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Editorial

Iconoclasts topple adaptive myocardial hypertrophy in aortic stenosis

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This editorial refers to 'Left ventricular hypertrophy in aortic valve stenosis: preventive or promotive of systolic dysfunction and heart failure?'† by M. Kupari *et al.*, on page 1790

For more than 30 years, the development of concentric left ventricular (LV) hypertrophy in pressure overload was considered adaptive because the parallel deposition of new sarcomeres and the corresponding LV wall thickening succeeded in normalizing LV systolic wall stress despite the high intracavitary systolic pressure.[1] In aortic stenosis, the validity of this paradigm was demonstrated by haemodynamic studies, which established an inverse relationship between LV systolic wall stress and LV ejection fraction (EF) and by clinical outcome studies, which demonstrated worse post-operative prognosis if LV performance fell below this inverse LV wall stress–LVEF relationship.[2,3] This clinical paradigm of adaptive myocardial hypertrophy developing during progression of aortic stenosis clearly withstood the test of time despite the mounting epidemiological evidence of LV hypertrophy being associated with excess cardiac mortality and despite the ominous significance of LV hypertrophy in congenital aortic stenosis.

Kupari *et al.*[4] were the first to challenge the time-honoured concept of adaptive LV hypertrophy in aortic stenosis. In a carefully designed prospective study of patients with isolated aortic stenosis, they observed an inverse relationship between LV mass index and LVEF and a higher prevalence of LV hypertrophy in patients suffering of heart failure. They therefore concluded that the development of LV hypertrophy was actually promoting heart failure instead of preventing it.

Basic inspiration

When Kupari *et al.*[4] started their prospective study 5 years ago, they were well ahead of the crowd in appreciating emerging basic evidence on pressure overload-induced myocardial hypertrophy and in translating it to clinical cardiology.[5] During LV pressure overload, the raised biomechanical stress on the cardiomyocytes stimulates various signal transduction pathways to the nucleus[6] and induces autocrine production and secretion of angiotensin II and endothelin, whose receptors are coupled to G_q proteins. It was in a mouse model with cardiorestricted deficiency in G_q signalling that the paradigm of adaptive LV hypertrophy during pressure overload received a first serious blow.[7] After 1 week of aortic constriction, control mice showed complete normalization of LV systolic wall stress in contrast to the cardiac gene-targeted mice, which had a blunted hypertrophic response and were unable to reduce LV systolic wall stress. After 8 weeks of aortic constriction, despite initial normalization of wall stress, control mice developed an increase in chamber dimensions and progressive deterioration of LV function with echocardiographic fractional shortening falling from 59 to 35%. In contrast, cardiac gene-targeted mice with blunted LV hypertrophy and persistent elevation of LV systolic wall stress showed, after 8 weeks, only limited LV dilatation and preserved LV function with an echocardiographic fractional shortening of 52%. From these experiments, it was concluded that in pressure overload, the left ventricle is better off being 'stressed out' than being hypertrophied.

In other models of experimental pressure overload, investigators, however, clearly succeeded in creating adaptive or physiological hypertrophy. One of these models was a rat model of right ventricular (RV) hypertrophy caused by monocrotaline (MCT)-induced pulmonary hypertension.[8] When rats were given 30 mg/kg of MCT subcutaneously, they developed slow-onset pulmonary hypertension and adaptive RV hypertrophy, but when rats were given 80 mg/kg of MCT, there was rapid development of pulmonary hypertension, which was accompanied by RV failure and premature death. Fourteen days after MCT injection, RV hypertrophy was still identical in rats having received 30 or 80 mg/kg of MCT. However, when RV myocardium was subjected to a microarray analysis 14 days after MCT injection, 63 genes out of the 3010 cardiac genes screened were already differentially expressed between rats that had received 30 mg/kg of MCT and were going to develop adaptive RV hypertrophy and rats that had received 80 mg/kg of MCT and were going to develop RV failure. This study implies that adaptive hypertrophy does not precede maladaptive hypertrophy in pressure overload and that the magnitude of the initial

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pressure overload stimulus pre-destines the myocardium to development of an adaptive or maladaptive phenotype. In accordance with these results, development of heart failure in the mice-aortic constriction model and in the clinical aortic stenosis is related, respectively, to the tightness of the aortic band and to the progression of valvular stenosis. Clinical trials, which try to slow the progression of valvular stenosis with statins or angiotensin converting enzyme inhibitors, could test the validity of this assumption by demonstrating slower progression of valvular stenosis to be accompanied by reduced incidence of heart failure.

Clinical translation

Before converting to the iconoclastic view that aortic stenosis in LV hypertrophy is maladaptive, a critical appraisal of the evidence provided by Kupari *et al*. seems justified. The following issues are of concern: (i) failure to identify and to characterize aortic stenosis patients with LV hypertrophy and no heart failure, i.e. with adaptive LV hypertrophy; (ii) no demonstration of a persistent elevation of LV wall stress in the aortic stenosis patients without LV hypertrophy, and (iii) presence of discordant LVEF–LV hypertrophy relationships when LV hypertrophy is assessed either by LV mass index or by relative wall thickness.

Sixty-three aortic stenosis patients were free of heart failure and had evidence of LV hypertrophy defined by an LV mass index $>110\,g/m^2$ in women and $>134\,g/m^2$ in men. This group was larger than the group of aortic stenosis patients presenting with heart failure and similar evidence of LV hypertrophy ($n = 39$). Aortic stenosis patients with adaptive LV hypertrophy, therefore, outnumbered aortic stenosis patients with maladaptive LV hypertrophy in this prospective study population. The investigators failed to look for clinical features discriminating patients with adaptive LV hypertrophy from patients with maladaptive LV hypertrophy. Such discriminating clinical features could have identified a hormonal or an environmental background, which predisposes pressure overload hypertrophy to evolve into a maladaptive phenotype. In this respect, body mass index and arterial blood pressure were significantly higher in patients who developed heart failure. Obesity and hypertension are established risk factors for LV diastolic dysfunction[9] and as aortic stenosis progresses, these comorbidities can direct LV hypertrophy towards a maladaptive phenotype with diastolic heart failure. Obesity and hypertension are both associated with insulin resistance, which lowers myocardial nitric oxide (NO) content by reducing protein kinase B-mediated endothelial NO synthase (NOS3) phosphorylation. Myocardial NO content is a potent modulator of the hypertrophy process as recently demonstrated in transgenic mice with cardiomyocyte-restricted NOS3 overexpression.[10] Hence, development of maladaptive LV hypertrophy should not necessarily be ascribed to the hypertrophy gene programme but could also result from deleterious modification of its expression by hormonal and environmental factors.

Normalization of LV wall stress is a key feature of the adaptive hypertrophy paradigm in pressure overload. In the original studies that applied this paradigm to aortic stenosis, failure to normalize LV wall stress was considered to be responsible both for contractile dysfunction[2] and for poor post-operative outcome.[3] The study by Kupari *et al*.[4] comes to the opposite conclusion as they observe better contractile function in the absence of LV hypertrophy. Absence of LV hypertrophy in their study does not, however, imply persistent elevation of LV wall stress, which they unfortunately failed to measure. As mentioned earlier, LV hypertrophy was diagnosed when LV mass index exceeded pre-set values. Because LV mass index also depends on LV end-diastolic volume index, its use to categorize patients for LV hypertrophy can cause patients with small LV volumes and moderate increase in LV wall thickness to end up in the group 'without LV hypertrophy'. This indeed happened as evident from *Table 3*, which shows patients 'without LV hypertrophy' to have elevated septal (13 ± 0.3 mm) and posterior (12 ± 0.4 mm) wall thickness and an LV end-diastolic diameter smaller than the patients 'with LV hypertrophy'. Patients labelled as having no LV hypertrophy could well have developed sufficient LV hypertrophy to normalize LV wall stress for a small LV cavity and their superior contractile performance was therefore no surprise. To clarify this issue, the study needs to be implemented with an invasive assessment of LV wall stress.

Finally, because LV mass index depends on LV end-diastolic volume index and because LV end-diastolic volume index was significantly larger in the heart failure group, the inverse relation between LV mass index and LVEF can also be explained by an inadequacy of LV hypertrophy to normalize LV wall stress for a large LV cavity. In fact, when LV mass index was replaced by relative wall thickness (i.e. septal and posterior wall thickness divided by end-diastolic diameter), this inadequacy of LV hypertrophy was accounted for and the relation between LVEF and LV hypertrophy actually reversed, with a higher LVEF now being observed at a higher relative wall thickness.

Conclusions

Avoidance or modification of maladaptive LV hypertrophy remains a major clinical challenge. The study by Kupari *et al*.[4] deserves credit for being the first to translate recent basic evidence on maladaptive myocardial hypertrophy to the clinical setting of valvular heart disease. At present, their iconoclastic idea on LV hypertrophy in aortic stenosis awaits further confirmation by invasive studies. As with all iconoclastic acts, history will tell whether it cleared perspectives or spoiled the view.

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