Is treating cardiac hypertrophy salutary or detrimental: the two faces of Janus

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LEFT VENTRICULAR (LV) hypertrophy (cardiac hypertrophy) is generally considered a compensatory response of the heart to a variety of stimuli, most commonly altered workload. Although the most common cause of cardiac hypertrophy is essential hypertension in Western countries, virtually all forms of cardiac diseases, including valvular dysfunction, coronary artery disease, and arrhythmias, can stimulate development of cardiac hypertrophy. Hypertrophy also occurs in several systemic diseases, such as endocrine disorders and chronic renal disease, in response to neural/humoral factors, independent of load. More recently, it has been determined that hypertrophy occurs through stimulation or deletion of specific signaling pathways (17, 32, 38). Importantly, however, it remains to be established whether hypertrophy is adaptive or maladaptive.

It is well known that mechanical loading is one of the most critical determinants of cardiac muscle mass (38). For example, right ventricular pressure overload induced by pulmonary artery banding causes right ventricular hypertrophy, whereas the papillary muscle undergoes atrophy when it is unloaded by transection of the chordae tendineae (13). According to Laplace’s law, increased wall thickness of the LV chamber reduces the wall stress, thereby reducing oxygen consumption in the heart. According to this view, development of cardiac hypertrophy can be considered as an adaptive response, and the impairment of this compensatory mechanism can lead to transition from cardiac hypertrophy to LV dysfunction. For instance, Meguro et al. (29) have demonstrated, using a mouse model of pressure overload, that attenuation of cardiac hypertrophy by administration of cyclosporine A, an inhibitor of Ca2+-regulated phosphatases (calcineurin), was associated with increased mortality of the animals because of heart failure. This result supports the concept that cardiac hypertrophy is a beneficial compensatory mechanism that protects the heart in the face of increased cardiac workload.

Epidemiological studies have demonstrated, however, that chronic cardiac hypertrophy is a major independent risk factor for the morbidity and mortality in the general population (33, 49), in patients with essential hypertension (10, 21, 48), and also in a variety of clinical settings (5, 25, 35). In fact, whereas cardiac hypertrophy is initially compensatory, the continued presence of hypertrophy leads to dilated cardiomyopathy, heart failure, ischemic heart disease, and sudden death (22, 23). The LV diastolic and systolic dysfunction and subsequent development of congestive heart failure start from hypertrophic remodeling of the heart. Accumulation of fibrillar collagen in the interstitial space of the hypertrophied LV accounts for the abnormal myocardial stiffness and for the impairment of diastolic function (19, 20, 36), which precedes the occurrence of the systolic dysfunction. Chronic pressure overload increases cardiac myocyte apoptosis through increases in the ratio of proapoptotic (such as bax) and antiapoptotic (such as bcl-2) gene expression (12), which may lead to systolic LV dysfunction.

Impaired subendocardial coronary reserve is one of the hallmarks of cardiac hypertrophy (28). Structural variables proposed to explain reduced subendocardial coronary reserve include 1) an inadequate growth of the capillary vascular bed while ventricular mass is increasing (6, 7, 37), 2) a reduction in the luminal cross-sectional areas of resistance vessels (28, 45), 3) an increase in the medial area of resistance vessels (2, 8, 46, 52), and 4) failure of the large epicardial conductance arteries and cross-sectional area of the vascular bed to enlarge in proportion to the degree of hypertrophy (27, 42, 51). In our laboratory, we have studied models of both right ventricular and LV severe pressure overload hypertrophy (16, 34), where subendocardial coronary reserve was reduced >50% during adenosine-induced vasodilatation. Despite the extensive hypertrophy, capillary density was equally reduced by only 10–15% in endo-, mid-, and epicardial LV regions compared with control dogs, whereas increased capillary cross-sectional area resulted in no change in capillary surface area/myocyte volume or volume percentage capillary space (3). Thus the mechanism of reduced subendocardial reserve is complex and can be explained...
plained only partially by structural alterations in the chronic setting where angiogenesis also occurs. This was confirmed in our laboratory (16) by demonstrating that the reduction in subendocardial reserve in LV hypertrophy is markedly attenuated, when compressive forces were mitigated, by unloading the heart. Perivascular fibrosis and medial thickening of intramyocardial coronary arteries also account, in part, for the impairment of coronary vasodilator reserve, which is commonly seen in cardiac hypertrophy (2, 30). Endothelium-dependent and -independent coronary vasorelaxation are also impaired in cardiac hypertrophy (18). Finally, cardiac hypertrophy compromises the neural control of coronary blood flow through alterations of cardiopulmonary baroreceptor functions (47). Thus the reduction of LV mass must be considered to be a primary end point for the treatment of patients with cardiac hypertrophy. In fact, several studies (33) have demonstrated that the regression of cardiac hypertrophy appears to be a favorable prognostic marker independent of the treatment-induced reduction in blood pressure.

Although the aforementioned salutary and detrimental aspects of cardiac hypertrophy seem contradictory, one important issue is the difference in the role of hypertrophy in response to acute versus chronic loads. Clearly, the normal heart cannot develop the same systolic pressure as can a hypertrophied heart. Patients with significant aortic stenosis often have pressure gradients over 100 mmHg and with stress or vasoconstrictors may achieve systolic pressures >300 mmHg. This load cannot be tolerated in a nonhypertrophied heart. In fact, the lack of ability to mount a compensatory hypertrophic response may argue for a poor prognosis. This must be distinguished from the chronic effects of severe hypertrophy that may be deleterious as we discussed above.

Although it is established that chronic severe cardiac hypertrophy enhances cardiovascular risk, our hypothesis is that acute cardiac hypertrophy is compensatory. At variance with this hypothesis, recent studies have demonstrated that inhibition of load-induced cardiac hypertrophy may lead to preserved cardiac function despite sustained elevation of the LV wall stress (14, 15). In transgenic mice with cardiac-specific expression of a carboxyl terminal peptide of Goq (Tg-GqI), which specifically inhibits Goq-mediated signaling (1), as well as in mice deficient in dopamine β-hydroxylase gene (Dbh−/−) (44), resulting in lack of endogenous norepinephrine and epinephrine, pressure overload caused a blunted hypertrophic response. In these studies, although wall stress was completely normalized in banded wild-type mice due to the induction of adequate hypertrophy, it remained elevated in banded Tg-GqI mice due to lack of adequate hypertrophy. Interestingly, wild-type mice with normalized LV wall stress showed an increase in chamber dimensions and a progressive deterioration of the LV function. By contrast, indexes of LV function in Tg-GqI and Dbh−/− mice showed significantly less deterioration. These data suggest that cardiac hypertrophy may be simply maladaptive. It should be noted, however, that although modification of the signaling mechanism in these cases caused both reduction of cardiac hypertrophy and maintenance of cardiac function, reduction of cardiac hypertrophy could be an epiphenomenon. In other studies, some forms of cardiac hypertrophy, including those induced by cardiac-specific overexpression of extracellular signal-regulated protein kinase (ERK) (9), Akt (11, 41), or phosphoinositide-3 kinase (40), are adaptive and do not show long-term decompensation. Thus it remains to be elucidated if the maintenance of cardiac function seen in Tg-GqI and Dbh−/− mice is mediated through inhibition of cardiac hypertrophy.

We have recently (43) found that mice deficient in adenylyl cyclase type 5, a major isoform of adenylyl cyclase in the heart, can tolerate pressure overload, thereby exhibiting well-maintained LV ejection fraction and LV chamber size compared with wild-type littermates. In contrast, we have also shown (39) that mitogen-activated protein kinase and ERK kinase kinase 1 (MEKK1) knockout mice are more susceptible to pressure overload and develop cardiac dysfunction compared with the control wild-type (MEKK1+/+) mice. These studies suggest that modifying a particular signaling mechanism could exhibit profound effects on the maintenance of cardiac function in response to hemodynamic overload than normalizing the wall stress. In this regard, we should keep in mind that cardiac hypertrophy occurs in response to a wide variety of stimuli, each of which activates an intricate network of signaling molecules, involving protein kinases, protein phosphatases, and other second messengers (26, 32, 38). These molecular pathways not only mediate cardiac hypertrophy but are also responsible for activation of deleterious mechanisms for the heart (i.e., apoptosis and impairment of contractility), which results in development of LV dysfunction and heart failure (4). If one signaling molecule stimulates both hypertrophy and cell death, inhibiting such molecule would reduce cardiac hypertrophy and, at the same time, maintain cardiac function, thereby showing beneficial effects. In contrast, if another signaling molecule stimulates cardiac hypertrophy and cell survival, inhibiting such molecule may not be necessarily beneficial because it could potentially promote cell death and cardiac dysfunction despite reduction in cardiac hypertrophy. Therefore, it is important to identify which molecular mechanisms make cardiac hypertrophy good or bad. Furthermore, the important target of treatment of cardiac hypertrophy is not necessarily the reduction of LV mass itself but rather may be the correction of the molecular pathways that account for the cardiac hypertrophy-related complications and/or the enhancement of the activity of cellular signals mediating cytoprotective actions.

Figure 1 summarizes the role of representative molecules in cardiac hypertrophy and apoptosis. Each signaling molecule does not necessarily affect cardiac hypertrophy and apoptosis in the same direction. It should be noted that the role of each signaling molecule is not identical when it is studied by using distinct
upstream stimuli. For example, although mice deficient in MEKK1 (the upstream kinase of c-Jun NH2-terminal kinase) exhibited pronounced dilation of cardiac chambers, reduction of LV ejection fraction, increased apoptosis, and premature death in cardiac hypertrophy in response to pressure overload (39), cardiac hypertrophy and development of cardiomyopathy are attenuated in the same mice when hypertrophy was induced by cardiac-specific overexpression of Gqq (31). Cardiac function of some molecules remains unclear because experimental results obtained from loss of function studies and those from gain of function studies have shown contradictory results (24, 50). It is possible that the extent and the timing of expression of the molecule significantly affect the function of the molecule in a given pathological condition. For example, it is possible that one molecule may mediate hypertrophy alone in the normal heart, whereas the same molecule may mediate cell survival when it is activated in a heart that already has hypertrophy. In this regard, it will be important to establish the conditional expression system to precisely control both expression levels as well as the timing of expression of the molecule of one’s interest.

A number of studies performed in the last decade have demonstrated that the development of cardiac hypertrophy is a complex process involving changes in hemodynamics, genetic background, neurohormonal activation, growth factors, and cytokines, which stimulate different signaling pathways resulting in increases in cardiac myocyte cell size, sarcomere assembly, and induction of the “fetal”-type cardiac genes (reviewed in Refs. 32 and 38). It is likely that cardiac hypertrophy in each patient possesses a distinct phenotype depending on how cardiac hypertrophy is stimulated. Therefore, a new challenge in the treatment for cardiac hypertrophy is 1) to better characterize the different phenotypes of cardiac hypertrophy caused by

Fig. 1. Physiological hypertrophy [compensated left ventricular (LV) hypertrophy] and pathological hypertrophy (decompensated LV hypertrophy) are caused by a balance between the cell death-promoting mechanism and the cell survival mechanism. Although many signaling molecules listed in the text are involved in cardiac hypertrophy, some molecules promote cell death, thereby causing pathological hypertrophy, whereas other molecules promote cell survival, thereby causing physiological cardiac hypertrophy. PKA, protein kinase A; PKC, protein kinase C; CaMK, Ca2+/calmodulin-dependent protein kinase; ERK5, extracellular signal-regulated protein kinase 5; MEKK1, mitogen-activated protein kinase kinase kinase 1; JNK, c-Jun NH2-terminal kinase; NF-AT3, nuclear factor of activated T cells 3; PI3K, phosphoinositide 3-kinase; CREB, cAMP response element binding protein; STAT3, signal transduction and activation of transcription 3.

Second messengers and G proteins: Gs, Gi, Gq, Ras, cAMP

Kinases or phosphatases: PKA, PKC, CaMK, ERK5, MEKK1-JNK, PTEN

Transcription factors: NF-AT3, MEF 2, AP-1

Others: SOCS3

Second messengers and G proteins: Gβγ, Gi

Kinases or phosphatases: Akt, PI3K, MEK1-ERK1/2, MEKK1-JNK, ErbB2

Transcription factors: GATA4, CREB

Others: gp130, STAT3
distinct pathological stimuli, 2) to understand the relative contribution of each biochemical pathway in the pathogenesis of different forms of cardiac hypertrophy, and finally, 3) to find molecular markers specifically associated with the different phenotypes of cardiac hypertrophy to evaluate the effectiveness of the treatment of cardiac hypertrophy. Therefore, we propose that we should preserve the beneficial component of cardiac hypertrophy and target detrimental components when we treat patients with cardiac hypertrophy. The prognosis of chronic cardiac hypertrophy patients can be affected significantly by modulation of the signaling mechanisms rather than reduction of cardiac hypertrophy itself. Therefore, what we should treat in patients with chronic cardiac hypertrophy may be the signaling mechanisms mediating cardiac hypertrophy, which have more pronounced effects upon cell survival and death of individual cardiac myocytes. Precise understanding of the function of each signaling molecule in the heart and identifying how and when those signaling molecules are activated or inactivated will be essential to better control cardiac function and survival of the patient.

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