Is There an Unrecognized Epidemic of Primary Aldosteronism? (Con)

Norman M. Kaplan

My answer is “no.” Although primary aldosteronism (PA) is likely more common than most experts believed in the 1960–1990 interval, it is not nearly as common as Dr Calhoun and other investigators report from 1990 until now. As many younger clinicians may not remember, this same issue arose soon after Dr Jerome Conn characterized this disease in 1955.1 Reporting on the prevalence of PA in his highly referred population of likely suspects, Dr Conn and coworkers’ estimates were as high as 20%.2 Subsequently, studies on unreferred patients supported a prevalence of <1%.3

Start of the Epidemic

The lower estimate was commonly accepted until Gordan and colleagues started screening for PA with the plasma aldosterone:renin ratio (ARR) first described in 19764 and expanded by Hiramatsu et al in 1981.5 In 1993, Gordon et al6 reported an elevated ARR in 20% of 199 patients, with 8.5% having an abnormal saline suppression test and 2.5% proven to have an aldosterone-producing adenoma.

Since then, numerous series have been reported (Table). As seen in Table 1, the prevalence of an elevated ARR has varied from 5.5% to 39.0%. Part of the wide variation rises from the use of varying thresholds; more of the variation rises from inclusion of various types of patients. The latter point must be recognized, because most patients in these series were referred to specialized centers, just as Dr Conn’s high numbers were largely derived from a referred population.

An Examination of 2 Recent Series

Two recently published series epitomize the vagaries of most series listed in the Table. The first is a study of 1125 recently diagnosed subjects with hypertension referred to 14 specialized hypertension clinics throughout Italy.27 Plasma renin activity and plasma aldosterone were measured at baseline and again 60 minutes after administration of 50 mg of captopril. The subjects then had a saline suppression test, although the results of the saline suppression test were not used to decide on further workup. Abdominal computed tomography and/or MRI were then performed. In 4 of the 14 centers where adrenal venous sampling was available, this was then performed. Of the 126 with presumed PA by ARR, who represented 11.2% of the total group, an aldosterone-producing adenoma was found in 43%, with the remainder considered to have idiopathic hyperaldosteronism (IHA).

The authors found more PA and APA in patients with more serious hypertension but an even higher prevalence of IHA with increasing severity of hypertension. Hypokalemia was seen in half of the patients with APA but in 17% of those with IHA compared with 7% of those with primary hypertension. This study has a number of problems that question the reported prevalence of PA in 11.2% of hypertensive patients. First, the patients were referred, presumably because of concern by the primary care physician that they might have PA or because of more resistant hypertension wherein a higher prevalence of PA has been reported.18 Second, only 1 set of ARRs was performed. The variability of repeated ARRs in patients proven to have PA has been shown.28 Third, no sodium suppression test for aldosterone autonomy was used in making the decision to proceed with workup. The captopril suppression test used in this study may be as good as tests of sodium suppression,29 but there are inadequate comparative data to be certain. Fourth, a computed tomography or MRI was used to make the definitive diagnosis in most patients, because only 43 of the 126 said to have PA had adrenal venous sampling. Virtually all of the experts have observed that computed tomography/MRI scans can accurately differentiate the type of adrenal pathology in only ≈50% of PA.30,31 Thus, despite the size of the study population, we are left with uncertainty as to the true prevalence of PA as would be found in unselected patients studied in a more definitive manner.

The second recent article describing the presumed prevalence of PA26 differs in many ways from that of Rossi et al.27 First, the enrollees “were recruited through a number of mechanisms, including mass-mailings, newspaper and posted...
advertisements, and referred from other study participants," adding up again to a selected population. However, those with an initial serum potassium of $\geq 3.5$ milliequivalents per liter were excluded, thereby deleting those most likely to have PA from an APA and perhaps IHA. Third, the 2 ARR tests were done under different conditions than the others in the table, once after 7 days of high-sodium ($\geq 200$ mmol/d) and once again after 7 days of low-sodium ($<10$ mmol/d) diets, while maintaining potassium balance. Fourth, the renin and aldosterone measurements were done in a centralized laboratory, and 24-hour urine aldosterone measurements were added.

The results of this smaller but more tightly controlled study were as follows: 20% had an elevated ARR ($>25$), but of these, only 7.5% had a serum aldosterone $>8$ ng/dL, the combination required for a "positive ARR screen." Of the 7.5% with a positive ARR screen, only 11 (3.2% of the entire 347 subjects with hypertension) had an elevated 24-hour urine aldosterone ($>17 \mu g$ per 24 hours). Thus, the authors conclude "that the prevalence of PA in a population with mild to moderate hypertension without hypokalemia was at most 3.2%." No further studies were done on those with elevated ARR and urinary aldosterone, so no information on the type of PA is available.

Although this study support a much lower prevalence of PA than Rossi et al, the data cannot be used as evidence for the prevalence in a nonselected population nor can the presence of APA be documented as it can in some of the patients in the study by Rossi et al.

### How to Screen for PA

These conflicting data point to an unanswered but fundamental problem: how to do the ARR. As seen in the Table, few investigators use the same criteria for an abnormally high ARR. Moreover, as shown by Hirohara et al, the ARR varies from high to normal on repeated study, even in patients with proven APA. As noted in another study, both the time of day and the posture of the participants induce marked variability. Furthermore, in a study of the ARR in 3326 participants in the Framingham Offspring Study, these features were found to be positively associated with the ARR: age, female sex, untreated hypertension, total:high-density lipoprotein cholesterol ratio, hormone replacement therapy, and $\beta$-blocker use, whereas angiotensin converting enzyme inhibitor and diuretic therapy were negatively associated. ARR was heritable with modest linkage to chromosome 11p but no association with 17 common variants of the REN locus.

As if these problems weren't enough to raise serious concerns, researchers have written about the technical problems of the renin and aldosterone assays. Gordon notes that "due to the wide availability of commercial kits, the

### Prevalence of Autonomous Hyperaldosteronism and APAs in Patients Tested by ARR

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Type</th>
<th>ARR Threshold*</th>
<th>Raised ARR, %</th>
<th>Abnormal Suppression by Salt Loads, %</th>
<th>Proven APA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiramatsu et al</td>
<td>349 R</td>
<td>40</td>
<td>7.4 NA</td>
<td></td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>Gordon et al</td>
<td>199 R</td>
<td>30</td>
<td>20.0 8.5</td>
<td></td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>Lim et al</td>
<td>125 P</td>
<td>27</td>
<td>14.0 NA</td>
<td></td>
<td></td>
<td>NA</td>
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<tr>
<td>Lim et al</td>
<td>495 R</td>
<td>27</td>
<td>16.6 9.2</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Nishikawa et al</td>
<td>1020 R</td>
<td>20</td>
<td>6.4 NA</td>
<td></td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Loh et al</td>
<td>350 R</td>
<td>$20 + PA &gt;15$</td>
<td>18.0 4.6</td>
<td></td>
<td></td>
<td>1.7</td>
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<tr>
<td>Rayner et al</td>
<td>216 R</td>
<td>$36 + PA &gt;18$</td>
<td>32.0 NA</td>
<td></td>
<td></td>
<td>2.3</td>
</tr>
<tr>
<td>Fardella et al</td>
<td>305 P</td>
<td>25</td>
<td>9.5 4.9</td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>Douma et al</td>
<td>978 R</td>
<td>$30 + PA$</td>
<td>21.2 13.8</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Rossi et al</td>
<td>1046 R</td>
<td>35</td>
<td>12.8 6.3</td>
<td></td>
<td></td>
<td>1.5</td>
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<tr>
<td>Hood et al</td>
<td>835 P</td>
<td>40</td>
<td>12.3 NA</td>
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<td>0.7</td>
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<tr>
<td>Mulato et al</td>
<td>2160 R</td>
<td>50</td>
<td>10.6 7.0</td>
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<td></td>
<td>1.6</td>
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<tr>
<td>Bernini et al</td>
<td>125 Inc</td>
<td>112</td>
<td>5.5 4.0</td>
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<td>0.8</td>
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<td>Calhoun et al</td>
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<tr>
<td>Girerd et al</td>
<td>143 R</td>
<td>NA</td>
<td>39 NA</td>
<td></td>
<td></td>
<td>6</td>
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<tr>
<td>Fogari et al</td>
<td>750 P</td>
<td>25</td>
<td>12 6</td>
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<td></td>
<td>2</td>
</tr>
<tr>
<td>Strauch et al</td>
<td>403 R</td>
<td>50</td>
<td>21.6 19</td>
<td></td>
<td></td>
<td>6.5</td>
</tr>
<tr>
<td>Stowasser et al</td>
<td>$\approx300$ R</td>
<td>30</td>
<td>18.6 17.7</td>
<td></td>
<td></td>
<td>5</td>
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<tr>
<td>Mosso et al</td>
<td>609 P</td>
<td>25</td>
<td>10.2 6.1</td>
<td></td>
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<td>0</td>
</tr>
<tr>
<td>Olivieri et al</td>
<td>287 P</td>
<td>50</td>
<td>32.4 NA</td>
<td></td>
<td></td>
<td>NA</td>
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<tr>
<td>Giragetti et al</td>
<td>157 R</td>
<td>40 + PA after IV saline</td>
<td>38.8 100</td>
<td></td>
<td></td>
<td>16.6</td>
</tr>
<tr>
<td>Williams et al</td>
<td>347 P/R</td>
<td>25 + PA &gt;8</td>
<td>7.5 3.2</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Rossi et al</td>
<td>1125 R</td>
<td>40</td>
<td>11.2 NA</td>
<td></td>
<td></td>
<td>4.8</td>
</tr>
</tbody>
</table>

Only those studies providing essential data are included. NA indicates not available; $\uparrow$, increased; R, referred; P, primary care; Inc, adrenal incidentaloma.

*ARR was expressed as plasma aldosterone in nanograms per deciliter, divided by PRA in nanograms per milliliter per hour.
measurement of the ARR has moved from the basic research laboratory, with meticulous quality control, clinical feedback and long experience, to the busy shrinking budget-driven general hospital laboratory.” Stowasser and Gordon further note “the ratio should be repeated until it unmistakably is, or is not, raised, with medications and conditions of collection adjusted if indicated. . . A single measurement of ARR should never be relied on.” Consider how far Gordon’s meticulous studies are from what goes on in Plano, Tex, or Mobile, Ala.

Why Not to Do the ARR
The previous litany of the problems with the use of ARR as a screening test leads to the next issue: what to do after an elevated ARR is documented. Most experts advise a 4-hour intravenous or a 3-day oral sodium load suppression test, but the Brisbane investigators report that only a 4-day high-salt diet plus daily fludrocortisone suppression test is accurate. Adrenal venous sampling is required to determine the type of hyperaldosteronism, because APAs should almost always be surgically removed, but the easily confused enlarged glands of IHA should never be removed unless the hyperplasia is unilateral, a very rare finding.

Everyone, including Dr Calhoun, recognizes the cost and potential hazards of both sodium loading and adrenal venous sampling that are needed to confirm the presence of PA and, even more importantly, to determine its cause. Therefore, in view of the high number of false-positives that high ARR will incorrectly mark for additional testing, why do it as a routine procedure unless there really is an epidemic of PA in ≥20% of patients? I argue that there is no such epidemic. But what if Dr Calhoun is correct and I am wrong?

The Consequences of Missing PA
Over the past 10 years, aldosterone in even presumably normal levels has been recognized to be an evil hormone. Although essential for survival in mankind’s early history when salt was scarce, now it is known to have little physiologic value but lots of pathologic associations. First recognized by Weber and Brilla in 1991, the evidence for a pathologic effect from aldosterone is strong, as expressed nicely by Dr Calhoun, “that underneath much of the smoke surrounding aldosterone, there is true fire.”

In view of its independent pathologic effects, the even higher levels of aldosterone in patients with PA have been shown to induce more bad cardiovascular consequences than those seen in patients with primary hypertension. These include stroke, heart attack, atrial fibrillation, metabolic syndrome, renal damage, and hypertensive emergency.

The issue now turns to a logical question, “If high levels of aldosterone are bad, should not a thorough search for PA in all subjects with hypertension be justified, even if in doing so, considerable mischief will have been caused?” The answer is contained in observations by Dr Calhoun and many others: if aldosterone receptors are effectively blocked with either spironolactone or eplerenone, the hypertension, hypokalemia (if present), and presumably all of the other bad consequences are prevented. This benefit from aldosterone receptor blockers has been documented in animals and humans, and they have been shown to be particularly helpful in overcoming resistant hypertension.

Therefore, even if Dr Calhoun is correct and there is an epidemic of PA, the way to stop the (unlikely) epidemic is easily at hand—inexpensive, rarely bothersome, and effective, as shown in the long-term benefit with spironolactone in patients with IHA. Dr Calhoun is among the first to show how well even low doses of spironolactone work, so I hope that my argument will convince him to use it even more and thereby avoid the costs, inconvenience, and potential dangers of looking for PA in more and more patients.

The Problem of the Incidentally Discovered Adrenal Mass
In addition to the increased surveillance of subjects with hypertension, even if normokalemic, that Dr Calhoun advocates, another large pool of suspects has appeared: patients with an adrenal mass recognized incidentally when computed tomography or MRI scans are done for other reasons. As reviewed by Young, ≈1% of adrenal incidentalomas turn out to be APAs. As do many others, he recommends an ARR for screening.

The Results of Surgery
The enthusiasm to uncover PA is partly based on anticipation that, if the cause is an APA, lifelong cure of hypertension can be guaranteed by surgical removal of the tumor. In fact, in long-term follow-ups of 420 patients who had unilateral adrenalectomy for APA in papers published from 1987 to 2001, only 52% were improved or cured. With laparoscopic or open adrenalectomy at the Mayo Clinic, only one third of 93 patients were cured.

To be sure, 20% to 30% of all patients with PA also have primary hypertension and would not be cured by any procedure. However, maybe a little less enthusiasm should be shown for finding an APA if its removal often does not relieve the patient of having to continue to take lifelong medications. A little spironolactone or eplerenone is likely as easy (and less expensive) than any other antihypertensive medication.

Summation
PA is likely more common than I believed in years past but is nowhere near as common as many, including Dr Calhoun, now claim. The prevalence of PA is likely <1% of the total unselected hypertensive population, and APA is likely the cause in approximately half of them.

Regardless, if the true prevalence is <1% or >20%, there is no need to screen for it by an ARR or any other maneuver unless the patient has an adrenal incidentaloma, unprovoked hypokalemia, or truly resistant hypertension. In these circumstances, finding PA can lead to appropriate therapy and serve the patient well. If indicated, the ARR must be done correctly, not the way it is now being done in most clinical settings.

A very wise and seasoned clinician, the late John Swales, said it very well 25 years ago, “The harder we look, the more patients with aldosteronism we are likely to find, though the yield in terms of disorder correctable by surgery is likely to decline spectacularly, the more widely we cast our net.”
Disclosures
N.M.K. has received modest payments as a speaker for Pfizer, Inc., and Boehringer Ingelheim Pharmaceuticals, Inc.

References

Kaplan Epidemiology of Primary Aldosteronism

Response to Is There an Unrecognized Epidemic of Primary Aldosteronism? (Con)

David A. Calhoun

“PA is likely more common than I believed in years past...”1 With that admission, I declare victory and will return to the clinic to resume writing prescriptions for spironolactone. Obviously, such a change of opinion cannot be credited to my forceful review, because Dr Kaplan would not have had benefit of it before composing his own, so instead, this change of heart but must be a consequence of the now compelling body of evidence demonstrating PA to be much more common than thought historically. Admittedly, there are wide variances in the estimated prevalence of PA, but differences would be anticipated based on the recognition that aldosterone excess undoubtedly represents a physiological continuum reflected by progressively smaller subgroups of patients if relying, respectively, on suppressed renin levels, an elevated ARR, or confirmatory suppression testing to index aldosterone status. A similar diminishing gradation in prevalence would be expected when evaluating patients with resistant versus moderate versus mild hypertension.

It is important from a clinical standpoint to recognize that Dr Kaplan and I are in agreement in suggesting that patients presenting with an adrenal incidentaloma, hypokalemia, and resistant hypertension warrant screening for PA given the increased risk of an APA, and, conversely, given the relatively low risk of an APA, patients with hypertension otherwise need not be routinely tested for aldosteronism. Furthermore, Dr Kaplan’s suggestion for broader use of mineralocorticoid receptor antagonists without previous assessment of aldosterone status is intuitive of evolving tendencies in our clinic for treatment of presumed primary hypertension.

Reference

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