

The changes in left ventricular structure-function relationship in aortic valve stenosis

WP Mistiaen^{1,2}

Abstract

Introduction

AVR in patients with calcified aortic valve stenosis relieves the left ventricle from pressure overload. Yet, congestive heart failure (CHF) is one of the complications observed, even years after the operation. The main questions are: why do patients still develop CHF? Which types of CHF can be expected? Which predictors are known?

Discussion

It has become clear that decrease in ejection fraction, which is the most commonly used parameter, occurs late in the course of aortic valve stenosis, when damage to the left ventricle has already been inflicted on this cardiac cavity. Several more sensitive imaging and Doppler parameters can demonstrate this damage earlier in the course of CAVS. This damage proves to be irreversible, at least in part. This explains the appearance of heart failure after aortic valve replacement. Although this type of heart failure is “diastolic” in nature, a continuum with the systolic type probably exists, at least in patients with aortic valve stenosis.

Conclusions

Damage to the left ventricle in patients with aortic valve stenosis can go unnoticed if only ejection fraction is used as parameter. Detection of more subtle changes, even in asymptomatic patients with severe aortic valve stenosis might lead to early replacement and hence less postoperative heart failure.

Introduction

Calcified aortic valve stenosis (AS) is the third most common acquired heart disease, which has a highly lethal course once it becomes symptomatic. Aortic valve replacement (AVR) is the only way to improve survival and to diminish symptoms such as exercise intolerance and dyspnea¹. These symptoms can be related to congestive heart failure (CHF) and appear late in the course of the disease. Occurrence of postoperative mortality² and CHF³ could indicate that such advanced changes of the left ventricle (LV) induced by AS are not fully reversible after AVR and that even diastolic CHF, with early changes of the LV, is not a benign condition. Therefore, patients who may benefit from AVR need to be identified before such changes

occur. Documenting the early changes in the structure-function relationship of the LV in patients with AS can be a first step. This involves the description of 1) morphological changes of the LV and 2) the repercussion on its function.

Discussion

Morphological changes of the LV

These changes include left ventricular hypertrophy (LVH), LV fibrosis and stiffness. LVH has been recognized as a repercussion of AS on the LV. It compensates for overload on the LV and helps to maintain LV ejection fraction (LVEF) and wall stress^{4,5,6}, at least in an initial phase⁷. LVH is the result of hypertrophy of the myocytes⁶ and of fibrosis^{5,8} and progresses as long as the overload continues. The ratio between LV mass (LVM) and LV end-diastolic volume increases in patients with AS. This indicates that the increment in LV mass exceeds the increase in LV dimension. Concentric and eccentric LVH can be distinguished and be related to diastolic and systolic CHF respectively⁹. LVH can be estimated by measuring the septal and posterior wall thickness using echocardiographically derived validated formulae^{4,5,10}. It can also be estimated reliably by cardiac MRI¹¹. Higher LVM is associated with lower LVEF and an increase in CHF, independent from the severity of AS. Absence of LVH, even in patients with critical AS, is considered favorable. LVH can be considered as maladaptive and not merely compensatory in patients with AS⁴. Fibrosis can be quantified by cardiac MRI^{12,13} as well as through biopsy¹⁴. It is the result of increase in collagen content of the myocardium. This can serve as measure for the severity of overload on the LV. Fibrosis can be considered as maladaptive LV remodeling⁶, and is multifocal¹². This process starts at the subendocardium and affects mainly longitudinal LV function (LVF), contributing to diastolic and systolic dysfunction^{8,14}. Although, there is a wide overlap in degree of fibrosis between healthy controls and patients with AS, fibrosis is more present with the latter¹³. This overlap might be due to the wide variation in fibrosis in patients with AS but a preserved LVEF. The degree of fibrosis does not correlate to the severity of AS. An elevation of several factors within the plasma correlates with collagen synthesis. Transforming growth factor-beta 1 and cardiotrophin-1 are cytokines which are implicated in the cellular and extracellular remodeling of the LV by inducing hypertrophy of myocytes and growth of fibroblasts⁶. Matrix metalloproteinases and their tissue inhibitors are involved in the remodeling of the cardiac extracellular matrix during overload conditions. These enzymes are in a delicate balance, which shifts to inhibition

*Corresponding author

Email: wilhelm.mistiaen@uantwerpen.be

¹ Artesis-Plantijn University College of Antwerp, Belgium

² University of Antwerp, Belgium

of matrix metalloproteinases during pressure overload of the ventricle. This results finally in accumulation of collagen⁶. Endothelin-1 has a pathologic effect on the cardiomyocytes and on the cardiac extracellular matrix¹⁵. Stiffness of the LV can be a surrogate for fibrosis and can be derived from pressure – volume relations as well as from echocardiographic studies⁶. Concentric LVH as well as stiffness can be considered as important contributors to increased LV end-diastolic pressure and to a delayed relaxation⁵. Changes in isoforms of titin contribute to stiffness of the LV wall. Titin is the largest sarcomeric protein and functions as a spring. It also limits the range of motion of sarcomeres under tension. This is responsible for the passive elasticity and stiffness of the myocardium. Titin connects the Z-line to the M-line within one sarcomere, thereby contributing to the transmission of forces at the Z-line and the I-band. The shorter isoform N2B is responsible for a higher degree of stiffness compared to the longer isoform N2BA. In patients with LV overload due to AS, the total content of titin does not alter, but the shorter isoform increases. This increase in stiffness can occur in the early stage of LVH, resulting in an increase in “passive tension” for any given length of sarcomeres. This might affect LV function¹⁶. Postoperative reversal of fibrosis and its consequences are not complete, in spite of normal LVEF¹⁷.

Functional changes of the LV

These parameters include LVEF, Tei-index, torsion-to-shortening ratio, longitudinal LVF, changes in the motion of the mitral annulus, and functional mitral regurgitation. The LVEF is widely used as estimation of LVF⁸ but this is only a crude measure. Normally, LVEF is considered above 50%¹⁸, but this has low discriminatory power to detect diastolic CHF⁹. The myocardium is not compressible. Hence, the subendocardial layers of a hypertrophied LV are pushed more inward, thereby squeezing its content in a larger degree (Figure 1). Therefore, one could expect that an LVEF of 50% already indicates a decrease in systolic LVF. The degree of reduction of LVEF is less in diastolic CHF compared to systolic CHF¹⁹. This has its importance: myocardial dysfunction starts early in the course of AS and can remain subclinical for some time. LVEF can remain above 50% during these changes. Hence, early irreversible damage to the LV needs detection by more sensitive methods such as estimation of a longitudinal LVF⁸. A large LV end systolic volume index predicts a loss in contractile reserve and a poor recovery of diastolic LVF¹⁸. A worse outcome can be predicted in patients with poor LVF and severe fibrosis¹². The isovolumetric contraction time (ICT) increases in patients with severe AS. This indicates a slower systolic contraction. A prolonged effort of the LV can present itself as a delayed peak of contraction. Subendocardial ischemia can be a possible mechanism⁷. The isovolumetric relaxation time (IRT) and reflects the diastolic emptying¹⁹. This is slower in patients with AS⁷. The Tei-index is the ratio between ICR+ICT and ejection time. This sensitive parameter is increased in patients with



Figure 1: shows the transection of the heart from caudal view. Note the thick-walled left ventricle with a small cavity. The inner part is displaced inside and squeezes blood out during systole. A part of the right ventricular wall is clearly visible.

AS and decreased LVEF. It analyses global LVF and is rather independent from heart rate, systolic and diastolic blood pressure²⁰. The Tei-index is decreased in patients with AS and still normal LVEF since IRT shortens and ejection time is prolonged. This index distinguishes between normal and decreased LVF in patients with symptomatic AS²¹. The Tei-index cannot be used in patients with arrhythmias and conduction defects²⁰. In patients with poor imaging qualities, the dP/dt ratio or the rate of pressure rise in the LV is an alternative index for LV performance. It is sensitive to changes in contractility²⁰. Determination of LV end-diastolic filling pressure on echocardiography can confirm the diagnosis of diastolic LV dysfunction in symptomatic patients with preserved LVEF²¹.

Torsion is caused by the counterclockwise rotation of the apical part of the LV while the basal part rotates clockwise, in apical view. This phenomenon is due to the spiral arrangement of the myocardial fibers, whereas the epicardial and endocardial helices are wound in an opposite direction: the subendocardial fibers are right-hand-oriented, the subepicardial are left-handed (Figure 2). All fibers experience the same force, but the epicardial fibers have a larger lever arm. Torsion contributes to the systolic thickening of the LV wall and to ejection of blood²². The torsion-to-shortening ratio (TSR) is consistent during systole. A uniform shortening of cardiac fibers is maintained by the relation between torsion and ejection. Torsion results in coiling of the LV. The energy stored during systole is released during isovolumetric relaxation. This results in a suction and rapid filling of the LV²². A change of TSR indicates differences in trans-mural fiber contractions, for example by subendocardial ischemia in patients with AS. The peak systolic twist and the peak apical rotation of the LV increase proportionally with the severity of AS: subendocardial ischemia results in loss of the inhibiting effect of the subendocardial fibers²².

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Stiffening of the valvular plane and LVH might result in a decrease in basal rotation, with a compensatory increase in apical rotation, in order to maintain LVEF. Concentric LVH itself also leads to an increased torsion. AS also leads to a delay in relaxation and to a delay in the reverse of the apical twist²². Longitudinal LVF is determined by longitudinally oriented fibers. These subendocardial fibers are vulnerable to microvascular ischemia, resulting in contractile and relaxation abnormalities¹⁹. AS selectively decreases longitudinal LVF and strain²³ by a reduced coronary flow reserve and ischemia. Longitudinal LVF is not well reflected by LVEF, since the latter remains normal for a longer time²³. Hence, longitudinal LVF is more sensitive in detecting early myocardial damage in patients with AS^{8,24}. Longitudinal systolic LVF also correlates with fibrosis²⁴. Increase in circumferential and rotational strain can compensate the loss of longitudinal LVF, in order to maintain LVEF⁸, but in patients in patients with severely decreased LVF, this compensation is lost²³.

Longitudinal dyssynchrony is an important contributing mechanism in the progression of CHF and of LV remodeling⁸. LVH and fibrosis can lead to distorted electrical activation and hence impaired LV filling and dilatation of the LA¹⁷. Non-uniformity in the damage of cardiomyocytes may lead to dyssynchrony and non-uniform regional LV dysfunction. Longitudinal dyssynchrony has an adverse effect on diastolic and systolic LVF. Radial and circumferential strain seem to be less affected by AS. Time course indicated that with increasing severity of AS, longitudinal LV dysfunction leads to dyssynchrony⁸. Connexin 43 is an important protein in the gap junctions and is up-regulated as a response to

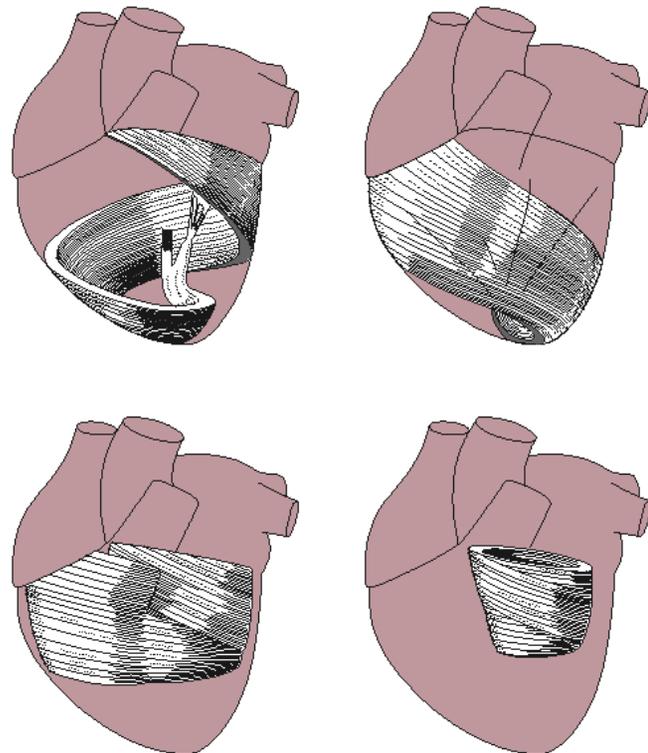


Figure 2: The orientation of the cardiac muscle fibers is shown. The top right explains the counterclockwise rotation of the apical part – seen from apical view. The top left shows fibers, which originate from the papillary muscles. The lower right part gives an indication of the subendocardial fibers (source: <http://www.bem.fi/book/06/06.htm>).

overload of the LV. In compensated LVH, cardiomyocytes enlarge, with increase in contractile proteins, assembly of new sarcomeres and improved contractility. There is also an increase in gap junctions and connexin 43 and hence, improvement in conduction. However, the more lateral location of connexin 43 might contribute to ventricular arrhythmias²⁵. When LVH decompensates, the expression of connexin 43 reduces and the distribution of gap junctions becomes heterogeneous. Non-uniform distribution of connexin 43 can lead to a non-uniform propagation of the electrical stimulation, to conduction defects and fatal arrhythmias²⁵.

Systolic displacement of the mitral annular ring towards the apex reflects global long axis (Figure 3) LVF^{20,24} and can be used as surrogate for LV longitudinal strain²⁶. The velocity of the mitral annulus displacement does not depend on pressure gradients, as is the case for blood flow²⁷. This velocity reflects the rate of change in LV long-axis dimension and LV volume, which on its turn is related to global LVF and to myocardial relaxation²⁰. In a diseased LV, relaxation can become non-uniform, which lessens the correlation between mitral annular velocity and global LV relaxation²⁷. Velocities and amplitudes of the mitral annulus seem to be more sensitive for systolic LVF compared to LVEF. This mitral annular plane systolic excursion (MAPSE) has several components: longitudinal, rotational and translational. MAPSE decreases in AS. Some

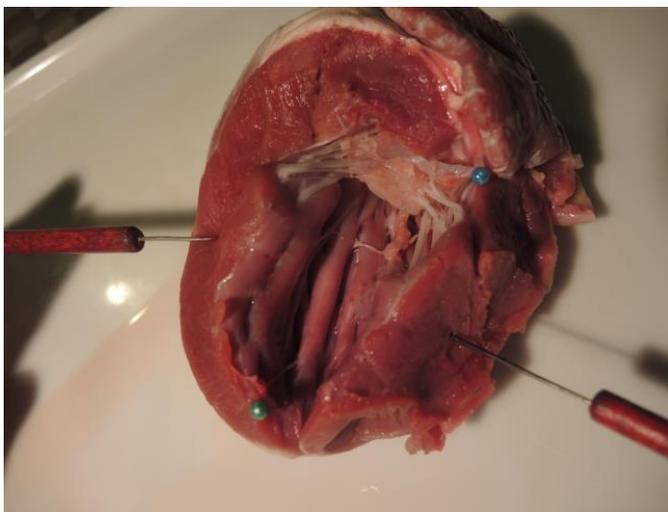


Figure 3: The left ventricle is opened and a part of the antero-lateral half is removed. The posterior half is visible and the thickened wall can clearly be seen. The mitral valve, with both leaflets and chordae tendineae is also visible. The longitudinal axis is indicated by the distance between the green pinhead, located at the apex and the blue pinhead, at the mitral annulus. This distance represents the long axis, which shortens during systole. This shortening gives an indication of the mitral annular plane systolic excursion (MAPSE). This relative shortening represents the longitudinal left ventricular function.

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cut-off values have been determined. If it is below 7 or 8 mm, it indicates an LVEF below 50%, a value of 10 mm or more is linked to a LVEF of at least 55%. It is doubtful, however if this relation is valid in LVH and hence, in most patients with AS. Moreover, MAPSE cannot detect small myocardial abnormalities²⁰. Deceleration time can be measured from the mitral annular excursion¹⁹ and represents diastolic LVF. A shortened deceleration time during mitral inflow indicates a restrictive filling. The parameter E is the early diastolic peak of trans-mitral flow²⁷ and could represent LA pressure and diastolic LVF^{18,28}. The parameter E', represents early diastolic lengthening⁹ or mitral annular motion and serves as indicator for diastolic dysfunction²⁸. The early annular diastolic velocity decreases in AS²⁹. The parameter A is the late trans-mitral diastolic filling, which increases in AS²⁷. Therefore, the E/A ratio or the ratio between early and late trans-mitral LV filling velocity^{10,15} decreases in AS. The E/E' ratio corrects for the influence of myocardial relaxation on the trans-mitral flow E. Since it combines the influence of the trans-mitral driving pressure with myocardial relaxation, E/E' is a better parameter for diastolic dysfunction^{9,27,28} and for LV end-diastolic pressure²⁹. E/E' is increased in patients with AS and rises more during exercise, compared to healthy controls. A value of 8 or less predicts normal mean LV diastolic pressure, while a value of 15 points to an increased mean diastolic LV pressure⁹. In patients with a value between 8 and 15, the parameter A can be an alternative²⁷.

Functional mitral regurgitation (FMR) is rather common in patients with AS³⁰. It is the consequence of tethering of the chordae tendineae during dilatation of the LV or of LVH. It can be graded from absent, mild, moderate to severe³¹. FMR is associated with larger ventricles. Patients with FMR have a tendency for more co-morbid conditions³⁰. The close anatomical and physiological relationship, the so-called aorto-mitral coupling could add to FMR in patients with AS²⁶. There is a fibrous continuity between the mitral and the aortic valve³². AS affects the mitral annulus dynamics. During LV systole, the mitral annulus contracts and pulls at the fibrous region, enlarging the aortic annular area. This facilitates systolic ejection. Conversely, during LV diastole, the mitral annular area expands. This improves LV filling. Hence, there is a mutual facilitation of the function of both valves²⁶. FMR leads to a reduced torsion and recoil rate²².

Conclusion

AS causes a remodeling of the complete left sided heart. The LV becomes stiff and fibrotic. The filling pressure increases and subtle changes of the LVF might occur in the earliest stage. When the LVEF starts to drop, the changes in the LV might already be irreversible, even when the patient is still asymptomatic. A high number of mutually related and partly overlapping imaging and Doppler derived parameters have been developed in order to detect these early subclinical changes. These parameters might be

helpful in more accurate timing of AVR and hence, improving postoperative results. The early stages of CHF might be called "diastolic". When LVEF drops, CHF could be called "systolic". Although some consider both types of CHF as two separate disorders, it seems reasonable to consider in the framework of AS, both conditions of a continuum: the diastolic type can evolve in the systolic type, during the progress of the valve disease. In patients with dyspnea and known AS with still preserved LVEF, increased volumes of LV, increased LV mass and increased E/E' or other Doppler derived parameters can establish the diagnosis of diastolic CHF. This has some importance since the prognosis of diastolic CHF is also ominous, even after AVR.

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