Laragh's Lessons in Pathophysiology and Clinical Pearls for Treating Hypertension

Introduction to Lessons X to XII

Last month, we presented the evidence implicating plasma renin-angiotensin excesses (ie, excess plasma renin activity levels) as the cause of malignant hypertension and of its cardiac, cerebral, and renal vessel damage, which lead rapidly to fatal heart attack or stroke, or heart or kidney failure. We also showed that milder but inappropriate excesses of plasma renin angiotensin directly sustain part or all of the hypertension of patients with medium and high renin essential hypertension but plays little or no role in causation of the other 30% of patients who have low renin essential hypertension, in whom a sodium volume excess instead sustains the hypertension. Accordingly, this hypertension is correctable instead by sodium depletion and is not responsive to anti-renin system drugs.

This month in Lessons 10, 11 and 12 we present clinical and experimental evidence indicating that the milder excesses of plasma renin, which cause and sustain most essential hypertension, are also highly associated with later more gradual occurrences of heart attacks and strokes, not observed in patients with low renin hypertension. These differences occur even though the low-renin patients are older by some 12 years and had even higher blood pressures. These findings implicating plasma renin levels in subsequent vascular injury are buttressed by our experiments in genetic hypertensive animal models and by many large clinical trials in the worlds of cardiology and nephrology, in all of which progression of coronary or of diabetic or nondiabetic small vessel renal diseases are uniquely arrested by treatment with specific anti-renin system drugs.

In our original renin-profiled hypertensive patients we needed to do a natural history study (now called “outcomes” research) to determine whether the amounts of renin in the blood of patients with essential hypertension might, over time, cause cardiovascular events. This concept was at odds with traditional thinking, which dictates that the height of the blood pressure per se is what causes hypertensive vascular damage and it also runs counter to the belief that essential hypertension is a single process. However, there were enough exceptions to these views for us not to be deterred.

I assigned a young fellow, Hans Brunner, to analyze our records on some 219 untreated hypertensive patients in whom we had been accumulating plasma renin levels. We needed to see what happens to these patients. His chart reviews turned up some very exciting and important new information, reported in 1972,1 which was reconfirmed in 19912 by Michael Alderman and colleagues using a modern prospective randomized trial design (Fig. 1). Both studies of patients followed for 8 years, demonstrated a close association between the later occurrence of heart attack and the height of the baseline plasma renin level but only in medium and high renin patients. In both studies, no heart attacks or strokes occurred in 259 consecutive low renin patients who had no other risk factors. This was in sharp statistical contrast to the progressively greater occurrence of these events in the medium and high renin patients.

Animal Models Confirm the Vasculotoxic Role of Plasma Renin-Angiotensin Levels in Hypertensive Vascular Damage

In parallel studies of genetic stroke-prone or Dahl-S hypertensive animals,3-5 we demonstrated that suppression or inhibition of their very high prestroke plasma renin either by K+ feeding4 or by giving a specific type 1 angiotensin II antagonist losartan4,5 caused striking arrest of their ischemic cardiac, cerebral, and renal vascular lesions and proteinuria, even when hypertension was not corrected. Altogether, these animal data reinforce our proposed role for plasma renin activity in causing medium and high renin essential hypertension per se and also for causing their subsequent heart attack, stroke, and heart failure or kidney failure.

Lesson X: Inappropriately High Plasma Renin Levels That Sustain Medium and High Renin Essential Hypertension Are Also Associated With Later Heart Attacks or Strokes Not Observed in Low Renin Essential Hypertension

Lesson XI: Low Renin Essential Hypertension is Sodium Mediated and Lacks Subsequent Cardiovascular Sequelae

It is noteworthy that in both of our 8-year clinical trials1,2 no heart attacks occurred in patients with low renin levels despite their even higher blood pressures and significantly greater age than the rest. The first study1 involved 219 patients with advanced hypertension, the second2 was a prospective randomized trial of 1717 patients with mild...
hypertension. In both studies, this lack of cardiovascular sequelae in the equally hypertensive low renin patients strengthens and focuses the positive relationship between the presence and the levels of renin and the subsequent occurrence of potentially fatal vascular sequelae—heart attack or stroke.

**Clinical Pearl #8: “Benign” Essential Hypertension Really Is a Discrete Pathophysiologic Entity: It Is Low Renin, Sodium-Mediated Essential Hypertension**

Clinicians like myself have long known that essential hypertension is heterogeneous in its outcomes. Thus, we have all observed patients with extremely high blood pressures who survive to a ripe old age, whereas others with much less hypertension may die prematurely of a heart attack or a stroke. Two of many examples make this point: When I was a resident I observed the care of Arturo Toscanini. He regularly had blood pressures in the region of 230/140 mm Hg in an era before drug treatments were available. He did have left ventricular hypertrophy as shown on the electrocardiogram, but other laboratory tests were normal. He died in his nineties while still conducting regularly.

Another patient of mine, Mary Thomas, had similar, persistent (for about 40 years) striking hypertension. On three occasions she was given a nitroprusside drip in an emergency room where she had gone for other problems. When the resident called me, each time I told him to desist. Each time he obliged but seemed to think I was nuts. Later on, Mary tried many drugs, but never felt good on them and respectfully discarded them. Maybe she knew more than I did. She lived without morbid events until her late eighties.

**Lesson XII: Confirmations From Clinical Trials in Cardiology and Nephrology: Only Anti-Renin System Drugs Arrest Progression of Cardiac or Diabetic or Nondiabetic Renal Disease**

Sometimes the most convincing results of a study are the unexpected findings not sought by the investigators because they reveal themselves without the assistance of any investigator bias. Accordingly, consistent findings demonstrating arrest of progression of either coronary or renal small vessel disease have emerged from large clinical trials designed primarily to evaluate the efficacy of various new converting enzyme inhibitors (CEI) by comparing them with or adding them to β blockers in patients after an acute myocardial infarction (MI), or with congestive heart failure, or in patients with chronic diabetic or nondiabetic renal diseases.

These trials indicate that, among the antihypertensive
drugs, only β blocker or CEI therapy, or a combination of the two, can significantly protect from a subsequent MI or other coronary events in post acute MI patients or in CHF. Thus, in the post MI patients, when either β blocker or CEI therapy, or both, is superimposed on their treatment regimen, mortality and reinfarction rates are promptly and persistently reduced, survival prolonged, and left ventricular remodeling and CHF are prevented. This was shown in BHAT, SOLVD, SAVE, GISSI-3, and ISIS-4,6–10 in studies altogether involving more than 100,000 patients. Moreover, in patients with CHF these benefits were shown (Fig. 2) here to be confined entirely to patients whose entry baseline angiotensin II levels were above the median (CONSENSUS I 1990).11

In clinical trials of renal failure patients, CEI therapy strikingly arrests the progression of the small vessel renal disease in both diabetic12 and nondiabetic13 patients. Thus, these findings too, using either β-blockers or CEI, each of which are potent anti-renin system drugs in either cardiac or renal failure patients, support the concept of an active antecedent role for excess endogenous plasma renin activity in causation of such coronary or renal vascular disease. The recent HOPE trial14 further indicates that CEI therapy can prevent coronary events even when blood pressure is not reduced. Altogether, these clinical trials in either cardiology or nephrology patients by showing unique and significant treatment benefits for two different anti-renin drug types, β blockers or CEI, and the additive effects of their combination (eg, SAVE)6 thereby implicate antecedent overactivity of the renin system for causing or hastening the progression of heart attack or heart failure, or for causing or hastening progression of nondiabetic as well as diabetic small vessel renal diseases. By deductive reasoning, it is diagnosis ex juvantibus all over again. Thus, the response to specific pharmacologic probes informs the pathophysiologic diagnosis (see introduction to the lessons).

Next month in these lessons we will consider the great salt debate and the central role of dietary and hence, body sodium, in the renin–sodium interaction that supports all normotension and hypertension. This leads directly to the use of our renin–sodium equation to assess the two final determinants of all blood pressures—the sodium volume factor and the renin factor—both of which can be simply evaluated by plasma renin testing of individual patients. Using this information everyday is the key to rational biochemically based treatment of all patients with hypertension. Accordingly, I consider the next three lessons on the roles of salt and renin as revealed by plasma renin testing as our most important lessons for all clinicians interested in treating hypertension.

JOHN LARAGH
Editor-in-Chief
American Journal of Hypertension
515 Madison Avenue, Suite 1212
New York, NY 10022

Address correspondence and reprint requests to Dr. John Laragh, American Journal of Hypertension, 515 Madison Avenue, Suite 1212, New York, NY 10022, e-mail: jsealey@mail.med.cornell.edu

This article is a continuation of a monthly series that began with the January, 2001, issue.
References