

# Aldosteronism and Hypertension

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A growing body of evidence suggests that hyperaldosteronism contributes significantly to the development and the severity of hypertension as well as to resistance to antihypertensive treatment. In cross-sectional analyses, plasma aldosterone levels have been shown to relate to BP levels, particularly in obese individuals. In these same individuals, BP was not related to plasma renin activity, suggesting an effect of aldosterone on BP independent of renin-angiotensin II. In a recent prospective analysis from the Framingham investigators, baseline serum aldosterone was strongly associated with development of hypertension during a 4-yr follow-up.

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Historically, primary aldosteronism has been thought to be an uncommon cause of hypertension. Recent studies, however, suggest that 10 to 15% of individuals with hypertension fulfill the biochemical criteria for primary aldosteronism. Demonstration of such a high prevalence of primary aldosteronism in patients with presumed primary hypertension suggests that aldosterone excess is a common contributing cause to the development of hypertension.

Primary aldosteronism is particularly common in patients with resistant hypertension, with prevalence of approximately 20%. An important role of hyperaldosteronism in contributing to the development of treatment resistance is suggested further by the broad antihypertensive benefit of aldosterone antagonists as add-on therapy in patients who are resistant to multi-drug regimens. The antihypertensive benefit in this setting is not limited to patients with classically defined primary aldosteronism, suggesting aldosterone excess as a cause of resistant hypertension to a degree that is greater than is indicated by measurement of either plasma or urinary aldosterone levels.

## Aldosterone and Incident Hypertension

Multiple, independent studies suggest that aldosterone contributes broadly to the development of hypertension separate from cases of classically defined primary aldosteronism. The role of aldosterone in causing hypertension is supported by cross-sectional studies that relate plasma aldosterone levels to ambulatory BP measurements, by prospective analyses that indicate that aldosterone levels predict development of hypertension, and by studies that confirm the broad antihypertensive efficacy of aldosterone antagonists in treating presumed primary hypertension. Importantly, in these studies, indices of renin activity were not related to BP levels, suggesting an

autonomous role of aldosterone in causing hypertension that is independent of renin-angiotensin II.

Cross-sectional studies demonstrate a significant correlation between plasma aldosterone and 24-h ambulatory BP levels. The relation is particularly strong in black individuals. In an analysis of black American and white French Canadian patients with primary hypertension, supine and standing plasma aldosterone levels were significantly correlated with daytime and nighttime systolic and diastolic BP levels in the black patients (1,2). In the French Canadian patients, standing plasma aldosterone levels were consistently related to both daytime and night BP, and supine aldosterone related significantly to nighttime systolic BP. In both ethnic groups, BP levels were unrelated to plasma renin activity. These results suggest that aldosterone, more so than renin-angiotensin II, contributes to worsening hypertension.

A recent prospective analysis lends strong support to the role of aldosterone in causing hypertension. As part of the ongoing Framingham Offspring Study, serum plasma aldosterone levels in normotensive individuals were related to subsequent increases in BP (increment of at least one BP category as defined by the Sixth Joint National Committee [JNC VI]) and development of sustained hypertension (>140/90 mmHg or use of antihypertensive medications) (3). During a 4-yr follow-up, a 16% increase in the risk for a significant elevation in BP and a 17% increase in the risk for development of hypertension was observed per quartile increment in the serum aldosterone level. Overall, the highest serum aldosterone quartile, relative to the lowest, was associated with a 1.60-fold risk for an elevation in BP and a 1.61-fold risk for development of hypertension. Renin activity was not measured in this study, so the independent predictive value of aldosterone *versus* renin could not be compared.

The role of aldosterone in contributing to hypertension is suggested further by the broad antihypertensive effectiveness of mineralocorticoid antagonists in treating unselected hypertensive individuals. Studies of spironolactone and eplerenone clearly demonstrate antihypertensive benefit that is not limited

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to patients with classical primary aldosteronism. In a blinded comparison of the two agents in unselected patients with mild to moderate hypertension, the highest doses of either agent reduced 24-h ambulatory BP by approximately 16/9 mmHg (4). In a separate study, eplerenone lowered systolic BP by an additional 5 to 6 mmHg in patients who received an angiotensin-converting enzyme (ACE) inhibitor receptor or an angiotensin receptor blocker (ARB) (5). It is interesting that in patients with primary hypertension, the BP response that was induced by eplerenone was not predicted by plasma aldosterone levels, plasma renin activity (PRA), or the plasma aldosterone/PRA ratio (6). The broad antihypertensive benefit of spironolactone and eplerenone in patients with presumed primary hypertension, the further reductions in BP that were induced by eplerenone even after renin-angiotensin blockade, and antihypertensive benefit of eplerenone independent of aldosterone-renin status support the hypothesis that aldosterone contributes broadly to the development of hypertension much beyond demonstrable cases of classical primary aldosteronism.

### Hypertension and Primary Aldosteronism

Primary aldosteronism as described by Conn (7) in 1955 had been thought to be an uncommon cause of hypertension, with a prevalence of <1% among general hypertensive patients (7–9). However, beginning in the early 1990s with reports from Gordon and associates in Brisbane, Australia, the prevalence of primary aldosteronism has been found to be considerably higher. In the earliest study, Gordon *et al.* (10) screened 52 hypertensive individuals who responded to a newspaper advertisement for participation in a hypertensive drug trial and found that 12% of the individuals were positive for primary aldosteronism. In a subsequent evaluation of 199 individuals who were referred to the hypertension clinic in Brisbane, the prevalence of primary aldosteronism was found to be at least 8.5% and probably 12% (11). These results were remarkable in suggesting that primary aldosteronism was not rare but rather a common cause of hypertension.

Since these earlier studies by Gordon, multiple investigators worldwide have confirmed a prevalence of primary aldosteronism of 5 to 15% in general or selected hypertensive populations (12–20). Two of these studies are particularly noteworthy because of their scientific rigor and because of the clinical implications of the results.

The studies that reported a high prevalence of primary aldosteronism have been criticized for lax diagnostic criteria, confounding effects of ongoing treatment, and/or lack of testing to confirm absence of aldosterone suppression with volume expansion. Schwartz and Turner (18) avoided such limitations by prospectively evaluating 118 individuals who had primary hypertension after withdrawal from antihypertensive treatment and who had confirmation of the diagnosis of primary aldosteronism with demonstration of lack suppression of aldosterone excretion after 4 d of dietary salt loading. With application of these very strict diagnostic criteria, primary aldosteronism was diagnosed in 13% of individuals.

In the study by Mosso *et al.* (20), >600 hypertensive patients were screened for primary aldosteronism by measurement of

plasma aldosterone/PRA ratio. Patients with a high ratio then were evaluated by fludrocortisone suppression testing to confirm the diagnosis of primary aldosteronism. At some point before their biochemical evaluation, all patients had their anti-hypertensive medications withheld such that the authors were able to relate the prevalence of primary aldosteronism to the severity of hypertension. Overall, the prevalence of primary aldosteronism was 6.1%. However, the prevalence increased in relation to the severity of the hypertension (Figure 1). In patients with mild hypertension (<160/100 mmHg), primary aldosteronism was uncommon (2%). In patients with moderate hypertension (160 to 179/100 to 109 mmHg), the prevalence of primary aldosteronism was 8%, and in patients with severe hypertension ( $\geq$ 180/110 mmHg), aldosteronism was diagnosed in 13% of patients. These results of these two studies are clinically very important in providing rigorous confirmation of a high prevalence of primary aldosteronism in general hypertensive populations and in demonstrating that the likelihood of primary aldosteronism is much higher in patients with more severe hypertension.

Although originally defined as an essential characteristic of Conn's syndrome, the recent evaluations indicate that when not part of the diagnostic criteria, hypokalemia is uncommon in patients with demonstrable aldosterone excess. In the study by Schwartz and Turner, none the patients who had a diagnosis of primary aldosteronism had a history of unprovoked hypokalemia. Of the 37 patients who were confirmed to have primary aldosteronism by Mosso *et al.* (20), all but one had normal potassium levels at the time of the diagnosis. These results suggest that hypokalemia is a late manifestation of aldosterone excess that is long preceded by the development of hypertension.

### Resistant Hypertension and Primary Aldosteronism

Resistant hypertension is defined as BP that remains elevated despite use of three antihypertensive agents, ideally one of which is a diuretic. The prevalence of resistant hypertension is unknown; however, cross-sectional and hypertension outcome studies suggest that it is a common clinical problem. In the most recent National Health and Nutrition Examination Survey

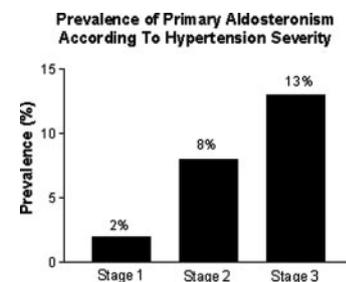


Figure 1. Prevalence of primary aldosteronism in patients according to Sixth Joint National Committee (JNC VI) stages of severity of hypertension (stage 1, 140 to 159/90 to 99 mmHg; stage 2, 160 to 179/100 to 109 mmHg; stage 3,  $\geq$ 180/110 mmHg) (20).

(NHANES 1999 to 2000), only 53% of individuals who were being treated for hypertension were controlled to <140/90 mmHg (21). Among older individuals ( $\geq 60$  yr), control rates were worse, with only 44% at or below 140/90 mmHg. In a cross-sectional evaluation of patients with diabetes, only 23% of black and 31% of white patients were controlled to <130/80 mmHg despite being prescribed an average of 2.7 and 2.2 antihypertensive medications, respectively (22).

Prospective hypertensive trials confirm a high occurrence of treatment resistance. In Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in which participants were provided medications at no charge, titration was dictated for uncontrolled hypertension, and medication adherence was monitored, at the end of the study, 34% of participants' hypertension remained uncontrolled, with an average use of 2.0 antihypertensive medications, and 27% of participants were receiving three or more medications (23). These studies indicate that resistant hypertension is common and undoubtedly will become even more so as the population ages and becomes increasingly obese, two of the strongest predictors of development of resistant hypertension (24).

Studies from separate laboratories suggest that primary aldosteronism is a common cause of resistant hypertension, with a prevalence of approximately 20% in patients with difficult-to-control hypertension (Figure 2). In an evaluation of 88 consecutive patients who were referred to the University of Alabama at Birmingham for resistant hypertension, primary aldosteronism was diagnosed in 18 or 20% of the patients on the basis of a suppressed PRA ( $<1.0$  mg/ml per h) and high urinary aldosterone excretion ( $>12$   $\mu\text{g}/24$  h) during high dietary salt intake (sodium  $> 200$  mEq/24 h) (25). In this evaluation, which included an equal number of black and white patients, primary aldosteronism was equally common regardless of race.

Gallay *et al.* (26) screened for primary aldosteronism 90 individuals who had been referred to a university hypertension clinic for poorly controlled hypertension despite use of multiple antihypertensive medications. Individuals with a high aldosterone/PRA ratio underwent further diagnostic workup, including adrenal computed tomography or magnetic resonance imaging and adrenal iodine<sup>131</sup> norcholesterol uptake scanning. Primary aldosteronism was found in 15 or 17% of the evaluated individuals. Ten of the 15 individuals with primary

aldosteronism had an aldosterone-producing adenoma confirmed by surgical resection.

In an evaluation of 90 treatment-resistant hypertensive individuals, investigators in Oslo, Norway, found a prevalence of primary aldosteronism of 23% on the basis of a high serum aldosterone and/or urinary aldosterone excretion (27). Of these individuals, almost 40% had evidence of an adenoma by computed tomography imaging. Last, investigators in Prague, Czech Republic, evaluated  $>400$  patients who were referred to a university hypertension clinic for moderate to severe hypertension. On the basis of a high aldosterone/PRA ratio and failure to suppress plasma aldosterone with saline infusion, 19% of the patients were found to have primary aldosteronism (28).

These four studies are consistent in reporting a prevalence of primary aldosteronism of approximately 20% in patients with resistant hypertension. This figure, however, likely underestimates the role of aldosterone excess in causing treatment resistance as suggested by the suppressed renin activity beyond those with confirmed primary aldosteronism and the broad antihypertensive benefit of aldosterone antagonists in patients with resistant hypertension.

In the evaluation conducted at the University of Alabama at Birmingham, 75% of the patients with resistant hypertension had suppressed renin activity despite that all patients received a diuretic and an ACE inhibitor or ARB, classes of agents that increase renin activity (29). Similarly, the investigators in Oslo reported that 67% of their patients with resistant hypertension had suppressed renin activity also despite use of diuretics and blockers of the renin-angiotensin system (27). There are multiple reasons for suppressed renin levels in patients with resistant hypertension (older age, high dietary salt ingestion, and, in the Birmingham study, inclusion of a large percentage of black patients); however, the persistently low renin activity in the large majority of patients in both studies likely reflects, in part, mineralocorticoid excess beyond the 20% of patients who were identified to have true primary aldosteronism. As discussed next, benefit of aldosterone antagonists in treating resistant hypertension is not limited to patients with confirmed primary aldosteronism. Broad antihypertensive benefit is reported in patients with resistant hypertension, supporting a larger contributory role of mineralocorticoids in causing treatment resistance than is suggested by application of classical criteria for hyperaldosteronism.

The findings of a high prevalence of primary aldosteronism in patients with resistant hypertension is consistent with longstanding observations that primary aldosteronism often presents with severe or refractory hypertension (30–34). Bravo *et al.* (30) in 1988 reported that patients with primary aldosteronism often presented with severe hypertension that was resistant to multidrug regimens. In a landmark study that was reported in 1993 and described diagnostic criteria to distinguish aldosterone-producing tumors from adrenal hyperplasia, Weinberger and Fineberg (34) found that patients with primary aldosteronism of either subtype generally had severe hypertension when withdrawn from treatment, with a mean value of approximately 175/110 mmHg. Suggestion that the high occurrence of

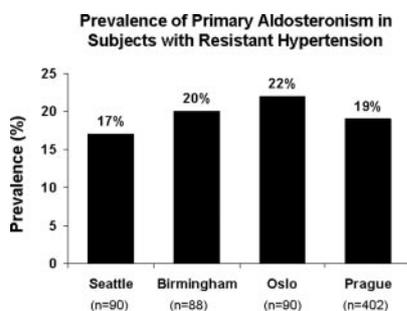


Figure 2. Prevalence of primary aldosteronism in patients with resistant hypertension from multiple clinics worldwide (25–28).

low renin levels in patients with resistant hypertension reflects a broader role of mineralocorticoid excess than indicated by measurement of aldosterone levels is likewise consistent with multiple studies over many decades supporting the concept of low-renin hypertension as a variation of aldosterone-induced hypertension (35–38).

## Aldosterone Antagonists and Treatment of Resistant Hypertension

Concomitant with reports indicating that primary aldosteronism is a common cause of resistance to treatment were studies describing the antihypertensive benefit of aldosterone antagonists in treating resistant hypertension. In an open-label evaluation, the antihypertensive benefit of spironolactone 25 to 50 mg was assessed prospectively when added to the existing regimen of patients whose BP was uncontrolled on three or more antihypertensive agents (29). A total of 76 patients, including an equal number of black and white patients were included in the analysis. Patients were on an average of four medications, including a diuretic and an ACE inhibitor or ARB. The mean daily dose of spironolactone at study end (6 mo) was approximately 31 mg, so the majority of patients remained on 25 mg. At 6 mo of follow-up, the mean BP reduction was  $25 \pm 20/12 \pm 12$  mmHg (Figure 3). The BP reduction that was induced by spironolactone was similar in black and white patients. It is interesting that the BP reduction was not predicted by plasma aldosterone, renin activity, or 24-h urinary aldosterone excretion. That is, patients with high *versus* normal or low aldosterone levels responded equally well, although patients with hyperaldosteronism were more likely to be titrated to the 50-mg dose of spironolactone.

Mamhud *et al.* (39) evaluated the BP response to adding 50 mg of spironolactone to patients whose BP was uncontrolled on three agents. At 14 wk of follow-up, the mean BP reduction was  $28 \pm 3/13 \pm 2$  mmHg. In this study, the BP response also was not predicted by the baseline aldosterone/PRA ratio. However, in a separate analysis of patients who were untreated with other antihypertensive medications, the aldosterone/PRA ratio was predictive of the BP reduction that was induced by spironolactone. This differential relationship between the baseline aldosterone/PRA ratio and response to aldosterone blockade in treated *versus* untreated patients suggests two possibilities that

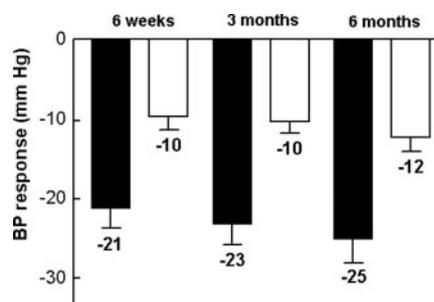


Figure 3. Spironolactone-induced reduction in systolic (■) and diastolic BP (□) at 6-wk, 3-mo, and 6-mo follow-up in patients with resistant hypertension (29).

are not necessarily exclusive: (1) A greater role of aldosterone in causing resistant hypertension than is reflected by plasma levels, and/or (2) the effects of antihypertensive medications on the aldosterone/PRA ratio alter its predictive value in relation to the BP response to spironolactone.

Other investigators have described the benefit of amiloride as add-on therapy in treating resistant hypertension. By blocking the epithelial sodium channel (ENaC), amiloride acts as an indirect aldosterone antagonist as aldosterone induces sodium and fluid retention, in part, through up regulation of ENaC. Eide *et al.* (27) evaluated the BP response of adding amiloride 2.5 mg to existing multidrug regimens, including a diuretic, in patients with resistant hypertension. Thirty-eight patients, all of whom had suppressed renin activity at baseline, were included in the analysis. After 2 wk of treatment, mean BP was reduced by  $31 \pm 31/15 \pm 11$  mmHg. In a subset of 26 patients, after doubling the amiloride/diuretic dose, an additional reduction in systolic and diastolic BP of 11 and 4 mmHg, respectively, was observed.

Saha *et al.* (40) compared the BP effects of amiloride 10 mg/d, spironolactone 25 mg/d, or a combination of both agents when used as add-on therapy in black patients whose BP was uncontrolled on a two-drug regimen that consisted of a diuretic and a calcium channel blocker. Ninety-eight patients were randomly assigned among the three treatment groups or placebo in a  $2 \times 2$  factorial design with a treatment period of 9 wk. The systolic and diastolic BP decreased an average of  $12.2 \pm 2.2/4.8 \pm 1.3$  mmHg in the amiloride arm,  $7.3 \pm 2.3/3.3 \pm 1.4$  mmHg in the spironolactone arm, and  $14.1 \pm 2.3/5.1 \pm 1.4$  mmHg in the combination arm *versus* placebo. Although amiloride was somewhat better than spironolactone in reducing BP, it was noted that amiloride use was associated with significant increases in PRA, whereas spironolactone was not, suggesting that the spironolactone may have been underdosed such that, with further up-titration, additional BP benefit might have been observed.

In these studies of spironolactone and amiloride, both agents generally were well tolerated. The most common adverse effect of spironolactone is breast tenderness with or without gynecostasia. It occurs more commonly in men but not exclusively. Studies indicate that approximately 10% of men will complain of breast tenderness with use spironolactone at the 25-mg dose (29). A sharp increase in the occurrence of breast tenderness can be anticipated with doses above 25 mg/d. Other adverse effects that are associated with spironolactone include sexual dysfunction and menstrual irregularities. Eplerenone is much more specific for the mineralocorticoid receptor than spironolactone. In avoiding stimulation of progesterone and androgen receptors, it is better tolerated than spironolactone, with a low occurrence of breast tenderness or sexual dysfunction. Although the efficacy of eplerenone has been established in the treatment of mild to moderate hypertension, it has not been evaluated specifically for treatment of resistant hypertension.

With use of either aldosterone antagonist, hyperkalemia can occur (41). The risk is increased in the setting of ACE inhibitor or ARB use and/or in patients with chronic kidney disease, including patients with diabetes and elderly patients. Accord-

ingly, monitoring for hyperkalemia is essential when beginning either spironolactone or eplerenone. In patients who are at increased risk, initiation of treatment with reduced doses of the aldosterone antagonist and assessment of serum potassium levels as soon as 1 wk of starting treatment is recommended.

## Screening Recommendations

Although some experts recommend screening all hypertensive patients for primary aldosteronism, given the costs and potential for false-positive assessments, it seems more prudent to reserve diagnostic evaluation for patients who are at increased risk. Accordingly, it is recommended that screening be limited to patients who present with hypokalemia, including when associated with diuretic use, and/or patients with severe or resistant hypertension. An elevated plasma aldosterone/PRA ratio (cutoff values will vary according to assay units and reported ranges) is an effective screen in having a high negative predictive value (18,19). However, false-positive values are common, likely reflecting the high prevalence of low-renin hypertension, particularly in patients with resistant hypertension, such that suppression testing with volume expansion is necessary to confirm the diagnosis of primary aldosteronism. False-positive results are less likely if when calculating the ratio, the PRA value is limited to no less than 0.7 ng/ml per h and the plasma aldosterone to >15 ng/dl; however, such maneuvers will reduce the sensitivity of the screening test, *i.e.*, resulting in more false-negatives. The plasma aldosterone/PRA ratio can be tested during ongoing antihypertensive treatment, although  $\beta$  antagonists can suppress renin levels, increasing the likelihood of a falsely high ratio. Low serum potassium levels will suppress aldosterone release such that screening should be repeated after correction of the hypokalemia if the initial ratio was low.

## Conclusion

Until recently, aldosterone excess was thought to play a minor role in the development of hypertension. Beginning in the early 1990s, however, reports from investigators worldwide have found that primary aldosteronism is common in patients with hypertension, with prevalence rates of 10 to 15%. In patients with severe or resistant hypertension, the prevalence of primary aldosteronism is even higher, with a prevalence of approximately 20%. Such figures, however, likely underestimate the degree to which aldosterone contributes to the development of hypertension, in particular resistant hypertension, given the persistence of suppressed renin levels beyond those in patients who receive a diagnosis of primary aldosteronism and given the broad antihypertensive benefit of aldosterone antagonists in treating both uncomplicated and resistant hypertension.

Why primary aldosteronism and, more broadly, milder forms of aldosterone excess seemingly are so much more common now than thought historically is unclear. Likely, primary aldosteronism was underestimated previously as early evaluations of prevalence often were limited to patients who presented with hypokalemia, which now is recognized as a late manifestation of the disorder. Furthermore, diagnosis of pri-

mary aldosteronism and, more important, screenings of large numbers of patients was facilitated by standardization of aldosterone and renin activity measurements as well as by recognition of the diagnostic screening value of the aldosterone/PRA ratio. These technical advancements allowed for screening of larger, unselected cohorts as opposed to assessments of small numbers of patients who are at high risk for having severe disease. Consequently, in screening much broader cohorts, earlier and/or milder manifestations of the disease are identified.

Beyond these technical reasons as to why the prevalence of primary aldosteronism seemingly is increased, the studies discussed herein clearly indicate that aldosterone excess, whether true primary aldosteronism or a milder variant, is common. Like classical primary aldosteronism, the aldosterone excess described here seems to occur independent of renin-angiotensin II, because the high aldosterone levels and the physiologic effects of the aldosterone excess are not related to concomitant measurements of plasma renin activity. So an important question in terms of treatment and perhaps prevention is what is the cause of the aldosterone excess that is now being so widely reported?

Stimuli that underlie the increasing occurrence of hyperaldosteronism remain obscure; however, recent studies suggest that obesity may be an important contributing factor. Biopsies of human adipose tissue indicate reduced activity of the renin-angiotensin system within adipocytes with weight loss (42). Separately, factors that have been isolated from human adipocytes have been shown to function as aldosterone secretagogues independent of renin-angiotensin II (43,44). Last, preliminary data link aldosterone levels to severity of obstructive sleep apnea in individuals with resistant hypertension (45). Although none is definitive, these studies are provocative in potentially relating the seeming increase in aldosteronism to concurrent increases in obesity.

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