

Mineralocorticoid Hypertension: Common and Treatable



Hypertension is the most common chronic disease treated by the primary-care physician. It is now evident that mineralocorticoid hypertension, which is most commonly caused by primary aldosteronism, is much more prevalent and can be readily diagnosed and treated.

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Introduction

About 20% of the Canadian population suffers from hypertension. Individuals with this disease are at higher risk of developing heart disease, stroke and renal failure. Hypertension accelerates the process of atherosclerosis and is the most important modifiable risk factor for coronary artery disease and stroke.¹ Fortunately, it is relatively easily diagnosed and often easily treated.²

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Case

John, a 41-year-old man, was referred to the Cardio-vascular Risk Factor Reduction Unit (clinic) for assessment of hyperlipidemia and hypertension. He had been found to have a blood pressure (BP) of 148-160/90-100 mmHg on several visits to his doctor. Medications he was taking included pravastatin 10 mg daily. He had no other complaints, no clinical evidence of atherosclerosis, and his family history was benign for early cardiovascular events. His body mass index was 27 and his waist measurement was 92 cm. His BP averaged 154/102 mmHg. His blood count and urinalysis were normal, the serum potassium 3.6 mmol/L, and serum creatinine 89 μ mol. His fasting glucose was 5.8 mmol/L, total cholesterol 7.3 mmol/L, triglycerides 3.31 mmol/L, high density lipoprotein 1.3 mmol/L and low density lipoprotein 4.5 mmol/L. He was instructed in a weight-reducing, low-fat diet, the pravastatin dosage was increased to 20 mg, and he was also prescribed acebutolol 200 mg daily. Three months later, his BP was 148/98 mmHg. His medication regime was augmented by felodipine ER 5 mg daily. After a further three months, his BP was still about 150/100 mmHg and hydrochlorothiazide 25 mg daily was added to his medications. After two weeks his serum potassium was 3.1 mmol/L.



Question: *What is the next step?*

Discussion *on page 40*

Table 1

Criteria for the Diagnosis of Primary Aldosteronism

Old Criteria for Primary Aldosteronism*

- Hypertension
- Hypokalemia
- Low plasma renin activity
- High aldosterone excretion

New Criteria For Primary Aldosteronism**

- Hypertension
- High plasma aldosterone/renin ratio (ARR)

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Adapted from:

* Conn JW: The evolution of primary aldosteronism: 1954-1967. *Harvey Lect* 1966; 62:257-91.

** Lim PO, Jung RT, MacDonald TM: Raised aldosterone to renin ratio predicts antihypertensive efficacy of spironolactone: A prospective cohort follow-up study. *Br J Clin Pharmacol* 1999; 48:756-60.

Among hypertensive patients, 85% to 90% are classified as having primary or essential hypertension, when a cause for their hypertension cannot be identified. The remainder are classed as having secondary hypertension, because a cause for the condition can be identified. Causes of secondary hypertension include the following:

- Ingestion of substances known to increase blood pressure (BP);
- Pheochromocytoma;
- Cushing's syndrome;
- Renal hypertension (which can be parenchymal or renovascular);
- Acromegaly;
- Coarctation of the aorta; and,
- Mineralocorticoid hypertension.

Once thought to be rare, mineralocorticoid hypertension has emerged as the most common of secondary causes. This article will review recent literature and discuss the authors' experiences with this condition.

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The steroid hormones produced by the adrenal gland include mineralocorticoids

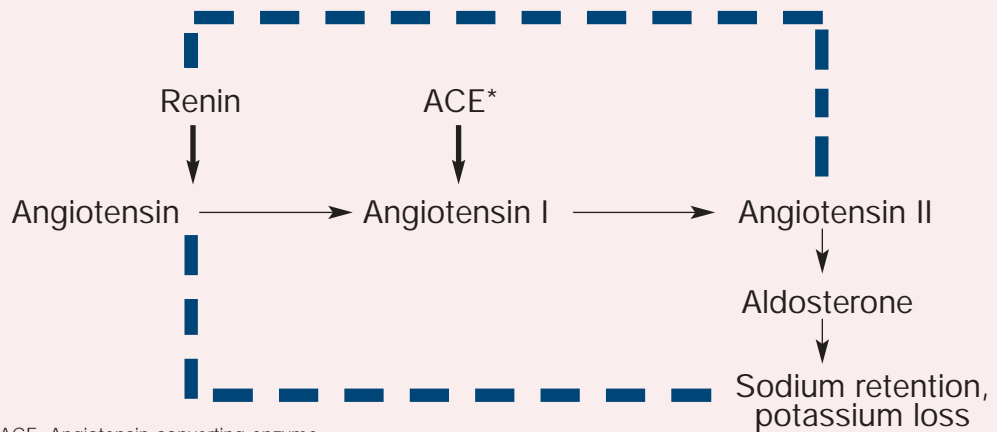
and glucocorticoids. Both act on intracellular receptors. Mineralocorticoid hypertension results from the inappropriate activation of the mineralocorticoid receptor, particularly in the kidney. This leads to increased sodium and water retention, increased potassium excretion, and suppressed plasma renin activity. Intravascular volume is reset at a higher level, leading initially to increased cardiac output and increased BP. Chronically, there are other mechanisms involved in raising BP, as the increase in intravascular volume is not always maintained.³

The majority of mineralocorticoid hypertension is due to primary aldosteronism (PA). Aldosterone-producing adenoma, first described by Dr. Jerome Conn over 40 years ago, accounts for 10% to 50% of the cases of primary aldosteronism.⁴ Bilateral adrenal hyperplasia (also called idiopathic hyperaldosteronism), unilateral (or primary) adrenal hyperplasia, glucocorticoid remediable and adrenal carcinoma, are other causes. Until recently, PA was felt to be rare, with a prevalence of 0.5% to 2.0% among hypertensive patients.⁵ We now diagnose PA in 5% to 12% of our hypertensive patients.⁶ This difference is due

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Figure 1

The Renin-Angiotensin-Aldosterone System



to new criteria for the diagnosis (Table 1). The lack of hypokalemia in the new diagnostic criteria increases the prevalence tenfold, making PA the most common cause of secondary hypertension by far. One out of every 10 hypertensive patients may have this disorder. It is important to recognize PA for several reasons. First, patients with PA may respond better to certain classes of antihypertensive drugs than others. Secondly, some cases are curable, and thirdly, most patients will develop hypokalemia if prescribed a thiazide diuretic. Recent data from the Systolic Hypertension in the Elderly Program (SHEP) suggest elderly hypertensives who are treated with thiazides and who become hypokalemic derive no benefit from antihypertensive therapy, even though BP is reduced.⁷ Finally, untreated PA may lead to a higher incidence of hemorrhagic stroke and renal failure, as compared to essential hypertension.⁸

Diagnosis

While some suggest screening for mineralocorticoid hypertension be carried out in all

hypertensives, this is not likely to be cost effective. Certain clinical clues should improve the efficiency of testing. Suspect PA when a patient develops hypokalemia on diuretic therapy. Remember the level of serum potassium may drop to, or below, the lower limit of normal. Also, if an angiotensin converting enzyme (ACE) inhibitor is used as first-line therapy, patients with PA will have little or no change in BP.

As the name implies, PA is characterized by the overproduction of aldosterone. It is further characterized by suppressed plasma renin activity (PRA). Under normal physiologic conditions, aldosterone secretion is under the control of the renin-angiotensin system, shown in Figure 1. Decreased blood flow to the kidney, due to dehydration for example, causes increased production of renin. This, in turn, leads to increased levels of angiotensin I and angiotensin II, which increases production of aldosterone. In PA, aldosterone production is autonomous. Renin is then suppressed due to the salt-retaining effects of aldosterone and increased renal arterial pressure.

Neither a random level of serum aldosterone, nor PRA by itself, is of much use in

screening for PA. In the case of aldosterone, both day-to-day and diurnal variations of serum levels are considerable. Levels are also affected by antihypertensive medications and serum potassium. PRA is modified by antihypertensive treatment and the position of the patient (supine or standing).⁹ When used together to calculate an aldosterone/renin ratio (ARR), however, screening has proven more successful. It has been shown that the ARR can be used as a random screening test and continues to be valid even in the presence of antihypertensive medications.¹⁰ One caveat is that profound hypokalemia can reduce aldosterone secretion — this should be corrected before measuring the ratio.

Furosemide Stimulation And The ARR

Autonomous production of aldosterone means that not only is renin activity suppressed, but it does not increase in response to various stimuli. Normally, the loop diuretic furosemide, given orally, stimulates PRA in two to four hours because of natriuresis. Upright posture can also stimulate PRA. When obtaining the ARR, many physicians measure plasma aldosterone and PRA after the administration of 40 mg to 60 mg of oral furosemide, followed by three to five hours of upright posture. Recently, however, suppression of serum aldosterone after oral captopril has been proposed as a diagnostic tool for PA.¹¹ Non-suppressible serum aldosterone, after captopril, correlated well with the level of aldosterone in plasma after salt-loading. Whether this single measurement will be a better screening test than the ARR is unknown.

The authors prefer to use the intravenous furosemide test, then calculate the ARR. It



has been shown that, in both normotensive and hypertensive subjects, intravenous furosemide stimulates a rapid increase in PRA.¹² Peak increases occur at about 10 minutes. In PA however, PRA does not increase after intravenous furosemide (see Figure 2). In the authors' clinic, they obtain plasma aldosterone and PRA at 0, 10, and 30 minutes after the administration of 40 mg of intravenous furosemide. The value of this method is twofold. First, it greatly reduces the time required to obtain values and eliminates the necessity of having the patient remain upright for such an extended period. Second, the diagnostic value of the ARR is enhanced because it is measured not once, but three times, increasing the accuracy of the estimate of the true ratio.

Two difficulties arise with the use of the ARR for the diagnosis of PA — inconsistency in the way plasma aldosterone is reported and the lack of consensus on the value that should be considered diagnostic of PA. In the U.S., plasma aldosterone is reported

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Table 2

Results of Furosemide Stimulated Renin-Testing

Group (range)	Age (range)	Male/Female	SBP (range)	DBP (range)	Serum K (range)	ARR (range)
Positive ARR	60 (36 to 77)	10/4	158 mmHg (128 mmHg to 190 mmHg)	87 mmHg (70 mmHg to 102 mmHg)	3.5 mmol/L (2.8 mmol/L to 4.3 mmol/L)	93 (13 to 562)
Negative ARR	67 (50 to 80)	6/7	154 mmHg (124 mmHg to 182 mmHg)	83 mmHg (56 mmHg to 104 mmHg)	3.7 mmol/L (3.1 mmol/L to 4.7 mmol/L)	8 (0.2 to 42)

SBP: Systolic blood pressure DBP: Diastolic blood pressure Serum K: Serum potassium concentration
ARR: Average plasma aldosterone/renin mass ratio. Range indicates extremes of individual values.

in units of ng/dL and PRA as ng/ml/h, whereas elsewhere it is reported in SI units: pmol/L and ng/L/sec. respectively. The threshold level of ARR in American units varies from 20 to 45, the most common being 30. In SI units, this translates to 900. A further complication has recently arisen: many labs in Canada (including the authors') measure not PRA, but renin mass. Renin mass consists of both active (*i.e.*, that contributing to PRA) and inactive renin. The relation between renin mass and PRA is complex — the higher the renin mass, the greater the percentage of renin that is active. At high renin mass concentrations (as might be seen in shock or scleroderma), therefore, up to 95% of it is active, while at low renin mass, as little as 1% is active. For patients with primary hypertension, about 5% of renin is active.¹³ Accordingly, the authors submit that a reasonable threshold ARR in SI units is 45 (900/[100/5]).

The results of the authors screening with the intravenous furosemide stimulation test are shown in Table 2. In each of these

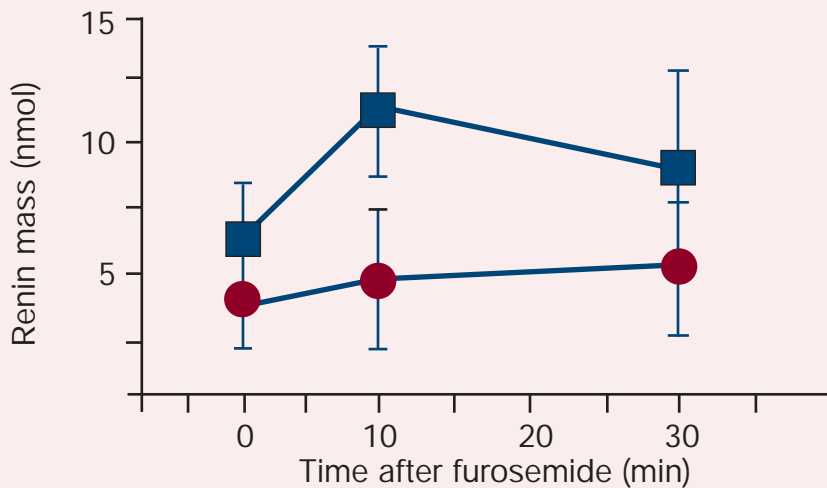
patients, the test was performed because of hypokalemia on diuretics, resistant hypertension, or both. Of these 27, 14 had ARR values deemed to be consistent with PA (1 or more ARR > 45), while 13 had a negative test which was considered to rule out PA (all ARR < 45). All "positive" patients were offered spironolactone and all but one had reduced BP or needed fewer antihypertensive drugs within three to six months. Subsequently, all had abdominal computed tomography (CT) scanning. Two patients were found to have adrenal masses and both underwent surgical resection and had a dramatic fall in BP. None of the "negative" patients were started on spironolactone or subjected to CT scanning.

Finding the Cause of Primary Aldosteronism

In Conn's original series of patients with primary aldosteronism, about 75% of patients with PA had an adenoma. When

Figure 2

Renin Mass in Patients Screened For Primary Aldosteronism



Renin mass after furosemide stimulation. Filled squares are patients whose average ARR was < 45; open circles are patients whose ARR was > 45. Error bars are standard deviation.

these were resected, about 80% of patients showed a drop in BP. Now that the diagnostic standards for PA have been relaxed, we find fewer adenomas. Unfortunately, the technology to determine whether or not an adenoma is present remains imperfect. CT, magnetic resonance imaging (MRI), scanning with 125-iodine labeled cholesterol, and differential adrenal vein sampling for aldosterone, have all been utilized — none are perfect. The authors believe if an adrenal mass > 2.5 cm is found on CT, it should be resected. Laparoscopic surgery is generally safe and well-tolerated. Otherwise, the authors use spironolactone.

Treatment

Spironolactone, a mineralocorticoid antagonist, remains the drug of choice for PA. Lim

et al found doses of 25 mg/day to 200 mg/day reduced BP to <160/90 mmHg in about 80% of patients, while reducing the need for other antihypertensive drugs.¹⁴

Spironolactone is also an androgen receptor antagonist and produces painful gynecomastia, particularly at higher doses. Usually these symptoms can be controlled with a one-month course of tamoxifen 20 mg daily. Many patients require a

repeat course once or twice per year. If the patient cannot tolerate spironolactone, anecdotal evidence suggests amiloride 10 mg to 30 mg daily might be useful. Finally, a new, not yet marketed mineralocorticoid antagonist, eplerenone, is devoid of anti-androgen effects.

Case Discussion


After correction of the low serum potassium with supplements, John underwent measurement of the aldosterone/renin ratio before and after furosemide 40 mg intravenously. The results:

Time after furosemide	Renin mass	Serum aldosterone	Aldosterone/renin ratio
0 minutes	< 1 μmol	391 pmol	> 391
10 minutes	< 1 μmol	285 pmol	> 285
30 minutes	< 1 μmol	273 pmol	> 273

The high aldosterone/renin ratios are suggestive of primary aldosteronism. Felodipine was discontinued and spironolactone 100 mg daily begun. A computed tomography scan of the abdomen showed normal adrenal glands. Six months later, his BP was 128/86 mmHg on spironolactone alone.

Conclusion

Hypertension is the most common chronic disease treated by the primary-care physician. Published guidelines provide direction for its diagnosis and treatment, but often, the decision to investigate for secondary causes is left to the specialist. It is now evident that mineralocorticoid hypertension, the most common cause of which is primary aldosteronism, is much more common and readily diagnosed.

Primary aldosteronism can be suspected in those with difficult to control BP and/or hypokalemia. Suspicion warrants measuring the ARR, the efficiency of which is enhanced with the intravenous furosemide stimulation test. This provides a fairly easy and robust screening test. If “positive,” further testing to detect a resectable (and possibly curable) adrenal adenoma, is indicated. Glucocorticoid remediable hyperaldosteronism can now be confirmed by genetic testing, which might best be done under the guidance of a specialist. 

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