Mineralocorticoids

Vascular Remodeling and Duration of Hypertension Predict Outcome of Adrenalectomy in Primary Aldosteronism Patients

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Abstract—Remodeling of the resistance arteries is a hallmark of arterial hypertension and predicts cardiovascular events, but it was unknown whether it could also predict the blood pressure response to adrenalectomy of patients with an aldosterone-producing adenoma. Therefore, we investigated the outcome of adrenalectomy as a function of vascular remodeling in the context of the preoperative features of aldosterone-producing adenoma patients. At 2 referral centers for hypertension, we prospectively measured the media:lumen ratio of small arteries from fat tissue of 50 consecutive aldosterone-producing adenoma patients treated with adrenalectomy. The blood pressure response to adrenalectomy was assessed by considering the blood pressure values and the number and dosages of antihypertensive medications. Adrenalectomy significantly (P<0.001) lowered plasma aldosterone (from 27.3±4.9 ng/dL to 8.3±11.2 ng/dL), the aldosterone:renin ratio (from 117±35 to 11±2), and blood pressure (from 163±22/98±2 mm Hg to 133±2/84±1 mm Hg), even despite a reduction (from 141±14 to 100±15; P=0.02) of the score of antihypertensive treatment. It provided cure of hypertension in 30% of the aldosterone-producing adenoma patients, normotension with less antihypertensive therapy in 52%, and improved blood pressure control in the rest. The media:lumen ratio and the known duration of hypertension significantly predicted the blood pressure response to adrenalectomy at univariate and multivariate analyses. Because a long duration of hypertension and/or the presence of vascular remodeling imply lower chances of blood pressure normalization at long-term follow-up postadrenalectomy, these findings emphasize the importance of an early diagnosis of aldosterone-producing adenoma. (Hypertension. 2008;51:1366-1371.)

Key Words: secondary hypertension ■ aldosterone ■ aldosteronism ■ adrenalectomy ■ outcome ■ vascular remodeling

Primary aldosteronism (PA) is far more common than usually perceived and is attributable to an aldosterone-producing adenoma (APA) in approximately half of the patients.1 Thus, it entails the most common endocrine form of secondary arterial hypertension (HT) that is curable by adrenalectomy in many patients.2

Identification of an APA, or unilateral primary adrenocortical hyperplasia,3 requires adrenal vein sampling (AVS) that, being minimally risky, should be reserved for patients who are candidates for adrenalectomy and, more importantly, can benefit from it.4 However, the identification of patients who will benefit more remains a challenging task, because the blood pressure (BP) response to adrenalectomy varies widely across patients. In fact, despite many efforts over the years, only age and lack of family history of HT were suggested to significantly predict the BP response.5–8 Nevertheless, the large uncertainties in the prediction estimates render them of little, if any,8 value on an individual basis.

The remodeling of resistance arteries is a hallmark of arterial HT and can be implicated in the excess cardiovascular damage associated with HT. Hence, it was shown to predict cardiovascular events independent of the major risk factors.9 It was also found to vary across secondary forms of HT in relation to activation of the renin-angiotensin system: an increased media:lumen ratio (M/L) with increased cross-sectional area of the media (hypertrophic remodeling) has been associated with an activated renin-angiotensin system in renovascular HT,10 whereas an increased M/L with an unchanged media cross-sectional area (eutrophic remodeling) was reported in PA,10 where the renin-angiotensin system is shut off. Moreover, vascular remodeling contributes to maintaining high BP values, even when the triggering mechanisms

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have vanished.11 Thus, we tested the hypothesis that, in APA patients, vascular remodeling predicts the BP outcome to adrenalectomy by measuring prospectively the M/L of resistance arteries and carefully assessing the outcome after adrenalectomy in the context of several other potentially relevant variables.

**Subjects and Methods**

We enrolled all of the consecutive consenting patients diagnosed with an APA who underwent adrenalectomy. The protocol of the study was approved by the institutional ethical committees and followed the requirements of the Declaration of Helsinki. The exclusion criteria comprised the patient’s refusal to participate in the study and the concomitance of major diseases, as diabetes mellitus, that might affect the M/L.12

**Diagnostic Tests and Criteria**

All of the patients underwent measurement of the aldosterone (nanograms per deciliter)/plasma renin activity (PRA; nanograms per milliliter per hour) ratio (ARR) and assessment of the Na⁺ intake by the 24-hour urine excretion, as described.1 The captopril and/or the saline infusion test were used as exclusion tests, as described.13 Before all of the tests, treatment with mineralocorticoid receptor antagonists was withdrawn for ≥6 weeks; other agents, such as diuretics, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin type 1 receptor blockers, were stopped ≥2 weeks before. A long-acting calcium channel blocker and/or doxazosin were allowed to minimize the risks of uncontrolled HT.1

The patients who were positive at these tests underwent a high resolution computed tomography and/or magnetic resonance for identification of adrenocortical nodules.4 Regardless of these results, they were submitted to AVS or NP99 scintigraphy to attain evidence for a lateralization of aldosterone secretion.4,14 Corticotropic stimulation was not systematically used during AVS because, albeit improving ascertainment of selectivity of catheterization, it did not, we also exploited use of the propensity score. This approach was found to be most useful for controlling for the effect of potentially significant covariates.16 We, therefore, created the propensity scores by using regression analysis and entering age, preadrenalectomy systolic and diastolic BP, body mass index, tumor diameter, and the overall score of ongoing antihypertensive treatment as independent variables in the model. The logistic regression analysis was then performed using the score of BP outcome as a dependent variable and the propensity score, the known duration of HT, and the M/L as covariates, with adjustment for duration of follow-up.

**Assessment of BP Outcome**

Recognizing the fact that patients often require antihypertensive treatment postadrenalectomy,5–8 a quantitative score that considered not only the number but also the dose of each antihypertensive agent was developed to assess the effect of adrenalectomy on BP. To this end, each antihypertensive drug was recorded; the dose prescribed was expressed as a percentage of the maximum recommended daily doses for that specific agent, and the percentage dose of all of the drugs was then summed up. A quantitative score of BP outcome was calculated by summing the absolute fall of systolic and diastolic BP and twice the change of the score of treatment.

A qualitative definition of outcome that considered cure and marked and mild improvement of HT was also seen, although they did not attain statistical significance. To obtain inferences about the effect of vascular remodeling and duration of HT on the BP outcome by effectively removing all of the bias in the background covariates, some of which were unbalanced between the groups that achieved normotension and the group that did not, we also exploited use of the propensity score. This approach was found to be most useful for controlling for the effect of potentially significant covariates.16 We, therefore, created the propensity scores by using regression analysis and entering age, preadrenalectomy systolic and diastolic BP, body mass index, tumor diameter, and the overall score of ongoing antihypertensive treatment as independent variables in the model. The logistic regression analysis was then performed using the score of BP outcome as a dependent variable and the propensity score, the known duration of HT, and the M/L as covariates, with adjustment for duration of follow-up.

**Results**

**Baseline Characteristics**

The anthropometric clinical and hormonal data of the APA patients overall and classified according to the BP outcome postadrenalectomy are shown in Tables 1 and 2, respectively. As anticipated by definition, baseline, the PAC and ARR were high, and PRA and serum K⁺ levels were low in all of the patients (Table 2); however, the mildly improved patients had high body mass index, systolic BP, and a longer known duration of HT than the cured patients. A stepwise increase in the preadrenalectomy, the left ventricular mass index, and treatment score from the cured to the mildly improved patients was also seen, although they did not attain statistical significance (Table 2).
Table 1. Baseline Anthropometric and Clinical Features of the 50 Patients With APA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men/women, n (%)</td>
<td>20/30 (40/60)</td>
</tr>
<tr>
<td>Age, mean±SEM, y</td>
<td>54.7±1.7</td>
</tr>
<tr>
<td>BMI, mean±SEM, kg/m²</td>
<td>27.2±0.7</td>
</tr>
<tr>
<td>Systolic BP, mean±SEM, mm Hg</td>
<td>162±3</td>
</tr>
<tr>
<td>Diastolic BP, mean±SEM, mm Hg</td>
<td>98±2</td>
</tr>
<tr>
<td>Serum K⁺, mean±SEM, mmol/L⁻¹</td>
<td>3.3±0.1</td>
</tr>
<tr>
<td>Left ventricular mass index, mean±SEM g/m²</td>
<td>121±4</td>
</tr>
<tr>
<td>Tumor size, mean±SEM, mm</td>
<td>17.0±1.0</td>
</tr>
<tr>
<td>Known duration of hypertension, median (range), mo</td>
<td>50 (1 to 491)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; K⁺, potassium level.

Effect of Adrenalectomy
Correction of the biochemical features of PA was consistent across groups, as evidenced by a fall in plasma aldosterone and the ARR and an increase of PRA and serum K⁺ levels (Table 3). A highly significant decrease of both systolic and diastolic BPs was seen, notwithstanding a significant tapering of the antihypertensive treatment. Considering the BP outcome, 29.5% of the APA patients were cured, 53% were markedly improved, and 18.2% showed a mild improvement. There were no significant differences of duration of follow-up among the patients who were cured (984±403 days), those who were markedly improved (885±264 days), and those who were mildly improved (493±156 days).

Arterial Remodeling
The result of the in vitro measurements in the arteries obtained ex vivo showed a eutrophic type of arterial remodeling (Table 2) when compared with those obtained in a series of control normotensive patients (data not shown). A stepwise increase of arteriolar media thickness, M/L ratio, and cross-sectional area of the media from the cured to the mildly improved patients was noticed; however, statistical significance was achieved only for the latter variable.

Predictors of Outcome of Adrenalectomy
The variables that did not show any significant collinearity could be examined in a multivariate logistic regression model in the context of background variables and after adjustment for the duration of follow-up. Only the M/L and the known duration of HT remained in this model, along with the propensity score. Overall, these 3 covariates allowed a correct prediction of achievement of normotension in 93% of the patients (Table 4).

The M/L and the known duration of HT were useful predictors of achievement of normotension also at the univariate ROC analysis: the AUC for both variables was significantly (P<0.005) greater than that under the identity line (Figure). The AUC under the M/L (0.827±0.082) was slightly higher than that under the known duration of HT (0.785±0.096), but the comparison between the ROC curves

Table 2. Preadrenalectomy Variables in the 3 Different Outcome Groups of APA Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cured</td>
</tr>
<tr>
<td></td>
<td>Markedly Improved</td>
</tr>
<tr>
<td></td>
<td>Mildly Improved</td>
</tr>
<tr>
<td></td>
<td>P vs Cured</td>
</tr>
<tr>
<td>Age, mean±SEM, y</td>
<td>50.5±3.4</td>
</tr>
<tr>
<td>Sex, men/women, %</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, mean±SEM, kg/m²</td>
<td>24.8±1.2</td>
</tr>
<tr>
<td>Systolic BP, mean±SEM, mm Hg</td>
<td>151±6</td>
</tr>
<tr>
<td>Diastolic BP, mean±SEM, mm Hg</td>
<td>95±3</td>
</tr>
<tr>
<td>Serum K⁺, mean±SEM, mmol/L⁻¹</td>
<td>3.2±0.3</td>
</tr>
<tr>
<td>ARR, mean±SEM, (ng/dL⁻¹)·(ng/mL/h)⁻¹</td>
<td>151.0±38.0</td>
</tr>
<tr>
<td>Tumor size, mean±SEM, mm</td>
<td>19.0±2.0</td>
</tr>
<tr>
<td>Known duration of HT, mean±SEM, mo</td>
<td>31.0±11.0</td>
</tr>
<tr>
<td>Treatment score, mean±SEM</td>
<td>110.0±24.0</td>
</tr>
<tr>
<td>Left ventricular mass index, mean±SEM, g/m²</td>
<td>112±8</td>
</tr>
<tr>
<td>Arterioles media thickness, mean±SEM, μm</td>
<td>23.4±2.4</td>
</tr>
<tr>
<td>Mean arterioles cross-sectional area, mean±SEM, μm²</td>
<td>22 057±3357</td>
</tr>
<tr>
<td>Arterioles M/L ratio, mean±SEM, %</td>
<td>9.57±0.78</td>
</tr>
</tbody>
</table>

K⁺ indicates potassium level. Normal values for PAC are 0.8 to 15.0 ng/dL⁻¹; PRA: 0.51 to 2.64 ng/mL·h⁻¹; ARR: <26 on 100 to 300 mEq Na⁺ per day⁻¹.
of the M/L and the known duration of HT in terms of BP outcome prediction showed no significant differences (Figure part A). A cutoff value of 9.12% for the M/L provided a sensitivity of 64% and a specificity of 100%, for the identification of the achievement of normotension postadrenalectomy. Likewise, a cutoff value of 38 months for the known duration of HT furnished the best trade-off of sensibility (49%) and specificity (100%; Figure part B and part C).

**Discussion**

The first finding of our study was that practically all of the APA patients showed correction of the biochemical features of PA postadrenalectomy. This observation accords with our long-standing experience in a larger cohort of APA patients and with available, albeit not all, previous reports. Thus, cure of hyperaldosteronism can be consistently achieved when the diagnosis of APA is corroborated by the demonstration of a lateralized aldosterone excess.

The second result entailed the demonstration that normotension can also be obtained postadrenalectomy in the vast majority of the APA patients, eg, ~82%, notwithstanding the tapering (in 52%) or the withdrawal (in ~30%) of the antihypertensive treatment. Even in the few (18%) not achieving normotension, a prominent decrease of both systolic and diastolic BP values was observed (Table 3). These results are striking considering that primary (essential) HT involves as many as 38% of the patients with an APA,22 thus, suggesting that cure or a prominent BP could theoretically occur in no more than 62% of the patients with documented APA,7 and many of our patients had a long-known history of HT, which might have been associated with target organ damage in the kidney and vasculature, thus contributing to persistent HT despite removal of the triggering mechanism.

This clear-cut effect of adrenalectomy on BP in a series of APA patients who were carefully diagnosed preoperatively is consistent with previous reports: an improvement of HT was observed (in up to 99% of the patients, and cure rates ranging between 33% and 82% were reported,5,6,8,23–25 as well as with the documented remarkable regression of left ventricular hypertrophy.26,27 It can also resolve previous controversies on the BP effect of adrenalectomy that might have risen from hypokalemia,28 or as a categorical outcome. For both of these independent variables, which were not intercorrelated, the AUC ROC was significantly greater than under the identity line (Figure part A). We also found that an M/L >9.12% and a known duration of HT >38 months provided the best combination of sensitivity and specificity for predicting the achievement of normotension postadrenalectomy (Figure part B and part C).

**Clinical Relevance**

It has been claimed that the BP response to adrenalectomy can be disappointing,28 particularly in older patients with APA, thus leading some to argue that clinicians should not bother to waste time in the attempt to identify the adrenal pathology underlying PA.28 The present results document instead that the biochemical picture of PA was corrected in all of the patients, thus eliminating the risks associated with severe hypokalemia, and a fall in BP could be obtained in practically all of the patients, with achievement of normal BP values in 82% of them, according to strict criteria.

It might be argued that, if adrenalectomy is so effective, why should one worry to develop strategies to predict its outcome on BP?5–8 There are, however, several circumstances where this can be relevant, as in the patients who are...
Identification of 93% of the patients who will be normotensive or will remain hypertensive after surgery. Moreover, the possibility of accurately predicting the outcome of adrenalectomy is important not only for choosing the most appropriate therapeutic strategy but also for selecting the patients for AVS. The latter is necessary to identify the surgically curable forms of PA, but because of costs and risks, should be reserved for PA patients who are candidates for adrenalectomy and are likely to benefit from it. The fact that noninvasive techniques are being made available for assessing vascular remodeling lends further support to the clinical relevance of the present results.

**Limitations and Strengths of the Study**

Exhaustive information on family history of HT in first-degree relatives could be obtained only in a proportion of the patients. Therefore, we could not confirm the usefulness of this variable as a predictor of BP normalization.

Myogenic response is a pressure-induced vasoconstriction that plays a key role in blood flow autoregulation and in the stabilization of capillary pressure. Hence, a failure to autoregulate blood flow efficiently might lead to increased high BP flow to target organs, effecting downstream damage. An impaired myogenic response can also lead to increased wall stress, thus triggering a hypertrophic microvascular remodeling, as shown in diabetic patients. It would, therefore, be interesting to determine the myogenic tone in the blood vessels, which could be expected to be deranged in those PA patients who can be more exposed to target organ damage and only get mild improvement postadrenalectomy. Unfortunately, because the myogenic tone can be assessed only by perfusion/pressure myography and not by wire myography, we could not collect enough data to address this hypothesis.

Although 50 APA patients with exhaustive follow-up data are an accomplishment, the limited size of this study suggests caution in drawing conclusions. Nonetheless, the tight criteria used to diagnose APA, the completeness of information on predictors and follow-up, and the accurate measurement of quantitative variables as the duration of HT and vascular M/L ratio are the major strengths of this study.

**Conclusions and Perspectives**

Unilateral adrenalectomy for APA resolves HT in ≈82% of patients, even when the HT is so severe as to require preoperative use of multiple antihypertensive agents, particularly when the known duration of HT does not exceed 38 months and the M/L ratio of small resistance arteries does not exceed 9.12%. The identification of the M/L of resistance arteries and the known duration of HT as predictors of outcome postadrenalectomy can allow an accurate estimate of the probability of achieving an optimal BP control with surgery. It is likely that measurement of the M/L ratio, which can be crucial for selecting the patients for AVS with the aim of identifying a surgically curable subtype of PA, will be feasible in the near future, with noninvasive techniques applied to the retinal arteries, as shown recently. Moreover, the fact that a long known duration of HT and the presence of vascular remodeling predicted a worse BP outcome emphasizes, in our view, the crucial importance of an early diagnosis of APA.
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Disclosures
None.

References
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