Clinical Value of Plasma Renin Estimation in the Management of Hypertension

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In physics, pressure is defined as force/area (Figure 1). From this, a number of further elegant equations can follow. John Laragh’s acuity was to recognize the intrinsically binary nature of blood pressure. In medicine today, our ability to discover individual molecules contributing to disease has had the opposite impact to what was perhaps anticipated: the sheer number discovered by techniques such as genome-wide association studies has rendered common diseases even more complex than anticipated.¹ But however complex and continuous the spectrum, the rainbow reminds us that there are just 2 ends to a spectrum and some remarkably distinct patterns in between.

John’s elucidation of the volume/vasoconstriction dichotomy was a direct descendant from Poiseuille’s physics, followed by a lifetime—indeed 2 lifetimes by ordinary career-length standards!—of experiment and teaching.² My own rainbow vision was a more Damascene moment, following a study that started with a completely different hypothesis. In 1996, the prevailing view was that essential hypertension might be due to allelic differences in about 5 main genes, with angiotensinogen recently reported as one of these. I wished to test first whether there is true variability between patients in their responsiveness to different antihypertensive drug classes and, if so, whether there might be 4 patterns of response corresponding to the mechanism of action of the 4 main drug classes. To detect and measure variability, we designed what I came to call rotation studies—crossover comparison of multiple drugs.

AB/CD—RULE OR PREDICTION?

In the event, we did confirm variability in response. However, there were not 4 patterns of response, but 2. This manifested as significant correlations between 2 pairs of drug classes but none of the other permutations. The 2 pairs worked best at opposite ends of the renin spectrum. One pair was ACE inhibitor and beta-blocker; the other was calcium channel blocker and diuretic. Two things stood out. One was that the first pair blocked the renin-angiotensin system, whereas the second blocked sodium retention. The other was the serendipity that the names of the 2 pairs of drug classes started, respectively, with A, B and C, D. Because we had chosen a young cohort of previously untreated patients to study and found that the first pair was on average almost twice as effective in reducing blood pressure as the second, the results could be summarized as an “AB/CD” rule. Using age as a surrogate for plasma renin, we recommended A or B for the typical younger patient, and C or D for the older.³ Perhaps the rule was more a prediction than a rule, although it was on fairly safe ground given John’s work a quarter-century earlier, using just beta-blockade and diuretics.² A number of morbidity/mortality outcome trials were in progress, which compared A or B with C or D drugs in patients of an age to sustain a morbid event—usually >55 years; in each case, blood pressure reduction proved greater in the C or D arm.⁴

In the subsequent decade, there has been slow, and still not universal, recognition by national and international guideline committees that initial treatment of hypertension should vary with surrogate markers of renin.⁵ ⁶ The United Kingdom, where AB/CD was adopted and modified first by the British Hypertension Society, then by the National Institute for Clinical Excellence, has seen a dramatic increase in levels of hypertension control.⁷ ⁸ Ironically, however, the basis of the AB/CD dichotomy was slightly blurred in the National Institute for Clinical Excellence’s drive for a simplified guideline, in 2011, which reduced the older members of each pair (beta-blockade and diuretic) to 3rd or 4th choices, rather than equi-effective choices for patients intolerant of A or C.⁹ No guideline committee has yet been inclined to recommend routine renin profiling. The challenge to those of us who do measure renin in most patients is to show that this practice is a cost-effective improvement on using the cost-free—but clearly imperfect—surrogates of age and ethnicity.
Figure 1. Pressure = force/area: the garden hose. As every gardener knows, the throw of water from the hose can be increased either by narrowing the outlet (as in a sprinkler) or by turning up the tap.
American Journal of Hypertension 27(8) August 2014 1015

Clinical Value of Renin Estimation

In 2008, the British Hypertension Society decided to address this challenge with a trio of publicly funded studies, PATHWAY 1–3, which will report next year. Each addresses a different group of patients, ranging from never-treated through treatment resistant, and asks whether baseline renin predicts response. In PATHWAY 1, 300 patients crossover between losartan and hydrochlorothiazide before progressing to combination, whereas a further 300 are randomized to initial combination and will answer the question of whether this is the superior strategy for the majority of patients, whose plasma renin is not at the extremes. PATHWAY 2 is a crossover comparison in 350 patients between the 3 recommended options for resistant hypertension and tests whether high and low renin will predict, respectively, good responders to bisoprolol and spironolactone. Most patients today are on combination therapy, and plasma renin may ultimately be of most value predicting response of 3rd- or 4th-line therapy. Therefore PATHWAY 3, although primarily a study of glucose tolerance, will tell us the value of plasma renin, both in prediction of initial blood pressure response and in titration of dose, following randomized addition of hydrochlorothiazide, amiloride, or hydrochlorothiazide + amiloride to common permutations of A, B, and C in 450 patients.

In the United Kingdom, the availability of a robotic renin mass assay has rendered renin measurement relatively cheap, about $35. But this is also the cost of a year’s treatment with many of the generic drugs, so that the cost of preferring a predictive test to systematic trial and error may not be rapidly recouped. A strength and weakness of plasma renin as clinical predictor is the breadth of its distribution in the population (Figure 2). At 3–4 log units, this is much broader than the single log unit of most hormones. Most patients are in the body of the distribution, where predictive value will be less than at the extremes. However, the practical impact is that almost an entire log unit can be assigned to high-renin and low-renin patients, sufficient to eradicate the clinical impact of variation due to stress or recent activity at the time of blood sampling. The textbook precautions of yesteryear are unnecessary, and in reality, renin is one of the easiest hormones to measure during short office visits.

**SUPPRESSED RENIN = PRIMARY ALDOSTERONISM, UNTIL PROVEN OTHERWISE**

So, it is the categorically opposite extremes of renin that are most informative, and the assimilation of renin into everyday practice may be most readily accepted when it commonly enables the detection of categorical, secondary causes of hypertension. Although high renin is arguably the most sensitive, if not particularly specific, test for renal artery stenosis, routine renin estimation is most easily justified by the frequency with which low renin points to primary aldosteronism (PA) and aldosterone-producing adenomas. Recognition that most PA patients are normokalemic and often have normal aldosterone leaves inappropriately suppressed plasma renin as the most sensitive test for PA. It was pursuit of such patients, even when the initial computed tomography or magnetic resonance imaging scan was ambiguous, that led to recognition of a common zona glomerulosa subtype of aldosterone-producing adenomas with their hallmark somatic mutations. Once it was apparent that small size was no bar to being a curable cause of severe hypertension—indeed mutations of zona glomerulosa cells are probably selected for aldosterone synthesis rather than proliferation—we have used our 11C-metomidate positron emission tomography computed tomography to detect ever-smaller adenomas and challenge whether low-renin is ever normal (Figure 3).

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**Figure 2.** Distribution of plasma renin—categorical separation of high-renin from low-renin patients. Plasma renin was measured in 850 treated patients in primary care after 10 minutes in the seated position. The first 650 were measured over 2 years by an activity assay at St Mary’s Hospital in London. The final 200 were measured over 2 weekends by a robotic renin mass assay. Equivalence studies showed that 1 pmol/ml/hour (activity) = 18 mU/L (mass).
CONCLUSION

It is remarkable that in many advanced countries measurement of the only pre-20th-century hormone has yet to become a standard clinical test outside specialist centers. I believe the delay is due, paradoxically, to the enormous potential impact and the need to define this (and its cost) before general release. I am confident, however, that renin measurement will become widespread. And that at that point the protagonists of the cause will, to a man, pay tribute to John Laragh for opening our eyes to the rationale and potential for renin measurement.

ACKNOWLEDGMENTS

M.J.B. is a National Institutes of Health Senior Investigator. The PATHWAY programme of trials, and much of M.J.B’s research reported here, is supported by the British Heart Foundation. I thank Professor Kennedy Cruickshank of King’s College London for referring the patient in Figure 3.

REFERENCES


Figure 3. Detection of a small unilateral aldosterone-producing adenoma by 11C-metomidate positron emission tomography (PET) computed tomography (CT). A 48-year-old Afrocaribbean patient had poorly controlled hypertension on 5 drugs. Plasma renin was 0.3 pmol/ml/hour off beta-blockade. He had multiple CT scans of the adrenals over several years, reported variably as thickened left adrenal or small adenoma. Comparison showed no real change. He was referred for 11C-metomidate PET CT, which demonstrated a clear, 6-mm adenoma in the left adrenal. In retrospect, this was visible on previous CT.