

*Personal Opinion***The hypertensive patient with hypokalaemia: the search for hyperaldosteronism**

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**Introduction***Factitious normokalaemia*

The physical chemical determination of plasma potassium concentration is very precise. However, the matrix where potassium is determined, the plasma, is a notoriously unreliable partner. This fact is generally recognized when patients with hyperkalaemia are considered. Because potassium concentrations are 20-fold higher within the cell than outside, the potassium concentration is facticiously high whenever potassium shifts from the intra- to the extracellular compartment during or after venipuncture. As a corollary, in a subject with hypokalaemia *in vivo* one might measure 'normal' potassium concentrations when such a factitious potassium shift has occurred. Patients like this may in reality be hypokalaemic. Thus, in clinical practice we have to ascertain that normokalaemia is not an artifact in patients with hypertension. The mechanisms accounting for factitious normokalaemia are: (i) repeated fist clenching with or without tourniquet; (ii) traumata venipuncture with a small gauge needle; (iii) delayed centrifugation or placing the sample on ice; (iv) thrombocytosis or myeloproliferative disorders; (v) blood clotting; (vi) acute hyperventilation due to fear of venipuncture; and (vii) abnormal leak of potassium through red blood cell membranes at lower temperature as a consequence of hereditary stomatocytosis (rare) [1–9]. In view of all these caveats it is completely unknown how often we miss the diagnosis of hypokalaemia. Hypokalaemia has arbitrarily been defined as plasma potassium level less than 3.5 mmol/l.

**Transtubular potassium gradient (TTKG) and related tests**

In the distal nephron, mineralocorticoids increase reabsorption of sodium and secretion of potassium.

Therefore, three indirect markers of renal mineralocorticoid activity have been utilized in the past based on the urinary excretion of sodium and potassium. The fractional excretion of potassium (i.e. the fraction of the filtered potassium load excreted into the urine), is probably a poor reflection of aldosterone action because filtered potassium is almost completely reabsorbed and the amount of potassium detected in urine is almost exclusively the result of distal secretion. Under steady-state conditions urinary potassium excretion must equal dietary potassium intake [10]. The urinary potassium/sodium ratio depends on dietary sodium and potassium intake as well. For the same reasons it is not a reliable indicator of mineralocorticoid activity [11]. The transtubular potassium gradient (TTKG) derived from the urine/plasma potassium ratio divided by the urine/plasma osmolality ratio has been popularized [12,13]. This index provides a semi-quantitative assessment of the apparent transtubular potassium concentration gradient in the major distal nephron segment, where potassium is secreted. This index can be applied to situations where the urine is not hypotonic and distal nephron sodium delivery is not a limiting factor for potassium secretion. The utility of the TTKG for the detection of mineralocorticoid excess has recently been challenged based on the results obtained in normal volunteers treated with spironolactone or fludrocortisone [14]. During the administration of the mineralocorticoid, the TTKG as well as the urinary potassium/sodium ratio and the fractional excretion of potassium in urine increased in each subject. However, the differences between these indices in the fludrocortisone and spironolactone test periods were diminished by day 3 and were non-existent by day 4. Since the duration of the study was limited to 4 days it is unknown whether a discrimination between mineralocorticoid excess and mineralocorticoid antagonism would have been detected if the observation period had been prolonged beyond the time when mineralocorticoid escape is expected (> 10 days). Escape from relentless salt retention requires a balance between ingestion and excretion of electrolytes at steady state; therefore, the urine index will eventually reflect the daily intake of sodium, potassium and other osmotically active

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substances. Since the homeostasis of these electrolytes is regulated by various hormones, channels and carriers, it is highly unlikely that the analysis of serum or urine electrolytes alone will allow one to diagnose mineralocorticoid excess.

### Magnetic resonance angiography

Since the much beloved sodium and potassium measurements in serum and urine do not provide sufficient diagnostic power to confirm or exclude exaggerated renal sodium retention in response to mineralocorticoid excess as the cause of arterial hypertension, more sophisticated and expensive methods are required in the diagnostic work-up of subjects with hypertension. As the development of hypertension is usually a steadily advancing process, one cannot define the time point when these methods should be applied in a given person. Currently renal artery stenosis is the most common mechanism underlying hyperaldosteronism. Not surprisingly, specialists do not agree on the selection criteria for screening for renovascular hypertension. Many physicians still use the criteria proposed by Mann and Pickering [15]. Although renovascular hypertension is uncommon in comparison to essential hypertension, it is a potentially curable disease and therefore in my opinion should never be missed.

The many tests proposed in the past have been predominantly radiological and functional. For patients with normal renal function the first test recommended is ACE inhibitor renography, conventional renography, or colour Doppler sonography [16]. Since I try to avoid iodine-containing contrast media and the fluctuating competence of the Doppler sonographer, my preferred method for detection of the renal artery stenosis is magnetic resonance angiography although I acknowledge that this may be biased. The main advantage of this unusual sequence in the work up of hypertension is the possibility of visualizing adrenal adenomas with a sensitivity close to a 100% and a specificity between 64 and 70% during one and the same diagnostic procedure [17,18]. As an additional benefit this procedure allows one to exclude major renal parenchymal disease which might account for hypertension. Mahler [19] performed the first renal artery angioplasty in our institution in 1977 (and not Grüntzig as erroneously reported [20]). Ever since, and particularly after the development of the stent technology, whenever we decided to enhance renal blood flow to the kidney by using catheter techniques we do not ascertain the renin level. This strategy is based on the impression (though unfortunately based on little or no evidence), that: (i) the intervention has few major side effects; and (ii) power of the renin level to predict the change of blood pressure after dilatation of a stenosis is far from impressive. Furthermore, I believe that protecting renal parenchyma from hypoperfusion is beneficial for preservation of renal function in patients in whom impaired renal function is to a large extent attributable to a decreased blood supply

[21]. Note that the decision to perform angioplasty in order to prevent the loss of function of the heart and in the brain is also mainly based on radiological data exclusively. A note of caution is nevertheless necessary. My optimistic view that all renal arteries with a stenosis of more than 70% have to be opened up is not supported by evidence from studies analysed by traditional statistical methods and with, at least in my opinion, too short a follow-up of 12 months only. A beneficial effect on renal function and blood pressure of treating a unilateral renal artery stenosis in the presence of a normal contralateral kidney can probably be documented in no more than 10% of the patients and might be counterbalanced by complications resulting from the treatment particularly in patients with a non-disease (i.e. narrowing of the luminal diameter by 50% or less) [22].

### Hormones

The diagnostic hallmark for primary aldosteronism is subnormal renin activity in the presence of high-normal or increased aldosterone concentrations. About two-thirds of the patients have a solitary aldosterone-producing adenoma of the adrenal gland and one third exhibit bilateral adrenal hyperplasia. It is still controversial which method is optimal for this differential diagnosis. In most of the patients with an adenoma, aldosterone and renin do not increase by changing from the supine to the erect position, whereas in subjects with bilateral hyperplasia there is a concomitant increase of aldosterone and renin [23,24]. In patients with equivocal results, invasive adrenal vein cannulation or iodocholesterol scans or tests for angiotensin II responsiveness have been proposed.

An autosomal dominant form of low renin hypertension with normal or moderately increased aldosterone excretion is the so called glucocorticoid-suppressible hyperaldosteronism, a disease state which is best diagnosed by the increased urinary excretion of 18-hydroxycortisol. The molecular mechanism for this disease state is a cross-over between the genes encoding for the enzyme 11- $\beta$ -hydroxylase, which catalyzes the last step in cortisol biosynthesis, and the gene for aldosterone synthetase, [25]. This chimeric gene contains the promoter region of the 11- $\beta$ -hydroxylase which is under the control of adrenocorticotrophic hormone (ACTH). Therefore, mineralocorticoid hormone production is regulated by ACTH and can be inhibited by the administration of exogenous glucocorticosteroids such as dexamethasone in these patients. Since with this mutation aldosterone is synthesized in the zona fasciculata, hybrid steroids such as 18-oxocortisol which require the action of 17 $\alpha$ -hydroxylase, are excreted in the urine [26].

11-deoxycorticosterone (DOC) has mineralocorticoid activity and causes hypertension with increased urinary potassium excretion, low renin activity and decreased aldosterone production. DOC is increased in three disease states: (i) DOC producing

adrenal adenomas [27]; (ii) 11- $\beta$ -hydroxylase deficiency [28], an autosomal recessive disease state with low renin, low aldosterone hypertension with ACTH-induced hypersecretion of adrenal androgens; in its classic form (CYP11B1 deficiency) the diagnosis is best made by the demonstration of elevated DOC concentrations after administration of ACTH; and (iii) 17 $\alpha$ -hydroxylase deficiency [29], an autosomal recessive disease with low plasma renin activity and blockade of production of sex steroids with resulting sexual infantilism in females or male pseudohermaphroditism.

The enzyme 11- $\beta$ -hydroxysteroid dehydrogenase type 2, converts cortisol to cortisone in cells expressing mineralocorticoid receptors (MR). By this mechanism it protects the MR from promiscuous occupation by cortisol [30]. When this enzyme is inhibited by liquorice [31], or absent in the rare patient with a loss of function mutation of the 11- $\beta$ -hydroxysteroid dehydrogenase [32], cortisol activates MR and causes a low renin, low aldosterone hypertension. The diagnosis can be made from an increased urinary ratio of tetrahydrocortisol plus 5 $\alpha$ -tetrahydrocortisol to tetrahydrocortisone or of cortisol to cortisone [33]. In the past, the loss of function mutation of the 11- $\beta$ -hydroxysteroid dehydrogenase type 2 had been called apparent mineralocorticoid excess.

### Personal history or therapy 'exjuvantibus'

Recently, a gain of function mutation has been found in the mineralocorticoid receptor. This mutation results in a constitutively active MR. The receptor is then further activated by progesterone and other steroids including, paradoxically, the MR antagonist spironolactone [34]. Therefore, such patients may paradoxically develop severe hypertension when treated with spironolactone and women with this mutation develop severe progesterone-induced hypertension during pregnancy. On the basis of the underlying mechanism, one can predict that subjects with a gain of function mutation in the MR have low renin activity and low aldosterone concentration.

Patients with Liddle's syndrome have hypertension with hypokalaemia and low renin and aldosterone concentrations and respond to inhibitors of epithelial sodium transport such as triamterene or amiloride, but not to mineralocorticoid receptor antagonists such as spironolactone [35,36]. The underlying mechanism is a gain of function mutation producing an epithelial sodium channel that allows an increased sodium passage from the tubular lumen into the blood compartment. Patients with Liddle's syndrome also exhibit low renin activity and low aldosterone concentrations.

### Conclusions

Steadily increasing innovations in the field of mineralocorticoid-induced hypertension currently preclude

an economically sound and epidemiologically founded recommendation on diagnostic work-up and therapy of the hypertensive patient with hypokalaemia. Nevertheless, since secondary hyperaldosteronism due to increased renal renin production is still the number one cause of mineralocorticoid-induced hypertension, radiological investigation of the kidney remains the corner stone. Renal artery stenoses can be corrected by angioplasty or stents without surgical intervention. Therefore this diagnosis should not be missed.

Provided that the radiological investigations are performed by non-nephrotoxic magnetic resonance angiography, adrenal adenomas can be detected during the same procedure. Since laparoscopic removal is now possible, such adenomas should no longer be missed. Comparison of laparoscopic *vs* open adrenalectomy has revealed that the time to resumption of diet (1.6 *vs* 6.1 days) and independent activity (1.6 *vs* 7.9 days), inpatient length of stay (1.7 *vs* 7.8 days) and total hospital patient charges (reduced by one third) were all significantly reduced in patients undergoing laparoscopic instead of open adrenalectomy at the Johns Hopkins University, School of Medicine [37]. As a consequence of the much reduced trauma of the surgical intervention, I am now more easily convinced to transfer a patient to a surgeon even when there remains some doubt whether the adenoma is the culprit for hypertension. Although the response of aldosterone and renin to posture is still regarded to be of pivotal relevance in our institution, one has to be aware that this test does not provide 100% certainty in distinguishing between bilateral adrenal hyperplasia and aldosterone-producing adenomas. The traditional view is that adrenal imaging should be undertaken only when primary aldosteronism has been biochemically confirmed. Since I suggest that the exclusion of renal artery stenosis should be a very early step during diagnostic work-up, the result from the adrenal imaging is usually available before the biochemical data are obtained. Nevertheless, before the final decision for or against laparoscopic intervention is made, both the biochemical data and the radiological result should be available to allow appropriate interpretation of the case.

The molecular defects of several forms of monogenic mineralocorticoid-like hypertension have recently been characterized. In screening in our own laboratory, we use gas chromatography-mass spectrometry to measure: (i) urinary DOC to find patients with hypertension related to congenital adrenal hyperplasia (11- $\beta$ -hydroxylase or 17 $\alpha$ -hydroxylase deficiency) or DOC secreting adenomas; (ii) 18-hydroxycortisol to diagnose glucocorticoid-remediable hyperaldosteronism; and (iii) the urinary ratios of cortisol/cortisone or tetrahydrocortisol plus 5 $\alpha$ -tetrahydrocortisol divided by tetrahydrocortisone for the diagnosis of 11- $\beta$ -hydroxysteroid dehydrogenase deficiency (Table 1).

When all these investigations are negative we go on to a therapeutic trial and prescribe triamterene with the intention of diagnosing Liddle's syndrome. Whether or not such therapeutic trials are relevant

**Table 1.** Parameters considered during the search for mineralocorticoid hypertension

Cause	Diagnostic parameter
Secondary hyperaldosteronism	renin magnetic resonance angiography
Aldosterone-producing adenoma Bilateral hyperplasia Adrenal carcinoma	renin/aldosterone: supine and erect magnetic resonance angiography
Deoxycorticosterone-producing adenoma	deoxycorticosterone* magnetic resonance angiography
11- $\beta$ -hydroxylase/aldosterone synthase chimeric gene (Glucocorticoid-remediable hyperaldosteronism)	18-hydroxycortisol*
11- $\beta$ -hydroxysteroid dehydrogenase deficiency (apparent mineralocorticoid excess)	(THF + 5 $\alpha$ THF)/THE*** or cortisol/cortisone*
11- $\beta$ -hydroxylase deficiency (congenital adrenal hyperplasia)	deoxycorticosterone*
17 $\alpha$ -hydroxylase deficiency	deoxycorticosterone*
Activated epithelial Na <sup>+</sup> channel (Liddle's syndrome)	amiloride-test
Activating mineralocorticoid receptor mutation	spironolactone-test? progesterone/pregnancy?

\*Determined in urine; \*\*THF, tetrahydrocortisol; 5 $\alpha$ THF, 5 $\alpha$ -tetrahydrocortisol; THE, tetrahydrocortisone.

for the detection of activating mineralocorticoid receptor mutations by prescribing spironolactone or progesterone is unknown at the present time. Furthermore, it is an open question whether or not these mutations should be identified at the DNA level as we do in our laboratory. Such characterizations are useful for several reasons; first, for the understanding of the clinical phenotype, a prerequisite for rational therapy and genetic counselling [23,24,38]; second, for the mechanistic analysis of structure and function of the enzyme/channel [25,34,35,39]; and third, most importantly, for the detection of genotypes with a less aggressive phenotype compared to the mutations described so far. This might lead to an increased understanding of more common forms of (essential) low renin, low aldosterone hypertension.

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