Endocrine Causes of Hypertension

A large number of secondary causes of hypertension are known (see table 1). Hyperaldosteronism is probably the commonest secondary cause of hypertension and appropriate investigation requires a careful understanding of the physiology of aldosterone secretion and the effects of anti-hypertensive medications on regulation of the renin-angiotensin system.

Aldosterone, a salt retaining hormone produced by the adrenal cortex, may be secreted in excess and independent of salt, water balance or renin/angiotensin\(^1\). Consequently, in appropriately prepared patients, the measurement of renin plus aldosterone and the calculation of the aldosterone renin ratio (ARR) is extremely helpful in the initial investigation of patients suspected of suffering from primary hyperaldosteronism (PHA)\(^2\).

ARR as a screening test was first introduced in 1983\(^3\). With the use of ARR, it was recognised that PHA was more common than previously appreciated (>5% of hypertensive patients) and the presence of hypokalemia was less common than normokalemia in patients proven to have PHA (10-30% have hypokalemia in PHA)\(^4\). More recently, PHA has been associated with excess cardiovascular morbidity due to cerebrovascular disease, myocardial infarction or arrhythmia compared to patients with essential hypertension and similar blood pressure control\(^5\). The frequency of these co-morbidities is reversed by surgery or specific medications that antagonise aldosterone action\(^6\). Case detection therefore offers the dual potential of surgical cure of the patient and/or minimisation of morbidity.

When should you test the ARR?

Recent guidelines have suggested the following patient categories should be considered for screening for PHA\(^7\):

1. Moderate, severe or resistant hypertension: BP > 160/100 or BP >140/90 despite 3 anti-hypertensive medications
2. Hypertension with spontaneous or diuretic induced hypokalemia
3. Presence of adrenal adenoma: note such adrenal masses could represent non-functioning “incidentalomas”- see later.
4. Hypertension and family history of early onset hypertension or CVA at age < 40
5. Hypertensive 1st degree relatives of patients with previous proven PHA

Some have argued that all hypertensive patients should be screened for PHA as the longer the diagnosis is missed, the higher likelihood of irreversible morbidity, the lower likelihood of curative surgery and screening before the introduction of anti-hypertensive medications makes ARR interpretation easier\(^8\).

### Table 1 – Secondary Causes of Hypertension

- Hyperaldosteronism: Primary 5%
- Phaeochromocytoma
- Cushings syndrome
- Congenital Adrenal Hyperplasia
- Adrenal virilising tumours
- Acromegaly
- PCOS: metabolic syndrome complication
- Thyroid disease
- Primary hyperparathyroidism: not used as criteria for surgery
- B-type naturetic peptide

Measuring renin and aldosterone

Whilst renin is the main regulator of aldosterone secretion, serum potassium, ACTH and changes in hepatic blood flow can also effect aldosterone secretion. A number of factors can affect renin release as well as aldosterone secretion and consequently the ARR. There is a need to control these extraneous factors, where possible.

The ARR is a simple ratio of the serum aldosterone, usually measured in pmol/L divided by the plasma renin, usually measured in mU/L. Consequently, similar to other ratios, such as FAI etc, it is the denominator, that is the plasma concentration of renin, that dominates the calculation of the ratio. Consequently, one limitation of ARR is that the ratio can be elevated purely in the presence of a very low renin concentration, such as occurs in advancing renal failure or in low renin, essential hypertension. Some laboratories, therefore, don’t report the ratio when the aldosterone values are very low (<300 pmol/L) to minimise the risk of over-interpretation of the result.

In a patient with PHA, renin is usually less than 10mU/L and typically often less than 5 mU/L. Serum aldosterone is typically greater than 420 pmol/L and as a consequence, an ARR of >50-70 is used by some laboratories. The lack of consensus regarding the specific value of the ratio can be partially explained by some differences between methods of renin and aldosterone analysis but also emphasises the divided literature in this area of diagnosis\(^7\).
Posture

Upright posture results in a rise in serum aldosterone due to a secondary increase in renin release. This effect occurs in healthy normotensive individuals as well as most patients with PHA. In practice, most centres measuring ARR use a mid-morning ambulant sample usually obtained after sitting for 5 to 10 minutes.

Time of day

In patients with PHA, renin is suppressed so aldosterone concentration may be influenced by ACTH levels which show a circadian rhythm. Consequently, ARR is more likely to be elevated in the morning in PHA as ACTH is highest at this time of day.

Dietary Na and serum/plasma K

Dietary sodium restriction may stimulate renin release and consequently lower the ARR. The sensitivity of the ARR can be improved by ensuring a liberal dietary salt intake.

Since potassium can stimulate aldosterone secretion, hypokalemia can be associated with a false negative ARR in PHA. Consequently, correction of serum K before assessing ARR is important. Concomitant assessment of creatinine and K with renin and aldosterone measurement is advisable.

Anti-hypertensive medications: beware the false positives!

Beta blockers inhibit renin output as sympathoadrenal function is an additional important regulator of rennin. Renin output can be reduced with aldosterone concentrations being less affected. The latter may be due to continued stimulatory effects of serum potassium and ACTH on aldosterone production. As a consequence, false positive ARR may occur. Methylaopa and clonidine may have similar effects to beta blockers on the ARR.

Anti-hypertensive medications: beware the false negatives!

Diuretics, dihydropyridine calcium antagonists (DHCA’s), angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB’s) can all increase renin more than aldosterone and in cases with PHA can result in false negative diagnoses. Diuretics induce volume contraction and consequent sympathoadrenal activation, DHCA’s induce reflex sympathoadrenal activation and ACE inhibitors or ARB’s may potentially interfere in the negative feed-back effect of angiotensin II on renin production.

Other medications

NSAID’s can suppress renin while concomitantly promoting potassium retention leading to stimulation of aldosterone production and an elevation in the ARR. Oral contraceptive agents probably have little effect on ARR when older renin activity assays were in use. However, newer mass renin assays could be affected as potentially, oestrogen could increase hepatic production of angiotensinogen resulting in increased angiotensin I, angiotensin II and consequently, greater feedback inhibition on renin. Newer oral ocs containing drospierone or gestodene (Yasmin, Yaz,) could equally and falsely increase ARR.

Other physiological effects

One recent study has indicated that ARR is higher in the luteal compared with the follicular phase but only when measuring renin using a mass and not an activity assay. Further studies are needed, but it is probably preferable to measure ARR in the follicular phase pending further data. Renal failure may result in false positive ARR due to reduction in renin secretory mass or salt and water retention. Pregnancy or renal artery stenosis may result in false negative ARR due to physiological renin stimulation.

Suggested testing of ARR and correction of pre-analytical factors

It is preferable to correct serum K before analysis of ARR and collect a sample for serum K and creatinine whenever measuring ARR. Normal unrestricted diet is preferred and medications which significantly affect the ARR should be listed on the request form.

If, for example, renin is relatively high (>10mU/L) whilst taking beta blockers, clonidine or methylaopa and assuming no other medication use or physiological effects, then the likelihood of PHA is low if the ARR is low. Consequently, further investigation may be unnecessary. Alternatively, if the ARR is high in the presence of diuretics, DHCA’s or ARB’s then PHA is likely.

If anti-hypertensive medication effects are causing possible interference then withdrawal of beta blockers plus most other agents for at least two weeks, diuretics for at least four weeks and specifically spironolactone for 6 weeks may be required. Prazosin, verapamil SR or hydralazine have been shown to have least effects on the ARR and can be used as alternative anti-hypertensive agents in the meantime.

A number of additional tests including oral salt loading, saline suppression, fludrocortisone suppression and captopril challenge are currently used to confirm PHA with recent consensus guidelines concluding that there is insufficient direct evidence to recommend one specific test.
Lateralisation and the role of imaging

Adrenal CT scanning is recommended once the ARR has been proven to be consistently and unequivocally elevated. Unfortunately, some aldosterone producing adenomas (APA’s) are too small to identify, small APA’s can be misinterpreted as representing hyperplasia and non-functioning, incidentalomas cannot be distinguished from APA’s on CT imaging. MR imaging has no advantage over CT imaging and is more expensive. However, CT imaging will exclude adrenocortical carcinomas which are fortunately rare.

Further testing is required in order to confirm lateralisation of aldosterone production. Adrenal venous sampling (AVS) involves bilateral adrenal vein cannulation to confirm unilateral as opposed to bilateral aldosterone production. The interpretation of AVS is beyond the scope of this article but it should be performed in a centre with extensive radiological experience and interpreted by pathologists with an understanding of the limitations of this methodology. Consequently, referral to an endocrinologist with experience and understanding of AVS is advisable when a diagnosis of PHA is suspected in general practice.

Treatment

Unilateral, laparoscopic adrenalectomy is advisable if unilateral aldosterone production is confirmed by AVS. 50% of patients may be cured of hypertension (BP<$140/90 without anti-hypertensive agents) following successful surgery and 100% have improvement in BP control and serum potassium concentration. Laparoscopy compared to open adrenalectomy is associated with shorter hospital stay and fewer complications.

In patients who decide against surgery, where AVS fails to lateralise aldosterone production or if AVS is unsuccessful due to lack of successful cannulisation of both adrenal veins, medical management can be pursued with either spironolactone, amiloride or eplerenone. Whilst eplerenone is a newer and more selective aldosterone antagonist it is only PBS listed in Australia for the management of heart failure so there are cost implications for patients who chose this treatment.

Conclusions

PHA should be considered in higher risk groups of hypertensive patients and in the presence of spontaneous or diuretic induced hypokalemia. ARR is ideally measured in the morning, in the early follicular phase of pre-menopausal women and should be interpreted carefully taking into consideration the effects of anti-hypertensive and other medications which can alter the renin-angiotensin system. Withdrawl of interfering medications should be considered where appropriate. All patients with PHA should undergo CT imaging and the presence of unilateral aldosterone production should be established or excluded by AVS. Laparoscopic unilateral adrenalectomy is optimal management for PHA due to an APA. Patients with bilateral adrenal hyperplasia or who are unsuitable for surgery should be offered medical treatment with mineralocorticoid receptor antagonists.

References


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