Hypertension and Sudden Cardiac Death

Franz H. Messerli

Left ventricular hypertrophy (LVH) has been identified as one of the strongest blood pressure-independent risk factors for sudden death, acute myocardial infarction, congestive heart failure, and other cardiovascular morbidity and mortality. Hypertensive patients with LVH have a significantly greater prevalence of premature ventricular contractions and complex ventricular arrhythmias than do patients without LVH or normotensive patients. Antihypertensive therapy reduces LVH, although not all antihypertensive drugs are equipotent in this regard. Angiotensin-converting enzyme inhibitors are probably the most effective in reducing LVH, followed by calcium antagonists, diuretics, and β-blockers. The effect of angiotensin receptor blockers on left ventricular mass is unclear at the present, some studies showing a reduction, some studies showing no effect. A reduction in LVH has been shown to diminish LVH-associated arrhythmias. However, it remains to be shown that patients with LVH and ventricular ectopy are at a higher risk for sudden death than those without ventricular ectopy and that the reduction of LVH-associated ventricular ectopy indeed confers a clinical benefit that exceeds the one from the reduction of arterial pressure alone. Am J Hypertens 1999;12:181S–188S © 1999 American Journal of Hypertension, Ltd.

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The clinical spectrum of hypertensive heart disease ranges from impaired-filling ventricular remodeling to left ventricular hypertrophy (LVH) to congestive heart failure. LVH has been identified as one of the strongest blood pressure-independent risk factors for sudden death, acute myocardial infarction, congestive heart failure, and other cardiovascular morbidity and mortality.1–3 These findings abolish the concept of LVH being a benign adaptive process serving to compensate for the increased hemodynamic burden (Figure 1).3 On the basis of these epidemiologic observations, a pathophysiologic or electrophysiologic chain of evidence linking hypertension, LVH, and sudden death has been proposed. Although it is unclear whether a reduction in LVH confers benefit over and above the benefit of lowering blood pressure alone, the effects of various antihypertensive agents on LVH have come under scrutiny.

LEFT VENTRICULAR HYPERTROPHY AND VENTRICULAR ARRHYTHMIAS

As early as 1984, we reported that hypertensive patients with LVH have a significantly greater prevalence of premature ventricular contractions (PVC) and complex ventricular arrhythmias than do patients without LVH or normotensive subjects,3 a finding that was later expanded to obese patients with eccentric LVH5 and confirmed in large population-based studies.6,7 Although it is still controversial whether these findings could explain, at least in part, the higher incidence of sudden cardiac death in these patients, a
study from the Framingham cohort recently indicated that in patients with LVH, the presence of asymptomatic ventricular arrhythmias was indeed associated with a nearly twofold increase in mortality.

In our study, ventricular ectopic activity was increased in patients with echocardiographically demonstrated LVH (475 ± 852 PVC/24 h), as compared with normotensive patients (8.17 ± 20.1 PVC/24 h) or hypertensive patients without LVH (10 ± 22.1 PVC/h) (both P < .01 vs the hypertensive patients with LVH).

As of this writing, several independent studies have been published (Table 1); all but one found a higher percentage of patients with ventricular arrhythmias in the LVH group than in patients with normal hearts, although the correlation between pressure levels, LVH, and ventricular arrhythmias was rather weak. In contrast to ventricular arrhythmias, the data regarding the association of LVH and atrial arrhythmias are sparse. Data from the Framingham cohort support evidence of an increased prevalence of atrial fibrillation among patients with hypertensive cardiovascular disease as compared with control subjects, both in men (risk ratio, 2.1) and in women (risk ratio, 1.9). Moreover, when different cardiovascular risk factors were taken into consideration, LVH was found to be a better predictor of atrial fibrillation than smoking, hypertension, or diabetes.

ETIOLOGY OF VENTRICULAR ARRHYTHMIAS IN HYPERTENSION

The mechanism by which LVH leads to increased arrhythmogenicity and ultimately to increased mortality remains unknown. A variety of factors associated with LVH are currently being considered as possible mechanisms (Figure 2):

1. LVH and hypertension without LVH are commonly associated with subendocardial ischemia. Microvascular angina has been reported to be common in hypertensive patients even in the absence of LVH.

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**TABLE 1. LEFT VENTRICULAR HYPERTROPHY AND VENTRICULAR ECTOPY**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Criterion</th>
<th>Normal LV Mass</th>
<th>LV Hypertrophy</th>
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<tr>
<td></td>
<td></td>
<td>PVC/24 h</td>
<td>% Patients With PVC</td>
<td>PVC/24 h</td>
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<tr>
<td>Messerli et al³⁹</td>
<td>1981</td>
<td>Lown &gt;2</td>
<td>10</td>
<td>475*</td>
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<tr>
<td>Loaldi et al¹⁰</td>
<td>1983</td>
<td>PVC/h &gt;10</td>
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<td>McLenachan et al⁷</td>
<td>1987</td>
<td>Couplets</td>
<td>16</td>
<td>36‡</td>
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<tr>
<td>Aronow et al¹³</td>
<td>1987</td>
<td>Couplets</td>
<td>44</td>
<td>75‡</td>
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<tr>
<td>Levy et al¹²</td>
<td>1987</td>
<td>PVC/h &gt;1</td>
<td>30</td>
<td>35‡</td>
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<tr>
<td>Lavie et al¹³</td>
<td>1988</td>
<td>Lown &gt;2</td>
<td>24</td>
<td>291*</td>
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<tr>
<td>Papademetriou et al¹⁴</td>
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<td>Lown &gt;2</td>
<td>65</td>
<td>346*</td>
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<tr>
<td>Szlachcic et al¹⁵</td>
<td>1989</td>
<td>PVC/h &gt;30</td>
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<td>1989</td>
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<td>412*</td>
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<td>Lown &gt;2</td>
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<td>46‡</td>
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<td>Vardas et al²⁵</td>
<td>1994</td>
<td>Lown &gt;1</td>
<td>25</td>
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<td>1996</td>
<td>Lown &gt;1</td>
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LV, left ventricular; PVC, premature ventricular contractions.

* Significant vs patients with normal LV mass.
† P < 0.05 vs patients with normal LV mass.
In the course of hypertensive cardiac hypertrophy, the coronary arteries fail to grow at a rate sufficient to compensate for the muscular hypertrophy, and the myocardium becomes relatively underperfused.32 Hypertension by itself, irrespective of LVH, is a major risk factor for coronary artery disease.34 The three mechanisms mentioned thus far result in decreased coronary reserve and chronic ischemia, which is a well-recognized stimulus for arrhythmias of all types.

The irregular hypertrophy pattern2,35 could, indeed, impede the homogeneous propagation of the electric impulse throughout the myocardium. Any disturbance of impulse propagation can give rise to reentry mechanisms and thereby lead to ectopic impulse formation. The pattern of hypertrophy detected on echocardiography is considered to be related to the prognosis and type of cardiovascular complications one may expect to encounter in the course of hypertension, although the exact mechanism is not understood.2,36 Thus, eccentric hypertrophy has been associated with more severe ventricular arrhythmias,35 whereas concentric hypertrophy is more closely related to ischemic events resulting from abnormal coronary autoregulation.37 Even the less frequently detected isolated septal hypertrophy is associated with an increased prevalence of atrial and ventricular arrhythmias, although its significance is unknown.38

The amount of fibrosis within the myocardium is also known to vary, depending primarily on the pathophysiologic mechanism accounting for hypertension in each patient. Increased fibrosis is a well-recognized factor accounting for nonhomogeneous propagation of electrical impulses throughout the myocardium. Any disturbances of impulse propagation can give rise to reentry mechanisms and thereby lead to ventricular arrhythmias.

The hypertrophied cardiac myocyte has been documented to be electrophysiologically different from and more arrhythmogenic than the normal myocyte.39 A number of structural changes that occur in hypertrophy have been related to the susceptibility of the hypertrophied myocardium to arrhythmias. Low-resistance pathways through the intercalated discs of the hypertrophic myocardium undergo changes that serve to increase the surface of the gap region involved in cell-to-cell communication.40 In addition, dilatation of the transverse tubule system (involved in the transmission of the surface action potential to the sarcomere)41 and an increase in the number of mitochondria (responsible for the cell energy status) are commonly found. However, it has not yet been shown whether these structural changes correlate with electrophysiologic abnormalities.

Excessive fluctuation in arterial pressure, as occurs in labile hypertension, may be arrhythmogenic41–43 because it continuously changes the loading conditions of the left ventricle. The cardiac myocyte is capable of reacting to a variety of external stimuli by modifying its structural and functional behavior.44 The stretch-activated channel in the cytoplasmic membrane detects external physical stimuli (ie, in the form of pressure changes), giving rise to a sequence of intracellular ionic events that affect the electrical stability of the cell. Both experimental and clinical studies have shown that mechanical stretching of the myocyte induces a decrease in the electric threshold, as was shown by James and Jones,43 who, gradually increasing afterload by pharmacologic means, demonstrated a positive correlation between this parameter and the rate of ventricular ectopic activity. Conversely, work from other laboratories has shown that acute reductions in afterload caused by electrically inactive drugs, such as nitroprusside, in patients with a high basal rate of ventricular ectopy drastically diminish the prevalence of arrhythmias. Thus, this mechanism is regarded as one of the factors implicated in the genesis of ventricular arrhythmias in patients with LVH.

Excessive activity of the sympathetic nervous system and the renin-angiotensin system has been implicated in the pathogenesis of essential hypertension and may play a particularly important role in the development of LVH. Sympathetic stimulation has been well documented to exert a direct proarrhythmic effect.45–48 Although the renin-angiotensin system has been implicated in the pathogenesis of LVH49,50 the evidence that angiotensin II may exert direct arrhythmogenic effects is somewhat less conclusive.

It seems, therefore, that the arrhythmogenicity of LVH is multifactorial in origin. However, regardless of the exact or predominant electrophysiologic mech-
anism, it is clear that the hypertrophied myocardium provides fertile soil for the sprouting of ventricular arrhythmias.

VENTRICULAR ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

The fact that ventricular ectopy is common in patients with LVH does not prove that these irregular heartbeats herald ventricular fibrillation or other fatal electric events. Several electrophysiologic studies carried out in patients with LVH have had contradictory results. Vester et al documented enhanced arrhythmogenicity in a series of 40 hypertensive patients in whom coronary heart disease had been previously excluded. The authors found a significantly higher left ventricular mass index (158 ± 44 vs 222 ± 112 g/m²) and lower ejection fraction (71 ± 17 vs 47 ± 18) in the group of patients in whom malignant arrhythmias (ventricular tachycardia or ventricular fibrillation) were induced by programmed electrical stimulation.

A study by Aronow et al, in a geriatric population followed for an average of 27 months, showed that hypertensive patients without documented coronary artery disease and with echocardiographic LVH were significantly more likely to experience ventricular fibrillation or sudden death than their counterparts without LVH (31% vs 10%). It stands to reason (but remains unproved) that in a population documented to be at a very high risk for sudden cardiac death (such as patients with LVH), individuals with the greatest degree of electric instability are likely to be at highest risk.

ANTIHYPERTENSIVE TREATMENT AND REDUCTION OF LEFT VENTRICULAR HYPERTROPHY

Of all antihypertensive drugs, angiotensin-converting enzyme (ACE) inhibitors are probably the most effective in reducing LVH. Recently, Schmieder et al performed a meta-analysis that included only prospective randomized studies comparing the effects of two or more therapies by assessing LVH and structure with blindly read echocardiograms. Of more than 400 studies, only 50 clinical trials fulfilled these criteria. As in previous meta-analyses, the decrease in left ventricular mass was greater with active drug treatment than with placebo and was directly related to the pretreatment left ventricular mass, control of pressure, and duration of treatment. When the analysis was adjusted for several factors, ACE inhibitors were most efficient in reducing LVH, followed by calcium antagonists, the diuretics, and the β-blockers (Figure 3). Indeed, some reports suggest that ACE inhibitors may lower blood pressure more than one would expect from their unloading properties alone. The ability of ACE inhibitors to produce regression in LVH at a dose that does not lower blood pressure supports the hypothesis that the local cardiac angiotensin system is a significant determinant of heart structure and function. As a class, calcium antagonists seem slightly less potent in reducing LVH than do the ACE inhibitors, with heart rate–lowering agents possibly having a greater effect than the dihydropyridines. A lesser effect on LVH is, in general, assigned to the β-blockers, the postsynaptic α-blockers, and the diuretics. However, recent findings in 690 men, a high percentage of whom were black, from the VA cooperative study showed hydrochlorothiazide to be as efficacious as captopril, and more efficacious than atenolol, diltiazem, prazosin, and clonidine in reducing LVH. Of note, there is uncertainty as to exactly what a drug-induced reduction of LVH means in terms of morbidity and mortality, and there are no conclusive data that a reduction in LVH would confer a benefit exceeding that conferred by the reduction in arterial pressure per se. These drawbacks notwithstanding, it can be extrapolated that the combination of an ACE inhibitor and a calcium antagonist ought to be particularly efficacious with regard to a reduction of LVH. Because these two drug classes have the potential to interfere with the pathogenesis of LVH at a similar level, one can argue that this combination will reduce LVH more than one would expect from its blood pressure–lowering effects alone.

Whether angiotensin receptor blockers (ARB), either in monotherapy or in combination, are as efficient as ACE inhibitors in reducing LVH remains questionable. Blockade of the angiotensin II type 1 (AT1) receptor is accompanied by an increase in plasma levels of angiotensin II and its metabolites. This could stimulate the angiotensin II type 2 (AT2) receptors, which

FIGURE 3. Reduction of left ventricular mass with various drug classes in prospective, double-blind, randomized studies. LVMI = left ventricular mass index. Adapted from Schmieder et al.59,60
are not blocked by ARB. It appears that activation of the AT2 receptors inhibits proliferation and stimulates apoptosis, which prevents myocardial hypertrophy. Moreover, Mizuno et al64 found that the angiotensin II in cardiac tissue, rather than circulating angiotensin II, plays an important role in the pathophysiology of LVH in spontaneously hypertensive rats. If this is the case in humans, ARB should be superior to ACE inhibitors in reducing left ventricular mass (LVM). In various animal models, ARB prevented or caused regression of LVH.65–68 In one study, candesartan cilexetil reduced LVM even at a dose that did not lower blood pressure.68 In another recent study, blocking the renin-angiotensin-aldosterone system with the combination of ACE inhibitor and ARB reduced blood pressure and LVM more than did blocking the system with either drug alone.69 Unlike the convincing results from animal models, no data from large clinical studies are available to support regression of LVM with ARB. In two small clinical studies, no reduction in LVM with losartan was observed.70,71 However, in a recent double-blind trial in 58 patients, valsartan seemed to reduce LVM more than did atenolol.72 Further, in another double-blind trial with 115 patients, irbesartan provided quicker and greater LVH regression than did the β-blocker atenolol.73 This would indicate that losartan is less effective than some of the newer, longer-lasting ARB in reducing LVM. The results from the large ongoing prospective clinical study—Losartan Intervention for Endpoint Reduction in Hypertension (LIFE)—will clarify this dilemma.74

**EFFECT OF REDUCTION OF LEFT VENTRICULAR HYPERTROPHY ON VENTRICULAR ARRHYTHMIAS**

The reduction of LVH in hypertensive patients has been shown to diminish the ventricular arrhythmias.75 This antiarrhythmic effect seems to be nonspecific and independent of the drug used to reduce LVH. We have documented that a reduction of LVH as the result of 3 months’ treatment with a calcium antagonist significantly diminished ventricular ectopy.79 In contrast, in the very same study, the patient group treated with a diuretic exhibited no decrease in either LVM or in ventricular ectopy. One might argue, however, that calcium antagonists are electrophysiologically active drugs, and therefore the decrease in ventricular ectopy could be directly related to an antiarrhythmic effect of the drug on the ectopically firing myocardium. However, González-Fernández et al.76 in a double-blind study, showed that use of an ACE inhibitor led to a marked reduction in LVH and, at the same time, to a marked reduction in ventricular ectopy, whereas in the placebo group LVH progressed, and there was no change in ventricular ectopy. Because a reduction in ventricular ectopy has been found with use of a calcium antagonist, an ACE inhibitor, and a β-blocker, it seems safe to assume that the decrease in ventricular ectopy associated with a reduction in LVH is not related to a direct antiarrhythmic effect of the drug only. That hemodynamic unloading and improvement of latent subendocardial ischemia were responsible for the reduction in arrhythmias seems unlikely in view of the fact that in our study and in others, despite their similar reduction of the hemodynamic burden, diuretics had no antiarrhythmic effect. However, the potential proarrhythmic effects of diuretics might have outweighed the beneficial hemodynamic effects induced by this class of agents.76 Diuretics have been shown to increase ventricular ectopy, both at rest and during exercise.77,78 This proarrhythmic effect may result from an intracellular electrolyte shift.

**DECREASE IN LEFT VENTRICULAR HYPERTROPHY AND THE RISK OF SUDDEN CARDIAC DEATH**

Studies of the effects of the reduction of LVH on cardiovascular morbidity and mortality are rare. Preliminary reports from Framingham79 have documented that a decrease of LVH as assessed by electrocardiographic criteria does, indeed, lead to a decrease in the risk of sudden cardiac death, acute myocardial infarction, and congestive heart failure. The clinical outcome, as evaluated by the percentage of patients who developed a cardiovascular event (cardiac death, myocardial infarction, stroke, angina, or need for coronary revascularization) over a 10-year period, was drastically reduced in patients in whom LVH was reversed versus those in whom LVH persisted at the end of follow-up (3% versus 25%; P < .01). Similarly, a multicenter study in Eastern Europe80 showed that patients in whom LVM decreased during antihypertensive therapy had many fewer morbid cardiovascular events than did patients in whom LVM remained unchanged or increased. Although both of these studies provide encouraging results, they do not allow the firm conclusion that a reduction of LVH per se prolongs life. To sustain such a conclusion, a study would have to show that a reduction in LVH confers a clinical benefit over and above the reduction in blood pressure alone. Until such data are presented, we should remain cautious in making reduction of LVH the sole therapeutic goal.

**REFERENCES**

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