Primary aldosteronism (PA), the most common endocrine cause of curable arterial hypertension, is usually attributed to aldosterone-producing adenoma (APA) and, less commonly, to unilateral or bilateral adrenal hyperplasia. The former two conditions are characterized by lateralized aldosterone secretion and are best treated by adrenalectomy, whereas the latter, featuring bilateral aldosterone excess, requires lifelong antihypertensive therapy on the basis of mineralocorticoid receptor antagonists.

Discrimination between unilateral aldosterone excess and bilateral adrenal hyperplasia is feasible with NP59 scintigraphy or adrenal vein sampling (AVS). Because NP59 has a low sensitivity and is not generally available, AVS is currently considered the gold diagnostic standard for identifying the surgically curable forms of PA.

However, interpretation of AVS results requires attention to several issues and particularly to the criteria to be used for assessing selectivity and establishing the lateralization of aldosterone excess. With regard to selectivity, experience has shown that selective catheterization can be consistently achieved on the left side, whereas on the right side the success rate is lower. The difficulty of selectively cannulating the right adrenal vein, is due to its brevity and direct draining into the inferior vena cava (IVC), while the training and experience of the operator do not seem to fully account for this lower success rate.

Because, on the right side, the adrenal vein often shares egress in the IVC with accessory hepatic veins, we hypothesized that the dilution of adrenal vein blood with blood draining from the liver, which carries a low cortisol concentration, might account for the lower success rate of catheterization on this side. However, there was no information on how common accessory hepatic veins are and on their impact on the selectivity of an AVS index. Therefore, this study was designed to prospectively investigate these questions.

**Patients and Methods**

The patients to be submitted to AVS were selected among those with a diagnosis of PA, as described previously, who had no contraindications to general anesthesia and surgery. They were asked to sign a written consent to undergo not only AVS but also laparoscopic adrenalectomy in case a lateralized aldosterone secretion was eventually identified.

**Abstract**—Adrenal vein sampling is the gold standard for identification of surgically curable primary aldosteronism, but its accuracy might be hindered by blood dilution from accessory vein blood. We prospectively investigated the presence of accessory veins draining into adrenal veins and their effect on the selectivity index (SI) in 74 consecutive patients undergoing adrenal vein sampling. On the right side, the venous anatomic pattern could be conclusively determined in 91.8% of the cases: we detected hepatic accessory veins in 12.1%, no accessory veins in 42.4%, and renal capsular veins in 45.5%. On the left side there was a phrenico-adrenal trunk in 89.4% and renal capsular accessory veins in 10.6% of the cases. On both sides, renal capsular and phrenic accessory veins did not affect the SI. At variance, on the right side, hepatic accessory veins were associated with SI values ∼3-fold lower than that found when such accessory veins were absent (median: 3.10 [range: 0.80 to 84.2] versus median: 1.10 [range: 0.70 to 2.20]; P=0.01). However, superselective adrenal catheterization resulted into higher SI values (median: 23.88; range: 4.80 to 84.20) in these cases. Thus, hepatic accessory veins sharing egress into the inferior vena cava with the right adrenal vein occurred in ∼12% of the patients and imply a low SI, likely because of adrenal blood dilution by hepatic blood carrying a low cortisol concentration. In the presence of this anatomic variation, superselective catheterization of the right adrenal vein should be undertaken to determine the lateralization of aldosterone secretion. (Hypertension. 2009;54:885-889.)

**Key Words:** adrenal vein sampling ■ aldosterone ■ aldosteronism ■ adrenocorticophic hormone ■ catheterization
Before planning AVS, a 64-slice multislice computed tomography scan with 2- or 3-mm examination and 3D reconstruction was performed to identify adrenocortical nodules, identify the right adrenal vein drainage in the IVC, and exclude major anatomic variations. Two months before the scheduled date of AVS, the patients were put on a normal (100 to 300 mEq/d) Na\(^+\) intake; \(\geq6\) weeks before the test, they were asked to stop treatment with mineralocorticoid receptor antagonists, because these agents can stimulate aldosterone secretion to a greater extent from the unaffected than from the APA side, at least in the considerable proportion of APAs that are unresponsive to angiotensin II.\(^\text{1,10}\) Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, \(\beta\)-blockers, and direct vasodilators was also withdrawn \(\geq2\) weeks before AVS.\(^\text{1}\) When necessary, a nifedipine gastrointestinal therapeutic system and/or doxazosin were allowed to control blood pressure, because these agents negligibly affect the plasma aldosterone and cortisol secretion rates under the study conditions.\(^\text{1}\) To avoid the blunting of aldosterone secretion, hypokalemia, if present, was systematically corrected before AVS with oral or intravenous potassium ion supplementation.\(^\text{1}\)

AVS and Assessment of Accessory Adrenal Veins

Bilateral simultaneous AVS was performed by the same experienced interventional radiologist (D.M.), as reported.\(^\text{7,11}\) The procedure was carried out between 8:00 AM and 12:00 PM to minimize effect attributed to circadian variations of cortisol and aldosterone, after a 3-hour rest in the supine position. To cannulate the right adrenal vein, which is technically more difficult than the left one because the central vein is short, tiny (2 to 3 mm in caliber), and drains directly into the posterior wall of the IVC, we more commonly used a Simmons 1 (5- to 6-F) catheter (Cordis) and less frequently a Cobra 2 (C2) or a Cobra 1 (C1) catheter (Cordis), all with a side hole at 2 mm from the tip to facilitate blood collection. On the left side, the venous anatomy shows minimal variations: there are no hepatic accessory veins, and the adrenal vein joins \(\geq1\) inferior phrenic vein, giving origin to the phrenico-adrenal trunk, which drains into the left renal vein. Moreover, the central adrenal vein can communicate with some renal capsular veins. On this side, we used a Simmons 2 or 3 (5- to 6-F) catheter or, less often, a C2 catheter. To evaluate the adequacy of the catheterization and the presence of accessory veins draining into the adrenal veins, a small amount, usually \(<3\) mL, of ionic contrast material (37 g/dL of Iopamidolo, Iopamiro 370, Bracco) was used. Injection was performed very gently manually, under fluoroscopic control, to minimize the risk of rupture of small intraglandular veins. The patterns of adrenal vein drainage were identified at phlebography and coded as follows: on both sides, the failure to achieve selective catheterization was coded as 0; the lack of accessory veins was coded as 1. On the right side, the presence of accessory hepatic veins was coded as 2, accessory renal capsular veins as 3, and accessory phrenic veins as 4. On the left side, the presence of accessory phrenic plus renal capsular veins was coded as 3 and a phrenico-adrenal trunk as 4. The coding was performed blindly from the patient’s hormonal data and clinical outcome; its accuracy by independent observers was determined by the \(\tau\) statistics. After placing a catheter in each adrenal vein, blood for the measurement of plasma aldosterone (PAC) and cortisol concentration (PCC) was simultaneously collected from both sides by gravity or, if necessary, gentle negative pressure. Immediately after withdrawing the catheter tip from the right adrenal vein, blood was obtained from the IVC. AVS was repeated with identical procedures after stimulation with adrenocorticotropic hormone with different doses as described\(^\text{6,8}\); however, for the purpose of this study, only the baseline data were used. Aldosterone and Cortisol Measurement

PAC and PCC were measured with radioimmunoassay as described\(^\text{1}\); the intra-assay and interassay coefficients of variation of our assay for PAC and PCC were both \(<5.6\%\), and the cross-reactivity of the antibody for aldosterone for the other adrenal steroids was \(<0.001\%\).

AVS-Derived Indices

The selectivity index (SI) was calculated as follows: \(\text{PCC}_{\text{side}}/\text{PCC}_{\text{IVC}}\), where \(\text{PCC}_{\text{side}}\) and \(\text{PCC}_{\text{IVC}}\) are the PCC in adrenal vein blood and in the IVC, respectively. The lateralization index was calculated as follows: \(\text{PAC}_{\text{dominant}}/\text{PCC}_{\text{dominant}}/\text{PAC}_{\text{nondominant}}/\text{PCC}_{\text{nondominant}}\), where \(\text{PAC}_{\text{dominant}}\) and \(\text{PCC}_{\text{dominant}}\) are PACs on the side with higher and lower aldosterone secretion, respectively, and \(\text{PCC}_{\text{nondominant}}\) are PCCs on the side with higher and lower aldosterone secretion, respectively. Adrenal blood sampling was considered bilaterally selective when the SI on both sides was \(>1.1\). A lateralization index \(\geq2.0\) was considered indicative of lateralized aldosterone excess secretion, as described.\(^\text{5,7}\)

Diagnosis of APA

The diagnosis of APA required all of the following criteria: (1) biochemical evidence of PA; (2) lateralization of aldosterone secretion at AVS (see above); (3) adenoma at pathology; and (4) demonstration of normokalemia and cure, or improvement, of hypertension at follow-up, \(\geq120\) days after adrenalectomy.\(^\text{1}\) Cure was defined as a systolic blood pressure \(<140\) mm Hg and/or a diastolic blood pressure \(<90\) mm Hg without medications; improvement as a systolic and/or a diastolic blood pressure \(<140/90\) mm Hg, respectively, on the same and/or reduced number of daily doses of antihypertensive medication. Patients with biochemical evidence of PA, but without conclusive evidence for a lateralized aldosterone excess on the basis of previously published criteria,\(^\text{5,7,8,11}\) were presumed to have IHA.

Statistical Analysis

Results are expressed as mean\(\pm\)SEM or median and interquartile range, when appropriate. For serum potassium ion, plasma renin activity and PAC data were log transformed to attain a Gaussian distribution, as verified by the Kolmogorov-Smirnov test. Baseline and postadrenalectomy values were compared with a paired \(t\) test, except for serum potassium ion, which required a Wilcoxon non-parametric test. For comparison of the SI across different adrenal vein patterns, 1-way ANOVA, followed by Bonferroni post hoc test, was used. A \(P<0.05\) (2-sided) was considered statistically significant; analysis was performed with SPSS for Windows statistical package (version 17.0, SPSS).

Results

Patients and Diagnosis

Between June 2003 and January 2009, we performed AVS in 74 consecutive white patients without any complications. Of these patients, 53 (71.6%) had an APA by the aforementioned criteria, and 21 (28.4%) had bilateral adrenal hyperplasia. The main anthropometric data of the patients are shown in the Table.

Identification of Adrenal Vein Patterns

At phlebography, the catheterization was judged to be inadequate for the assessment of the venous drainage pattern in 6.8% of the cases on the right side and in 1.4% of the cases on the left side. Therefore, the analysis of the anatomic vein pattern was limited to 91.8% of the cases. Overall, these cases did not differ significantly from the whole cohort in terms of anthropometric and clinical features. To test the concordance of 2 radiologists in independently establishing the adrenal vein pattern, we calculated the Kendall \(\tau\), which gave a value of 0.98 (\(P<0.001\)), indicating that the methodology used allowed for accurate assessment of
The anatomic variation of adrenal vein drainage with negligible between-observer variability.

The distribution of the type of venous pattern on the right and left sides is shown in Figure 1: on the right side we detected no accessory veins in 42.4% (n=28) and hepatic and renal capsular accessory veins in 12.1% (n=8) and 45.5% (n=30), respectively; no phrenic accessory veins were detected on this side. On the left side, the central vein joined inferior phrenic vein (phrenico-adrenal trunk) in 89.4%, whereas renal capsular accessory veins were seen in 10.6% (n=7); no cases of an isolated left adrenal vein were detected.

Effect of Adrenal Vein Patterns and Accessory Vein Number and Caliber on Selectivity

Figure 2 shows the SI value as a function of the venous drainage pattern on the right side. There were significant differences in SI across venous patterns, because the presence of accessory hepatic veins implied significantly lower values of the SI as compared with the other patterns (median: 1.10 [range: 0.70 to 2.20] versus median: 3.10 [range: 0.80 to 84.2]; P=0.01). On the left side, no significant differences across different venous drainage patterns were found (capsular accessory veins: median: 3.1 [range: 1.4 to 4.8]; phrenico-adrenal trunk: median: 3.7 [range: 1.0 to 109.3]). At variance, we could detect no significant effect of the number and caliber of these accessory veins on the SI (data not shown).

Superselective Catheterization of the Right Adrenal Vein in Patients With Hepatic Accessory Veins

After an ad interim evaluation of results, we decided to undertake superselective catheterization of the right adrenal vein in the patients with hepatic accessory veins. This approach furnished values of the SI that were significantly higher (median: 23.88 [range: 4.80 to 84.20]) than those obtained without superselective catheterization and not dissimilar from, or even higher than, those attained from patients without accessory hepatic veins (Figure 2). Figure 3 shows the different position of the catheter tip in the case of nonselective and superselective catheterization of the right adrenal vein sharing egress with hepatic accessory veins.

Discussion

Despite the importance of AVS for identifying the surgically curable subtypes of PA, the impact of adrenal vein anatomic variations on AVS results has never been assessed thus far. This study shows that the type of adrenal accessory veins has a significant impact on the diagnostic performance of AVS, albeit with marked differences between sides. On the left side, successful selective catheterization was almost the rule, likely because of the greater length of the left adrenal vein and its drainage into the left renal vein. Moreover, on this side, the occurrence of accessory veins, regardless of their type, had no significant effect on the SI. Thus, dilution of adrenal vein blood with systemic venous blood (from phrenic and renal capsular veins) does not affect the adrenal vein-to-IVC cortisol gradient, likely because this blood does not carry adrenocortical hormones at a concentration much lower than that in adrenal vein blood.

Table. Clinical Features of the Patients With PA Who Underwent AVS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Summary Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51±12</td>
</tr>
<tr>
<td>Sex, male:female, n (%)</td>
<td>37:37 (50/50)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>160±17</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>96±13</td>
</tr>
<tr>
<td>K⁺, mEq/L</td>
<td>3.36 (2.66 to 4.06)</td>
</tr>
<tr>
<td>s-Aldosterone, ng/dL</td>
<td>22.9 (11.3 to 33.0)</td>
</tr>
<tr>
<td>s-PRA, ng/mL per h</td>
<td>0.43 (0.20 to 1.07)</td>
</tr>
<tr>
<td>s-ARR, ng/dL-ng/mL per h⁻¹</td>
<td>52.8 (25.0 to 158.0)</td>
</tr>
</tbody>
</table>

K⁺ indicates serum potassium level; s-aaldosterone, supine plasma aldosterone; s-PRA, supine plasma renin activity; s-ARR, supine aldosterone/renin (PRA) ratio. Normal values are as follows: s-aaldosterone, 0.8 to 15.0 ng/dL; s-PRA, 0.51 to 2.64 ng/mL per h; s-ARR, <25.86.

*Data are mean±SD, except for K⁺, s-aaldosterone, and s-PRA, where median (range) are shown.
presence of hepatic accessory veins on the right side can inadequate catheterization of a right adrenal vein sharing egress with hepatic accessory veins in 888/1000 of the cases. Moreover and of note, the occurrence of these veins implied significantly lower values of the SI (Figure 2), which would indicate nonselective catheterization, even when the tip of the catheter was shown to be placed inside the adrenal vein at phlebography.

By contrast, on the right side we found that the adrenal vein shares egress in the IVC with accessory hepatic veins in ≤12% of the cases. Moreover and of note, the occurrence of these veins implied significantly lower values of the SI (Figure 2), which would indicate nonselective catheterization, even when the tip of the catheter was shown to be placed inside the adrenal vein at phlebography.

This observation might explain why AVS was judged previously to be selective on the right side, on the basis of the values of the SI, in only ≈85% to 90% of the cases, even at most experienced centers.12,13 More importantly, because bilaterally selective AVS studies are held to be necessary for diagnostic use of this test,5,6,13 this finding suggests that the presence of hepatic accessory veins on the right side can preclude the use of AVS results to determine lateralization of aldosterone excess in many cases.

Mechanisms of the Low SI With Accessory Hepatic Veins
The following explanations can be offered for the association of a low SI with hepatic accessory veins. Samples collected from the adrenal vein draining into hepatic veins compose an admixture of blood with a high cortisol (and aldosterone) concentration draining the adrenal gland with blood coming from the liver. Because of hepatic metabolism of steroids, the latter blood carries a cortisol concentration much lower than systemic and adrenal blood, resulting in a significant decrease of cortisol gradient, and thereby of the SI, between the adrenal vein and the IVC.

At least 3 lines of evidence support this contention. First, on both sides, the occurrence of accessory veins that carry systemic venous blood, other than the hepatic veins, had no effect on the SI. Second, in the patients with hepatic accessory veins, superselective catheterization of the right adrenal vein (Figure 3) resulted in values of the SI similar to, or even higher than, those attained from patients without hepatic accessory veins (Figure 2). Third, in our experience, blood samples obtained from the hepatic accessory veins showed a cortisol concentration that was much lower than that detectable in systemic vein blood from the same patients (data not shown).

Of note, the fact that superselective catheterization increased the SI by 5-fold (Figure 2) indicates that a large decrease in cortisol levels takes place between venules close to the adrenocortical cells and veins at the ostium into the vena cava, thus depending on the position of the catheter tip. This is why, in our view, when estimating selectivity, the absolute PCC concentration is meaningless, and the SI should be used instead.

Practical Implications and Limitations of the Study
This study provides further evidence and a rationale as to why high values of the SI cannot conceivably be expected on the right side. Hence, use of tight cutoffs for assessing selectivity, at least when AVS is performed under unstimulated conditions,8 would result in discarding many AVS data from diagnostic use. Conversely, the adoption of less restrictive cutoffs for the SI can permit the use of >90% of the studies for diagnostic purposes, as previously shown.7

In addition, in the presence of hepatic accessory veins, attempts to achieve superselective catheterization of the right adrenal vein should systematically be undertaken, because they can provide much higher selectivity and, therefore, a better diagnostic accuracy. The importance of this should be emphasized, because its adoption can furnish SI values far above the 1.1 cutoff, which corresponds to a concentration gradient that is close to the level of variability of the cortisol assay.

Conclusions
This study shows that the right adrenal vein shares drainage with hepatic accessory veins in ≤12% of the patients and that
blood sampling from this common vein drainage implies values of the SI similar to those obtained with unselective AVS studies. Therefore, identification of such accessory veins at phlebography indicates the need to undertake superselective catheterization, which was feasible with a simple rotation and withdrawal of the catheters and usually required only a few seconds to diagnose lateralized aldosterone excess.

**Perspectives**

Future research should be aimed at developing reliable imaging techniques for identifying right adrenal vein anatomic variation before and during AVS to allow superselective catheterization of the adrenal vein whenever a hepatic accessory vein is identified. The use of C-arm computed tomography\(^1\) can be a promising strategy in this direction. Moreover, improved shape of the catheter’s tip might contribute to increase the success rate of AVS on the right side. Finally, the impact of hepatic accessory veins with or without superselective catheterization needs to be determined in a series of patients undergoing AVS much larger than the present series.

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**Disclosures**

None.

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