Curable Renal Hypertension: Renin, Marker or Cause? Question Answered.

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I arrived in Dr Laragh's unit in 1971 having just completed my urology residency at the University of Virginia. While there, I became interested in the role of the renin-angiotension system in the vasoconstriction that accompanied unilateral ureteral occlusion in the dog.[1] In addition, I had collaborated in the laboratory of Dr Carlos Ayers working with his elegant model studying the role of the renin system in control of renal hemodynamics in the dog.[2] In fact, it was Dr Ayers who facilitated my obtaining the fellowship in Laragh's lab.

My first assignment when I arrived was to assist Dr Laragh in drafting an editorial for the *Journal of the American Medical Association* to accompany an original article from Dr Thomas Stamey concerning a refinement of the use of split renal function studies to identify patients with potentially curable renal hypertension. I prepared a draft and after several revisions submitted it to Dr Laragh. I received back a dramatically revised version with the implication that I really could not write very well! The editorial eventually was published.[3] I did not know at that time that manuscripts went through extensive revisions before leaving the lab, and during these group "bible readings," as the fellows called them, we learned to be precise in interpreting the data, to clearly and repeatedly iterate our main conclusions, and to particularly pay attention to the abstract. In addition, the discussions would wander, and new questions and studies would be proposed. Taken altogether, although tedious, they were wonderful learning experiences.

Why an editorial titled "Renin, Marker or Cause?" Although almost 100 years had passed since renin was identified by Tigerstedt and Bergman and 40 years had passed since Goldblatt accidently created the 2 kidney–1 dog model of renovascular hypertension (Goldblatt hypertension),[4] the cause of renal hypertension was unclear. It was logical that oversecretion of renin should have been the hallmark of the disease. However, the literature was inconclusive. In fact, a subsequent large review by Marks and Maxwell found "normal" peripheral renin levels in 44% of patients verified to have renovascular hypertension.[5] Moreover, in the large cooperative study, Foster found a disappointing reversal of hypertension rate of 51% after revascularization or nephrectomy.[6]Finally, the Cooperative Study of Renovascular Hypertension, which involved 502 patients, also revealed that none of the commonly used tests to identity patients for surgical correction, the hypertensive intravenous program, the renal nuclear scan, or differential renal function studies had sufficient positive predictive value to identity accurately patients for surgical renal artery correction or nephrectomy.

A major advance in the lab had occurred just before I arrived. Laragh's group received samples of the angiotensin analog Saralasin (Sar1, Val5, Ala8-AII) from Norwich Eaton.[7] In an elegant study in the 2 kidney–1 clip rat model, Hans Brunner showed a dramatic drop in blood pressure with the infusion of saralasin.[8] Thus the role of angiotension as the causative factor of the hypertension was established. Subsequently, Ed Miller in Boston showed similar results in the same model using the angiotensin-converting enzyme inhibitor SQ20881.[9] In the Laragh lab, Harry Gavras added another piece to the puzzle, showing that the 1 kidney–1 clip rat model, when sodium replete, did not show a blood pressure response to saralasin, the hypertension was supported by volume in the absence of the opposite kidney. However, when the animal was sodium depleted, the renin-angiotensin system was activated, and then the blood pressure fell dramatically with the infusion of saralasin.[10] These observations also gave experimental evidence for Laragh's vasoconstriction-volume construct for the understanding and treatment of hypertension.[11] Thus the stage was set for the verification of these findings in patients with renal or renovascular hypertension.

After the approval of an IND by the Food and Drug Administration, phase I studies were begun on the 9th-floor metabolic ward at Columbia-Presbyterian Medical Center. Again Hans Brunner was the fellow in charge. Twelve patients were studied, and the 8 with high peripheral renin activity levels (PRA) had dramatic falls in blood pressure with the saralasin infusion, whereas those with normal or

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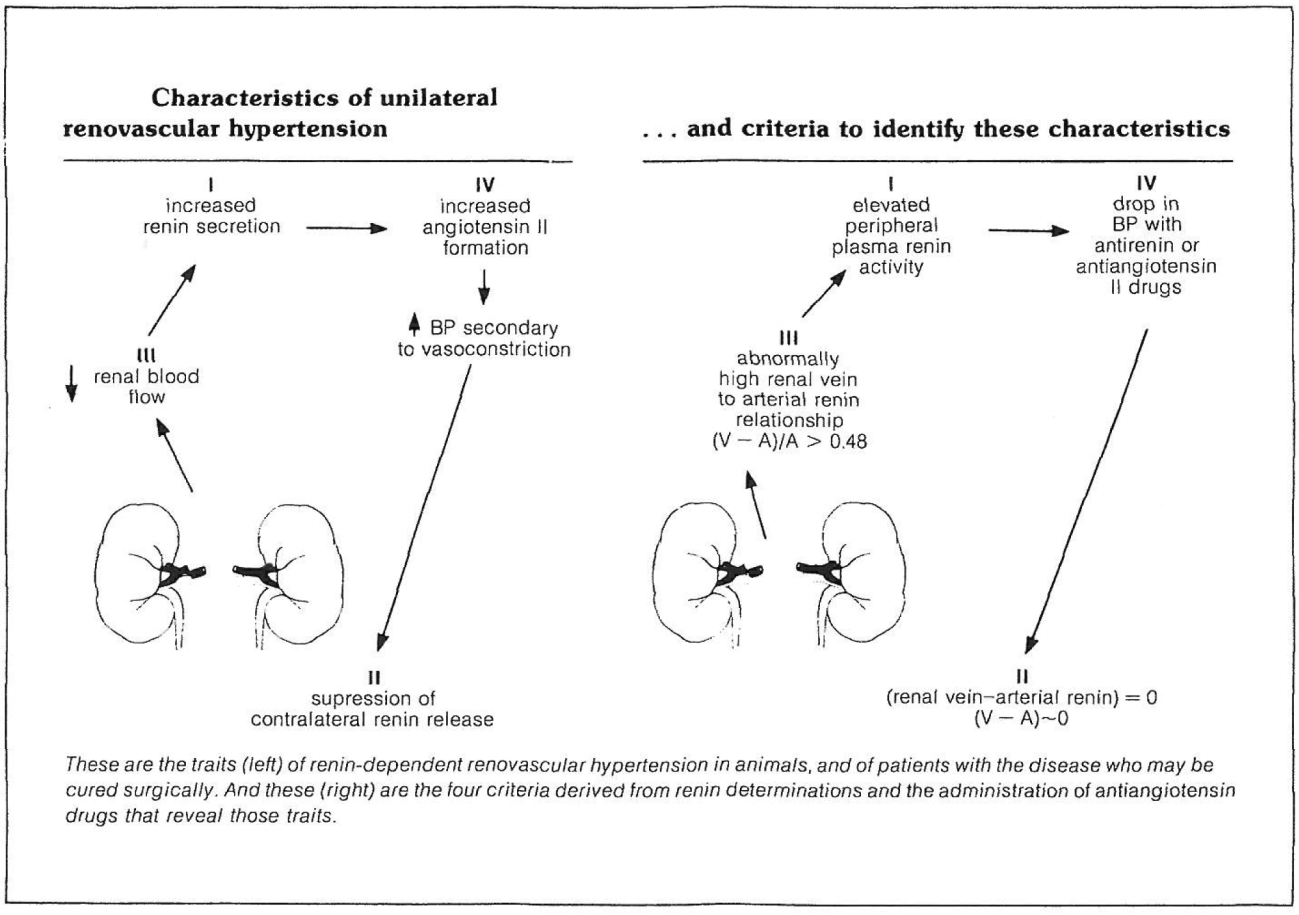
low PRA did not respond with a fall in blood pressure.[12] An early patient studied was a 21-year-old female patient of mine who was admitted with malignant hypertension (Figure 1). At the time of infusion, her blood pressure was 210/135 mm Hg, and during the infusion it fell to 160/90 mm Hg. Her headache was relieved, and she cried when we stopped the infusion and the hypertension returned. The supine PRA rose from 9 ng/ml/hour to 28 ng/ml/hour. We did not recognize the importance of the reactive rise in PRA at that time, but the fall in blood pressure and the reactive rise in PRA in response to saralasin were subsequently used in conjunction with renin measurements to identify patients with curable renovascular hypertension.[13] The use of saralasin to identify these patients was eventually replaced by the angiotensin-converting enzyme inhibitor captopril.[14]

With this better understanding of the role of the renin-angiotensin system in experimental models of renovascular hypertension (Figure 2), we needed to return to renal vein renin analyses to develop a more accurate means to identify patients with renal artery lesions or renal disease potentially curable by surgery or angioplasty. At that time the major discussion revolved around what was the appropriate cut point in interpreting renal vein renin ratios—1:1.5, 1:2, or another ratio of renin from the normal kidney to the kidney with the arterial lesion that would predict a favorable response to intervention.[15] In the review of a dormant manuscript of our experience with renal vein renin in patients with renal vascular disease, we realized that we did not have a clear understanding of renin secretion in hypertensive patients without renal disease. Accordingly, under the leadership of Jean Sealey, we measured renin in blood collected from the aorta, inferior vena cava, and renal veins in 43 patients with essential hypertension, normal renal vasculature, and most with normal renal function.[16] The first observation was that the renin activity in the aorta and that in the inferior vena cava were not different from each other over a wide range of values. Thus when calculating the increase of renin activity across the kidney (V − A), we did not have to obtain an arterial value, which simplified the blood collections. More important, again over a wide range of renin levels, the relationship of renal vein renin to arterial (or venous) renin was a constant, with the renal vein level being 24% higher from each kidney. Finally, in the absence of liver disease, normal clearance of renin, and the constant 25% increment from the kidneys, then the peripheral PRA is the indicator of renin secretion. Any further elevation of the renal vein renin is an indication of decreased renal renin blood flow (Figure 2).

Taking these observations into account with the leadership of Jean Sealey and Fritz Buhler, we then returned to our review of renin determinations in our patients with renal



These are the traits (left) of renin-dependent renovascular hypertension in animals, and of patients with the disease who may be cured surgically. And these (right) are the four criteria derived from renin determinations and the administration of antiangiotensin drugs that reveal those traits.

Figure 1. Blood pressure response to saralasin infusion in a patient with malignant hypertension. Abbreviation: Ang II Inh, angiotensin II inhibitor.

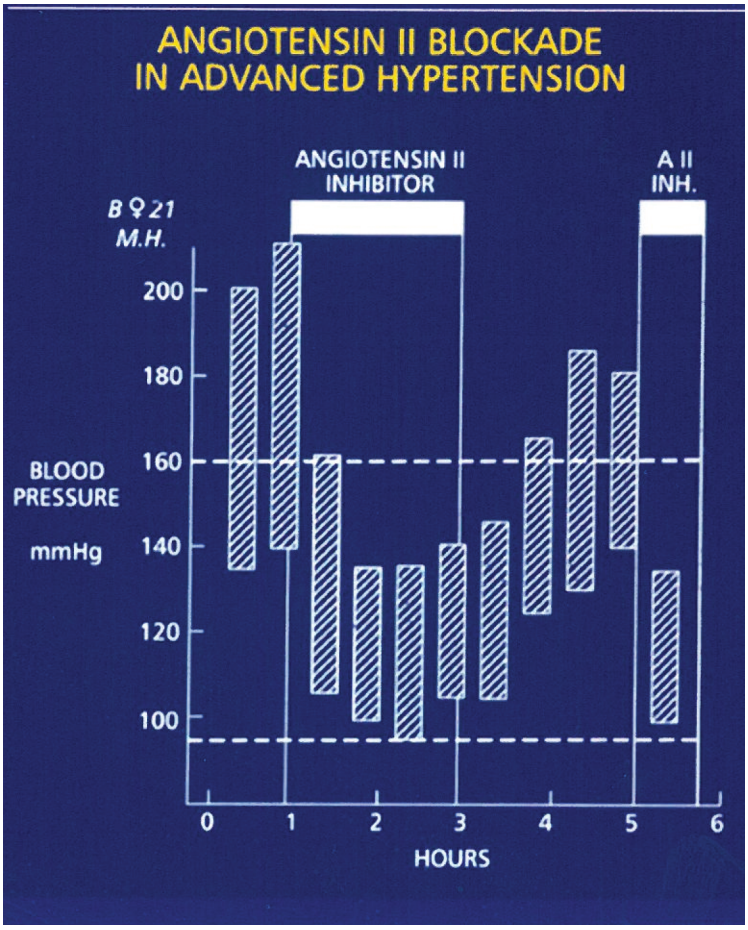


Figure 2. Characteristics of unilateral renovascular hypertension and criteria to identify these characteristics. Abbreviation: BP, blood pressure. (Adapted from ref. 19.)

vascular disease. Based on the animal date and the observations in the patients with essential hypertension, we postulated that patients with curable renovascular hypertension should have an elevated peripheral PRA related to their 24-hour sodium excretion, indicating renin oversecretion from the affected kidney. In our review of 29 patients who had undergone surgical correction of their lesion, 86% of the cured patients had an elevated peripheral PRA. Further evidence for the peripheral PRA being an indicator of increased renin secretion was the demonstration, in patients where values were available, that the PRA normalized in all cured patients after corrective surgery. Second, we knew that in the animal model of 2 kidney–1 clip Goldblatt hypertension the contralateral kidney suppressed its renin secretion in face of the hypertension, a phenomenon termed contralateral suppression of renin secretion (V – A = 0).[17] A similar finding had also been reported by Stockigt in patients with renovascular hypertension.[18] In all cured patients in our study, the renal vein renin relative to the arterial renin from the contralateral uninvolved kidneys approached zero (mean V – A = 0.08). We also postulated that a failure to demonstrate contralateral suppression was an indicator of occult bilateral disease, which might limit the success of renal revascularization of the affected kidney. Finally, the third criteria was that the increased renal vein renin content relative to arterial renin from the suspect kidney should be ((V – A)/A > 48)) which could be used to estimate the degree of renal ischemia—the higher the value, the lower the renal blood flow.[19] We felt that this physiological interpretation of renal vein renin and peripheral PRA taken together would enhance our ability to identify patients with curable renal hypertension. Furthermore, this patient analysis supported the view that abnormal renin secretion was intimately involved in curable renovascular hypertension in man, confirming the experimental animal data. Later, as discussed previously, the captopril test became an additional tool, with a fall in blood pressure and a reactive rise in PRA being an indicator of renin-dependent hypertension.

Thus in a short period of time with the combination of excellent methods, animal experiments, a robust patient database, and a talented and dedicated group of investigators, the question, "Renin, marker or cause?", was answered. Unfortunately, with the ease of angioplasty and renal artery stenting at the present time, the rigor necessary to clearly identify patients with curable renovascular hypertension is not uniformly carried out before the procedure. Perhaps this is the reason that the results of intervention in patients with renovascular disease is no better than medical management, as shown in some publications. A step back in time may be indicated.

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