Role of Angiotensin and Its Inhibition in Hypertension, Ischemic Heart Disease, and Heart Failure

Haralambos Gavras, Hans R. Brunner

Abstract—This is a personal historical account relating the events that led to the first application of angiotensin inhibition (either by ACE inhibitors or by angiotensin receptor blockade) to the investigation of the pathogenesis and treatment of hypertension, ischemic heart disease, and heart failure. Included are animal experiments, clinical observations, and the earliest clinical experimental studies that helped define some of the detrimental effects of angiotensin II and the beneficial hemodynamic results of its inhibition, which have been subsequently corroborated and amplified by large randomized outcome trials. (Hypertension. 2001;37[part 2]:342-345.)

Key Words: renin-angiotensin system ■ myocardial infarction ■ heart failure ■ angiotensin-converting enzyme inhibitors ■ receptors, angiotensin

Despite impressive biochemical and technological advances in recent years—or, maybe, because of them—cardiovascular disease and its end result, heart failure, continues to be the most common ailment of advanced age. Among the various pharmacological approaches introduced for its treatment, one of the most successful in terms of improving and maintaining functional capacity as well as prolonging life was the suppression of the renin-angiotensin system (RAS).

Scientific advances do not occur in a vacuum, and this one was no exception. Work by many investigators all over the world (such as Irvine Page and his group in the Cleveland Clinic, Braun-Menendez and his team in Argentina, Lever and his MRC Blood Pressure Unit in Glasgow, Laragh and his colleagues in New York, and many others) had been exploring and elucidating various aspects of the RAS. The role of RAS activation in hypertension, hypertensive/ischemic heart disease, and its corollary, congestive heart failure (CHF) was still hotly debated in the early 1970s but was gradually coming into focus. We had been approaching the subject from two different angles: experimental studies in animals, in which infusions of angiotensin II caused extensive necrotic lesions in the myocardium, replacing myocytes by fibrotic scar tissue, and epidemiological studies in hypertensive populations, in which normal or high-renin patients were far more prone to develop heart attacks than patients with hypertension of similar severity but with suppressed renin. We therefore reached the same conclusion, that is, that relative renin-angiotensin excess is a cause of ischemic heart disease and myocardial infarction. It would be a small leap from that point to suppose that suppression of the RAS might be beneficial by reversing the pathogenic process. The following is a personal account of the background and circumstances that led us to conduct the first clinical experiments with angiotensin inhibition in heart failure and hence crystallize that notion.

The idea of afterload reduction to relieve CHF was not new. It was first proposed by Fries (Keely et al.), who used ganglionic blocking agents, the only dependable antihypertensive drugs available at that time. However, it remained relatively unnoticed for many years, and it was much later that the hemodynamic benefits of treating CHF with vasodilators were convincingly demonstrated. Several vasodilators were tested, some working mostly directly against the resistance arterioles, others mostly venodilators, others working indirectly through α-adrenergic blockade. All remained largely in the realm of clinical research because of side effects or difficulties that made them impractical for long-term routine use; problems included need for intravenous drip, tachyphylaxis with loss of efficacy, activation of neurohormonal factors (particularly the renin-angiotensin/aldosterone axis and catecholamines) that offset their initial benefit by causing retention of salt and fluid with further enhancement of edema, reflex tachycardia, and diminished perfusion of coronary, renal, and cerebral circulation in patients who may have had already impaired perfusion of vital organs at baseline.

In retrospect, elimination of one of the major vasopressor systems would appear to be the obvious rational choice for treatment of CHF. After all, the hallmark of CHF is elevated systemic vascular resistance, and all three major pressor hormones—catecholamines, renin-angiotensin, and vaso...
pressin—had been implicated as contributing to this situation. Abnormal activation of these vasoconstrictors already had been described as a common although inconsistent finding in decompensated CHF. However, the interpretation of these findings was still a matter of debate, because prior experience had already shown that circulating levels of a vasoactive substance do not necessarily indicate its functional significance (hence, for example, the debate about the role of renin in hypertension in the 1960s).

Be that as it may, activation of the renin-angiotensin system had been described several years earlier as one of the features of decompensated CHF. Many of the undesirable effects of vasodilators (such as retention of salt and fluid or diminished perfusion of vital organs) would be eliminated if vasodilation were associated with blockade of angiotensin actions. However, the first clinical application of this logical concept was not the result of rational design. It was the result of serendipity.

We had the opportunity to study the pathogenesis of experimental renovascular hypertension by using angiotensin II antiserum, and—more importantly—the angiotensin II receptor antagonist saralasin. In a first set of experiments, 2 kidney–1 clip (2K1C) hypertensive rats and 1 kidney–1 clip (1K1C) hypertensive animals were treated either by injection of angiotensin II antiserum or infusion of saralasin. Both treatments yielded the same results, that is, normalization of blood pressure in the 2K1C model but no blood pressure reduction in the 1K1C animals. In a follow-up experiment, 1K1C hypertensive animals were fed a low-sodium diet, which per se did not reduce their blood pressure but rendered their hypertension exquisitely sensitive to angiotensin II, reflected by blood pressure normalization during saralasin infusion. A third set of experiments demonstrated that with prolonged time (15 weeks), even 2K1C hypertensive animals needed simultaneous salt depletion to normalize blood pressure during saralasin infusion. These experiments demonstrated for the first time that renin secretion is often inappropriate, even though salt retention caused by a reduced renal excretory capacity for sodium may let it appear “normal.” This salt-mediated—apparent normalization of renin secretion is readily unmasked by dietary salt depletion, which reveals the true angiotensin mechanism of hypertension.

This string of seminal observations opened the possibility of a more important contribution of the RAS to sustaining the increase in blood pressure in patients with essential hypertension and normal or even low plasma renin activity. We were accordingly eager to infuse saralasin to hypertensive patients. In a first observation, we were thus able to demonstrate for the first time in some severe hypertensive patients with mostly high renin levels that specific angiotensin II blockade by saralasin could indeed substantially reduce or even normalize blood pressure. This finally provided the final proof that angiotensin II—at least in some special cases—could represent the key hypertensive mechanism.

Of even greater interest was the question of whether our concept of unmasking the renin component by simultaneous salt depletion would work equally well in normal or low-renin essential hypertensive patients as in 1K1C hypertensive rats. To our great satisfaction, we found that in hypertensive patients, angiotensin II dependency of blood pressure could be exquisitely accentuated or attenuated by varying relatively moderately their sodium balance. Indeed, similar studies conducted subsequently in hypertensive patients with extremely suppressed renin levels established the concept of a reciprocal relation between renin and sodium balance.

We were in the midst of these exciting studies in the laboratory of Dr John Laragh, at the Columbia-Presbyterian Hospital in New York, using the angiotensin-receptor antagonist saralasin, when late one afternoon of 1972, at the end of a regular clinic session, a new patient (patient AD), age 41, was evaluated for severe headache and increasing dyspnea. He had a blood pressure in the range of 250/150, with typical signs of malignant hypertension, and appeared to be suitable for our new antihypertensive treatment. Only there was a problem: Even though he was already taking furosemide and digitalis, he was also in florid pulmonary edema. We decided to go ahead and set up a drip of the experimental drug, while starting a urine collection. We sat up all night and watched as his blood pressure came down within minutes, accompanied by profuse diuresis, his headache and orthopnea diminished, and by morning he was sleeping peacefully flat on one pillow. The drip continued for 7 days, at the end of which he had a negative cumulative sodium balance of 760 mEq. He had not even been in a cardiac care unit, and we did not have any other objective evidence of his improvement except for the clinical signs, that is, reduced blood pressure and heart rate, loss of edema, and clear lungs. What we really needed was a formal protocol to measure changes in hemodynamic parameters to move on from this anecdotal report to a controlled clinical experiment.

Over the next few years, we struggled with research proposals and grant applications to funding agencies, the pharmaceutical industry, and the Institutional Review Boards for Human Studies. Most were rather reluctant—perhaps understandably—to allow experimentation in such high-risk patients with a novel approach of unproven value and inadequate documentation, let alone fund it. Some reviewers pointed out potential scientific flaws in our reasoning: Could we guarantee, for example, that angiotensin II blockade would not open up pulmonary shunts and cause a ventilation-perfusion imbalance that would further worsen hypoxemia? We could not, of course, but we knew that patient AD had not become cyanotic; on the contrary, he had improved dramatically. Still, the concerns were legitimate, and we had to settle for a very restricted protocol, where our measurements could be performed over a short period of time on a patient who would require the necessary invasive instrumentation as part of his routine care and would not have to undergo additional manipulations. We drafted a detailed protocol and agreed to continue our collaborative effort, although our careers were now at crossroads: One of us was about to move to Boston, and the other was returning home to Switzerland.

The right opportunity presented in 1975, when a patient with resistant hypertension secondary to renal artery obliteration, in need of uninephrectomy, was scheduled to first undergo diagnostic cardiac catheterization for evaluation of coronary disease associated with chronic CHF. This was one of the rare cases in which a single clinical observation may
provide invaluable insights in the pathogenic mechanism of a disease process. It illustrates how a clinical experiment properly conducted can open up new avenues of research—something frequently forgotten in this age of high technology and “evidence-based medicine,” when scientific validity is only accepted if based on cellular and molecular studies or randomized multicenter trials. The unique hemodynamic observations made after angiotensin inhibition on that patient initiated the work that subsequently led to the concept of cardioprotection through diminished cardiac work, enhanced myocardial perfusion, and improved myocardial metabolism. A 30-minute infusion of saralasin during patient L’s catheterization produced an immediate drop in systemic and pulmonary vascular resistance, with fall in left ventricular end-diastolic pressure and pulmonary capillary pressure. The increase in cardiac output was accompanied by decrease in heart rate, diminished left ventricular stroke work index, and reduced myocardial oxygen extraction. Yet, despite these metabolic changes and the marked fall in systemic blood pressure, there was clear increase of the coronary blood flow.12 All of the changes reverted to baseline within minutes after stopping the infusion of saralasin.

This last observation, that is, the increase in coronary blood flow despite diminished myocardial oxygen consumption, was particularly intriguing because it went against the rules known to govern the autoregulation of coronary circulation. It did, however, tie in with our previous experimental animal and clinical work that had linked renin-angiotensin excess with the development of myocardial infarcts.1,2 Efforts to further clarify this odd phenomenon led to a series of highly informative experiments that revealed a difference in sensitivity of various vascular trees to the constrictor effect of angiotensin II. This difference caused a fractional redistribution of the cardiac output after blockade of angiotensin II, with increase in regional blood flows to the sensitive vital organs (heart, kidney, brain) at the expense of musculoskeletal and cutaneous blood flows.3,14 Moreover, the enhanced coronary blood flow was associated with improved myocardial metabolic parameters. This would later explain how nonhypertensive patients with CHF and with actually low-baseline blood pressures could tolerate some further lowering of their systemic pressure after angiotensin II blockade without symptoms of cerebral, cardiac, or renal ischemia, because the perfusion of these angiotensin-sensitive organs was maintained at an adequate level. Indeed, hypertension was by no means a prerequisite for successful treatment of CHF by angiotensin inhibition. Normotensive patients with CHF were also shown to have considerable hemodynamic and metabolic improvement in response to saralasin, but this observation was not accepted for presentation at the annual meeting of a prestigious society, and the report had to be submitted consecutively to three journals until one agreed to publish it.15

Saralasin was not a practical drug. Being a peptide with a very short half-life, it had to be given by constant infusion under close monitoring. Moreover, by that time, it was also known that saralasin could under certain circumstances act more as an angiotensin-receptor agonist than antagonist if the blood pressure was not renin-dependent and therefore could not always be counted on to perform as expected. On the other hand, a marvelous new experimental tool, the ACE inhibitor teprotide, had been synthesized by scientists at the Squibb Research Institute and become available for clinical use. It was not only effective in inhibiting formation of angiotensin II for several hours but was a far more reliable blood pressure-lowering drug. We had already tried it in various types of human hypertension and had found its effects to be predictable and long lasting after a single-bolus intravenous injection.16 It was perfect for our protocol. We approached our friend, Dr Juan Guerrero at Squibb with this idea. He was enthusiastic about the science of this project and willing to provide us with enough substance for a trial. However, his company’s administration had already decided that teprotide was not a drug with commercial future and was not prepared to financially support such studies; neither were other funding agencies, although saralasin had already given us preliminary positive results that were encouraging enough to warrant further research.

Nevertheless, with persistence in our conviction and with a great deal of encouragement and cooperation from our cardiologist colleagues Drs D. Faxon, G. Turini, and T. Ryan, we somehow managed to complete the first short-term clinical trial, whose results showed that our optimism was amply justified. However, it proved to be far more difficult to convince the editorial board of a medical journal to publish those results. After being summarily rejected by another prestigious journal, the paper remained under consideration by Circulation for a whole year and raised a lot of arguments. It did not gain acceptance until after another similar report, submitted later independently by Dr Jay Cohn and his team, corroborated its findings. The two papers were finally published back to back in the same issue.17,18

The rest, as the saying goes, is history. The rapid succession of biochemical advances, with the design and synthesis of orally active ACE inhibitors that were safe, effective, and convenient for chronic administration,19 led many cardiologists throughout the United States and Europe to repeat these studies and confirm and amplify their results. Captopril, the first orally active ACE inhibitor, was released commercially in 1981 and was immediately adopted by clinicians as treatment for CHF as well as hypertension, even though originally only the latter indication was officially sanctioned by the Food and Drug Administration. Within another 4 years, this approach was regarded as a breakthrough in the treatment of CHF and came to be considered as the standard therapy that might be unethical to withhold for purposes of further research. The subsequent introduction of many “second-generation” ACE inhibitors, with improved pharmacokinetic properties, led to numerous multicenter outcome trials funded by their respective manufacturers, thus firmly establishing the validity of this approach. More recently, a new class of orally active, nonpeptide, selective antagonists of the angiotensin II type 1 receptor was introduced,20 and the first multicenter outcome trials with various members of this class suggest that their benefits in hypertension and heart failure are comparable to those of ACE inhibition, thus providing further evidence—if still at all needed—that angio-
tensin II is a dominating culprit in hypertension and congestive heart failure.

It was the combination of careful clinical observation and metabolic measurements, together with the use of novel, highly selective pharmacological probes, that allowed us to identify key pathogenic mechanisms involved in the development of hypertension and cardiac failure and at the same time to completely change the treatment of these diseases.

References
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