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

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As evidenced by this debate, controversy persists as to the true prevalence of primary aldosteronism (PA) and, perhaps more importantly, concerns regarding the clinical rationale of evaluating large numbers of hypertensive patients for evidence of aldosterone excess. In regard to the former controversy, it has been suggested that reports of a high prevalence of PA exaggerate the true value for a variety of methodologic shortcomings, including overreliance on the plasma aldosterone/plasma renin ratio (ARR) to estimate the prevalence of PA; a selection bias from estimating the general prevalence of PA based on patients referred to hypertension specialty clinics; and because of inappropriately considering idiopathic hyperaldosteronism (presumed secondary to adrenal hyperplasia) to be a type of PA.1–3 Suggestions to broadly screen hypertensive patients for PA have led to the latter controversy as to whether the costs and risks of potentially evaluating large numbers of hypertensive patients for the presence of PA are clinically justified.1 The controversies are obviously related but especially so for clinicians treating hypertension, because they reflect different strategies as to how and when to screen patients for PA.

Early Estimates of PA Prevalence

Early studies indicated that PA was an uncommon cause of hypertension with a prevalence of <1% to 2%.4–7 However, in these studies, testing for PA was primarily limited to patients presenting with hypokalemia. Consistent with the initial description of the syndrome, hypokalemia was thought to be an obligatory characteristic, such that normal potassium levels were thought to reliably exclude PA. However, as later reported by Conn et al,5 hypokalemia is likely a late manifestation of aldosterone excess, if it occurs at all. Recent studies evaluating consecutive patients, regardless of serum potassium levels, have consistently found that hypokalemia occurs in a minority of patients with biochemical PA.9,10 Although a history of hypokalemia is much more common in patients with PA secondary to an adrenal tumor, it still occurs in ≤50% of such patients.11 Therefore, the early studies assessing the occurrence of PA, in only testing patients with spontaneous hypokalemia, undoubtedly underestimated the true prevalence of PA. So in considering the current “epidemic” of PA, it is difficult to say to what degree current estimates represent a true increase in prevalence versus differences in methodology.

Recent Estimates of PA Prevalence

Previous criticisms leveled against some of the recent studies reporting a high prevalence of PA represent legitimate concerns. Relying solely on a high ARR to estimate the prevalence of the PA will likely result in an inflated value. We and others have shown the ARR to have a relatively poor positive predictive value.10,12 That is, there is a high percentage of falsely high ratios (depending on the cutoff value used) such that studies that did not confirm PA with volume suppression testing would have overestimated the presence of PA. Likewise, assessments of PA done in specialty clinics would have reflected a referral bias, particularly in selecting patients with more severe and/or resistant hypertension in whom the prevalence of PA is much higher compared with general hypertensive populations. Lastly, according to current convention, aldosterone excess, whether confirmed to be secondary to an aldosterone-producing adenoma (APA) or presumed to be idiopathic, is broadly labeled as PA. Accordingly, studies that have not distinguished between the 2 etiologies will have reported a higher prevalence of PA compared with studies that restricted the definition of PA to true Conn’s syndrome, that is, PA secondary to an APA.

As described by Padfield3 in an earlier iteration of this same debate, idiopathic PA is physiologically different from an APA in that the former manifests a hypersensitive response to angiotensin II compared with the latter, leading Padfield to suggest that idiopathic PA is, in reality, more of a secondary aldosteronism mediated by renin-angiotensin II. Although patients with PA secondary to an APA compared with patients with idiopathic PA tend to have higher aldosterone levels, lower potassium levels, and more severe hypertension,1 these characteristics are not diagnostic enough to confirm or exclude the presence of an APA on an individual
PA Prevalence in General Hypertension

In a study by Schwartz and Turner10 conducted at the Mayo Clinic, 118 patients with hypertension who had been part of a larger epidemiologic study of patients with hypertension in Olmsted County, Minn, were evaluated for PA. The ARR was measured during the subject’s normal antihypertensive treatment; 2 weeks after withdrawal from his or her antihypertensive treatment; after 4 days of dietary sodium loading; and after acute diuresis. The investigators found that the positive predictive value of the ARR was $\geq0.95$% under all of the test conditions. This comparison demonstrates that the ARR is an effective screening test (negative value reliably excludes the disease) even during normal antihypertensive treatment. Equally significant was demonstration of the poor positive predictive value of ARR. Regardless of the test conditions, the positive predictive value was $\leq0.41$%, emphasizing that a high ARR does not reliably indicate PA and that confirmation with suppression testing is necessary. Importantly, hypokalemia had been corrected in all of the subjects before testing, and medications during testing did not include mineralocorticoid receptor antagonists.

Mosso et al9 evaluated $>600$ patients with hypertension for PA. This study is clinically informative in being able to relate the prevalence of PA to the severity of hypertension in untreated patients. Subjects were recruited from 2 outpatient primary care centers. The severity of hypertension was staged in the absence of treatment according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (stage 1: 140 to 159/90 to 99 mm Hg; stage 2: 160 to 179/100 to 109 mm Hg; stage 3: $\geq180/110$ mm Hg). All of the subjects were screened by an ARR. If high ($>25$), PA was confirmed or excluded by fludrocortisone suppression testing. Overall, 6.1% of subjects were confirmed to have biochemical PA. Important from a clinical perspective was that the prevalence of PA increased with increasing severity of hypertension. In patients with mild hypertension (stage 1), the prevalence of PA was not different from normotensive patients ($\approx2$%). In subjects with more moderate hypertension (stage 2), the prevalence of PA increased to 8%. In subjects with severe hypertension (stage 3), PA was present in 13% of subjects (Figure 1).

By having recruited subjects from primary care clinics, this study minimized any referral bias. The study is also strengthened by the large number of subjects evaluated and by having confirmed the diagnosis of PA by fludrocortisone suppression testing. Clinically the results are particularly informative in demonstrating that the likelihood of PA increases with increasing severity of hypertension. In patients with untreated blood pressure $<160/100$ mm Hg, PA is unlikely, but in...
patients with severe hypertension (>180/110 mm Hg) the likelihood of PA is substantially increased (>10%).

Until recently, all of the studies determining the prevalence of PA were limited in reporting the presence of biochemical PA by having not systematically distinguished idiopathic PA from true Conn’s syndrome. Impressively, that limitation was recently overcome by the Primary Aldosteronism Prevalence in Hypertensives (PAPY) investigators. In this study 1125 Italians newly diagnosed with hypertension agreed to be screened for PA including, if biochemical PA was confirmed, localization studies (either AVS or adrenocortical scintigraphy) and adrenalectomy. PA was confirmed based on a high baseline ARR and high ARR after captopril suppression testing or with application of a previously validated logistic function. APAs were confirmed by positive localization, surgical resection, pathological examination, and clinical outcome after adrenalectomy. Subjects with confirmed PA but without confirmed adrenal adenomas were diagnosed as having idiopathic PA.

Overall, the prevalence of biochemical PA was 11.2%. Approximately 43% of these cases could be attributed to an APA, with the remaining 57% considered idiopathic in etiology. Accordingly, in this cohort of newly diagnosed patients with hypertension, the overall prevalence of PA secondary to an adrenal adenoma was 4.8%, and the prevalence of idiopathic PA was 6.4%.

These 3 studies add to a now large body of evidence indicating that PA is common among patients with general hypertension with a prevalence of ~10%. This rate is considerably higher than the 1% to 2% observed in the very early studies of PA prevalence. Collectively, these studies avoid limitations of some of the earlier studies by having enrolled generally broad cohorts of patients with hypertension, confirming the diagnosis of PA with suppression testing, and with publication of the PAPY study, having anatomically and clinically distinguished Conn’s syndrome from idiopathic PA.

**PA Prevalence in Resistant Hypertension**

Multiple studies indicate that PA is particularly common in patients with resistant hypertension. At the University of Alabama at Birmingham, we screened 88 consecutive patients referred to us for resistant hypertension (clinical blood pressure >140/90 mm Hg on ≥3 antihypertensive medications). Based on a suppressed plasma renin activity (PRA; <1.0 mg/mL per hour) and high urinary excretion of aldosterone (>12 μg per 24 hours), in spite of dietary sodium loading (>200 milliequivalents per 24 hours), 18% or 20% of patients were diagnosed with PA. In a separate analysis, we found that, in patients with resistant hypertension, the ARR at a cutoff value of 20 had a high negative predictive value (93%) but low positive predictive value (56%), similar to the results of Schwartz and Turner in patients with more general hypertension. These results suggest that PA commonly contributes to resistance to antihypertensive treatment. The ARR is an effective screen for PA without withdrawal of antihypertensive treatment but has a high rate of falsely positive results, such that suppression testing is necessary to confirm the diagnosis of PA.

A prevalence of PA of ~20% in patients with resistant hypertension has been a very consistent observation from different laboratories worldwide. Gallay et al found, in Seattle, Wash, that, among 90 consecutive patients referred to a hypertension specialty clinic for severe and/or poorly controlled hypertension, the prevalence of PA was 17%. Among 90 patients referred for resistant hypertension to a university hypertension clinic in Oslo, Norway, 23% were confirmed to have PA. In an evaluation of >400 patients referred to a university specialty clinic in the Czech Republic for moderate-to-severe hypertension, 19% were found to have PA.

These multiple studies agree in demonstrating a prevalence of PA of ~20% among patients with resistant hypertension (Figure 2). This percentage, however, likely underestimates the role of aldosterone excess in contributing to resistant treatment in that the PRA remains persistently suppressed in 60% to 70% of patients with resistant hypertension in spite of the use of antihypertensive agents that typically increase renin activity (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics). Admittedly, there are multiple reasons in these cohorts for suppressed PRA other than hyperaldosteronism, but a greater role of aldosterone excess in causing resistant hypertension beyond the 20% of patients with confirmed PA is also suggested by studies indicating broad antihypertensive benefit of mineralocorticoid receptor antagonists in patients resistant to conventional antihypertensive regimens.
The relative prevalence of APAs compared with idiopathic PA is likely higher in patients with resistant hypertension than the 43% found in subjects with newly diagnosed hypertension reported by the PAPY investigators, because patients with resistant hypertension are more likely to have characteristics suggestive of an APA (higher aldosterone levels, lower potassium levels, and more severe hypertension). A higher occurrence of true Conn’s syndrome was found in the study by Gallay et al,15 in which 10 of the 15 or 66% of patients with biochemical PA were confirmed to have adrenal adenomas by surgical resection and pathological confirmation. Overall, the results of these studies are clinically relevant in demonstrating that 1 in 5 patients with resistant hypertension have PA and that, of these patients, >50% are likely to have an APA. These recent results are consistent with early studies of PA indicating that it was often associated with severe and/or difficult-to-treat hypertension.21–23

Screening for PA
Given that the prevalence of PA secondary to an APA in general patients with hypertension is likely <5% (as suggested by the PAPY study of patients with newly diagnosed hypertension), I will agree in advance with Dr Kaplan and suggest that we need not be evaluating all patients with hypertension for PA. The costs and risks of identifying biochemical PA and then distinguishing adrenal adenomas from hyperplasia with radiographic imaging and AVS in order to identify the small percentage of patients that will benefit from adrenalectomy are prohibitive in such a large number of patients. Given that a large percentage of patients with general hypertension can be controlled with 1 or 2 antihypertensive agents, this should be attempted, reserving screening for PA for those patients who fail this routine approach. Exceptions would include patients at increased risk of having an APA, including patients presenting with hypokalemia, patients suspected of having a secondary cause of hypertension (particularly onset of hypertension at a young age), and patients who present with severe hypertension.

Patients with resistant hypertension do warrant routine evaluation for PA. Given that ≥10% of patients with resistant hypertension may have an APA, and, by definition, such patients are failing medical therapy, the opportunity for clinic benefit is high in being able to control blood pressure and avoid lifelong use of multidrug regimens.

It might be argued that we should just empirically begin mineralocorticoid receptor antagonists in patients with resistant hypertension, reserving evaluation for PA for those who cannot be managed medically. Such an approach would not be unreasonable, but I would suggest at least checking an ARR to see if PA can be excluded, because once the mineralocorticoid receptor antagonist is started, PRA and aldosterone levels cannot be reliably interpreted. So, to avoid having to later withdraw therapy, it seems more practical to at least identify in advance those patients who are not likely to have PA.

The other problem with beginning treatment without screening is that, whereas mineralocorticoid receptor antagonists are broadly effective in patients with resistant hyperten-

tion, many patients, at least with the use of doses of spironolactone that are tolerable, will require lifelong use of multiple drugs to control their blood pressure. In many cases, the dose of spironolactone needed to achieve full benefit will not be tolerated (most often because of breast tenderness without or without gynecomastia). This is particularly true of men even with use of relatively modest doses of spironolactone. Avoiding or at least minimizing the costs, inconvenience, and adverse effects of such long-term dosing by looking for and removing an APA would seem to be an appropriate consideration on an individual patient basis. This approach could change with the use of more selective and better tolerated mineralocorticoid receptor antagonists, such as eplerenone, but first the efficacy of such agents in treating resistant hypertension needs to be established.

If not necessary to screen for PA in patients with general hypertension, might checking an ARR be recommended to guide the use of mineralocorticoid receptor antagonists? Although there are some data to suggest that a high ARR, a suppressed PRA,24 and/or a low serum potassium level19,25 predict a favorable response to aldosterone blockade, such predictive value has not been definitively established in blinded studies that included active comparators, and in fact, was specifically absent in the multicenter studies leading to approval of eplerenone, at least in patients already receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.26 Accordingly, it is premature to recommend using the ARR to guide preferential use of mineralocorticoid receptor antagonists. That having been said, we find ourselves more often initiating thiazide therapy in combination with a low-dose mineralocorticoid receptor antagonist (in the absence of chronic kidney disease) without measuring the ARR. This approach helps prevent thiazide-induced hypokalemia (particularly with chlorthalidone), provides additional blood pressure benefit allowing for use of smaller doses of the thiazide diuretic, and, we hope, minimizes some of the other metabolic adverse effects associated with thiazide use. In doing this, we typically begin with just 12.5 mg of chlorthalidone or hydrochlorothiazide and 12.5 mg of spironolactone. In the United States, there is a fixed-dose combination of hydrochlorothiazide and spironolactone that has been available for many decades, suggesting that with this “evolving” approach we may in fact be rediscovering the wheel.

Although we are not recommending screening all patients with hypertension with an ARR, we do think there is therapeutic value in measuring the ARR in patients with resistant hypertension even when complete evaluation for PA is not being considered. The value is not in initiating therapy with a mineralocorticoid receptor antagonist, because, interestingly, we and others have found that the blood pressure response to aldosterone blockade in patients being treated for resistant hypertension is not predicted by the ARR, PRA, or by urinary or plasma aldosterone levels.18,24 This lack of predictive value is likely in part a consequence of confounding effects of ongoing treatment but also suggests a role of aldosterone in contributing to treatment resistance that is not reflected in the measurement of circulating levels.

The therapeutic value of measuring the ARR is not in initiating but in dosing mineralocorticoid receptor antagonists.
when treating resistant hypertension. Clinical data clearly establish the medical benefit of using mineralocorticoid receptor antagonists as fourth-line agents in treating resistant hypertension.\textsuperscript{18–20} What those trials do not establish, however, is the appropriate dose range of spironolactone for treatment of resistant hypertension, particularly if PA is not present. The studies confirming the efficacy of spironolactone in treating resistant hypertension have been mostly limited to 25 to 50 mg daily, whereas true PA may require doses as high as 400 mg daily for effective treatment. So in having ruled out PA with a low ARR, use of spironolactone $\leq 50$ mg is supported by recent clinical trials. The risk versus benefit of using higher doses in the absence of PA has not been determined. Accordingly, in patients in whom PA is unlikely (a low ARR), we are typically dosing spironolactone $\leq 50$ mg daily. In patients with a high ARR but in whom we are not continuing the evaluation for PA, we are much more comfortable continuing to titrate the spironolactone up to 100 mg daily or higher. Such an approach is supported by our experience in showing that, whereas the degree of blood pressure reduction with spironolactone is similar in resistant patients with hypertension with or without confirmed PA, the subjects with PA will require higher doses to achieve that same level of blood pressure reduction.\textsuperscript{19}

Because many patients with resistant hypertension have already developed significant complications of their poorly controlled hypertension (ie, left ventricular hypertrophy, proteinuria, or retinopathy), it does not seem prudent to wait until resistant hypertension is fully manifest to begin testing for PA. However, at what point along the progression from general to resistant hypertension it is cost and risk efficient to begin testing for PA is not established by clinical data and, thus, will be arbitrary. At risk of splitting hairs, I would recommend sooner compared with later screening all patients as they progress from needing 2 to 3 antihypertensive medications. Such early screening is recommended to identify PA before the complications of poorly controlled hypertension have developed.

PA can be reliably excluded by a low ARR (usually <20 to 30 if plasma aldosterone is measured in nanograms per deciliter and PRA is measured in nanograms per milliliter per hour). The ratio should be measured in the early morning in ambulatory patients. Risk of a falsely high ratio because of an extremely low PRA can be minimized by using a minimum PRA of 0.5 ng/mL per hour. Alternatively, requiring a plasma aldosterone of $\geq 12$ to 15 ng/dL will lessen the risk of false-positive values. Such maneuvers do improve the specificity of PA screening but at the expense of lowering sensitivity. For example, PA has been confirmed in patients with plasma aldosterone levels as low as 9 ng/dL.\textsuperscript{27}

Falsely high serum potassium levels can occur if patients are asked to repeatedly clinch their fists to facilitate blood collection, which, in turn, may obscure evidence of PA.\textsuperscript{28,29} To avoid such an effect, blood should ideally be collected without use of this maneuver.

Future Needs

Whether an epidemic or not, PA is common in patients with hypertension. A critical unanswered question concerns the cause of the inappropriate aldosterone release. If the underlying stimuli of the aldosterone excess were identified, they might allow for better treatment and/or effective prevention. Recent in vitro studies suggest that adipocytes may release aldosterone secretagogues independent of renin-angiotensin II.\textsuperscript{30,31} If true, it would link the seemingly growing burden of aldosterone excess to worldwide increases in obesity. Genetic variations within and separate from the renin-angiotensin-aldosterone pathway have been linked to fluctuations in aldosterone levels,\textsuperscript{32–34} but the clinical significance of these variants needs clarification.

An important clinical question needing elucidation is whether mineralocorticoid receptor antagonists provide unique antihypertensive benefit in treating resistant hypertension or is it a nonspecific benefit that could be achieved with addition of any of the other classes of agents. The degree of benefit (\textasciitilde 20/10 mm Hg) seemingly exceeds what would be expected with titration or addition of other agents, but this needs to be established both for clinical clarification and for confirmation of the role of aldosterone excess in causing resistant hypertension. Also needed is determination of the effective dose range of spironolactone for treatment of resistant hypertension, particularly in the absence of PA.

Lastly, biochemical parameters to guide the use of mineralocorticoid receptor antagonists would be of significant clinical value. Presently, aldosterone and/or renin levels have not been shown to convincingly predict blood pressure response to aldosterone blockade, but if such a parameter could be identified, it should allow for more timely use of mineralocorticoid receptor antagonists in treating both general and resistant hypertension.

Summary

A large body of evidence clearly establishes that PA is common, with a prevalence of \textasciitilde 10% among general hypertensive populations and \textasciitilde 20% among patients with resistant hypertension. Results of the recently published PAPY study indicate that, among patients with general hypertension, <5% will have an APA.\textsuperscript{11} Given this small percentage, it is not likely to be cost or risk efficient to fully evaluate all patients with hypertension for PA in order identify the few that will benefit for adrenalectomy. In contrast, because patients with resistant hypertension are by definition failing medical therapy, evaluation for PA seems appropriate to identify the 10% who likely have an APA and to guide dosing of mineralocorticoid receptor antagonists in the 10% who have idiopathic PA.

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References


Response to Is There an Unrecognized Epidemic of Primary Aldosteronism? (Pro)
Norman M. Kaplan

I am pleased that Dr Calhoun is not among those who believe that there is a real epidemic of primary aldosteronism, necessitating screening of all hypertensive subjects.\(^1\) We also agree that adrenal venous sampling is essential to distinguish between adenomas (primary aldosteronism) and bilateral hyperplasia (idiopathic hyperaldosteronism) certainly before adrenalectomy is performed.

However, we disagree on 3 issues. First, he believes primary aldosteronism is present in \(\geq 10\%\) of all subjects with hypertension, based largely on the finding of the Italian Primary Aldosteronism Prevalence in Hypertensives Trial.\(^2\) As I noted, there are multiple problems with the trial that preclude its use to establish the true prevalence of primary aldosteronism in an unselected hypertensive population. Similar problems are present in most of the trials shown in my table, leading to my conviction that the true prevalence is unknown but almost certainly is much lower than 10%.

Second, he defends the use of the ARR for screening. By his own calculations, the ARR has a false-positive rate of \(\geq 5\%\) to 7%. Because he would focus primarily on patients with resistant hypertension or those whose control requires going from 2 drugs to 3, it should be noted that the number of false-positives among those patients would number around 900,000 in the United States alone. Taking the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial data,\(^3\) >30% required 3 drugs. If 30% of the 60 million hypertensive subjects in the United States would be subject to screening, and 5% would have a false-positive test, there would be 900,000 who would require at least a salt suppression test and, because it too has some false-positives, a large number of adrenal vein sampling studies would then be unnecessarily performed.

Third, Dr Calhoun exaggerates the need for increasingly large doses of an aldosterone receptor blocker that would be needed to control idiopathic hyperaldosteronism and protect those with an unrecognized adenoma. In a long follow-up of patients with idiopathic hyperaldosteronism, an average dose of only 37.5 mg per day was needed for control.\(^4\) To be sure, men should be warned about gynecomastia even with small doses of spironolactone, but now that eplerenone is generic, it can be used without that concern.

There is more to be said about where we disagree but space is limited. Lastly, thanks to the editors of Hypertension for providing a forum to air out such controversies.

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