More about plasma renin and cardiovascular mortality

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This editorial refers to ‘Association of plasma renin with 10-year cardiovascular mortality, sudden cardiac death, and death due to heart failure’, by A. Tomashitz et al., on page 2642

Renin, the renal pressor substance, was discovered and described by Tigerstedt and Bergman in classic experiments published in 1898. It was not, however, until 1934 that Goldblatt identified the relevance of renin by showing that renal secretion of renin caused sustained renovascular hypertension in dogs. Others subsequently demonstrated that renin itself is not the pressor element, but rather is the rate-limiting component of the newly defined renin–angiotensin–aldosterone control system (RAAS). This RAAS has since become recognized as a key regulator of blood pressure control and a participating factor in its pathological consequences.

In the past half century, the role of the RAAS in the pathophysiology of hypertension and as a basis for antihypertensive drug development was established. Plasma renin has also been associated with cardiovascular morbidity and mortality in hypertensive patients (Figure 1). Tomashitz et al. have now extended that finding to patients in whom plasma renin was measured while taking antihypertensive drugs.

Tomashitz et al. measured the plasma renin concentration (PRC) using a sensitive automated immunoreactive chemiluminescence method that is comparable with the more traditional enzyme kinetic radioimmunoassay renin activity (PRA) assay. An exception is that very high PRC values (PRA > 40 ng/mL/h; PRC > 300 pg/mL) are proportionally higher because they deplete plasma angiotensinogen, the renin substrate, in vivo, resulting in a reactive increase in renal renin secretion. Thus, at high levels, the PRA assay continues to reflect the in vivo rate of angiotensin formation.

Tomashitz et al. examined the 10 year mortality experience of 3316 Caucasian men and women referred to a single hospital for coronary angiography (the LURIC group). At baseline, participants were free of serious non-cardiovascular disease (CVD), had normal liver function, and, except for the 30% with ‘acute coronary syndrome’ (ACS), were in stable condition. Interval history is unavailable.

Subjects were mostly males (70%) with an average age of 63 years. Stratification by ascending PRC quartiles revealed that at baseline PRC correlated with plasma angiotensin II, plasma aldosterone, C-reactive protein, uncontrolled hypertension, and heart failure.

The principle finding was that, independent of traditional risk factors and antihypertensive drug therapy, a one standard deviation increase in PRC predicted 23% higher CVD mortality—mostly heart failure or sudden cardiac death. However, addition of PRC did not significantly improve prediction of CVD mortality beyond that provided by conventional risk factors.

This prospective cohort study raises questions and generates fresh hypotheses. The authors accurately present this as a prospective cohort study of patients referred for coronary angiography. Not surprisingly, the population studied had a high degree of coronary artery disease. However, to better understand the issue in question—the relationship of renin to CVD mortality—it is important to note that nearly 90% were taking antihypertensive medications and so were most probably hypertensive patients.

Measurements of renin have different meanings in normotensive and hypertensive individuals. In both cases volume contraction and/or falling blood pressure causes a reactive increase in plasma renin levels thereby increasing angiotensin II to increase arterial vasoconstriction; this response maintains an adequate blood pressure to ensure appropriate levels of tissue perfusion—a priori this is both an appropriate and beneficial response. At the same time, in normal circumstances, rising blood pressure suppresses renin secretion, leading to suppressed plasma renin levels. Renin becomes pathological whenever it fails to fall appropriately in response to the rising blood pressure. This suggests that in normal circumstances renin ought not to be associated with CVD. In fact no relationship of PRA levels to CVD was found in cohort studies of general populations.

In contrast, plasma renin levels bear a continuous relationship to CVD in hypertensive patients, and those with the highest plasma renin levels have been shown to have a markedly increased CVD...
Thus, the strong association of PRC with CVD in the LURIC study, seen as a hypertensive cohort, is wholly consistent with virtually all previous research.

Unfortunately, however, the LURIC study cannot be precisely compared with previous studies because plasma renin was measured in their patients while they were taking antihypertensive drugs, and antihypertensive drugs influence plasma renin levels. Neither the factors influencing drug assignment, nor details of usage, nor the frequency of combination prescription is reported. In fact, drug use varied strongly by renin quartile. Medications that increased renin were more frequent in the highest renin quartile [diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs)] while those that suppressed renin were used more frequently in the lowest quartile (β-blockers). Another confounding effect of drug use is that plasma renin levels measured in the face of ACEI or ARB blockade overestimate by $\approx 10$-fold the true activity of the circulating renin–angiotensin system in vivo. Thus the ‘effective’ activity of renin in vivo might have been only 10% of the measured level in up to 80% in the highest renin quartile. If that is indeed the case and had it been taken into account, the results might have been quite different. In short, drug use almost certainly influenced renin levels, but, with available data, it is impossible to determine its extent or significance.

Nevertheless, in the absence of pre-treatment values, it is unlikely that those who fall in the lowest quartile (75% on a β-blocker) would have fallen in the highest quartile in the untreated state, or that those taking an ACEI or ARB in the highest quartile (nearly 80%) would have fallen in the lowest quartile at baseline. Assuming this, it is reassuring that, notwithstanding the possibility of confounding, these findings are consistent with those previously observed in other studies of hypertensive subjects based upon pre-treatment PRA.

The foregoing addresses the epidemiological association of renin with health outcomes. However, renin also has physiological meaning. For example, an elevated renin level does not invariably signify the need for additional renin system blockade. Instead, it could reflect a physiological response to intravascular and intracellular volume contraction, perhaps due to aggressive diuretic therapy and/or excessive dietary sodium restriction. This is particularly likely in patients with heart failure. In such circumstances, reactive increases in plasma renin–angiotensin II-mediated vasoconstriction may be a beneficial effect that is sustaining pressure to maintain tissue perfusion. Liberalizing sodium intake can be an effective way to suppress plasma renin levels in patients with heart failure. Thus, under special circumstances, increasing salt intake may be more beneficial than blocking renin pharmacologically. A randomized clinical trial in patients with compensated heart failure and aggressive diuretic therapy found that sodium restriction to 80 mmol/day significantly increased hospitalization and mortality compared with sodium intakes of 120 mmol/day.

What’s next?

These data again raise the possibility that plasma renin measured while patients are taking their medications can contribute to more effective drug therapy while illuminating prognosis.
However, the appropriate circumstances for measuring renin during treatment and its application need further definition. More information is also needed to define fully the place of renin testing as a tool for improving antihypertensive therapy. Barely half of all hypertensive patients now achieve blood pressure control. Would a renin-based treatment paradigm—as we believe—significantly improve that which has been achieved by adherence to the stepped care approach? Further studies are also required to determine whether and to what extent the association of renin with mortality might be exposed in patients with coronary artery disease, but without heart failure or hypertension.

Finally, the $64 question. Does the RAAS have, as we believe, a causal role in the development of CVD in hypertensive patients? CVD remains the world’s greatest killer overall, and hypertension is its most prevalent risk factor. Robust randomized clinical trials are urgently needed to determine whether, in appropriate patients, blockade of the RAAS can confer cardioprotection beyond that ascribed to blood pressure reduction, and to define when subtraction of medications that induce reactive increases in renin secretion might be the appropriate treatment strategy. Meanwhile, assessment of plasma renin status provides an additional tool for regular assessment of each patient, particularly those with hypertension, heart failure, and now perhaps coronary heart disease, to identify new opportunities and improve treatment success.

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References