart Association class
BNP	Brain natriuretic peptide

pVO$_2$	Peak oxygen consumption
Ex	Exercise
ECC	Extracorporeal circulation time
OT	Occlusion cross-clamping time
CABG	Coronary artery bypass grafting
STS score	Society of Thoracic Surgeons scoring system
EuroSCORE	European system for cardiac operative risk evaluation
ROI	Region of interest
ECG	Electrocardiogram
TDI	Tissue Doppler imaging
STE	Speckle tracking echocardiography
AVC	Aortic valve closure time
MRI	Magnetic resonance imaging
CT	Computed tomography
AF	Atiral fibrillation
CAD	Coronary artery disease
LDL	Low density lipoprotein
ACE-inhibitor	Angiotensin-converting enzyme inhibitor
BAV	Balloon aortic valvuloplasty
RVP	Rapid ventricular pacing

Twist: The myocardium rotates around the long axis of the left ventricle during the cardiac cycle "rotation". Normally, the LV base (clockwise, negative value) and apex (counter clockwise, positive value) rotates in the opposite directions. The absolute LV apex-to-base rotation difference is referred to as twist (degree).

Septal radial motion: Measurement of the extent of systolic anterior septal motion with respect to its position in end-diastole using the M-mode technique from the parasternal long axis view. Positive (+) motion towards the LV cavity and negative (-) motion towards the RV cavity.

Peak displacement: The LV wall peak movement during the cardiac cycle which is measured in millimetre (mm) or centimetre (cm).

Time to peak displacement: Time interval from the onset of QRS to LV wall peak displacement, represented in millisecond (ms).

ε (Strain): The deformation of the myocardium relative to its original length. Strain is expressed in percent (%), the positive strain is lengthening, stretching or thickening and negative strain is shortening with compression of the myocardium, in relation to its original length.

Strain rate: The rate of myocardial deformation. Strain rate reflects the deformation or strain per time unit (1/s).

Introduction

Aortic stenosis (AS) is the commonest valve disease in the West, with a prevalence varying between 0.02% in adults under 44 years and 3-9% in those over 80 years of age (1, 2). The disease may remain "silent" and hence unnoticed for years, particularly in the elderly with naturally limited exercise. With the development of symptoms, patients may carry a mortality of 36-52%, 52-80% and 80-90% at 3, 5 and 10 years, respectively if left untreated, even carrying a high risk of sudden death (3). Aortic valve replacement (AVR) is the only effective treatment for severe AS, it is indeed the second indication for open heart surgery after coronary artery bypass grafting (CABG) (4).

Pathophysiology

Aetiology: The most common cause of AS in adults is calcification of a trileaflet or congenital bicuspid valve (5). Calcific AS is a progressive pathology, starting with simple leaflet thickening, fibrosis then eventually severe calcification, small valve area and tight stenosis. The exact pathology of AS is not clearly understood. Studies have shown that the risk factors for AS are similar to those of atherosclerosis, hence the suggestion that the pathology is likely to be similar (6, 7). Histological studies of valve specimens also demonstrated inflammation, lipid accumulation and fibrosis on the stenotic aortic valve, taking similar morphology to those seen in atherosclerotic disease (8). Less common causes of acquired AS is rheumatic valve disease, although much less prevalent than rheumatic mitral valve disease (2). Rheumatic AS presents with typical pathological leaflets, thickened and calcified with fused commissures resulting in additional regurgitation. Isolated congenital AS is a rare pathology, with bileaflet aortic valve being the commonest and sub or supra aortic valve stenosis the less common. Although can result in similar pathophysiology, subaortic membrane may cause severe narrowing of the left ventricular outflow tract (LVOT) early in life and cause a serious need for surgical removal (9). Finally, aortic valve stenosis should be differentiated from subaortic basal septal

hypertrophy, causing LVOT narrowing and potential obstruction, particularly at fast heart rate (10).

Pathology: As a result of the stenotic aortic valve, the left ventricle (LV) faces a significant pressure afterload which is known to affect LV structure and function as is the case with long standing hypertension (11, 12). The raised intracavitary pressure raises wall stress which affects first the function of the subendocardial layer of the myocardium followed by the transmural layer (13). As the pressure increases and becomes significant, LV wall thickness increases and consequently the overall LV mass increases too. This is a potential compensatory mechanism to the LVOT obstruction and resistance as well as the exponential increase in wall stress, in order to maintain overall systolic LV function. Since the disease is progressive, eventually subendocardial dysfunction occurs. The degree of subendocardial dysfunction usually correlates with the severity of the AS (13). This can easily be studied by accurate assessment of LV long axis function which reflects the subendocardium (14). Long standing conditions may result in irreversible subendocardial dysfunction which affects the conduction system and hence broadening of the QRS duration, commonly seen in severe AS. The LV hypertrophy should then be seen as having a compensatory beneficial effect as well as a damaging effect on the subendocardium as it compromises its blood supply hence, a perpetual subendocardial ischemia even in the absence of epicardial coronary artery disease (15). LV hypertrophy and increase in muscle mass affects also diastolic cavity function and causes global slow relaxation (16). This is bound to affect the overall LV performance with most filling volume occurring during late diastole rather than early diastole as is the case in normal hearts. These functional disturbances have been shown by various echocardiographic techniques including M-mode and tissue Doppler (17). With further deterioration of diastolic LV function, the cavity becomes stiff and filling pressures rise, which affect further the subendocardial function and patients may develop rather serious arrhythmia as a result. Furthermore, raised LV filling pressures themselves destabilize the left atrial (LA) function and increase LA size, hence the potential development of atrial fibrillation (AF). Most patients with raised LA pressures present with exertional breathlessness and signs of secondary raised systolic pulmonary artery pressure. Finally, late ventricular disease results in a fall in LV systolic function as shown by

reduced ejection fraction (EF) and development of heart failure symptoms and signs. These patients may present with masked signs of AS which, again, could be inappropriately diagnosed and managed. It should be mentioned that fast developing AS resulting from aggressive leaflet calcification process usually causes disproportionate hypertrophy and fast pressure build up in the LA and atrial arrhythmia.

Mechanism of calcific AS

A number of theories have been proposed but none is entirely satisfactory. As mentioned above, the most popularly accepted pathophysiology is that of atherosclerosis and inflammation. Genetic studies demonstrated that lipids, Vitamin D receptor gene, estrogen receptor, and Notch1 signaling in addition to a familial aggregation have important implications in the development of AS (18), but no specific gene has yet been identified. Lack of clear understanding of the exact mechanism and pathophysiology of aortic valve calcification makes disease prevention difficult, and even management might also be inappropriate in some cases.

Treatment

While mild and moderate AS are monitored and followed up by regular echocardiographic assessment, severe AS is an indication for valve surgery particularly in symptomatic patients, according to the current guidelines (19, 20). Asymptomatic patients with severe AS remain a dilemma, although evidence exists confirming a significantly poor clinical outcome, if left unattended to (21). Another dilemma is symptomatic patients with only moderate AS, in the presence of good LV function. The general belief is that the native valve should be preserved for as long as possible. Such patients with moderate AS who are limited by symptoms, particularly those with additional systemic hypertension have been shown to have worse LV and LA function compared to those without hypertension (22). Controversies remain regarding the best management plan for such patients since most hypertension medications are vasodilators with their known effect on AS physiology. These patients with moderate AS are commonly seen in

cardiology clinics and more critical studies need to be properly designed to determine best management policies for them.

Medical treatment

ACE-inhibitors: For aortic stenosis, ACE inhibitors and statins are the two controversial medications which have been tested. A limited evidence suggests that ACE-inhibitors might improve exercise tolerance in AS patients with preserved LV systolic function (23). However, ACE-inhibitors are known for their vasodilatory effect and hence are traditionally a contraindication because they reduce the peripheral resistance resulting in increased transaortic valve gradient and reduced coronary perfusion.

Statins: The use of statins in AS is based on the shared risk factors, found in AS and coronary atherosclerosis. These findings lead investigators to hypothesize that the two conditions are similar, and AS should benefit from statins and reduction of low density lipoprotein (LDL) cholesterol as coronary atherosclerosis does. A number of observational studies and trials have been conducted to objectively test this hypothesis, but failed to prove it. The most important is the SEAS trial being the largest study which showed no effect on severity of AS despite successful fall in LDL with simvastatin and ezetimibe (24). A recent meta-analysis also showed that AS does not respond to statins (25). If the early hypothesis proves true, the failure of response to statins could then be explained on the basis of commencing them in already late matured disease and calcified leaflets. In fact, these findings are not surprising since they mirror the results of using statins in calcific coronary artery disease shown by a number of randomized trials and a recent meta-analysis which showed no structural benefit (26).

Beta blockers: The pressure gradient and its drastic effect on LV function are very well known. A resting gradient of 60 mmHg in an asymptomatic patient is likely to double with increase in heart rate. Therefore, beta blockers have traditionally been used for heart rate control in AS patients. In asymptomatic AS patients, it may be useful since it can potentially reduce sudden death, ischemic events or artial fibrillation, but are poorly tolerated by severe AS patients (27).

Aortic valve replacement (AVR)

Valve substitutes

AVR is the conventional treatment for severe symptomatic AS. It is performed either in isolation or concomitantly with CABG surgery, which is known to take place in almost 50% of patients with AS. The overall mortality of isolated AVR is 3-5% in patients below 70 years and 5-15% in older adults (20). After successful AVR, long-term survival rate becomes close to that expected in age matched controls, symptoms are less marked, and quality of life is largely improved (20). Some patients may be completely discharged from cardiology clinics to be followed up in the community. Various valve substitutes have been developed over the years, varying from mechanical, bioprostheses, homografts and autografts, with the objective of inserting the ideal valve which causes the least possible resistance to the left ventricle. Clear differences, advantages and disadvantages between them exist. The life span of the mechanical valves is the longest, but it has a need for life-long anticoagulation with its known potential problems, particularly in the elderly. Anticoagulants are also difficult to manage appropriately in patients living in rural areas in developing countries, with poor anticoagulation control. The life span of the biological prostheses is around 10-15 years. Getting old, the bioprostheses disintegrate and cause fast developing significant aortic stenosis/regurgitation which may need life saving redo valve replacement (28). The main advantage of bioprostheses is the lack of the need for using anticoagulants. Aortic homografts are ideal in terms of hemodynamics of the LVOT. They result in similar clinical outcome to bioprostheses without a need for anticoagulation. It must be mentioned that homografts are the ideal valve substitute for patients with recurrent or resistant aortic valve endocarditis, particularly when mechanical valves have previously been used. Despite that, aortic homografts are known for their potential problems including calcification and availabilities. Homografts do calcify at a similar rate to bioprostheses, but no exact predictors for aortic calcification have been identified yet. In order to offer an optimal aortic homograft service, a well organized homograft bank needs to be established. Aortic autograft (Ross procedure) is another potentially viable valve substitute. The procedure involves replacing the calcified aortic valve by the patient's own pulmonary valve and inserting a homograft in the pulmonary position. This

operation is ideal for young patients because it allows the patient's own valve to grow. Autografts do not need anticoagulation, but need homograft banks as well as optimally experienced surgeons who are trained to undertake such procedure.

Mechanical prostheses have better long-term survival than biological prostheses mainly because of the absence of primary valve failure while bleeding complications are more frequent (28). On the other hand, biological prostheses have better hemodynamics than mechanical prostheses (29). Despite that, biological prostheses have no difference on the rate of LV hypertrophy regression at long-term follow-up compared to mechanical prostheses (30). For biological prostheses, the stentless valve has a greater reduction in peak aortic velocity and a greater increase in indexed effective orifice area than the stented valve, despite similar reduction of LV mass at intermediate and long-term follow-up after AVR (31, 32). Similar findings are reported in a meta-analysis which showed that although LV mass index is significantly lower in a stentless group after 6 months of AVR, differences disappear after 12 months (33). Full aortic root replacement and reimplantation of the coronary arteries either with the stentless or the homograft valve produces near-normal transvalvular velocities and less than the stentless implanted in the subcoronary position (34). The Ross procedure, compared with homograft aortic root replacement, improves survival in adults, and is associated with improved freedom from reoperation and quality of life in long-term follow-up. The proportion of patients who survive after the Ross procedure is similar to that in the general population. The autografts have better hemodynamic outcome which does not change during follow-up compared with homografts which have a steady increase in transvalvular pressure up to 13 years after surgery (35).

Clinical outcome after AVR

After successful AVR, symptoms become less marked, if do not disappear, and the quality of life greatly improves. The long-term survival after 5, 10 and 15 years is 94.6%, 84.7% and 74.9% respectively (36). Factors affecting short-term mortality and long-term survival after AVR include age (≥70 years), NYHA functional class Ⅲ and Ⅳ, aortic regurgitation, concomitant CABG and AF. Patients in a good NYHA functional class (Ⅰ and Ⅱ) before

surgery usually have low operative mortality and excellent long-term survival, not different from the expected in the control population (36). Despite various scores currently used to assess surgical risk, optimally timed AVR remains a dilemma for some patients such as the elderly and those with LV systolic dysfunction.

AVR in high-risk patients: In elderly AVR patients, the early mortality is approximately 4%-9% (37, 38). Studies have shown that the 5, 10 and 15 years late postoperative survival (68%, 34% and 8%) is lower than the expected in elderly population (70%, 42% and 20%) (37). While, the overall postoperative survival in elderly patients at low risk is similar to that of age- and sex-matched general population (37). Although AVR in the elderly can be performed with acceptable mortality and excellent long-term survival and functional recovery, the European Heart Survey on valvular heart disease demonstrates that 33% of patients over 75 years of age are not considered for surgical AVR because of age and LV systolic dysfunction or other co-mobidities (39), such as kidney impairment, chronic obstructive pulmonary disease and neurological dysfunction. Another survey in U.S. shows that half of symptomatic AS patients with quoted operative risks of 5-12% did not undergo AVR mainly because of other co-morbidities (40).

In severe AS patients with poor LV function, AVR has significantly better outcome compared to those treated medically (41). Undoubtedly, such patients are likely to carry a significantly higher surgical risk (amounting for up to 10%) compared to those with maintained LVEF, with an estimated in-hospital mortality of 8-9%. However, the gain benefit in terms of clinical outcome outweighs the surgical risk. In fact, guidelines support AVR in such patients (20).

Left ventricular function after AVR

Left ventricular hypertrophy (LVH) regression: AVR decreases the LV afterload, resulting in regression of cavity hypertrophy. LV mass regression predominantly occurs within the first 6 months of surgery, late regression is slow and might not become significant on long-term follow-up. Studies reported controversial results regarding the effect of age and gender on LV hypertrophy regression (30). However a systematic review has shown

no statistical association between age and sex with the rate of LV mass regression and change in EF (42).

LV function: LVEF may remain normal in more than 90% of AS patients. However, the long-axis systolic function has already been shown to be significantly decreased in AS patients with normal LVEF as assessed by either M-mode or tissue Doppler imaging (TDI) velocities (13, 43). During the cardiac cycle, the myocardial fiber length changes are not only in the longitudinal direction, but also in the radial and circumferential direction. Analysis of the changes in these three directions in AS patients gives profound information on LV function performance during the disease process. The new echocardiographic techniques e.g. TDI and speckle tracking echocardiography (STE) provide accurate evaluation of LV global and segmental myocardial motion (velocity and displacement) as well as deformation (strain and strain rate). In AS patients, the longitudinal velocity, strain and strain rate are significantly decreased even in mild aortic stenosis and deteriorate further as AS becomes severe, similar to the findings of M-mode and pulsed TDI. The reduction in long-axis function is related to the extent of LV hypertrophy (44, 45) and the severity of AS (13, 46). The radial and circumferential strain and strain rate changes usually occur later than the longitudinal function, which may remain normal in mild AS patients, but decrease in moderate and severe AS (47). This has been shon by *Delgado et al* who demonstrated significantly decreased radial and circumferential strain and strain rate in severe AS patients with preserved LVEF (48). While another study showed supernormal circumferential strain in patients with normal EF and decreased function when LV systolic dysfunction is present, suggesting that the high circumferential strain may serve as an initial compensatory mechanism for maintaining normal LVEF (49). The differential changes in longitudinal, radial and circumferential fibers reflect the myocardial dysfunction beginning at the subendocardium in mild AS and progressing to mid-wall and eventually transmural impairment in severe AS.

After surgery, LV pressure overload immediately decreases, resulting in rapid increase of LV myocardial velocities, strain and strain rate in all three directions, as early as 1 week of surgery before global systolic function and LV mass significantly change (50, 51, 52). These improvements may be due to the increased coronary artery reserve secondary to increased valve

effective orifice area, resulting in a more effective myocardial blood supply (53). During mid-term and long-term follow-up, the strain and strain rate in all directions increase gradually and eventually normalize (48, 53, 54). The recovery of strain and strain rate in radial and circumferential direction are usually earlier than that in the longitudinal direction.

LV twist function: The heart normally rotates along its long-axis forming a wringing (twisting) motion during the cardiac cycle. Looking from the apex, the LV base rotates clockwise (negative value) and the apex rotates counter-clockwise (positive value), resulting in a wringing motion. The net rotation difference between apex and base is called twist. During isovolumic relaxation, the rapid untwisting occurs before cavity filling.

Studies using magnetic resonance imaging (MRI) in AS patients with preserved LVEF demonstrate that in AS the apical rotation and LV twist are increased and untwist is delayed compared to normals (55, 56). Furthermore, the increased apical rotation and LV twist correlate with the severity of AS (57). These changes are considered as compensatory mechanisms for the increased intracavitary pressure overload and the subendocardial ischemia (57). Another explanation is the potentially rearranged fiber architecture in AS patients which may alter the torsional deformation of the heart (56). LV twist has also been shown to increase significantly in women with congenital AS and further increase during pregnancy (58) confirming that LV twist is altered in response to varying ventricular loading conditions (50). However, this compensatory mechanism is lost in patients with severe LV dysfunction (49). After surgery, the twist function may normalize (59).

Septal radial motion and right ventricular function after AVR

AS has no effect on right ventricular (RV) function unless complicated by secondary pulmonary hypertension or additional coronary artery disease affecting the RV. However, AVR is known to affect RV function with reduced amplitude of the free wall motion, clinically described as RV long axis function or tricuspid annulus peak systolic excursion (TAPSE), the exact explanation of such disturbance has not been successfully established. Some suggestions for potential mechanisms have been reported such as right atrial cannulation, suboptimal RV myocardial preservation or sternal opening (60,

61). However, none of these hypotheses has yet proved a satisfactory explanation. A recent study shows that the reversed septal motion after AVR is related to TAPSE (60). With the reversed septal motion after AVR, the mechanism of how LV could maintain its global EF remains unknown as well as the relationship between LV twist and segmental function.

Trans-catheter aortic valve implantation (TAVI)

TAVI is a recently developed procedure which aims at non-surgical aortic valve replacement in patients with severe, symptomatic and calcified AS who carry high surgical risk because of either poor LV function or other significant co-morbidities e.g. previous CABG surgery and/or aorta or other heart valve surgery, patients with LVEF <50%, impaired kidney function or pulmonary hypertension and patients older than 80 years old (62). Currently, this technology is not recommended in bicuspid AS patients due to the risk of incomplete and incorrect deployment of the aortic prostheses (63). TAVI avoids open heart surgery and hence is likely to protect myocardial perfusion function.

TAVI procedure

Current TAVI practice uses two types of valves: the ballon-expandable Edwards Sapien (Edwards Lifesciences, Irvine, California) and the self-expandable CoreValve (Medtronic, Irvine, California). Both valves consist of three equal pericardial leaflets. TAVI is performed through either the retrograde trans-femoral (Edwards Sapien and CoreValve) or by the antegrade trans-apical (Edwards Sapien) approach. While trans-femoral approach is usually favored for most patients, the trans-apical approach is recommended for those in whom the trans-femoral access is suboptimal or difficult.

The trans-femoral approach requires an adequate peripheral vascular access (more than 6mm diameter, no more than mildly diseased and tortuous vessels, no significant aortic disease or previous aortic surgery) and can be performed fully percutaneously under general or local anesthesia. The alternatives for trans-femoral approach are iliac artery, subclavian artery or

ascending aorta when the femoral artery is not suitable. The trans-apical approach requires a left anterolateral mini-thoracotomy through the 5th or the 6th intercostal space and general anesthesia. During procedure, both approaches might need balloon aortic valvuloplasty (BAV) to predilate the native valve. It is essential for increasing the effective orifice area of the aortic valve and allowing for easy placement of the prosthetic valve. After balloon predilatation, the prosthetic valve with its delivery system is introduced and advanced to the aortic valve. The prosthetic valve, then, is deployed either balloon-expanded or self-expanded depending on the valve design. BAV and balloon-expandable valve deployment must be performed under rapid ventricular pacing (RVP) with a temporary pacemaker which paces the heart at 180-220 beats per minute, usually the pacing is for less than 15 seconds. The RVP induced ventricular tachycardia accomplishes an optimal reduction of the cardiac output, creating a transient cardiac standstill (64).

TAVI procedure is performed under X-ray monitoring and transoesophageal echocardiography is also recommended for accurate monitoring of valve positioning, evaluating the LV function before and immediately after valve implantation as well as detecting any early procedure related complications e.g. para-valvular regurgitation (65).

Clinical outcome of TAVI

Since the first introduction of TAVI in patients by Cribier in 2002 (66), the interest in this catheter-based treatment for high-surgical-risk AS patients is increasing (67, 68) and a number of clinical trails have been designed to assess the safety and efficacy of this new technique, some of them compared TAVI with medical treatment or conventional surgical AVR. The procedure's efficacy has been proved with overall procedural success rates ranging between 74% and 100%. The short-term (30 days) overall mortality is 0-25% (69), 1, 2 and 3 years survival rates are 76.1%, 61.9% and 57.0%, respectively (70, 71, 72). Survival after TAVI is not different between trans-apical and trans-femoral approach at short and mid-term follow-up (73, 74).

Compared with conventional treatment (medical and balloon aortic valvuloplasty), TAVI has been shown to improve the one-year survival by

20% in high risk inoperable patients, and significantly reduces repeat hospitalization and cardiac symptoms (PARTNER trial) (75). TAVI and surgical AVR have shown similar 1 year survival rates in high risk patients despite TAVI remains carrying more periprocedural risk (76, 77). In patients with severe AS and reduced LV systolic function, TAVI has resulted in better LVEF improvement (△LVEF: 14±15 vs. 7±11%, p=0.005) than surgical AVR with similar baseline LVEF (78).

LV function after TAVI

In addition to the favorable clinical outcome of TAVI, the procedure has significant effect on LV function. The LV function changes after TAVI are similar to those of after surgical AVR, LVH significantly regresses although not complete after 1 year follow-up (79). Despite remarkable drop of transvalvular gradient, significant improvement of EF and posterior wall myocardial velocity, strain and strain rate have already been observed 24 hours after procedure (80). After 8 weeks of procedure, TAVI results in similar increase of LV lateral wall longitudinal amplitude and myocardial velocity compared to AVR (81). Meanwhile, similar to surgical AVR, the decreased longitudinal systolic strain and strain rate in severe AS patients increased after 1 month of TAVI with unchanged EF. The unchanged radial and circumferential strain and strain rate after procedure may be due to the near-normal values before TAVI (82). It seems that the changes of LV myocardial motion and deformation after TAVI or surgical AVR are more dependent on the baseline patients' characteristics than the procedure itself since they both decrease the afterload immediately. Up till now, there is no study on the twist function after TAVI, since TAVI and surgical AVR both relieve the LVOT obstruction. The twist function changes after TAVI are expected to be the same as with AVR. This remains to be proved.

RV function after TAVI

In contrast to AVR, TAVI has proved to have no negative effect on RV function with TAPSE remaining well preserved and RV free wall systolic velocity increased compared with gender, age and LV function matched AVR patients after 8 weeks of procedure (81). But the septal radial motion after TAVI has never been studied, as well as its relationship with TAPSE.

Assessment of AS and ventricular function

Cardiac catheterization: Historically, cardiac catheterization used to be the "gold standard" technique for evaluating valvular and LV function. Precise transvalvular and intra-cardiac gradients, LV volumes, systolic and diastolic functions were determined based on invasive hemodynamic findings. Cardiac catheterization also provides direct accurate assessment of coronary artery disease using selective injection of contrast into the right and left coronary arteries. Although cardiac catheterization has now been replaced by Doppler echocardiography for assessing valve and ventricular function, it remains of specific value for assessing the coronary circulation before AVR (19). Because of its known limitations, namely its invasive nature, the need for arterial access, risking blood loss and technical difficulties, cardiac catheterization for coronary studies has now been replaced by computed tomography (CT) coronary angiography, particularly in patients with negligible risk for coronary artery disease.

Doppler Echocardiography: Echocardiography is recommended as the prime non-invasive imaging technique for the assessment of cardiac function, particularly the left ventricle and the aortic valve (19, 20). Compared with other imaging modalities, echocardiography is patient friendly, provides bed side diagnosis, accurate estimation of the degree of AS, even in patients with poor LV function and masked signs of AS. It is a tool which could be used for pre- as well as post- operative assessment of the valve and ventricular function, even in patients with pacemakers. Routine echocardiographic examination includes assessing the size and function of ventricles, the size of the atria as well as valve leaflet pathology, mobility and severity of stenosis and regurgitation. After surgery, echocardiography is unique in assessing prosthetic valve function. TDI and 2D STE can provide details on segmental and global myocardial function as well as synchronous behavior.

Magnetic Resonance Imaging (MRI): Having high spatial and temporal resolution, MRI provides precise non-invasive hemodynamic information on cardiac structure and to some extent its function. MRI displays exquisite anatomical images of the heart which allow accurate volume and ejection fraction estimation. It does not require any contrast or the use of radiation and calculations of volumes do not depend on geometric

assumptions. The natural contrast between blood and tissue allows accurate assessment of regional wall motion and chamber size. In addition, cardiac MRI can measure segmental myocardial deformation, strain and strain rate, throughout the cardiac cycle as well as twist function of the heart, using tagging technology. MRI can also assess aortic valve function on two-dimensions before and after AVR (83), despite being an indirect estimation rather than direct velocity and pressure gradient calculation as is the case with continuous wave Doppler (84). The main disadvantages of MRI are long acquisition and processing time, cost and availability. At present, MRI is not routinely indicated for AS patients before and after surgery in clinical practice.

Computed Tomography (CT): CT scanning enables accurate assessment and quantification of aortic valve calcification, which has been shown to correlate with severity of AS (85). CT also helps in excluding significant coronary artery disease in AS, particularly in patients who are at low risk of atherosclerosis. CT measurements of ventricular volumes prove to be very accurate when compared with MRI. CT permits high spatial, temporal resolution and contrast for delineation of endocardial and epicardial borders. In addition, it provides information on the anatomic details of the valve leaflets, in those with no calcification. The main drawbacks of CT are radiation and lack of trasvalvular pressure gradient information in AS patients (86).

Echocardiographic evaluation

Valve function

Echocardiography is recommended to be used in the diagnosis and follow-up of AS patients and after intervention. The valve calcification is easily detected on the 2D imaging but can only be qualitatively evaluated. Doppler flow velocity is conventionally used to evaluate the severity of valve stenosis, from which the peak transaortic valve velocity is measured. Peak pressure drop is calculated using the modified Bernoulli equation ($P=4V^2$), where P is transaortic valve pressure and V is the peak transaortic valve velocity by continuous-wave Doppler. The aortic valve area (AVA) is then calculated

from the LVOT diameter and velocity-time integral (VTI) using the continuity equation (AVA=CSA$_{LVOT}$×VTI$_{LOVT}$/VTI$_{AV}$) (87). A simplified method is the direct comparison of the peak flow velocity at the subvalve area and that across the aortic valve. Severe stenosis is present when the velocity ratio is 0.25 or less, corresponding to a valve area of 25% normal. This method has also been proved to be very accurate in confirming severe AS in patients with poor overall LV systolic function (88). The principles of imaging prosthetic valve function are similar to those used in the native valve (89).

Patients with poor LV systolic function may present with low-flow low-gradient state (effective AVA <1.0cm², LVEF <40% and mean gradient pressure <30-40mmHg), peak gradient across the valve becomes not accurately representative of the stenosis severity. Mild-to-moderately diseased valves may not open fully due to depressed LV function, resulting in a "functionally small valve area" (pseudosevere AS). In these patients dobutamine stress echocardiography is recommended to differentiate true severe AS from pseudosevere AS (20).

LV function

LV hypertrophy in AS results in a small ventricular cavity with thick walls and diastolic dysfunction. The cavity size and volume can be easily measured from M-mode and 2D imaging. LVEF, a marker of global systolic function, is usually measured using the modified Simpson's model. The LV diastolic function is evaluated from ventricular filling pattern; transmitral E wave, A wave, E/A ratio and E/Em. Myocardial velocities, displacement, strain and strain rate even twist function are measured during systole and diastole using TDI and 2D STE giving more information of LV function. Thus, Doppler echocardiography is an ideal non-invasive imaging technique for evaluating ventricular function before and after AVR.

RV function

The right ventricle is an integral part of the cardiac pump function. It is commonly normal in size and function in AS, except patients with severe LV disease and secondary pulmonary hypertension or those with coronary

artery disease, affecting the right ventricle. AVR has been shown to result in reversed septal motion which has previously been shown to correlate with the extent of drop in RV free wall amplitude of motion after surgical AVR (60).

Exercise echocardiography

Exercise echocardiography is now recommended in asymptomatic, normal LVEF AS patients for clinical decision-making (20). It provides prognosis information for such patients. The exercise capacity improves after AVR with the removal of LVOT obstruction, but the myocardial function during exercise remains unknown.

Based on the above knowledge of AVR and TAVI and their effect on ventricular function, the scientific motivation behind my four prospective studies in this thesis is:

I.   There is no direct comparison between AVR and TAVI with regard to their effect on septal motion and RV function.

II.   There is no evidence about the effect of AVR on LV twist function and its relationship to segmental function.

III.   The reversed septal motion after AVR results in potential loss of myocardial power of LV despite maintained overall systolic function, the exact explanation of this is not known. Therefore, we analyzed the LV function in great detail particularly of the lateral and septal wall in a group of AVR patients with normal EF.

IV.   AVR improves systolic and diastolic function. However, no objective study addressed the effect of AVR on patients' exercise capacity.

Objectives

The objectives of this thesis were to evaluate the left and right ventricular function after AVR compared to TAVI, and the patients' exercise capacity after AVR.

Study Ⅰ

To compare the LV and RV function after AVR and TAVI. AVR is known to result in reversed septal motion and reduced RV function. Our hypothesis is TAVI may improve LV and preserve RV function at early stage.

Study Ⅱ

To assess the effect of AVR on LV twist function. The twist function is exaggerated in AS patient, so we were set to assess the relationship between LV twist, global and segmental function and the effect of AVR on them.

Study Ⅲ

To assess in detail segmental LV function after AVR and potential relationships between septal and LV lateral wall. Our hypothesis is that LV free wall (lateral) may compensate for the loss of septal contribution to LVEF and stroke volume (SV) by its post-operatively reversed motion.

Study Ⅳ

To evaluate patients' exercise capacity after AVR, we hypothesized that despite complete alleviation of symptoms following AVR and normal LVEF, patients remain with compromised myocardial functional reserve.

Material and Methods

Study population

The studied AVR patients in the four studies are listed in figure 1. The 30 studied controls are the same in study Ⅰ-Ⅲ. The 20 TAVI patients were recruited especially for study Ⅰ. Another control group (n=21) who underwent exercise echocardiography participated in study Ⅳ.

AVR patients: I studied 30 consecutive symptomatic severe AS patients (mean age 62±11 year, 19 male) who underwent conventional AVR by the same surgeon (A. H.) and were recruited between 2007 and 2009. Severe AS was taken as a mean trans-valvular pressure drop (gradient) ≥40 mmHg and/or AVA <1.0cm². All patients had undergone cardiac catheterization before surgery to exclude high grade lesions, >50% narrowing, in any of the epicardial coronary arteries. Before surgery, all patients were in sinus rhythm, had normal LV dimensions and systolic function (EF>50%) and none had more than mild additional valve disease, or had underwent other valve or coronary artery bypass procedures. Other exclusion criteria included signs of raised left atrial pressure (E/A>2 and isovolumic relaxation time <50 ms), pulmonary hypertension (RV-RA peak pressure drop >40 mmHg), severely impaired RV function, or chronic obstructive pulmonary disease. Patients' clinical data were collected including New York Heart Association functional class (NYHA), EuroSCORE, pulmonary function, kidney function, history of hypertension, arrhythmia, stroke, diabetes or smoking. The AVR patients were followed up to 2 years after surgery and recalled for resting echocardiographic examination at 6 months, 1 year and exercise echocardiography at 2 years after surgery.

TAVI patients: In addition, I studied 20 consecutive symptomatic severe AS patients (mean age 79±6 year, 14 male) who were deemed unsuitable for surgical AVR because of either technical reasons or serious co-morbidities as judged by EuroSCORE or the Society of Thoracic Surgeons (STS) scoring system. The patients had mean trans-valvular pressure gradient ≥ 40 mmHg and/or AVA <0.8cm². They were carefully studied by the Heart Centre multidisciplinary team and recruited for TAVI procedure, having fulfilled the
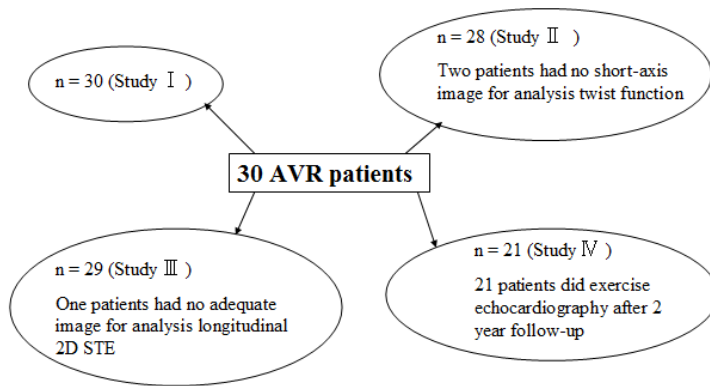
Figure 1 AVR patients in the 4 studies

published suggestions for inclusion (62). Seven patients were operated on for being technically high risk/inoperable (5 with earlier CABG with midline left internal mammary artery (LIMA) and 2 with porcelain aorta). The remaining 13 were recruited based on a EuroSCORE >20% and/or STS score >10%. The TAVI patients were followed up for six weeks after procedure.

Controls: Healthy individuals were randomly selected from the Swedish tax bureau register constituted the control group, none of whom had any cardiovascular or systemic disease or risks. Thirty controls (mean age 63±11 year, 16 male) were enrolled in study I -III and another 21 controls (mean age 57±9 years, 14 male) who underwent exercise echocardiography were included in study IV.

All studied subjects had given an informed consent to participate in the study, which was approved by the Regional Ethics Committee of Umeå.

AVR and TAVI procedure

Surgical AVR

Conventional surgical procedure for AVR was adopted in AVR patients group. The aorta was cannulated just proximal to the innominate artery and the

right atrium was cannulated in the area of the appendage using a two-staged venous cannula. Extracorporeal circulation was then established with mild to moderate hypothermia and a standard AVR procedure was performed during cardioplegic arrest. Cold crystalloid or cold blood cardioplegia was delivered antegradely and/or retrogradely. Both mechanical and bioprostheses were used according to the surgeon's own assessment and preference.

TAVI procedure

All TAVI patients received general anesthesia and a left sided anterolateral mini-thoracotomy was performed, opening the anterolateral segment of the pericardium near the apex to avoid puncture of the septum and to guarantee an adequate wall thickness where healing of the ventricular wound can be guaranteed. External temporary pacing wires were attached to the LV and the thin portion of the apex was identified by finger palpation and confirmed by transesophageal echocardiography. Two orthogonal U-shaped sutures were then placed in the myocardium and passed through tension tourniquets. An arterial needle puncture allowed placement of a 6F sheath through the apex into the LV cavity using a standard over-the-wire technique. A stiff support wire was passed to the descending aorta and the sheath was upgraded to 26F. Under rapid ventricular pacing, balloon aortic valvuloplasty was performed. The valve was delivered under fluoroscopy and transesophageal echocardiography guidance for optimum positioning.

Echocardiography

Echocardiographic examination

A Vivid 7 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with a phased array transducer (1.5-4 MHz) (Study Ⅰ-Ⅳ) and an IE33 ultrasound system (Philips, Bothell, WA USA) equipped with a broadband (1–5 MHz) S5-1 transducer (Study Ⅰ) were used. All images were acquired from the standard cardiac views according to the guidelines of the American Society of Echocardiography and were digitally stored for offline analysis (90). All recordings were made at a fast speed of 100 mm/s with a superimposed ECG. Off-line analysis was made using commercially available software (General Electric, EchoPAC version 8, Waukesha, WI, USA).

Conventional echocardiographic measurements

LA and LV cavity dimensions including septal and posterior wall thickness were taken from the parasternal long-axis view using the M-mode technique, according to the conventionally published criteria by the American Society of Echocardiohraphy (91). LV fraction shortening (FS) was calculated as the percentage fall of LV systolic dimension with respect to diastolic dimension. LV long-axis amplitude (mitral annulus peak systolic excursion -MAPSE) and RV long-axis amplitude (free wall tricuspid annulus peak systolic excursion -TAPSE) were obtained from the apical 4 chamber view with the M-mode cursor placed at the LV lateral and septal angles of the mitral annulus and RV free wall tricuspid annulus, respectively. MAPSE and TAPSE were measured as the distance between the innermost point and outermost point of the motion displacement. Trans-aortic valve velocity, peak gradient, and velocity-time integral (VTI) were obtained from the apical five-chamber view using pulsed and continuous wave Doppler, respectively. The aortic valve area (AVA) was calculated from LVOT diameter and VTI using the continuity equation (87):

$AVA = CSA_{LVOT} \times VTI_{LOVT} / VTI_{AV}$.

CSA_{LVOT} (cross sectional area) is calculated by $\pi \, (d/2)^2$ with d is LVOT diameter. VTI_{LOVT} and VTI_{AV} are flow velocity-time integral derived from Doppler LVOT and trans-aortic valve velocities.

LV volumes were measured at end–systole and end–diastole from the apical 4 chamber view and LVEF was calculated using biplane or single plane Simpson's model. SV was measured as the product of LVOT cross sectional area multiplied by its VTI. Cardiac output (CO) was determined as the product of the SV and heart rate. All volumetric data were adjusted to body surface area (BSA). LV filling velocities were acquired using the pulsed wave Doppler recording of the transmitral early (E) and late (A) diastolic velocities, then E/A ratio was calculated (92). LV filling time (FT) and ejection time (ET) were measured and relative filling and ejection times with respect to R-R interval were calculated and expressed as percentage (%). In addition, they were both multiplied (in seconds) by heart rate and then expressed as total ejection and filling times (s/min). From these measurements global synchronous LV function was assessed using the following parameters:

a) total isovolumic time (t-IVT) calculated as 60-[total ejection time + total filling time] (93)

b) Tei index calculated as the ratio between IVT and ejection time (94).

LV long-axis myocardial velocities Sm and Em were measured in systole and early diastole, respectively using pulsed TDI technique with the sample volume placed at the basal segments of the lateral and septal wall. E/Em was also calculated with Em was the average of septal and lateral values.

Septal radial motion

Systolic septal radial motion was measured as the extent of anterior septal motion with respect to its position in end-diastole using the M-mode technique from the parasternal long-axis view. Positive (+) motion was towards the LV cavity and negative (-) motion was towards the RV cavity.
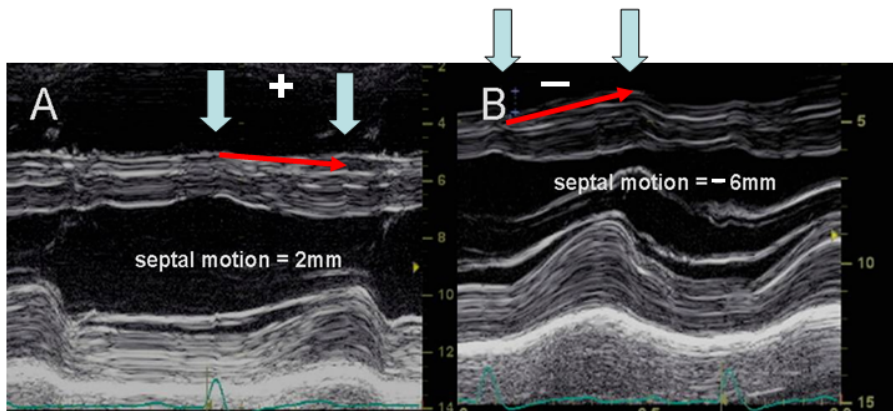

Figure 2 The measurement of septal radial motion in a healthy control (A) and an AS patient after AVR (B). In the control, it is towards the LV cavity (+2mm) and in the patient towards the RV cavity (-6mm) at end-systole with respect to end-diastole. AS = aortic stenosis; AVR = aortic valve replacement,

Speckle tracking echocardiography (STE)

Gray scale digital cine loops triggered to the QRS complex were acquired from the LV apical 4-chamber view and from the two LV short-axis planes at the basal and apical levels. Care was taken to ensure that the basal short-axis

plane contained the mitral valve. The apical plane was acquired as previously described (95). Segmental systolic strain, peak displacement and time from the onset of QRS to peak displacement were analyzed from the LV apical 4-chamber view. Rotation and twist were measured from the short-axis views. At each plane, three consecutive cardiac cycles were acquired during quiet breath-hold at a frame rate of approximately 70 f/s, without using dual focus, and were stored on a hard disk for off-line analysis.

Twist function (Study Ⅱ)

It has been known for years that the heart rotates along its long-axis and a wringing (twisting) motion. Non-invasive echocardiographic measurement of rotation and twist function is an optimal tool for studies of cardiac mechanics of diseased and healthy hearts. Looking from the apex, the LV base rotates clockwise (negative value) and the apex rotates counter-clockwise (positive value), producing a wringing motion. The net rotation difference between apex and base is called twist.

The twist function before and 6 months after AVR were measured in this study. From the two LV short-axis planes at the basal and apical levels, rotation and twist were measured from STE. The region of interest (ROI) of the LV was set between the endocardial and epicardial borders, thus delineating the entire myocardial segmental circumference. The ROI width was adjusted as needed to fit the wall thickness, as previously described (96). The tracking quality of each segment was indicated by the software, and segments with insufficient tracking quality were excluded. Averaged apical and basal rotation data were used for calculating LV twist as previously proposed (96). Cavity systolic twist was calculated as the net difference of peak systolic LV rotation between the apical and basal short-axis planes (Figure 3).
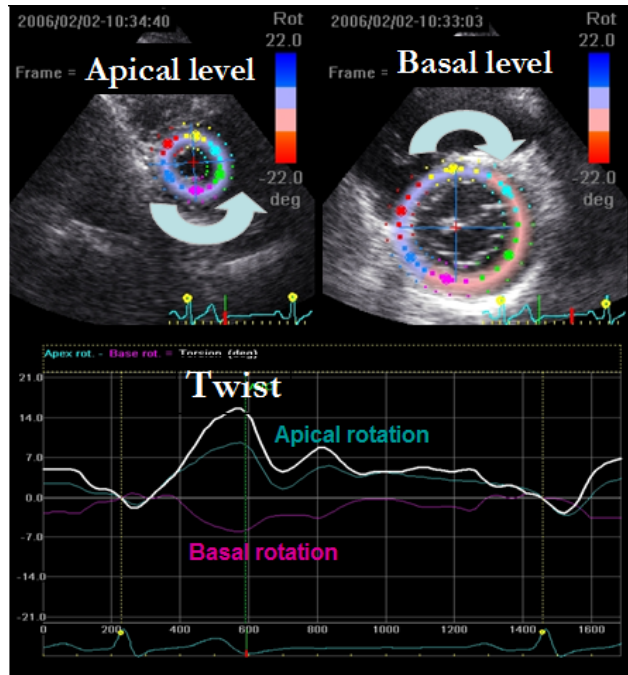
Figure 3 Systolic rotation and twist measurements by speckle tracking echocardiography. The twist is the net difference between apical rotation and basal rotation. The blue curve is apical rotation, the purple curve is basal ration and white curve is twist.
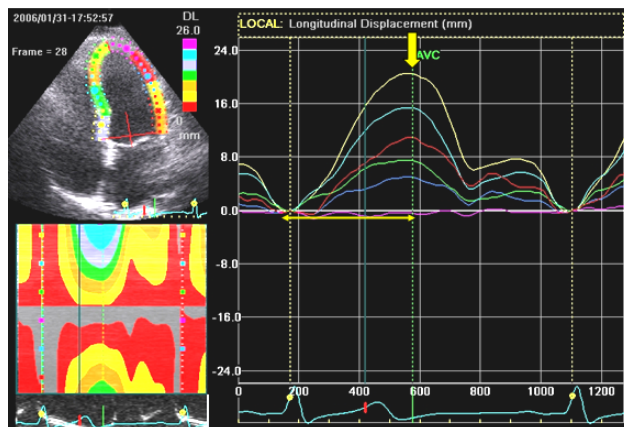

Figure 4 The measurement of peak longitudinal systolic displacement (vertical arrow) and time to peak displacement (horizontal arrow). The colored curves represent LV segments.

Strain and displacement (Study Ⅲ)

Through the cardiac cycle, the myocardial fiber length change in longitudinal, radial and circumferential direction. These changes can be measured by myocardial motion (velocity and displacement) and deformation (strain and strain rate). Strain (ε) represents the dimensional changes in myocardial fiber length relative to resting condition, strain rate (SR) reflects the speed at which such deformations take place. As the ventricle contracts, muscle shortens in the longitudinal and circumferential directions (negative value) and thickens or lengthens in the radial direction (positive value). The measurement of myocardial ε and SR offers a series of regional and global parameters that are useful in the assessment of myocardial intrinsic function. Currently, the ε and SR can be assessed by TDI and speckle tracking echocardiography (STE).

The velocity and displacement represent the motion of ventricular wall. Because of the relatively fixed position of the apex in the thorax, the mitral annular ring is pulled down toward the apex during systole. As a result, it has a base-to-apex gradient with higher velocity and displacement at LV base than near the apex. Beside the magnitude, velocity and displacement also have direction and can measure the longitudinal, radial and circumferential components which are especially relevant to the characteristics of myocardial mechanics. It should be noted that completely passive segments can show motion due to tethering, but without deformation.

In this study, we measured the LV segmental strain and displacement as well as time to peak displacement before, 6 months and 12 months after AVR. From LV apical four-chamber view, the LV cavity was traced manually from the innermost endocardial edge at end-systole from STE. The software automatically divided the LV long-axis into six segments (basal, mid-cavity and apical segments of the septal and lateral walls, respectively). LV systolic strain, peak displacement and time interval from the onset of QRS to peak displacement were measured from each segment of the LV. Mean septal and lateral systolic strain, peak displacement and time to peak displacement were calculated as the average of basal, mid-cavity and apical measurements, respectively (Figure 4). The time difference between septal and lateral wall peak displacement was also calculated. End systole was marked by the aortic valve closure time (AVC), defined as the artifact on the aortic pulsed Doppler velocity recording.

Exercise echocardiography (Study IV)

Supine ergometer exercise test

The AVR patients were recalled to perform exercise echocardiography after 2 years follow-up in this study. A semi-supine (slightly left lateral) bicycle exercise test (GE ergometer, model 900, Ergoline GmbH, Germany) with an increasing workload (10 watt) every 2 minutes was used. The workload started at 30 watt and the Borg scale for exertion level was reported and blood pressure was taken using cuff sphygmomanometer. Oxygen consumption (VO_2) measurements were continuously collected using Metamax breath by breath system (CORTEX Biophysik GmbH·Nonnenstrasse 39·D-04229 Leipzig·Germany). The mean value of VO_2 was continuously calculated within 10 seconds and the peak exercise value (pVO_2) was taken. A 12-lead ECG was continuously monitored throughout the exercise, and recorded on paper at the end of each stage to exclude any evidence for exercise related myocardial ischemia or arrhythmias. The exercise was stopped if the patient developed limiting breathlessness/chest discomfort, ST segment depression of ≥1mm, more than three consecutive ventricular premature beats, or hypotension (defined as a fall in systolic blood pressure of at least 20 mmHg from baseline). Exercise end point for controls was exhaustion. Brain natriuretic peptide levels (BNP) from venous blood sample were also analyzed before and at peak exercise.

Exersise echocardiographic measurements

Beside the resting echocardiography, additional five consecutive loops of the 4-chamber view with and without color Doppler were acquired at the last minute of each work load and were stored digitally. Measurements were made at all exercise (Ex) stages. In this study, I presented data from the following stages:

1) Pre Exercise = immediately before exercise (resting echo)

2) Submaximal Exercise = at a heart rate (HR) of 100-110 bps

3) Peak Exercise = at Borg scale of level 17

4) at 4 minutes after Peak Exercise

From the apical 4 chamber view, global longitudinal strain rate (GLSR) was studied using STE with the same technique described in study Ⅲ. GLSR was measured as the mean of six segments from the apical 4 chamber view (basal, middle and apical level of septal and lateral walls). From the acquired recordings, systolic (GLSRs), early (GLSRe) and late diastolic (GLSRa) strain rate were measured (Figure 5). When filling was of the summation pattern, the single diastolic wave was taken as the GLSRe. LV longitudinal SR was a negative value during systole (SRs) and positive value during diastole (SRe and SRa). In this study, the systolic SR was presented as positive value in order to avoid any potential confusion when the linear regression model is performed.
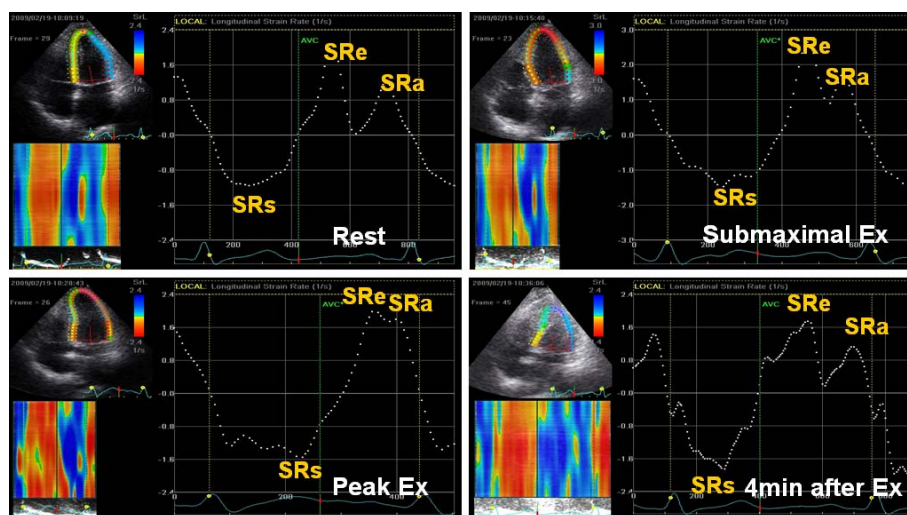

Figure 5 The measurements of systolic and diastolic global longitudinal strain rate during exercise (Rest, Submaximal Ex, Peak Ex and 4 minutes after Ex).

Statistical analysis

The statistical analysis was undertaken using a standard statistical software package (SPSS 18.0, SPSS Inc.). Normally distributed data was presented as mean ± standard deviation (SD) to describe a central tendacy and variation. Categorical variables were expressed as percentage (%). Unpaired Student *t*-test was used to compare the data between different groups. Paired Student *t*-test was used to compare the data before and after AVR or TAVI. Linear regression (Pearson's coefficient) was performed to identify the correlations. A p<0.05 was considered as statistical significance.

Study Ⅰ

Because of the different patients' number in TAVI and AVR group, the non-parametric Mann-Whitney U test was additionally used to recheck the significance of differences.

Study Ⅲ

Repeated measures ANOVA with Tukey post-hoc test was used to test difference between before, 6 months and 12 months after AVR in patients.

Study Ⅳ

Univariate linear regression (Pearson's coefficient) was performed to study the correlation between pVO_2 and echocardiographic parameters. The variables in the univariate regression model which reached p<0.05 entered into multiple regression model.

Reproducibility

In study Ⅲ and Ⅳ, intra- and inter-observer variabilities were assessed in 10 randomly chosen subjects for STE LV wall peak displacement and time to peak displacement measurements, and LV GLSR measurements at rest and during exercise, respectively. The variability was presented as coefficient of

variation which was calculated as the ratio of the standard deviation of the variables to their corresponding mean from the original data set (97).

Results

Clinical characteristics of the studied population

All AS patients had degenerative aortic valve stenosis.

TAVI patients were significantly older than AVR patients (p<0.001) and had more risk factors (high NYHA, higher EuroSCORE and createnine, p<0.05 for all). Eleven patients (55%) had coronary artery disease (CAD). Two of the TAVI patients had atrial fibrillation before and 1 week after procedure, at the time of echocardiographic examination. All 20 TAVI patients survived a successful procedure and up to 6 weeks and 90% of them achieved six weeks (6.7±2.2 week) follow-up.

Twelve patients in the AVR group proved to have bicuspid aortic valve at the time of surgery. Two patients had paroxysmal atrial fibrillation immediately after AVR, which recovered before hospital discharge. No patient developed bundle branch block or interventricular conduction delay during the 2 years follow-up period.

Table 1 Clinical characteristics of AVR, TAVI patients and controls in study Ⅰ-Ⅲ

	Controls (n=30)	TAVI (n=20)	AVR (n=30)	p (TAVI vs. AVR)
Age, years	63±11	79±6	62±11	<0.001
Male/Female	16/14	14/6	19/11	0.13
NYHA I,II,III,IV	-	0,0,13,7	1,17,12,0	<0.001
Diabetes	-	4 (20%)	5 (17%)	0.72
Smoking	-	7 (35%)	16 (53%)	0.27
Hypertension	-	15 (75%)	16 (53%)	0.07
Stroke	-	6 (30%)	4 (13%)	0.13
Createnine, μmol/ml	-	104±48	79±21	0.02
EuroSCORE	-	19.3±8.3	4.0±2.1	<0.001
STS	-	17.1±5.6	-	-
ECC, min	-	-	95.9±24.8	-
OT, min	-	-	70.5±18.4	-

All values are presented as mean ± SD. NYHA=New York Heart Association clinical class; STS = the Society of Thoracic Surgeons scoring system; ECC = extracorporal circulation time; OT = occlusion cross-clamping time; TAVI = trans-catheter aortic valve implantation; AVR = aortic valve replacement.

Study Ⅰ: Trans-catheter aortic valve implantation – early recovery of left and preservation of right ventricular function

Purpose

To compare the LV and RV function after AVR and TAVI. AVR is known to result in reversed septal motion and reduced RV function. Our hypothesis is TAVI may improve LV and preserve RV function at early stage.

Before procedure

Seven patients (14%) had LVEF <50% in the TAVI group and hence the LVEF was lower than that in the AVR group in which LVEF was normal (54±8.3 vs. 65±6.7%, p<0.001). E/A ratio (1.3±0.7 vs. 0.9±0.2, p=0.04) was higher and LA was larger (42±5 vs. 36±5 mm, p=0.001) in the TAVI patients indicating worse LV systolic and diastolic function than AVR patients. The two patient groups had similar AS severity and degree of LV hypertrophy. The LV and RV long-axis function, septal radial motion as well as relative filling time (FT) were not different between the two patient groups although they were all lower than controls (p<0.05). TAVI patients had longer t-IVT (9.3±3.2 vs. 7.2±2.3 s/min, p<0.05) than AVR patients, while the Tei index was not different between groups.

After procedure

LV function: After 1 week of procedure, the two patient groups had similar drop in aortic valve gradient (14.7±5.7 vs. 16.8±6.3 mmHg, p=ns). Although LVEF remained unchanged after 1 week of both procedures, the patients with lower LVEF (in the TAVI group) showed significant rise from 46±5.7 to 57±4.5% (p=0.02). The LV long-axis amplitude of motion was not changed in both group after procedure except AVR resulted in a slight increase in lateral long-axis amplitude (12.4±1.9 vs. 11.4±1.5 mm, p=0.03). At 6 weeks of TAVI, the LVEF had increased (60±5.3 vs. 54±8.3%, p=0.05) as well as long-axis amplitudes (p<0.05), LV E/A fell (p=0.01), relative FT increased (p=0.04) and LA diameter decreased (p=0.04). NYHA class fell from 3.3±0.5 to 1.9±0.4 (p<0.001) compared to before procedure.

Septal radial motion and RV function: AVR resulted in approximately 70% drop in TAPSE from 21.6±5.0 to 9.2±3.2 mm (p<0.001) and significantly reserved septal radial motion (-2.6±3.8 vs. 4.5±1.4 mm, p<0.001) as shown 1 week after surgery (Table 2). Neither of these changes occurred in the TAVI patients (Figure 6). The extent of reversed septal radial motion correlated closely with that of TAPSE in the patients group as a whole (r=0.78, p<0.001), showing significant downward sliding of the post-AVR values along the line of identity compared to those of TAVI which did not change after procedure (Figure 7). TAPSE and septal radial motion remained unchanged in the TAVI group up to 6 weeks after procedure.

Table 2 Septal radial motion and TAPSE in patients before and after TAVI and AVR

	TAVI (n=20)			AVR (n=30)		
	before	1 week	p	before	1 week	p
Septal motion, mm	5.0±2.9	4.4±2.8	0.19	4.5±1.4	-2.6±3.8	<0.001
TAPSE, mm	19.8±4.6	17.6±2.5	0.06	21.6±5.0	9.2±3.2	<0.001

All values are presented as mean ± SD. TAVI = trans-catheter aortic valve implantation; AVR = aortic valve replacement; TAPSE = tricuspid annulus peak systolic excursion.
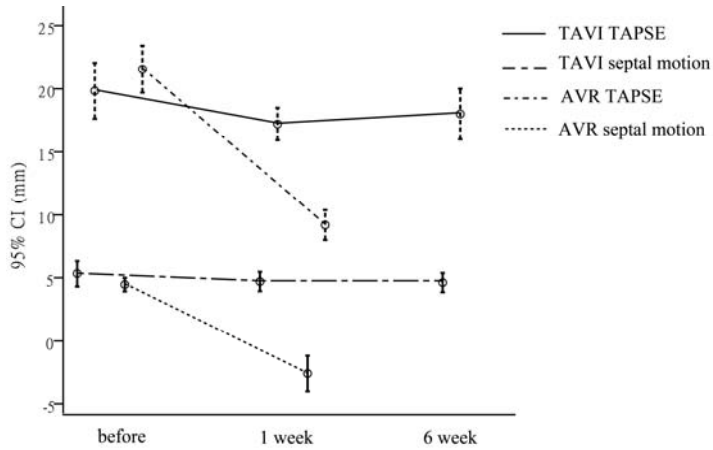
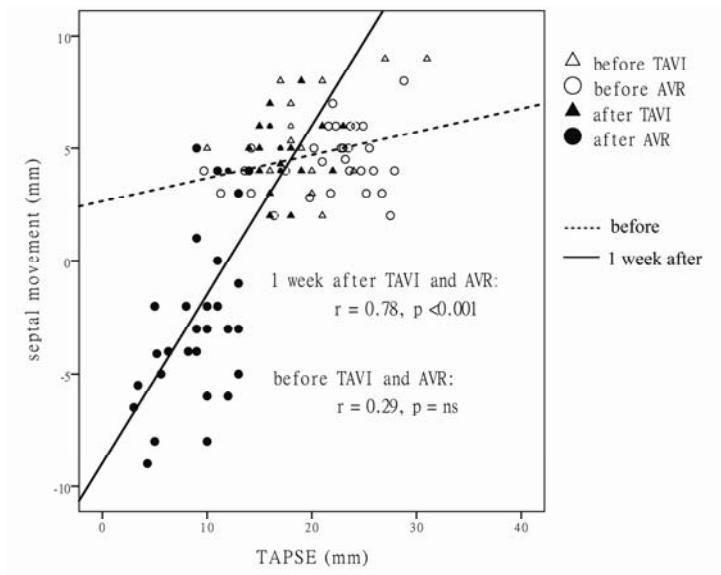**Figure 6** The changes of septal radial motion and RV TAPSE in TAVI and AVR patients.

Figure 7 Correlation between septal radial motion and TAPSE before and 1 week after TAVI and AVR.

Study Ⅱ: Aortic valve replacement normalizes left ventricular twist function

Purpose

To assess the effect of AVR on LV twist function. The twist function is exaggerated in AS patient, so we were set to assess the relationship between LV twist, global and segmental function and the effect of AVR on them.

Before AVR

Despite preserved LV dimensions, EF and FS, patients had reduced LV lateral and septal systolic long-axis amplitudes and myocardial velocities (p<0.05) before AVR. LV hypertrophy (p<0.001), reduced E/A (p<0.01) and increased E/Em (p<0.001) indicating abnormal systolic and diastolic function at baseline. Peak apical systolic rotation (13.0±5.8° vs.7.6±2.6°, p<0.001) and cavity twist (19.7±5.7° vs. 12.9±3.2°, p<0.001) were significantly increased but not basal systolic rotation when compared to controls.

6 months after AVR

LV dimensions and EF did not differ from before. FS increased (43±5 vs. 38±7%, p<0.01) and LV hypertrophy regressed (p<0.001). LV lateral and septal systolic long-axis amplitudes and myocardial velocities all significantly increased (p<0.05) and E/Em decreased (p<0.01). The exaggerated apical rotation and LV twist normalized (Table 3).

Relationship between components of LV function (Figure 8&9)

LV twist correlated strongly with LVFS (r=0.81, p<0.001) in controls. This relationship was significantly less in patients before AVR (r=0.52, p<0.01) and was completely lost after AVR (r=0.34, p=ns). While, LV twist (r=0.19, p=ns) was not related to EF in controls, it was modestly related in patients pre-operatively (r=0.53, p<0.01) and less so after AVR (r=0.40, p<0.05).

Table 3 LV rotation and twist function in controls and patients before and after AVR

	Controls (n=28)	Pre AVR (n=28)	p	Post AVR (n=28)	p (pre vs. Post AVR)
Basal rotation, °	-5.3±2.5	-6.2±3.0	ns	-5.8±2.7	ns
Apical rotation, °	7.6±2.6	13.0±5.8	<0.001	8.6±4.6	<0.001
Twist, °	12.9±3.2	19.7±5.7	<0.001	14.4±5.2	<0.001

All values are presented as mean ± SD. AVR = aortic valve replacement.
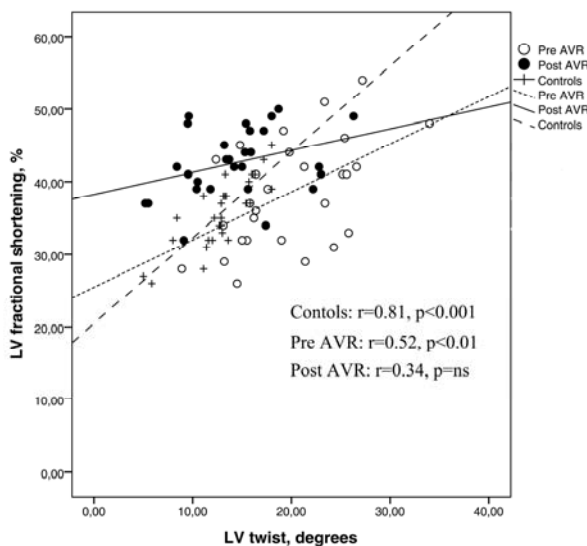

Figure 8 Scatter plot between LV fractional shortening (LVFS) and LV twist in controls and in patients before and after AVR.
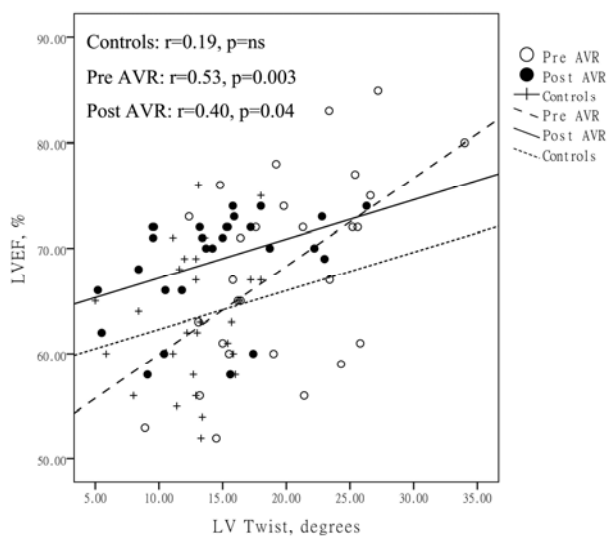
Figure 9 Scatter plot between LV ejection fraction (LVEF) and LV twist in controls and in patients before and after AVR.

Study Ⅲ: Accentuated left ventricular lateral wall function compensates for septal dyssynchrony after valve replacement for aortic stenosis

Purpose

To assess in detail segmental LV function after AVR and potential relationships between septal and LV lateral wall. Our hypothesis is that LV free wall (lateral) may compensate for the loss of septal contribution to LVEF and SV by its post-operatively reversed motion.

LV structure and function

Patients had maintained LV cavity size, EF and SV before, 6 and 12 months after AVR. Before surgery, LV mass and wall thickness were increased ($p<0.001$), septal and lateral Sm ($p<0.05$) and Em ($p=0.01$) were reduced hence E/Em was raised ($p<0.001$). Six months after AVR, LV hypertrophy regressed ($p<0.01$), Sm, Em and E/A were all increased ($p<0.05$) and E/Em reduced ($p<0.05$). Twelve months after AVR, all these measurements remained unchanged with the LV wall thickness, mass and E/Em were still higher than controls ($p<0.05$). There was no difference in cycle length between the recordings we made the measurements from.

Septal radial motion

Before AVR, septal radial motion was reduced (4.5 ± 1.5 vs. 6.7 ± 1.9 mm, $p<0.001$) and fell further (0.5 ± 3.4 mm, $p<0.001$) at 6 months after surgery. At 12 months, it increased, towards the LV cavity but still remained significantly less than controls (3.5 ± 2.9 vs. 6.7 ± 1.9 mm, $p<0.001$).

LV segmental longitudinal function (Table 4 and Figure 10)

Septal and lateral strain were less than controls ($p<0.001$) before AVR and the lateral strain increased ($p<0.05$) after surgery. Before AVR, peak septal and lateral wall longitudinal displacement and time to peak displacement were not different from controls. Six months after AVR, peak septal displacement decreased ($p<0.001$) but lateral wall displacement increased

(p<0.01), with the time to septal peak displacement prolonged (p<0.05) and that of the lateral wall becoming early (p<0.05). The septal-lateral time difference between the two segments became significantly prolonged than before AVR and controls (p<0.001). Twelve months after AVR, septal peak displacement remained lower (p<0.05) and lateral wall peak displacement higher than pre-op values (p<0.01). The time to septal peak displacement recovered to pre-operative values while that of the lateral wall remained earlier (p<0.01 compared with pre-op). The net septal-lateral time difference was not different from pre-operative values but remained longer than controls (71±71 vs. 23±46 ms, p<0.01).

Table 4 LV segmental function before and after aortic valve replacement (AVR)

	AS	6 months after AVR	12 months after AVR	p
Septal strain, %	-16.1±3.1	-17.2±3.6*	-17.8±3.6	0.10
Lateral strain, %	-17.2±4.7	-20.1±4.8*	-19.6±4.8	0.03
Peak displacement, mm				
septal	11.3±2.6	8.3±2.5*	9.1±3.3*	<0.001
lateral	9.3±2.6	11.4±3.8*	11.3±3.8*	<0.001
Time to peak displacement, ms				
septal	414±56	456±66*	419±68#	0.03
lateral	373±32	355±42*	349±27*	0.02
septal and lateral difference	41±62	101±54*	71±71	<0.001

All values are presented as mean ± SD. AS = aortic stenosis; AVR = aortic valve replacement.

*: compared with before, p<0.05

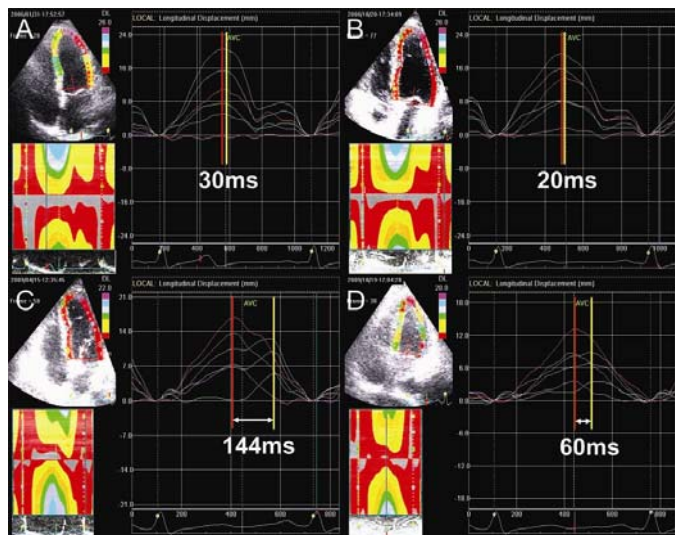#: compared with 6 months, p<0.05

Figure 10 An example of the time to septal (yellow line) and lateral wall (red line) peak displacement and time delay between the two segments. The septal-lateral time delay was 30ms (A) in controls, 20ms, 144ms and 60ms before (B), 6 months (C) and 12 months (D) after AVR, respectively.
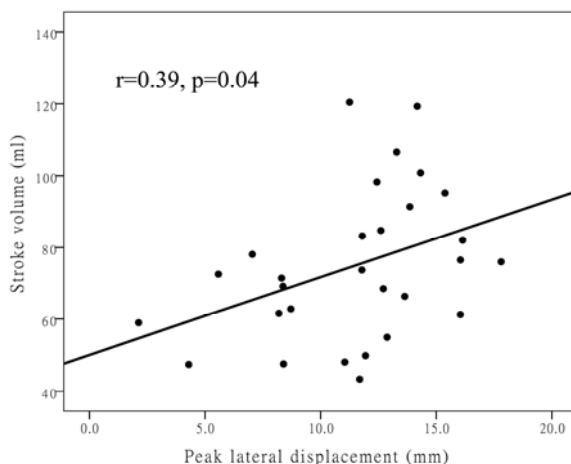

Figure 11 Relationship between LV stroke volume and lateral wall peak displacement (r=0.39, p=0.04) after 6 months of AVR.

The relationship between LV global and segmental function

After 6 months of AVR, the lateral wall peak displacement was correlated with SV (r=0.39, p<0.05), time to septal peak displacement (r=0.60, p<0.001) and septal-lateral time delay (r=0.64, p<0.001) and septal strain (r=-0.40, p<0.05) (Figure 11&12). The lateral strain correlated with septal displacement (r=-0.58, p=0.001). There was no correlation between these measurements before and 12 months after AVR.
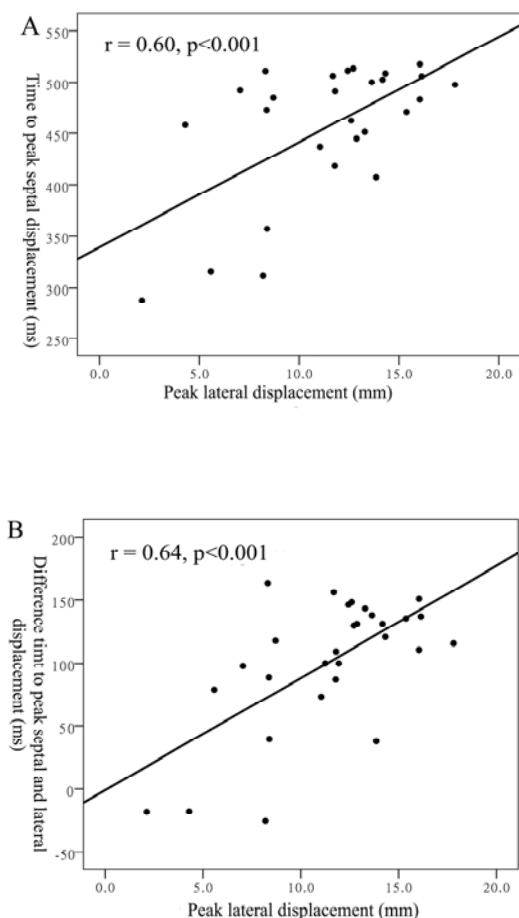

Figure 12 The relationship between lateral wall peak displacement and time to septal peak displacement (A) and the time difference between septal and lateral walls (B) 6 month after AVR.

Study Ⅳ: **Residual compromised myocardial contractile reserve after valve replacement for aortic stenosis**

Purpose

To evaluate patients' exercise capacity after AVR. We hypothesized that despite complete alleviation of symptoms following AVR and normal LVEF, patients remain with compromised myocardial functional reserve.

Baseline data

Age and gender were comparable between patients and controls. Ten of the 21 AVR patients had additional systemic hypertension causing a slightly raised mean systolic blood pressure values compared with controls ($p<0.05$), 3 had diabetes, 3 had previous strokes. BNP was significantly raised in patients (73 ± 72 vs. 14 ± 11 ug/ml, $p<0.001$) but remained within conventional limits of LV dysfunction. LV cavity dimensions and EF were not different between groups, but septal and posterior wall thickness were still higher ($p<0.01$) in patients than controls after 2 years follow-up. E/A was not different.

Exercise echocardiography (Table 5)

Exercise echocardiography was successfully performed in all subjects who reached Borg scale of level 17, without any complications. Peak VO_2 was lower (18.5 ± 4.5 vs. 22.1 ± 4.3 l/min/kg, $p<0.05$) and the BNP level was higher at peak exercise (103 ± 82 vs. 25 ± 22 ug/ml, $p<0.001$) in patients compared to controls.

Conventional echocardiographic measurements

LVEF, HR and LV volume indices were not different between the two groups at rest. However, at submaximal and peak exercise, patients had significantly lower EF ($p<0.001$) and higher indexed LVESV ($p<0.05$) although they achieved similar HR, CO and indexed SV with respect to controls. Patients had limited increase in EF ($p<0.05$) and CO ($p<0.05$) than controls during exercise. 4 minutes after exercise, all these parameters recovered to normal level.

Septal and lateral Sm, E/Em were comparable between the two groups but patients had lower Em (p<0.01) at rest. At submaximal and peak exercise, septal and lateral Sm and Em in patients were lower (p<0.01) and E/Em higher than controls (p<0.01). Consequently, the delta change of these parameters between rest and peak exercise were less (p<0.05) but E/Em was higher (p<0.05) in patients. The change in Em was not significant but had a tendency to be lower in patients (p=0.08). 4 minutes after exercise, septal and lateral Sm, Em were still lower (p<0.01) and E/Em higher (p<0.01) than controls but within normal range.

LV longitudinal strain rate

GLSRs and GLSRe were not different between groups at rest. At submaximal and peak exercise, both systolic and early diastolic SR were significantly lower (p<0.01) in patients than controls. The magnitude of increase in GLSRs and GLSRe between rest and peak exercise was also lower (p<0.05) in patients than controls. 4 minutes after exercise, the longitudinal strain rates had recovered to normal values with no difference from controls (Figure 13).

Table 5 The cardiac function parameter changes between rest and peak exercise in patients and controls

	Patients (n=21)	Controls (n=21)	p
EF, %	6.68±9.60	13.97±9.10	0.02
CO, l/min	2.49±3.02	4.43±2.68	0.04
Lateral Sm, cm/s	3.57±3.98	5.74±2.09	0.03
Septal Sm, cm/s	2.29±2.23	4.63±2.29	0.002
E/Em	1.66±2.73	-0.33±3.11	0.03
GLSRs, 1/s	0.18±0.32	0.68±0.27	<0.001
GLSRe, 1/s	0.14±0.48	0.70±0.93	0.03

All values are presented as mean ± SD. LVEF = left ventricular ejection fraction; CO = cardiac output; Sm = systolic myocardial velocity; Em = early diastolic myocardial velocity; GLSRs = global longitudinal systolic myocardial strain rate; GLSRe = global longitudinal early diastolic strain rate.
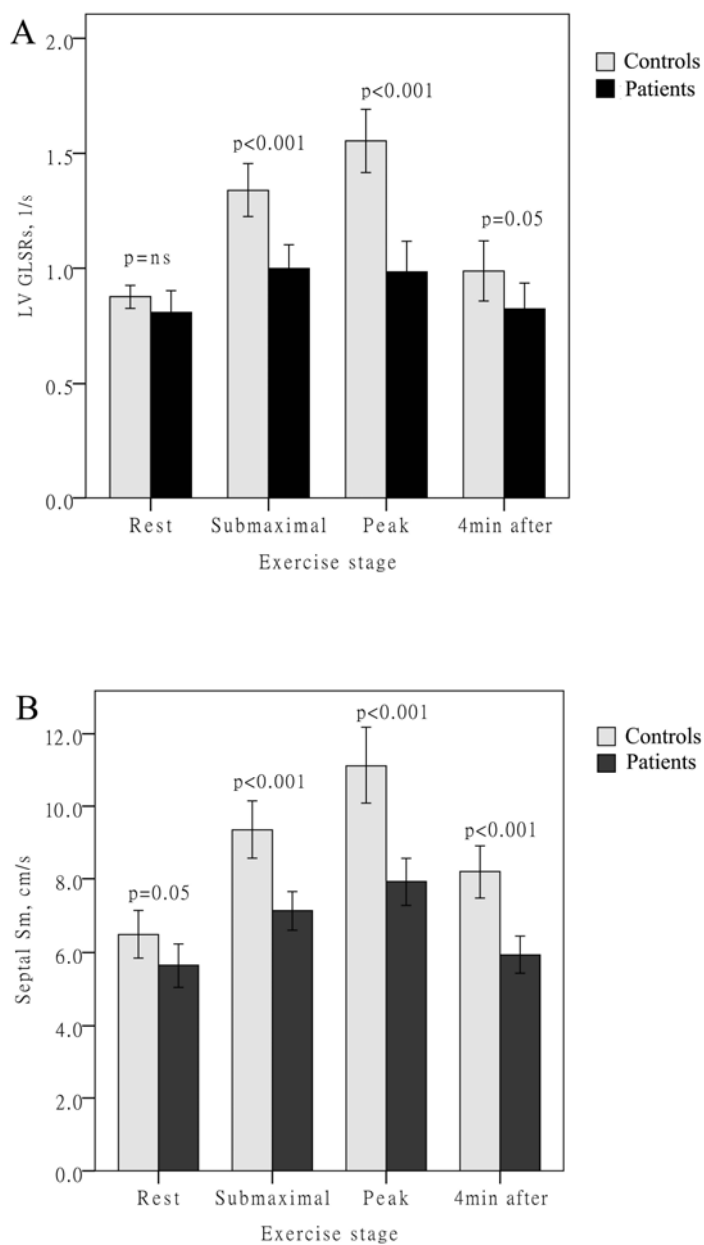
Figure 13 LV GLSRs (A) and septal Sm (B) comparison between patients and controls during exercise.

Relationship between pVO₂ and cardiac function parameters (Figure 14)

There was no correlation between pVO₂ and any echocardiographic measurements in controls. In patients, pVO₂ correlated with peak exercise GLSRs (r=0.60, p=0.007), septal Sm (r=0.65, p=0.002), and Em (r=0.57, p=0.009) in the univariate regression analysis but not resting measurements. In the multivariate analysis, GLSRs at peak exercise (β=7.18, p=0.03) was the only independent predictor of pVO₂ in patients.
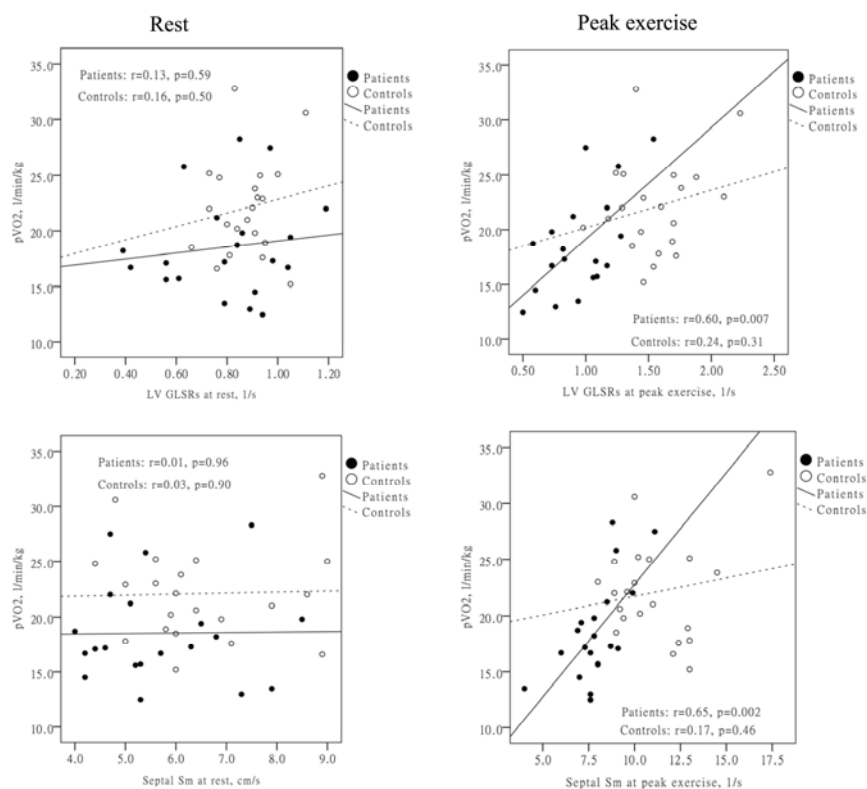

Figure 14 Correlations between pVO₂ and LV GLSRs, septal Sm at rest and peak exercise in patients and controls. In controls, there is no correlation between pVO2 and GLSRs and septal Sm at rest or at peak exercise. In patients, pVOs is correlated with GLSRs and septal Sm at peak exercise but not at rest.

Reproducibility

Twist: The reproducibility of cardiac rotation and twist measurements of our laboratory has been previously reported, being 5-19 % (98).

Displacement: The coefficient of variation of septal and lateral peak displacements and their timings were: 2.9%, 3.1%, 7.1% and 5.7% for intra-observer. Respective values for the inter-observer reproducibility were 3.2%, 3.5%, 8.8% and 9.1%.

Exercise strain rate: For intra-observer reproducibility, the coefficient of variation of GLSRs at rest, submaximal exercise, peak exercise and 4 minutes after exercise were: 8%, 10.4%, 8.6% and 8.8%. GLSRe at rest, submaximal exercise, peak exercise and 4 minutes after exercise were: 9.1%, 9.8%, 11.1% and 8.7%. Respective values of GLSRs for the inter-observer reproducibility were 12.6%, 12.1%, 11.1% and 11.9%. GLSRe were 8.6%, 12.9%, 13.4% and 10.4%.

Discussion

In this thesis, we focused on the ventricular function after AVR in a series of severe AS patients, the recovery of LV and RV function compared to TAVI procedure (study Ⅰ), the twist function (study Ⅱ), the mechanism of the LV maintaining global EF and SV (study Ⅲ) and the exercise capacity after AVR procedure (study Ⅳ). The main findings in these studies are the different effect of AVR and TAVI on LV and RV function. AVR results in significantly reserved septal radial motion and depressed RV long-axis function, while after TAVI, septal radial motion and RV long-axis function were fully preserved. TAVI patients also had early recovery of LV function particularly in those with reduced EF. The exaggerated twist function preoperatively also normalized after AVR, but the twist lost its relationship with the basal LV function, represented by FS. Furthermore, the septal peak displacement decreased and became delayed after AVR due to the reversed septal radial motion. The LV lateral wall peak displacement became augmented and peaked early, in order to maintain the global EF and SV, this enhanced function correlated with the SV and septal time delay. Finally, the exercise capacity (pVO_2) after AVR was limited as was the increase in EF, longitudinal strain rate and myocardial velocities during exercise compared to controls. In multiple regression analysis, the systolic global longitudinal strain rate at peak exercise was the only independent predictor of pVO_2 in the patients group.

TAVI protection of RV function

Although LVEF was maintained after AVR, the reversed septal radial motion and reduced RV long-axis amplitude of motion were well known (61). In contrast to AVR, TAVI patients had fully preserved septal radial motion and RV long-axis function and these findings were confirmed by Forsberg et al (81). Efforts were exhausted to explain the exact mechanism behind such LV and RV functional disturbances after AVR but without great success (99, 100, 101). Recently it has been suggested that such changes are related to opening the pericardium (102). We are somewhat sceptical about this idea for a number of reasons. First, we have previously shown in a controlled trial format that leaving the pericardium open or repairing it after AVR does not

affect early RV functional disturbances (60). Second, we have also shown that intrinsic RV function in a similar group of patients remained intact after AVR, but what really holds the tricuspid annular motion was the reduced right atrial myocardial strain as a result of intra-operative cannulation (60). Third, our findings in the TAVI patients further support this argument, since all patients had small pericardiotomy, although at a different site from that of the AVR, and the right atrium was not cannulated, hence the preserved RV long-axis motion.

The pattern of LV function recovery after TAVI is of interest, showing early improvement of systolic and diastolic function, particularly in patients with low EF before procedure. The continued improvement of function in those patients and the prolongation of filling time highlight the important role of the 'time factor' for reverse remodelling. It seems therefore that early functional recovery is related directly to the outflow tract obstruction and the delayed ones, i.e. total isovolumic time (t-IVT), reflect normalized synchronous LV function, as previously shown after AVR (103). Finally, the difference in the effect of the two procedures on RV function is similar to previous findings in patients undergoing surgical and device closure of atrial septal defects (104).

Twist function after AVR

The twist function was increased in AS patients as a compensation for the reduced longitudinal function. This exaggerated function normalized after AVR, however, the relationship between LV twist and basal region, shown by FS, was lost. To interpret our results, a clear appreciation of LV normal anatomy, in particular myocardial fibre architecture is essential, with the basal circumferential, longitudinal and oblique fibres controlling basal, long axis and rotation function, respectively. In our patients with AS and normal EF, the nature of long axis and cavity twist abnormalities were similar to what has previously been described, with the long axis function reduced and apical rotation and cavity twist function exaggerated (55, 57, 59). The apical rotation is commonly noticed by cardiac surgeons as soon as the chest is opened, and tends to reduce by the end of procedure. We have noticed similar findings in our patients in whom the apical rotation and cavity twist

normalized after AVR as did long axis amplitude and velocity, while EF remained unchanged. This behaviour suggests a potential interaction between long axis function and twist function although we could not demonstrate such relationship statistically in our relatively small group of patients. Also, the relationship between twist and EF before AVR suggested that the exaggerated twist compensated for the decreased long-axis function in order to maintain a normal global cavity function. As long-axis dysfunction improved after AVR, this relationship became weak. On the other hand, there was a dynamic relationship between the three different LV functional components according to individual events. These changes might be related to the removal of the high LV afterload by AS. While normally twist correlated strongly with basal systolic function (LVFS), this relationship fell in patients and was lost after AVR. The loss of such relationship after AVR suggests a surgery related additional factor which has interfered and disturbed the preoperative synchronous function. It is known that septal motion, which contributes to the twist function, becomes reversed after AVR (61), and hence, redirecting systolic myocardial power to the right side and consequently affecting the twist function. The increased FS after AVR might be related to the augmented posterior wall motion as an attempt to compensate for the disturbed septal motion and to maintain global systolic function after AVR.

Accentuated lateral wall displacement after AVR

As shown above, the septal radial motion reversed and RV long-axis function reduced after AVR as well as the twist function lost its relationship with the basal LV function. These results showed subclinical LV disturbances after surgery, despite preserved global function throughout the study. The mechanism of how LV could maintain its function had never been studied. In this study, we showed the depressed and delayed septal peak displacement which may be related to the reversed septal motion after AVR. Most interestingly was the accentuated and earlier peaking of LV lateral wall after AVR which was maintained up to 12 months. This accentuated behavior correlated with the SV and septal time delay as well as the septal-lateral time difference. These findings suggested that the lateral wall which is relatively distant from the direct site of potential myocardial injury is compensating

for the loss of myocardial power generation by the septum. Furthermore, our results demonstrate that this is not a mere suggestion but is indeed an evidence for segmental interaction based on the correlation between lateral wall peak displacement and the degree of septal-lateral dyssynchronous time relation. Such relationship appeared only after AVR and was not there pre-operatively neither was it there in controls, thus suggesting the development of post-operative functional dependence between the two segments. The obvious aim for it is maintaining overall LV pumping function i.e SV. This was proved by the modest relationship we found between the SV and the lateral wall peak displacement. Finally, since these changes existed even at 12 months after AVR, we suggest that they could be considered as a manifestation of continuous LV reverse remodeling in order to maintain optimum SV, independent of mass regression which is known to be completed by the 6th month after AVR (42). This has clearly been confirmed in our patients who showed progressive fall in LV mass for 6 months after AVR. Finally, the correlation we found between systolic strain and the opposite wall displacement confirms a significant inter-segmental relationship which matures at 6 months after AVR but becomes less so at 12 months, by the time reverse remodeling is potentially completed.

Limited exercise capacity after AVR

Exercise provokes greater peripheral oxygen demands which requires reciprocal increase in myocardial global and segmental function (105). Our AVR patients had normal systolic and diastolic function at rest. At peak exercise, patients had less pVO_2 than controls. Also with exercise, patients demonstrated global as well as segmental systolic and diastolic dysfunction in the form of attenuated increase in EF, global strain rate as well as segmental myocardial velocities at both submaximal and peak exercise. During recovery, myocardial velocity measurements remained abnormal while the GLSRs and GLSRe had already recovered to resting values. And in a multivariate regression model, only GLSRs at peak exercise correlated with pVO_2 in the patients group.

Our patients showed attenuated change of CO with stress but no difference at the same exercise and heart rate level from controls, suggesting maintained myocardial oxygen demand-supply balance, similar to controls.

No patient had symptoms during exercise or signs of myocardial dysfunction based on ECG and 2D echo analysis. However, we found clear evidence for global myocardial dysfunction, in the form of limited EF rise, and global strain rate as well as indirect signs of raised filling pressures. In addition, there was clear evidence for abnormal segmental function in the form of limited rise of myocardial velocities with exercise. The combination of these disturbances was not an incidental finding but was related to pVO_2 suggesting a direct relationship. Furthermore, myocardial function disturbances were the main predictor of pVO_2.

In the absence of exercise induced ischemic dysfunction, particularly in the setting of aortic stenosis and dramatic increase of pre-operative afterload we can not ignore the potential role of subendocardial fibrosis in explaining our findings. With disease progression, the myocardial perfusion is decreased and systolic wall stress is increased due to myocardial hypertrophy. These disturbances predominantly affect the subendocardial layer in the form of ischemic dysfunction followed by fibrosis (106). The extent of myocardial fibrosis has been found to closely correlate with longitudinal myocardial function "subendocardial" in patients with increased pressure-afterload (107, 108). This has been previously reported at rest, but now it seems to have a significant effect on patients' exercise capacity. Such disturbances of LV function is unlikely to be related to AVR, which itself resulted in myocardial mass regression and improvement of overall cardiac function, but more likely reflect the chronic effect of outflow tract obstruction on the myocardium. The current guidelines recommendation of AVR for AS depends on symptoms, which commonly occur when patients develop ventricular disease, which might be, to some extent, irreversible despite maintained EF, at rest (19, 20). Our findings therefore, reflect those disturbances in the form of compromised myocardial longitudinal SR reserve and limited EF increase with exercise. Although after AVR, the wall stress is hypothetically still higher than normal due to incomplete recovery of LV hypertrophy and the presence of fibrotic myocardium, the modest normal rise in BNP levels with stress roles out the possibility of significant residual raised wall stress as a potential mechanism. With a mean follow-up period of 2 years after AVR, it seems unlikely for such changes to recover. This finding is supported by the previously reported lack of improvement of exercise capacity after AVR despite improvement of resting systolic function (109). It

is also supported by histological findings after AVR, which showed incomplete regression of structural abnormalities of LV hypertrophy at intermediate follow-up and residually increased relative interstitial fibrosis which existed even 6-7 years after surgery (110).

Few studies have used exercise/stress echocardiography in assessing aortic valve substitute function (111, 112, 113). Most of them aimed at comparing patients exercise capacity and ventricular functional parameters' response to various valve substitutes. Our study is the first of its nature to assess objectively patients exercise capacity and cardiac function after AVR in comparison with normal. It is also the first to indentify significant myocardial functional disturbances which predicted exercise capacity. Similar findings need to be reproduced in a larger cohort of patients.

Clinical implications

Currently available guidelines recommend AVR for aortic stenosis only in symptomatic patients. The high-risk patients who are not suitable for surgery are recommended to receive TAVI. The TAVI procedure proved to result in better clinical outcome compared with both medical and surgical treatment, in high risk patients. Our studies demonstrated early post TAVI and AVR differences in LV and RV response to removal of outflow tract obstruction. In addition to the positive effect of TAVI on EF, its preservation of septal function favours it, particularly in patients with prior myocardial infarction who need the septum to optimize LV stroke volume. Although trans-apical TAVI approach involves apical myotomy it preserves the full integrity of the two ventricles. The lost relationship between LV twist and basal FS after AVR, and the accentuated lateral wall motion after AVR provide a clear understanding for the differential segmental behavior of the LV after AVR for AS and the means by which the left and right ventricles interact in order to maintain normal physiological SV. Follow up of such patients after AVR on the basis of the demonstrated segmental function changes is of particular importance. A fall in lateral wall displacement or delay in its peaking time suggests the likelihood of myocardial dysfunction eg. ischemia. Likewise, a completely normalized septal radial function may suggest a volume overload from either the mitral or aortic valve. Since reversed septal motion appears also in CABG patients (61, 100, 114), we presume that if patients did not have myocardial infarction before CABG,

these findings should be also applicable. Aortic stenosis results in reduced myocardial functional reserve which is likely to be irreversible, even after AVR. These disturbances could not be detected at rest but were associated with limited increase of exercise capacity. Therefore, they stress the hypothesis that earlier removal of the outflow tract obstruction even before symptoms develop might limit the irreversible myocardial damage.

Limitations

Despite the heterogeneity of this small cohort of patients, selected according to the current guidelines, findings seem to be consistent. The incidence of coronary artery disease was higher in the TAVI compared to the AVR group, but since the mechanical procedure in the two groups succeeded to equally remove the LV outflow tract obstruction and none of the patients underwent additional revascularisation, the changes we documented can only be seen to be directly related to AS procedures. There was significant age difference between TAVI, AVR and controls. This difference however, cannot explain the different response of LV and RV to the two procedures, since patients were their own controls for post-procedural comparison. We were unable to determine the exact post AVR time required by the septal and lateral walls to fully normalize since the follow up end-points were fixed. Likewise, we were uncertain whether the radial septal motion will continue to normalize after 12 months. Finally, our patients did not have an exercise test before AVR, since they all had symptoms which justified direct surgical intervention. We wished to assess the relationship between pVO_2 and the chronicity of aortic stenosis severity before surgery but these data were not available, since patients had most pre-operative studies at the referring centre/hospital. We can not exclude the impact of hypertension on the LV remodelling, twist function and longitudinal dysfunction at rest and during exercise, since 50% of our patients had documented hypertension. It is well known that there is normal difference in gender response to exercise (115), we were unable to assess similar difference in our study because of the small cohort. The small study number carries with it the common statistical limitations in the thesis.

Conclusion

AVR is an effective treatment for AS patients, but results in reversed septal motion and reduced TAPSE. The newly developed TAVI procedure improves LV systolic and diastolic function and maintains RV function which results in preservation of septal motion. In AS with maintained EF, the LV twist function is exaggerated and AVR normalizes it but loses its relationship with basal LV function. The reversed septal motion results in depressed septal displacement and time delay which are compensated for by the accentuated lateral wall displacement and the early time peaking. These disturbances almost normalize at 12 months of AVR. But the patients remain suffering from limited exercise capacity years after AVR. With the growing evidence on LV dysfunction in asymptomatic AS patients, similar findings may assist in identifying those needing surgery before LV damage becomes irreversible.

Acknowledgments

Fundings

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