Introduction: The Hemodynamic and Vascular Effects of Angiotensin II: Managing the Consequences

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The renin-angiotensin system mediates pathophysiologic mechanisms affecting the cardiovascular system and the kidneys. The vasoconstrictive effects of angiotensin II contribute to increased blood pressure (BP) levels in at least two-thirds of patients with hypertension and play a major role in increasing cardiac afterload in congestive heart failure.

There is now compelling evidence that the direct effects of angiotensin II on the vasculature, independent of its hemodynamic actions, accelerate arterial disease. It mediates such adverse effects as endothelial dysfunction and oxidative stress, which lead to premature atherosclerotic changes, and it has prothrombotic actions that further endanger vascular integrity. Angiotensin II also works directly on the myocardium to stimulate left ventricular hypertrophy, which, in turn, is a major risk factor for clinical cardiovascular events and is associated frequently with both the systolic and diastolic forms of left ventricular dysfunction. Likewise, angiotensin II has deleterious effects on the kidney. It appears to increase intraglomerular pressure through its vasoconstrictor effects on the efferent arterioles, and it stimulates such factors as transforming growth factor–β, further hastening degenerative changes in the kidney and a subsequent loss of function.

The relevance and importance of these observations have been heightened by the development of drugs that interrupt the renin-angiotensin system. The angiotensin converting enzyme (ACE) inhibitors are now widely used for the routine management of hypertension, and their use for treating congestive heart failure is now regarded as mandatory. Beyond improving hemodynamics and symptoms in patients with this condition, the ACE inhibitors have been shown to improve survival and to decrease major clinical events. The Heart Outcomes Prevention Evaluation (HOPE) trial, which was based on high-risk patients with histories of previous coronary disease, strokes or transient ischemic episodes, peripheral arterial disease or complicated diabetes, recently demonstrated that an ACE inhibitor, when compared with placebo, provided powerful survival benefits and protection from further clinical events.

The angiotensin receptor blockers are a newer class of drugs that are already in wide use for treating hypertension. There is preliminary evidence that they may have similar benefits to those of ACE inhibitors in the management of congestive heart failure, though definitive trials are still awaited. Interestingly, though, recent trials in patients with type 2 diabetes and evidence of renal impairment have shown that these agents have powerful renal protective effects that are additive to their antihypertensive properties. Several ongoing clinical trials with these newer agents could well propel them into preferred status for a wide range of cardiovascular conditions, particularly as they are so well tolerated.

The Symposium

This special publication of the American Journal of Hypertension is based on a symposium held at the Annual Scientific Meeting of the American Society of Hypertension, May 15–19, 2001 in San Francisco, California. Four members of the symposium faculty have prepared articles based on their presentations, documenting the data they shared during the meeting.

The article by Dr. Douglas Vaughan details innovative work that he and his colleagues have carried out to explore the ways in which the renin-angiotensin system influences vascular fibrinolytic mechanisms. A focal point of this research is that angiotensin II stimulates release of plasminogen activator inhibitor-1 (PAI-1), thus reducing fibrinolytic activity. Patients in whom this occurs have an increased risk of cardiovascular events. Dr. Vaughan suggests that some of the clinical outcomes benefits observed with ACE inhibitors may be due to the fact that these
drugs have desirable effects on measurements of such key mediators of fibrinolysis as PAI-1 and tissue plasminogen activator (tPA).

The role of the renin-angiotensin system in promoting atherosclerosis is the principal subject of the article by Dr. Carlos Ferrario. He reviews the changes in vascular biology induced by angiotensin II, including changes in the vascular endothelium and the upregulation of angiotensin converting enzyme in affected artery walls. Dr. Ferrario also examines recent evidence that angiotensin receptor blockers can reduce atheromatous changes in susceptible animals such as the cynomolgus monkey and the hypercholesterolemic Watanabe rabbit. A new agent of this class, olmesartan medoxomil, has been shown to be effective in protecting the vascular wall in both of these models independent of its effects on BP or cholesterol levels. Dr. Ferrario evaluates the mechanisms by which these potential benefits might occur.

The still uncertain status of angiotensin receptor blockers for the treatment of congestive heart failure is addressed by Dr. Bertram Pitt. Taken together, clinical trials completed thus far have been inconclusive, and it has not yet been possible to determine whether there is any additional benefit of angiotensin receptor blockers over ACE inhibitors for the treatment of this condition. Such issues as trial design or the choice of drug doses in comparative studies of the two drug classes has made it difficult to reach firm conclusions. Dr. Pitt points out that ACE inhibitors should remain the drugs of choice in congestive heart failure for the time being, although important ongoing clinical trials with angiotensin receptor blockers could help resolve this issue.

At this relatively early stage of their existence the angiotensin receptor blockers are indicated primarily for the treatment of hypertension, and in her article Dr. Suzanne Oparil explores the principal considerations in treating this condition. She discusses recent clinical trials suggesting that tight BP control, of itself, is an important factor in preventing clinical events. At the same time, interrupting the renin-angiotensin system with selective agents such as the angiotensin receptor blockers could add an additional measure of target organ protection. As with heart failure, clinical trials under way with the angiotensin receptor blockers should soon determine their place in managing hypertension and in affecting clinical events. Dr. Oparil also examines the interesting question of whether there might be differences among the angiotensin receptor blockers in their BP lowering efficacies. Some of the newer agents, including olmesartan, appear to be particularly effective and well tolerated antihypertensive agents.

The availability of the angiotensin receptor blockers, like the ACE inhibitors before them, has helped to stimulate continued interest and research in the role of the renin-angiotensin system in cardiovascular disease. This symposium has focused on evaluating several important ways in which the renin-angiotensin system can contribute to the pathogenesis of clinical events, and how management with these innovative agents can modify this process. The data and ideas presented by the authors of this supplement should prove most interesting to the reader.

References