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Editorial Comment

Left Ventricular Hypertrophy and Sudden Death*

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Much interest has been engendered in recent years about the pathogenesis and risk of left ventricular hypertrophy (LVH) in patients with hypertension and its related outcomes with respect to left ventricular failure, cardiac dysrhythmias and sudden cardiac death (1–5). The risk associated with LVH is very real and severe, even greater than that of the increased systolic or diastolic pressures that are associated with this complication. Nevertheless, the fundamental physiologic mechanism(s) explaining that risk remain(s) to be defined clearly (6). Most important, it still remains abundantly clear that, to date, there have been no major definitive studies reported that demonstrate reversal of the risk associated with

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LVH can be reduced by decreasing the increased left ventricular mass therapeutically independent of the coexistent reduction in arterial pressure or other effects of the antihypertensive drugs. Several multicenter studies are presently in progress to arrive at this conclusion; but, as yet, a large, well-controlled pharmacologic trial has not demonstrated such a reduction in either total or cardiovascular morbidity and mortality associated with reduction of left ventricular mass. To be sure, all antihypertensive agents (including the diuretics and even the direct-acting vascular smooth muscle relaxants) have been shown to reduce left ventricular mass given a sufficiently long enough period of treatment (3). Thus, to demonstrate that reversal of LVH per se is associated with reduced risk, the effect must be independent of the decreased arterial pressure, the antiarrhythmic effect of some of the antihypertensive drug classes, as well as from other actions of the antihypertensive drugs even though those effects may also be beneficial (6).

Throughout all of the reports that have demonstrated the pharmacologic and clinical effects of antihypertensive drug treatment on the course of hypertensive heart disease, one very clear and reasoned epidemiologic voice has rung out clear and true; and this has emanated from the constant flow of illuminating reports of the Framingham Heart Study. At first, there was the major signal study that indicated that a number of "factors of risk" can be identified that predispose the patient to premature morbidity and mortality from coronary heart disease (7). Incidently, this exposition of specific risk factors by Dr. William B. Kannel was the first use of the term "risk factors;" and it has been adopted ever since throughout the various medical disciplines for "risk factors" underlying other diseases. Shortly after the introduction of this term, the Framingham Heart Study identified electrocardiographic evidence of LVH as yet another independent "factor of risk" for extremely severe adverse cardiovascular events (8,9). More recently, the Framingham investigators generated another important series of publications that demonstrated that the more sensitive echocardiographic techniques confirm the increased risk of LVH—but at a much earlier clinical stage of LVH development (10–12).

The Framingham Heart Study had already demonstrated that the most common cause of congestive heart failure in this country was hypertension; the second most common cause was hypertension associated with ischemic heart disease; and the third cause was hypertension associated with other cardiac diseases (13,14). More recently, the Framingham Heart Study demonstrated further that not only was hypertension the most common cause of cardiac failure, but that it is importantly contributed to and exacerbated by hypertensive LVH, which in turn resulted in impaired left ventricular function (5).

And, now, in this issue of the Journal, the Framingham Heart Study provides us with still another "gem" that extends their experience with LVH from their remarkable cohort (15). Until this time, there had been no report of the risk of sudden cardiac death in individuals with echocardiogram-positive LVH. This report demonstrates very clearly that increased left ventricular mass and LVH are associated with increased risk for sudden cardiac death (15). That LVH predisposes the patient with hypertension to coronary heart disease, left ventricular failure and sudden cardiac death only underscores the severe clinical outcomes of hypertensive heart disease; it does not define the underlying functional mechanism(s) of death from LVH.

In early clinical studies LVH had been shown to be associated with a greater prevalence of left ventricular dysrhythmias (16–18); but this clinical observation has not been useful in explaining the underlying mode of death pathophysiologically (19,20). Several more recent reports have demonstrated that the earlier experimental findings of reduced left ventricular flow and flow reserve (21,22) also occur in patients with hypertensive LVH (23,24). Still more recently, one clinical study demonstrated significant improvement in left ventricular flow and flow reserve that was associated with pharmacologically induced reduction in left ventricular mass with an angiotensin-converting enzyme (ACE) inhibitor (25) and experimentally, even more so, still more effectively with the concurrent use of an ACE inhibitor and an angiotensin II (type 1) receptor antagonist than when either of these agents was used alone (26). Perhaps this results from the multiplicity of

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actions of this drug combination including: reduced local generation of and receptor stimulation by angiotensin II; the potential of local coronary vasodilation promoted by increased bradykinin resulting from ACE inhibition (27,28); additional angiotensin II receptor (type I) inhibition, especially in the patient in whom its generation from angiotensin I may be greater quantitatively as a result of ventricular chymase action (29); and the local effect of ACE inhibition on the endothelial dysfunction of the coronary circulation associated with hypertensive coronary arterial disease (30).

Still another mechanism may participate in the increased risk associated with LVH; and this relates to increased myocardial fibrosis and collagen deposition in the ventricular wall chamber (31). Left ventricular dysfunction (especially diastolic) has been an important finding in patients with hypertensive LVH, particularly those who are elderly or with concurrent ischemic heart disease resulting from either coexisting coronary epicardial occlusive atherosclerosis or the coronary arteriolar disease of severe hypertension with LVH (32). The fibrosis promotes a stiffer and less distensible left ventricular chamber that, in turn, impairs its functional performance. Experimental studies in our laboratory involving progressively aging spontaneously hypertensive rats (SHR) have demonstrated that both the aging process itself as well as coronary hypertensive vascular disease adversely affected coronary circulation and that these affects were at least additive (33). These studies demonstrated that myocardial fibrosis and collagen deposition were closely associated with the progressive deterioration of the coronary hemodynamics of the aging normotensive control rats as well as of the SHR. Moreover, the fibrosis affected the right ventricle as well as the left. These findings may provide a fundamental mechanistic explanation for the diastolic dysfunction and cardiac dysrhythmias that are encountered clinically in the older patients with hypertensive LVH studied echocardiographically (5). Indeed, we must keep these potential findings in mind when we observe the increased mass of the left ventricle observed echocardiographically; it may not only be hypertrophied left ventricular myocardium, but also increased amount of deposited collagen tissue and fibrosis associated with aging, hypertension and ischemia. Hence, the diastolic dysfunction may not result only from the LVH per se in these elderly patients, but also from the impaired coronary hemodynamics and reduced ventricular contractility associated with aging and fibrosis. Moreover, the findings reported herein concerning the increased risk of sudden cardiac death in patients with LVH may also be explained by these recent pathophysiologic findings. Remaining to be explained, however, is the apparent significantly greater incidence of sudden cardiac death in the male patients with LVH reported therein; but, as the authors suggested, there may also be other confounding variables, some of which they have identified as well as others that still remain to be sorted out (15).

Nevertheless, once again cardiovascular medicine (and medicine in general) has been the beneficiary of the outstanding forethought and wisdom of the earlier Framingham Heart Study investigators and the remarkable and productive team that has succeeded them.

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