Angiotensin II, through its effects at the angiotensin-type 1 receptor, elevates arterial pressure and exacerbates hypertensive heart disease. Alterations in coronary hemodynamics, including reductions in coronary blood flow and flow reserve promotes coronary insufficiency and contributes to the increased cardiovascular risk associated with these conditions. In spontaneously hypertensive rats, coronary flow reserve, the difference between basal coronary blood flow and the flow achieved during maximal coronary vasodilation achieved by dipyridimole, was increased to a greater extent after treatment for 3 months with an angiotensin II receptor blocker as compared with an angiotensin converting enzyme inhibitor. The combination of the two agents, in equidepressor doses, almost restored coronary flow reserve to levels seen in normotensive Wistar Kyoto rats. This finding suggests a possible advantage of combination angiotensin converting enzyme inhibitors and angiotensin II receptor blocker therapy in patients with hypertension and hypertensive heart disease.

KEY WORDS: Left ventricular hypertrophy, hypertensive heart disease, hypertension, coronary flow reserve, angiotensin II.

The renin-angiotensin system, through the actions of angiotensin II, plays an important role in increasing arterial pressure and regulating cardiovascular function in patients with hypertension. However, the impact of the renin-angiotensin system in hypertension extends beyond the increase in arterial pressure to encompass several aspects of hypertensive heart disease (HHD), including left ventricular hypertrophy (LVH), coronary insufficiency, ventricular fibrosis, diastolic dysfunction, endothelial dysfunction, and occlusive coronary artery disease. Angiotensin II stimulates angiotensin-type 1 (AT₁) receptors to exacerbate each of these cardiac aspects of HHD. The additional increase in arterial pressure and total peripheral resistance further increases left ventricular afterload and any existing LVH and coronary arterial disease associated with HHD.

Several factors contribute to the development and progression of HHD. First, arteriolar disease, the hemodynamic hallmark of hypertension increases vascular resistance, arterial pressure, and left ventricular afterload. It also produces coronary vasoconstriction with attendant ischemia, thereby decreasing coronary flow and flow reserve and increasing coronary vascular resistance and minimal vascular resistance. Second, hypertension produces endothelial dysfunction of the coronary arteries and arterioles, which further exacerbates myocardial ischemia. Third, hypertension accelerates the progression of atherosclerosis in the epicardial coronary arteries, which further aggravates the endothelial dysfunction, ischemia, and impaired coronary flow reserve. Furthermore, LVH develops as the ventricle attempts to compensate for

From the Alton Ochsner Medical Foundation, New Orleans, Louisiana.
Address correspondence and reprint requests to Edward D. Frohlich, MD, Alton Ochsner Medical Foundation, 1514 Jefferson Highway, New Orleans, LA 70121.
the progressively increasing pressure overload and increased wall stress imposed by the elevated arterial pressure and total peripheral resistance in hypertension. This increased left ventricular wall mass and wall thickness in LVH may also result from a direct mitogenic effect of locally produced angiotensin II on the heart, further aggravating the myocyte hypertrophy and collagen deposition in the ventricular wall. Although LVH allows the heart to efficiently develop the ventricular forces needed to maintain stable contractile function, left ventricular function will ultimately deteriorate and cardiac failure will supervene unless arterial pressure is appropriately controlled.2–4

LEFT VENTRICULAR HYPERTROPHY

The prevalence of LVH varies widely depending on the patient population and the diagnostic method used to detect its existence. LVH is found in 1% to 8% of hypertensive patients by electrocardiography in relation to the severity of hypertension, but it is rarely detected in normotensive subjects.5 The prevalence of LVH is much greater, of course, when echocardiography is used for diagnosis. Thus, it is found in 12% to 20% of patients with mild hypertension, but it may be present in almost 90% of patients with severe disease.3,6,7 Moreover, some hypertensive patients have increased ventricular wall thickness, although their left ventricular mass index does not meet the criteria for the diagnosis of LVH (ie, 131 g/m² in men and 100 g/m² in women).

Risk for LVH is associated with several factors, older age, race, and obesity, and is independent of level of arterial pressure.2,5,8 The relative risk for LVH increases by 43% among men and 25% among women with every 20 mm Hg increase in systolic pressure. Similarly, the risk for LVH increases with age. In the Framingham population, for example, LVH was detected by echocardiography in 3% to 7% of adults under 50 years of age and in 12% to 40% of those between 50 and 80 years of age.6 The relationship between LVH and systemic hemodynamics appears more pronounced in African Americans than in whites.9 In patients with mild hypertension, African Americans are twice as likely as whites to have echocardiographic evidence of LVH.10 Finally, obesity, which is commonly seen in hypertensive patients, doubles the prevalence of LVH.11

The structure of LVH is determined by the relationship between the left ventricular mass and the thickness of the ventricular wall relative to the radius of the ventricular chamber.3 Whereas left ventricular mass is more closely related to the systolic pressure, the relative thickness of the left ventricular wall may be more closely related to the diastolic pressure.3 A concentric pattern of hypertrophy develops when the increase in left ventricular mass is accompanied by an increase in the relative wall thickness without a concomitant increase in the volume of the ventricular cavity. Concentric LVH is related more to the increased left ventricular afterload and may be the predominant form seen in middle-aged and elderly patients with hypertension.5 In comparison, an eccentric pattern of LVH occurs when left ventricular mass increases without an increase in the relative wall thickness. In this case, the end-diastolic volume of the left ventricle increases due to the preload or volume overload. This eccentric pattern develops in 10% to 20% of hypertensive patients older than 60 years of age, but less frequently in those less than 50 years of age.3,6

Epidemiologic studies have demonstrated that LVH increases risk for cardiovascular morbidity and mortality in a manner that is independent of the elevations in systolic or diastolic pressure.12,13 Although the exact mechanisms by which LVH conveys increased cardiovascular risk remains to be defined, several possibilities have been suggested.4,14 First, patients with LVH have a greater prevalence of cardiac dysrhythmias, which may lead to the increased prevalence of sudden death associated with LVH.15,16 However, abnormal coronary hemodynamics are likely to be more closely related to risk for cardiac dysrhythmias.4 The increased coronary arteriolar resistance and reduced blood flow to the hypertrophied myocardium in LVH lead to a state of coronary insufficiency, which is more fundamentally related to the increased cardiovascular risk. Coronary insufficiency results from increased myocardial oxygen demand and coronary vascular resistance, reduced coronary flow and flow reserve, and probably increases in flow viscosity. Moreover, hypertension, in conjunction with endothelial dysfunction and a coexistent occlusive epicardial artery, exert a multiplicity of effects on the coronary circulation and ventricles and, thereby, exacerbate the existing coronary insufficiency of HHD.4

Endothelial dysfunction is associated with reduced nitric oxide synthesis and increased production of a variety of mediators and growth factors, including angiotensin II, and is another mechanism that may play a role in the increased cardiovascular risk associated with LVH.4 The endothelium in the coronary arteries of patients with hypertension, as well as older individuals and those who have atherosclerosis or smoke cigarettes and other comorbid conditions, has an impaired ability to produce nitric oxide, a potent vasodilator that plays an important role in the local regulation of blood flow as well as platelet aggregation and smooth muscle cell growth. Furthermore, in experimental models, a reduction in nitric oxide production and the resulting impairment in coronary blood flow is associated with increased myocardial fibrosis and myocardial infarction.17

Patients with hypertension and LVH typically have
Impaired coronary flow reserve, which is defined by the difference between basal coronary blood flow and the maximal blood flow achieved during maximal coronary vasodilation.\(^2\)\(^-\)\(^4\) For example, Scheler et al\(^{18}\) measured coronary flow and flow reserve in 43 hypertensive patients with normal epicardial coronary arteries, who were not receiving antihypertensive medications. The hypertensive patients were stratified according to the presence of ST-segment depression on 24-h Holter monitoring. Coronary flow reserve was determined from the coronary resistance before and after dipyridamole. \(^*\)After dipyridamole (0.5 mg/kg body weight). Data from Scheler S et al: Mechanism of angina pectoris in patients with systemic hypertension and normal epicardial coronary arteries by arteriogram. Am J Cardiol 1994;73:478–482.

The diminished coronary flow reserve in patients with LVH is associated with a disproportionate increase in extracellular matrix protein deposition in the hypertrophied left ventricle.\(^19\) This remodeling may be characterized by changes in the patterns of the collagen strands and in the relative types of collagen that are produced.\(^20\)\(^-\)\(^21\) A relative decrease in capillary density may ensue when the rate of capillary growth cannot keep up with the developing hypertrophy. In this case, patients may exhibit increased minimal coronary vascular resistance and reduced coronary flow reserve. As a result, myocardial ischemia may develop even in the absence of atherosclerotic coronary artery disease.\(^2\)\(^-\)\(^4\) However, in cases where LVH is complicated by occlusive atherosclerotic disease, the clinical and functional relevance of the reduced coronary flow reserve becomes even more pronounced.\(^4\)

**ROLE OF ANGIOTENSIN II IN LVH**

Angiotensin II is believed to contribute to the development of LVH by both hemodynamic and nonhemodynamic mechanisms.\(^1\)\(^-\)\(^4\) Hemodynamically, angiotensin II activates vascular AT\(_1\) receptors to increase arterial pressure, which increases the afterload, and it activates renal AT\(_1\) receptors to cause sodium retention and volume expansion, which increases the preload. However, angiotensin II also stimulates cardiac myocyte hypertrophy, and it increases production of extracellular matrix proteins by cardiac fibroblasts.\(^22\)\(^-\)\(^25\) Angiotensin II may also activate cardiac myocytes indirectly by facilitating the release of catecholamines from myocardial nerve terminals. At the cellular level, angiotensin II binds to AT\(_1\) receptors to promote transient expression of several early activation genes (fos, jun, myc, and egr-1).\(^26\)\(^-\)\(^28\) These, in turn, control expression of other genes that are involved in cell growth and extracellular matrix protein production.

Two general pharmacologic approaches are available for regulating the effects of angiotensin II. The angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I to angiotensin II, but angiotensin II generation in the heart and vasculature is not only dependent on the actions of ACE. Other enzymes, notably chymase, are also capable of producing angiotensin II. Using membrane preparations from left ventricles, Balcells et al\(^{29}\) demonstrated that angiotensin II production in human heart is approximately fourfold higher than in dog heart, and at least 13 times higher than in mouse, rat, or rabbit heart. Notably, chymase appeared responsible for 97% and ACE for 3% of angiotensin II production in human heart. Chymase was also responsible for the majority of angiotensin II production in dog heart, but in rat, rabbit, and mouse heart, ACE was responsible for 76%, 90%, and 94% of angiotensin II production, respectively. Thus, chymase may play a greater role in cardiac angiotensin II production in humans than may be predicted from experimental models in animals.
An alternative pharmacologic strategy is to selectively block the ability of angiotensin II to activate AT1 receptors. Several angiotensin II receptor blockers (ARB) have been approved for the treatment of hypertension, including candesartan cilexetil, irbesartan, losartan, and valsartan. These agents block the hemodynamic and nonhemodynamic effects of angiotensin II that contribute to LVH, regardless of whether the angiotensin II is generated by ACE, chymase, or other enzymes. Moreover, these agents do not antagonize the angiotensin-type II (AT2) receptor, which mediates antiproliferative and vasodilatory actions and appears to be important during differentiation.30,31

**EFFECT OF ACE INHIBITORS AND ARB ON CORONARY FLOW AND FLOW RESERVE**

Studies in animal models indicate that angiotensin II contributes to impaired coronary flow and flow reserve in hypertension and LVH.32,33 In untreated Wistar-Kyoto normotensive rats, left ventricular coronary blood flow was increased and coronary vascular resistance decreased by maximal exercise on a treadmill.32 After administration of dipyridamole, coronary blood flow was further increased and vascular resistance further decreased, indicating that normotensive animals had a significant degree of flow reserve. In spontaneously hypertensive rats (SHR), however, the coronary flow reserve was greatly reduced. At baseline, SHR had coronary blood flow similar to that in age-matched normotensive animals, but the coronary vascular resistance was greatly increased. Coronary blood flow did not increase substantially with either exercise or dipyridamole, and although coronary vascular resistance declined, it still remained higher than that seen in normotensive animals.

The impact of angiotensin II on coronary flow reserve was investigated by treating 23-week-old SHR for 12 weeks with either the ACE inhibitor enalapril (30 mg/kg/day), the ARB losartan (30 mg/kg/day), or a combination of these agents (15 mg/kg/day each).33 Left ventricular coronary flow did not increase after exercise in animals treated with the ACE inhibitor, but flow reserve was significantly increased as reflected by greater flow after dipyridamole (Figure 2). In comparison, losartan produced the same reduction in blood pressure and decrease in left ventricular mass as enalapril; however, the ARB produced a greater increase in left ventricular coronary blood flow and flow reserve than the ACE inhibitor. Most intriguing, the combination of losartan and enalapril produced the most dramatic effects. The combination reduced blood pressure and left ventricular mass to a greater degree than either agent alone, but more importantly, it restored coronary flow reserve to a level close to that for an untreated normotensive Wistar-Kyoto rat. Moreover, coronary vascular resistance was also restored to a level only slightly higher than that seen in normotensive animals. These results indicate that an ARB either alone or in combination with an ACE inhibitor improves systemic and coronary hemodynamics to a greater extent than the ACE inhibitor alone. This difference likely reflects the impact of angiotensin II generated by non-ACE pathways in the heart. Similarly, studies in the same animal model with the same ARB (in another laboratory) recently demonstrated inhibition of posttranscriptional synthesis of collagen type I and reversal of left ventricular fibrosis.34

In man, blood pressure lowering with antihypertensive agents usually reduces LVH mass provided treatment is continued for a long enough time.2–4 Indeed, when certain classes of antihypertensive agents are used (eg, ACE inhibitors, ARB, calcium antagonists), this reduction in left ventricular mass may precede the hemodynamic effects of those agents suggesting an important nonhemodynamic effect of these agents in reducing cardiovascular mass.35–39 Reduction of LVH has not yet been shown to reduce cardiovascular risk related to LVH. Indeed, multicenter trials designed specifically to measure reductions in cardiovascular morbidity and mortality in association with reversal of LVH have not yet been reported. LVH usually pre-
cedes the development of congestive heart failure with diastolic dysfunction, a major hypertensive heart problem in the elderly. We believe that the associated ventricular fibrosis and impaired coronary hemodynamics are directly associated with the risk from LHV. The improvement in coronary flow and flow reserve seen in animal models with the ARB and reduction in ventricular fibrosis, if demonstrated clinically, should be especially beneficial clinically.

REFERENCES