Adaptive and Maladaptive Cardiac Hypertrophy: What Is the Effective Role of Heat Shock Transcription Factor 1?

To the Editor:

In the recent interesting article by Sakamoto et al.,1 the authors found that rats undergoing exercise training showed lower degree of left ventricular (LV) hypertrophy, higher expression and activity of heat shock transcription factor 1 (HSF1), and preserved LV systolic function in comparison with rats exposed to sustained pressure overload by surgical constriction of the transverse aorta (TAC). They also observed that transgenic mice expressing constitutively active HSF1 showed less evidence of hypertrophic response and better systolic function than their wild-type littermates 5 weeks after TAC. Conversely, HSF1-deficient mice showed similar degree of LV hypertrophy but worse systolic function in comparison with their wild-type littermates after 4 weeks of exercise or 1 week after TAC. These data support the intriguing hypothesis that HSF1 upregulation in cardiomyocytes may play a key role in preventing LV systolic impairment in the exercise-induced hypertrophy model, and in determining the adaptive or maladaptive nature of the hypertrophic response.

An important issue in the interpretation of these findings derives from the method used for the assessment of LV systolic performance. The use of unadjusted echocardiographic indices measured at the level of endocardium, such as the M-mode-derived fractional shortening used by the authors, overestimates the real performance of circumferentially oriented LV fibers, that are mostly distributed within the midwall layers.2,3 Determination of fractional shortening at the midwall is a more reliable method to explore effective LV systolic function, particularly in the presence of LV hypertrophy or altered LV geometry, and its feasibility in mice has been previously validated.4,5 Also, because of the negative effect of LV afterload on systolic shortening and ejection,5 particularly relevant when pharmacological or surgical manipulation of hemodynamic status is performed, eg, by TAC, adjustment to end-systolic LV wall stress is required to provide a load-independent index of LV systolic performance.7 This point may represent a major drawback for the main message of the study. For instance, the authors reported lower fractional shortening in pressure-overloaded (41.20±2.33%) than exercised rats (53.42±0.94%), but it should be considered that blood pressure, a major determinant of LV afterload, was considerably higher in the former (144.6±9.0 mm Hg) than in the latter group (84.4±4.3 mm Hg). Similar considerations can be made for the differences in fractional shortening observed between transgenic and wild-type mice, even considering that blood pressure was not significantly different in the 2 groups, and between HSF1-deficient and wild-type mice, as in both comparisons the potential discrepancies in LV afterload related to different end-systolic LV diameter and wall thicknesses have not been taken into account. Adjustment to wall stress is therefore necessary to exclude that any observed reduction in LV shortening might be a pure reflection of increased afterload.8 Moreover, heart rate may act as an additional confounding factor, particularly when relatively fast frequencies are analyzed.6 To date, stress- and rate-adjusted extent or velocity of midwall shortening is often used in clinical research as an echocardiographic measure of effective circumferential LV myocardial contractility.9 In this view, a study aimed at exploring the role of HSF1 in modulating LV myocardial contractility, rather than LV fractional shortening, in exercise-induced and pressure overload hypertrophy could provide new insights into the mechanisms of cardiac adaptation to different types of overload. Considering the potential importance of HSF1 in cardiac stress response,10 even in the chronic stage of myocardial hypertrophy, such analysis might also help clarifying our previous finding that increasing levels of LV afterload in a population of hypertensive humans with LV hypertrophy were associated with more evident reduction in LV myocardial contractility than in highly trained subjects with physiologic LV hypertrophy.11

Additionally, it should be taken into account that circumferential systolic indices do not provide a complete description of LV systolic dynamics. Tissue Doppler imaging and strain analysis of long-axis myocardial velocities have recently gained ground as reliable methods to assess longitudinal LV systolic function,12 and their feasibility in mice has been recently demonstrated.13,14 An impairment in longitudinal LV systolic function is often found despite normality of circumferential performance,13 and has been shown to allow early detection of contractile dysfunction and prediction of mortality in mice exposed to drug-induced cardiac injury better than circumferential indices.16 Furthermore, recent evidences obtained by cardiac MRI in humans suggest that longitudinal left atrioventricular plane excursion is the most important determinant of LV pump function, as it accounts for approximately 60% of the total LV stroke volume.17 Based on these considerations, the nice study by Sakamoto et al suggests a potential involvement of HSF1 in determining the different hypertrophic response to exercise and chronic pressure overload, but further studies are needed to investigate its effective role in affecting LV systolic function and in characterizing the adaptive or maladaptive nature of LV hypertrophy in these conditions.

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