

## Adrenal Venous Sampling: Where Is the Aldosterone Disappearing to?

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Received: 28 July 2009 / Accepted: 14 September 2009 / Published online: 1 October 2009  
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**Abstract** Adrenal venous sampling (AVS) is generally considered to be the gold standard in distinguishing unilateral and bilateral aldosterone hypersecretion in primary hyperaldosteronism. However, during AVS, we noticed a considerable variability in aldosterone concentrations among samples thought to have come from the right adrenal glands. Some aldosterone concentrations in these samples were even lower than in samples from the inferior vena cava. We hypothesized that the samples with low aldosterone levels were unintentionally taken not from the right adrenal gland, but from hepatic veins. Therefore, we sought to analyze the impact of unintentional cannulation of hepatic veins on AVS. Thirty consecutive patients referred for AVS were enrolled. Hepatic vein sampling was implemented in our standardized AVS protocol. The data were collected and analyzed prospectively. AVS was successful in 27 patients (90%), and hepatic vein cannulation

was successful in all procedures performed. Cortisol concentrations were not significantly different between the hepatic vein and inferior vena cava samples, but aldosterone concentrations from hepatic venous blood (median, 17 pmol/l; range, 40–860 pmol/l) were markedly lower than in samples from the inferior vena cava (median, 860 pmol/l; range, 460–4510 pmol/l). The observed difference was statistically significant ( $P < 0.001$ ). Aldosterone concentrations in the hepatic veins are significantly lower than in venous blood taken from the inferior vena cava. This finding is important for AVS because hepatic veins can easily be mistaken for adrenal veins as a result of their close anatomic proximity.

**Keywords** Adrenal venous sampling · Primary aldosteronism

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### Introduction

In primary aldosteronism (PA), the choice of treatment depends on the lateralization of aldosterone secretion. In cases with unilateral aldosterone overproduction, adrenalectomy leads to improvement or even a complete cure of high blood pressure. Therefore, it is important to differentiate between bilateral and unilateral forms of PA [1, 2].

The only diagnostic method that can recognize unilateral aldosterone hypersecretion is adrenal venous sampling (AVS) [3, 4]. The adequacy of adrenal blood sampling is evaluated by the ratio of cortisol concentrations in the adrenal vein and in the inferior vena cava ( $C_{\text{adrenal}}/C_{\text{ivc}}$ ). The higher the  $C_{\text{adrenal}}/C_{\text{ivc}}$  is, the less is the dilution of blood from adrenal veins, which results in a more representative sample of adrenal venous blood. The published criteria for appropriate adrenal vein sampling range from

**Table 1** AVS results of a patient with marked variability in aldosterone concentration in samples thought to come from the right adrenal vein (see samples 2, 3, and 4)

Sample no.	Sample identification	Aldosterone (pmol/l)	Cortisol (nmol/l)	$C_{\text{adrenal}}/C_{\text{ivc}}$	AC	Appropriate adrenal sampling <sup>a</sup>
1	Left adrenal vein	49,000	7,950	15.29	6.16	Yes
2	Right adrenal vein	390	930	1.79	0.42	No
3	Right adrenal vein	150	680	1.31	0.22	No
4	Right adrenal vein	47,800	8,100	15.58	5.90	Yes
5	Inferior vena cava <sup>b</sup>	1,310	520		2.51	

AVS adrenal venous sampling, AC ratio of aldosterone to cortisol concentration,  $C_{\text{adrenal}}/C_{\text{ivc}}$  ratio of the cortisol concentrations in the adrenal vein and the inferior vena cava

<sup>a</sup> Appropriate adrenal sampling was defined as  $C_{\text{adrenal}}/C_{\text{ivc}}$  values of  $>5$

<sup>b</sup> A sample from the inferior vena cava was taken below the renal veins

$C_{\text{adrenal}}/C_{\text{ivc}}$  is  $\geq 2$ –5 with cosyntropin [3, 5] and from  $C_{\text{adrenal}}/C_{\text{ivc}}$  is  $\geq 1.1$ –3 without cosyntropin [1, 6].

The ratio of aldosterone to cortisol (AC) is the parameter used to compare both adrenals in order to eliminate variable dilution of adrenal venous blood. The lateralization of aldosterone secretion is assessed by the ratio  $AC_{\text{dominant adrenal}}/AC_{\text{nondominant adrenal}}$ . The reported criteria for abnormal lateralization of aldosterone secretion also vary significantly, with the ratio  $AC_{\text{dominant adrenal}}/AC_{\text{nondominant adrenal}}$  varying from  $\geq 2$  to  $\geq 5$  [7]. Moreover, some centers require the suppression of the nondominant adrenal glands ( $AC_{\text{nondominant adrenal}} < AC_{\text{ivc}}$ ) to confirm abnormal lateralization of aldosterone secretion [8].

When analyzing the AVS results of some patients, we noticed considerable variability in aldosterone concentrations among samples thought to have come from the right adrenal glands. Table 1 presents the AVS data of one such patient as an example. These findings raised doubts about the validity of some of our AVS examinations.

Repeated measurements of hormone concentrations in individual samples excluded laboratory errors. Instead, we hypothesized that some right adrenal samples were actually taken not from adrenal glands but from hepatic veins, which are located nearby. To avoid any further confusion, we implemented hepatic vein sampling into our routine standardized AVS protocol. This approach was chosen primarily to explain the data acquired from individual patients. By using these methods, we were able to systematically analyze the origin of the aldosterone variability among samples thought to come from the right adrenals.

## Materials and Methods

Data from 30 consecutive patients referred to AVS were analyzed. The patients' characteristics are shown in Table 2.

**Table 2** Principal characteristics of the study population<sup>a</sup>

Characteristic	Value
No. of patients (no. women)	30 (4)
Age (years)	52 (33–71)
Systolic blood pressure (mmHg)	133 (112–200)
Diastolic blood pressure (mmHg)	84 (68–110)
No. of antihypertensive drugs	4 (2–7)
Serum aldosterone (pmol/l) <sup>b</sup>	510 (240–1070)
Plasma active renin (ng/l) <sup>b</sup>	2.10 (0.48–7.15)
Aldosterone to renin ratio <sup>c</sup>	77 (25–762)

<sup>a</sup> Values are expressed as median (range) unless otherwise indicated

<sup>b</sup> Screening values

<sup>c</sup> Ratio of aldosterone to renin concentration was calculated in conventional units (ng/l)

Indication of AVS resulted from a high clinical suspicion of PA, which was based on a previous noninvasive diagnostic workup. Withdrawal of aldosterone antagonists for 2 months was required before the procedures were initiated. The ratio of aldosterone to active renin concentration (ARR) was used to screen patients for PA. Blood sampling for ARR was always performed in the morning hours (7–10 a.m.) with the patients in the upright position for at least 30 min before sample collection. For calculation of ARR, both serum aldosterone and plasma renin concentrations were expressed in ng/l. ARR values of  $>20$  were considered to be abnormal, and on the basis of our observations in 69 healthy volunteers (unpublished data), 20 was set as the cutoff value. Before sampling for ARR, no specific changes in antihypertensive medication were initially required (except for the withdrawal of any aldosterone antagonists as mentioned above).

However, if the patient had an ARR of  $>20$ , adrenal adenoma, or hypokalemia, ARR sampling was repeated after 2 weeks of withdrawal from any medication that could interfere with the renin–angiotensin–aldosterone system.

Only doxazosin and verapamil were allowed for patients who were considered at risk from uncontrolled hypertension.

On the basis of persistent increase of ARR ( $>20$ ), the patients were referred for suppression testing. Verapamil and doxazosin were the only antihypertensive drugs allowed. Blood samples for serum aldosterone were taken in the supine position after a 4-h saline infusion (2000 ml) and a previous period of high salt intake. Aldosterone was considered nonsuppressible when it was  $>100$  pmol/l, which, on the basis of our observations from 32 healthy volunteers (unpublished data), was the cutoff value.

All AVS procedures were performed according to the routine standardized protocol used in our center. No changes in concomitant medications were required, except for oral anticoagulants and aldosterone antagonists that had to be withdrawn before the procedure. All of the patients provided informed written consent for the AVS procedure according to the following protocol. To minimize stress-induced fluctuations in adrenal hormones secretion, an infusion of cosyntropin was administered 1 h before and during the procedure, at the rate of 160  $\mu\text{g/h}$ . The design of the cosyntropin dosing scheme was inspired by previous reports [9, 10].

Samples were taken step by step from both adrenal veins, one of the hepatic veins, and the inferior vena cava below the renal veins [11, 12]. Because cannulation of adrenal veins, especially the right one, is technically difficult, multiple samples were taken in order to increase the success rate of the procedure.

Angiographic verification of the catheter placement into adrenal and hepatic veins was required both before and just after the sampling in order to exclude the possibility of catheter displacement during blood sampling [12]. Small amounts of contrast agent were used to minimize the risk of adrenal injury.

Aldosterone and cortisol concentrations were measured in all the acquired samples. Commercially available radioimmunoassay kits were used both to measure aldosterone (Diagnostic Products Corporation, Los Angeles, CA) and cortisol (Immunotech, Beckman Coulter, Marseille, France). In the long term, the observed intra-assay coefficients of variation were less than 7% for aldosterone and no more than 5% for cortisol. The cross-reactivity of the diagnostic antibodies for other corticosteroids was low.

AVS was considered successful when samples with  $C_{\text{adrenal}}/C_{\text{ivc}}$  values of  $>5$  were obtained from both adrenals. Abnormal lateralization of aldosterone secretion was defined by  $AC_{\text{dominant adrenal}}/AC_{\text{nondominant adrenal}}$  values of  $>4$  [5]. These criteria were chosen to avoid uncertainties when indicating adrenalectomy.

All the patients provided written informed consent to the AVS procedure according to the above-mentioned protocol. Institutional review board approval was not required.

Nonparametric tests were used for statistical analysis of the acquired data (MedCalc, Mariakerke, Belgium).

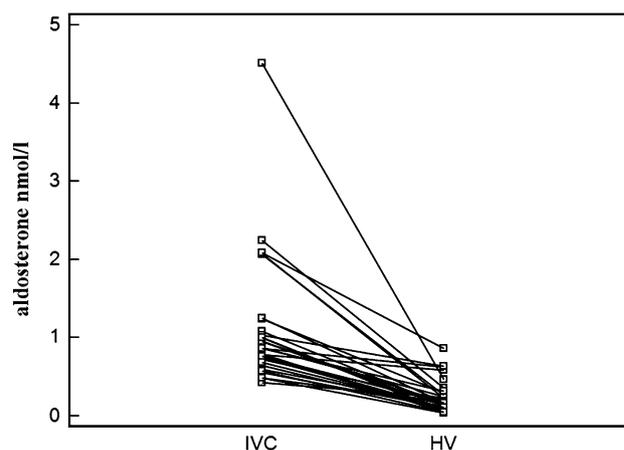
## Results

The AVS procedure was successful in 27 patients (90%) when samples with a  $C_{\text{adrenal}}/C_{\text{ivc}}$  value of  $>5$  were obtained from both adrenals. One patient was catheterized twice because the first catheterization failed to yield adequate samples. No complications were noted. By using samples with the highest  $C_{\text{adrenal}}/C_{\text{ivc}}$ , a lateralization of aldosterone secretion ( $AC_{\text{dominant adrenal}}/AC_{\text{nondominant adrenal}} > 4$ ) was diagnosed in eight cases (26.7%).

Hepatic vein cannulation was successful in all AVS procedures performed. The aldosterone concentration was uniformly lower in hepatic veins than in the inferior vena cava. The medians of aldosterone concentrations in hepatic venous blood and the inferior vena cava were 170 (range, 40–860) pmol/l and 860 (range, 460–4510) pmol/l, respectively (Fig. 1). The observed difference was highly statistically significant ( $P < 0.001$ ) by the Wilcoxon test.

In contrast, no significant difference in the cortisol concentrations was observed between hepatic veins (median, 810 nmol/l; range, 510–1 350 nmol/l) and inferior vena cava (median, 790 nmol/l; range, 540–1 500 nmol/l).

In patients with successful AVS, the ratio of cortisol concentrations in the hepatic vein and inferior vena cava ( $C_{\text{hepatic}}/C_{\text{ivc}}$ ) was calculated as a parameter, in a manner analogous to  $C_{\text{adrenal}}/C_{\text{ivc}}$ . Marked variability in  $C_{\text{hepatic}}/C_{\text{ivc}}$  was noted (range, 0.74–2). In eight patients (29.6%), the  $C_{\text{hepatic}}/C_{\text{ivc}}$  value was  $\leq 0.9$ , and in seven patients (25.9%), the  $C_{\text{hepatic}}/C_{\text{ivc}}$  value was  $\geq 1.1$ .



**Fig. 1** Aldosterone concentrations in the HV and in the IVC. Graph compares the aldosterone concentrations in the HV and in the IVC. Aldosterone concentration in HV was uniformly and significantly ( $P < 0.001$ ) lower than in the IVC. HV hepatic vein, IVC inferior vena cava

If hepatic samples with  $C_{\text{hepatic}}/C_{\text{ivc}}$  values of  $\geq 1.1$  had been considered to be from the right adrenal, the lowest published criterion for appropriate AVS [6] would have been satisfied.

Replacing the right adrenal samples with the corresponding hepatic samples with  $C_{\text{hepatic}}/C_{\text{ivc}}$  values of  $\geq 1.1$  would have led to changes in the AVS interpretation in all seven patients. In six patients without lateralization of aldosterone secretion, false hypersecretion from the left adrenal would have been detected. Moreover, in one patient with right-side aldosterone overproduction, accidental hepatic vein sampling would have masked the lateralization of aldosterone secretion.

## Discussion

Implementation of hepatic sampling into our routine AVS protocol cleared up some of our doubts about the clinical interpretation of the data acquired. By taking one additional control sample from the hepatic veins during AVS, we were able to explain the observed discrepancies in aldosterone concentrations among “right adrenal” venous samples in individual patients.

When we analyzed the data from hepatic samples, we observed that liver metabolism of aldosterone exceeded that of cortisol. Aldosterone concentrations found in the hepatic venous blood were only a fraction of those found in the inferior vena cava, whereas cortisol levels were not significantly different. The high metabolic rate of aldosterone in the liver is well known [13, 14]. However, to our knowledge, it has not been mentioned in the context of AVS. In particular, a low aldosterone concentration in the hepatic venous blood may have implications for AVS interpretation if a sample of hepatic venous blood is mistakenly thought to come from the right adrenal vein. Cortisol concentration does not enable the differentiation of adrenal and nonadrenal samples when the lowest recommended  $C_{\text{adrenal}}/C_{\text{ivc}}$  cutoff criterion [15] is used. In a quarter of the examined patients, the estimated cortisol concentration in the liver was at least 10% higher than that in the inferior vena cava. In our opinion, there are several reasons that may explain this finding.

First, the most obvious explanation seems to be the inherent imprecision of laboratory assays of cortisol. The precision of a laboratory test describes a coefficient of variation that is defined by the ratio of the standard deviation (SD) to the mean. According to statistics, 68.3% of values measured from one sample are within the range of one SD from the mean, and 99.7% of measured values are within the range of 3 SDs. Therefore, when the coefficient of variation of the cortisol laboratory assessment is 5%, 31.7% of the measured values (from one

sample) lie more than  $\pm 5\%$  away from the mean. Consequently, it is not unlikely that the estimated cortisol concentrations in two nonadrenal samples could differ by more than 10%. Second, despite continuous cosyntropin infusion during sampling, we remained unable to exclude small fluctuations in serum cortisol. These arguments support the fact that the number of hepatic samples with  $C_{\text{hepatic}}/C_{\text{ivc}}$  values of  $\geq 1.1$  (25.9%) corresponds to the proportion of examinations (29.6%) with  $C_{\text{hepatic}}/C_{\text{ivc}}$  values of  $\leq 0.9$ .

Adrenal samples containing a significant portion of nonadrenal blood can influence the results, especially when they are contaminated with hepatic venous blood, which has a low concentration of aldosterone. As a potential cause, the anomalous confluence of adrenal and hepatic vein has been described [16]. However, the frequency and the clinical significance of this anomaly are poorly understood [17, 18]. In our study, we did not systematically assess adrenal venous anatomy. Retrograde venography with a large volume of contrast agent would greatly increase the risk of adrenal hemorrhage. Moreover, venography itself cannot depict related parenchymatous organs or differentiate anomalous hepatic veins from right adrenal veins [19].

In practice, displacement of the catheter during sampling can occur. High concentrations of adrenal hormones can be found in the blood taken from the inferior vena cava above the adrenal veins [18] because the laminar blood flow may prevent complete dilution of blood coming from adrenal veins. However, this may also be true for blood with a low concentration of aldosterone coming from hepatic veins lying close to the adrenal veins.

We tried to eliminate this effect by performing adrenal angiography not only before but also after sampling, but adherence to this rule was not absolute. As an example, we present AVS data of one patient in whom it was difficult to cannulate a right adrenal vein (Table 3). Inconsistently with our protocol, not all samples were taken under predefined angiographic guidance. Cortisol-corrected aldosterone concentrations (AC) differed greatly between samples with moderate and high  $C_{\text{adrenal}}/C_{\text{ivc}}$  values. Moreover, marked AC differences were observed among samples with moderate  $C_{\text{adrenal}}/C_{\text{ivc}}$  values (Table 3, samples 2, 6, 7, and 8), which can be explained by variable dilution of adrenal venous blood. In fact, as demonstrated in Table 3, two samples ascribed to right adrenal veins were taken not from the adrenal but from the liver (Table 3, samples 3 and 4).

Therefore, the only principal determinant of successful adrenal sampling is a high concentration of cortisol. The recent guidelines on PA [20] report an adrenal/peripheral vein cortisol ratio that is typically more than 10:1 with the continuous cosyntropin infusion protocol, and more than

**Table 3** AVS results of one patient in whom it was difficult to cannulate a right adrenal vein<sup>a</sup>

Sample no.	Sample identification	Aldosterone (pmol/l)	Cortisol (nmol/l)	$C_{\text{adrenal}}/C_{\text{ivc}}$	AC	Appropriate adrenal sampling <sup>b</sup>
1	Left adrenal vein	87,100	23,500	25.54	3.71	Yes
2	Right adrenal vein	12,100	3,800	4.13	3.18	No
3	Right adrenal vein	470	920	1.00	0.51	No
4	Right adrenal vein	360	800	0.87	0.45	No
5	Right adrenal vein	101,600	26,700	29.02	3.81	Yes
6	Right adrenal vein	4,400	2,800	3.04	1.57	No
7	Right adrenal vein	2,010	3,100	3.37	0.65	No
8	Right adrenal vein	7,400	2,800	3.04	2.64	No
9	Hepatic vein	270	970	1.05 <sup>c</sup>	0.28	
10	Inferior vena cava <sup>d</sup>	2,070	920		2.25	

AVS adrenal venous sampling, AC ratio of aldosterone to cortisol concentration,  $C_{\text{adrenal}}/C_{\text{ivc}}$  ratio of the cortisol concentrations in the adrenal vein and the inferior vena cava

<sup>a</sup> Cortisol-corrected aldosterone concentrations (AC) differed greatly between samples with moderate or high  $C_{\text{adrenal}}/C_{\text{ivc}}$ . Marked AC variability was observed among samples with moderate  $C_{\text{adrenal}}/C_{\text{ivc}}$  (samples 2, 6, 7, and 8). Samples 3 and 4 were unintentionally taken not from the right adrenal but from the liver; their aldosterone concentrations are markedly lower than those of samples from the inferior vena cava and from the right adrenal vein

<sup>b</sup> Appropriate adrenal sampling was defined by  $C_{\text{adrenal}}/C_{\text{ivc}} > 5$

<sup>c</sup>  $C_{\text{hepatic}}/C_{\text{ivc}}$

<sup>d</sup> A sample from the inferior vena cava was taken below the renal veins

3:1 without the use of cosyntropin. In fact, the published criteria for adequate adrenal sampling, with or without adrenal stimulation, are based primarily on local experience and personal opinions. They vary greatly from  $C_{\text{adrenal}}/C_{\text{ivc}}$  values of  $\geq 1.1$  [6] to  $C_{\text{adrenal}}/C_{\text{ivc}}$  values of  $>5$  [5].

It is unclear to what extent our findings are applicable to AVS procedures performed without adrenal stimulation [21, 22]. However, our data clearly show that appropriate choice of a  $C_{\text{adrenal}}/C_{\text{ivc}}$  cutoff should at least eliminate the inherent imprecision of cortisol laboratory estimation.

To conclude, we found that aldosterone concentration in hepatic veins is uniformly lower than in mixed venous blood taken from the inferior vena cava; however, no difference in cortisol concentrations was observed between the two veins. This finding may have implications for AVS because unintentional cannulation of hepatic veins instead of right adrenal veins can occur during adrenal catheterization. Caution should be taken when samples characterized by only mild increase in cortisol concentration (compared with inferior vena cava) are used for the interpretation of the results.

**Acknowledgment** This work was supported as part of research projects MZO00179906 and MSM0021620817.

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