Fibrosis and Ischemia: The Real Risks in Hypertensive Heart Disease

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The increased cardiovascular morbidity and mortality in hypertension are related to the target organs (i.e., heart, brain, kidneys) involvement from vascular disease. Left ventricular hypertrophy (LVH), the major expression of cardiac involvement, is both a structural and functional adaptation to the afterload imposed by the vascular disease. Without this adaptation, cardiac failure would result much earlier in the natural history of hypertensive heart disease (HHD). However, LVH imposes an independent risk that is even greater than the risk associated with the height of systolic or diastolic pressure. The mechanisms that explain this risk have not been defined precisely; several have been postulated. Among these are the following: 1) coronary hemodynamic alterations associated with HHD (i.e., increased coronary vascular and minimal vascular resistance, reduced coronary blood flow and flow reserve, and increased blood viscosity); 2) enhanced predisposition for lethal cardiac arrhythmias, cardiac failure, and accelerated atherosclerosis of the coronary arteries (with exacerbation of the ischemia); and 3) collagen deposition and ventricular fibrosis. From the earliest controlled therapeutic trials, deaths from stroke and coronary heart disease were significantly reduced. However, more recent data have indicated that the prevalence of cardiac failure (CHF) continues to rise progressively. The nature of the CHF is no longer primarily from systolic dysfunction, but is now chiefly from diastolic dysfunction. Diastolic dysfunction occurs primarily in the elderly hypertensive patient or in the patient with ischemic heart disease, both of which are associated with increased collagen deposition. Indeed, these effects continue to be suggested by the data from the Framingham Heart Study as well as NHANES-III that indicate CHF is the most common diagnosis occurring in hospitalized patients over 65 years of age. In this report, both experimental and clinical evidence demonstrating that increased ventricular fibrosis occurs in the spontaneously hypertensive rats and in hypertensive patients are provided, and that treatment with the newer antihypertensive agents reduce ventricular hydroxyproline (i.e., collagen) content while, at the same time, improve coronary hemodynamics. Am J Hypertens 2001;14:194S–199S © 2001 American Journal of Hypertension, Ltd.

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The benefits derived from antihypertensive therapy have truly been one of the success stories of 20th century medicine. Thus, over the past four decades, clinical outcome studies have demonstrated a remarkable and progressive reduction in morbidity and mortality from stroke as well as from coronary heart disease (CHD) by approximately 70 and 55 percent, respectively, in the United States. Reduction in deaths from stroke most likely reflect the greater responsiveness of cerebral circulation to antihypertensive therapy. On the other hand, the response with respect to CHD has been more complex. Although not as great as had been predicted from the data of the original 14 multicenter studies, when diuretic doses were reduced according to present-day recommenda-

tions, the very same predicted reduction of CHD deaths of 26% were observed, even in elderly patients. In contrast to these foregoing responses with respect to stroke and CHD, there has been a continuous and progressively steady rise in numbers of patients with hypertension who develop cardiac failure (CHF) and end-stage renal disease. However, with respect to the subject of this article, the nature of CHF in the pre-antihypertensive drug therapy era is very different today, although hypertension continues to remain its most common cause. In the early years, CHF resulted from untreated hypertension and its associated increased left ventricular afterload, leading to ventricular systolic dysfunction; today, however, the problem occurs most frequently in older patients with ventric-

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ular ischemia and diastolic dysfunction.6–8 To explain this seeming paradox, one of the best means to explore the fundamental answers to this problem is to seek out the underlying “factors of risk,” a concept introduced by Kannel et al in 1961.9 We have been systematically exploring several of the potential mechanisms of risk (eg, aging, ischemia, and fibrosis) in our laboratory; and this discussion summarizes our recent experience in the naturally occurring adult spontaneously hypertensive rats (SHR), studied over a broad age range from 23 to 85 weeks of age. Our findings of the past continue to demonstrate a remarkable similarity between our observations in the SHR with those of hypertensive heart disease in the patient with essential hypertension.10 The more recent findings from our laboratory, summarized herein, continue to support that contention.

Coronary Heart Disease

In earlier years, deaths termed as those resulting from CHD had been defined by the epidemiologists to include those from the following causes: myocardial infarction; angina pectoris without proved myocardial infarction; lethal cardiac dysrhythmias; congestive heart failure; and sudden cardiac death without any other demonstrable cause.1,11 Today, CHD deaths of patients with hypertension still include these events, but they also result from hypertensive disease involving the smaller (ie, nonepicardial vessels) coronary arterioles and from endothelial dysfunction of the coronary arteries, arterioles, and endocardium.12

Pathophysiological Alterations

The clinical endpoints of hypertensive heart disease identified above can be explained by structural, functional, and endothelial pathophysiological mechanisms that alter coronary hemodynamics and ventricular function. Among the structural alterations associated with hypertension are changes in coronary arterial flow that involve ventricular wall compression, luminal obstruction, and, of course, the increased wall thickening of the hypertensive arteriole that diminish the wall:lumen ratio.13 In addition, recent reports have documented reduced ventricular wall vascularity (ie, rarefaction) in patients with essential hypertension.14 It is important at this juncture to emphasize that ventricular enlargement not only relates to myocytic hypertrophy, but also to the increased ventricular intramural deposition of protein and collagen in the extracellular matrix of the chamber.12,15–17 These changes promote alterations in left ventricular function that include reduced resting coronary blood flow and diminished coronary blood flow reserve, which have been assessed experimentally and clinically by physiological and pharmacological stimuli.18–21 As a result of the increased coronary blood flow demand imposed by the provocative disease, resting coronary blood flow and coronary vascular resistance of the hypertensive left ventricle are diminished (although not to levels achieved in normotensive patients); and these findings are expressed as coronary flow reserve and minimal coronary vascular resistance. In addition to the well-established techniques used to assess coronary flow reserve (ie, exercise, dipyridamole, and adenosine), recent reports have also demonstrated coronary arterial and other organ endothelial dysfunctions that now appear to be reversible therapeutically.22–35

A number of potential causes of coronary vascular insufficiency and mechanisms for ischemic heart disease in patients with essential hypertension have been postulated, including comorbid atherosclerotic epicardial disease and cardiac involvement associated with diabetes mellitus, hyperlipidemia, exogenous obesity, and excess dietary sodium intake.12 However, this ischemia may also occur in hypertensive patients with pure hypertensive heart disease with left ventricular enlargement but without coronary epicardial arterial atherosclerosis, and this condition coexists with endothelial dysfunction of the coronary arteries, perivascular fibrosis, with intraventricular and collagen deposition. These pathophysiological alterations are frequently associated with symptomatic or asymptomatic ischemic heart disease, increased risk for sudden cardiac death, and other endpoints that can be attributable solely to hypertensive heart disease.19–26,29,35,36 Our laboratory has reported a series of studies supporting these concepts that provides a clearer understanding of the coronary arterial insufficiency associated with experimental hypertensive heart disease.12,27,33,37 These observations have been supported by recent clinical observations that offer new insight concerning specific hemodynamic abnormalities in hypertensive heart disease that need not incriminate coexisting atherosclerotic heart disease.

Cardiac Involvement

In Hypertension

Left Ventricular Hypertrophy

Until recently, general thinking concerning cardiac involvement in hypertension had been considered to be manifested solely by left ventricular hypertrophy (LVH) or, perhaps with other evidence of coronary arteriolar insufficiency.8,12,38 The presence of LVH does indeed confer a severe risk of premature morbidity and mortality, an independent risk that exceeds even that of the height of either the systolic or diastolic pressure elevation.6,9,38,39 However, with respect to the risk of LVH, we still must know whether currently employed antihypertensive pharmacotherapy diminishes that risk. If this is so, it is necessary to demonstrate that risk reversal is actually due to the diminished left ventricular mass or to its associated effects of pressure reduction, improved coronary hemodynamics, or the antiarrhythmic effects of the drugs employed.40 Personally, I believe that antihypertensive therapy will ultimately be shown to reduce the risk associated with LVH, but those studies that will demonstrate that risk
reduction must also explain all of the potential mechanisms involved.

Our recent clinical and experimental observations have emphasized the multifactorial nature of the myriad of hemodynamic and nonhemodynamic factors involved with the development of LVH. Among them are the obvious pressure (and, possibly, volume) overload, sex, ethnicity, age, and comorbid pathophysiological entities (eg, atherosclerosis, obesity, and diabetes mellitus). Experimentally and, more recently, clinically, two important factors that have been demonstrated are altered coronary flow reserve and increased collagen deposition in the extracellular left ventricular matrix. Although many reports have also emphasized progressive impairment of myocytic contractile function, a mechanism not to be minimized, this discussion focuses on altered coronary hemodynamics and ventricular fibrosis, with an emphasis on our recent experimental findings.

The Aging Factor

We have focused on normotensive rats (WKY) and spontaneously hypertensive rats (SHR) in our experimental efforts. In these studies we have consistently shown reduced left ventricular coronary blood flow and flow reserve, as well as increased coronary vascular resistance and minimal vascular resistance in the SHR at any age (from 20 through 65 weeks of age). These very same coronary hemodynamic alterations that are present in the hypertrophied left ventricle also occur in the nonhypertrophied right ventricle; and, most intriguingly, they are also impaired in the left and right ventricles of 65-week-old normotensive WKY. Thus, altered coronary hemodynamics result from aging in both the hypertrophied and nonhypertrophied ventricles of the SHR as well as in the aged WKY. Most notable were observations that associated with these hemodynamic changes with aging and with the progression of myocytic hypertrophy was a progressive increase in the deposition of hydroxyproline in the left and right ventricular walls of these normotensive and hypertensive rats. Moreover, it is particularly significant that these findings of the parallel progressive increases in fibrosis and myocytic hypertrophy have also been well documented in patients with essential hypertension. Thus, in both natural forms of hypertension (ie, in patients with essential hypertension and in the SHR), ventricular fibrosis accompanies the development of hypertrophy, and these changes are associated with diminished coronary flow reserve of both ventricles.

Diastolic Dysfunction

The development of LVH in essential hypertension has been associated with demonstrable events suggesting that the premature cardiovascular morbidity and mortality are related to the LVH per se. Whereas the myocytic hypertrophy could, in fact, be associated with that increased risk, this problem must also be considered physiologically as an adaptive response to the increased demands of pressure overload; and, as already stated, this adaptive change is associated with ischemia and fibrosis. However, the LVH that occurs in the well trained athlete is associated neither with ischemia nor with fibrosis. Moreover, when one compares left ventricular diastolic function of the athlete with LVH and patients with essential hypertension having similarly increased left ventricular mass, left ventricular diastolic function is normal in the athlete but is impaired in the patient with essential hypertension and LVH. These findings are of particular relevance to the elderly patient with hypertension and LVH who also has diastolic dysfunction, the most common cause of cardiac failure. Thus, the elderly patient with hypertension and LVH typically has extraventricular fibrosis associated with impaired diastolic function and ventricular ischemia.

Role of Pharmacotherapy

Because both left and right ventricular hemodynamics are altered in hypertension and with aging, it is of vital importance to ascertain their respective responses to therapeutic interventions. This is a particularly relevant question inasmuch as cardiac complications from hypertensive heart disease are exceedingly common, occurring more frequently in elderly individuals. Using previously published techniques developed in our laboratory for assessing basal coronary (and other organ) hemodynamics and flow reserve adapted for the rat using radioactive microspheres, we have evaluated a variety of pharmacologic agents that are currently used for the treatment of hypertension and altered coronary hemodynamics. These studies were designed not only to determine changes in resting and stimulated coronary flow reserve, but also to determine whether they had any effect on the fibrosis of the two ventricles. Therefore was of great interest to learn that both of these pathophysiological alterations associated with hypertension (ie, coronary ischemia and fibrosis) improved significantly after prolonged administration of an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II (type I) receptor antagonist, a calcium antagonist, or L-arginine. These observations in the SHR have recently been demonstrated in the patient with essential hypertension treated with an ACE inhibitor, a calcium antagonist, spironolactone, or L-arginine. That the angiotensin II type 1 receptor was not the sole effector of ventricular fibrosis was demonstrated when a type 2 receptor antagonist was administered long term together with a type 1 receptor blocker. Similarly, qualitative (although not necessarily quantitative) effects were shown by the beneficial hemodynamic and antifibrotic ventricular responses to calcium antagonists. This latter class of agents also increased left and right ventricular flow reserves and reduced minimal coronary resistances while decreasing left ventricular hydroxyproline content.
Moreover, each calcium antagonist that we studied experimentally decreased left ventricular hydroxyproline while increasing right ventricular content in the SHR\textsuperscript{39,60} and also increased right ventricular wall thickness in human subjects.\textsuperscript{61} Furthermore, the increased right ventricular collagen in the SHR was prevented by the coadministration of an ACE inhibitor, although left ventricular collagen was not reduced further.\textsuperscript{59,60} The mechanisms for these actions remained unexplained at present.

**Endothelium**

We have only recently appreciated that the hemodynamic changes associated with hypertension are also complicated by endothelial dysfunction.\textsuperscript{22–25,29,62–66} Alterations of endothelial function are distinctly different from the previously described arteriolar changes associated with the above hypertensive vascular disease. Endothelial dysfunction also seems to occur in many other naturally occurring, pathological, and clinical conditions including atherosclerosis, hyperlipidemia, cardiac failure, diabetes mellitus, obesity, smoking, menopause, and aging. Many of these entities have been shown to be responsive to a variety of therapeutic interventions, so that it might be more reasonably considered as a spectrum of endothelial dysfunctional states produced by a variety of endothelial alterations that respond to specific therapies. In this respect, it was of particular interest to find that the changes in coronary hemodynamics and fibrosis associated with hypertension were improved after administration of the nitric oxide precursor amino acid L-arginine\textsuperscript{33,34} alone as opposed to the alterations that were solely produced by the aging.\textsuperscript{33} However, when L-arginine was administered together with an ACE inhibitor, the changes associated with aging were significantly improved.\textsuperscript{66}

**Conclusion**

Cardiac enlargement—which, clinically, is more commonly termed left ventricular hypertrophy—is a major risk factor of premature cardiovascular morbidity and mortality. However, the clinical diagnosis of LVH, whether by electrocardiographic or echocardiographic techniques, not only reflects ventricular myocytic hypertrophy, but also the associated alterations of extramyocytic collagen deposition in both ventricles and the effects of impaired blood flow to both chambers. Likewise, ischemia not only reflects the systemic arteriolar constriction resulting from hypertensive vascular disease, but also perivascular as well as subendocardial fibrosis, endothelial dysfunction, and increased myocardial oxygen demand of an enlarged hypertensive left ventricular chamber subjected to increased tension. Thus, hypertrophy of the left ventricle myocytes undoubtedly exists, with its attendant increased risk for premature morbidity and mortality. This muscle hypertrophy is subject to impaired myocytic function. However, two major underlying associated mechanisms also occur that impart increased risk: diffuse left and right ventricular fibrosis, and ischemia. Experimental studies of the SHR with naturally occurring hypertension as well as recent studies of essential hypertensive patients with LVH provide encouraging data that the current antihypertensive therapy presently available is capable of reversing these changes and, hopefully, of reducing the risk associated with LVH.

**References**


