special medical editorial

Am J Physiol Heart Circ Physiol 284: H1043–H1047, 2003;
10.1152/ajpheart.00990.2002.

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

Carmine Morisco,[1,3] Junichi Sadoshima,[1] Bruno Trimarco,[3] Rohit Arora,[2] Dorothy E. Vatner,[1] and Stephen F. Vatner[1]

[1]*Cardiovascular Research Institute, Department of Cell Biology and Molecular Medicine, and* [2]*Division of Cardiology, Department of Medicine, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey 07101-1709; and* [3]*Department of Internal Medicine, Cardiovascular and Immunological Sciences, University of Federico II, 80131 Naples, Italy*

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 Ca^{2+}-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 ex-

Address for reprint requests and other correspondence: S. F. Vatner, Dept. of Cell Biology and Molecular Medicine, Univ. of Medicine and Dentistry of New Jersey, New Jersey Medical School, 185 South Orange Ave., MSB G-609, Newark, NJ 07101-1709 (E-mail: vatnersf@umdnj.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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 Gαq (Tg-GqI), which specifically inhibits Gαq-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 those 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

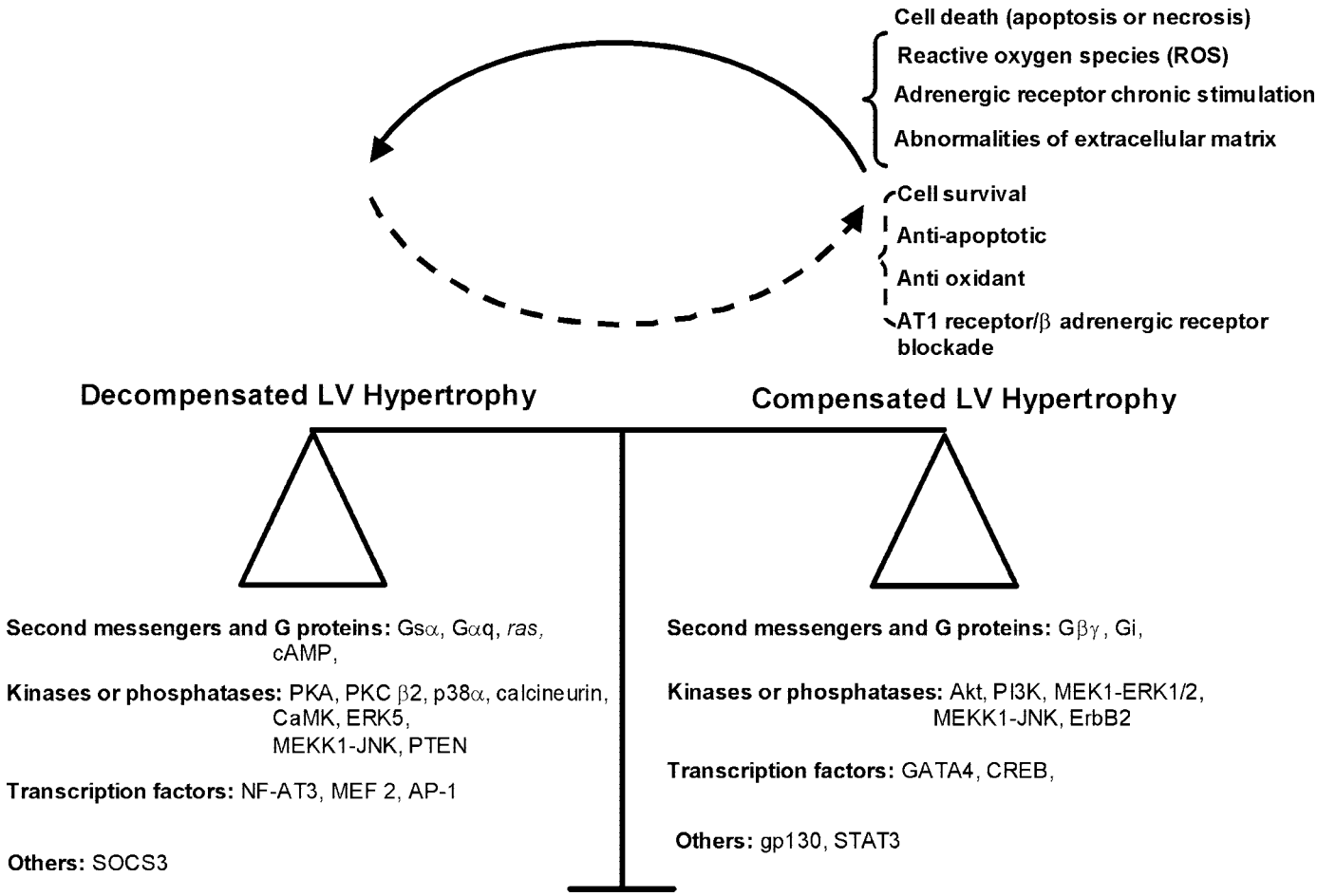

Fig. 1. Physiological hypertrophy [compensated left ventricular (LV) hypertrophy] and pathological hypertrophy (decompensated LV hypertrophy) are caused by a balance between the cell death-promoting mechanism and the cell survival mechanism. Although many signaling molecules listed in the text are involved 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, Ca^{2+}/calmodulin-dependent protein kinase; ERK5, extracellular signal-regulated protein kinase 5; MEKK1, mitogen-activated protein kinase kinase kinase 1; JNK, c-Jun NH_2-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.

upstream stimuli. For example, although mice deficient in MEKK1 (the upstream kinase of c-Jun NH_2-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 Gαq (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

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.

This work is supported by National Institutes of Health Grants HL-59139, HL-33107, HL-33065, HL-65182, HL-65183, AG-14121, HL-69020, HL-67724, and HL-67727 and American Heart Association (AHA) National Grant 9950673N. C. Morisco is a recipient of AHA Mid Atlantic Postdoctoral Fellowship.

REFERENCES

1. **Akhter SA, Luttrell LM, Rockman HA, Iaccarino G, Lefkowitz RJ, and Koch WJ.** Targeting the receptor-Gq interface to inhibit in vivo pressure overload myocardial hypertrophy. *Science* 280: 574–577, 1998.
2. **Anderson PG, Bishop SP, and Digerness SB.** Vascular remodeling and improvement of coronary reserve after hydralazine treatment in spontaneously hypertensive rats. *Circ Res* 64: 1127–1136, 1989.
3. **Bishop SP, Powell PC, Hasebe N, Shen YT, Patrick TA, Hittinger L, and Vatner SF.** Coronary vascular morphology in pressure-overload left ventricular hypertrophy. *J Mol Cell Cardiol* 28: 141–154, 1996.
4. **Bishopric NH, Andreka P, Slepak T, and Webster KA.** Molecular mechanisms of apoptosis in the cardiac myocyte. *Curr Opin Pharmacol* 1: 141–150, 2001.
5. **Bolognese L, Dellavesa P, Rossi L, Sarasso G, Bongo AS, and Scianaro MC.** Prognostic value of left ventricular mass in uncomplicated acute myocardial infarction and one-vessel coronary artery disease. *Am J Cardiol* 73: 1–5, 1994.
6. **Breisch EA, Houser SR, Carey RA, Spann JF, and Bove AA.** Myocardial blood flow and capillary density in chronic pressure overload of the feline left ventricle. *Cardiovasc Res* 14: 469–475, 1980.
7. **Breisch EA, White FC, and Bloor CM.** Myocardial characteristics of pressure overload hypertrophy. A structural and functional study. *Lab Invest* 51: 333–342, 1984.
8. **Brilla CG, Janicki JS, and Weber KT.** Impaired diastolic function and coronary reserve in genetic hypertension. Role of interstitial fibrosis and medial thickening of intramyocardial coronary arteries. *Circ Res* 69: 107–115, 1991.
9. **Bueno OF, De Windt LJ, Tymitz KM, Witt SA, Kimball TR, Klevitsky R, Hewett TE, Jones SP, Lefer DJ, Peng CF, Kitsis RN, and Molkentin JD.** The MEK1-ERK1/2 signaling pathway promotes compensated cardiac hypertrophy in transgenic mice. *EMBO J* 19: 6341–6350, 2000.
10. **Casale PN, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, and Laragh JH.** Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. *Ann Intern Med* 105: 173–178, 1986.
11. **Condorelli G, Drusco A, Stassi G, Bellacosa A, Roncarati R, Iaccarino G, Russo MA, Gu Y, Dalton N, Chung C, Latronico MV, Napoli C, Sadoshima J, Croce CM, and Ross J Jr.** Akt induces enhanced myocardial contractility and cell size in vivo in transgenic mice. *Proc Natl Acad Sci USA* 99: 12333–12338, 2002.
12. **Condorelli G, Morisco C, Stassi G, Notte A, Farina F, Sgaramella G, de Rienzo A, Roncarati R, Trimarco B, and Lembo G.** Increased cardiomyocyte apoptosis and changes in proapoptotic and antiapoptotic genes bax and bcl-2 during left ventricular adaptations to chronic pressure overload in the rat. *Circulation* 99: 3071–3078, 1999.
13. **Cooper GT, Kent RL, Uboh CE, Thompson EW, and Marino TA.** Hemodynamic versus adrenergic control of cat right ventricular hypertrophy. *J Clin Invest* 75: 1403–1414, 1985.
14. **Esposito G, Rapacciuolo A, Naga Prasad SV, Takaoka H, Thomas SA, Koch WJ, and Rockman HA.** Genetic alterations that inhibit in vivo pressure-overload hypertrophy prevent cardiac dysfunction despite increased wall stress. *Circulation* 105: 85–92, 2002.
15. **Hill JA, Karimi M, Kutschke W, Davisson RL, Zimmerman K, Wang Z, Kerber RE, and Weiss RM.** Cardiac hypertrophy is not a required compensatory response to short-term pressure overload. *Circulation* 101: 2863–2869, 2000.
16. **Hittinger L, Mirsky I, Shen YT, Patrick TA, Bishop SP, and Vatner SF.** Hemodynamic mechanisms responsible for reduced subendocardial coronary reserve in dogs with severe left ventricular hypertrophy. *Circulation* 92: 978–986, 1995.
17. **Hoshijima M and Chien KR.** Mixed signals in heart failure: cancer rules. *J Clin Invest* 109: 849–855, 2002.
18. **Houghton JL, Smith VE, Strogatz DS, Henches NL, Breisblatt WM, and Carr AA.** Effect of African-American race and hypertensive left ventricular hypertrophy on coronary vascular reactivity and endothelial function. *Hypertension* 29: 706–714, 1997.
19. **Jalil JE, Doering CW, Janicki JS, Pick R, Clark WA, Abrahams C, and Weber KT.** Structural vs. contractile protein remodeling and myocardial stiffness in hypertrophied rat left ventricle. *J Mol Cell Cardiol* 20: 1179–1187, 1988.
20. **Jalil JE, Doering CW, Janicki JS, Pick R, Shroff SG, and Weber KT.** Fibrillar collagen and myocardial stiffness in the intact hypertrophied rat left ventricle. *Circ Res* 64: 1041–1050, 1989.
21. **Koren MJ, Devereux RB, Casale PN, Savage DD, and Laragh JH.** Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 114: 345–352, 1991.
22. **Levy D, Garrison RJ, Savage DD, Kannel WB, and Castelli WP.** Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 322: 1561–1566, 1990.
23. **Levy D, Salomon M, D'Agostino RB, Belanger AJ, and Kannel WB.** Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 90: 1786–1793, 1994.
24. **Liao P, Georgakopoulos D, Kovacs A, Zheng M, Lerner D, Pu H, Saffitz J, Chien K, Xiao RP, Kass DA, and Wang Y.** The in vivo role of p38 MAP kinases in cardiac remodeling and restrictive cardiomyopathy. *Proc Natl Acad Sci USA* 98: 12283–12288, 2001.
25. **Liao Y, Cooper RS, McGee DL, Mensah GA, and Ghali JK.** The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. *JAMA* 273: 1592–1597, 1995.
26. **MacLellan WR and Schneider MD.** Genetic dissection of cardiac growth control pathways. *Annu Rev Physiol* 62: 289–319, 2000.
27. **Marchetti GV, Merlo L, Noseda V, and Visioli O.** Myocardial blood flow in experimental cardiac hypertrophy in dogs. *Cardiovasc Res* 7: 519–527, 1973.
28. **Marcus ML.** *Coronary Circulation in Health and Disease*. New York: McGraw-Hill, 1983.

29. **Meguro T, Hong C, Asai K, Takagi G, McKinsey TA, Olson EN, and Vatner SF.** Cyclosporine attenuates pressure-overload hypertrophy in mice while enhancing susceptibility to decompensation and heart failure. *Circ Res* 84: 735–740, 1999.
30. **Michel JB, Salzmann JL, Ossondo Nlom M, Bruneval P, Barres D, and Camilleri JP.** Morphometric analysis of collagen network and plasma perfused capillary bed in the myocardium of rats during evolution of cardiac hypertrophy. *Basic Res Cardiol* 81: 142–154, 1986.
31. **Minamino T, Yujiri T, Terada N, Taffet GE, Michael LH, Johnson GL, and Schneider MD.** MEKK1 is essential for cardiac hypertrophy and dysfunction induced by Gq. *Proc Natl Acad Sci USA* 99: 3866–3871, 2002.
32. **Molkentin JD and Dorn IG, II.** Cytoplasmic signaling pathways that regulate cardiac hypertrophy. *Annu Rev Physiol* 63: 391–426, 2001.
33. **Muiesan ML, Salvetti M, Rizzoni D, Castellano M, Donato F, and Agabiti-Rosei E.** Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment. *J Hypertens* 13: 1091–1095, 1995.
34. **Murray PA and Vatner SF.** Reduction of maximal coronary vasodilator capacity in conscious dogs with severe right ventricular hypertrophy. *Circ Res* 48: 25–33, 1981.
35. **Parfrey PS, Harnett JD, Griffiths SM, Taylor R, Hand J, King A, and Barre PE.** The clinical course of left ventricular hypertrophy in dialysis patients. *Nephron* 55: 114–120, 1990.
36. **Pfeffer MA, Pfeffer JM, and Frohlich ED.** Pumping ability of the hypertrophying left ventricle of the spontaneously hypertensive rat. *Circ Res* 38: 423–429, 1976.
37. **Roberts JT, Wearn JT, and Boten I.** Quantitative changes in the capillary muscle relationship in human hearts during normal growth and hypertrophy. *Am Heart J* 21: 617–633, 1941.
38. **Sadoshima J and Izumo S.** The cellular and molecular response of cardiac myocytes to mechanical stress. *Annu Rev Physiol* 59: 551–571, 1997.
39. **Sadoshima J, Montagne O, Wang Q, Yang G, Warden J, Liu J, Takagi G, Karoor V, Hong C, Johnson GL, Vatner DE, and Vatner SF.** The MEKK1-JNK pathway plays a protective role in pressure overload but does not mediate cardiac hypertrophy. *J Clin Invest* 110: 271–279, 2002.
40. **Shioi T, Kang PM, Douglas PS, Hampe J, Yballe CM, Lawitts J, Cantley LC, and Izumo S.** The conserved phosphoinositide 3-kinase pathway determines heart size in mice. *EMBO J* 19: 2537–2548, 2000.
41. **Shioi T, McMullen JR, Kang PM, Douglas PS, Obata T, Franke TF, Cantley LC, and Izumo S.** Akt/protein kinase B promotes organ growth in transgenic mice. *Mol Cell Biol* 22: 2799–2809, 2002.
42. **Stack RS, Rembert JC, Schirmer B, and Greenfield JC Jr.** Relation of left ventricular mass to geometry of the proximal coronary arteries in the dog. *Am J Cardiol* 51: 1728–1731, 1983.
43. **Takagi G, Okumura S, Kawabe J, Hong C, Yang G, Meguro T, Takagi I, AY Gaussin V, Vatner DE, Sadoshima J, Homcy CJ, Ishikawa Y and Vatner SF.** Adenylyl cyclase type 5 disruption preserves cardiac function in response to pressure overload (Abstract). *Circulation Suppl* 106: 11–59, 2002.
44. **Thomas SA, Matsumoto AM, and Palmiter RD.** Noradrenaline is essential for mouse fetal development. *Nature* 374: 643–646, 1995.
45. **Tomanek RJ.** Response of the coronary vasculature to myocardial hypertrophy. *J Am Coll Cardiol* 15: 528–533, 1990.
46. **Tomanek RJ, Wangler RD, and Bauer CA.** Prevention of coronary vasodilator reserve decrement in spontaneously hypertensive rats. *Hypertension* 7: 533–540, 1985.
47. **Trimarco B, Lembo G, De Luca N, Volpe M, Ricciardelli B, Condorelli G, Rosiello G, and Condorelli M.** Blunted sympathetic response to cardiopulmonary receptor unloading in hypertensive patients with left ventricular hypertrophy. A possible compensatory role of atrial natriuretic factor. *Circulation* 80: 883–892, 1989.
48. **Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, and Santucci A.** Ambulatory blood pressure an independent predictor of prognosis in essential hypertension. *Hypertension* 24: 793–801, 1994.
49. **Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, Reboldi G, and Porcellati C.** Prognostic significance of serial changes in left ventricular mass in essential hypertension. *Circulation* 97: 48–54, 1998.
50. **Wang Y, Huang S, Sah VP, Ross J Jr, Brown JH, Han J and Chien KR.** Cardiac muscle cell hypertrophy and apoptosis induced by distinct members of the p38 mitogen-activated protein kinase family. *J Biol Chem* 273: 2161–2168, 1998.
51. **Woods JD.** Relative ischaemia in the hypertrophied heart. *Lancet* 1: 696–698, 1961.
52. **Yamori Y, Mori C, Nishio T, Ooshima A, Horie R, Ohtaka M, Soeda T, Saito M, Abe K, Nara Y, Nakao Y, and Kihara M.** Cardiac hypertrophy in early hypertension. *Am J Cardiol* 44: 964–969, 1979.