Primary hyperaldosteronism—seek and you may find

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Abstract: Primary hyperaldosteronism (PHA), also referred to as primary aldosteronism (PA), remains a largely under-recognized and suboptimally managed secondary cause of hypertension, associated with significant cardiovascular morbidity and mortality. When caused by a classical unilateral Conn’s adenoma, it is potentially curable with adrenalectomy. However, identifying this remains problematic and acts as a barrier to best management. The gold-standard investigation to determine lateralization is adrenal vein sampling (AVS). This procedure is invasive and technically challenging, and results can be inconclusive. Hence, there has been much interest in finding a noninvasive yet reliable alternative to this, and the most promising candidate at present is 11C-metomidate positron emission tomography-computed tomography (PET-CT) scanning. We present the case of a patient with PHA in whom initial imaging revealed bilateral adrenal pathologies: however, after having both AVS and 11C-metomidate PET-CT which showed unilateral overproduction of aldosterone, the patient had an adrenalectomy with improvement of blood pressure. We discuss the benefits of this investigation and the potential impact it could have on managing PHA. ▪ Heart Metab. 2019;79:30-33

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Case report

A 66-year-old retired quality surveyor was referred to the Guy’s Hospital (London, UK) hypertension clinic in 2011. His general practitioner had been struggling to control his high blood pressure (BP), which was not causing symptoms. He was diagnosed with hypertension in his early 20s during a routine medical check for work. He had a background history of hypercholesterolemia, and had been diagnosed with colonic adenocarcinoma in 2011, which was managed by surgery followed by radiotherapy and chemotherapy.

At his first clinic visit, he was taking four antihypertensive medications, namely bumetanide 1 mg od, lisinopril 20 mg od, diltiazem modified-release 120 mg od, and doxazosin 4 mg od. His lowest clinic BP was 156/88 mm Hg. He was investigated for secondary causes of hypertension. Renin was 7.4 mU/L and aldosterone 277 pmol/L, giving an aldosterone:renin ratio (ARR) of 37.4, all of which were in the normal ranges. He had mild renal impairment with creatinine 99 μmol/L and eGFR 66 mL/ min, but potassium was within normal at 4.3mEq/L. Thyroid-stimulating hormone (1.47mIU/L) was also normal.

As no secondary cause for hypertension was revealed, he was managed with adjustment of his medications. Doxazosin was initially increased to 8 mg od and reduced as his BP control improved. However, in attempts to adequately control his elevated BP over the subsequent years, the daily dose of diltiazem gradually increased to 300 mg. Bumetanide was replaced by bendroflumethiazide. He developed
a dry cough attributed to the angiotensin-converting enzyme (ACE) inhibitor and was switched to the angiotensin receptor blocker losartan at a dose of 100 mg od. Despite these changes in his medications, his home BPs remained high and his clinic BP was 152/94 mm Hg.

It was decided to reinvestigate for secondary causes in 2016. At this point, renin was suppressed at 4.3 mU/L and aldosterone raised at 641 pmol/L, giving an elevated ARR of 149. He remained normokalemic (4.2 mEq/L). A saline suppression test confirmed failure to adequately suppress aldosterone following a 2-hour saline load. Adrenal magnetic resonance imaging (MRI) revealed bilateral adrenal body adenomas, measuring 11 mm on the right and 12 mm on the left.

At this point he was enrolled into the MATCH (Is Metomidate PET-CT superior to Adrenal venous sampling to predict outcome of adrenalectomy in Hyperaldosteronism?) study. He underwent successful adrenal vein sampling (AVS, Figure 1) which demonstrated raised aldosterone concentration in the right adrenal vein with an elevated lateralization index (LI) of 1.1. The cortisol-corrected aldosterone concentration is calculated in both adrenal veins and the LI is the ratio of the higher value over the lower. LIs greater than 2 to 4 (depending on the center) indicate unilateral disease.

Following AVS, he underwent 11C-metomidate positron emission tomography-computed tomography (PET-CT), which identified a single right-sided 14x14 mm tumor with SUV$_{max}$ of 1.18 (Figure 2). This corresponded to a medium probability of a right-sided aldosterone-producing adenoma (APA).

Both tests therefore suggested right-sided primary hyperaldosteronism (PHA). He underwent an uncomplicated laparoscopic right adrenalectomy and was discharged home 2 days later. He did not exhibit postoperative hypoadrenalism, nor did he require mineralocorticoid replacement.

In the weeks preceding his adrenalectomy, the patient’s plasma aldosterone concentration was 991 pmol/L and renin 1 mU/L. Home BPs averaged 180/95 mm Hg. 10 months post-adrenalectomy, his home BP was 134/91 mm Hg on average and his medications had reduced to losartan 50 mg od and lercanidipine 20 mg od. Aldosterone had reduced to 191 pmol/L and renin to 0.9 mU/L.

Whilst the patient tolerated the AVS and did not experience any adverse events or complications relating to this, he expressed a preference for the 11C-metomidate PET-CT scan as this was a more straightforward and familiar procedure which was relatively quick and noninvasive. Post-adrenalectomy, he was pleased that that the number of medications had reduced significantly and that his blood pressure was better controlled.

**Discussion**

An important stage in the management pathway for patients with suspected PHA is to subtype this as either unilateral or bilateral disease. The significance of identifying lateralization is in the subsequent management. In patients with unilateral disease, adrenalectomy can be offered with the potential to cure hypertension (in 30% to 60%) and/or correct hypokalemia.
In bilateral disease or in patients with unilateral disease who do not want or are not suitable for surgery, the management is targeted drug therapy with a mineralocorticoid receptor antagonist.1

The current gold standard investigation to differentiate unilateral from bilateral pathology is AVS, wherein the adrenal veins are catheterized and samples taken for cortisol and aldosterone measurement. An elevated aldosterone: cortisol ratio on one side indicates unilateral PHA, whereas elevation of this ratio on both sides indicates bilateral disease.2,3 AVS has a sensitivity of 95% and a specificity of 100% for detecting unilateral aldosterone excess.1

However, there are significant disadvantages to AVS. It is an invasive and expensive investigation. There are substantial technical challenges, particularly regarding successful cannulation of the right adrenal vein, which is much smaller than the left and drains directly into the vena cava rather than into the renal vein.2 The right adrenal vein is successfully cannulated in 74% of procedures.1 The main complication is adrenal vein rupture, which occurs in 0.51% to 0.61% of cases.3 There is much heterogeneity in how AVS is performed and how results are interpreted. The adrenal veins can either be sampled simultaneously or sequentially, and sampling can be done with or without cosyntropin.2,3 Cosyntropin use minimizes stress-induced and time-related fluctuations in aldosterone secretion.2 Prior to the AVS, hypokalemia should be corrected, and medications known to stimulate renin should be stopped, which may prove challenging in patients with severe hypertension. If the AVS result shows that both adrenals were not successfully catheterized, the procedure may need to be repeated.3

Given the multiple challenges that AVS poses, eligible patients may not even undergo the procedure. These patients may be managed medically and not offered the unilateral adrenalectomy which could potentially cure them. There may also be a resistance from clinicians to initially screen for PHA but also to improve the willingness of clinicians to investigate for it.11C-metomidate PET-CT is a promising rival to the current gold standard of AVS. Historically, metomidate was used as a veterinary anesthetic but later found to be a potent inhibitor of the human adrenal steroidogenic enzymes CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase). Metomidate can be labeled as a PET radiotracer that selectively accumulates in tissue that secretes aldosterone to excess. The 11C-metomidate PET-CT combines noncontrast CT images with dynamic PET images to create standardized uptake value (SUV) maps. The maximum uptake (SUVmax) is higher in APAs than normal adrenal tissue.7,8 Dexamethasone can be given to suppress background adrenal CYP11B1, enhancing the selectivity of metomidate for CYP11B2, which is ACTH-independent and preferentially expressed in APAs.9 Several studies have assessed the usefulness of 11C-metomidate PET-CT in PHA subtyping.7-12 The largest study included 39 patients with PHA.12 The investigators determined that using an SUVmax ratio of 1.25 provided a specificity of 87% (95% CI 69-104) and a sensitivity of 76% (95% CI 59-93) for identifying APAs.12 In areas with a SUVmax >17, the specificity rose to 100%. This study concluded that 11C-metomidate PET-CT is non-inferior to AVS and should be considered as a noninvasive alternative.

Conclusion

We describe the case of a patient in which PHA was discovered over 45 years after his initial hypertension diagnosis. There were bilateral adrenal changes on
standard (MRI) imaging, but AVS and a novel investigation, 11C-metomidate PET CT, showed right-sided PHA, which was managed by adrenalectomy, with resultant improvement in blood pressure control.

For patients with unilateral PHA, adrenalectomy offers superior health outcomes compared to medical management alone. Proving lateralization with AVS has its challenges, however 11C-metomidate PET-CT may be a useful noninvasive alternative to this. Current available evidence for this imaging modality is based on small patient numbers, and further studies are required to determine its true usefulness in wider clinical practice. As a noninvasive investigation, it may prove to be a powerful tool to break down the barriers in detecting unilateral PHA in the hypertensive population and to better managing this underdiagnosed, potentially curable condition.

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REFERENCES


