Antihypertensive Therapy—Going to the Heart of the Matter

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The heart is but one of several target organs that is damaged by long-standing arterial hypertension. Unlike the diagnosis of functional and structural changes in the brain and kidneys the diagnosis of such changes in the heart can be made early and quantified accurately at the bedside by echocardiography, Holter monitoring, and radionuclide studies. In hypertension, the heart not only suffers from elevated arterial pressure (as a target organ), but it also generates the force needed to keep arterial pressure at these elevated levels. This dual role is of central importance in understanding the pathogenesis and the specific treatment of hypertensive heart disease. Clearly, such specific treatment should not only abolish the main pathogenetic factor (i.e., elevated arterial pressure) but also prevent or lead to a reversal of cardiac structural and functional changes that are the result of long-standing arterial hypertension. What then are the major sequelae of long-standing arterial hypertension in the heart?

Cardiac Sequelae of Long-standing Hypertension

Left Ventricular Hypertrophy

The main structural adaptation to an increased pressure load consists in concentric left ventricular hypertrophy (LVH), that is, an increase in wall thickness at the expense of chamber volume.1-4 However, an increase in arterial pressure may also be sustained by enhanced left ventricular contractility with little or no LVH.5,6 Conversely, hypertensive patients with concomitant volume overload states such as obesity develop predominantly eccentric LVH, that is, wall thickening and chamber dilation.7,8 Myocardial structural adaptation of hypertensive cardiovascular disease occurs early in the course of disease, and increased wall thickening can be found even in adolescents whose blood pressure is between the 75th and the 95th percentile for age, which are values considered within the normal range in adults.9,10 Impaired left ventricular filling, because of decreased relaxation in early diastole, is often present in hypertensive patients before other arbitrary criteria of LVH are present, such as posterior wall thickness exceeding 1.1 cm, a ventricular mass exceeding an arbitrary value of 134 g/m², or equally arbitrary voltage and vector criteria on the electrocardiogram.11-15 In early hypertensive heart disease, impaired filling is predominantly caused by decreased relaxation during early diastole,16-18 whereas in more severe hypertensive heart disease, compliance during late diastole becomes impaired because of an increase in myocardial wall thickness.

The prevalence of LVH is greatly affected by age, and after the age of 65 years, more than 50% of patients with mild essential hypertension may have echocardiographic evidence of LVH.19,20 We recently reported a close correlation between 24-hour urinary sodium excretion levels and left ventricular mass in patients with essential hypertension, indicating that a high salt intake may facilitate the development of LVH, and conversely, a low salt diet could prevent or slow down this process.21 The Framingham Study has clearly indicated that LVH according to electrocardiographic or echocardiographic criteria can no longer be considered a benign compensatory process. Independent of the degree of hypertension, LVH importantly increases cardiovascular morbidity and mortality.22-24 Recent data have documented that patients who have evidence of LVH by echocardiographic criteria share the same unfavorable prognosis.25 Clearly, the occurrence of LVH must be considered an ominous prognostic sign that greatly increases a given patient’s risk for sudden death, congestive heart failure, and coronary artery disease. What are the mechanisms that connect LVH with an increased cardiovascular morbidity and mortality?

Ventricular Dysrhythmias

We have documented that patients with LVH (by electrocardiographic criteria) have a distinctly higher prevalence of premature ventricular contractions and more serious arrhythmias than do patients without LVH or normotensive subjects.26 Similarly, obese patients with eccentric LVH (increased wall thickness and chamber dilatation) exhibited increased ventricular ectopy when compared with obese patients without LVH or with lean subjects.27 Recent data28,29 have corroborated and expanded our find-
ings, thereby further attesting to the arrhythmogenicity of the hypertrophied myocardium even, at least in one study, in the presence of normal coronary arteries. The exact electrophysiologic mechanism by which an increase in left ventricular mass leads to ectopy is unknown. Conceivably, the distorted myocardial structure caused by LVH may interfere with homogeneous impulse propagation, give rise to reentry mechanisms, and thereby become arrhythmogenic. Indeed, McLenachan et al demonstrated an excess of fibrosis and interstitial tissue in endomyocardial biopsy samples from patients who had severe LVH, normal coronary arteries, and episodes of ventricular tachycardia. In a recent electrophysiologic study, nonsustained ventricular tachycardia was induced in three of six patients with LVH according to echocardiographic and electrophysiologic criteria, whereas the same stimulus failed to induce ventricular tachycardia in patients with echocardiographically indicated LVH only or without LVH. Although a relation between increased ventricular ectopy and sudden death is far from established, it seems logical to assume that within a population that has been documented to be at risk (i.e., patients with LVH), those persons who have the highest grades of electric instability of the ventricle may also have the highest risk of more serious arrhythmias and sudden death.

**Myocardial Ischemia**

LVH is not only associated with an increase in ventricular ectopy, but it is also a predisposing condition to myocardial ischemia. Five pathogenetic mechanisms may lead from hypertension and LVH to myocardial ischemia: 1) An elevation in arterial pressure will (if not offset by appropriate LVH) increase left ventricular wall stress, wall tension, and stroke work, thereby augmenting myocardial oxygen demand. 2) An increase in myocardial mass that has occurred as an adaptation to an increased pressure load will, by itself, require more tissue perfusion. 3) The growth of the coronary vascular bed does not keep pace with increases in cardiac mass. Although coronary flow per unit muscle at rest usually remains normal in LVH, this imbalance between the vascular proliferation and muscle growth is a predisposing condition to relative ischemia. Indeed, Strauer et al has shown that coronary reserve becomes decreased in patients with left ventricular hypertrophy even when their coronary arteries are patent, as documented by coronary angiograms. Similarly, Tomanek et al and Marcus et al demonstrated that certain types of cardiac hypertrophy are associated with major abnormalities in coronary reserve. 4) Long-standing arterial hypertension promotes arteriosclerosis in systemic and coronary arteries, thereby impeding coronary blood flow and diminishing myocardial oxygen supply. Although arterial hypertension has been identified as a relatively mild risk factor for the occurrence of coronary artery disease, it must be remembered that rarely can arteriosclerotic changes be found in vascular beds with low pressure (pulmonary circulation, poststenotic arterial segments). 5) Finally, it must be emphasized that the presence of LVH is not a prerequisite for the occurrence of angina in hypertensive patients without coronary disease. Myocardial ischemia due to an abnormally elevated resistance of the coronary microvasculature ("microvascular angina") has recently been documented in hypertensive patients without LVH.

Myocardial ischemia and, as a consequence, angina pectoris are therefore common sequelae of long-standing hypertension. Indeed, the Framingham Heart Study documented that the risk of acute myocardial infarction and angina pectoris increased sixfold to eightfold with the occurrence of LVH.

**Congestive Heart Failure**

As arterial hypertension becomes progressively more severe, the heart, despite adaptive hypertrophy, is less able to carry the burden of an ever-increasing afterload. Congestive heart failure with its dire consequences eventually ensues. The left chamber becomes dilated, and cardiac output falls. Vasodilatation, mediated by an increased activity of the renin-angiotensin system, as well as the sympathetic nervous system, attempts to maintain arterial pressure at its preset levels. Clearly, the presence of latent or overt myocardial ischemia will further impair the pump function and accelerate the fall in contractility. However, a decline in systolic function is not always the sole culprit leading to pump failure in essential hypertension. For even in the presence of normal systolic function, impaired ventricular filling as the result of impaired relaxation and increased chamber stiffness can lead to clinically manifest heart failure. Topol et al described a subset of elderly hypertensive patients with heart failure whose conditions were characterized by excessive ventricular emptying by a small chamber volume and by impaired early diastolic filling. Whether systolic or diastolic dysfunction is more important or prevalent in the pathogenesis of congestive heart failure in patients with long-standing hypertension remains to be documented.

Congestive heart failure is a common complication of untreated long-standing hypertension: Data from the Framingham cohort have shown that over 80% of patients with manifest congestive heart failure had elevated blood pressure values in the past.

**Cardiac Sequelae and Therapeutic Approach**

At least to the extent that antihypertensive drugs (irrespective of their blood pressure–lowering effects) affect the above-mentioned four cardiac sequelae (i.e., left ventricular hypertrophy, ventricular dysrhythmias, myocardial ischemia, and congestive heart failure), they clearly have to be considered when selecting therapy. Although all antihypertensive drugs will lower arterial pressure (by definition), their effects on LVH, ventricular ectopy, congestive heart failure, and coronary artery disease may sharply differ. In the following, the effects of antihypertensive drugs on these sequelae are described.
pertensive monotherapy on these four cardiac sequelae of arterial hypertension are discussed, and advantages and disadvantages of various antihypertensive drug classes are critically analyzed. For the purpose of this analysis, each of these cardiac sequelae will be considered as a separate clinical entity, although clearly they are pathogenetically interrelated (Figure 1).

**Thiazide Diuretics**

The antihypertensive effect of the thiazide diuretics has been more extensively documented than for any other drug class. Quick response rate, good efficacy, convenient dosage, and inexpensiveness seem, at first glance, to make the thiazide diuretics an excellent choice as the first-line class of antihypertensive agents. Thiazide diuretics not only lower arterial pressure but also get rid of salt and water, thereby improving the fluid overload state commonly present with congestive heart failure. However, they may be less useful in patients exhibiting congestive heart failure from predominantly diastolic dysfunction, because any contraction of intravascular volume will further diminish left ventricular filling.

With regard to other cardiac sequelae of hypertension, diuretics have a much less favorable effect. Despite a fall in arterial pressure, left ventricular mass usually remains unchanged or decreases only marginally as reported in several studies.\(^{44-46}\) Moreover, thiazide diuretics induce hypokalemia, hypomagnesemia, and hypernatremia, and these electrolyte shifts could exacerbate ventricular dysrhythmias and thereby increase the risk of sudden death. A variety of studies have attested to the arrhythmogenicity of thiazide diuretics,\(^{47-51}\) although this has not been the experience of all investigators.\(^{52,53}\) Nevertheless, most clinicians would agree that a patient with electrocardiographic abnormalities at rest, such as LVH and manifestations of ventricular ectopy, should not be exposed to significant diuretic-induced hypokalemia. Of note, diuretic-induced hypokalemia may be drastically aggravated under conditions of catecholamine excess such as those elicited by stimuli like severe pain or stress.\(^{54}\)

Thiazide diuretics also have an unfavorable effect on other risk factors for coronary artery disease such as blood lipids, glucose intolerance, and uric acid. Total cholesterol and triglyceride levels have been documented to increase when thiazide diuretics are given, whereas high density lipoprotein (HDL) levels tend to fall (for reviews, see References 55 and 56). These changes have been reported to be most pronounced during the first few weeks of therapy and seem to become somewhat less important with prolonged therapy.

In contrast, impairment of glucose tolerance has been documented to become more severe with prolonged therapy, as was shown in patients who were receiving thiazides for up to 7 years.\(^{57-59}\) Once diuretic therapy was discontinued, the impaired glucose tolerance reverted to normal, clearly indicating that it was not the result of either progressive aging or an increase in adipose tissue.\(^{59}\)

An increase in uric acid commonly occurs with diuretic therapy, probably because of a fall in renal blood flow and a reduction in uric acid clearance.\(^{60}\) Although hyperuricemia has been suggested to be a risk factor for coronary artery disease, it remains highly questionable whether diuretic-induced mild hyperuricemia must be considered as a risk as well.

Thus, when a thiazide diuretic is selected as the first-line antihypertensive agent, only one cardiac sequela of hypertension potentially improves (congestive heart failure as long as it is not due to predominantly diastolic dysfunction), one may remain unchanged (LVH), whereas two others (ventricular dysrhythmias and myocardial ischemia) may even worsen. Therefore, it is not surprising that most studies in the United States or abroad have failed to show that the lowering of arterial pressure with thiazide diuretics has any preventive effect with regard to coronary artery disease.\(^{51-67}\) Conceivably, the induction of dysrhythmias and enhancement of cardiovascular risk factors such as hyperlipidemia, hypokalemia, hyperglycemia, and hyperuricemia by diuretic therapy may override the beneficial effects of a lowered blood pressure on the heart.

**β-Adrenoceptor Blockers**

β-Adrenoceptor blockers have been used as antihypertensive agents for almost 20 years. With the notable exceptions of pindolol, labetalol, and dilevalol their blood pressure–lowering effect occurs mainly by a reduction in cardiac output and in the activity of the renin-angiotensin-aldosterone system. Total peripheral resistance may remain unchanged or may even increase to some extent during the initial period of therapy or even later with long-term therapy.\(^{68}\) Given the knowledge that an elevated total peripheral resistance is the hemodynamic culprit of established essential hypertension, β-blockers become considerably less attractive because they...
merely shift the patient from one pathologic state (elevated total peripheral resistance and normal cardiac output) to another one (same or higher levels of peripheral resistance and a low cardiac output), the long-term consequences of which are ill defined.

In young patients with borderline and early established hypertension, who are hemodynamically characterized by an increase in heart rate and cardiac output, \( \beta \)-blockers remain an excellent choice. \( \beta \)-Blockers have been documented to reduce LVH in parallel with the fall in arterial pressure.\(^{69-71}\) Their effect-on ventricular ectopy is not entirely clear, although one would expect ventricular ectopy to decrease in parallel with the decrease in left ventricular mass. Of course, \( \beta \)-blockers are good agents for patients concomitantly suffering from myocardial ischemia, because they decrease heart rate and arterial pressure and thereby reduce the double product and myocardial oxygen demand. The cardioprotective effect of timolol and certain other \( \beta \)-blockers for secondary prevention of myocardial infarction has been extensively documented.\(^{72-75}\) However, these \( \beta \)-blockers should be used only with great caution in the elderly hypertensive patient who is hemodynamically characterized by a low cardiac output and a high peripheral resistance,\(^{19}\) and they should be avoided altogether in patients with latent or overt congestive heart failure resulting from systolic dysfunction. In contrast, \( \beta \)-blockers may be useful in some patients for the treatment of congestive heart failure from diastolic dysfunction. Thus, \( \beta \)-blockers prevent or reverse two cardiac sequelae of hypertension (LVH and myocardial ischemia), possibly improve the third (ventricular dysrhythmias), and either worsen or improve the fourth (congestive heart failure) depending on its predominant pathogenesis.

Centrally and Peripherally Acting
Antiadrenergic Drugs

Centrally acting antiadrenergic drugs (methyldopa, guanabenz, guanfacine, and clonidine) and the peripherally acting agents (prazosin, guanadrel, trimazosin, and doxazosin) are effective antihypertensive agents. The centrally acting agents have been documented to reduce LVH.\(^{40,76,77}\) Methyldopa, in particular, seems to reduce LVH in some patients more profoundly than is expected from its antihypertensive effect alone.\(^{76}\) In contrast, for the peripherally acting antiadrenergic drugs, only prazosin has been shown to have some efficacy in reducing LVH.\(^{78}\) Because most centrally acting antiadrenergic drugs reduce LVH, they will probably also improve ventricular ectopy, at least to the extent that ventricular ectopy is the result of long-standing LVH.

Antiadrenergic drugs have little documented effect on manifestations of coronary artery disease. Prazosin, trimazosin, and doxazosin have a favorable effect on the plasma lipid profile.\(^ {79,80}\) which may, at least to some extent, reduce the risk of coronary artery disease. With regard to congestive heart failure, the effects vary from one drug to the other. Whereas clonidine may exert some negative inotropic properties, methyldopa seems to have little effect, and prazosin, as well as other peripherally acting agents, may even unload the left ventricle and thereby favorably influence the hemodynamic condition, at least over a short period of time.

Thus, centrally acting agents reduce LVH and probably improve ventricular dysrhythmias but have little effect on myocardial ischemia and congestive heart failure. The peripherally acting agents may reduce LVH or LVH-associated dysrhythmias, may be useful in congestive failure, and may exert some preventive effect on myocardial ischemia by virtue of their lipid-lowering properties.

Angiotensin Converting Enzyme Inhibitors and Calcium Channel Blockers

Angiotensin converting enzyme inhibitors and calcium channel blockers are relatively new in the antihypertensive arsenal. Angiotensin converting enzyme inhibitors are somewhat more effective in the younger, white patient\(^{81,82}\) (characterized by an activated renin-angiotensin system), whereas blood pressure response to calcium channel blockers has been shown to increase with age in the experience of some,\(^ {83}\) but not all,\(^ {84}\) investigators. In contrast to the use of angiotensin converting enzyme inhibitors, no racial difference in blood pressure responsiveness has been documented with use of calcium channel blockers.\(^ {85}\)

Both drug classes seem to reduce LVH in parallel with their antihypertensive effect.\(^ {86-92}\) We recently documented that a reduction in LVH induced by calcium channel blockers is associated with suppression of ventricular ectopy exceeding 75\%.\(^ {93}\) In contrast, patients who were treated with a thiazide diuretic had neither a reduction in LVH nor a suppression of ventricular ectopy despite an equipotent fall in arterial pressure. Whether this reduction in ectopy with calcium channel blockers was related to 1) a decrease of the hemodynamic burden and improved subendocardial perfusion, 2) the regression of LVH, 3) direct electrophysiologic effects of the calcium channel blocker, or, perhaps most likely, 4) a combination of these factors, remains unknown at present. Clearly calcium channel blockers are the agents of choice for use in the patient with hypertension who simultaneously has manifestations of myocardial ischemia. Even in patients with coronary artery disease, experimental and human studies\(^ {94-98}\) indicate that angiotensin converting enzyme inhibitors have some cardioprotective and perhaps antiangiial effects. A multicenter study to evaluate the effect of captopril on progressive ventricular dilatation and its remodeling effect after a myocardial infarction is currently in progress.\(^ {99}\) In contrast to data with \( \beta \)-blockers, most attempts to document cardioprotection with either calcium channel blockers or angiotensin converting enzyme inhibitors have yielded disappointingly mixed results even in patients with coronary arterial disease.
artery disease. Neither of these two classes of drugs had cardioprotective efficacy evaluated in large-scale trials of hypertensive patients. Clearly, however, patients who have symptoms of myocardial ischemia due to microvascular angina might be expected to respond to any potent vasodilating agent.40

In patients with arterial hypertension and congestive heart failure, angiotensin converting enzyme inhibitors are clearly the drugs of choice. In these patients, a short-acting drug (such as captopril) has been reported to be preferable to a long-acting compound, at least initially.106 However, the first study showing that angiotensin converting enzyme inhibition prolongs life in patients with class IV congestive failure was performed with enalapril.101 The unloading effect of calcium entry blockers often,102–104 but not always,105 overrides the direct negative inotropic effect of these drugs, and some of these agents have been used successfully in some patients with hypertension and congestive heart failure. A particular point in this case must be made in patients suffering from congestive failure on the basis of predominantly diastolic dysfunction (impaired left ventricular filling). Recent data have documented that calcium channel blockers improve ventricular relaxation in early diastole, restoring ventricular filling toward normal values.106–108 Ventricular filling was already improved after intravenous applications of verapamil, indicating that this effect is independent of myocardial structural changes. Conceivably, calcium channel blockers have a dual effect on ventricular filling: initially, they improve early diastolic relaxation; with time, they also improve late diastolic compliance as a result of their LVH-reducing properties.

Thus, it seems fair to state that calcium channel blockers, as well as angiotensin converting enzyme inhibitors, potentially improve all four cardiac sequelae of essential hypertension: LVH, ventricular dysrhythmias, myocardial ischemia, and congestive heart failure. However, this improvement varies from one drug to the other and is clearly not equipotent for all four sequelae. It is, therefore, not surprising that both of these drug classes have evolved within a very short period of time to become the most attractive agents currently used for the first-line treatment of essential hypertension.

Conclusions

Cardiac target organ damage from long-standing hypertension can be diagnosed early and quantified accurately by echocardiography, Holter monitoring, and radionuclide studies. The four commonly encountered cardiac sequelae of long-standing essential hypertension are left ventricular hypertrophy, ventricular dysrhythmias, myocardial ischemia, and congestive heart failure. Left ventricular hypertrophy, even though clinically silent, has an ominous prognosis and is, independent of arterial pressure, a harbinger of sudden death, myocardial infarction, congestive heart failure, and morbidity and mortality from other cardiovascular etiologies. Although these four cardiac sequelae may not always be clinically overt in a given patient, they are a foundation on which the therapeutic approach should be based. All antihypertensive drugs lower arterial pressure (by definition), however, their effect on left ventricular hypertrophy, ventricular dysrhythmias, congestive heart failure, and myocardial ischemia may sharply differ. Despite lowering arterial pressure, certain drugs will adversely affect cardiovascular risk factors and function and structure of the heart and other target organs. It is proposed that a close match between the natural history of cardiovascular disease in a given patient and a particular pharmacologic effect of an antihypertensive drug will not only reduce arterial pressure but, more importantly, will prevent or reverse hypertensive heart disease and its inherent excessive morbidity and mortality.

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