State-of-the-Art Lecture

Risk Mechanisms in Hypertensive Heart Disease

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Abstract—In this report, some of the underlying pathophysiological alterations associated with the independent risk from hypertensive heart disease and left ventricular hypertrophy are discussed. Emphasized are the classically described coronary hemodynamic alterations of decreased coronary blood flow and flow reserve with increased coronary vascular resistance and minimal coronary resistance; more recent concepts of endothelial dysfunction are emphasized. Additionally, increased collagen deposition within the ventricular walls and perivascularly participates importantly. These changes are exacerbated by the aging process and perhaps by increased dietary salt intake. Consequences of these functional and structural changes include further endothelial dysfunction, impairment of coronary hemodynamics, and ventricular contractile function (diastolic as well as systolic). The clinical consequences of these alterations are angina pectoris (with or without atherosclerosis), myocardial infarction, cardiac failure, lethal dysrhythmias, and sudden cardiac death. Thus, not all that is clinically recognized as “left ventricular hypertrophy” is true myocyte hypertrophy with structural remodeling; other important comorbid changes occur that directly affect risk, including ventricular fibrosis, impaired coronary hemodynamics, and endothelial dysfunction. (Hypertension. 1999;34[part 2]:782-789.)

Key Words: left ventricular hypertrophy ■ coronary heart disease ■ coronary hemodynamics ■ fibrosis ■ sudden death ■ risk

Some time has passed since I summarized my thoughts on the multifactorial nature of the development and reversal of left ventricular hypertrophy (LVH) and on the underlying mechanisms of risk associated with hypertensive heart disease.1,2 During these years, and before, a tremendous body of information has appeared on this subject, including epidemiological data confirming the concept that LVH is, indeed, an independent factor of risk conferring increased mortality3,4; newer biological information about the underlying fundamental mechanisms associated with developing LVH and with ventricular remodeling6-14; the role of powerful local autocrine and paracrine mechanisms within the left ventricle (LV)5,6,8,9,11; and, of course, the persistent problem of silent ischemia, cardiac failure, and sudden death in hypertensive patients with LVH.13-18 Still persistent is the unresolved issue of pharmacological reversal of LVH and whether the phenomenon simplistically termed pharmacological “regression” of LVH is, in fact, solely reduction and remodeling of LV muscle mass.2,19,20 Furthermore, the more complete elucidation of pathophysiological mechanisms associated with the underlying risk of LVH demands our attention. This overall concern is the primary focus of this report.

Earlier-Described Mechanisms Underlying LVH Risk

In our previous reports, several mechanisms were offered to explain the underlying risk associated with LVH.2,19,21 Because relatively little was known about LVH as a cardiovascular risk factor until recently, the intrinsic alterations associated with the hypertrophied myocyte and its epiphenomena were not considered. Evidence was cited from experimental studies suggesting that pathological hypertrophy was associated with a different myosin isozyme that might predispose the heart to cardiac failure or sudden death,22 but this concept has not remained a viable option. A second possibility, supported by a flurry of reports, suggested that LVH predisposed the ventricle to arrhythmias and sudden death23-26; however, this explanation was later deemed incomplete and less satisfying, particularly as these dysrhythmias relate to ventricular ectopy.27 Whereas sudden death is clearly associated with LVH,18 it hardly provides the underlying pathophysiological mechanism of the risk.

Still highly attractive as an underlying pathophysiological mechanism of risk is impaired coronary hemodynamics, most effectively explained and accepted as being manifested by inadequate coronary flow reserve.28-32 Indeed, this alteration of coronary hemodynamics could very well explain the increasing prevalence of cardiac dysrhythmias, silent ischemia, and sudden cardiac death associated with LVH. Compounding the increasing complexity of this problem is the relatively recent concept of endothelial dysfunction and other altered coronary hemodynamic factors in hypertension. Thus, a defect in the local generation of nitric oxide relating to endothelial dysfunction has also been offered to explain impaired coronary blood flow and relaxation of human coronary resistance vessels.33-35 Other factors have been
suggested for impaired coronary hemodynamics, including coronary arteriolar compression by the hypertrophied and stiffer LV with a fibroed ventricular wall (see below); occlusive epicardial coronary arterial disease by an atherosclerotic lesion, which has long been known to be exacerbated by hypertension; increased arteriolar wall thickening and arteriolar wall-to-lumen diameter associated with hypertensive vascular disease; inadequate sizing of coronary vessels; increased blood viscosity in hypertension; and an increased left ventricular chamber diameter reflecting not only myocytic hypertrophy but also collagen deposition and an increased protein matrix.

Perhaps better appreciated are the underlying functional mechanisms that have been emphasized clinically over the past several decades. Of these, the most accepted alteration of coronary hemodynamics is the increased coronary arteriolar resistance associated with hypertension in all organ circulations. However, this need not be associated with increased resting coronary blood flow, although resting ischemia may be important, particularly if associated with occlusive atherosclerotic epicardial coronary arterial disease. However, reduced coronary flow reserve in patients with LVH can be demonstrated relatively early in the asymptomatic stage of the disease by estimating coronary blood flow before and after certain physiological and pharmacological interventions that promote increased demand for coronary flow.

These alterations in coronary hemodynamics may now be assessed more completely (clinically as well as experimentally) to explain coronary insufficiency and silent ischemia. In this respect, impairment of coronary arteriolar dilation may be engendered not only by the coronary arteriolar constriction of hypertension but also by the endothelial dysfunction.

The remainder of this discussion will focus on some of the newer and current issues related to the intrinsic cardiac alterations associated with hypertensive heart disease: a clear definition of coronary heart disease (CHD), coronary insufficiency, diastolic dysfunction and cardiac failure, ventricular fibrosis, and perhaps the long-standing controversial concern of salt excess (Table). Each of these factors is intimately and directly related to the underlying pathophysiology of hypertensive heart disease and the risk associated with LVH. Some have been summarized before; some should be reassessed into our current base of knowledge; several have recently emerged into our thinking; and, no doubt, all may be readapted to our future thinking of risk mechanisms as they, too, evolve.

**Coronary Heart Disease**

Much confusion appeared after the first well-designed meta-analysis in which efficacy of antihypertensive therapy was demonstrated through the initial 14 multicenter control drug trials. The meta-analysis predicted that this therapy would reduce deaths from stroke and CHD by 35% to 40% and 20% to 25%, respectively. In fact, this analysis demonstrated highly significant reductions of both lethal hypertensive end points. Death from stroke was actually reduced by 43%; however, reduction of CHD deaths declined by only 14% ($P<0.01$). This latter reduction of CHD deaths suggested to many (through lectures, editorials, and other reports) that the antihypertensive therapy (ie, diuretics and β-blockers) used failed to prevent deaths from myocardial infarction. This conclusion was erroneous on several bases: the deaths were from CHD and not only from myocardial infarction; the suggestion that the therapy used neither raised serum lipid levels nor exacerbated the atherosclerotic process; and the data did not demonstrate failure to reduce CHD deaths. Moreover, reduction of stroke deaths has been shown to be reduced even before death from CHD in all subsequent analyses, thereby suggesting that the cerebral circulation may be more pressure-related than the coronary circulation.

Most important for consideration is the definition used for CHD. Thus, deaths attributable to CHD by the epidemiologists in these multicenter studies included more end points than just myocardial infarction. Myocardial infarction did not explain all deaths from CHD; other CHD deaths resulted from unstable angina pectoris or unremitting chest pain unconfirmed by autopsy, lethal cardiac dysrhythmias, cardiac failure, or sudden cardiac death. Furthermore, after publication of that meta-analysis, reports appeared relating sudden cardiac death to the higher doses of hydrochlorothiazide (or its equivalents) used for treatment of hypertension and use of potassium-sparing agents to prevent hypokalemia. In addition, shortly after completion of the initial 14 multicenter trials in which the thiazides were used in daily doses equivalent to 100 mg hydrochlorothiazide, national recommendations advocated reduction of the initial diuretic dose to 12.5 or 25 mg with subsequent increases to 50 mg as the full doses; this recommendation has persisted. Thus, when a subsequent meta-analysis was reported, involving elderly hypertensive patients (a population certainly with higher prevalence of atherosclerotic CHD), the actual reduction of CHD was precisely what was predicted originally, 26%; and reduction of deaths from stroke was 40%. Hence, the issue raised of failure of therapy to protect from CHD has not been supported. In addition, subsequent studies have demonstrated significant reduction of deaths from CHD as well as from stroke.

**Left Ventricular Hypertrophy**

The Framingham Heart Study and other important prospectively designed studies have clearly demonstrated that LVH is a major cardiovascular risk factor that is independent of height of both systolic and diastolic pressures. Related to this concept, many studies have reported reduced LV mass and wall thicknesses resulting from antihypertensive therapy. However, to date no prospective study has clearly demonstrated that associated with reduced LV mass is a proportionate reduction in risk from LVH, although a few have suggested that this may be so. Moreover, no clinical
study demonstrating so-called regression of LVH is actually synonymous with reduced hypertrophy unless pathological or other biological evidence is corroborative. Notwithstanding, several meta-analyses have suggested that certain classes of antihypertensive agents may be more effective than others in promoting regression of LVH. Indeed, these analyses are complicated by inherent demographic, biological, or pharmacological variables, since included in the studies of these analyses are patients of dissimilar gender, race, age, and number; treated over varying times using unlike doses and with different compounds of the same therapeutic class (with perhaps dissimilar physiological, pharmacodynamic, and pharmacokinetic actions); and having varying treatment histories (in which past therapeutic effects may be of extreme importance). We do not know at this time whether changes induced directly by prior pharmacological treatments or indirectly by the biological change produced by therapy have a prolonged effect mediated by biologically altered cellular memory. Nevertheless, it is possible (and perhaps even probable) that some antihypertensive drug classes may be more effective than others in diminishing electrocardiographically or echocardiographically measured indices of LVH (ie, mass, wall thicknesses). Thus, it is far too premature to conclude that certain drugs (or classes of drugs) are more effective than others in reducing the risk from LVH simply because their cardiac mensurations may be less than before treatment.

**Coronary Insufficiency**

**Coronary Flow**

As already suggested, resting coronary blood flow may be normal in experimental hypertensive models as well as in patients with hypertension, even in the presence of profound LVH. Of course, as also stated, associated with the markedly elevated arterial pressure there is an increased total peripheral resistance that is shared with all component organ circulations, including the coronary. However, because of the early work of Marcus and associates and others, the appealing concept of coronary flow reserve has become well established. This consideration has been extremely useful in understanding the clinical concerns of coronary insufficiency and silent ischemia associated with hypertensive heart disease as well as other cardiovascular diseases. Thus, coronary blood flow can be measured before and after certain physiological (eg, exercise, ventricular pacing) or pharmacological (eg, carbochrome, papaverine, dipyridamole, adenosine) interventions. The differences between the 2 determined coronary flows and vascular resistances provide excellent indexes of coronary flow reserve and minimal coronary vascular resistance. These hemodynamic indexes have been extremely useful in explaining the phenomena of silent ischemia and microvascular angina that occur in patients with hypertensive heart disease, especially when occlusive atherosclerotic epicardial coronary arterial disease cannot be demonstrated cineangiographically. Not only is it possible to determine quantitatively actual impairment in coronary flow reserve, even if occlusive atherosclerotic disease is not present, it is also possible to assess hemodynamic impairment and the effect of therapy on improving flow reserve, if present. This has been demonstrated in experimental hypertension as well as clinically. For example, in the spontaneously hypertensive rat (SHR) treated with either an ACE inhibitor, an angiotensin II (type 1) receptor antagonist, or both (in studies designed to produce equivalent reductions in arterial pressure with each of these 3 treatment options), it was possible to demonstrate significant physiological improvement using these therapies. Most intriguing was the greater-than-additive flow reserves with combination therapy. This can be explained by the coronary vasodilation induced by inhibition of angiotensin II-mediated constriction with the ACE inhibitor, further inhibition of additionally generated angiotensin II by intracardiac chymase, augmented bradykinin-induced vasodilation induced by the ACE inhibitor, as well as the beneficial effect on the endotheli ally produced natural vasodilator nitric oxide. Other studies, in patients with hypertensive heart disease, have also demonstrated increased coronary flow reserve with an ACE inhibitor.

**Endothelial Dysfunction**

Whereas this new concept of endothelial dysfunction is not intended to be the primary focus of the present discussion, it has become an extremely important mechanism underlying many aspects of hypertensive cardiovascular disease and related complicating comorbid disorders. Endothelial dysfunction has been shown experimentally and clinically to be a major component of the vascular disease in hypertension. Other cardiovascular risk factors, diseases, and conditions that have been implicated in producing endothelial dysfunction include aging, menopause, tobacco abuse, diabetes mellitus, hyperlipidemia, atherosclerosis, hyperhomocysteinemia, vessel injury, and cardiac failure. Intrinsically to this concept is impaired synthesis of nitric oxide from its amino acid precursor L-arginine by the endothelium of the coronary vasculature as well as by the myocytic endothelium in hypertension. Many studies have focused on involved potentially related mechanisms, including a defect in the gene nitric oxide synthase, increased symmetrical dimethyl arginine, enhanced local participation (ie, autocrine, paracrine, or intracrine) of the renin-angiotensin system, or conversely, diminished participation of the local bradykinin-kinin system. With respect to the latter 2 local autocrine/paracrine (and even intracrine) peptide systems, it is well known that angiotensin II inhibits nitric oxide synthesis and that bradykinin promotes local nitric acid synthesis in the endothelium.

Most exciting are recent observations, experimental as well as clinical, that ACE inhibition and probably angiotensin II type 1 receptor inhibition, which have already been discussed, reduce LV mass and improve LV coronary flow reserve in older SHR. These findings suggest augmented local endothelial production of nitric acid synthesis and improvement of endothelial dysfunction of the coronary circulation. Furthermore, we have recently reported that prolonged L-arginine administration also induces similar improvement in intra-coronary hemodynamics and other pathological alterations induced by hypertensive coronary
vascular disease as well as by agents chronically administered experimentally that inhibit nitric oxide synthase endothelially. Furthermore, recent clinical studies have shown that prolonged administration of L-arginine to patients with hypertensive or atherosclerotic vascular disease improve the clinical and hemodynamic alterations associated with these diseases.

**Ventricular Fibrosis: Diastolic Dysfunction and Cardiac Failure**

**Epidemiological Information**

From the earliest Framingham Heart Study report on the prevalence of congestive heart failure to the most recent report, hypertension remains the most common cause of cardiac failure. In the earlier years, however, hypertensive heart failure resulted primarily from impaired systolic contractile function. Thus, the development of LVH served as a structural and functional cardiac adaptation to the ever-increasing LV afterload associated with systemic arterial hypertension. Indeed, most of the earlier antihypertensive drug studies demonstrated significant prevention of this expression of congestive heart failure that was associated with the reduction in deaths from stroke and CHD. More recently, however, cardiac failure has been developing in the elderly hypertensive patient and has been manifested predominantly by diastolic dysfunction. Although diastolic dysfunction is being increasingly recognized and its pathophysiological and etiological mechanisms continue to be well studied, there is still a need to characterize its incidence, prevalence, and natural history. Diastolic dysfunction may be defined as impaired ventricular filling during diastole preceding impaired systolic function. This phenomenon seems to occur predominantly in elderly patients or those other patients with evidence of ischemic heart disease without hypertension. However, it seems to occur particularly in those patients with hypertensive heart disease having reduced coronary flow reserve with or without associated occlusive atherosclerotic coronary artery disease who have silent ischemia and are potential victims of sudden cardiac death and left ventricular failure. These pathophysiological characteristics are consistent with current reports that congestive heart failure is the most common diagnosis reported in hospitalized patients over the age of 65 years.

**Ventricular Fibrosis**

One distinct and striking factor associated with LVH and hypertensive heart disease that is not present in exercise-induced (ie, physiological) LVH is the presence of collagen deposition and ventricular fibrosis. Although this aspect of hypertensive heart disease is now well accepted, it had been relatively neglected in the past. Not only is LV collagen deposition increased in hypertensive, but it is also increased with aging. In this respect, our recent experimental studies involving the SHR and normotensive Wistar-Kyoto rats of increasing ages have shed new light on these LV coronary hemodynamic and structural changes. These studies have demonstrated a striking and progressive impairment not only in LV coronary blood flow and flow reserve but also of the right ventricle with advancing age from 23 to 80 weeks in the SHR as well as in their normotensive and age- and gender-matched controls. Moreover, these alterations in ventricular hemodynamics were associated with a parallel increasing deposition of collagen (ie, hydroxyproline) in both ventricles. These findings in LVH of the SHR have been confirmed in human beings, in whom hypertrophied myocytes have been directly correlated with collagen deposition. Furthermore, these hemodynamic and structural alterations that have been associated with aging and with hypertension do not appear to be fixed and uncorrectable by therapeutic interventions. Thus, our earliest studies demonstrated that LV mass could be reduced by most antihypertensive agents. Specifically, LV mass has been reduced within 3 weeks, as demonstrated by studies from our laboratory using an identical protocol and in short courses of therapy in patients with a centrally acting adrenergic inhibitor, β-adrenergic receptor inhibitors, calcium antagonists, or with ACE inhibitors or an angiotensin II (type 1) receptor antagonist alone or in combination. Furthermore, associated with ACE inhibitor–induced or calcium antagonist–induced reductions in LV muscle mass was a concomitant reduction in LV collagen; however, there was a concurrent increase in right ventricular mass only with calcium antagonists. This early (within 3 weeks) development of increased right ventricular mass was confirmed clinically by demonstrating increased wall thickness. When the ACE inhibitor was administered together with the calcium antagonist, the increased RV mass resulting from collagen deposition in the SHR was prevented even though there was no further decrease in LV mass. Thus, the RV mass increase was related solely to increased RV collagen (or hydroxyproline concentration).

More recently, we have reported increased coronary flow reserve and reduced hydroxyproline concentration (and content) associated with reduction in arterial pressure, LV afterload, and LV mass after prolonged treatment with an ACE inhibitor or a type 1 angiotensin II receptor antagonist (alone or in combination). In support of these findings, another report, by Varo et al., demonstrated reversal of fibrosis and suggested that prolonged type 1 angiotensin II blockade diminished the posttranscriptional synthesis of fibril-forming collagen type 1 molecules in adult SHRs receiving the agent from 16 to 30 weeks of age. Furthermore, we reported similar decreases in arterial pressure, total peripheral resistance, and LV mass after prolonged L-arginine treatment associated with a reduction in LV collagen (ie, hydroxyproline), although right ventricular collagen was not as markedly decreased. These improvements in LV structure and function with L-arginine were observed only in the hypertensive (SHR) rats, suggesting that the alterations related to endothelial dysfunction responding to L-arginine may have been more related to the hypertensive disease rather than to aging. However, it must be emphasized that all antihypertensive drug classes reduce LV mass (and occasionally RV mass) and that these changes frequently occurred with certain agents in normotensive rats. Hence, the mechanisms involved require much further biochemical and biological study and should not be ascribed simply to regression of LVH.
A current report from the Framingham Heart Study indicated that there has been a very real and significant decrease in the prevalence of hypertension in that community as well as a coincident reduction in the prevalence of severely elevated pressures and LVH.\textsuperscript{119} A cause-effect relationship for these associations may appear to be a logical assumption. However, rather than concluding that effective control of blood pressure elevation reversed the incidence of LVH by regressing LVH, it is also reasonable to conclude that with more widespread recognition of patients having elevated arterial pressure, the prevalence of LVH diminished through prevention of development of LVH. Thus, with early recognition of hypertension in patients, there was a reduced prevalence in the progression of the disease that resulted in fewer patients with more severe stages of blood pressure elevation as well as in the incidence of LVH.\textsuperscript{119} Indeed, as suggested in our earlier report concerning prevention of LVH, to my way of thinking, the best means of treating LVH is the early recognition of patients with hypertension, prompt institution of a rigorous and effective antihypertensive treatment program that is designed to prevent development of LVH, and hence, prevention of the consequences of the risk from LVH in the first place.\textsuperscript{2} However, once LVH has been recognized in a hypertensive patient, an equally vigorous antihypertensive therapy is a necessity designed to control the elevated systolic and diastolic goal pressures to levels <140 and <90 mm Hg, respectively. In these patients, prevention of cardiac dysrhythmias by taking specific precautions to protect the patient from developing and reversing hypokalemia and hypomagnesemia is essential. Of course, agents that provide increased coronary blood flow and flow reserve and, if possible, reduce ventricular fibrosis should protect the patient against other mechanisms of risk associated with the LVH.

It is appropriate to comment at this point on the effects of excessive dietary sodium intake on LV structure. Several years ago, we observed that increased dietary salt intake in the SHR was associated with increased LV mass even when the salt excess did not increase arterial pressure or total peripheral resistance.\textsuperscript{120} The LV and total cardiac mass increased further with a higher salt intake; this was associated with a further rise in arterial pressure and total and regional vascular resistances in most organ circulations. More recently, others have reported that, with similar salt excess, an increased LV mass was associated with severe ventricular fibrosis as well as perivascular fibrosis in the coronary and renal circulations.\textsuperscript{121} We believe that these findings have particularly important implications for our developing concepts concerning hypertensive heart disease, sudden cardiac death, CHF, and perhaps the persistently increasing incidence of end-stage renal disease in patients with hypertension in recent years.\textsuperscript{2,160}

Concluding Hypothesis

Despite the continuing reduction in morbidity and mortality from stroke and CHD associated with hypertension, there have been persistent increases in morbidity and mortality associated with CHF and end-stage renal disease. The disturbing findings with respect to CHF can be closely related to the risks associated with LVH. Thus, it would appear that the major underlying pathophysiological mechanism associated with risk from LVH appears to be progressive impairment of intracranial hemodynamics associated with a remarkable deposition of collagen in the ventricular wall. These alterations, affecting the LV in hypertension, seem to also involve the right ventricle as part of the aging process and may also be exacerbated by excessive dietary salt intake. Thus, both the aging process and excessive dietary salt intake may participate in promoting increased collagen deposition perivascularly and within the ventricle as well as in the kidney. These changes, together with impaired left (and right) ventricular blood flow reserves, further increase LV mass and the overall risk associated with LVH, which, of course, is not solely the result of hypertrophied LV muscle. It also is the collagen deposited within the ventricular wall and around the coronary vessels. The results of these hemodynamic and structural alterations affecting the LV are usually recognized as electrocardiographic and echocardiographic LVH, which may be manifested clinically by angina pectoris, cardiac dysrhythmias, systolic or diastolic dysfunction, and cardiac failure as well as by silent ischemia, myocardial infarction, and, of course, sudden cardiac death.

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