Primary aldosteronism and low-renin hypertension: a continuum?

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Primary aldosteronism (PA) was first described by Jerome Conn almost 60 years ago, and is thus sometimes called Conn’s syndrome. Although Conn believed that PA may constitute 20% of all hypertension, within a decade of his initial findings, it was thought (and taught) that PA was relatively benign, accounted for <1% of hypertension, with hypokalaemia required for diagnosis, none of which we now know to be the case. PA is now recognized as causing ~10% of hypertension, frequently occurring with normokalaemia, and to carry a much higher level of cardiovascular risk—atrial fibrillation, non-fatal myocardial infarction and stroke—than age, sex and blood pressure (BP)-matched essential hypertensives [1].

The radically revised figure for the prevalence of PA reflects the currently widely accepted use of the plasma aldosterone to renin ratio (ARR) for potential case detection. If a patient has low levels of plasma renin activity (PRA: reflecting generation of angiotensin II from endogenous angiotensinogen) or of plasma renin concentration per se, coupled with a plasma aldosterone concentration (PAC) in the upper levels of the normal range or higher, they are candidates for the diagnosis of PA. PA is thus defined as inappropriate aldosterone secretion despite suppressed levels of renin plus normal or low levels of plasma [K⁺], the two major stimuli of aldosterone secretion. Although the definition of a cut-off for normal versus elevated ARR varies between laboratories, most find ~20% of hypertensives to have a raised ARR, of whom approximately half have PA as confirmed by subsequent testing, commonly involving PAC being less than normally responsive to acute sodium loading, or other tests (captopril challenge, fludrocortisone suppression).

While levels of aldosterone in PA rarely equal those found in profound chronic sodium deficiency, the clinical picture differs markedly between the two. In sodium deficiency, the elevated PAC is homeostatic, to maximize epithelial sodium retention, and BP is low normal; in PA, the elevated PAC causes inappropriately high epithelial sodium retention and volume expansion. The vascular wall is a physiological target tissue for aldosterone, with the high PAC in sodium deficiency serving to maintain the vascular tone in the face of a reduced circulating volume; in PA, the elevated PAC is inappropriately vasoconstrictor, in the face of the expanded plasma volume. Taken together, the epithelial and vascular actions of inappropriately elevated aldosterone levels in PA provide a cogent explanation of the resultant BP elevation.

This contrasts with low-renin hypertension (LRH), in which renin is suppressed (as is the case for PA), but PAC levels are apparently normal. This appears to be the case for ~30% of hypertensives; given that renin is secreted in response to sympathetic stimulation, the elevated BP prima facie appears not to reflect increased systemic sympathetic overactivity; low renin rules out direct effects of angiotensin on sodium retention or vascular tone, as similarly do the apparently normal levels of PAC. In contrast with PA, then, LRH is a description of rather than a mechanism-based diagnosis for the observed BP elevation.

In a recent issue of the journal, Ori et al. [2], from the Sackler School of Medicine in Tel Aviv, make a very important contribution to the elucidation of the possible mechanisms underlying the elevated BP in LRH. The authors detail very impressively that the two conditions—PA and LRH—are indistinguishable in terms of response to mineralocorticoid receptor (MR) antagonists. What this may suggest is that the two conditions represent a continuum in terms of pathogenesis; in addition, it suggests that, in a world with an elevated salt intake, we may need to redefine both normal aldosterone levels and what in fact constitutes PA.

The results (in 48 patients: 24 with PA, 24 with LRH) of low-dose treatment with spironolactone (or in two patients, eplerenone) are as follows. First, BP fell from systolic (SBP) of 149 to 126 mmHg, and diastolic (DBP) from 88 to 78 mmHg after 1 year, with a substantial decrease in the average number of other antihypertensives (2.6–1.5); this effect persisted over the longer term (3 years), despite a reduction in MR antagonist dose (from a mean of 34 to 29 mg/day). Secondly, by a number of indices of cardiac function, low-dose MR antagonists produced major improvement, mainly within this first
year, but maintained or improved thereafter: of the 48 patients, 39 had left ventricular hypertrophy, for instance, at baseline, which was normalized in 16 of 39 at 1 year and 22 of 39 at 3 years. Similarly, left ventricular mass index decreased in 44 of 48 patients, from 143 g/m² at baseline to 118 g/m² at 1 year.

The most interesting finding is that absolutely no difference apart from initial PAC, and in consequence ARR, was seen between the 24 patients with PA and the remaining 24 with LRH.

To gauge the full implications of this, it is necessary to consider the cohort under study, and whether or not some form of selection bias may have contributed to this potentially prismatic finding. Of the group as a whole, the average age was high (61.4 years, range 47–64), and the history of hypertension very variable (11.4 years, range 0.5–40). Diagnosis of the seven cases of unilateral aldosterone producing adenoma (APA) was (presumably) made on the basis of imaging, in that only one subject underwent adrenal venous sampling, with unsatisfactory results and with the remaining 17 (presumably) bilateral adrenal hyperplasia (BAH). Only seven subjects were hypokalaemic (<3.6 mEq/L), and those with APA had a mean plasma [K⁺] of 3.9 mEq/L, not different from the remainder (4.1 mEq/L). All 48 patients required an elevated ARR for inclusion in the study (11 of the initial 35 patients with LRH and baseline cardiovascular studies were excluded on the basis of an ARR < 830); the sole discriminant between PA and LRH was thus a PAC of 440 pM, equal to 14.5 ng/100 mL. PAC levels in patients with PA averaged 576 ± 174 pM, and those in LRH 280 ± 75 pM.

What, then, can be said of the two groups? First, none of the 24 PA patients is recorded as having a confirmatory/exclusion test, so that the diagnosis is one that is (very) probable, rather than confirmed. Conversely, patients with a PAC just under the arbitrary cut-off, but with profoundly suppressed plasma renin and a plasma [K⁺] < 4 mEq/L, for example, may in fact turn out to have a PAC only minimally lowered by sodium loading. That said, the average ARR values (PA: 3626, LRH 1821) are telling—perhaps particularly in the absence in most patients of hypokalaemia. These caveats notwithstanding, on the basis that the two groups do differ clearly in terms of PAC and ARR, what can these studies tell us?

The first is that patients respond differently to medication dosage. In the study, all were started on 12.5 or 25 mg spironolactone per day (two on eplerenone, generously taken to have 75% of the potency of spironolactone). Four stayed on 12.5 mg, 24 on 25 mg, 7 on 37.5 mg, 12 on 50 mg and 1 on 75 mg. No correlation was sought between antagonist dosage required and baseline PAC; whether this was the case or not would be of interest—though in other circumstances, as noted below, no correlation could be found.

In a study [3] on unremarkable essential hypertensives, ~40% of 397 patients attained goal DBP (<90 mmHg) after 4 weeks monotherapy on 50 mg eplerenone/day. Those who did not respond received 100 mg/day for weeks 5–8, and approximately one-third attained goal DBP; the remainder went on to 200 mg/day for weeks 9–12, with approximately half of the reaching goal DBP, and the other half (~20% of the total) totally unresponsive. In this study, no correlation was found between any two variables, except that at each dose, those with a lower starting DBP were not surprisingly slightly more likely to respond. The equivalence of the BP and other cardiovascular responses in the two groups studied by Ori et al., with PAC levels in the PA patients twice those in those with LRH, suggest a similar disconnect between starting PAC levels and response to MR antagonists.

What this brings into focus is three things. The first is whether a cut-off of 14.5 pg/mL as the upper limit of PAC in the normal range is today appropriate. Aldosterone secretion is sensitive to angiotensin II, plasma [K⁺] and (acutely) ACTH. In the study under consideration, values of plasma [K⁺] are surprisingly normal (in 41/48 subjects). In the PAPY study (Primary Aldosterone Prevalence in Italy: [4]), a multicentre study of a total of 1125 hypertensive patients with PA, half of those with an APA were hypokalaemic on presentation, and ~16% of those with BAH; there is clearly a difference in baseline [K⁺] (and perhaps diet/K supplementation) between Israel and Italy, in that the seven patients with an adrenal adenoma had an average plasma [K⁺] of 3.9.

ACTH has long been neglected as a potential confounder of ‘normal’ aldosterone levels: recently, by using dexamethasone suppression in control subjects to define the range of normal aldosterone levels, Gouli et al. [5] suggested that approximately one-third of hypertensives have autonomous aldosterone secretion, i.e. that PA is three to four times as prevalent as currently recognized. The findings by Gouli et al. dotevalt neatly with those of Ori et al., and lend weight to the proposition that most patients with LRH have a degree of autonomous aldosterone secretion—albeit within the currently defined normal range—which is responsible for their elevated BP and other cardiovascular sequelae. What this means, in fact, is that they have hitherto unrecognized PA.

The second issue is thus how it is that many patients with an ARR ≥ 830 but a PAC < 14.5 pg/mL might have PA. Some laboratories use 0.5 mg/mL/h as the lowest level of PRA which can be measured accurately, which is no longer the case. The fact that a PRA of 0.2 will give an ARR double that of one of 0.4 for the same PAC level is discounted on the basis that it means nothing, which is untrue. What it means is that in the first, patient suppression of renin activity is twice as sensitive to aldosterone as in the second, and that in the first, a PAC of 13 is consistent with PA, whereas in the second, a PA of 20 is not (necessarily).

The third finding is that modest levels of spironolactone are sufficient to control not only BP but also cardiovascular damage in both PA patients, some of whom had markedly elevated PAC levels, and in those with LRH. Very importantly, even at these modest doses (average at 3 years 29 mg/day), renal function was considerably improved, with urinary albumin to creatinine ratio falling from 42 to 11 µg/mg, despite a (predictable) fall in eGFR from 72 ± 19 to 69 ± 18 mL/min/1.73 m³. The efficacy of such a modest dose makes the likelihood of its acting as an MR blocker—i.e. acting to deny aldosterone access to MR—vanishingly unlikely.

Recent ischemia–reperfusion studies in experimental animals using a Langendorf preparation of rat hearts have shown that spironolactone, unsurprisingly, antagonizes the
effect of added aldosterone (or cortisol) to aggravate infarct size and area at risk. Surprisingly, spironolactone itself, absent any other steroid (and also in hearts from adrenalectomized animals), is protective in its own right at very low (nanomolar) concentrations—i.e. acts as an inverse agonist, rather than by denying steroids which are agonist in the context of tissue damage access to cardiomyocyte MR [6, 7].

The study by Ori et al. focused on the cardiovascular—in particular the cardiac—effects of low-dose MR antagonist administration in two groups—those with presumptive PA, and those LRH patients with the combination of both low renin and an ARR ≥ 830, who constituted ∼70% of the LRH patients screened. The authors’ findings—of the efficacy of low-dose MR antagonists in equivalently ameliorating the cardiovascular and renal sequelae of both conditions—contain a variety of challenging implications for endocrinologists managing PA. These include,

(i) that in some populations, even fewer patients with PA present with hypokalaemia than the 25–30% in the PAPY study;
(ii) that the indistinguishable pattern of response to MR antagonists implies an equivalent role for aldosterone in both PA and LRH;
(iii) that across LRH and PA, individual patients vary in terms of sensitivity to MR antagonists (as they do in essential hypertension, as noted above);
(iv) that our current definition of a single upper limit of 'normal' value for PAC may be misleading, given the multi-factorial inputs to aldosterone secretion, and the probability of wide variation in sensitivity to agonists as well as antagonists;
(v) that given that currently ∼10% of hypertensives are regarded as having PA, and another ∼30% LRH, the true figure for inappropriately elevated aldosterone secretion, i.e. PA may be of the order of 30%, i.e. 10% plus the two-thirds of those categorized as LRH with an ARR ≥ 830 as in the Ori et al. study;
(vi) that low-dose MR antagonists do not result in dangerous hyperkalaemia, even in patients concurrently on ARB/ACEI treatment, and even in patients with only moderate eGFR values; in fact, they are clearly renoprotective;
(vii) that massive-dose MR antagonist therapy for PA should be a thing of the past, and that, save in exceptional patients, a maximum daily dose of 50 mg spironolactone should be used, with over half of the patients needing 25 mg/day or less; and finally,
(viii) that the guidelines for the case detection, diagnosis and management of primary aldosteronism [8] published in 2008, need to be updated in the light of the data that have been since presented, including those described by Ori et al.

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CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Ori et al. Regression of left ventricular hypertrophy in patients with primary aldosteronism/low-renin hypertension on low-dose spironolactone. Nephrol Dial Transplant 2013; 28: 1787–1793.)

REFERENCES


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