Primary Aldosteronism

Clinical Management and Outcomes of Adrenal Hemorrhage Following Adrenal Vein Sampling in Primary Aldosteronism

Silvia Monticone,* Fumitoshi Satoh,* Anna S. Dietz, Remi Goupi, Katharina Lang, Francesca Pizzolo, Richard D. Gordon, Ryo Morimoto, Martin Reincke, Michael Stowasser,* Paolo Mulatero*

Abstract—Aldosterone-producing adenoma and bilateral adrenal hyperplasia account for >90% of all primary aldosteronism cases. Distinguishing between bilateral and unilateral disease is of fundamental importance because it allows targeted therapy. Adrenal vein sampling (AVS) is the only reliable means to preoperatively differentiate between unilateral and bilateral subtypes. A rare but serious complication of AVS is an adrenal hemorrhage (AH). We retrospectively examined in detail 24 cases of AH during AVS in 6 different referral hypertension centers. AH more often affected the right adrenal (n=18) than the left (n=5, P<0.001); 1 bilateral. Median duration of experience of the radiologist in AVS at the time of AH was 5.0 years (0.6–7.8) and AH occurred with both highly experienced (>10 years) and less experienced radiologists. Of 9 patients who suffered AH in the gland contralateral to an aldosterone-producing adenoma and who underwent complete (n=6) or partial (n=3) unilateral adrenalectomy, only one required long-term corticosteroid replacement for adrenal insufficiency. No reduction in blood pressure or biochemical resolution of primary aldosteronism occurred in any of those patients who experienced AH in the gland ipsilateral to an aldosterone-producing adenoma (n=6) or who had bilateral adrenal hyperplasia (n=9). No patient required invasive treatments to control bleeding or blood transfusion. In conclusion, AH usually has a positive outcome causing either no or minor effects on adrenal function, and AVS should remain the best approach to primary aldosteronism subtype differentiation. (Hypertension. 2016;67:146-152. DOI: 10.1161/HYPERTENSIONAHA.115.06305.) * Online Data Supplement

Key Words: adrenal hemorrhage ■ adrenal vein sampling ■ aldosterone-producing adenoma ■ bilateral adrenal hyperplasia ■ primary aldosteronism

S tudies both in vivo and in vitro have demonstrated that aldosterone plays a detrimental role on the cardiovascular system, and patients affected by primary aldosteronism (PA) have an increased rate of cardio- and cerebrovascular complications compared with essential hypertensives with a similar blood pressure levels.1,2 In light of these considerations, the early identification of PA is crucial to enable targeted treatment to reverse the excess of organ damage in affected patients. As detailed by the Endocrine Society3 and by the Japanese Endocrine Society Guidelines,4 optimal management of PA patients is dependent on the differentiation between aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia (BAH), the 2 most common subtypes of sporadic PA.

Adrenal computed tomography (CT) scanning with contrast and fine cuts is recommended in all confirmed PA patients to rule out malignancy (aldosterone-producing adrenocortical carcinoma), but it is otherwise unreliable for subtype differentiation because it lacks both sensitivity and specificity. In particular, microadenomas (<1 cm in diameter) can be overlooked, and it is not possible to distinguish between nonsecreting incidentalomas and APAs by adrenal CT scanning alone.5

Adrenal vein sampling (AVS) is a demanding procedure consisting of the selective cannulation of the adrenal veins to identify the source of aldosterone overproduction. It was first described in the 1960s as a technique to localize APAs preoperatively,6 but its inherent invasiveness, lack of standardized criteria for interpretation of the hormonal results, and the reported high complication rates at that time were major factors in hindering its employment in the clinical management of PA. A complication of AVS is adrenal hemorrhage (AH), secondary to adrenal vein rupture or, less frequently, to dissection, infarction, or thrombosis.7

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Historically, complication rates ranged between 5% and 10% and were reportedly associated with complete and permanent destruction of the gland. More recent studies, however, report a substantially lower rate of complications of between 0.2 and 0.9%. In part, this is likely to be related to the advent of CT for the imaging of adrenal lesions and the consequent abandonment of the practice of retrograde adrenal venography, which required injection of a relatively large amount of contrast under considerable pressure, and was associated with an increased risk of AH. Interestingly, a recent observational, retrospective, multicenter study demonstrated that the rate of adrenal vein rupture was not predicted by the method of cannulation, but rather by the experience of the radiologist, that is, the number of AVS performed by each radiologist.

Despite an impressive number of studies comparing the performances of imaging techniques and AVS in the subtype differentiation of PA, a systematic study on AH has never been performed, and uncertainties in the clinical management of this complication still remain. The aim of this study was to describe the clinical presentation, management, and outcome of 24 AH cases, collected from 6 different tertiary referral hypertension centers, to help clinicians decide whether to use AVS in their PA patients.

Materials and Methods

Patient Selection

We retrospectively evaluated 24 cases of AH after AVS that occurred in 6 tertiary referral hypertension centers in Italy (Torino, 1994 to January 2015, 427 AVS; Verona, 2000–2014, 31 AVS), Germany (Munich, December 2009 to January 2015, 255 AVS; Wuerzburg December 2009 to January 2015, 69 AVS), Japan (Sendai, April 2007 to December 2014, 640 AVS), and Australia (Brisbane, 1990–2014, 1446 AVS).

The control group comprised 1388 PA patients who underwent AVS in the different centers participating in the study during a similar period of time as when the patients experienced AH during AVS (Table S1 in the online-only Data Supplement).

The diagnosis of PA was made according to the Endocrine Society and the Japanese Endocrine Society Guidelines. Confirmatory testing and synacthen test were performed as detailed elsewhere.

All patients included in the analysis gave written informed consent, and approval from the local ethics committees was obtained for the use of these retrospective data. The study adheres to the principles of the Declaration of Helsinki and to institutional guidelines.

An expanded methods section is given in the online-only Data Supplement.

Statistical Analyses

IBM SPSS Statistics 19 (SPSS INC, Chicago, IL) was used for statistical analyses. Data are presented as mean±standard error or median (25th–75th percentile). Data were analyzed with the Kolmogorov–Smirnov and Shapiro–Wilk tests to determine their distributions. Statistical significance between groups was calculated in normally distributed data by the Kruskal–Wallis test, using Bonferroni corrections for multiple comparisons. The χ2 test of the Fisher exact test was used for qualitative variables. A probability value of <0.05 was considered statistically significant.

Results

General Description of the Cases

We retrospectively identified 24 cases of AH that occurred during AVS in 6 different referral hypertension centers in Italy, Germany, Japan, and Australia. Clinical and biochemical characteristics (before and after AVS) of the patients included in the study are summarized in Tables 1 and 2.

In our series, AH was more frequent in the right adrenal (n=18) than in the left (n=5, P<0.001), and in one case, AH was bilateral. In one case (MU-01), the patient was referred for super-selective AVS because of bilateral nodules at adrenal CT scanning but lack of lateralization at previous, nonselective AVS. Hemorrhage occurred during the catheterization of side branches of the right adrenal vein. AVS showed highest aldosterone/cortisol ratios in a vein draining the lateral limb of the right adrenal which bore an adenoma. In another case of right AH (BR-1), for the AVS procedure, gadolinium was used instead of iodinated contrast because of concerns about contrast allergy.

CT scanning of a patient (TO-01) with right AH and left APA is shown in Figure.

Patients experiencing AH were older than patients who underwent uncomplicated AVS procedures. None of the other assessed clinical or biochemical and hormonal parameters were significantly different between the AH and the controls (Table S1). Of the 24 patients included in the study, 2 were taking aspirin 100 mg/d (MU-01 and MU-03), one of whom was also under treatment with enoxaparin 0.4 mg (MU-03); of note, the percentage of patients on aspirin was not significantly different from the percentage of total PA patients receiving aspirin treatment within the Torino unit; data not shown); no other patients were receiving medications that are likely to have affected coagulation or platelet aggregation, thereby facilitating the occurrence of AH. In our series, there were no significant comorbidities other than diabetes mellitus in 1 patient (BR-10) and polymyalgia rheumatica treated with steroids in another (MU-03).

According to AVS results, the final diagnosis was BAH in 9 patients, left APA in 8 patients, and right APA in 7 patients. In 2 patients (BR-7 and SE-03), the first AVS was not diagnostic: in BR-7, the right adrenal vein was not cannulated, and in SE-03, the AVS was stopped after the occurrence of adrenal vein rupture. Repeated AVS revealed a final diagnosis of BAH in SE-03 and left APA in BR-7.

The median duration of experience of the radiologist in AVS at the occurrence of the AH was 5.0 years (0.6–7.8, 25th–75th percentile) and, at the time of AH, 33% (8/24) of the radiologists performed <10 AVS/y, whereas 67% (16/24) performed >10 AVS/y.

In all but 2 patients, the occurrence of AH required hospitalization or a prolongation of hospital stay compared with noncomplicated procedures for an average of 1.9±1.3 days. Overall, 54% (13/24) of the patients required the administration of a strong opioid (morphine, pethidine, piritramide, and fentanyl) for efficient pain management, 8% required the administration of a weak opioid (codeine and tramadol), whereas 38% (9/24) required no analgesic medications. After the diagnosis of AH, adrenal CT was performed in 16 patients, one of whom also underwent 131I-nor cholesterol adrenal scintigraphy, to evaluate the residual activity of the affected adrenal gland. In 8 patients, imaging was not performed. In our series, none of the patients required invasive treatments to control bleeding or blood transfusion because of anaemia.
Final Diagnosis of Unilateral PA, AH Contralateral to the Adenoma

Of the 15 patients displaying unilateral disease, AH occurred in the contralateral side to the adenoma in 9 cases. None of the 9 patients with AH contralateral to the side of lateralization showed BP reduction after the occurrence of the AH. Three of these 9 patients underwent nodulectomy and 6 underwent total laparoscopic adrenalectomy. In all patients who underwent total adrenalectomy and had AH contralateral to the adenoma, adrenal function was tested to rule out adrenal insufficiency. Plasma cortisol at 8:00 AM was within the normal range (5–25 mg/dL) in all patients; rapid synacthen test was normal in 5 of the 6 tested patients (normal values >500 nmol/L, 18.1 μg/dL). In 2 patients (with right AH, BR-01 and BR-10) left adrenalectomy was performed under hydrocortisone cover. In the immediate postoperative period, patient BR-10 received ongoing treatment with dexamethasone while undergoing a short synacthen test (which showed a blunted response from <35 to 83 nmol/L) followed by a long synacthen test (0900 h cortisol levels basally and daily for 2 days after commencement of intramuscular depot tetracosactrin, 1 mg 12 hourly). Because the latter demonstrated a definite (albeit modest) cortisol response (from <35 to 306 nmol/L by day 1 and 271 nmol/L by day 2), dexamethasone was gradually withdrawn, but an adrenal crisis occurred after subsequent shoulder surgery, and the patient was, therefore, commenced (and remains) on cortisol and fludrocortisone supplementation. In patient BR-01, the test was performed 5 days after adrenalectomy and demonstrated a subnormal response (from 303 to 484 nmol/L), and he, therefore, remained on glucocorticoid supplementation with plans for repeat testing in 6 weeks’ time. Adrenal function was also assessed in all patients who underwent nodulectomy (n=3; in 1 case, WU-01, the tests were performed and reported as normal, but hormonal values were not available) and was found to be normal in each case (in BR-11, short synacthen test 1 month after adrenalectomy showed a partially blunted response after 60 minutes; the test was repeated 4 months later and showed an adequate response). In one patient (TO-01), 131I-nor cholesterol adrenal scintigraphy performed without dexamethasone suppression demonstrated a focus of tracer uptake by the right adrenal in agreement with residual right adrenal cortex function (Figure S1): this patient had a normal synacthen test after nodulectomy. Of the 3 patients who underwent nodulectomy,
2 became normotensive without any antihypertensive medication and 1 displayed significant improvement of hypertension (normotensive on irbesartan 150 mg/d, before adrenalectomy, SBP 180 mmHg and DBP 100 mmHg on 3 anti-hypertensive medications). Of the 6 patients who underwent total unilateral adrenalectomy, 1 displayed long-term adrenal insufficiency (BR-10) but BR-01, who demonstrated a blunted cortisol response to synacthen in the early postoperative period, requires repeat testing to assess whether normal adrenal function has returned (adrenalectomy performed in March 2015).

Table 2. Outcome Parameters After Adrenal Hemorrhage

<table>
<thead>
<tr>
<th>Patients</th>
<th>Hospitalization Requirement (days)</th>
<th>Drugs for Pain Control</th>
<th>Follow-Up Imaging</th>
<th>Adrenalectomy</th>
<th>Same Side/CL Side</th>
<th>SBP/DBP (no of classes of drugs) after AVS/ADX</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR-01</td>
<td>Yes (1)</td>
<td>Morphine s/c, paracetamol</td>
<td>CT scan</td>
<td>Yes</td>
<td>CL side</td>
<td>182/116 (3)</td>
</tr>
<tr>
<td>BR-02</td>
<td>Yes (2)</td>
<td>Pethidine, paracetamol</td>
<td>CT scan</td>
<td>No</td>
<td>NA</td>
<td>160/80 (4)</td>
</tr>
<tr>
<td>BR-03</td>
<td>Yes (3)</td>
<td>Pethidine, omnopon</td>
<td>CT scan</td>
<td>Yes</td>
<td>Same side</td>
<td>156/110 (1)</td>
</tr>
<tr>
<td>BR-04</td>
<td>Yes (1)</td>
<td>Pethidine</td>
<td>CT scan</td>
<td>No</td>
<td>NA</td>
<td>160/80 (1)</td>
</tr>
<tr>
<td>BR-05</td>
<td>Yes (2)</td>
<td>Morphine s/c, paracetamol</td>
<td>CT scan</td>
<td>No</td>
<td>NA</td>
<td>192/96 (5)</td>
</tr>
<tr>
<td>BR-06</td>
<td>No</td>
<td>Pethidine, paracetamol</td>
<td>None</td>
<td>No</td>
<td>NA</td>
<td>130/68 (2)</td>
</tr>
<tr>
<td>BR-07</td>
<td>No</td>
<td>None</td>
<td>None*</td>
<td>Yes</td>
<td>Same side</td>
<td>164/88 (2)</td>
</tr>
<tr>
<td>BR-08</td>
<td>Yes (1)</td>
<td>Pethidine, paracetamol</td>
<td>CT scan</td>
<td>Yes</td>
<td>Same side</td>
<td>124/84 (0)</td>
</tr>
<tr>
<td>BR-09</td>
<td>Yes (1)</td>
<td>Pethidine, paracetamol</td>
<td>CT scan</td>
<td>No</td>
<td>NA</td>
<td>157/94 (3)</td>
</tr>
<tr>
<td>BR-10</td>
<td>Yes (5)</td>
<td>Codeine, paracetamol</td>
<td>CT scan</td>
<td>Yes</td>
<td>CL side</td>
<td>134/78 (0)</td>
</tr>
<tr>
<td>BR-11</td>
<td>Yes (2)</td>
<td>Paracetamol, pethidine</td>
<td>CT scan</td>
<td>No (nodulectomy)</td>
<td>CL side</td>
<td>140/80 (0)</td>
</tr>
<tr>
<td>BR-12</td>
<td>Yes (3)</td>
<td>Paracetamol, pethidine</td>
<td>CT scan</td>
<td>Yes</td>
<td>CL side</td>
<td>128/85 (0)</td>
</tr>
<tr>
<td>MU-01</td>
<td>Yes (1)</td>
<td>Metamizol</td>
<td>None</td>
<td>No (nodulectomy)</td>
<td>Same side</td>
<td>113/76 (0)</td>
</tr>
<tr>
<td>MU-02</td>
<td>Yes (1)</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>Same side</td>
<td>130/85 (0)</td>
</tr>
<tr>
<td>MU-03</td>
<td>Yes (3)</td>
<td>Paracetamol</td>
<td>CT scan</td>
<td>No</td>
<td>NA</td>
<td>145/65 (3)</td>
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<tr>
<td>MU-04</td>
<td>Yes (3)</td>
<td>Piritramid</td>
<td>CT scan</td>
<td>Yes</td>
<td>Same side</td>
<td>152/96 (4)</td>
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<tr>
<td>WU-01</td>
<td>Yes (4)</td>
<td>Phetidine, fentanyl</td>
<td>CT scan</td>
<td>No (nodulectomy)</td>
<td>CL side</td>
<td>140/85 (0)</td>
</tr>
<tr>
<td>SE-01</td>
<td>Yes (1)</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>CL side</td>
<td>127/78 (0)</td>
</tr>
<tr>
<td>SE-02</td>
<td>Yes (1)</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>CL side</td>
<td>122/79 (0)</td>
</tr>
<tr>
<td>SE-03</td>
<td>Yes (1)</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>NA</td>
<td>117/70 (3)</td>
</tr>
<tr>
<td>SE-04</td>
<td>Yes (1)</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>CL side</td>
<td>126/82 (1)</td>
</tr>
<tr>
<td>SE-05</td>
<td>Yes (1)</td>
<td>None</td>
<td>CT scan</td>
<td>No</td>
<td>NA</td>
<td>120/68 (2)</td>
</tr>
<tr>
<td>TO-01</td>
<td>Yes (3)</td>
<td>Morphine, paracetamol</td>
<td>CT scan</td>
<td>No (nodulectomy)</td>
<td>CL side</td>
<td>135/85 (0)</td>
</tr>
<tr>
<td>VE-01</td>
<td>Yes (4)</td>
<td>Tramadol</td>
<td>CT and Scinti scan</td>
<td>No</td>
<td>NA</td>
<td>120/80 (1)</td>
</tr>
</tbody>
</table>

All 1.9±1.3

ADX indicates adrenalectomy; AVS, adrenal vein sampling; CT, computed tomography; DBP, diastolic blood pressure; NA, not applicable; and SBP, systolic blood pressure.

*Minor asymptomatic extravasation of contrast was seen at the time of AVS, and further imaging was not considered clinically indicated.

Figure. Computed tomography (CT) scan just after adrenal vein sampling (AVS) in patient TO-01. A, Left adrenal gland with a discrete 1-cm-diameter nodule at the lateral gland limb (arrow). B, Right suprarenal space is almost completely filled by an oval hematoma (arrow head). Two different cuts are shown because adrenal glands were situated in on different CT planes.
Four patients were cured of PA and hypertension, 1 displayed significant amelioration of blood pressure levels and biochemical cure of PA, and 1 was operated only in March 2015 and has not been fully reevaluated after the operation.

**Final Diagnosis of Unilateral PA, AH Ipsilateral to the Adenoma**

Of the 15 patients displaying unilateral disease, AH occurred in the side of the adenoma in 6 cases. According to the historical reports indicating permanent adrenal dysfunction after AH, we would have expected that AH in the side of the adenoma to have resulted in cure of PA without further treatment. However, in our series, none of the patients displayed cure of PA or improvement of hypertension after AH, and all patients, therefore, still required unilateral adrenalectomy. Consistently, aldosterone levels did not change significantly after the AH but before the adrenalectomy in the 4 out of 6 patients who had the hormone tested (Table S2). The occurrence of the AH was confirmed in all cases by histology report, clearly showing presence of recent bleeding in both the tumor and the adjacent adrenal tissue. None of these patients had evidence of adrenal insufficiency, as expected.

**Final Diagnosis of BAH**

In a recent report, hypertension was improved in 14 of 40 patients with BAH who underwent unilateral adrenalectomy. We analyzed the post-AVS parameters of the 9 BAH patients who experienced unilateral AH. Of note, none of the patients displayed any degree of blood pressure reduction or amelioration of PA or improvement of adrenal function after AH and all patients, therefore, still required unilateral adrenalectomy. Consistently, aldosterone levels did not change significantly after the AH but before the adrenalectomy in the 4 out of 6 patients who had the hormone tested (Table S2). The occurrence of the AH was confirmed in all cases by histology report, clearly showing presence of recent bleeding in both the tumor and the adjacent adrenal tissue. None of these patients had evidence of adrenal insufficiency, as expected.

**Discussion**

The diagnosis of PA is a 3-step process (screening, confirmation, and subtype differentiation), and AVS is recognized by the Endocrine Society and Japanese Endocrine Society Guidelines as the gold standard test to distinguish between unilateral and bilateral disease. It is a demanding interventional procedure where the adrenal veins are accessed through a femoral vein approach and cannulated to identify the source of aldosterone overproduction. The left adrenal vein almost always drains into the left renal vein, and it is, therefore, usually relatively easy to cannulate. On the contrary, the right adrenal vein is small, drains directly into the inferior vena cava, and it is, therefore, more difficult to cannulate. Moreover, despite significant efforts toward standardization, AVS protocols and interpretation of hormone results vary widely across centers.

Adrenal vein rupture and subsequent AH represent the most serious complication of AVS. Despite being now widely recognized that the prevalence of AH is not as high as suggested by historical reports, the clinical outcomes of this complication have never been systematically investigated, and evidence on the subsequent optimal management is still lacking.

In this study, we collected 24 cases of AH through 6 different referral hypertension centers in Italy, Germany, Japan, and Australia and retrospectively investigated the clinical management and the outcomes in terms of hospital stay, need for medications/interventional procedure, and the rate of complete and permanent destruction of the affected adrenals. Interestingly, as suggested by historical reports, we observed that AH occurred more frequently in the right adrenal vein, suggesting that the anatomy, unfavorable for cannulation, can at least partially account for this difference. In addition, the higher number of attempts necessary to cannulate the right adrenal vein may have contributed to the higher rate of AH. Overall, abdominal pain was the most common symptom associated with the occurrence of AH and required treatment with strong opioids in the majority of the patients. Follow-up imaging was performed in most patients, mainly by CT scanning. Only in one case was functional evaluation by adrenal scintiscan performed. In this patient, the uptake of the tracer in the adrenal containing the AH demonstrated that the complication did not result in loss of functional activity of the gland.

A recent observational retrospective multicenter study showed that the rate of adrenal vein rupture was inversely correlated with the number of procedures performed by each radiologist and directly with the number of AVS procedures performed per center. However, in our series, AH occurred with both experienced radiologists (>5 years of experience and >10 procedures/y) and inexperienced ones, consistent with experience of the operating being not the only important factor associated with the occurrence of AH.

It should be noted that in 2 patients with AH, AVS was successfully and uneventfully repeated without complication, showing that a previous AH does not necessary exclude the feasibility of a subsequent AVS.

The most important finding of this study is represented by the outcome data regarding the residual function of the affected adrenal. In our series of 24 AH, only one patient, after removal of the adrenal contralateral to the AH, displayed signs and symptoms of adrenal insufficiency, requiring long-term therapy with replacement doses of hydrocortisone. In another case operated in March 2015, the synacthen test was slightly suboptimal, and the patient will be subsequently reevaluated by repeat testing. These findings show that the functional activity of the adrenals after the hemorrhage is in most cases not markedly impaired by this complication. In agreement with these findings, we did not observe a blood pressure reduction after the AH when the event involved the adrenal bearing the APA or in BAH patients.

In clinical practice, when the AH involves the contralateral adrenal to an APA, the clinician may be concerned about the residual adrenal function of the affected adrenal gland and, hence, whether corticosteroid replacement will be required perioperatively and long term after unilateral adrenalectomy. One option is to perform an adrenal-sparing nodulectomy to save part of the functioning cortex surrounding the APA. However, this surgical option has the potential disadvantage of PA persisting if the removed nodule was not the sole source of excessive aldosterone production. In fact, aldosterone production outside the main nodule of the removed adrenal was observed in immunohistochemistry studies using specific antibodies for CYP11B2. To overcome this disadvantage, super-selective segmental adrenal vein branches AVS would be required. However, this technique is highly demanding and is only available in few specialized centers.
to performing short synacthen testing postoperatively, preoperative testing for residual adrenal function in the gland bearing the AH by performing adrenal scintiscan using 131I-Nor cholesterol without dexamethasone suppression could be considered. This procedure has been suggested previously and successfully undertaken in one of our patients (TO-01) before contralateral adrenalectomy to the AH. Furthermore, the identification of the anatomy of right adrenal vein by contrast-enhanced multidetector CT before AVS may be helpful to shorten the time required for AVS performance, thereby reducing the AH risk. Finally, in some selected cases in which the clinical, radiological, and biochemical information point strongly toward unilateral APA, a case for avoiding AVS could be made.

The main limitation of the present study is the retrospective nature of data collection; therefore, the evaluation of patients’ outcome after the AH was not standardized.

In conclusion, to the best of our knowledge, this represents the first study undertaken primarily to explore the management and the outcomes of AH occurring during AVS. AH, despite being the most dreaded complication of AVS, usually has a positive outcome causing minor or no permanent effects on adrenal function and should not discourage clinicians from using AVS to correctly diagnose the PA subtype.

Perspectives
A wealth of studies clearly demonstrated that PA is the most frequent cause of secondary hypertension. AVS is the only reliable way of differentiating unilateral PA forms from bilateral forms that benefit from adrenalectomy from bilateral forms that are treated pharmacologically. AVS is currently performed in few referral centers: one of the obstacles to the wide acceptance of this technique is the invasive nature of the procedure that in some cases is complicated by AH. In the present study, this rare complication usually had a positive outcome in terms of adrenal function. Therefore, AVS should be offered to all PA patients considered for unilateral adrenalectomy.

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Disclosures
None.

References


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**Novelty and Significance**

**What Is New?**

- Adrenal hemorrhage (AH) after adrenal vein sampling in primary aldosteronism is a rare event and is more frequent in the right adrenal than in the left and in older patients.
- None of the patients affected by AH on the side of the adenoma displayed cure of primary aldosteronism or improvement of hypertension after AH.
- The occurrence of AH required hospitalization or a prolongation of hospitalization compared with uncomplicated procedures and required treatment with strong opioid for efficient pain management in the majority of patients.
- Only one patient, after removal of the adrenal contralateral to the AH, displayed signs and symptoms of adrenal insufficiency, requiring long-term therapy with replacement doses of hydrocortisone.

**What Is Relevant?**

- AH usually has a positive outcome causing either none or only minor permanent effects on adrenal function. Therefore, adrenal vein sampling should remain the favored approach to primary aldosteronism subtype differentiation.

**Summary**

AH is a rare complication of adrenal vein sampling for subtype diagnosis of primary aldosteronism and usually is followed by a favorable outcome in terms of adrenal function.
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Clinical management and outcomes of adrenal haemorrhage following adrenal vein sampling in primary aldosteronism.


* and ** equal contribution

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Short title: Adrenal haemorrhage in primary aldosteronism

Key words: primary aldosteronism, adrenal vein sampling, aldosterone-producing adenoma, bilateral adrenal hyperplasia, adrenal hemorrhage

Abbreviations: PA: primary aldosteronism; EH: essential hypertension; AVS: adrenal vein sampling; APA: aldosterone producing adenoma; BAH: bilateral adrenal hyperplasia; AH: adrenal hemorrhage.

Supplemental Methods

The diagnosis of adrenal haemorrhage was suspected by relentless pain during and after the procedure and confirmed by fluoroscopic evidence of adrenal gland or retroperitoneal haemorrhage or by computed tomography/magnetic resonance. The diagnosis of PA was made according to the Endocrine Society and the Japanese Endocrine Society Guidelines (3,4). In particular, interfering medications were withdrawn at least 4 weeks prior to testing and the aldosterone to renin ratio (ARR) was used as a screening test. The diagnosis of PA was confirmed using fludrocortisone suppression testing, the intra-venous saline loading test or the captopril challenge test, as detailed elsewhere (13, 14). All patients with a confirmed diagnosis of PA underwent adrenal CT scanning or MRI and AVS for subtype differentiation. AVS was performed under basal conditions in all units, while in one AVS was performed both under basal conditions and after intravenous bolus injection of cosyntropin (0.25 mg). In all centers, AVS was performed using sequential catheterization of the adrenal veins.

To evaluate the presence of adrenal insufficiency, synacthen (tetracosactide) stimulated (0.25 mg iv) peak serum cortisol <500 nmol/L (18.1 mcg/dL) was considered diagnostic of adrenal insufficiency (15). One patient (TO-01) underwent adrenal cortical scintigraphy with $^{131}$I-nor cholesterol (NP59) without dexamethasone suppression to evaluate the functional activity of the adrenals.

All patients included in the analysis gave written informed consent and approval from the local ethics committees was obtained for the use of these retrospective data. The study adhere to the

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AH cases (n=24)</th>
<th>AVS control group (n=1388)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57±10</td>
<td>51±11</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/17</td>
<td>638/750</td>
<td>0.12</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>154±20</td>
<td>155±22</td>
<td>0.73</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>89±12</td>
<td>94±13</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum aldosterone (ng/dL)</td>
<td>18.3 [15.3-29.0]</td>
<td>23.1 [15.5-34.3]</td>
<td>0.13</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>0.2 [0.10-0.48]</td>
<td>0.3 [0.10-0.47]</td>
<td>0.37</td>
</tr>
<tr>
<td>Renin (ng/L)</td>
<td>1.2 [1.0-3.7]</td>
<td>2.54 [1.26-5.39]</td>
<td>0.16</td>
</tr>
<tr>
<td>Anti-hypertensive medications (n°)</td>
<td>2.0 [1.0-3.0]</td>
<td>2.0 [1.0-3.0]</td>
<td>0.4</td>
</tr>
<tr>
<td>Plasma K⁺ (mmol/L)</td>
<td>3.49±0.56</td>
<td>3.55±0.50</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**Supplemental Table S1.** Preoperative clinical and biochemical parameters of AH cases and the randomly selected control group. SBP = systolic blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Aldosterone at diagnosis (ng/dL)</th>
<th>Aldosterone after AH but before adrenalectomy (ng/dL)</th>
<th>Aldosterone (ng/dL) after adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MU-02</td>
<td>29.4</td>
<td>21.1</td>
<td>7.4</td>
</tr>
<tr>
<td>BR-03</td>
<td>18.7</td>
<td>18.6</td>
<td>1.5</td>
</tr>
<tr>
<td>BR-07</td>
<td>15.1</td>
<td>24.6</td>
<td>7.4</td>
</tr>
<tr>
<td>BR-08</td>
<td>29.7</td>
<td>32.6</td>
<td>&lt;2.5</td>
</tr>
</tbody>
</table>

**Supplemental Table S2.** Hormonal parameters of patients with AH on the same side of the APA, after the AH but before adrenalectomy.

MU-01 and MU-04 data are not available.
Supplemental Figure S1.
NP-59 scanning after AVS in patient TO-01, posterior view. A focal uptake of $^{131}$I- iodomethyl-norcholesterol is seen at level of the right adrenal gland, suggesting residual viable cortical adrenal tissue.