



Chemiluminescence immunoassays: aldosterone and direct renin measurement

Fast and reliable identification of endocrine hypertension

Renin and aldosterone measurement in hypertensive patients

Both renin and aldosterone must be measured for the diagnosis of the two most frequent forms of secondary hypertension, i.e. primary aldosteronism (PA) and renovascular hypertension. Renin and aldosterone should also be determined in cases of hypertension caused by liquorice or contraception, which occur less frequently, as well as in patients with resistant hypertension. In addition, evaluation of the renin-angiotensin-aldosterone system (RAAS) is useful for selecting the most appropriate antihypertensive treatment for the individual patient.¹⁻³

Primary aldosteronism

It is estimated that around 10% of hypertensive patients who are referred to hypertension centres have PA, with 40% of those cases being caused by an aldosterone-producing adenoma and 60% by bilateral adrenal hyperplasia.⁴ Due to the aldosterone-mediated blood volume expansion and the subsequent blood pressure elevation, renin secretion is suppressed. The combination of a high plasma aldosterone concentration (PAC) and a low plasma renin concentration (PRC) is therefore recognised as characteristic of PA; it is often but not always associated with a low plasma potassium level.

Accordingly, in its recently published guidelines, the Endocrine Society⁵ reiterates the recommendation to evaluate the aldosterone-to-renin ratio (ARR) for all groups of hypertensive patients with increased risk for PA (s. table 1) using blood collected in the seated position.

The Endocrine Society Guidelines for primary aldosteronism recommend screening using the ARR in patients with:

- Moderate/severe hypertension
- Drug-resistant hypertension
- Hypertensive patients with spontaneous or diuretic-induced hypokalemia
- Hypertension with adrenal incidentaloma
- Hypertension with obstructive sleep apnea

Table 1: Recommended screening for hypertensive patients with high risk of PA

The ARR is the concentration of aldosterone, expressed in ng/dl, divided by the concentration of renin, expressed in $\mu\text{U/ml}$, both of which can be determined using chemiluminescence immunoassays (ChLIAs). Instead of PRC, it is also possible to use the plasma renin activity (PRA) expressed in ng/ml/hr for ARR calculation.

ARR values must be interpreted carefully, since their ranges differ greatly depending on the units used to express renin and aldosterone concentration. There are also many factors that might lead to false-positive or false-negative ARR results,⁵ especially the antihypertensive drug classes of β -blockers and anti-aldosterone medication, which should be stopped before blood collection for ARR determination.

Effect of gender and postural changes on PRC, PAC and the ARR

Gender may affect renin and aldosterone levels due to a number of humoral factors. Therefore, we evaluated both parameters as well as the ARR in a randomly selected cohort of 106 hypertensive patients (37 male, 69 female). The median values of PRC measured in blood collected in seated position were similar in males (10.7 $\mu\text{U/ml}$) and females (11.3 $\mu\text{U/ml}$) (Fig. 1a). The corresponding median values of PAC were also similar (male 5.0 ng/dl, female 6.3 ng/dl) (Fig. 1b). Consequently, there was no significant difference in the median ARR value of the two groups (0.39 (ng/dl)/($\mu\text{U/ml}$) in males and 0.60 (ng/dl)/($\mu\text{U/ml}$) in females) (Fig. 1c).

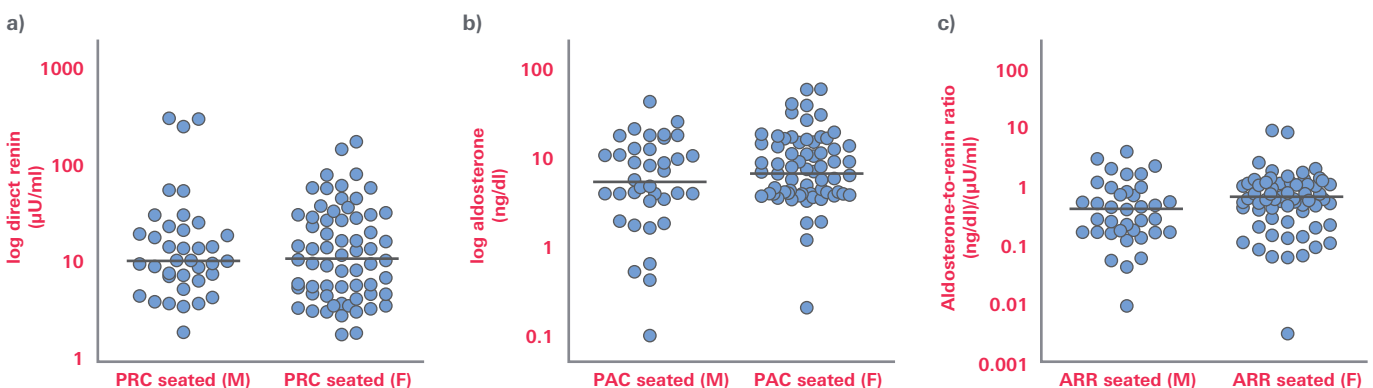


Figure 1: Plasma renin and aldosterone concentrations as well as ARR in male (M) and female (F) patients in a seated position, measured with the respective IDS assays

Postural changes are commonly used to assess the integrity of RAAS response to changes in blood volume following the assumption of an upright posture. If renin and aldosterone fail to increase in response to standing, this is a confirmation of PA. In a subcohort of 22 patients with essential hypertension (15 female, 7 male), PRC and PAC responded physiologically to one hour of active standing with an increase from $21.4 \pm 3.5 \mu\text{U/ml}$ to $36 \pm 5.3 \mu\text{U/ml}$ (Fig. 2a) and from $10.8 \pm 1.1 \text{ ng/dl}$ to $23.7 \pm 3.9 \text{ ng/dl}$ (Fig. 2b), respectively (mean \pm standard error of the mean). As a result of the PRC and PAC increases, values of ARR were similar in supine and standing positions (0.69 and $0.82 \text{ (ng/dl)/}(\mu\text{U/ml)}$ respectively) (Fig. 2c).

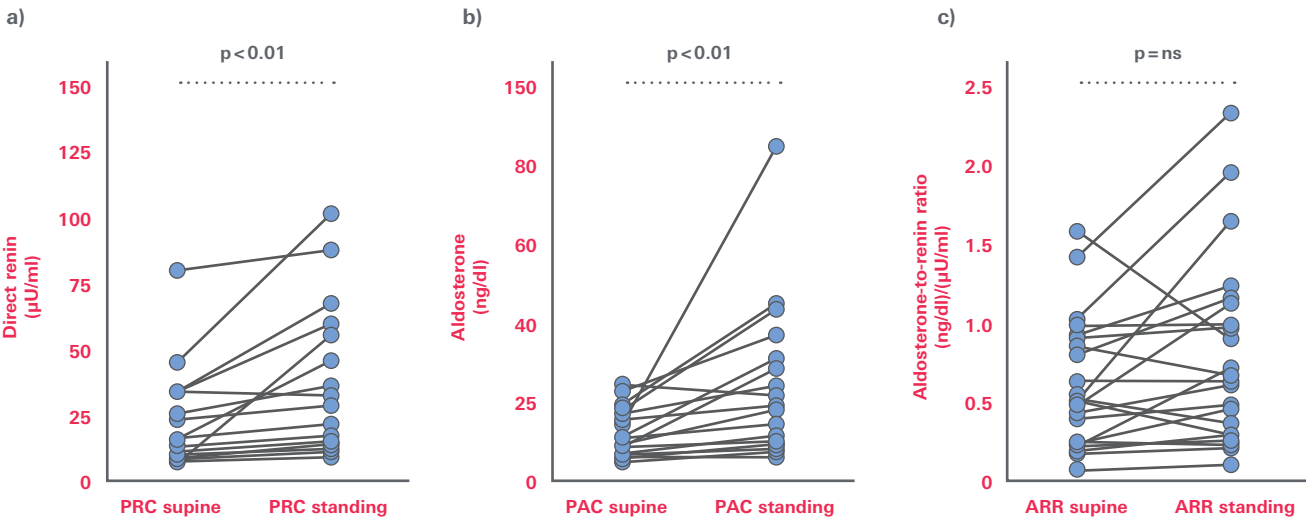


Figure 2: Plasma renin and aldosterone concentrations (PRC, PAC) and ARR values in supine and standing position

ARR cut-off values for PA diagnostics

Values of PRC and PAC measured with the IDS ChLIA and the calculated ARRs were evaluated in 93 patients with PA, in 152 with essential hypertension and in 147 healthy controls⁶. At a cut-off of $1.12 \text{ (ng/dl)/}(\mu\text{U/ml)}$, the sensitivity and specificity of ARR for detecting PA were 98.9% and 78.95% respectively. In patients with an aldosterone-producing adenoma (APA), ARR values ranged from 1.1 to $52.1 \text{ (ng/dl)/}(\mu\text{U/ml)}$ with an average of $6.8 \text{ (ng/dl)/}(\mu\text{U/ml)}$, significantly greater than that observed in patients with a bilateral adrenal hyperplasia (BAH) (average $2.1 \text{ (ng/dl)/}(\mu\text{U/ml)}$, range $1.1 - 11.2 \text{ (ng/dl)/}(\mu\text{U/ml)}$) (Fig. 3).

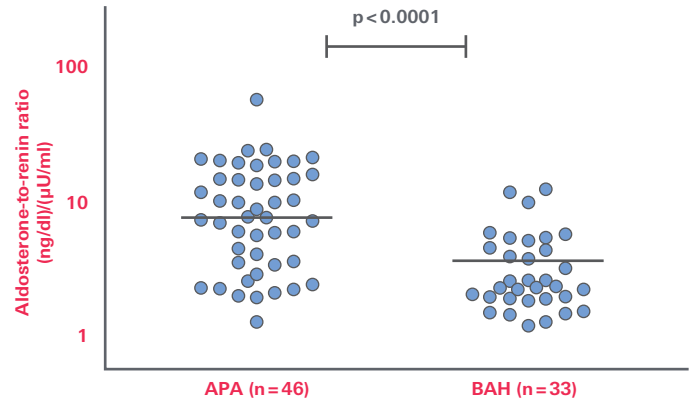


Figure 3: The ARR in primary aldosteronism patients with APA and BAH

Confirmatory test for PA

Patients with an elevated ARR should undergo confirmatory testing. The saline infusion test (SIT) is the most frequently used confirmatory test and involves the evaluation of the suppression of aldosterone in response to the IV infusion of 2 litres of saline over 4 hours. In non-PA patients, PAC should decrease to values below 5 ng/dl . Figure 4 shows SIT results measured using the IDS ChLIA: aldosterone was not suppressed in all 46 patients with previous PA diagnosis, whereas PAC decreased below 5 ng/dl in all 73 non-PA patients with essential hypertension.

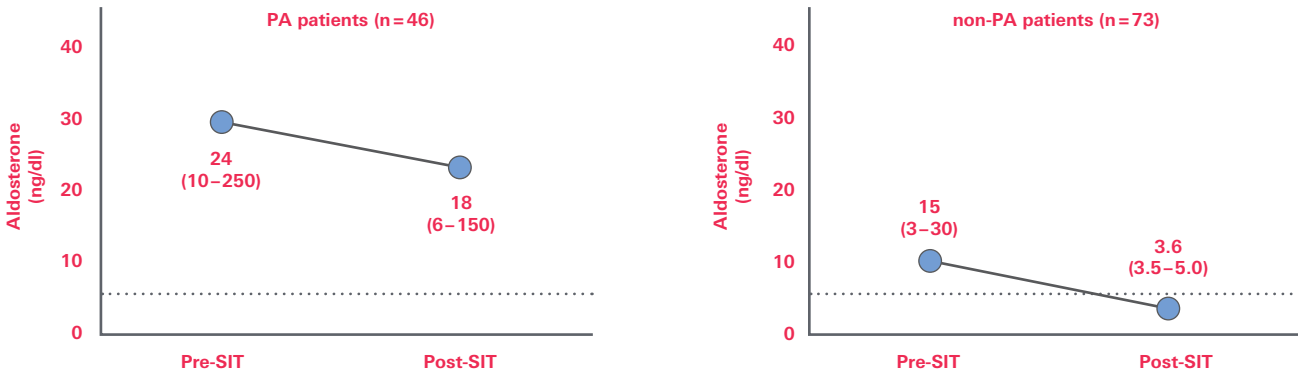



Figure 4: PACs during the saline infusion test in PA and non-PA patients given as mean values and ranges

Conclusions

- IDS Aldosterone and IDS Direct Renin are fast and reliable ChLIAs for the measurement of aldosterone and renin from the same plasma sample.
- In both ChLIAs, International Standard Reference Preparations and gold-standard calibration methods are used.
- PRC and PAC measured in hypertensive patients in seated position with these two ChLIAs are similar in males and females. In addition, with both assays the PRC and PAC response to the postural stimulus is similar to that described with conventional methods.
- In a large cohort of hypertensive patients the ARR determination using these ChLIAs has detected PA cases with a high degree of sensitivity and specificity.
- Aldosterone suppression in response to blood volume expansion with saline infusion is a reliable confirmation method for PA diagnostics in patients with high ARR.
- Both ChLIAs have higher inter-laboratory reproducibility than conventional radioimmunoassays, do not require radioactive material and have the additional advantage of being processed on a fully automated analyzer platform that allows the simultaneous determination of hundreds of samples in less than one hour.
- The technical features of the renin and the aldosterone ChLIA are included in the tables in reference 6.

Endocrine hypertension

 Product name	Description	Code*
Aldosterone	100 tests, calibrators included	IS-3300/IS-3330
Direct Renin	100 tests, calibrators included	IS-3400/IS-3430

* IS-##30 are the corresponding control sets

References

1. Laragh, J.H. and J.E. Sealey Abnormal sodium metabolism and plasma renin activity (renal renin secretion) and the vasoconstriction volume hypothesis: implications for pathogenesis and treatment of hypertension and its vascular consequences (heart attack, stroke). Clin Chem 37(10 Pt 2): 1820–7 (1991).
2. Alderman, M.H., et al., Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. N Engl J Med 324(16): 1098–104 (1991).
3. Laragh, J.H., Renin profiling for diagnosis, risk assessment, and treatment of hypertension. Kidney Int 44(5): 1163–75 (1993).
4. Rossi, G.P., et al., A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. J Am Coll Cardiol 48(11): 2293–300 (2006).
5. Funder, J.W., et al., The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 101(5): 1889–916 (2016).
6. Manolopoulou, J., et al., Clinical validation for the aldosterone-to-renin ratio and aldosterone suppression testing using simultaneous fully automated chemiluminescence immunoassays. J Hypertens 33(12): 2500–11 (2015).

Connect with us



 +44 191 519-6155

 www.idsplc.com

 Follow us

Global Headquarters

Immunodiagnostic Systems
10 Didcot Way, Boldon Business Park
Boldon, Tyne & Wear, NE35 9PD,
United Kingdom

Tel: +44 191 519-0660
Fax: +44 191 519-0760

IDS Germany

Herriotstraße 1
60528 Frankfurt
Germany

Tel: +49 69 26019-0940
Fax: +49 69 26019-0949

EUROIMMUN



 +49 451 2032-0

 www.euroimmun.com

 Follow us

Global Headquarters

EUROIMMUN Labordiagnostika AG
Seekamp 31
23560 Lübeck
Germany

Tel: +49 451 2032-0
Fax: +49 451 2032-100