Impact of Accessory Hepatic Veins on Adrenal Vein Sampling for Identification of Surgically Curable Primary Aldosteronism

Diego Miotto, Renzo De Toni, Gisella Pitter, Teresa Maria Seccia, Raffaella Motta, Matteo Vincenzi, Gianpietro Feltrin, Gian Paolo Rossi

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: 0.70 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 ▪ adrenocorticotrophic hormone ▪ catheterization

P

rimary 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 in 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.
Before planning AVS, a 64-slice multisectored 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; ≥6 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. Treatment with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, β-blockers, and direct vasodilators was also withdrawn ≥2 weeks before AVS. 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. To avoid the blunting of aldosterone secretion, hypokalemia, if present, was systematically corrected before AVS with oral or intravenous doses as described; however, for the purpose of this study, only the SI on both sides was ≥1.1. A lateralization index ≥2.0 was considered indicative of lateralized aldosterone excess secretion, as described.

**AVS-Derived Indices**

The selectivity index (SI) was calculated as follows: PACside/ PCCside, where PACside and PCCside are the PAC in adren al vein blood and in the IVC, respectively. The lateralization index was calculated as follows: PACdominant/PACnondominant, where PACdominant and PACnondominant are PACs on the side with higher and lower aldosterone secretion, respectively, and PCCdominant and PCCnondominant 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 ≥2.0 was considered indicative of lateralized aldosterone excess secretion, as described.

**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, ≥120 days after adrenalectomy. 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, were assumed to have IHA.

**Statistical Analysis**

Results are expressed as mean±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 τ, 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 the 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-aldosterone, supine plasma aldosterone; s-PRA, supine plasma renin activity; s-ARR, supine aldosterone/renin (PRA) ratio. Normal values are as follows: s-aldosterone, 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-aldosterone, and s-PRA, where median (range) are shown.

![Figure 1. Percentage distribution of different types of venous drainage on the right (A) and left (B) and the corresponding aspect at phlebography.](http://hyper.ahajournals.org/)

**Figure 1.** Percentage distribution of different types of venous drainage on the right (A) and left (B) and the corresponding aspect at phlebography.
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 vein and adrenal vein 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 access-
ory 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 detect-
able 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 condi-
tions, 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.

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 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.

Sources of Funding
The studies herein described were supported by research grants from the Foundation for Advanced Research in Hypertension and Cardiovascular Diseases, the University of Padua, and the Società Italiana dell’Ipertensione Arteriosa.

Disclosures
None.

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Hypertension. 2009;54:885-889; originally published online August 17, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.134759

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