


Elvin Kedhi
Department of Cardiology
AZ Middelheim Lindendreef Nr. 1
2020 Antwerp Belgium
Tel: +32 32803255
E-mail address: ekedhi@yahoo.com

Paul Vermeersch
Department of Cardiology
AZ Middelheim Antwerp Belgium

doi:10.1093/eurheartj/ehi623

Online publish-ahead-of-print 24 October 2005

Left ventricular hypertrophy, apoptosis, and progression to heart failure in severe aortic stenosis

We read with great interest the article by Kupari et al. In supporting the concept that left ventricular (LV) hypertrophy in severe aortic stenosis is a predisposing factor rather than a protective one against the development of systolic dysfunction and heart failure, the authors discuss in detail the relationship between hypertrophy and progression through failure from a clinical/instrumental point of view, but fail to indicate a pathophysiological mechanism responsible for such transition. Indeed, evidence is accumulating that a common molecular pathway mediates both hypertrophy and myocardocyte apoptosis. The upregulation of local angiotensin-converting enzyme and of norepinephrine release have been revealed in animal models of chronic pressure overload. The same factors are well-established promoters of apoptosis. The upregulation of p38 MAPK pathway has been suggested as the link between (i) angiotensin II/norepinephrine and (ii) alterations of gene expression profile associated to both hypertrophy and apoptosis. In animal model of chronic pressure overload, apoptosis has revealed as a pivotal trait of myocardial damage together with overproduction of extracellular matrix. In the same model, the role of angiotensin system in promoting apoptosis has been demonstrated by the ex adiuvantibus criterion. Furthermore, in our recent study, we have for the first time disclosed an inverse correlation between indices of myocardial perfusion and myocardocyte apoptosis in the hypertrophied human heart with severe aortic stenosis. Demand ischaemia is a key feature of severe hypertrophy and a well-established stimulus to apoptosis. Given the analogy in inclusion criteria between the study by Kupari et al. and our own, we believe that the results of these two investigations may be complementary and that taken together they support the hypothesis of myocardial apoptosis as a key element of histological damage and a main determinant of clinical course in these patients.

Moreover, the finding that no surgical variable (i.e. the size of implanted prosthesis) influences the degree of LV mass regression after aortic valve replacement, but that the determinants of such regression are medical (i.e. coexistence of hypertension and pre-operative LV mass index), suggests that (i) the cause-effect link between pressure overload and hypertrophy is more complex and recognizes more co-factors than a direct linear relationship; (ii) the structural deterioration of the myocardium occurs first at all at a cellular/molecular level; (iii) a threshold in myocardial derangement exists beyond which the hypertrophy process is not reversible. These elements are compatible with the hypothesis of the ‘apoptotic cardiomyopathy’ in chronic pressure overload. The sudden development of symptoms and failure in unoperated aortic stenosis should mark the moment in which myocardocyte loss reaches a critical threshold; the same hypothesis can explain why late valvular replacement when failure has developed is unable to revert the unfavourable evolution of the disease.

References


