Primary Aldosteronism: Seismic Shifts

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Jerome Conn, the father of primary aldosteronism (PA), proposed that the syndrome may account for approximately 20% of patients with blood pressure (BP) elevation. For decades thereafter, conventional wisdom considered PA a rare (<1%) and relatively benign form of hypertension, which we now know is not the case. The first seismic shift came with the introduction of screening for PA by the aldosterone-to-renin ratio (ARR); on this basis, followed by confirmatory/exclusion testing, it is now recognized that PA represents 5–10% of hypertension.

Over the past 5 years, there have been two more major advances. The first is the demonstration that a variety of somatic—ie, confined to the adrenal cortex—mutations have been found in what are now most aldosterone-producing adenomas. The first, and most common, mutation was that in KCNJ5, a component of the Kir3.4 potassium channel; subsequently, mutations in Na+/Ca2+/ATPases, Ca2+ channels, and β-catenin have been described. The initial findings have been confirmed and replicated worldwide (1), ongoing exploration is intense, and the diagnostic and therapeutic aspects are yet to be determined.

The second seismic shift is an increasing body of evidence that the current figures for the prevalence of PA are far too low. This has attracted much less attention than the somatic mutations, which are novel and exciting, as again challenging received wisdom, always to some extent threatening. The mutations are a tour de force of laboratory-based molecular medicine; the expanded prevalence, in contrast, is the result of demanding clinical studies. Over the past decade, the groundbreaking insights—including those in the paper by Markou et al (2) in this issue of the JCEM—have come from Athens. If the results of that study (2) and the previous studies from Athens (3, 4) can be generalized, Conn’s figure of approximately 20% will be shown to be a very conservative estimate.

Before the discussion of all three papers, a review of additional background is necessary. Currently, the 5–10% prevalence figure reflects differences in cutoff values for ARR, different normal ranges for plasma aldosterone concentration (PAC), plus variability in assay accuracy and reproducibility. Patients with an ARR above the local cutoff, plus at least modestly elevated levels of PAC, constitute 10–20% of hypertension cases, necessitating confirmation/exclusion by one of at least five commonly used tests, determined by historic local usage and to some extent by cost. The most expensive test—sometimes called the “gold standard”—is the 4-day fludrocortisone plus saline test (FST); a diagnosis of PAC is confirmed if after 4 days PAC is not suppressed to very low levels.

Key to understanding the first two of the contributions (3, 4) is their modification of the FST by the addition of 2 mg of dexamethasone at midnight on the last day of testing to produce a dexamethasone-enhanced fludrocortisone suppression test (FDST), in recognition that the levels of PAC are regulated by ACTH, in addition to plasma [K+] and angiotensin. In 80 control subjects—normotensive, negative on adrenal screening, standard exclusion criteria—the FDST produced a range of PAC values, with the upper limit of normal set at the 97.5th percentile value of the group.

When the FDST was applied to a group of outpatients referred to the endocrine clinic for evaluation of thyroid function or osteoporosis, 29–32% showed PAC levels above the 97.5 upper limit of normal. Whatever the genesis, almost one-third of unselected hypertensives appear to have inappropriate aldosterone secretion independent of the classic regulators—ACTH, plasma [K+], and angiotensin.

History has a habit of repeating itself: there is nothing new under the sun. Thirty years ago, Helber et al (5) com...
pared 24-hour urinary aldosterone levels in response to sodium loading in normotensives, patients with confirmed PA, and “essential hypertensives.” Among this latter group of 100 patients, 36 had urinary aldosterone levels above the upper limit of the range in control subjects—10.0 ± 3.0 vs 2.7 ± 1.4 μg/d in the remaining 64 essential hypertensives—and with mean plasma [K+] levels of 3.81 vs 4.26 meq/L in the essential hypertensives. Finally, the 36 with higher urinary aldosterone levels and lower plasma [K+] responded to spironolactone by an average fall in BP of 21 mm Hg, vs 9 mm Hg in the remaining hypertensives.

The inference from the original FDST studies was that under the circumstances of testing, ACTH plays a considerable role in raising PAC, which distorts the normal range of basal, unstimulated aldosterone secretion; thus, many of the less florid cases of PA are missed because their post-FST PAC values fall in the upper level of this distorted range. The paper under review (2) proposes an additional role for ACTH in the genesis of another, distinct cohort of patients with inappropriate aldosterone secretion—patients who are hyper-responsive (HYPER) to low levels of ACTH stimulation of PAC over the remaining 83 “essential hypertensives” but they leave open the question of a (probably) lesser role in raising PAC, which distorts the normal range under the circumstances of testing, ACTH plays a considerable role in raising PAC, which distorts the normal range of basal, unstimulated aldosterone secretion; thus, many of the less florid cases of PA are missed because their post-FST PAC values fall in the upper level of this distorted range.

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Briefly, the entire cohort (113 hypertensive subjects, 61 normotensive controls) underwent baseline clinical evaluation and blood sampling. This was followed in order by a 4-day sodium loading period (Table 1 in Ref. 2; 155/92 mm Hg) to 124/77 mm Hg. In 25 of the 30 hyper-responders, MRAs as monotherapy (spironolactone, 12.5–100 mg/d; median, 50 mg/d in 18 of 25; eplerenone, 25–100 mg/d; median, 100 mg/d in seven of 25) were sufficient. In five subjects, addition of a calcium channel blocker (three of the five), a beta blocker, or an angiotensin receptor blocker was necessary.

It would have been useful to parse the group of 30 further and give both baseline and post-medication BP values for those on monotherapy and those requiring additional agents. The choice of a comparator group among the 83 hypertensives was suboptimal for reasons that are not clear. The authors chose 22 subjects with average BP of 134/84 mm Hg (in contrast with the group as a whole, baseline BP of 152/90 mm Hg) on MRAs as monotherapy, their BP “rebounded” to 143/88 mm Hg. A cleaner comparison would have been made by choosing a group of essential hypertensives with baseline BP equivalent to the HYPER group; the patients chosen do not vitiate the impressive BP-lowering effect of MRAs in the HYPER group, but they leave open the question of a (probably) lesser effect in essential hypertensives.

As acknowledged by the authors, there is clear evidence for a major effect of eplerenone titrated to effect on BP in a majority of essential hypertensives (6). In subjects with PA excluded on criteria current more than a decade ago, eplerenone at 50/100/200 mg/d as monotherapy lowered BP to below the goal (<90 mm Hg diastolic BP) in 44, 61, and 80%, respectively. This was then, and continues to be, attributed to antagonizing a major role in mineralocorticoid receptor activation not by aldosterone but by normal levels of cortisol, acting as a mineralocorticoid receptor agonist in the context of hypertension-induced tissue damage. Such essential hypertensives may well have included patients with PA on the FDST and hyper-responders in the.
study under review; the authors’ claim of approximately 60% total, on median daily doses of 50 mg spironolactone or 100 mg eplerenone, is essentially identical to the figure of 61% for 100 mg/d eplerenone in the dose-titration study.

One final question remains—that of a possible overlap between the two groups, the PA post-FDST and the hyper-responders. In the present study, all the patients are stated to have “... normal aldosterone suppression post-FDST and normal adrenal computerized tomography.” In the following paragraph, “the diagnosis of PA was based on the combination of a post-FDST ARR ≥ 26 pmol/mIU, and post-FDST ald ≥ 82 pmol/L.” This cutoff value for PAC is 3 mg/dL; the values for PAC post-FDST in Table 1 (Ref. 2) are 2.8 ± 1.8 (SD) for hyper-responders, 2.4 ± 1.3 for essential hypertensives, and 1.7 ± 0.6 mg/dL for normotensive controls. At least for the hyper-responders, it is difficult to see how such a mean ± SD value does not include a substantial minority with PAC > 3 mg/dL, who on the cutoff proposed levels have PA. They may be “saved” from the diagnosis of PA on the basis of their ARR values after FDST, given that elevations of both are deemed necessary for a diagnosis of PA. In this context, it would be interesting to know the lower limit of the renin assay.

None of the above commentary detracts from the impact and potential importance of the findings in the paper under review (2). Like all novel findings, they need to be independently replicated; given the nature of the FST/FDST, additional studies might usefully compare the seated saline suppression test (SSST) (7) with a dexamethasone-enhanced SSST to establish range and cutoffs in both controls and hypertensives. The latter might be screened de novo, in higher probability subjects, or routinely after ARR to compare with the previous findings. Hypertensives who do not have PA on the dexamethasone-enhanced SSST should then undergo an ultra-low ACTH test, again to compare with findings in the present paper; subjects should include both sexes (no reference is made to gender in the study under review [Ref. 2]). When validated, attention should focus on ACTH as the secretagogue appearing to compromise current confirmatory testing, and on the mechanism(s) whereby it elicits an exaggerated aldosterone response in a substantial minority of patients otherwise classified as essential hypertensives.

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**References**


