Primary Aldosteronism: Results of Adrenalectomy for Nonsingle Adenoma

Amy R Quillo, MD, Clive S Grant, MD, FACS, Geoffrey B Thompson, MD, FACS, David R Farley, MD, FACS, Melanie L Richards, MD, FACS, William F Young, MD

BACKGROUND: Historically, treatment of confirmed primary aldosteronism has been adrenalectomy for unilateral adenoma; bilateral hypersecretion is treated medically. Increasingly, we use adrenal venous sampling (AVS) to define unilateral hypersecretion. Histology of glands resected based on AVS often reveals multiple nodules or hyperplasia. The aim of this study was to compare patients with multiple nodules or hyperplasia with those with single adenoma with regard to cure, preoperative imaging, AVS ratio, and biochemical evaluation to determine if a nonsingle adenoma (NSA) process could be predicted to impact extent of adrenalectomy.

STUDY DESIGN: This was a retrospective study reviewing a single-institutional surgical experience at a tertiary academic center from 1993 to 2008, during which 215 patients with primary aldosteronism underwent unilateral adrenalectomy based on imaging of a single adenoma (normal contralateral gland) or AVS ratios. Histology included single adenoma versus NSA; cure was defined as normal immediate postoperative plasma or urine aldosterone level, normal aldosterone:renin ratio, or normotension without antihypertensive medications.

RESULTS: Follow-up (mean 13 months, range 0 to 185 months) was available for 167 patients: 132 (79%) single adenoma and 35 (21%) NSA. All 35 patients with NSA and 128 patients (97%) with single adenoma were cured. Imaging studies correctly predicted NSA in 29% and 57% when combined with AVS. Identifying patients with NSA preoperatively was impossible biochemically: mean serum and urinary aldosterone levels and AVS ratios were not different than those of the single adenoma group.

CONCLUSIONS: Twenty-one percent of patients had NSA, all cured by unilateral adrenalectomy. No preoperative evaluation reliably predicted NSA. Therefore, total unilateral adrenalectomy was safest given the potential for incomplete resection with partial adrenalectomy. Accurate AVS is highly predictive of cure irrespective of the unilateral adrenal histology. (J Am Coll Surg 2011;213: 106–113. © 2011 by the American College of Surgeons)
ognized to counteract the deleterious effects on the heart, kidney, and peripheral vascular system, and even to improve the quality of life.

APAs are usually small (≤2 cm in diameter) adrenal nodules, hypodense on CT scan, and distinctly golden yellow on gross pathology. IHA adrenal glands usually appear either normal or nodular bilaterally on imaging studies. Where distinguishing these 2 conditions preoperatively might seem straightforward with modern, high-definition imaging such as CT or MRI, 46% of patients in the Mayo Clinic experience with PA would have been incorrectly managed on the basis of CT findings alone. These patients were appropriately managed with the use of bilateral adrenal venous sampling (AVS), now incorporated as a crucial step in discrimination of unilateral aldosterone hypersecretion in patients with PA. The importance of AVS in the management of PA has been verified in other studies; management plans based initially on CT scan required alteration following AVS in 36% of patients in one report and in 50% of the patients reported by the NIH.

During a retrospective review of the pathology of the 110 patients with unilateral aldosterone hypersecretion in the previously cited Mayo Clinic study, 8 were found to have primary adrenal hyperplasia. With unilateral adrenalectomy, 6 of the 8 had early postoperative complete resolution of their hypertension without need for medication. Because of this group of patients who did not fit into either an APA or IHA subtype, the aim of this study was to compare patients with multiple nodules or hyperplasia with those with a single adenoma with regard to cure, preoperative imaging, AVS ratio, and biochemical evaluation, and to determine if a nonsingle adenoma (NSA) process could be predicted preoperatively to prevent performing a less than total adrenalectomy that might not cure the PA if NSA were the pathology.

METHODS

A computerized medical record database was used to identify 215 patients (mean age 50 years; range 17 to 80 years; 142 men) with the confirmed biochemical diagnosis of PA who had undergone unilateral adrenalectomy at the Mayo Clinic in Rochester, Minnesota. The clinical protocol was approved by our IRB. The database had been prospectively collected but was then retrospectively reviewed for purposes of this study.

Criteria used to establish a biochemical diagnosis of PA in a patient with hypertension included a PAC of greater than 15 ng/dL and a PAC to PRA ratio of more than 20. The suspected diagnosis was confirmed by an inability to suppress the aldosterone level despite saline load.

Generally, once the diagnosis of PA was established, patients underwent abdominal imaging with CT with our adrenal protocol. In patients younger than 40 years, if a CT scan showed a definitive unilateral adenoma with a completely normal contralateral adrenal gland, the patient was selected for unilateral adrenalectomy. In patients older than 40 years or in those who had bilateral abnormalities or normal-appearing adrenals on imaging, AVS was performed and surgery usually subsequently based on AVS lateralizing ratios of 3:1 or greater.

As described previously, AVS at the Mayo Clinic is performed successfully under a strict protocol. A continuous cosyntropin infusion is administered, and the adrenal veins are catheterized percutaneously through femoral vein access. A small amount of contrast is injected to confirm cannulation and delineate the anatomy. The right adrenal vein is sampled first because it is usually more time consuming, whereas the left is relatively easy to cannulate and can be performed rapidly soon after success on the right. The final “inferior vena cava” sample is taken from the external iliac vein. Aldosterone and cortisol concentrations are then measured in all 3 samples. Successful catheterization is confirmed by the cortisol concentrations. The right and left adrenal vein PACs are then divided by their respective cortisol concentrations, which corrects for the dilution of the left adrenal vein by inferior phrenic vein inflow. The values from each side are compared, and the larger PAC ratio is divided by the smaller ratio, resulting in the “AVS ratio” used to determine lateralization (see Table 1 for example). A ratio of greater then 4:1 is generally accepted to represent a unilateral process on the side of the larger PAC ratio. Values less than 3:1 signify a bilateral process. We did include all patients with ratios greater than 3:1 for this evaluation. Patients were then categorized based on histo-

### Table 1. Example of Adrenal Venous Sampling

<table>
<thead>
<tr>
<th>Vein</th>
<th>Aldosterone (A) mg/dL</th>
<th>Cortisol (C) μg/dL</th>
<th>A/C ratio</th>
<th>Adrenal ratio</th>
</tr>
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<tbody>
<tr>
<td>RAV</td>
<td>1,538</td>
<td>940</td>
<td>1.6</td>
<td>1</td>
</tr>
<tr>
<td>LAV</td>
<td>8,925</td>
<td>760</td>
<td>11.7</td>
<td>7.3</td>
</tr>
<tr>
<td>IVC</td>
<td>210</td>
<td>37</td>
<td>5.7</td>
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IVC, inferior vena cava; LAV, left adrenal vein; RAV, right adrenal vein.
logic findings into single adenoma or NSA process if multiple nodules or hyperplasia were found on final pathology.

The criteria for cure of PA was defined as a postoperative aldosterone level ≤ 5 ng/dL (drawn during the postoperative hospitalization), postoperative urinary aldosterone level of less than 12 μg, normal postoperative aldosterone to renin ratio (≤ 20) at any time after surgery, or normal blood pressure off all antihypertensive medication.

RESULTS

Of the 215 patients who underwent unilateral adrenalectomy for PA, 167 met the criteria for inclusion and had follow-up available (mean 13 months; range 0 to 185 months); data were obtained either through clinic visit or telephone interview with the patient.

Excluded from the study were those patients without postoperative biochemical evaluation of aldosterone who also did not have sufficient long-term follow-up by way of biochemistry or blood pressure to adequately assess cure or recurrence/persistence of PA. Only those patients with either documented biochemical normalization of aldosterone or normal blood pressure off all medications were included as cured, and recurrence or persistence of PA was documented by biochemical means or with no improvement/worsening of blood pressure. Of those excluded, there were 25 patients (23 single adenoma and 2 NSA) who had no biochemical evaluation after the operation and no follow-up information available. However, also excluded were 18 patients (17 single adenoma and 1 NSA) who had documented improvement in blood pressure control with fewer medications but continued to require antihypertensive medications at last follow up and had no documented biochemical normalization of aldosterone. These patients were therefore excluded from analysis. Five patients were excluded for AVS ratios of less than 3:1.

The group of 167 who did meet criteria for inclusion consisted of 108 men and 59 women with an overall mean age of 51 years (range 17 to 80 years). Of these, 132 (79%) had a single adenoma identified on final pathology, and 35 (21%) had an NSA process (11 with multiple nodules and 24 with hyperplasia, see Fig. 1 for an example). Demographics and biochemical evaluation of both groups are summarized in Table 2. Number of medications, preoperative serum and urinary aldosterone levels, and AVS ratios were not different between the 2 groups.

With respect to imaging results, the results for the NSA group are summarized in Table 3. Preoperative imaging in the form of adrenal CT scanning predicted the “correct side” (based on AVS results and later surgery and cure) in

<table>
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<tr>
<th>Table 2. Demographics and Biochemical Evaluation</th>
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<tr>
<td>Age, y (range)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>No. of preoperative antihypertensive medications</td>
</tr>
<tr>
<td>Serum aldosterone level, ng/dL</td>
</tr>
<tr>
<td>Urinary aldosterone level, μg</td>
</tr>
<tr>
<td>AVS ratios (AC larger:AC smaller)</td>
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Data are presented as means ± SD unless otherwise noted.
AC, aldosterone concentration; AVS, adrenal venous sampling; NSA, nonsingle adenoma.

![A example of a nonsingle adenoma process demonstrated in an intact adrenal gland after laparoscopic removal.](image1)

![B cross-section of a nonsingle adenoma process with at least 3 golden-yellow nodules identified, each consistent with an aldosterone-producing adenoma, apparent hyperplastic cortex.](image2)
only 54% of patients with the NSA process. Furthermore, although CT did correctly lateralize in these 19 patients, only about one-half of those (29% of total) had a CT scan that suggested the presence of an NSA process. Even with known AVS lateralization, reexamination of the CT scan predicted the presence of NSA in only 57%.

Based on the criteria outlined in the preceding text, all 35 patients (100%) of the NSA group met the criteria for cure, either biochemically or by follow up after at least 6 months with normal blood pressure off all antihypertensive medications. Of the single adenoma group, 128 (97%) met the criteria for cure. AVS sampling was obtained in 2 of the 4 patients not cured in the single adenoma group, with ratios of 8.7:1 and 7.6:1, both of which we would have expected cure.

DISCUSSION

Considerable progress has occurred over the last 15 years in virtually all aspects of primary aldosteronism. What was previously thought to represent a rare cause of hypertension—dominated since at least 1965, with a case report by Ross.15—has now been recognized worldwide to comprise up to 13%11,12 of patients with hypertension. It is now recognized that a single blood test—not serum potassium (as hypokalemia is most often not present)—to determine the ratio of PAC to PRA is highly sensitive in screening for the diagnosis. Once the diagnosis is confirmed by lack of aldosterone suppression in response to saline loading, appropriate treatment requires the pivotal distinction between medically treated IHA and surgically treated APA. However, the pathologic distinction between the 2 has been blurred by an additional group of patients found to have either nodular hyperplasia or multiple macronodules on final pathology following unilateral adrenalectomy. Of the overall 215 patients surgically treated for PA in our series, 40 (19%) were found to have NSA, of whom 35 met the study criteria. The unsettling discovery of either hyperplasia or multiple nodules on postoperative histology might reasonably raise concern that these patients actually had IHA and therefore would not be cured with unilateral adrenalectomy. However, even assessed by the exacting criteria of cure—either suppressed postoperative PAC or complete resolution of hypertension—all 35 of the NSA group were cured. Certainly, these results confirm unilateral aldosterone hypersecretion, which would not have been achieved in patients with IHA. Identifying these patients with NSA preoperatively was impossible biochemically: mean serum and urinary aldosterone levels and AVS ratios were not different than those of the APA group.

Preoperative imaging was also markedly unreliable because CT scans lateralized to the correct side in only 54% of the NSA group. Of those in the NSA group in whom CT did not lateralize correctly, most had imaging with bilateral abnormalities; however, 6% actually had an abnormality on the contralateral side. In only 29% of the patients did CT scan correctly predict or suggest the presence of an NSA process on the correct side. The emphatic conclusion is that surgical decisions cannot be based solely on traditional preoperative imaging, especially in older patients who have an increased frequency of “incidentalomas” that may confuse the picture.13 The inescapable key step principally responsible for the uniformly successful cure of PA in the patients with NSA was the use of AVS; it yielded unequivocal physiologic data that reliably predicted cure of PA with unilateral adrenalectomy.

Implicit in this patient cohort is the issue of partial adrenalectomy. In the past, there has been interest in partial or cortex-sparing adrenalectomy in patients with PA, especially in those whose preoperative imaging studies seem clear cut. However, as demonstrated in this series, even with lateralization by AVS coupled with preoperative imaging, only 57% were even suggestive of an NSA process. These results, as well as the incidence of NSA of 21% in our study and up to 27% in other reports,14 lead us to the general recommendation of total adrenalectomy based on accurate AVS, irrespective of preoperative imaging results.

Unilateral hyperplasia as a cause of PA has been recognized since at least 1965, with a case report by Ross.15 Additional individual case reports have been published,16,17 and a review of 30 cases from published reports was provided by Goh and colleagues in 2006.18 All 30 patients had

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<th>Table 3. CT Concordance and Prediction in Patients with Multiple Nodules and Hyperplasia on Final Pathology (NSA)</th>
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<tr>
<td><strong>Multiple nodules</strong></td>
</tr>
<tr>
<td>(n = 11)</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>CT predicted correct side</td>
</tr>
<tr>
<td>CT predicted correct side and NSA process</td>
</tr>
<tr>
<td>CT showed bilateral process</td>
</tr>
<tr>
<td>CT showed contralateral process only</td>
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<tr>
<td>Once AVS results known, CT suggested NSA process</td>
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*Two patients with nonsingle adenoma (NSA) process were treated before standardized use of adrenal venous sampling (AVS).
hypertension, most were hypokalemic, and most had postural response studies indicating a unilateral source of the aldosterone hypersecretion. In only 53% of the patients did the CT scan correctly localize. Adrenal scintigraphy localized correctly in only 50%, whereas in the 22 patients with AVS, all lesions were correctly predicted. With a median of 1-year follow-up, 50% were cured of their hypertension, with the remaining patients having improved blood pressure control. All were cured of hypokalemia. Unilateral hyperplasia has been thought to represent only 1% of PA,19,20 and determining whether the hyperplastic zona glomerulosa or nodules are actually responsible for aldosterone hypersecretion has been disputed. However, Shigematsu and colleagues19 demonstrated, by in situ hybridization and real-time polymerase chain reaction, that the hyperplastic zona glomerulosa cells rather than the adenoma cells demonstrated intense mRNA expression of steroidogenic enzymes necessary for production of aldosterone. Recently, a report by Novitsky and associates21 presented data on 15 patients with NSA, 60% of whom had normal abdominal imaging. Their outcomes were related to control of hypertension without postoperative aldosterone results, but they concluded that adrenalectomy for unilateral aldosterone hypersecretion by AVS provided cure or significant improved blood pressure control in a majority of patients.

In contradistinction to verification of a unilateral source of aldosterone hypersecretion by AVS, reports from Walz and colleagues22 and Tresallet and coworkers23 concluded that with imaging studies that demonstrate a clinically predominating nodule, approximately one-third of patients were cured of hypertension and the remaining had improved blood pressure control. Both studies involved approximately two-thirds of patients with APA and one-third with NSA. Tresallet and coworkers23 advised that only if CT scan findings were equivocal should AVS be undertaken. Any nodule of 1 cm or larger was sufficient to warrant adrenalectomy. The preoperative determination of APA versus NSA was not relevant; however, because his patients with NSA had a higher frequency of persistent hypertension, they would need to be warned. In the report by Walz and colleagues, only 10% of the patients in the hyperplasia cohort were normotensive without medication, and 20% remained hypertensive despite ongoing medical treatment.

Underscoring the importance of screening the hypertensive population for PA as well as evaluating those patients diagnosed with primary hyperaldosteronism for potential surgical cure are the recently understood implications of the target organ effects of chronically elevated serum aldosterone independent of blood pressure levels. Several studies over the past few years have linked PA to deleterious renal, cardiovascular, and metabolic effects as well as increased tissue damage, all independent of blood pressure.24 In 2005, Milliez and colleagues25 compared patients with both single adenoma and bilateral adrenal hyperplasia with controls with essential hypertension, looking at incidence of cardiovascular events independent of blood pressure levels. They found a significant increase in stroke, MI, and atrial fibrillation, all of which were increased in both subtypes of PA. This high prevalence of cardiovascular comorbidities in patients with PA was corroborated by a large cross-sectional study of 553 patients from the German Conn’s Registry.25 Moreover, patients with PA compared with those with essential hypertension showed dramatically higher cardiovascular disease risk with odds ratios of 4.93, 4.36, and 2.80 for sustained arrhythmias, cerebrovascular events, and coronary heart disease, respectively.26 The risks continue: more marked left ventricular hypertrophy, diastolic dysfunction, and alterations in left ventricular filling2; increased arterial stiffness27; and even increased synthesis of proinflammatory molecules and reactive oxygen species.28 Reversal of renal dysfunction owing to elevated aldosterone has been seen with surgical and medical treatment in patients with both APA and IHA according to animal and clinical studies.29 Suggested by some studies is an increase in insulin resistance and tendency to develop the metabolic syndrome, although there is conflicting evidence; further study in this area is needed to determine whether effects are truly independent of blood pressure.4 An observational study, however, did show an improvement in glucose tolerance after adrenalectomy over that seen with medical management in patients with PA,30 emphasizing the importance of evaluating possible surgical candidates. Additional evidence that aldosterone contributes to impairment in both insulin metabolic signaling and pancreatic beta-cell function31 supports the concept that aldosterone excess may factor into the development of the cardiometabolic syndrome. Besides its well-known role in causing hypertension in PA, aldosterone is linked to a multitude of deleterious effects contributing to cardiovascular and chronic kidney disease as well as the cardiometabolic syndrome, making it imperative to undertake adequate evaluation of hypertensive patients for PA and determination of potential surgical candidates for definitive cure.

Several studies addressing cure rates after unilateral adrenalectomy, regardless of subtype, have focused more on the resolution or improvement of hypertension as the final outcome to evaluate for cure.22,23 Although important, resolution of hypertension is an insufficient means by itself to assess cure of PA, given the multitude of other factors that may contribute to elevated blood pressure. Despite documented normalization of aldosterone levels, the majority of
patients will not be restored to a no-drug, normal blood pressure, even in patients with APA.\(^2\) Therefore, blood pressure alone cannot be used as the gold standard for determining cure. The definition of cure of PA is biochemical normalization of aldosterone levels. Complete normalization of blood pressure off all medications can act as a surrogate for cure. Therefore, we used the combination of these 2 criteria for cure in this study.

Considering limitations of this study, our 95% success rate in completing AVS is curiously both a major strength as well as a limitation. The aldosterone secretion data from AVS was a critical strength in defining the unilateral source but a limitation because this level of success is often not achieved in other centers, perhaps limiting its applicability. The Mayo Clinic is a referral center, which may have altered the overall patient population evaluated and treated. Excluded were those patients without sufficient proof of cure or recurrence of PA, which may be considered a limitation, although there were only 3 such patients excluded in the NSA group. Furthermore, 18 of the excluded patients, although they did not have documented cure of PA by our criteria, did show marked improvement in blood pressure control with a decrease in number of medications required. Although we did also exclude the very few patients with AVS ratios less than 3:1 who for various reasons underwent adrenalectomy, this is not necessarily a limitation because we are not recommending surgical intervention in such patients. Also, the likelihood of bilateral hyperplasia is higher in these patients; therefore, lack of normalization of aldosterone in these patients would not be unexpected. Finally, we do not have immunohistochemistry staining, aldosterone extraction data, or data from other methods that would define aldosterone secretion specifically from individual nodules or hyperplastic cortex from the adrenal glands of the patients with NSA. Therefore, we cannot establish multiple sites of excess aldosterone secretion within these adrenal glands, only that removal of these NSA adrenal glands resulted in cure of PA as we defined it in these patients. Moreover, whether development of additional nodules in the contralateral adrenal gland with recurrence of PA might eventually occur will require prolonged follow-up.

A major strength of the study was the extensive, relatively standard biochemical and imaging evaluation before the operation, ensuring the accuracy of the diagnosis. The pathology was well defined and thoroughly examined in all patients. The biochemical assessment of postoperative serum or urinary aldosterone levels or a normal PAC to PRA ratio was available in the majority of patients, and all of the remaining patients who were considered cured achieved a normal blood pressure off all antihypertensive medications.

**CONCLUSIONS**

We have not found a reliable method to detect preoperatively the presence of an NSA process; preoperative serum and urinary aldosterone concentrations, AVS ratios, and the number of blood pressure medications required for blood pressure control were not different than those in the APA group. Only in patients with confirmed PA who are being considered for surgical intervention, for whom a CT scan delineates a unilateral macroscopic nodule with a completely normal contralateral gland, would our preference be to proceed to unilateral adrenalectomy in a patient 40 years or younger (small likelihood of a nonfunctioning adrenal adenoma) without the addition of preoperative AVS. However, for the remaining patients with confirmed PA (>40 years or with questionable, bilateral abnormal, or normal CT findings), AVS provided a highly reliable method to predict unilateral aldosterone hypersecretion that can be uniformly cured with unilateral adrenalectomy. CT scan alone was again shown to be unreliable. Finally, total unilateral adrenalectomy is recommended based on results showing the inability to predict the presence of NSA with any current preoperative evaluation.

**Author Contributions**

Study conception and design: Quillo, Grant, Thompson, Young

Acquisition of data: Quillo, Grant, Thompson

Analysis and interpretation of data: Quillo, Grant, Thompson, Farley, Richards, Young

Drafting of manuscript: Quillo, Grant, Thompson, Farley, Richards, Young

Critical revision: Quillo, Grant, Thompson, Farley, Richards, Young

**REFERENCES**

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Discussion

INVITED DISCUSSANT: DR STEVEN DE JONG (Maywood, IL): This 15-year retrospective study examines and compares the cure rates of unilateral adrenalectomy for patients with multiple nodules or hyperplasia found on final histopathology with cure rates in patients found to have a single adenoma. Preoperative laboratories and imaging do not reliably identify or distinguish these patients, and the messages of the study are clear. Avoid partial adrenalectomy for this functional adrenal neoplasm because some single adenomas on CT may turn out to be multiple nodules or hyperplasia, and rely on preoperative adrenal venous sampling (AVS) as the most accurate tool for lateralization of excess aldosterone secretion to guarantee biochemical and clinical cure for these patients. I have the following questions.

First, it seems your findings advocate expanding the use of preoperative AVS in patients with primary hyperaldosteronism, yet it remains unnecessary in patients under 40 years of age with a single adenoma on CT, which, in this study, has limited predictive ability to identify multiple nodules or hyperplasia. How many patients in this analysis did not require or undergo preoperative AVS, and how has this study changed the criteria for and use of preoperative AVS at the Mayo Clinic?

Second, what do you expect to see in the early and late function of the contralateral remaining adrenal gland in patients with “non-single” adenomas causing hyperaldosteronism? Did this group require any immediate adrenal hormone supplementation?

Third, although preoperative laboratory and imaging data could not identify single versus “non-single” disease, did the time course of postoperative improvement in hypokalemia and hypertension differ between patients with single adenomas versus patients with unilateral multiple nodules or hyperplasia?

Finally, given the limited or lack of availability of adrenal scintigraphy and the variable technical success rates of AVS, are there future advancements in preoperative imaging that will accurately localize and lateralize excess aldosterone production in these patients?

DR CLIVE S GRANT (Rochester, MN): We have increasingly used and relied on AVS. Early in the series, we did not use it routinely; it has become almost the norm now. I don’t have the exact numbers, but as we have become comfortable and successful with it, and seen the value of it, it’s now almost routine.

The exception would be the relatively rare patient who is young,
perhaps less than 40, thereby with a low chance of having an adrenal incidentaloma, with more severe primary aldosteronism biologically (which is more typical of a single-adenoma patient) and a CT scan that just looks absolutely unequivocal for a single hypodense unilateral tumor with the opposite adrenal being completely normal. It’s in that pretty limited group of patients that we would go directly to the operating room rather than get venous sampling.

The main point is to avoid operating on a patient who has bilateral hyperplasia, as these patients should be treated medically. However, when AVS indicates unilateral aldosterone hypersecretion, even if we found more than one nodule in the affected adrenal, as this study points out, we should be curing that patient.

Regarding early and late function of the contralateral adrenal, there are 2 parts to that question. The first relates to the early postoperative function relative to aldosterone secretion. If the patient is prepared preoperatively with an aldosterone antagonist, such as spironolactone, the patient has an opportunity to restore his/her total body potassium, and postoperatively, the opposite adrenal gland takes over full function, usually without need for any medication.

If, on the other hand, there is no preoperative preparation, then a period of temporary replacement of potassium may be necessary. In fact, we have had patients who needed Florinef supplementation postoperatively for severe primary aldosteronism for a temporary period of time until the contralateral adrenal takes over normal aldosterone secretion. There has never been cortisol insufficiency.

The second part of that question relates to encountering unanticipated hyperplasia or multiple nodules in the resected adrenal, and what the likelihood is that the patient will eventually suffer relapse and redevelop primary aldosteronism from the other adrenal that is also nodular or hyperplastic. We have not seen that yet in this group of NSA patients. In contrast, 25 to 30 years ago, when either unilateral adrenalectomy or sometimes bilateral subtotal adrenalectomies were performed for bilateral idiopathic hyperplasia (before we knew that these patients were appropriately treated medically), those patients had neither biochemical cure nor resolution of their hypertension. We are reasonably confident that these non-single adenoma patients really do represent a unilateral process and will not have relapse in the future.

In answer to what is on the horizon that might give us an equally valuable answer as does AVS, we do not have a good alternative. We enjoy reasonably high success because we have an angiographer who, for years, has been practically the only one doing it at our institution. That’s not necessarily true across the country. We don’t use scintigraphy and haven’t for 2 decades or more. Unfortunately CT scan is not really not valuable at delineating this specific condition. For right now, we must rely on AVS.

DR THOMAS BIEHL (Seattle, WA): It seems that you are suggesting AVS on virtually every patient with hyperaldosteronism. But this is a challenging procedure, it’s expensive, and it’s not always diagnostic. Not only that, but it takes time, especially in a place like the Mayo Clinic, where patients are coming from far away. How often does the procedure really change your operative management, especially if you are going to do a unilateral complete adrenalectomy?

DR CLIVE S GRANT (Rochester, MN): We looked at that specifically with a previous study. Even in confirmed primary aldosteronism, CT scans may show normal adrenal glands, adrenal gland thickening, unilateral adenomas less than 1 cm, or bilateral nodules greater than 1 cm. In our earlier study of more than 200 primary aldosteronism patients, CT proved accurate in only 53%. On CT alone, 22% would have been excluded from a curative adrenalectomy, and another 25% might have undergone unnecessary or inappropriate adrenalectomy. A recent study from the NIH corroborated that CT scan was accurate in only about 50% of patients.

There are other studies, however, that suggest if a patient has a nodule on one side and no obvious nodule on the other side, adrenalectomy will be successful in about 80%.

DR THOMAS BIEHL (Seattle, WA): If you take all the patients who had adrenal sampling, how many times did you change your operative plan?

DR CLIVE S GRANT (Rochester, MN): I can’t recall exactly that specific number but it was substantial, 20% to 25%.

DR SAMUEL SNYDER (Temple, TX): Your results go a long way to alleviating a lot of fear postoperatively when we find multiple nodules in the adrenal gland that we just removed for primary aldosteronism. But the real crux of the matter is getting an accurate and reliable bilateral adrenal vein sampling; having trouble getting into the right adrenal vein is not uncommon. So my question is, do you have any tips for us to improve the results of getting that right adrenal vein sampling? And what do you do when you don’t have an adequate right adrenal vein sampling? Do you go back and repeat the study?

DR CLIVE S GRANT (Rochester, MN): What you need is to find an interventional radiologist, an angiographer who considers it a personal affront not to be successful. We have had that kind of person for more than two decades, and he’s had a 95% success rate. If he is unsuccessful, we redo it. With present catheter technology, strictly limiting this intervention to 1 or 2 of your angiographers is probably the best advice.

DR RICHARD A PRINZ (Chicago, IL): A number of patients were excluded from this study, including those who didn’t have follow-up, didn’t have biochemical data, or had failure. So how many failures do you have? And in that group, are there any who had what you would consider a technically successful venous sampling but a failed clinical outcome?

DR CLIVE S GRANT (Rochester, MN): The exclusions really relate to patients on whom we did not get postoperative aldosterone values and also did not have 100% cure of their hypertension off medications. Therefore, if we did not have an aldosterone level and they were not cured of hypertension, we did not know how to classify those patients regarding cure of their primary aldosteronism. There were a few patients on whom we just had no follow-up. The demographics of those patients were essentially identical to patients included in the study.

Is AVS absolutely always correct? No. I know of one patient on whom I operated who had lateralization, and we resected the adrenal nodule. But the aldosterone did not go down. I had actually performed only a partial adrenalectomy. We reoperated and took out the remaining remnant of that adrenal gland. Nevertheless, the patient’s blood pressure did not normalize, nor did the aldosterone. So even though AVS is highly effective and reliable, we have had a rare false positive.