Left ventricular hypertrophy in aortic valve stenosis: preventive or promotive of systolic dysfunction and heart failure?

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Aims In aortic stenosis (AS), left ventricular (LV) hypertrophy is considered a compensatory response helping maintain systolic function. Recent research in experimental AS suggests, however, that LV hypertrophy is not necessary to sustain LV contractions but may in fact be maladaptive. The present work aimed to clarify the role of LV hypertrophy in AS-related heart failure (HF) in man.

Methods and results We studied 137 adult patients with isolated AS undergoing pre-operative echocardiography and cardiac catheterization. HF was diagnosed by the European criteria and LV hypertrophy by sex-specific limits of echocardiographic LV mass. The higher the LV mass was, the poorer was the LV ejection fraction ($\beta = -0.26$, $P < 0.001$, linear regression) and the greater the likelihood of HF independent of the severity of AS ($P < 0.001$, logistic regression). In the subgroup of critical AS (valve area $<0.4 \text{cm}^2/\text{m}^2$, $n = 85$), patients with absent LV hypertrophy ($n = 19$) had better preserved ejection fraction (mean $\pm$ SE, $64 \pm 3$ vs. $57 \pm 2$, $P = 0.045$) and less HF (16 vs. 48%, $P = 0.025$) than patients with LV hypertrophy ($n = 66$).

Conclusion In isolated AS, increased LV mass predicts the presence of systolic dysfunction and HF independent of the severity of valvular obstruction. LV hypertrophy may be maladaptive rather than beneficial in AS in man.

Introduction

The paradigm of compensatory cardiac hypertrophy says that in pressure overload states like hypertension and aortic stenosis (AS), left ventricular (LV) wall thickness and mass increase to maintain normal wall stress and unimpaired contractions.1,2 Accordingly, hypertrophy is an appropriate adaptive response although it may also bring along adverse consequences like proneness to ischaemia and impairment of diastolic function.2 Inherent in this train of thoughts is that insufficient hypertrophy leads to LV systolic dysfunction and heart failure (HF). Recent animal studies have shown, however, that a hypertrophic response is not necessary to sustain LV contractions but may in fact be maladaptive.3,4,5 These observations, backed by the prognostic notoriety of LV hypertrophy in man6 and by new insight into its molecular mechanisms,7,8,9 are challenging the time-honoured paradigm of compensatory hypertrophy. To clarify this issue, we examined the associations among LV mass, LV systolic dysfunction, and HF in patients undergoing echocardiography and cardiac catheterization for isolated AS. We found that both LV systolic dysfunction and HF were associated with increased LV mass independent of the severity of AS. Even in critically severe AS, normal systolic function and freedom from HF were associated with absence rather than presence of LV hypertrophy. 'Compensatory' LV hypertrophy may not be beneficial in AS.

Methods

Patients

We considered for the present study each adult patient referred to our institution between August 2000 and January 2003 for the evaluation of symptomatic, clinically significant AS. The exclusion criteria were a history of myocardial infarction or otherwise established coronary artery disease (CAD), more than mild aortic or mitral regurgitation or mitral stenosis, previous cardiac surgery, complicated diabetes, and renal failure (serum creatinine $>170 \mu\text{mol}/\text{L}$). Of a total of 174 patients screened for the study (without a formal power calculation), 37 either had at least one of the exclusion criteria or failed to consent. The remaining 137 patients (65 men) participated and underwent clinical examination, 6 min walk test, echocardiography, and cardiac catheterization with blood sampling for laboratory analyses. Their mean age ($\pm$SD) was 69 $\pm$ 10 years (range, 39–83). These tests, save for cardiac catheterization, were repeated 3 and 12 months after aortic valve replacement in a subgroup of 85 patients who were free of significant CAD at angiography and consented to LV biopsy at surgery.
We planned and conducted this work in compliance with the Declaration of Helsinki. The Ethics Committee of our hospital approved the study protocol, and all participants signed an informed consent document. The present report is based on the pre-operative clinical, echocardiographic, and invasive data in the total study population and on data from the 3-month post-operative assessment in the subgroup undergoing long-term follow-up. Our previous publications from the present investigation have dealt with the diagnosis of HF and with the pathobiology of the valve lesion in AS.\textsuperscript{11,12}

**Echocardiography**

The echocardiographic studies were done with an Acuson Sequoia scanner. The aortic valve and the left ventricle were studied as previously detailed from our laboratory.\textsuperscript{13,14} LV mass was calculated from the parasternal M-mode measurements using an anatomically validated formula.\textsuperscript{15} LV hypertrophy was diagnosed when LV mass index (LV mass/body area) exceeded 110 g/m\textsuperscript{2} in women and 134 g/m\textsuperscript{2} in men.\textsuperscript{16} Relative wall thickness was calculated from end-diastolic M-mode measurements as \( \frac{\text{septal thickness} + \text{posterior wall thickness}}{\text{LV cavity diameter}} \). Ejection fraction was determined by the Gorlin formula and indexed to body area. In patients in whom we could not cross the valve (\( n = 6 \)), ejection fraction was calculated from m-mode measurements by Teicholz formula. The reproducibility of our echocardiographic measurements and the agreement between non-invasive and invasive aortic valve studies have been reported previously.\textsuperscript{13,14}

**Cardiac catheterization**

Pressures in the right heart and pulmonary artery, including the pulmonary wedge position, were measured using flow-directed balloon-tipped catheters. The aortic valve was crossed retrograde for pressure recording in the left ventricle and during catheter pullback into the aortic root. Determination of the pressure gradient was based on superimposition of the LV and aortic pressure tracings. All pressures were measured using fluid-filled catheters with the zero reference level at the mid-axillary line. Cardiac output was determined by the Fick method. The aortic valve area was calculated by the Gorlin formula and indexed to body area. In patients in whom we could not cross the valve (\( n = 16/137 \)), echocardiographic valve area and mean pressure gradient were substituted for the invasive data. Coronary angiograms were done using selective techniques. Luminal reductions exceeding 50\% of the reference diameter were considered to represent angiographically significant disease.

**Diagnosis of HF**

For a diagnosis of HF,\textsuperscript{17} the patient had to have both a history of dyspnea or a fatigue on ordinary effort (i.e. symptoms of HF) and a resting mean pulmonary wedge pressure \( \geq 15 \text{mmHg} \) at cardiac catheterization (i.e. objective evidence of cardiac dysfunction). HF was classified diastolic when LV ejection fraction was \( \geq 50\% \) and systolic with an ejection fraction <50\%.

**Statistical analysis**

Comparisons across group means were done with ANOVA. Frequency distributions were compared with the \( \chi^2 \) test. Univariate associations between continuous data were analysed by Pearson's correlation coefficients. Complete (instead of stepwise) multiple logistic and linear regression analyses were used to identify the independent correlates of HF and LV ejection fraction, respectively, from among the explanatory factors that showed statistically significant or borderline (\( p < 0.10 \)) associations with HF or ejection fraction in univariate analyses. Age, sex, LV mass index, aortic valve area index (AVAI), relative wall thickness, history of hypertension, presence of chronic atrial fibrillation (AF), and presence of CAD at angiography were included in these analyses as biologically plausible explanatory factors. Comparisons between the pre-operative and 3-month post-operative data in the same subjects were made using paired \( t \)-tests. The results are given as mean \( \pm \) SE unless indicated otherwise. Nominal two-sided \( P < 0.05 \) were considered statistically significant. All analyses were conducted using commercially available software (SYSTAT version 9.1, Systat Inc.).

**Results**

Forty-two out of the 137 patients had HF, which was classified diastolic in 26 patients and systolic in 16 patients. Tables 1 and 2 compare the clinical characteristics and findings at catheterization and echocardiography across patients without and with the two types of HF. For patients free of HF, the data are given both for the total group (\( n = 95 \)) and, for comparative purposes, separately for the subgroup with an AVAI < 0.40 cm\textsuperscript{2}/m\textsuperscript{2} (\( n = 51 \)).

**Predictors of HF and ejection fraction**

In univariate analyses (Tables 1 and 2), patients with HF had smaller aortic valve areas, higher LV mass index, higher prevalence of LV hypertrophy, and more often AF and history of hypertension than patients free of HF. Neither age or sex nor the prevalence of CAD at angiography was statistically significantly related to the presence of HF. In a multiple logistic regression analysis run in 136 patients with complete sets of data on these variables, HF was independently associated with a higher LV mass index (\( P = 0.0004 \)), smaller AVAI (\( P = 0.003 \)), history of hypertension (\( P = 0.0004 \)), and presence of AF (\( P = 0.016 \)). The result was essentially the same when LV hypertrophy as a dichotomous variable was substituted for LV mass index in an otherwise identical logistic regression model (\( P = 0.004 \) for LV hypertrophy as an independent predictor of the presence of HF).

LV ejection fraction correlated inversely with LV mass index (\( r = -0.30, P < 0.001 \)) and directly with relative wall thickness (\( r = 0.36, P < 0.001 \)). It showed borderline associations also with AVAI (\( r = 0.16, P = 0.059 \)) and sex (62 \% in women vs. 58 \% in men, \( P = 0.062 \)). In a multiple linear regression analysis in 131 patients with complete data sets, LV mass index (standardized coefficient \( \beta = -0.26, P < 0.001 \)), relative wall thickness (\( \beta = 0.40, P < 0.001 \)), and AVAI (\( \beta = 0.24, P = 0.004 \)) came out as independent correlates of ejection fraction. Figure 1 illustrates the directionally opposite relations of ejection fraction to LV mass index and relative wall thickness.

**Critical AS with absent LV hypertrophy**

Totally 85 (40 men) of the 137 patients had critically severe AS (valve area index < 0.4 cm\textsuperscript{2}/m\textsuperscript{2}). Nineteen of them (12 men) did not have LV hypertrophy at echocardiography. Their mean age was 71 \pm 2 years compared with 69 \pm 1 years in the 66 patients (28 men) with LV hypertrophy (\( P = 0.405 \)). Patients with absent LV hypertrophy had smaller LV cavities (LV diastolic diameter, 43 \pm 2 mm vs. 49 \pm 1 mm, \( P = 0.002 \)) and thinner LV walls (posterior wall, 12 \pm 0.4 vs. 15 \pm 0.2 mm, \( P = 0.00008 \)) than patients with LV hypertrophy. Relative wall thickness was nearly
Three-month post-operative changes in LV structure and function in relation to the presence of pre-operative LV hypertrophy

Seventy-seven of the 85 candidates for the long-term follow-up substudy (see Methods) underwent a 3-month post-operative assessment including an echocardiographic examination. Of the eight missing patients, six had died early post-operatively (all had LV hypertrophy preoperatively) and two did not want to participate. Table 3

identical in the absence (0.62 ± 0.03) and in the presence (0.63 ± 0.02) of LV hypertrophy, and all except one of the 19 patients with absent hypertrophy had concentric LV remodelling (relative wall thickness >0.45). LV ejection fraction was on average higher in patients free of LV hypertrophy (0.63 ± 0.02 vs. 0.57 ± 2%, P = 0.045), and not a single patient with absent hypertrophy had systolic dysfunction (Figure 2). Only three of 19 patients (16%) free of LV hypertrophy had HF when compared with 32 of 66 patients (48%) with LV hypertrophy (P = 0.025).
shows selected clinical and echocardiographic measurements and their 3-month post-operative changes by the presence of pre-operative LV hypertrophy. Of note, patients who did not have LV hypertrophy pre-operatively showed no post-operative changes in LV size, mass, or systolic function while LV mass index was markedly reduced and ejection fraction improved in patients with pre-operative LV hypertrophy. The regression of LV hypertrophy was due both to a decrease in the LV cavity size and to thinning of the LV walls (Table 3).

Discussion

Nothing in our data or analyses supports the idea of beneficial LV hypertrophy in AS. On the contrary, increased LV mass predicted the presence of LV systolic dysfunction and HF independent of the severity of AS. Even in critical AS, patients with LV hypertrophy were worse off in the sense of having more often impaired ejection fraction and a triple prevalence of HF compared with individuals free of LV hypertrophy.

Methodological considerations

The cross-sectional design of our study needs recognition as a potential source for biased associations. Above all, one may ask whether our main finding, the rarity of systolic dysfunction and HF in patients with absent LV hypertrophy despite critical AS, simply is an artefact attributable to a high death rate in such patients. We consider this a possibility, however, because mortality in asymptomatic AS is low and the patients were referred to us once they had developed symptoms. Furthermore, only two patients died on our waiting list. Our data should, therefore, reflect genuine associations instead of artefacts due to the cross-sectional study design. We also emphasize that a prospective follow-up study without surgery in symptomatic AS, or in any AS with systolic dysfunction or HF as endpoints, would have been ethically unacceptable.

We used echocardiographically determined LV mass to identify LV hypertrophy. The method is widely used, has been validated against autopsy measurements, and provides prognostically important data. As it is based on estimating LV myocardial volume, it takes into account not only the LV wall thickness but also the cavity size. In our work, patients with AS and LV hypertrophy had both thicker LV walls and larger LV cavities than patients free of LV hypertrophy (Table 3). Had we used mere LV wall thickness in our analyses, instead of LV mass, the association between HF and LV hypertrophy would have been obscured. The lack of data on LV systolic wall stress is a limitation of our analyses. Wall stress could not be reliably determined because LV echocardiography and cardiac catheterization (i.e. measurement of LV pressure) were made on different days.

Development and significance of LV hypertrophy in AS

Many studies have shown that the degree of LV hypertrophy is poorly related to the severity of flow obstruction in AS. Clearly, there are factors additional to the pressure overload influencing the LV response. Age and gender are of significance, as is genetic variation in the renin–angiotensin system, although the latter effect is controversial. Importantly, several studies have shown that 10–20% of patients with severe AS do not have LV hypertrophy, and even much higher per cent, up to 46% in men and 29% in women, have been reported.

Although the idea of LV hypertrophy as a compensatory mechanism in AS is widely accepted, not a single human study has shown that that deficient hypertrophy would lead to systolic dysfunction or predict bad prognosis. Only two genuinely prospective follow-up studies in AS have been published. Otto et al. found that echocardiographic LV mass had no predictive value in asymptomatic patients, whereas Rosenhek et al. included no assessment.
of LV mass or hypertrophy in their report. The other follow-up studies have been retrospective in design and mixed in findings suggesting that increased LV wall thickness predicts either neutral, more favourable or more worse outcome in AS.

The role of LV hypertrophy in AS has recently been studied in animal models where myocardial hypertrophy was prevented by either pharmacological or genetic manipulation (for in depth reviews, see Lips et al. and Frey et al.). A number of these works have shown that lack of LV hypertrophy does not cause deterioration of LV systolic function. In one remarkable study, aortic-banded animals with genetically blunted hypertrophy maintained normal LV size and contractions, whereas animals with wild-type hypertrophy developed LV dilatation and systolic failure. These findings challenge the time-honoured paradigm of compensatory LV hypertrophy. They also suggest that the development of LV hypertrophy may be an epiphenomenon the outcome of signalling pathways activated or arrested in the myocardium.

Critically severe AS with absent LV hypertrophy

One-fifth of our patients with critical AS did not have LV hypertrophy. They had both thinner LV walls and smaller diastolic LV cavity diameters than patients with LV hypertrophy. Yet, relative wall thickness was nearly identical in the presence and absence of LV hypertrophy, only it was mainly due to thickened LV walls in the former group and reduced cavity size in the latter. Experimental studies have shown that the LV cavity size can decrease in response to pressure overload resulting in concentric remodelling and preserved LV function without myocardial hypertrophy. We found that patients with LV hypertrophy before surgery had a marked reduction of LV mass with improvement of systolic function 3-month post-operatively, whereas patients with absent pre-operative hypertrophy had no post-operative change in LV structure or function (Table 3). These data further support the conclusion that the latter group truly was devoid of ‘compensatory’ LV hypertrophy and that there exist genuinely different modes of LV response to pressure overload in man.

LV ejection fraction was related directly to relative wall thickness and inversely to LV mass. This raises the idea that concentric LV remodelling may be the key compensatory mechanism in AS, LV hypertrophy (i.e. increase of LV mass) being a common but harmful byproduct. It is known that concentric LV geometry not only normalizes wall stress but also helps sustain endocardial shortening (and ejection fraction) even though mid-wall and longitudinal shortening would be depressed.

Prevention and treatment of LV hypertrophy in AS?

In experimental AS, angiotensin-converting enzyme (ACE) inhibition prevents or reverses LV hypertrophy, improves LV systolic and diastolic function, and prolongs survival. In human AS, ACE-inhibitors have been contraindicated due to the threat of hypotensive reactions and to the fear that regression of LV hypertrophy would lead to high wall stress and systolic HF. As these obstacles are not evidence-based and as small pilot studies have shown that ACE inhibition is well tolerated in AS, a therapeutic trial appears both warranted and timely.

Another incentive to study ACE inhibition in AS comes from the realization that inhibition prevents or reverses LV hypertrophy, improves LV systolic and diastolic function, and prolongs survival. In summary, prevention and treatment of LV hypertrophy in AS appears to be both feasible and timely.
Conclusion

Our study shows that increased LV mass is an independent predictor of the presence of LV systolic dysfunction and HF in severe AS. Although concentric LV remodelling may be adaptive and beneficial, LV hypertrophy may promote rather than prevent adverse cardiac consequences in AS.

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