Clarification of hypertension – Diagnosis of primary hyperaldosteronism

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The significance of the aldosterone/renin ratio (ARR) in the diagnosis of normo-alaeic and hypokalaemic primary hyperaldosteronism, the most common causes of secondary hypertension

Epidemiology of primary hyperaldosteronism

Primary hyperaldosteronism (PH) is the most common cause of secondary hypertension. Apart from hypertension, hypokalaemia was hitherto considered to be the classical cardinal symptom. Its presence was therefore also usually a prerequisite for further diagnostic clarification in respect of PH. However, numerous new studies in normokalaemic hypertension patients now show that serum potassium levels are within the reference range in approximately 90% of PH patients.

On the basis of the new data, which were obtained by determining the aldosterone/renin ratio (ARR), the frequency of PH in hypertensives – 5-13% – is much higher than previously suspected (0.1-1%) [1, 2, 3, 19].

On the cautious assumption that PH is the underlying cause in 5% of all hypertensives, over 800,000 people in Germany would be affected by this diagnosis. Aldosterone-producing adenoma as a cause of hypertension can in principle be cured by surgery.
Aetiology of primary hyperaldosteronism

- **Aldosterone-producing adenoma (APA = Conn’s syndrome) (approx. 30-40%), unilateral**
- **Idiopathic hyperaldosteronism (IH) (approx. 60%), bilateral**
- **Macronodular adrenocortical hyperplasia (MNH) (1-5%), unilateral or bilateral**
- **Aldosterone-producing carcinoma (adrenal or ectopic, e.g. ovarian) (1%)**
- **Familial hyperaldosteronism (FH)* (1-5%), type I (= GSH**) and II

Table 1: Classification of primary hyperaldosteronism (PH) [1, 2]
The stated frequencies refer to the total PH group (normokalaemic and hypokalaemic). If – as before – only the hypokalaemic PH patients are included, APA is the most common cause, at around 70% [3].
* For details of diagnosis and treatment, see [3]. ** GSH = glucocorticoid-suppressible hyperaldosteronism

Optimized PH screening: the aldosterone/relin ratio (ARR)

Since the diagnosis of PH opens up effective, inexpensive treatment options [4, 5], extended laboratory screening with additional determination of the aldosterone/renin ratio (ARR), including normokalaemic patients, is now generally accepted [1, 2, 17, 19]. The following antihypertensives should be discontinued before the aldosterone-renin ratio is determined: spironolactone – 4 weeks before blood sampling; beta blockers, AT2 antagonists, loop diuretics, imidazoline receptor agonists, and ACE inhibitors – 2 weeks before blood sampling in each case [15, 17 and Table 2]. Alternative medication for treating hypertension during diagnosis is available [17].

![Fig. 1](classification_of_disturbances_of_the_renin-angiotensin-aldosterone_system_using_the_aldosterone/relin_ratio(ARR)_and_aldosterone. Marked in are the limits recommended by our laboratory for the identification of patients with PH (ARR: 30; aldosterone 15 ng/dl), according to [2, 9, 10, 17]. If the ARR is > 30 and aldosterone is < 15 ng/dl, further clarification in respect of PH may also be indicated and successful.)
- **Optimized PH screening:**
  - **target groups**
  
  In the following groups of patients, optimized PH screening with additional determination of the aldosterone/renin ratio (ARR) is recommended [1, 17, 19]:
  
  - Hypertensives with hypokalaemia
  - Hard-to-stabilize hypertensives with a blood pressure > 140/90 despite treatment with three antihypertensive drugs
  - Young hypertensives (< 30 years of age) with a positive familial history or a cerebrovascular event
  - Incidentaloma (compressive process in the adrenal gland) with hypokalaemia or hypertension
  - Hypertensives with other signs of secondary hypertension
  - All hypertensives with first-degree relatives who had primary hyperaldosteronism
  - Young hypertensives (< 40 years of age) with a blood pressure > 160/100
  - Hypertensives with a blood pressure > 180/110

- **Procedure if a pathological result is obtained in the PH screening**

  - **Confirmation of diagnosis**

  After a positive result in screening, the diagnosis of PH must be confirmed with further testing.

  The principal confirmatory test recommended, on the basis of its practicability (for outpatients) and evaluation [15], is the salt loading test: 2 litres of isotonic saline is infused into the patient, in a recumbent position, between 8 and 12 o’clock (contraindication: heart failure, state after myocardial infarct; severe, uncontrolled hypertension).

  At 8 o’clock and 12 o’clock blood is collected for analysis of plasma aldosterone and plasma renin.

  In patients without autonomous aldosterone secretion, plasma aldosterone is suppressed by at least 50% by the infusion of saline, or aldosterone levels normalize. In PH, there is no, or no clear, suppression of the elevated baseline aldosterone values. The salt loading test should be performed under the same medication as the screening test [15]. The fludrocortisone suppression test, which has likewise been well evaluated in the literature, is very expensive, because of the need to spend 5 days in hospital. Analysis of aldosterone-18-glucuronide in 24-h urine under oral salt loading should only be carried out as an alternative if the salt loading test is contraindicated/impracticable. Administration of 3 x 2 g NaCl/day in addition to the normal diet (approximately 9 g NaCl/day) for a period of 3 days is recommended for this, to give a daily sodium intake of roughly 260 nmol/day. Since aldosterone-18-glucuronide represents only about 20% of total aldosterone secretion and there are no up-to-date evaluation studies, this test is less conclusive than the salt loading test [15]. On the 3rd day of oral salt loading, aldosterone-18-glucuronide must be in the normal range and urinary sodium in the check on salt supply must be > 200 mmol/24 h.

- **Clarification of the aetiology in cases of confirmed diagnosis**

  When the diagnosis of PH has been confirmed, the aetiology is further investigated using biochemical methods (analysis of aldosterone, renin, and cortisol in the orthostasis test; 8 o’clock (recumbent position), 12 o’clock (standing)) and imaging techniques (CT or MRI) [see 1, 2, 3]. For the orthostasis test, care must be taken to ensure that the patient remains constantly in horizontal position for at least 8 h before the start of the test, something which is only possible in an
inpatient setting. After collection of the first sample of blood in the recumbent position, the patient is to adopt an erect posture for 4 h. Another blood sample is then collected for the analysis of aldosterone, renin, and cortisol in the standing position.

A typical sign of an aldosterone-producing adenoma is an apparently paradoxical drop in the aldosterone concentration between 8 o’clock (recumbent position) and 12 o’clock (standing) in the orthostasis test, which can be explained by ACTH-dependence on aldosterone secretion.

In bilateral adrenocortical hyperplasia, on the other hand, preserved angiotensin II-dependence on aldosterone secretion with an increase of over 30% in aldosterone under orthostasis is typical. 30% of adenomas also show an increase in aldosterone in orthostasis, however. If the results of the orthostasis test and imaging techniques agree, the aim is to give the relevant specific therapy (adrenalectomy or spironolactone therapy). If a clear differential diagnosis between adenoma and hyperplasia is not possible with these tests, selective adrenal venous blood sampling with analysis of aldosterone and cortisol is indicated. Selective adrenal venous blood sampling should always be carried out, however, if surgical treatment is probable [17].

Patients with aldosterone-producing adenoma typically show an aldosterone/ cortisol ratio gradient of more than 5:1 to the adenoma-affected side. [2]. Other sources speak of more than 2:1 [15, 16] or more than 3:1 [18].

If an aldosterone-producing adenoma is present, the treatment of choice is (laparoscopic) adrenalectomy; long-term therapy with spironolactone is an alternative.

For patients with bilateral idiopathic hyperplasia, the only thing left is drug treatment with a mineralocorticoid receptor antagonist (e.g. spironolactone), possibly in combination with ACE inhibitors and beta blockers [2].

Pre-analysis and sampling for determination of the ARR

- The patient should have been in an erect position (sitting, standing, or walking) for at least 2 h before the blood sampling
- Blood (EDTA blood) to be collected from the patient in an erect sitting position between 8 and 10 o’clock in the morning after a 15-min phase at rest in a sitting position
- Since hypokalaemia leads to false-positive results, this must be compensated for beforehand through potassium supplementation [15]
- There should be no restriction of sodium in the period before blood sampling (sufficient salt)
- Obtain 2 ml EDTA plasma by centrifuging the EDTA blood
- Transfer the EDTA plasma into a new tube labelled with a bar code with the name of the material (“EDTA plasma”) and patient data on
- Send to Bioscientia FROZEN
- Some antihypertensives should be discontinued for a certain period before blood sampling [see Table 2]
- Request on the request form as: “Aldosterone/Renin ratio”
Flow diagram: Procedure to be followed if primary hyperaldosteronism is suspected/to be excluded

Screening

Aldosterone/Renin ratio

Salt loading test
(If the salt loading test is contraindicated or impracticable:
analysis of aldosterone-18-glucuronide in 24-h urine under oral salt loading)
or fludrocortisone suppression test

Confirmation of diagnosis

Differential diagnosis

CT or MRI of adrenals and renin-aldosterone orthostasis test

Results agree:
Unilateral tumour and decrease in aldosterone

Results differ:
Tumour, but increase in aldosterone
or
No tumour, but decrease in aldosterone

Adrenal vein catheterization to determine the aldosterone/cortisol ratio

Aldosterone-producing adenoma

Gradient

No gradient

Idiopathic hyperaldosteronism

Fig. 2: Differential diagnosis and clarification of PH [according to 1, 2]
Before surgical treatment, selective adrenal venous blood sampling with determination of the aldosterone/cortisol ratio should always be performed to confirm the diagnosis.
Medication group | Recommended break
---|---
Increase in aldosterone/renin ratio (false-positive results) |  
- Beta receptor blockers | At least 2 weeks  
- Imidazoline receptor antagonists (e.g. clonidine) | At least 2 weeks

Decrease in aldosterone/renin ratio (false-negative results) |  
- Thiazide diuretics |  
- Loop diuretics | At least 2 weeks  
- ACE inhibitors | At least 2 weeks  
- Calcium antagonists | -  
- Alpha receptor blockers (e.g. doxazosin) | -  
- Angiotensin II antagonists (sartans) | At least 2 weeks  
- Spironolactone, eplerenone, drospirenone, amiloride, triamterene | At least 4 weeks

Table 2: Effects of antihypertensives on the aldosterone/renin ratio [15, 17]

### References
