CLINICAL SIGNIFICANCE OF CONTRALATERAL ADRENAL SUPPRESSION DURING ADRENAL VEIN SAMPLING IN PRIMARY ALDOSTERONISM

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BACKGROUND

Adrenal vein sampling (AVS) is recognized by Endocrine Society guidelines as the only reliable mean to distinguish between aldosterone producing adenomas and bilateral adrenal hyperplasia, the two most common subtypes of primary aldosteronism (PA). However, AVS protocols are not standardized and vary between centers. in addition to the SI and lateralization index (LI) (see below), some authors have emphasized the importance and usefulness of contralateral (CL) adrenal suppression to identify the source of aldosterone production and currently many centers require this additional criterion together with a defined LI to suggest adrenalectomy to a PA patient.

	Measurement	Clinical significance	Suggested cut-off
Selectivity index (SI)	$Cortisol_{adrenal\ vein}/cortisol_{peripheral\ vein}$	Adequacy of cannulation of the adrenal veins	Minimum requirement of SI>2 under basal conditions, SI>3 during ACTH (1–24) (>3 and >5 respectively are preferable)
Lateralisation index (LI)	$(Aldosterone/cortisol_{adrenal\ vein})/(aldosterone/cortisol_{contralateral\ adrenal\ vein})$	Lateralisation of aldosterone production. To distinguish between unilateral and bilateral PA	LI >4 indicates unilateral PA; LI<3 indicates bilateral PA; 3<LI<4 is a grey zone
Contralateral ratio (CLR)	$(Aldosterone/cortisol_{nondominant\ adrenal\ vein})/(aldosterone/cortisol_{peripheral\ vein})$	Inhibition of aldosterone secretion in the non-dominant adrenal gland	CLR<1 can be thought of as indicative of unilateral PA in the opposite side; can be used when the other adrenal vein is not cannulated or when LI is in the grey zone
Ipsilateral ratio (ILR)	$(Aldosterone/cortisol_{dominant\ adrenal\ vein})/(aldosterone/cortisol_{peripheral\ vein})$	Gradient between the dominant adrenal and the peripheral vein	ILR>2 is required together with CLR<1 in some centres to diagnose unilateral PA

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OBJECTIVE

The objective of the present study was to assess whether the presence or absence of contralateral adrenal (CL) suppression has an impact on the postoperative clinical and biochemical parameters in patients who underwent unilateral adrenalectomy for PA.

DESIGN & METHODS

The study was retrospectively carried out in 8 referral hypertension centers in Italy, Germany and Japan. Screening and subtype differentiation were performed according to the Japan Endocrine Society and The Endocrine Society guidelines and a total of 234 AVS procedures were included in the study (**Figure 1**). CL suppression was defined as aldosterone/cortisol $_{non\ dominant\ adrenal\ vein}$ / aldosterone/cortisol $_{peripheral\ vein}$ < 1.

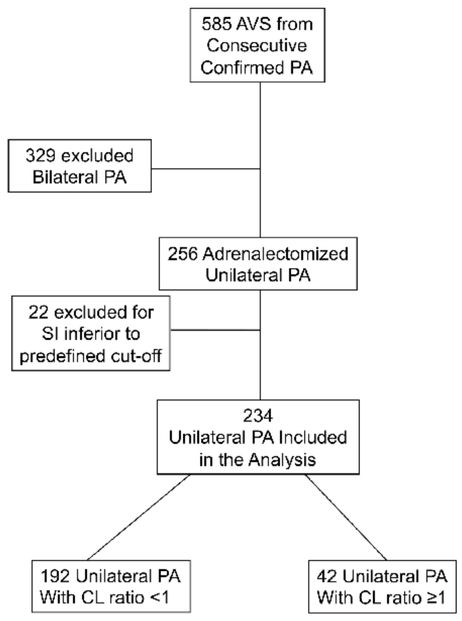

Figure 1. *Flow chart of the study.*

RESULTS

Clinical and biochemical parameters of patients participating in the study are summarized in **Table 1**. Clinical and biochemical parameters after adrenalectomy are summarized in **Table 2**. Overall, 192/234 (82%) of AVS studies displayed contralateral (CL) suppression, with no statistically significant differences among centers. ACTH stimulation was associated with a significant (p=0.014) increase in the percentage of AVS showing CL suppression, compared with basal studies (90% vs 77%). CL suppression was slightly but not significantly higher in studies with bolus ACTH vs basal studies (88% vs 77%, p=0.07), significantly higher in studies with continuous ACTH infusion vs basal (91% vs 77%, p=0.02) and similar in the two types of ACTH stimulation (88% vs 91%, p=0.44). Fifty-three AVS were performed both under basal conditions and after ACTH stimulation.

We observed a statistically significant inverse correlation between CL ratio and serum aldosterone levels at diagnosis (R2= 0.04; p=0.02), but not between CL ratio and systolic blood pressure, potassium and age at diagnosis of PA. Moreover, regression analysis showed that serum aldosterone levels but not SBP and potassium levels predicted CL suppression during AVS.

Among AVS parameters, CL ratio inversely correlated with lateralization index (R2=0.028; p=0.01) and patients with LI>4 displayed a significantly higher proportion of CL suppression compared to patients with 3<LI< 4 (184/211, 87% vs 8/23, 35%; p<0.001).

Patients with CL suppression had higher plasma aldosterone levels at diagnosis than patients who did not have suppressed CL aldosterone secretion, whilst we did not observe significant differences in systolic and diastolic blood pressure, potassium, PRA, PRC and number of class of drugs used to treat the patients (**Table 3**). Both in basal and ACTH stimulated conditions (p<0.001 and p=0.004 respectively), median lateralization index was significantly higher in patients who showed contralateral adrenal suppression (**Figure 2**). No differences were observed between the two groups for the main clinical and biochemical parameters (SBP, DBP, aldosterone, PRA, PRC, K+, number of drugs, reduction of blood pressure levels and number of classes of drugs assumed by the patients) but patients with CL suppression underwent a significantly larger reduction in aldosterone levels after adrenalectomy (**Table 4**).

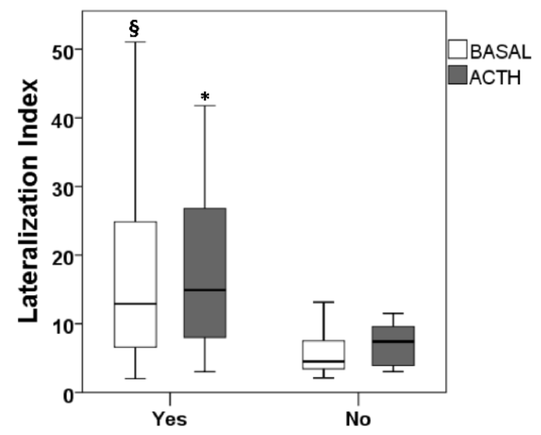

Figure 2. *Box plots of LI distribution between patients with and without CL suppression in basal (white) and ACTH (gray) stimulated studies. * p =0.004, § p < 0.001.*

	GERMANY	ITALY	JAPAN	Overall	GERMANY	GERMANY	ITALY
				p-value	*vs.* ITALY	*vs.* JAPAN	*vs.* JAPAN
Age at diagnosis (years)	52 ± 1.4	48 ± 1.0	53 ± 1.9	0.04	0.1	0.45	0.02
Sex (male/female)	33/26	67/64	23/21	0.83	0.32	0.43	0.52
Pre-op PRA (ng/ml/h)	0.2[0.2–0.5]	0.2[0.14–0.4]	0.1[0.1–0.3]	0.003	1.0	0.15	0.007
Pre-op PRC (mU/liter)	2.8[1.6–5–1]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Pre-op Aldosterone (ng/dL)	22.3 [14.5–38.1]	45.3[33.3–58]	39.9[26.9–60.9]	<0.001	<0.001	0.003	0.47
Pre-op K^+(mEq/liter)	3.1 ± 0.07	3.0 ± 0.06	3.4 ± 0.11	0.002	0.46	0.012	<0.001
Pre-op SBP (mmHg)	152 ± 3	169 ± 2	155 ± 3	<0.001	<0.001	0.57	0.001
Pre-op DBP (mmHg)	91 ± 2	103 ± 1	90 ± 2	<0.001	<0.001	0.77	<0.001
Nodule (mm)	15[11.7–19]	15[10–20]	15[10–19]	0.73	0.67	0.48	0.76
Pre-operative drugs (number)	3 ± 0.2	2.4 ± 0.1	2.2 ± 0.3	0.013	0.01	0.006	0.39

Table 1. *Clinical and biochemical parameters of APA patients included in the analysis. PRA =plasma renin activity; DRC = direct renin concentration: SBP = systolic blood pressure; DBP = diastolic blood pressure; n.a. = not available; n.s. = not significant. Nodule dimensions are obtained with CT scanning. Numbers are mean ± standard deviation or median [25th-75th percentiles].*

Pre adrenalectomy	Contralateral suppression:	Contralateral suppression:	p-value
parameters	**YES (*n* = 192)**	**NO (*n* = 42)**	
PRA (ng/mL/h)	0.2 [0.1–0.3]	0.2 [0.1–0.3]	0.6
PRC (mU/liter)	3.0 [2–5.1]	2.4 [1.3–13.5]	0.8
Aldosterone (ng/dL)	41.5 [26.2–58]	33.3 [22.3–48.8]	0.011
K^+ (mEq/liter)	3.1 ± 0.05	2.9 ± 0.1	0.2
SBP (mmHg)	161 ± 2	167 ± 4	0.2
DBP (mmHg)	96 ± 1	101 ± 3	0.1
Drugs number	2.5 ± 0.1	2.6 ± 0.3	0.9

Table 3. *Comparison of pre-operative parameters according to contralateral suppression status. PRA =plasma renin activity; PRC = plasma renin concentration; SBP = systolic blood pressure; DBP = diastolic blood pressure. P <0.05 was considered statistically significant.*

	GERMANY	ITALY	JAPAN	Overall	GERMANY	GERMANY	ITALY
				p-value	*vs.* ITALY	*vs.* JAPAN	*vs.* JAPAN
Post PRA (ng/ml/h)	1.6 [1.1–2.3]	2.1 [1.2–3.]	1.9 [1–3.9]	0.53	0.27	0.46	0.59
Post PRC (mU/liter)	20 [11–50]	n.a.	n.a.	n.a	n.a.	n.a	n.a
Post Aldosterone (ng/dL)	5.4 [3.5–8.4]	12.9 [8.7–19.1]	9 [5.9–12]	<0.001	<0.001	0.005	0.004
Post K^+ (mEq/liter)	4.3 ± 0.06	4.7 ± 0.04	4.4 ± 0.05	<0.001	<0.001	0.1	0.001
Post SBP (mmHg)	129 ± 2	127 ± 1	127 ± 2	0.55	0.28	0.45	0.92
Post DBP (mmHg)	82 ± 1	81 ± 1	79 ± 1	0.26	0.43	0.10	0.24
ΔSBP (mmHg)	23 ± 3	41 ± 2	28 ± 3	<0.001	<0.001	0.35	0.001
ΔDBP (mmHg)	9 ± 2	22 ± 1	11 ± 2	<0.001	<0.001	0.51	<0.001
Post-operative drugs (n)	1.6 ± 1.5	1.1 ± 1.2	1.5 ± 1.3	0.019	0.014	0.85	0.045

Table 2. *Clinical and biochemical post-adrenalectomy parameters of APA patients included in the analysis. PRA = plasma renin activity; DRC = direct renin concentration: SBP = systolic blood pressure; DBP = diastolic blood pressure; ΔSBP = systolic blood pressure reduction after adrenalectomy; ΔDBP = diastolic blood pressure reduction after adrenalectomy; n.a. = not available. Data were obtained between 12 and 18 months after adrenalectomy.*

Post adrenalectomy parameters	Contralateral suppression: YES (*n* = 192)	Contralateral suppression: NO (*n* = 42)	p-value
SBP (mmHg)	128 ± 11	127 ± 14	0.6 (n.s.)
DBP (mmHg)	80 ± 8	82 ± 8	0.2 (n.s.)
Aldosterone (ng/dL)	9.80 [5.65–17.40]	9.50 [6.90–20.00]	0.5 (n.s.)
K^+ (mEq/liter)	4.53 ± 0.4	4.52 ± 0.4	0.9 (n.s.)
PRA (ng/mL/h)	2.0 [1.20–3.08]	1.65 [1.09–3.08]	0.6 (n.s.)
PRC (mU/liter)	18.5 [9.2–30.0]	26.8 [13.0–63.2]	0.4 (n.s.)
Drugs number	1.35 ± 1.4	1.38 ± 1.5	0.9 (n.s.)
ΔSBP (mmHg)	33 ± 1.8	40 ± 4.0	0.1 (n.s.)
ΔDBP (mmHg)	16 ± 1.0	19 ± 2.6	0.2 (n.s.)
ΔAldosterone	28.6 ± 3.1	8.5 ± 9.9	0.015
Δ drugs number	1.2 ± 0.1	1.2 ± 0.3	0.8 (n.s.)
Number of Cured (%)	100 (52%)	22 (52%)	0.9 (n.s.)

Table 4. *Comparison of post-operative parameters according to contralateral suppression status. PRA = plasma renin activity; PRC = plasma renin concentration; SBP= systolic blood pressure; DBP = diastolic blood pressure; ΔSBP = systolic blood pressure reduction after adrenalectomy; ΔDBP = diastolic blood pressure reduction after adrenalectomy; Δ Aldosterone = plasma aldosterone levels reduction after adrenalectomy; Δ Drugs number = drugs number reduction after adrenalectomy. P < 0.05 was considered statistically significant.*

CONCLUSIONS

For patients with lateralization indices of > 4, CL suppression should not be required to refer patients to adrenalectomy because it is not associated with a larger blood pressure reduction and might exclude patients from curative surgery.

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