JACC Vol. 3, No. 5
May 1984:1349–51

EDITORIALS

Regression of Left Ventricular Hypertrophy: Partial Answers for Persistent Questions*

ROBERT C. TARAZI, MD, FACC

Cleveland, Ohio

The development and functional consequences of cardiac hypertrophy have long been a subject of intense interest; this interest was recently heightened by the demonstration that ventricular hypertrophy could be reversed by medical therapy (1). The clinical impact of these observations was further increased by the possibility of quantitating left ventricular hypertrophy noninvasively by echocardiography and, thus, of monitoring the effects of treatment on left ventricular structure and function in patients (2,3). The Framingham studies have added a new dimension to the question by stressing the role of systemic hypertension as a prime cause of left ventricular hypertrophy (4) and by reporting its early development in the offspring of hypertensive parents (5).

Complexities of Left Ventricular Hypertrophy

Studies from different centers succeeded each other rapidly and began to outline a picture of hypertensive left ventricular hypertrophy that was different and more complex than previously thought. Thus, the relation between hypertension and left ventricular hypertrophy, usually thought of as a direct response of the heart to a pressure overload, was observed from both experimental and clinical studies to involve more factors than blood pressure levels alone. Increases in left ventricular wall thickness and mass developed early in the evolution of the disease, and could be made to regress in relatively short periods with some, but not all, forms of equipotent antihypertensive therapy. Ventricular weight did not always correlate with arterial pressure levels; the correlation was better with diurnal averages than with single readings, but even then, the index of determination rarely exceeded 25 to 30% (6). Because of the poor prognosis associated with electrocardiographic left ventricular hypertrophy, and in view of the possibility of inducing its regression by antihypertensive measures, evaluation of the functional significance of increased left ventricular mass became more urgent for the large numbers of patients with hypertension. Is it a compensatory process to be left undisturbed, or does it bear the seeds of future decompensation and constitute both an indication for treatment and determinant of the choice of drugs?

The many questions raised by these rapid advances have been addressed in many recent reviews (1,7,8) as well as by Panidis et al. (9) in this issue of the Journal. An editorial on the subject can, therefore, only underline some of the still unanswered questions or point out current research directions with potentially important clinical implications. In this regard, it should also be noted that vascular hypertrophy is an important component of the hypertensive process; the pressure load is imposed on both the heart and the arterial system. Studies of the hypertrophic responses of each could benefit greatly from comparison of the results in both.

Multiple types of left ventricular hypertrophy. The first point to be underlined is a *caveat* regarding simplified or widespread extrapolations from one kind of experimental conditions to cardiac hypertrophy in general. The heterogeneity of cardiac hypertrophy is now well recognized (10); less well recognized perhaps is the presence of important structural and functional differences within the same "type" of hypertrophy (pressure overload). Indeed, recent studies (3) have demonstrated a wide spectrum of variations in hypertensive left ventricular hypertrophy (asymmetric, concentric or eccentric; inappropriate or inadequate to the load). The susceptibility of cardiac function to increased afterload or its dependence on adrenergic support also varied widely among patients; the level of afterload was more of a dominant factor when dilation was associated with hypertrophy (3).

Electrocardiographic versus echocardiographic diagnosis. This multiplicity of types of hypertensive left ventricular hypertrophy naturally raises a question about prognostic conclusions reached mainly on the basis of electrocardiographic left ventricular hypertrophy. The sen-

*Editorials published in *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or of the American College of Cardiology.

From the Department of Clinical Science, The Cleveland Clinic Foundation, Cleveland, Ohio. Manuscript received December 19, 1983, accepted January 11, 1984.

Address for reprints: Robert C. Tarazi, MD, Department of Clinical Science, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106.

0735-1097/84/$3.00

JACC Vol. 3, No. 5
May 1984:1349–51

sitivity and specificity of electrocardiographic signs of ventricular hypertrophy have been widely investigated, as have been the important pitfalls associated with voltage criteria and their dependence on body build and placement of precordial electrodes. The conclusion that changes in precordial voltage relate in some degree to changes in left ventricular mass is a reasonable extrapolation from autopsy correlations, but it has yet to be rigidly established. The superiority of echocardiography in recognizing left ventricular hypertrophy and in allowing a quantitative direct determination of left ventricular wall thickness and mass is widely recognized. Because the correlation in diagnostic power between the two methods favors echocardiography by a wide margin, we should critically examine the implications of those findings for therapy. Whether the serious prognosis associated with the detection of electrocardiographic left ventricular hypertrophy in patients with hypertension also applies to the diagnosis of left ventricular hypertrophy by echocardiographic criteria still remains to be determined.

Reversal of Left Ventricular Hypertrophy

Reversal of cardiac hypertrophy has definitely been demonstrated in both patients and experimental animals (1), but it has also been shown not to depend solely on reduction of the ventricular pressure load. It does not necessarily occur after otherwise successful surgery for aortic regurgitation or stenosis, as noted by Panidis et al. (9), and it is not closely related to blood pressure control in hypertensive subjects. Among the latter, the degree of regression in left ventricular mass varied with the type of antihypertensive agent used (11), but it also differed from patient to patient treated with the same drug (7). In some cases, there was an obvious reason for the lack of regression, such as associated myocardial or coronary disease or lack of maintained blood pressure control. More often than not, however, no apparent cause was found. Although it has been claimed that the greater the left ventricular mass before treatment, the more marked the regression of hypertrophy, exceptions are seen (6); it would be important to determine whether treatment can indeed reduce the mass of a "normal" ventricle. One of the main factors interfering with reversal of left ventricular hypertrophy during antihypertensive therapy appears to be the reflex sympathetic stimulation induced by some vasodilators (12–14). In summary, both the development and regression of left ventricular hypertrophy in response to variations in mechanical load are obviously modulated by many factors such as age, sex, adrenergic drive and humoral influences including the renin-angiotensin system (1,15). To the degree that those factors can be influenced by treatment and to the extent that reversal of hypertrophy might appear a desirable goal, future choices of therapy may be influenced by current research directed to those factors and to the functional consequences of reduction in left ventricular mass.

Is Reversal of Cardiac Hypertrophy Beneficial?

Left ventricular function. Whether regression of cardiac hypertrophy is beneficial or harmful still remains an unanswered question. Naturally, the first studies were directed to examination of the pumping efficiency of hearts demonstrating regression of hypertorphy; they revealed no impairment in ejection fraction, left ventricular fractional shortening (14,16) or peak cardiac output (17,18) after reduction of left ventricular mass. Neither ejection indexes nor cardiac output levels are sufficient by themselves to adequately describe cardiac performance and reserve. However, few studies have carefully differentiated the effects of regression of hypertrophy from those of blood pressure control on those results; it is essential to consider the effects of alterations in afterload (as evaluated from end-systolic left ventricular stress, for instance) on changes in cardiac function before drawing conclusions regarding the consequences of reduction in ventricular mass (7,14). Moreover, responses to sudden or rapidly developing increases in afterload or to different forms of exercise are needed to evaluate the heart's ability to withstand the stresses of everyday life or sudden exacerbations in hypertension. Still undetermined are the effects of regression of hypertrophy on abnormalities in diastolic function of the left ventricle that are common in hypertension and that have recently been reported to correlate with left ventricular mass (19).

Inotropic responses and coronary vascular reserve. At more basic levels, left ventricular hypertrophy has been associated with reductions in inotropic responses to catecholamines (20) and coronary vascular reserve (21). Both may play a role in the evolution of heart disease in ventricular hypertrophy; their responses to therapy still need further definition. A wide spectrum of alterations at various points in the adenylate cyclase system has been described in the myocardium of hypertensive rats (22); progressive reduction of inotropic response to activators of that system may rob the hypertrophied ventricle of adrenergic support and play a role in the eventual progression from hypertrophy to heart failure. Early reports suggest that some of those abnormalities may be corrected with regression of left ventricular hypertrophy. Reduction in coronary flow reserve is seen in severe hypertrophy. Of particular interest in relation to blood pressure control and changes in left ventricular mass is the balance that exists between coronary perfusion pressure and myocardial mass. A reduction in blood pressure without a concomitant reduction in hypertrophy can upset this balance and interfere with coronary flow reserve (23). If confirmed, these observations might have important clinical implications.

Regression of vascular hypertrophy. The question regarding coronary flow raises a wider question about the possibility of regression of vascular hypertrophy by antihypertensive therapy. Vascular lesions play a major role in the evolution of hypertension and its complications. Increased wall thickness of resistance vessels will amplify the effects of even normal vasconstrictor stimuli on peripheral resistance, so that vascular hypertrophy will help perpetuate hypertension (24). Early studies (25) showed a parallelism between variations in heart weight and indexes of protein synthesis in the mesenteric arteries of spontaneously hypertensive rats. Reports from Göteborg (26) suggest that regression of the structural component of peripheral resistance occurs along with reduction of cardiac mass during antihypertensive treatment in spontaneously hypertensive rats. However, significant differences in structural response to hypertension were found between the myocardium and the aorta.

Implications. All these questions obviously need more precise answers regarding the importance of modulating factors, the functional sequelae of regression of left ventricular hypertrophy and the parallelism or divergence between cardiac and vascular hypertrophy. As the picture becomes clearer, with more precise differentiation of various types of hypertensive disease, there is no doubt that considerations of regression of hypertrophy will be a major influence in the decision for and choice of therapy.

References

1. Tarazi RC, Sen S, Fouad FM, Wicker P. Regression of myocardial hypertrophy: conditions and sequelae of reversal in hypertensive heart disease. In: Alpert NR, ed. Myocardial Hypertrophy and Failure. New York: Raven, 1983:637–52. (Alpert NR, ed. Perspectives in Cardiovascular Research; vol 7.)
2. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1977;55:613–8.
3. Abi-Samra F, Fouad FM, Tarazi RC. Determinants of left ventricular hypertrophy and function in hypertensive patients: an echocardiographic study. Am J Med 1983;75(suppl 3A):26–33.
4. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram: prevalence, incidence and mortality in the Framingham study. Ann Intern Med 1969;71:89–105.
5. Savage DD, Abbott RD, Anderson SJ, Padgett S. Determinants of left ventricular mass and reference values based on a large population-based sample of apparently healthy subjects: the Framingham study (abstr). Circulation 1983;68(suppl III):III-336.
6. Rowlands DB, Glover DR, Stallard TJ, Littler WA. Control of blood pressure and reduction of echocardiographically assessed left ventricular mass with once-daily timolol. Br J Pharmacol 1982;14:89–95.
7. Tarazi RC, Foaud FM. Reversal of cardiac hypertrophy in man. Hypertension (in press).
8. Drayer JIM, Weber MA, Gardin JM, Lipson JL. Effect of long-term antihypertensive therapy on cardiac anatomy in patients with essential hypertension. Am J Med 1983;75(suppl 3A):116–20.
9. Panidis IP, Kotler MN, Ren JF, Mintz GS, Ross J, Kalman P. Development and regression of left ventricular hypertrophy. J Am Coll Cardiol 1984;3:1309–20.
10. Skelton CL, Sonnenblick EH. Heterogeneity of contractile function in cardiac hypertrophy. Circ Res 1974;34,35(suppl II):II-83–96.
11. Sen S, Tarazi RC, Khairallah PA, Bumpus FM. Cardiac hypertrophy in spontaneously hypertensive rats. Circ Res 1974;35:775–81.
12. Sen S, Tarazi RC. Regression of myocardial hypertrophy and influence of adrenergic system. Am J Physiol 1983;244:H-97–101.
13. Drayer JIM, Gardin JM, Weber MA, Aronow WS. Cardiac muscle mass during vasodilation therapy of hypertension. Clin Pharmacol Ther 1983;33:727–32.
14. Fouad FM, Tarazi RC, Bravo EL. Cardiac and haemodynamic effects of enalapril. Hypertension 1983;1(suppl 1):1-135–42.
15. Frohlich ED. Hemodynamics and other determinants in the development of left ventricular hypertrophy: conflicting factors in its regression. Fed Proc 1983;42:2709–15.
16. Wollam GL, Hall WD, Porter VD, et al. Time course of regression of left ventricular hypertrophy in treated hypertensive patients. Am J Med 1983;75(suppl 3A):100–10.
17. Spech MM, Ferrario CM, Tarazi CM, Tarazi RC. Cardiac pumping ability following reversal of hypertrophy and hypertension in spontaneously hypertensive rats. Hypertension 1980;2:75–82.
18. Kuwajima I, Kardon MB, Pegram BL, Sesoko S, Frohlich ED. Regression of left ventricular hypertrophy in two-kidney, one-clip Goldblatt hypertension. Hypertension 1983;4(suppl II):113–8.
19. Fouad FM, Slominski JM, Tarazi RC. Left ventricular diastolic function in hypertension: relation to left ventricular mass and systolic function. J Am Coll Cardiol (in press).
20. Ayobe MH, Tarazi RC. Beta-receptors and contractile reserve in left ventricular hypertrophy. Hypertension 1983;5(suppl I):192–7.
21. Marcus ML, Mueller TM, Gascho JA, Kerber RE. Effects of cardiac hypertrophy secondary to hypertension on the coronary circulation. Am J Cardiol 1979;44:1023–8.
22. Kumano K, Upsher ME, Khairallah PA. Beta-adrenergic receptor response coupling in hypertrophied hearts. Hypertension 1983;5(suppl I):174–83.
23. Wicker P, Tarazi RC, Kobayashi K. Coronary blood flow during the development and regression of left ventricular hypertrophy in renovascular hypertensive rats. Am J Cardiol 1983;51:1744–9.
24. Folkow B. Cardiovascular structural adaptation; its role in the initiation and maintenance of primary hypertension. Clin Sci Mol Med 1978;55:3s–22s.
25. Yamori Y, Nakada T, Lovenberg W. Effect of antihypertensive therapy on lysine incorporation into vascular protein of the spontaneously hypertensive rat. Eur J Pharmacol 1976;38:349–55.
26. Hallback-Nordlander M. Functional consequences of structural adaptation of the heart in hypertension. Hypertension (in press).