# Left ventricular hypertrophy in aortic valve stenosis: friend or foe?

## Raquel Yotti, Javier Bermejo

'How wonderful that we have found a paradox. Now we have some hope of making progress.'

Neils Böhr (1885—1962)

Concentric remodelling (reduction of the diameter/thickness ratio) and hypertrophy (increase of mass—left ventricular hypertrophy; LVH) have been classically interpreted as the physiological mechanisms used by the left ventricle to compensate for chronic pressure overload.[1] At the cellular level, increasing the number of contractile elements improves contractile force. At the organ level, a thicker myocardial wall reduces left ventricular radial, circumferential and meridional systolic stresses. Concentric remodelling and hypertrophy thus take advantage of Laplace's law to benefit systolic function. Even under extreme values of intraventricular pressure, overall systolic performance is maintained and pump function remains normal in terms of cardiac output and filling pressures. In the long term, if the systolic load is not relieved, this compensatory mechanism fails, hypertrophy switches towards eccentric remodelling, filling pressures rise and overt heart failure develops (a phase classically designated 'afterload mismatch'). This has been the classic conception of the favourable 'adaptive' effects of left ventricular remodelling under increased systolic stress.[1]

In their article published in this issue of *Heart*, Cioffi *et al*[2] (*see page 301*) analyse the prognostic value of LVH in a prospective cohort of patients with aortic valve stenosis (AS). The major finding of their study is related to adverse outcome if values are 110% higher than the values expected for wall stress, body size and gender. Importantly, such an inappropriate increase in left ventricular mass (LVM) was found in 59% of patients from an unselected cohort with asymptomatic AS. Multivariate analysis showed the independent predictive value of and inappropriate LVM, in addition to well established indices that influence outcome in AS such as baseline disease severity[3 4] or the degree of valve calcification.[5] Although a potentially maladaptive effect of hypertrophy in AS had already been reported,[6] this is the first study demonstrating its detrimental impact on patient outcome in a longitudinal design.

In hypertensive heart disease, the deleterious consequences of left ventricular remodelling have been unequivocally proved. Best evidence comes from pharmacological interventions showing a reduction of cardiovascular events parallel to the regression of LVH, independent of their effect on blood pressure.[7] A relatively large number of patients with hypertension also develop inappropriate hypertrophy for the degree of load and, as in AS, the correlation of LVM with outcome may not be linear. In fact, adverse inappropriate hypertrophy beyond a given threshold had previously been described in hypertensive heart disease, and excessive LVM correlates with cardiovascular outcome, independently of conventional risk factors.[8]

A number of genetic, molecular, and cellular mechanisms related to secondary LVH have been well characterised in the past few years. Interestingly, separate intracellular pathways have been identified to modulate adaptive and maladaptive hypertrophy.[9] Signalling molecules that involve the phosphoinositide-3-kinase cascade exert a protective role in progression towards heart failure, whereas pathways involving G-protein signalling enhance apoptosis and extracellular fibrosis. Further understanding of these molecular mechanisms will help drug development to prevent the transition from left ventricular concentric remodelling to heart failure. In addition, clarification of the signal pathways of LVH has allowed investigators to develop genetically modified murine models of blunted LVH response. Particularly striking has been the observation that outcome is improved in animals undergoing aortic binding by blocking the hypertrophic response to pressure overload.[10] Although genetically modified animals have higher left ventricular systolic stress than their wild-type counter mates, this has no consequence on long-term myocardial performance. In fact, knock-out animals lived longer. The conventional conception of physiological adaptation to pressure overload as a teleological mechanism to reduce wall stress thus calls for revision.[11 12]

There are several mechanisms by which excessive LVH may be related to the outcome of patients with AS. It has been shown that left ventricular systolic function declines as hypertrophy develops, increasing the risk of heart failure.[6] Due to afterload dependence, systolic chamber function may be difficult to quantify in the presence of AS. As left ventricular volumes become smaller due to concentric remodelling, stroke volume is reduced, sometimes leading to the 'paradoxical low-flow AS' phenomenon.[13] Despite normal ejection fraction, patients with this condition show higher values of concentric remodelling and smaller ventricles than their normal-flow counterparts. In paradoxical low-flow AS, reduced output is believed to result in the combination of systolic and diastolic dysfunction. Under stress situations, the heart may fail to provide adequate output, and patients with paradoxical low-flow AS show an adverse prognosis, particularly if they do not undergo valve replacement.[14]

Hypertension and AS frequently coexist, and both conditions share a number of common mechanisms. They also multiply their effect on the systolic burden of the left ventricle. In fact, AS patients with hypertension show more unfavourable remodelling than normotensive individuals.[15] This has led some authors to propose combined indices of systolic load such as the valvular—vascular impedance, which may allow prognosis to be stratified in given subsets of patients with AS.[16] However, even these more sophisticated measurements of systolic load only consider singular measurements at a given time point. Indices accounting for the degree of left ventricular remodelling and LVM may have the advantage of reflecting the effects of an abnormal load during a long period of time, acting as a 'cumulative systolic load dose' indicators.

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## Editorial

Localised LVH at the basal septum is particularly prevalent in hypertensive patients with AS,[17] and may occasionally cause associated subvalvular outflow obstruction ('double outflow stenosis'), thus accelerating patient symptom development. Even milder and non-obstructive degrees of basal septal hypertrophy may be detrimental.[18–20] Significant reductions of annular size (most frequently found in female patients with an advanced concentric remodelling pattern) may complicate therapeutic interventions, increasing the risk of patient—prosthesis mismatch,[18] or precluding transcatheter valve implantation. Importantly, LVH and concentric remodelling are associated with increased perioperative and mid-term mortality.[19 20]

The worse prognosis associated with inappropriately high LVM in AS may also be due to factors not related to the valve disease per se. Aortic valve sclerosis is associated with increased cardiovascular risk,[21] and this association may be particularly powerful in patients with excessive remodelling. Two recent studies have shown that obesity[22] and metabolic syndrome[23] correlate to LVM, in addition to conventional cardiovascular risk factors such as age, sex and low-density cholesterol. Inappropriately high LVM may thus be a flagging signal of a particularly high vascular risk factor profile in a given patient with AS.

Some therapeutic consequences may be considered in patients with AS showing inappropriate LVM. Concomitant hypertension deserves treatment, attempting to slow down the remodelling process. Importantly, AS severity may need to be reassessed once blood pressure is controlled.[24] ACE inhibitors show a suitable haemodynamic profile in asymptomatic hypertensive AS patients, if titrated with caution.[25] When present, hypercholesterolaemia and metabolic syndrome should also be intensively treated, despite the fact that statins will not slow valve disease progression.[26] [27] After valve replacement, pharmacological treatment should not be discontinued, as vasodilators may accelerate favourable reverse remodelling.[28]

Of particular controversy is how the degree of LVH should influence timing for surgery. Current decision making based on symptomatic status, disease severity and left ventricular ejection fraction works fine in most patients with AS. However, there is probably room for improvement, because patients still die from the complications of AS without ever undergoing surgery.[29] Patients are also sometimes operated on when myocardial damage is already irreversible. Current European practice guidelines accept severe LVH (in the absence of hypertension) as a IIb (level of evidence C) class recommendation for valve replacement in asymptomatic patients.[30] However, the study by Cioffi et al[2] suggests that efforts should be made to explore further the role of more refined measurements of ventricular remodelling in prospective clinical trials. The prognostic value of ventricular variables beyond ejection fraction need to be analysed, and surrogate indices such as systolic pulmonary artery pressure[31] or natriuretic peptides[32] are particularly promising. Although the level of evidence is currently too weak to recommend anticipating surgery in the asymptomatic patient based only on the degree of hypertrophy, the left ventricular remodelling response should no longer be considered only as a favourable adaptive mechanism to AS.

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