Review

The Renaissance of Primary Aldosteronism: What Has it Taught Us?

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The growing realisation since the early 1990s that primary aldosteronism (PA) is a much more common cause of hypertension than previously thought, and that aldosterone excess has adverse effects that are at least partly independent of blood pressure, has been the main driving force for a renaissance in clinical and research interest in PA. This has generated a wealth of new knowledge regarding (1) PA's high prevalence, (2) the extent of non-BP dependent cardiovascular and renal organ damage and morbidity and reduced quality of life associated with PA, all of which appear to be at least partly ameliorated by specific treatment (especially surgical) directed against excessive aldosterone action, (3) the diversity of adrenal histopathology associated with PA and the need to subdivide patients based on glucocorticoid remediability (by genetic testing for the hybrid gene mutation causing familial hyperaldosteronism type I, FH-I) and lateralisation on adrenal venous sampling in order to ensure optimal treatment, (4) the value of elucidating genetic bases for PA in terms of improving detection, understanding of pathogenesis and treatment, as illustrated by the determination of the genetic basis of FH-I, and (5) the genetic basis of more common forms including aldosterone-producing adenoma. From the clinical perspective, the principal lesson learnt is that PA, being a common cause of cardiovascular morbidity and reduced quality of life reversible by specific treatment, is worth looking for.

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Introduction

In primary aldosteronism (PA), production of the salt-retaining hormone aldosterone by the adrenal cortex is excessive for the body's prevailing sodium and volume status and autonomous of its usual main chronic regulator, renin/angiotensin II, circulating levels of which are usually suppressed [1]. Over time, the resulting excessive retention of sodium at the distal tubule leads to the development of hypertension. In exchange for the retained sodium, potassium and hydrogen ions are excreted, and, if this is prolonged and severe enough, hypokalaemia and metabolic alkalosis may occur [1]. Case detection is of considerable potential benefit to affected individuals, in that unilateral adrenalectomy results in cure or improvement in hypertension and correction of hypokalaemia (when present) in patients with unilateral PA and an improvement in quality of life, which is often marked [2–4]. In the remaining PA patients who do not have surgery, medical treatment with agents that antagonise aldosterone action will have very worthwhile beneficial effects on hypertension and hypokalaemia [5–7].

Over the more than 50 years since Conn originally described PA, interest in this condition has waxed and waned, with the principal deterrent to scientific attention being its perceived rarity as a clinical condition. The last 20 years, however, have seen a remarkable and sustained resurgence in clinical and research activity in this area which has brought with it a number of important new insights into the role of PA as a cause of cardiovascular morbidity, the extent of its diversity as a clinical disorder, and its likely pathogenesis. The following review will summarise some of the more significant of these.

Lesson 1 – PA is Not Rare

Throughout the 1970s to early 1990s, PA was considered a rare cause of hypertension (accounting for less than 1% of patients) and not worth looking for unless patients were hypokalaemic. In 1981, Hiramatsu et al. [8] reported on the use of the plasma aldosterone/renin ratio (ARR) to detect and remove aldosterone-producing adenomas (APAs) from nine (2.6%) of 348 "unselected" hypertensives. Only three of the nine were hypokalaemic. Given that these workers selected only patients with very high

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ratios for further investigation, and used only adrenal venography and scintigraphy to confirm the diagnosis, patients with bilateral PA and most with APAs less than 1 cm (which together make up at least 50% of patients in most series) would have escaped detection. Hence, the true prevalence of PA might have been at least double that reported.

At the Greenslopes Hospital Hypertension Unit (GHHU), after finding PA to be common in a small cohort of resistant hypertensives, in 1990 Gordon widened his screening by ARR, and in 1991 adopted the policy to screen all referred hypertensive patients for PA by ARR, and not just those with hypokalaemia or resistant hypertension. This was soon associated with a tenfold increase in the annual detection rate of PA (confirmed in each case by fludrocortisone suppression testing [FST]), which reached 94 patients in 1995 and has remained between 60 and 90 ever since [9–11]. Only 21% of patients diagnosed since 1992 were known to have been hypokalaemic up until the time of referral [9–11].

In 1994, the GHHU reported an 8.5% prevalence of PA (confirmed by FST) among 199 consecutively referred normokalaemic hypertensive patients who underwent ARR testing [12]. Although these patients were "selected" in that they had been referred to a hypertension unit, none were known to be hypokalaemic or were referred with the diagnosis of PA in mind, and less than half were taking more than one antihypertensive medication at the time of presentation. In an earlier study [13], 52 respondents to advertisements placed by the GHHU seeking volunteers for antihypertensive drug trials were screened for PA. Six (12%), all of them normokalaemic, had been found to have PA.

Since these initial reports, many other groups employing the ARR to screen for PA have independently reported evidence to suggest that PA is a not uncommon cause of hypertension, and probably the commonest cause of specifically treatable and sometimes curable hypertension. Most have reported prevalence rates between 5 and 15%, with most patients normokalaemic [14–20]. In resistant hypertensive cohorts, the prevalence rates have been consistently significantly higher and at least 20% [21–24].

Lesson 2 – PA Causes More Than Just Hypertension

It has long been established that hypertension is an almost invariable accompaniment of PA and responds well to unilateral adrenalectomy in those with unilateral forms (with cure in 50–80% and improvement in virtually all remaining operated patients in most studies) [2,3,6,25–27], and to aldosterone antagonist medications in non-surgically treated patients (including those with bilateral forms) [5,6,28]. More recently, however, it has become apparent that aldosterone excess in PA induces injury (inflammation, remodelling and fibrosis) in cardiovascular tissues in ways that are at least partly independent of its effect on blood pressure (BP). This concept, which had its beginnings in rodent models [29], has been greatly strengthened by cross sectional studies assessing markers of cardiovascular disease in humans with PA. Such studies have reported increased left ventricular (LV) dimensions [30,31] and myocardial backscatter [32] (as a marker of fibrosis) on echocardiography, increased carotid intima-media thickness [33,34], increased femoral pulse wave velocity [33] and reduced endothelial function [35]. Most importantly, there have been increased rates of cardiovascular events including arrhythmias, myocardial infarctions, strokes and mortality [36–38] when compared with matched essential hypertensives.

In 2005 we reported increased LV wall thicknesses and reduced diastolic function in eight normotensive individuals with genetically confirmed familial hyperaldosteronism type I (FH-I, also known as glucocorticoid-remediable PA). They were identified by screening affected families and compared with 24 age- and sex-matched normotensive controls with similar 24-h ambulatory BP levels [39]. They also had higher serum levels of interleukin 6, consistent with the hypothesis that inflammation is a key component of the non-BP dependent cardiovascular damage that occurs with aldosterone excess [40]. These findings raise the question whether it is sufficient to control only the hypertension in patients with PA and not address the effects of aldosterone excess *per se*, and, in normotensive subjects found to have PA through screening of pedigrees with familial forms, whether treatment (with aldosterone antagonists, or, in the case of FH-I, dexamethasone) should be commenced well before hypertension has developed.

Just as PA causes more than just hypertension, so does specific treatment against excessive aldosterone action provide more benefit than just lowering BP. Both unilateral adrenalectomy and spironolactone treatment led to improvements in endothelial function in patients with PA (which was worse than in essential hypertensives and correlated inversely with plasma aldosterone levels and ARR prior to treatment) in a study reported by Tsuchiya et al. [35]. Strauch et al. [41] reported reduced arterial stiffness (measured as carotid-femoral pulse wave velocity and augmentation index) at approximately one year following unilateral adrenalectomy in 15 patients with APA but not after a year of spironolactone treatment in 14 other subjects with PA treated medically. Catena et al. [42] similarly found surgery ($n = 24$) to be more effective than spironolactone ($n = 30$) in reducing left ventricular mass (which was greater prior to treatment in the patients with PA than in matched essential hypertensives) after one year, with significant decreases only seen in the surgically treated group. However, subsequent changes were greater in the medically treated group so that by the end of the study (mean follow-up 6.4 years) the overall reduction from baseline was comparable in the two groups. Most importantly, the excess in cardiovascular morbidity (see above) that was reported by this group in these same patients prior to treatment of PA was reversed following treatment, so that the proportion of patients with PA who reached the primary endpoint (comprising myocardial infarction, stroke, any type of revascularisation procedure and sustained arrhythmias) during a mean follow-up period of 7.4 years was similar to that of patients with essential hypertension (19% *versus* 18%) [36]. These data provide