



Nuclear imaging in the diagnosis of primary aldosteronism

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Purpose of review

Primary aldosteronism is increasingly recognized as a common secondary cause of hypertension. Successful demonstration of a unilateral cause (e.g. a classical 'Conn's adenoma') offers the potential for curative adrenalectomy. Adrenal vein sampling (AVS), in conjunction with cross-sectional imaging, remains the 'gold standard' for distinguishing unilateral and bilateral disease, but is technically demanding and frequently unsuccessful or inconclusive. As such, alternative strategies for lateralization, including nuclear medicine techniques, are being developed and brought into clinical practice.

Recent findings

Metomidate, a potent ligand of CYP11B1 and CYP11B2, can be C¹¹H₃-labelled as a PET tracer and has been shown to offer a rapid noninvasive alternative to AVS for localizing unilateral aldosterone-producing adenomas.

Summary

Increasing experience with ¹¹C-metomidate PET-CT supports its use as an adjunct to AVS when this has failed, is ambiguous, or cannot be undertaken.

Keywords

metomidate, PET-CT, primary aldosteronism/hyperaldosteronism

INTRODUCTION

Hypertension is a major determinant of excess cardiovascular morbidity and mortality, especially myocardial infarction, and stroke. Well established algorithms for stepwise pharmacological management of 'essential' hypertension exist, alongside lifestyle interventions [1]. However, identifying a specific cause for hypertension, such as primary (hyper)aldosteronism, yields the possibility of targeted drug therapy or, more enticingly, the potential for surgical cure. Indeed, the impetus to diagnose and manage primary aldosteronism is further strengthened by the recognition that aldosterone excess is associated with morbidity over and above that in a matched population with primary hypertension [2]. Primary aldosteronism is increasingly recognized as a common secondary cause of hypertension and is reported in approximately 5–10% of all hypertensive patients and in 20–25% of those with documented treatment-resistant hypertension [3,4]. In around half of all cases of primary aldosteronism, the hypersecretion is attributable to a single aldosterone-producing adenoma (APA) in one adrenal gland, and when this is the case

adrenalectomy offers the possibility of a cure of hypertension in a significant proportion of patients. However, currently only one in 10 eligible patients proceed to surgery [3]. Perhaps the most significant hurdle is the need to confirm that primary aldosteronism is indeed the result of unilateral disease, thus distinguishing an isolated APA from other causes of primary aldosteronism, including bilateral idiopathic hyperaldosteronism

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Curr Opin Endocrinol Diabetes Obes 2015, 22:150–156

DOI:10.1097/MED.0000000000000148

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KEY POINTS

- Unilateral primary aldosteronism is a common cause of hypertension and is potentially curable by adrenalectomy.
- Diagnosis of unilateral primary aldosteronism has conventionally relied on AVS, which is invasive and is often uninformative as a result of inherent technical challenges.
- ¹¹C-metomidate PET-CT offers a rapid noninvasive alternative to AVS for localizing unilateral APAs.

and familial syndromes, which may coexist with a nonfunctioning adrenal adenoma (incidentaloma) [5]. Currently, nonlateralizing primary aldosteronism is treated medically, but this has been shown to have poorer cardiovascular outcomes than surgery for unilateral disease [6,7].

ADRENAL VEIN SAMPLING IN THE DIAGNOSIS OF PRIMARY ALDOSTERONISM

The first step in establishing lateralization typically involves cross-sectional imaging [thin-slice computed tomography (CT) or MRI]. In patients under 35 years of age, the finding of a classical solitary Conn's adenoma (1–2 cm diameter), with an entirely normal contralateral gland may be sufficient to proceed direct to surgery [8]. In the majority of cases however, further proof of unilaterality is required, as several studies have shown that reliance on cross-sectional imaging alone is fraught with risk. This is nonspecific, as nonfunctioning adrenal incidentalomas are common in patients more than 40 years of age (4–7% of the population) [5]. It is also insensitive as small nodules (<1 cm in diameter) may be missed, especially if located within the body of the adrenal, and a common sub-tier of small APAs was recently identified through finding hallmark somatic mutations, distinct from those in classical Conn's adenomas [9]. The gold-standard lateralization procedure remains bilateral adrenal vein sampling (AVS) [10]. However, this is technically challenging and in many centres the right adrenal vein is successfully cannulated in only 50–80% of cases [11,12]. In addition, several different sets of criteria exist for defining both successful adrenal vein cannulation and subsequently lateralization, based on the measurement of plasma cortisol and aldosterone levels in both adrenal veins and in the inferior vena cava [13]. In recognition, that both cortisol and aldosterone secretion can be

pulsatile, some centres perform AVS with cosyntropin stimulation and/or sampling of the adrenal veins simultaneously, rather than sequentially. Both measures aim to reduce the risk of false lateralization [14,15].

The difficulties inherent in achieving successful AVS, coupled with the potential need for many more patients to be referred for lateralizing studies as primary aldosteronism is increasingly recognized, has led to a search for alternative strategies to circumvent the 'hurdle' of AVS in progressing patients to surgery. Küpers *et al.* [16] assessed the potential utility of a clinical scoring system in predicting unilateral disease. In 87 patients with primary aldosteronism and successful AVS, lateralization was demonstrated in 49 patients. All 26 patients with a typical Conn's adenoma and serum potassium level less than 3.5 mmol/l or estimated glomerular filtration rate at least 100 ml/min/1.73 m² (or both) had unilateral primary aldosteronism; this rule had 100% specificity and 53% sensitivity. However, subsequent studies from both the UK [17] and Germany (German Conn's Registry) [18] were unable to reproduce the 100% specificity (88.5 and 80%, respectively). Accordingly, interest has been rekindled in functional imaging techniques to complement cross-section imaging and AVS and which would allow a more definitive assessment of lateralization to be delivered to many more patients than is currently achievable in the majority of centres.

NUCLEAR MEDICINE IMAGING IN THE DIAGNOSIS OF PRIMARY ALDOSTERONISM

Norcholesterol scintigraphy

Historically, ¹³¹I-iodomethyl-norcholesterol (NP-59) and ⁷⁵Se-selenomethyl-19-norcholesterol have been used as scintigraphic tracers for the detection of APAs [19,20]. In both cases, high dose dexamethasone treatment (e.g. 8 mg per day for >1 week) to suppress tracer uptake by nonautonomous adrenal cortex is given, and patients are required to attend for image capture on several occasions. In addition, the accuracy of distinguishing an APA from bilateral hyperplasia is as low as 47% in studies using planar imaging, which in particular lacks the resolution to reliably detect lesions less than 1.5–2 cm in diameter. It may also erroneously identify gastrointestinal activity as adrenal uptake. Single photon emission computed tomography/CT has been proposed as a means of addressing these concerns, although significant numbers of false-positive and false-negative categorizations have been observed even in modern case series [21].

Although attempts have been made to improve sensitivity and specificity with semiquantitative approaches to this technique [22[■]], the requirement for prolonged dexamethasone suppression, sequential imaging, and limited tracer availability mean that it is unlikely to be considered a viable alternative to AVS in most centres.

¹¹C-metomidate PET-CT

Recent interest has focussed on the potential utility of PET-CT, with its increased spatial resolution, as an alternative imaging modality for the detection of functional autonomy in primary aldosteronism. Metomidate is a potent inhibitor of CYP11B1 (11 β -hydroxylase) and CYP11B2 (aldosterone synthase). It is the methyl analogue of etomidate, an ethyl-imidazole anaesthetic agent which is used clinically in subhypnotic doses as an inhibitor of adrenal steroidogenesis in the management of refractory Cushing's syndrome [23]. Metomidate (itself used as a veterinary anaesthetic until the 1970s) can be C¹¹H₃-labelled as a PET radiotracer (¹¹C-metomidate), and proof of concept of its high affinity binding to adrenal cortex was established *in vitro* and in primate studies as far back as 1998 [24]. In the first human application [25], 15 patients underwent ¹¹C-methionine PET-CT prior to surgery for a unilateral adrenal mass. The nine histologically diagnosed adrenocortical tumours each demonstrated high uptake and could be reliably discriminated from the six lesions that were not of cortical origin. In a larger follow-up series, comprising 73 patients who underwent surgery for suspected adrenal lesions, the six histologically confirmed APAs demonstrated the highest ¹¹C-metomidate uptake, with a standardized uptake value (SUV) of 30.7 compared with 18.4 in nonfunctional adenomas [26]. These findings suggested that ¹¹C-metomidate PET-CT might offer an alternative technique for the lateralization of Conn's adenomas and provided preliminary evidence to support a formal study of sensitivity and specificity in an unselected cohort of patients with unilateral and bilateral primary aldosteronism.

We recently reported the findings of such a study in which the potential utility of ¹¹C-metomidate PET-CT for establishing lateralization in primary aldosteronism was assessed through direct comparison with the current 'gold standard' of AVS in a prospective noninferiority trial [27[■]]. Based on the findings of a small pilot study, all patients received a short course of low-dose dexamethasone (0.5 mg 6-hourly for 72 h) immediately prior to undergoing a single PET-CT scan. This well tolerated pretreatment regimen improved the

signal to background ratio through suppression of ¹¹C-metomidate uptake by nonadenomatous adrenal cortex. Interestingly, pretreatment with fludrocortisone (400 μ g daily), either alone or in combination with the dexamethasone, showed no additional benefit. Of 44 recruited individuals, 39 had primary aldosteronism and five a nonfunctioning adrenal incidentaloma (these individuals were normotensive and had no clinical or biochemical evidence of adrenal hyperfunction). In the group with primary aldosteronism, 19 had a unilateral cause identified at AVS, and a further six were confirmed to have unilateral disease on the basis that subsequent unilateral adrenalectomy reversed their biochemical primary aldosteronism and cured their hypertension, despite a failure to conclusively lateralize on AVS (the decision to recommend surgery in these cases was taken independently by the referring physician with primary responsibility for the patient's care). Of those deemed to have unilateral primary aldosteronism on AVS, all but three proceeded to surgery. All operated cases demonstrated a histological adenoma with dominant CYP11B2 expression, and aldosterone production in primary culture of cells from the resected nodule, which exceeded that of adjacent normal tissue. Ten patients met the criteria for a diagnosis of bilateral primary aldosteronism. Four patients were excluded from the final analysis as they did not proceed to surgery, in the absence of a clear-cut AVS result and indication for surgery.

¹¹C-metomidate uptake was calculated as the SUV_{max} during the final 10 min of data acquisition. In patients with primary aldosteronism and a unilateral APA, the mean SUV_{max} over the adenoma [21.7 ± 1.6 (range 10.3–38.9)] was significantly greater than in the surrounding normal adrenal tissue SUV_{max} [13.8 ± 0.6 ($P < 0.00003$)] [27[■]]. Patients with an adrenal incidentaloma (and no clinical or biochemical evidence of primary aldosteronism) demonstrated a lower mean tumour SUV_{max} of 11.5 ± 3.3 (range 0–16.6). Patients with primary aldosteronism and bilateral adrenal hyperplasia or bilateral adenomas had a mean SUV_{max} of 17.3 ± 1.2 [27[■]]. Calculation of the ratio of tumour SUV_{max} to normal background adrenal SUV_{max} revealed that an SUV ratio greater than 1.25 afforded optimal sensitivity (76%) and specificity (87%). Importantly, specificity increased to 100% in patients with an SUV_{max} ratio greater than 1.25 and absolute tumour SUV_{max} of greater than 17 [27[■]].

Taken together, these findings provide confirmatory evidence that ¹¹C-metomidate PET-CT offers a noninferior alternative to AVS in the diagnosis of unilateral primary aldosteronism. Since our original

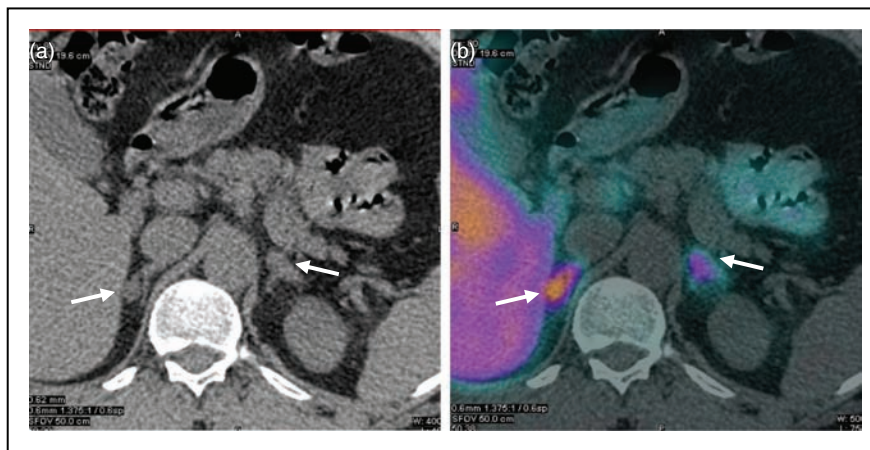


FIGURE 1. Case 1 – ^{11}C -metomidate PET-CT identifies unilateral primary aldosteronism in a patient with equivocal cross-sectional imaging. A 56-year-old man with significant ischaemic coronary disease had poorly controlled hypertension despite treatment with multiple agents. Further investigation confirmed a diagnosis of primary aldosteronism. CT revealed an 8 mm lipid poor right adrenal nodule, which could not be fully characterized because of its small size (a). In addition, the body of the left adrenal gland was noted to be bulky, but without a discrete lesion. Adrenal vein sampling (AVS) demonstrated a right-sided gradient ($>4:1$), but in light of the equivocal cross-sectional imaging findings the patient proceeded to ^{11}C -metomidate PET-CT. This confirmed increased tracer uptake [target:background standardized uptake value (SUV)_{max} ratio 1.44] in the right adrenal nodule only (b). The patient underwent laparoscopic right adrenalectomy, which confirmed a classical small Conn's adenoma. Postoperatively, he had complete resolution of his hyperaldosteronism and required just single agent therapy (amlodipine) to achieve satisfactory blood pressure control. This case illustrates how the increased spatial resolution of ^{11}C -metomidate PET-CT facilitates the reliable identification of subcentimetre Conn's adenomas.

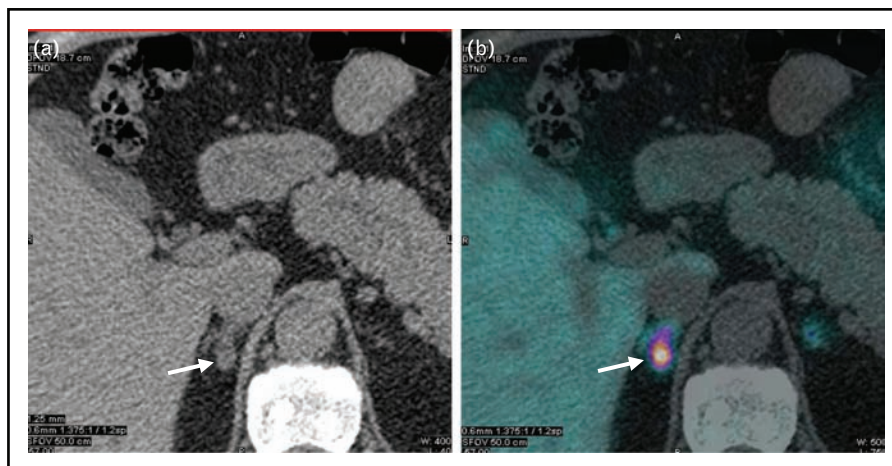


FIGURE 2. Case 2 – ^{11}C -metomidate PET-CT identifies unilateral primary aldosteronism despite mineralocorticoid receptor antagonist therapy. A 63-year-old man with a 10-year history of primary aldosteronism treated medically with mineralocorticoid receptor antagonist therapy was referred for reassessment and consideration of possible adrenalectomy. His blood pressure had previously proved difficult to control until the introduction of spironolactone, and the patient was reluctant to discontinue this to permit adrenal vein sampling (AVS). MRI demonstrated an 11 mm right adrenal nodule (a). ^{11}C -metomidate PET-CT confirmed avid tracer uptake within this lesion [target:background standardized uptake value (SUV)_{max} ratio 2.45] (b). He underwent laparoscopic right adrenalectomy, with histology confirming an adrenal cortical adenoma. Postoperatively, he had complete resolution of his biochemical hyperaldosteronism and hypertension with no requirement for antihypertensive therapy. This case illustrates the utility of ^{11}C -metomidate PET-CT in establishing unilateral primary aldosteronism even in patients who are unable or unwilling to discontinue mineralocorticoid receptor antagonist therapy.

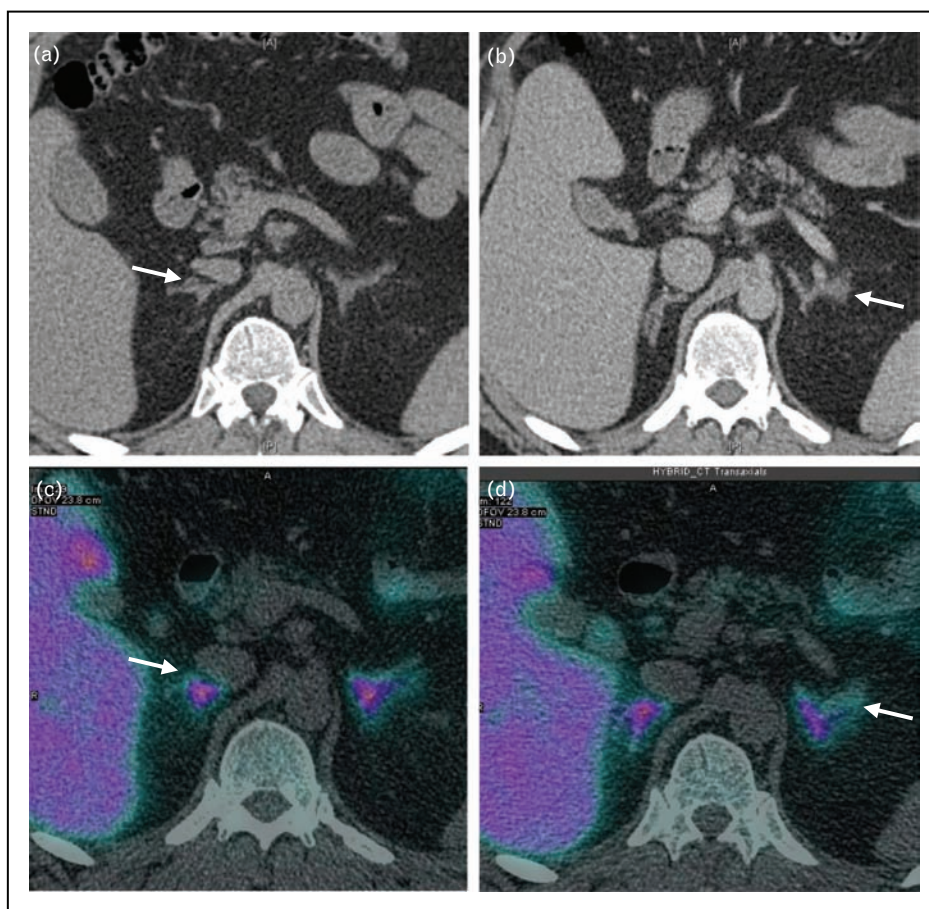


FIGURE 3. Case 3 – ^{11}C -metomidate PET-CT in bilateral primary aldosteronism with adrenal incidentalomas. A 52-year-old man was found to have primary aldosteronism during participation in a study of treatment-resistant hypertension. CT showed 7 mm right and 16 mm left adenomas (a and b), but with no lateralization on AVS. On ^{11}C -metomidate PET-CT, both adenomas were seen to be relatively cold, compared with adjacent adrenal (c and d), which was not, therefore, suggestive of a surgically-remediable unilateral cause. His blood pressure was subsequently controlled on conventional triple therapy (losartan, amlodipine, and bendroflumethiazide) with the addition of the mineralocorticoid receptor antagonist eplerenone, and amiloride. This case demonstrates how ^{11}C -metomidate PET-CT may be used in the confirmation of bilateral disease, and the distinction between aldosterone-producing adenomas (APAs) and nonfunctional incidentalomas.

study, we have confirmed and extended our findings in a much larger cohort of patients (illustrative cases, Figs. 1–4), with confirmation that PET-CT confers significant benefits particularly with respect to the identification of small APAs (where the enhanced spatial resolution compared with conventional scintigraphy is required), and in patients in whom AVS is technically challenging, inconclusive or not feasible.

The downside of ^{11}C -metomidate PET-CT is the 20-min half-life of ^{11}C -isotopes, mandating an on-site cyclotron. Two patients can be studied for each synthesis, making the costs comparable to, or lower than, those for AVS, and a number of centres in the UK and Scandinavia are now establishing and evaluating ^{11}C -metomidate PET-CT. Elsewhere, there is interest in radiolabels with longer half-lives, with ^{123}I -metomidate or ^{131}I -metomidate being used

in the diagnosis and therapy of malignant adrenocortical carcinomas [28^{***}]. However, the different analogues may vary in relative affinity for the aldosterone-producing and cortisol-producing enzymes (CYP11B2 and CYP11B1), with critical difference therefore in their ability to distinguish APAs from adjacent adrenal tissue [29]. They may also lack the spatial resolution afforded by PET-CT.

CONCLUSION

Primary aldosteronism is a common cause of hypertension and in unilateral disease, which accounts for approximately 50% of cases, is potentially curable surgically. Lateralization with AVS is technically demanding and invasive and in many centres is frequently unsuccessful. ^{11}C -metomidate PET-CT offers a rapid noninvasive alternative to AVS for

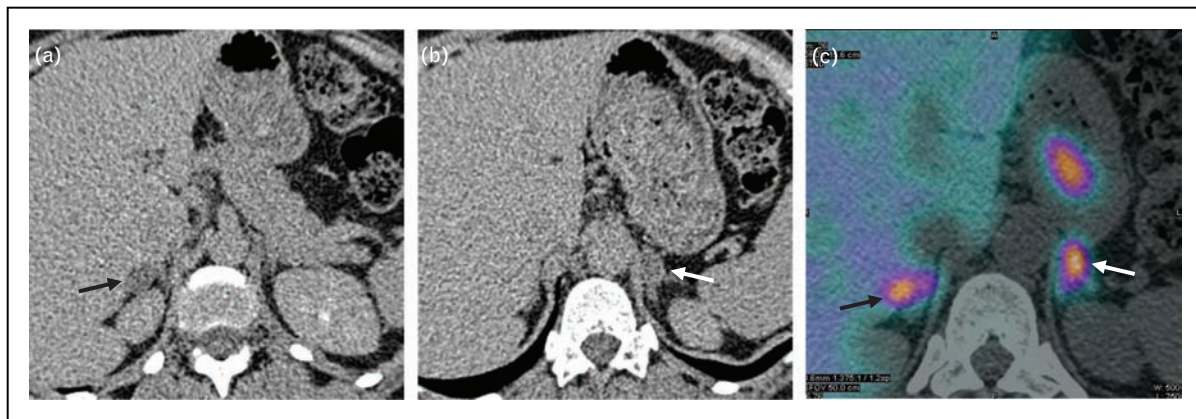


FIGURE 4. Case 4 – ^{11}C -metomidate PET-CT in bilateral primary aldosteronism with ‘hot’ aldosterone-producing adenomas (APAs). A 48-year-old woman with 10-year history of severe hypertension and primary aldosteronism had bilateral adrenal adenomas (a and b). AVS did not lateralize. ^{11}C -metomidate PET-CT shows bilaterally hot adenomas, with higher standardized uptake values (SUV_{max}) than adjacent adrenals (c). Her blood pressure was subsequently well controlled by spironolactone and amlodipine.

localizing unilateral APAs. Our increasing experience suggests it may have particular utility in certain settings, such as when mineralocorticoid receptor antagonists cannot be easily or safely withdrawn, or with subcentimetre lesions and equivocal cross-sectional imaging. Furthermore, in our experience patients universally prefer this noninvasive option.

Acknowledgements

The authors acknowledge the contribution of Dr H.K. Cheow and Dr J. Buscombe of the Departments of Nuclear Medicine and Radiology, Addenbrooke’s Hospital, Cambridge, UK.

Financial support and sponsorship

A.S.P. and M.G. are supported by the National Institute for Health Research Cambridge Biomedical Research Centre. M.J.B. is a National Institute of Health Research Senior Investigator.

Conflicts of interest

There are no conflicts of interest.

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