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VASCULAR-INTERVENTIONAL

# Simultaneous bilateral adrenal vein sampling for primary aldosteronism: useful tips to make it simple and safe

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## Abstract

Adrenal vein sampling (AVS) is the key test for subtyping patients with primary aldosteronism (PA) before referring those with unilateral disease for laparoscopic unilateral adrenalectomy. However, it is still not systematically used, despite guidelines recommendations, because it is still considered as an invasive, risky, and challenging procedure. Simultaneous bilateral catheterization is believed to add technical difficulties inherent with attempting to catheterize both adrenal veins at the same time, but can be useful to minimize differences between the sides due to timing. We herein report on the protocol for routine clinical use. Tips for preparation of the patient as well as optimal catheterization of adrenal veins and sampling are provided to propose a protocol that is easy, safe, and reliable.

### Key Points

- *Adrenal vein sampling is the reference standard in the case of primary aldosteronism to detect the hyper-functioning side and allow subsequent treatment.*
- *Simultaneous bilateral adrenal vein sampling avoids bias related to sampling timing.*
- *Some technical suggestions concerning patient preparation and catheterization are proposed to make simultaneous adrenal vein sampling easier and safer*

**Keywords** Adrenal vein sampling · AVS · Bilaterally simultaneous AVS · Interventional radiology · Primary aldosteronism

### Abbreviations

| | |
|---|---|
| ACTH | Adrenocorticotropic hormone |
| APA | Aldosterone-producing adenoma |
| AVS | Adrenal vein sampling |
| PA | Primary aldosteronism |
| PCC | Plasma cortisol concentration |

## Main text

Primary aldosteronism (PA) is highly prevalent among patients with drug-resistant hypertension [1] and derives from unilateral overproduction of the hormone aldosterone-producing adenoma (APA) or unilateral adrenal hyperplasia, or from bilateral causes like bilateral adrenal hyperplasia also known as idiopathic hyperaldosteronism.

To distinguish between these causes and to guide treatments, the Endocrine Society Guidelines advocate the use of adrenal vein sampling (AVS) [2], a procedure that should be performed only in patients with biochemically confirmed PA and who are reasonable candidates for general anesthesia and surgery. AVS allows the sampling of blood from adrenal veins via catheters with the aim of determining if the autonomous hormone production is unilateral or bilateral.

APA or unilateral autonomous adrenal hyperplasia can be cured with adrenalectomy, while bilateral nodular adrenal hyperplasia does not benefit from surgery. However, this is still controversial. As shown in a recent large survey, some major referral centers do not use AVS, considering that it is a risky and invasive procedure [3]. In addition, simultaneous catheterization [4, 5], which was introduced to minimize the differences related to timing [6], is considered technically difficult.

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In our tertiary center, we perform about 45 AVS examinations per year, and we have developed a simple, safe, and efficient technique.

### Necessity of an appropriate patient selection and preparation

A preliminary adrenal CT scan is recommended by the Endocrine Society guidelines before planning AVS, to exclude an adrenocortical carcinoma and evaluate the anatomy of adrenal veins including the presence of possible anatomical variants [7–13].

We routinely perform a venous phase CT acquisition 60″ after contrast medium injection with a slice thickness of 2 mm and coronal reconstruction for optimal visualization of adrenal veins.

The left adrenal vein exits the gland anteriorly and usually drains into the left renal vein forming a common trunk with the inferior phrenic vein; its variants include two adrenal veins or an adreal vein separate from the inferior phrenic vein. The right adrenal vein is short and exits the gland medially to enter the inferior vena cava (IVC); its variants include one central vein with multiple significant accessory veins or an adrenal vein that drains into the hepatic vein [14].

In the case of anatomical variants, different catheters could be necessary (see below), to carry out a superselective catheterization of the adrenal vein [15].

We perform the procedure early in the morning, to minimize the bias due to the circadian rhythm of aldosterone, and we instruct the patient to remain supine for the previous 3 h to avoid creating artificial gradients between sides due to standing up stimulation including during the transfer to the angiographic room and the positioning of the patient on the operating bed. For this purpose, the patient is moved with a slide sheet.

In addition, correction of hypokalemia during the week before AVS and fasting in the previous 6 h are required.

## Bilaterally simultaneous AVS

### Access

The right groin is preferred for venous access using the Seldinger technique after local anesthesia.

In order to avoid creating artificial gradients between the adrenal glands, given the pulsatile secretion of aldosterone [6, 16], bilaterally simultaneous AVS is performed through double right femoral venous access: the first puncture is done under ultrasound guidance, while the second one is carried out under fluoroscopic guidance in parallel and within half a centimeter cranially and medially from the first.

To proceed safely, we place two introducer sheaths: a 5-French introducer will be used for the right side, and a 6-French introducer will accommodate the catheter for the left adrenal vein (Fig. 1). Such calibers are necessary to collect samples by gravity (see below).

### Catheters

We use 5-French Simmons catheters, SIM 1 with end hole and two side holes close to the tip for the right adrenal vein, and SIM 2 for the left adrenal vein. Alternative catheters can be C1 or C2 cobra or shepherd hook for right adrenal vein and SIM 3 for left adrenal vein, e.g.

The evaluation of the CT images may help to identify possible anatomical variants and to choose different catheters (Fig. 2).

### Catheterization

The catheter for the left adrenal vein is positioned first, reforming the catheter tip in the right heart atrium or in the left iliac vein. One should look at the inferior phrenic-adrenal trunk on the left side of the IVC, slowly dragging the catheter downwards in the left renal vein and opacifying gently with small amounts of contrast medium. When the catheter tip fits somewhere, its correct positioning can be verified by very gentle manual injection of contrast medium and place the catheter tip upstream of the inferior phrenic vein orifice.

Please note that the inner caliber of the introducer (6 Fr) is a little larger than the outer caliber of the catheter (5 Fr), which allows collection of IVC blood from the introducer (see below).

Subsequently, the catheter for the right adrenal vein is introduced. The right adrenal vein generally flows into IVC posteriorly and is more challenging to detect. When the IVC is large, slightly widening manually the distal curve of the catheter can help to catheterize the vein.

### Sample collection

We routinely obtain two samples [17], the second of which after 15 min; a third sample could be obtained if pharmacological stimulation with cosyntropin is performed. This increases cortisol secretion, and thereby facilitates the ascertainment of success in achieving bilateral selectivity. However, it lowers the relative aldosterone secretion index [18] and thereby the lateralization index [19] which is why we do not use it.

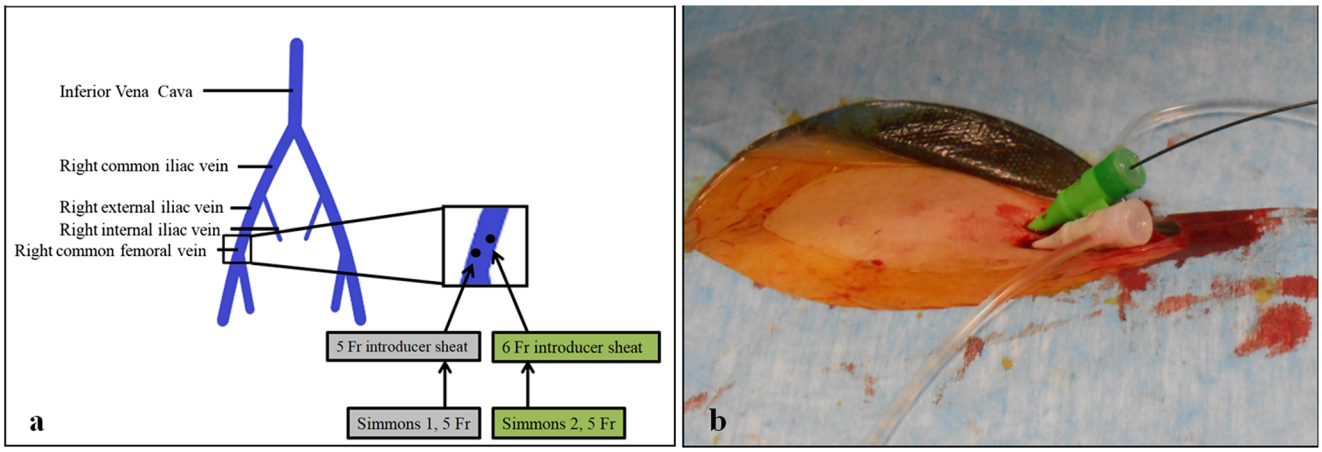


**Fig. 1** Double right femoral venous access. **a** Scheme. **b** The two positioned introducers

Samples are collected by dripping from the catheters into test tubes and, at the same time, are obtained from IVC by aspiration from the 6-Fr introducer. During the collection, catheters are left on free standing. It is important not to move the catheters and the introducers and not to touch catheter extremities with the test tube; the catheter tip position should be verified occasionally, checking that they will follow breathing movement (Fig. 3).

Finally, all test tubes should be labeled correctly, for instance, using a color-coded identification of catheters and tubes.

## After collecting the first samples…

On the left side, the catheter can remain in place, provided that gentle wash is performed after every sampling. On the contrary, on the right side, it is necessary to remove the catheter

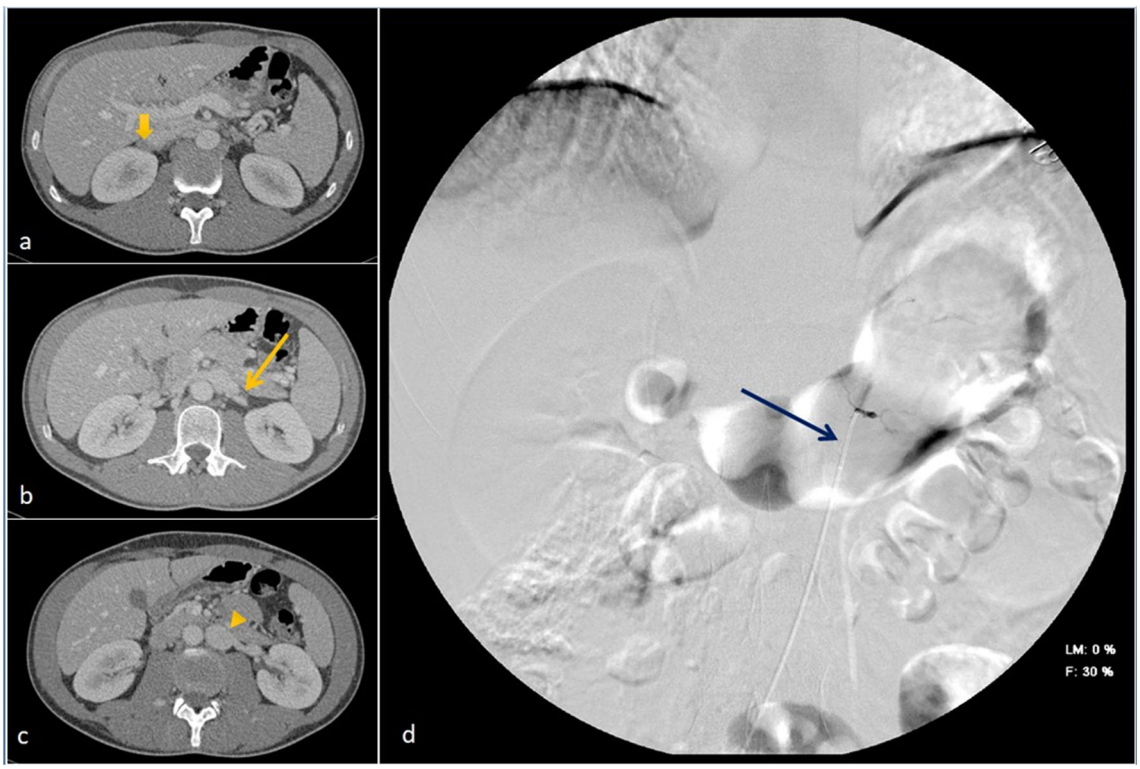


**Fig. 2** (**a**–**c**) Axial CT scan in a 35-year-old man with a right adrenal nodule (yellow arrow in (**a**) and a left inferior vena cava (yellow arrowhead in **c**). In order to catheterize the left adrenal vein (yellow thin arrow in **b**), it was necessary to use a BER catheter (blue arrow in **d**) in this case

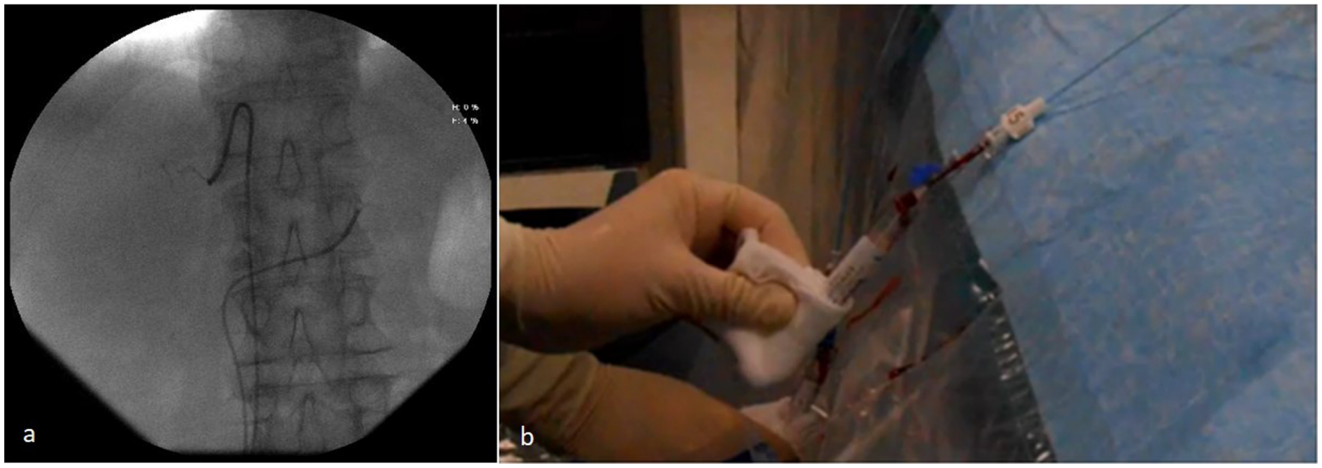


**Fig. 3** **a** Both catheters are positioned to perform bilaterally simultaneous adrenal vein sampling. **b** Samples are collected by gravity

from the vein, wash it, and reposition it again for the next sampling, owing to the much higher risk of thrombosis.

We perform a very gentle manual injection of a small amount of contrast medium, to reduce the risk of vein rupture, to verify again the position of the catheters tips before starting blood sampling.

### Intraprocedural rapid cortisol assay

The intraprocedural plasma cortisol concentration (PCC) assay is helpful to confirm the selectivity using a semi-quantitative kit assessing the step-up of cortisol between the adrenal veins and the IVC blood [20].

Its usefulness for increasing the success rate of AVS is currently investigated in a multi-center randomized clinical trial: the I-Padua Study [21].

It has to be considered, however, that this requires the presence of a dedicated laboratory technician during the procedure, because samples should be processed immediately after collection. The major advantage is that within a few minutes we know if the catheter is not selective, and another attempt of selective catheterization is undertaken [22, 23].

## Challenges

### Bilaterally simultaneous, and not sequential, AVS

It should be considered that, despite being minimally invasive, the procedure can trigger a stress reaction, resulting in the release of cortisol induced by ACTH.

The bilaterally simultaneous technique by nature is likely to minimize the artifactual differences related to stress and pulsatility of aldosterone secretion on the assessment of lateralization of excess aldosterone [17].

Moreover, with the protocol herein described, we did not observe any significant increase in costs and duration of the procedure, as compared with the sequential technique. Experienced interventional radiologists should be able to practice this procedure without any major difficulties.

### Double right femoral venous access

Even if double access may seem to be difficult, it is easier to work on one side. Our current protocol foresees the positioning of two different introducers, which help to keep the catheters steady during blood sample collection. We have not experienced any conflicts between the catheters thus far. However, should this happens, it can be swiftly resolved by removing and repositioning, the access being made safe by the introducers.

### Atrial fibrillation

Atrial stimulation, especially during the Simmons 2 tip reshaping, can cause tachycardia and caution is advised during this maneuver.

A valid option is to reshape the catheter in the contralateral common iliac vein rather than in the right atrium.

It is advisable to monitor the patient during the procedure by electrocardiogram. Occurrence of atrial fibrillation requires stopping the procedure.

### Sample

We found the two side hole catheter (Simmons 1) very useful to prevent vessel collapse during blood collection and, unlike what some authors have claimed, we did not experience dilution of adrenal blood samples from IVC blood.

### Allergy to contrast medium

In such cases, in order to avoid the confounding effect of antihistaminergic drugs and steroids, which would be necessary to prevent severe anaphylaxis, we reported the feasibility

of using carbon dioxide as a contrast medium [24]. Since this makes the identification of the vessels more difficult, we coupled this with intraprocedural rapid cortisol assay to confirm the achievement of selective catheterization [24].

### Vein rupture

It is essential to minimize the injection of contrast media and to carry it out as gently as possible. If hemorrhage occurs, it is advisable to perform a CT. The occurrence of a retroperitoneal hematoma, which causes acute pain, is rare (0.7%) and the complication usually resolves with conservative treatment [3, 25].

## Conclusions

Selective catheterization of both adrenal veins is a prerequisite for diagnostic clinical use of AVS. Bilaterally simultaneous sampling allows the elimination of the bias related to the different sampling times.

In our experience, with the precautions described above, it is possible to perform bilaterally simultaneous AVS correctly, optimizing the outcome and minimizing complications.

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### Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Prof. Emilio Quaia.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry** No complex statistical methods were necessary for this paper.

**Informed consent** Written informed consent was not required for this study because it concerns the development of a technique perfected over the years with the experience gained in our center; therefore, it is not focused on a patient population. However, all patients who are sent to our facility to undergo the procedure expressed their written consent to that.

**Ethical approval** Institutional Review Board approval was not required because this work describes our protocol to perform AVS procedure.

**Methodology**
• Performed at one institution

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