AJH 1989; 2:16S–23S

# Heart and Hypertension

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**The manifestations of cardiac involvement in hypertension include: (1) the development of hypertensive heart disease characterized by left ventricular hypertrophy (LVH), and (2) the consequences of coronary atherosclerosis, as angina pectoris, myocardial infarction, and sudden cardiac death. Whereas the former is directly related to increased blood pressure, the latter are sequelae of atherosclerosis per se, and hypertension acts only as a risk factor in this regard. This can partially explain why antihypertensive treatment is effective in diminishing the incidence of congestive heart failure, which is the final consequence of LVH, but is not very effective in preventing coronary complications.**

**It is generally accepted about LVH that increased arterial pressure is the major stimulus to cardiac hypertrophy in hypertension; however, there are a lot of both quantitative and qualitative events suggesting that other factors beside blood pressure levels can modulate the development of LVH, in particular neurohumoral influences. From a morphological point of view, hypertrophy of the cardiac muscle is defined as an increase in the size of existing myocardial fibers. In most experimental models, myocardial hypertrophy is associated with myosin isoenzymatic changes, consisting in a shift from the faster migrating isoenzyme $V_1$ to $V_3$, a form that migrates more slowly. However these changes do not occur in all animal species and particularly in humans. In the hypertrophied human ventricle, a decreased ATPase activity of myofibrils was observed, probably related to changes in myosin light chains. Presently the changes in ATPase activity and in ventricular contractility do not still have a clear molecular basis in humans. The main consequences of LVH on myocardial function include: (1) effects on contractility, (2) effects on myocardial response to adrenergic stimulation, (3) effects on diastolic function, and (4) effects on coronary blood flow. As LVH has been demonstrated to be associated with a high incidence of cardiovascular morbidity and mortality, the therapeutic goal for treating hypertension is not only to normalize blood pressure but also to prevent or reverse cardiac damage. Am J Hypertens 1989;2:16S–23S**

KEY WORDS: **Hypertensive heart disease, left ventricular hypertrophy, coronary atherosclerosis.**

The heart is the main target organ of hypertension (Figure 1); manifestations of its involvement include, on one hand, the development of hypertensive heart disease, characterized by left ventricular hypertrophy (LVH), and, on the other hand, the consequences of coronary atherosclerosis, such as angina pectoris, myocardial infarction, and sudden cardiac death. Indeed, hypertension is directly related only to cardiac hypertrophy; regarding coronary heart disease (CHD), hypertension acts indirectly as a risk factor of coronary sclerosis. In considering the frequency of these two main complications of hypertension, several epidemiological studies, first of all the Framingham Study,[1] have shown that the incidence of CHD is predominant; myocardial infarction turned out to be the most frequent among coronary complications followed by angina pectoris and sudden cardiac death.[2] It is important to keep these two different complications of hypertension quite distinct in order to better understand the effects of antihypertensive therapy. Lowering blood pressure values is clearly beneficial for the myo-

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0895-7061/89/$3.50

cardium, as suggested by the decreased incidence of heart failure in treated hypertensives, but there is currently no evidence of an impact of antihypertensive treatment on those structural alterations of arteries, such as atherosclerotic plaques, whose development is not directly related to hypertension. Several trials have indicated that antihypertensive therapy clearly diminished the incidence of heart failure, cerebral vascular accidents, renal damage, and accelerated hypertension,[3-7] but it had little effect on coronary complications.[8-10]

Only the European Working Party on High Blood Pressure in the Elderly trial (EWPPHY) has shown a significant reduction in the cardiac mortality rate (including sudden death), in patients treated with antihypertensive agents. However, this study was conducted in patients over the age of 60 recruited from clinics rather than by population screening.[11] An understanding of why antihypertensive therapy has not reduced the incidence of coronary heart disease is of great interest. Several hypotheses have been suggested: (1) CHD might not be a consequence of hypertension but simply a coexisting disease casually associated with hypertension; (2) the follow-up of most trials might be too short (three to five years) in order to evaluate the effects of blood pressure lowering on the course of atherosclerotic vascular alterations, which develop rather slowly; (3) there may be unfavorable metabolic effects associated with antihypertensive drugs that could counteract the benefit of lowering elevated blood pressure. The available data do not allow us to resolve this problem. The hypertensive heart disease is characterized by left ventricular hypertrophy (LVH). It is generally accepted that the main stimulus to the development of LVH is left ventricular wall stress, which in turn depends on left ventricular pressure and dimension, according to Laplace's law.[12,13] The increased left ventricular pressure and wall stress result in the addition of new myofibrils in parallel (with increased wall thickness and concentric hypertrophy) or in addition of new sarcomeres in series (with fiber elongation and chamber enlargement). The link between increased wall stress and the development of LVH has been well demonstrated in experimental hypertension.[14] However, the molecular signals regulating myocardial hypertrophy are still unknown, and it is not clear how the pressure load is transformed into sarcomerogenesis. According to Meerson,[15] the increased energy requirements resulting from the supranormal workload deplete high energy phosphate stores, and this in turn stimulates nuclear and mitochondrial protein synthesis. It has also been suggested that pressure overload induces a mechanical stretch of myocyte membrane that might represent a stimulus to protein synthesis.[16]

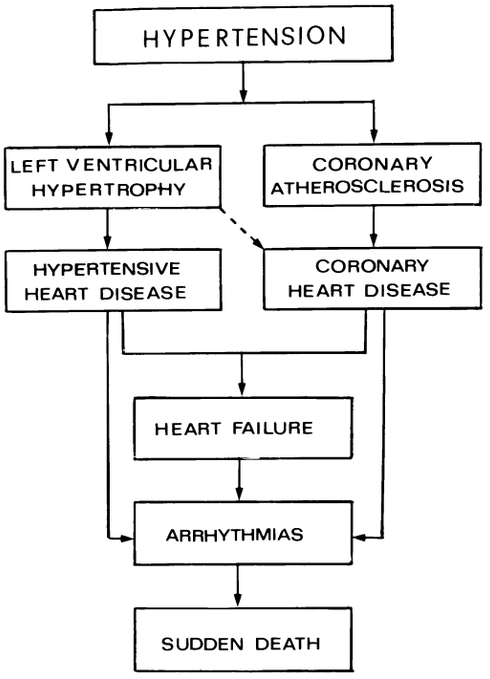


**FIGURE 1.** *Heart involvement in hypertension.*

Left ventricular hypertrophy in hypertension was usually viewed as a direct secondary effect of the increased pressure load. This traditional view has been questioned from time to time, and evidence has accumulated that the development of cardiac hypertrophy is probably due to multiple factors whose role is still debated.[17,18] It is generally accepted that increased arterial pressure is the major stimulus to cardiac hypertrophy in hypertension; however, there are a lot of both quantitative and qualitative events that cannot be explained by the pressure overload alone.

**Quantitative Events** Recent studies have repeatedly shown that the degree of hypertrophy correlated poorly with isolated casual blood pressure levels.[19,20] The average pressure value resulting from several measurements over the 24 hours seems to show a closer (but always weak) relationship with the degree of LVH.[21,22] The correlation index further ameliorates eliminating nighttime pressure as well as pressure measured during daytime rest.[23] A discrepancy between the degree of LVH and the pressure load has been shown also in the spontaneously hypertensive rats (SHR);[24,25] on the contrary, a good correlation between the degree of LVH and blood pressure levels was found in rats with renovascular hypertension.

**Qualitative Events** Recent studies have revealed a wide variability in incidence and pattern of LVH among hypertensive subjects.[26,27] Concentric and eccentric LVH appear to occur with almost the same frequency in hypertensives. These different types of LVH are not related to the degree and the duration of hypertension and are not chronologically related one to the other. These data have led to a departure from the classical

teaching of a progression from concentric hypertrophy (eventually preceded by asymmetric septal hypertrophy) to eccentric hypertrophy (considered as predisposing to heart failure) in the natural history of hypertension. The reasons and the significance of this variability in types of LVH among essential hypertensive patients are not evident; it is evident however that this heterogeneity cannot be explained by pressure overload alone.

All these findings suggest that other factors beside blood pressure levels can modulate the development of LVH in hypertension. Of particular importance seem to be the neurohumoral influences, namely the renin-angiotensin and the adrenergic system. As far as the renin-angiotensin system is concerned, it has been shown that the addition of angiotensin II to myocardial cell tissue culture increases cellular protein synthesis.[28,29] Besides, in the SHR, a positive correlation was found between the degree of LVH and plasma renin activity (PRA).[24] Despite these observations, there is no definite evidence of a role of the renin-angiotensin system in the development of LVH.

There is a great number of both experimental and clinical studies supporting a possible role of catecholamines as additional stimulus to LVH. In experimental animals, subhypertensive doses of norepinephrine (NE)[30,31] or isoproterenol[32] can directly induce ventricular hypertrophy, which is prevented by the contemporary administration of a $\beta$-blocker.[33] Simpson et al[34] have shown that isolated muscle cells from the neonatal ventricle, cultured in serum free medium, grow by hypertrophy when incubated with NE. The growth promoting effect of NE is inhibited by $\alpha_1$-antagonists but not by $\alpha_2$- and $\beta$-antagonists. In the same experimental model isoproterenol does not induce cell hypertrophy. Thus NE-stimulated hypertrophy seems to be mediated through the myocardial cell $\alpha_1$-adrenergic receptors. On the contrary, hypertrophy induced by $\beta$-stimulation seems to be absent or much less evident.[35] These data are not in agreement with previous observation in vivo.[32] In this regard, it has been suggested that hypertrophy induced by isoproterenol in vivo might be mediated indirectly, through increased release of NE facilitated by presynaptic $\beta_2$-adrenoceptor stimulation. Thus the inhibitory effect of $\beta$-blockers on isoproterenol-induced hypertrophy might be due to the inhibition of NE release from presynaptic $\beta_2$-adrenoceptors or to hemodynamic effects related to $\beta$-blockade (decreased heart rate, cardiac work, and $O_2$ consumption). The same cell culture model used by Simpson has allowed us to better define the role of adrenergic receptors.[36] Incubation with NE has been shown to increase myocardial cell size by 1.5 to two-fold and to induce spontaneous contractile activity in about 95% of cells, whereas less than 5% of cells are beating in control cultures. It has been demonstrated that the induction of beating activity requires both $\alpha_1$- and $\beta$-activation. Prevention of hypertrophy by inhibition of protein synthesis does not prevent the beating response. Thus contractile activity could be induced without hypertrophy.[36]

Several clinical studies provide indirect evidence of the role of the adrenergic system in LVH. First, LVH has often been demonstrated in patients with pheochromocytoma without hypertension.[37,38] Second, increased right ventricular wall thickness has been recently observed in patients with essential hypertension without any evidence of pulmonary hypertension;[39] such a finding can not be due to hemodynamic stimuli. In several studies carried out in patients with borderline hypertension, increased interventricular septal thickness was found; this increase was positive related to plasma NE.[40] A significant positive correlation was also found between left ventricular mass index and plasma NE in a subpopulation of hypertensive patients with elevated NE levels at rest.[41] Currently, evidence suggests that in humans as well as in experimental animals, hypertensive LVH is more likely to be reduced when blood pressure is controlled with drugs that blunt adrenergic activity or at least that do not stimulate it.[42,45] From a morphological point of view, hypertrophy of the cardiac muscle is defined as an increase in the size of existing myocardial fibers in contrast to hyperplasia, which implies an increase in the number of cells by mitotic division.[46] In fact, after birth, myocardial cell division progressively decreases in mammalian species and ceases at three to six months of age.[47] However, cardiac growth during fetal life is characterized by an additional hyperplastic phase in the SHR. Thus, in these animals, both the physiological postnatal hypertrophy and the eventual pathological hypertrophy involve a greater cell number as compared with normotensive rats.[48] As well as myocytes, fibroblasts increase their size by hypertrophy, and unlike myocytes, they also increase their number by mitotic division.[49] The rate of incorporation of $H^3$-proline in cardiac collagen and the proline-hydroxylase activity increase within a few days,[50] and collagen increases by ⅓-fold in compensated hypertrophy and by two-fold in dilated hypertrophy.[51] This increase in collagen content causes an increased distance between the capillaries, which do not develop in proportion to the degree of myocardial hypertrophy, an augmented muscle stiffness and a reduced diastolic compliance.[52] In the SHR, not only does the total collagen increase,[53] but the collagen phenotypes also change during development of hypertrophy.[54] In the six-month-old SHR type V collagen (type A and B), prevalent in normotensive rats, is almost undetectable. This decrease is associated with an increase in $\alpha$-III collagen. Currently we don't know the significance of these alterations in collagen phenotypes.

The increase in protein synthesis, which occurs rather early, is also related to contractile proteins so that in a

hypertrophied ventricle myofibrils increase by two-fold as compared with a normal ventricle.[55] In most experimental models, hypertrophy of the ventricular myocardium is associated with myosin isoenzymatic changes. In SHR, a shift from the faster migrating isoenzyme $V_1$ (prevalent in normotensive rats) to $V_3$, a form that migrated more slowly, was found during development of cardiac hypertrophy.[56,57] The shift from $V_1$ to $V_3$ is accompanied by a lower ATPase activity, a decrease in muscle contraction velocity, an economy of force generation, and a decrease in $O_2$ consumption.[58,59] Thus myosin isoenzymatic modifications constitute an adaptive change of the myocardial cell that contributes to adaptation of cardiac muscle to new functional requirements. However, these changes don't occur in all animal species[60] and particularly in humans. The immunological studies indicate that human myosins are composed mostly of a $V_3$ type, but contain also $V_1$ isomyosin (ranging from 0% to 15% of total myosin). Their relative proportion does not seem to vary during development of cardiac hypertrophy.[61-63] However in a hypertrophied human ventricle, a decreased ATPase activity of myofibrils was observed, whereas no significant changes in the actin-stimulated ATPase activity of purified myosin were observed.[64] These findings have been related to changes in myosin light chains,[65] namely to the presence of a light atrial chain $ALC_1$, which partially replaces the physiological light ventricular chain $VLC_1$. The appearance of $ALC_1$ might be an adaptive change of the ventricle in response to its increased workload.[66] However, nowadays the changes in ATPase activity and in ventricular contractility do not have a clear molecular basis in humans. Further important aspects of myocardial adaptation to hypertension are the alterations in the intracellular and membrane properties involved in excitation-contraction coupling. These alterations seem to be different in genetic hypertension as compared with other models of experimental hypertension (ie, renovascular or Doca-Na hypertension). About intracellular alterations, soluble proteinkinase (PK) seems to be reduced in SHR and increased in renovascular and Doca-Na hypertension.[67] As far as the membrane properties are concerned, in the SHR a decrease in ouabain-inhibited Na/K-ATPase activity, an increase in the number of $Ca^{++}$-channels and a decrease in $\alpha_1$- and $\beta$-adrenergic receptors have been reported.[68-70] The significance of these changes is currently unknown. The decrease in ATPase activity and the increase in $Ca^{++}$-channel number may represent a compensatory mechanism to the decreased phosphorylation-dependent opening of the slow $Ca^{++}$ channels, a way to augment the myocardial contractility, or a genetic defect. The reduced number of $\alpha_1$-adrenergic receptors, which seems related to the degree of myocardial hypertrophy, is likely to cause a decrease in $Ca^{++}$ influx across sarcolemma or $Ca^{++}$ release from the intracellular $Ca^{++}$ pools during excitation-contraction coupling.[68]

**TABLE 1. ALTERATIONS IN MYOCARDIAL $\beta$-ADRENERGIC RECEPTORS IN LEFT VENTRICULAR HYPERTROPHY.**

| | SHR | RHR and DOCA-Na |
|---|---|---|
| $\beta$-adrenoceptors number | ↓ | N |
| $\beta$-adrenoceptors affinity | N | N |
| Nucleotide regulatory protein | N | N |
| Adenylate cyclase | N | N |

Some differences in $\beta$-receptor systems were recently reported between SHR and renovascular and Doca-Na hypertension (Table 1) that suggest that patterns of cardiac hypertrophy are different within the various models of hypertension, at least in the early stages. However, the global significance of these alterations is still unknown. The main consequences of LVH on myocardial function include effects on contractility, myocardial response to adrenergic stimulation, diastolic function, and coronary blood flow.

Some investigators have found decreased indexes of contractility per load unit in isolated cardiac muscle from hypertrophied hearts.[71] In human subjects, the type of hypertrophy seems to greatly influence left ventricular performance. It has been shown that the indexes of systolic function are within the normal range in hypertensive subjects without LVH; these indexes appear to be normal or supranormal in hypertensive subjects with concentric hypertrophy, whereas systolic function is depressed in hypertensive subjects with cardiac hypertrophy and dilatation.[72-74] However, there is no definite evidence that development of myocardial hypertrophy is associated with increased ventricular performance.

Experimental studies have shown that the inotropic response to $\beta$-adrenergic stimulation is reduced in the hypertrophied heart.[75,76] This impairment of contractile response, which has been related to reduction in myocardial $\beta$-adrenergic receptors,[77] presents a positive correlation with the degree of cardiac hypertrophy. These observations were confirmed in man; in essential hypertensive patients, the chronotropic and inotropic response to isoproterenol has been shown to be depressed. This impairment was related to the degree of cardiac hypertrophy.[78,79]

Diastolic function is impaired early in the course of hypertension.[80,81] The abnormalities in diastolic function include both ventricular relaxation and compliance.[82-87] Prolonged isometric relaxation, decreased filling velocity, and reduced rapid filling fraction were found.[80] The mechanisms by which LVH impairs ventricular relaxation are not evident. Hypertrophy might induce a relative subendocardial underperfusion or a reduction in protodiastolic coronary flow; there might be also some alteration in intra-

cellular calcium pools.[88] The last phase of left ventricular filling is impaired too. Filling fraction secondary to atrial contraction is increased, which might be due to the Frank-Starling mechanism at the left atrial level. The last phase of ventricular filling is almost entirely influenced by reduction in ventricular compliance. This reduction induces an increase in left ventricular end-diastolic pressure which in turn influences left atrial dynamics.[80]

Left ventricular hypertrophy occurring in hypertension is accompanied by a significant decrease in coronary reserve even in the absence of coronary atheroma.[89–92] Several mechanisms may contribute to this reaction: inadequate growth of new vessels, increased coronary tone, obstacle to subendocardial flow as a consequence of increased ventricular systolic pressure, and augmented myocardial oxygen consumption due to increased myocardial wall tension and left ventricle stroke work. Thus coronary flow, which is sufficient under resting conditions, might be unable to supply increased metabolic demand elicited by a variety of stimuli. Anatomical, structural, and functional alterations of hypertrophied heart allow us to understand clinical consequences of advanced cardiac hypertrophy, first of all heart failure, arrhythmias, and acute coronary events.

Heart failure may develop in a subgroup of patients with hypertension. Possible mechanisms of development of heart failure include: lack of blood pressure control, functional consequences of LVH, inadequate hypertrophy, and association with coronary heart disease. The interrelation between ventricular hypertrophy and cardiac failure is a complex one, and little is currently known of the factors that produce the progression of the former in the latter.[93] It has been suggested that hypertension serves as a time accelerator of the physiological aging process of the heart; thus heart failure might develop earlier in life in the patients with hypertension.[94]

Several studies suggest that hypertensive patients with left ventricular hypertrophy have significantly more frequent ventricular arrhythmias than hypertensive patients without hypertrophy.[94–96] Little is known about the mechanisms by which myocardial hypertrophy predisposes to ventricular ectopy. Several hypotheses have been proposed. First, hypertrophied myocardial cells might be more vulnerable to arrhythmias; intracellular electric currents and conduction rate might be enhanced, leading to a re-entry mechanism. Second, patients with LVH usually have higher blood pressure values; it is possible that a greater stretch of myocardial cells lowers electric threshold as was demonstrated in an isolated cardiac cell. Finally, patients with LVH often show ECG manifestations of subendocardial ischemia. Experimental studies suggest that ventricular ectopy increases in relation to myocardial underperfusion. The data on increased premature ventricular contractions are in agreement with the findings of the Framingham Study, indicating that LVH is an independent risk factor for cardiovascular mortality and particularly for sudden cardiac death.[97]

Arrhythmias lead us to consider the last aspect of the relation of heart to hypertension: sudden cardiac death. In fact, it is widely accepted that ventricular tachyarrhythmias are responsible for most cases of sudden cardiac death. A correlation between hypertension and sudden death has been well-demonstrated in the Albany-Framingham Study where the annual rate of sudden death rose progressively with the blood pressure.[98] A history of hypertension has been shown in about one-third of sudden cardiac death victims, and a greater proportion (about 50%) have increased heart weight.[99]

Electrocardiogram evidence of LVH also has prognostic value. In the Albany-Framingham Study LVH on the ECG was associated with a five-fold increase in the risk of sudden death.[99] These findings suggest that hypertrophy per se may predispose to sudden death; however, autopsy studies indicate that 90% of cardiac sudden death victims have coronary damages, although no correlation has been found between heart weight and the degree of CHD.[100] It has been suggested that in the hypertensive patients cardiac hypertrophy probably increases the vulnerability to ventricular arrhythmias induced by CHD. This hypothesis seems to be confirmed by some of the few animal studies on this problem.[101]

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