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Impact of Associated Significant Aortic Regurgitation on Left Ventricular Remodeling and Hemodynamic Impairment in Severe Aortic Valve Stenosis

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Key Words
Mixed aortic valve disease · Aortic stenosis · Aortic regurgitation · Left ventricular remodeling

Abstract
Objectives: The left ventricular (LV) response to combined pressure and volume overload [aortic stenosis (AS) and aortic regurgitation (AR)] versus pressure overload (isolated AS) has not been systematically studied. We aimed to assess LV remodeling, functional and hemodynamic consequences in patients with mixed aortic valve disease versus patients with isolated AS. ***Methods:*** We enrolled 181 patients (67 ± 9 years, 109 men) with severe AS (aortic valve area indexed to body surface area <0.6 cm^2/m^2) who underwent preoperative cardiac catheterization and a complete echocardiogram. Pulmonary capillary wedge pressure (PCWP), LV end-diastolic pressure (LVEDP) and pulmonary artery pressure (PAP) were measured. ***Results:*** One hundred and ten patients (group A) had isolated severe AS (AR 0–1) and 71 patients (group B) had mixed aortic valve disease (severe AS plus AR 2–3). Patients in group B were younger and in a higher New York Heart Association class ($p < 0.01$). Severity of AS was similar in both groups. Patients in group B had a higher indexed LV mass, a lower LV ejection fraction, and higher PCWP, LVEDP and PAP (all $p \leq 0.01$). ***Conclusions:*** Patients with severe AS and significant AR are more symptomatic than patients with isolated severe AS. The increased burden due to the combined lesion induces pronounced LV remodeling and more severe hemodynamic consequences.

Introduction

Aortic valve disease is an ongoing research focus due to its high prevalence and common difficulties in clinical decision-making, particularly in asymptomatic patients. Aortic valve disease induces left ventricular (LV) overloading resulting in LV remodeling (changes in LV size, function and geometry). LV remodeling was investigated both in aortic stenosis (AS, pressure overload) and in aortic regurgitation (AR, combined pressure and volume overload) [1–3]. There is little research on LV remodeling features in patients with mixed aortic valve disease, who represent a challenge for clinical decisions because evidence about best management is lacking. As such, current guidelines [4] recommend the selection of therapeutic in-

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terventions mainly on the basis of symptoms and hemodynamic consequences and not on the parameters assessing specifically the severity of both stenosis and regurgitation. The purpose of this study is to characterize the pattern of LV remodeling and the hemodynamic consequences in patients with mixed significant aortic valve disease.

We sought to answer the following questions. (1) Is LV remodeling more pronounced in patients with severe AS and significant AR than in those with isolated severe AS? (2) How does the degree of LV hypertrophy (LVH) correlate with LV systolic function and which are the determinants of LV mass in patients with aortic valve disease? (3) Does the combined pressure and volume LV overload in patients with mixed aortic valve disease induce more significant changes in LV function and intracardiac pressures than pressure LV overload in isolated AS?

Methods

Study Patients

The study included consecutive patients with severe valvular AS referred for left- and right-heart catheterization and coronary angiography. All patients had a comprehensive transthoracic echocardiography available for off-line analysis. Severe AS was defined as an indexed aortic valve area (AVAi, measured by the continuity equation) less than 0.6 cm^2/m^2, (AVAi <0.6 cm^2/m^2) [4]. We excluded patients with mitral stenosis, more than mild mitral regurgitation or valvular prostheses. Patients with inadequate acoustic windows were also excluded. Clinical, echocardiographic and invasive data were obtained for all patients.

Clinical Data

Demographic data, medical history (e.g. history of hypertension and diabetes mellitus) and data regarding the presence of angina, heart failure signs and symptoms and functional New York Heart Association (NYHA) class were obtained for all patients.

Echocardiographic Data

Within 48 h prior to cardiac catheterization, all patients underwent a comprehensive echocardiographic examination, including 2-dimensional, M-mode, color-flow Doppler and pulse/continuous-wave Doppler echocardiography, using commercially available ultrasound instruments. All echocardiographic data were stored for off-line analysis. Standard views and techniques were used according to the guidelines of the European Association of Echocardiography/the American Society of Echocardiography [5]. All parameters were calculated as an average of at least three measurements.

LV Assessment

LV end-diastolic diameter (LVEDD), LV end-systolic diameter and end-diastolic LV wall thickness [interventricular septum and LV posterior wall (PW)] were measured according to the guidelines [5]. Relative LV wall thickness, i.e. relative wall thickness (RWT) was calculated according to the formula: RWT = 2 × PW/LVEDD. LV mass was calculated by the equation of Devereux et al. [6] and was indexed to body surface area (BSA). Biplane LV volumes (end-diastolic and end-systolic) and LV ejection fraction (LVEF) were measured using the modified Simpson's rule from apical 4-chamber and 2-chamber views and were normalized to BSA.

AS Severity Assessment

The peak and mean aortic valve flow velocities were determined by continuous-wave Doppler echocardiography by systematically sampling the flow from different windows and the highest values were considered for analysis. The maximal instantaneous gradient across the aortic valve and the mean gradient were derived from aortic Doppler velocities by the modified Bernoulli equation. The aortic valve area (AVA) was calculated from the continuity equation as previously described [7] and was indexed to BSA.

AR Severity Assessment

AR was assessed by color Doppler [8]. There was a qualitative assessment for the presence/absence of AR and semiquantitative or quantitative for estimation of AR severity using the jet width/LV outflow tract width ratio, vena contracta width and parameters derived from the PISA method (regurgitant volume and effective regurgitant orifice area), according to the guidelines [8]. Considering these parameters, as well as data derived from continuous-wave Doppler in 5-chamber apical view (pressure half-time of AR flow) and from pulsed-wave Doppler in suprasternal view showing diastolic flow reversal in the descending aorta, AR was graded as mild (1), moderate (2) or severe (3).

LV diastolic function was evaluated by considering E wave and A wave velocities, E/A ratio and the deceleration time of the E wave obtained by pulsed-wave Doppler in 4-chamber apical view.

Hemodynamic Data

Left- and right-heart catheterization was performed in all patients using standard techniques [9]. Intracardiac pressures were measured at the beginning of the procedure, before administering any contrast. For the pressure measurement during left-heart catheterization, fluid-filled catheters were used. For the measurement of pulmonary artery pressure (PAP) and of pulmonary capillary wedge pressure (PCWP), Swan-Ganz catheters were used. Systolic, mean and diastolic PAP were measured. Cardiac output was measured by the Fick method or thermodilution, simultaneously with the measurement of transaortic pressure gradient when pulling back the conventional catheter from the LV into the aorta (pull-back technique) [10]. LVEDP was measured before pulling back the catheter into the aorta. Cardiac index was calculated from the ratio between the cardiac output and BSA. AVA was calculated by the Gorlin equation [11]. Selective coronary angiography was performed in all patients. Coronary artery disease was defined as the presence of at least one stenosis ≥50% at the level of at least one epicardial coronary artery.

Statistical Analysis

Continuous data were expressed as mean ± SD, and categorical data as percentages. For analysis comparing the 2 groups, the χ^2 test was used for dichotomous variables and the Student t test for continuous variables. Linear regression analysis was used to iden-

Table 1. Clinical characteristics of the entire study population and of the 2 subgroups, A and B

	Study population (n = 181)	Group A (n = 110)	Group B (n = 71)	p value*
Age, years	67±9	68±8	65±9	0.005
Men, n (%)	109 (60)	67 (61)	42 (59)	0.81
Hypertension, n (%)	55 (30)	31 (28)	24 (34)	0.42
Diabetes mellitus, n (%)	35 (19)	27 (24)	8 (11)	0.027
Angina, n (%)	69 (38)	44 (40)	25 (35)	0.052
NYHA class	2.2±0.9	2.0±0.9	2.4±0.9	0.008
Atrial fibrillation, n (%)	17 (9)	10 (9)	7 (10)	0.86

* Displayed p values refer to the difference between group A and group B.

Table 2. Echocardiographic data in the entire study population and in the 2 subgroups, A and B

	Study population (n = 181)	Group A (n = 110)	Group B (n = 71)	p value*
LVEDD, mm	52±8	50±7	55±7	<0.001
LV end-systolic diameter, mm	34±8	33±8	36±8	0.004
Interventricular septum, mm	13±2	13±2	13±2	0.45
PW, mm	13±2	13±2	12±1	0.41
RWT	0.50±0.11	0.52±0.12	0.46±0.09	0.001
LVEF, %	63±12	65±13	60±11	0.005
LV shortening fraction, %	35±8	35±8	34±8	0.59
Indexed LV mass, g/m^2	162±44	153±42	175±45	0.001
Mean transaortic gradient, mm Hg	53±15	52±14	54±17	0.34
AVA, cm^2	0.73±0.17	0.73±0.16	0.73±0.17	0.95
AVAi, cm^2/m^2	0.41±0.08	0.41±0.09	0.41±0.09	0.90
Ascending aorta diameter, mm	34.3±5.0	34.0±5.1	34.7±4.8	0.34
Transmitral flow E/A ratio	0.9±0.7	0.9±0.6	1.0±0.8	0.48

Values are means ± SD. * Displayed p values refer to the difference between group A and group B.

tify correlation between different parameters, and correlation coefficients were calculated by the Pearson method. Step-wise multivariable linear regression analysis was used to identify the independent predictors of indexed LV mass. Variables introduced in this analysis were those which performed best in the univariable analysis (at a significance level of $p < 0.10$). Probability values <0.05 were considered to be statistically significant. The statistical analysis was performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, Ill., USA).

Results

Clinical Characteristics

The final study population consisted of 181 patients: 109 men (60%) and 72 women (40%) with a mean age of 67 ± 9 years (35–83 years). Clinical characteristics of the entire study population are displayed in table 1. Most patients were symptomatic, 70% experiencing NYHA class ≥ II heart failure at the moment of cardiac catheterization, and 30% presented with NYHA class III and IV despite adequate medical treatment.

Echocardiographic Data

Table 2 presents the main echocardiographic data. In the whole study population, there was an increased LV mass with normal linear dimensions of LV chamber, thus the RWT was also increased. LV shortening fraction and LVEF were in the normal range overall. All 181 patients included in the study had severe AS, while 71 (39%) also had significant AR. According to the presence of significant AR, we divided the study population into 2 groups. Group A consisted of 110 patients (67 men) with isolated

Table 3. Invasive data obtained during left- and right-heart catheterization in the entire study population and in the 2 subgroups, A and B

	Study population (n = 181)	Group A (n = 110)	Group B (n = 71)	p value*
Systolic PAP, mm Hg	37±12	34±10	40±15	0.01
Mean PAP, mm Hg	24±8	22±7	26±9	0.002
Diastolic PAP, mm Hg	16±6	15±6	18±7	0.001
PCWP, mm Hg	15±7	13±6	18±8	<0.001
LVEDP, mm Hg	25±9	24±8	28±11	0.01
CI, l/min/m^2	2.8±0.5	2.8±0.5	2.8±0.6	0.58
AVA[a]	0.61±0.20	0.61±0.20	0.60±0.19	0.86
Coronary artery disease	52 (29)	34 (31)	18 (25)	0.42

Values are means ± SD and number (%).
* Displayed p values refer to the difference between group A and group B.
[a] According to Gorlin [11].

Table 4. Correlates of indexed LV mass in univariable and multivariable analyses in the entire study population

	Univariable analysis		Multivariable analysis	
	r	p	r	p
Age	0.03	0.65		
LV shortening fraction	–0.18	0.013		
LVEF	–0.19	0.011	–0.24	0.001
Transmitral flow E/A ratio	0.09	0.38		
Mean transaortic gradient	0.29	<0.001	0.33	<0.001
AVA(according to Gorlin [11])	–0.15	0.049		
LVEDP	0.14	0.053		
PCWP	0.15	0.041		
Systolic PAP	0.13	0.088		
Mean PAP	0.13	0.075		
Diastolic PAP	0.16	0.031		
AR severity (2–3 vs. 0–1)			0.16	0.022

severe AS (associated AR 0–1). Group B consisted of 71 patients (42 men) with severe AS and significant AR (AR 2–3), defined as mixed aortic valve disease. The echocardiographic characteristics of the 2 groups are also displayed in table 2.

Invasive hemodynamic data obtained during cardiac catheterization are presented in table 3.

Determinants of Indexed LV Mass

Clinical, echocardiographic and hemodynamic correlates of indexed LV mass are shown in table 4. In the entire study population, there were no significant differences in indexed LV mass between men and women (165 ± 48 vs. 156 ± 37 g/m^2, p = 0.20), patients with or without a history of hypertension (159 ± 44 vs. 163 ± 45 g/m^2, p = 0.64) or diabetes mellitus (152 ± 36 vs. 164 ± 46 g/m^2, p = 0.15), or with or without documented coronary artery disease (158 ± 41 vs. 163 ± 46 g/m^2, p = 0.53).

Indexed LV mass was significantly higher in patients with mixed aortic valve disease than in patients with isolated severe AS: 175 ± 45 vs. 153 ± 42 g/m^2 (p = 0.001). Indexed LV mass correlated with the presence of significant AR (AR 2–3). Also, by univariable analysis, indexed LV mass correlated with parameters of AS severity, especially with mean transvalvular gradient, and had a statistically borderline correlation with increased intracardiac pressures (LVEDP, PCWP and PAP, especially diastolic PAP) (table 4).

Of note is the significant inverse correlation between indexed LV mass and the parameters of global systolic LV

function (LV shortening fraction and LVEF), suggesting a decrease in systolic LV function with increasing LV mass in the study population.

In the multivariable linear regression analysis, the only independent predictors of indexed LV mass were parameters of valve disease severity, i.e. mean transaortic gradient and AR severity (direct correlation) and parameters of global systolic LV function, i.e. LVEF (inverse correlation) (table 4).

Clinical, Echocardiographic and Hemodynamic Differences between Patients with Isolated AS and Those with Mixed Aortic Valve Disease

Patients with mixed aortic valve disease were more symptomatic, with a significantly higher NYHA class than those with isolated AS (table 1).

The echocardiographic characteristics of the 2 groups (table 2) show that patients with mixed aortic valve disease had a significantly higher indexed LV mass, due to the significantly higher LV diameters. The RWT was higher in patients with isolated severe AS, demonstrating a predominant pattern of concentric hypertrophy in these patients. Of note, LVEF was lower in patients with mixed aortic valve disease than in those with isolated severe AS. The E/A ratio was similar in both groups. There were no differences between the parameters of AS severity in the 2 groups, so the significantly higher indexed LV mass in group B could not be explained by a more advanced degree of AS.

Invasive hemodynamic data (table 3) show similar AVA and cardiac index values in both groups. All intracardiac pressures were significantly higher in patients with mixed aortic valve disease.

Discussion

The main finding of our study is that in patients with severe AS, the coexistence of significant associated AR impacts symptoms, LV remodeling, systolic and diastolic function and hemodynamic consequences. Due to its increasing prevalence and major health burden, nowadays, AS is the most studied valvular heart disease. The current practice guidelines contain precise recommendations regarding the diagnosis and indications for surgery in AS [4]. Conversely, there is a lack of data on mixed aortic valve disease and this is why there are currently no specific guideline recommendations in this particular setting. Current guidelines on the management of valvular heart disease state that when stenosis or regurgitation occur, management should follow the recommendations concerning the predominant abnormality [4]. However, when stenosis and regurgitation have the same severity, indications for surgery should be based upon symptoms and objective consequences rather than on the parameters of this severity [4]. In the light of these recommendations, it becomes important to determine whether mixed aortic valve disease has a different morphological pattern and functional consequences than isolated AS. Accordingly, our study aimed at identifying structural, functional and hemodynamic changes (i.e. LV remodeling, systolic LV function and intracardiac pressures) which could impact on prognosis and guide therapeutic interventions in mixed aortic valve disease.

LVH is a major predictor of cardiovascular morbidity and mortality [12–13]. Determinants of LV mass in different studies are age, gender, body weight, hypertension, coronary artery disease and valvular heart disease (AS, AR and mitral regurgitation) [14–17]. Aortic valve disease induces LV pressure and/or volume overload, resulting in LV remodeling with increased LV mass and changes in LV geometry and function. The pattern of LVH is characteristic to each specific valvular abnormality but there is also variation in the geometric type of hypertrophy between individuals with the same valvular heart disease. This different geometry results in a different degree of adaptation to LV overload.

In our study, the degree of LVH in the entire study population was not influenced by gender, history of hypertension or coronary artery disease. Instead, LV mass correlated significantly with AS severity: patients with a higher mean transaortic gradient had a more pronounced LVH. Also, LV mass was higher in patients with more severe AR. Moreover, in the multivariable analysis, only mean transaortic gradient and AR severity emerged as independent predictors of LV mass, demonstrating the major role of aortic valve disease in inducing significant LVH in this setting.

The geometric pattern of hypertrophy impacts on LV function according to the law of Laplace. The consequence of an increased ratio between chamber radius and wall thickness is an increased wall stress [17]. Concentric LVH development in LV pressure overloading was considered to be a compensatory mechanism due to the normalization of wall stress by the increased wall thickness despite increased intracavitary LV pressure [18]. This paradigm of compensatory hypertrophy was outlined in early hemodynamic studies showing an inverse correlation between systolic wall stress and LVEF in patients

with AS or in clinical studies demonstrating a worse postoperative outcome in patients with increased wall stress and a lower LVEF [19–20]. Conversely, other clinical studies denied this paradigm, showing a deleterious effect of LVH in conditions associated with pressure LV overload such as AS. In one study [21], assessing ejection LV performance (expressed as mean normalized systolic ejection rate), LV contractility (expressed as peak velocity of shortening) and afterload (expressed as peak systolic circumferential wall stress) in patients with AS, an inverse correlation between ejection performance and wall stress was found, irrespective of the normal or impaired contractile state. So, whether hypertrophy is adequate or inadequate in terms of maintaining normal wall stress, advanced myocardial hypertrophy ultimately leads to decreased contractility. In a subsequent prospective study in patients with isolated AS, Kupari et al. [22] showed an inverse correlation between indexed LV mass and LVEF and a higher prevalence of LVH in patients with heart failure, concluding that LVH development favors heart failure onset rather than being a compensatory mechanism.

The impact of LVH on myocardial function in different overloading states was studied by Krayenbuehl et al. [23] in patients with LVH due to chronic pressure or volume LV overload. LV mass was similar in both overload states. LV contractility was decreased in patients with LVH but there were no significant differences in contractility between patients with pressure or volume LV overload, showing that the degree of LVH has more impact on LV contractility than the etiology of hypertrophy.

In our study, we found a significant inverse correlation between indexed LV mass and the parameters of global systolic LV function, and LVEF emerged as an independent predictor of LV mass in the multivariable analysis. These results suggest that in patients with severe aortic valve disease (all patients in our study had severe AS and 39% of them also had significant AR), in its advanced stages, at least, severe LVH is no longer a compensatory mechanism and becomes a maladaptive one, with a deleterious effect on systolic LV function.

Few previous studies investigated the clinical, hemodynamic and prognostic characteristics of patients with mixed aortic valve disease compared to those with isolated AS. Postoperative outcome was assessed in patients with isolated severe AS (n = 63) and severe AS plus moderate or severe AR (n = 59) having a similar preoperative NYHA class, LVEF and mean transaortic gradient [24]. Operative mortality and NYHA class were similar in both groups at 12 months after surgery, but at 18 months NYHA class III and IV were more prevalent in the patients with mixed aortic valve disease [24]. In the multivariable analysis, preoperative significant AR emerged as an independent predictor of reduced postoperative functional capacity. This could be attributed, at least in part, to a lesser improvement or even a deterioration in LV diastolic function after surgery for significant AR [25]. A recent retrospective cohort study performed in 306 patients (232 with isolated severe AS and 74 with mixed aortic valve disease) showed that associated significant AR worsens survival without cardiac death and hospitalisation due to heart failure, and that concomitant AR was an independent predictor of adverse events [26]. These results suggest that patients with severe AS and significant associated AR may benefit from early surgery.

Our results confirm these findings and provide the pathophysiological background for the worse outcome of patients with mixed aortic valve disease. Thus, even though these patients were younger than those with isolated severe AS, they were more symptomatic at the same degree of AS severity. Also, patients with mixed aortic valve disease had more pronounced LVH, a lower LVEF and higher left- and right-heart pressures at cardiac catheterization. These data confirm the detrimental effect of combined pressure and volume overload on intracardiac hemodynamics, systolic and diastolic function in patients with severe AS and significant AR.

In the multivariable analysis, mean transaortic gradient and AR severity emerged as independent predictors of indexed LV mass, demonstrating that aortic valve disease is a major determinant of LVH, independent of the presence of hypertension, coronary artery disease or diabetes mellitus.

This study shows that significant AR associated with severe AS has an incremental deleterious effect on symptom severity and on the consequences of valve disease in terms of anatomic remodeling (LVH), functional impact (LVEF) and hemodynamic impact (LV filling pressures and pulmonary pressures). These results suggest that earlier surgery should be considered in these patients, probably even before the onset of relevant symptoms.

Study Limitations

Our study has some limitations. First, it is a retrospective study. However, it included a relatively large number of patients, all of them having invasive data obtained by left- and right-heart catheterization. This included mea-

surements of LV pressure after crossing the stenotic aortic valve, which are no longer routinely performed today except in selected cases. Moreover, echocardiographic data were available for all patients and analyzed by experienced observers blinded to the invasive data. Another limitation of the study is the lack of tissue-Doppler-imaging-derived parameters of systolic and diastolic LV function (not routinely performed at the time when these patients were scanned). Still, direct measurements of LV filling pressures were available for all patients. Despite these limitations, our study provides additional insights into the clinical picture and structural, functional and hemodynamic changes in patients with mixed aortic valve disease, for whom the current available evidence for guiding therapy is still scarce.

Conclusions

Patients with mixed aortic valve disease have more severe symptoms, more pronounced LV remodeling, more reduced LV function, both systolic and diastolic, and more severe hemodynamic consequences than patients with isolated AS. This suggests that in patients with combined severe AS and AR, early intervention should be considered, probably even before the onset of relevant symptoms.

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