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Response to Letter on use of functional imaging by ^{11}C -metomidate PET for primary aldosteronism subtyping

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We read the letter by Crimi *et al.* (1) and are thankful for the opportunity to discuss some comments. The authors highlight important points in our recent paper on whether functional imaging of adrenal cortex with ^{11}C -metomidate (^{11}C -MTO) could offer a non-invasive alternative to adrenal venous sampling (AVS) in the subtype classification of primary aldosteronism (PA) (2).

We acknowledge that the selectivity of isotope tracers for CYP11B1 and CYP11B2 is an obstacle for non-invasive subtype diagnostics in PA and have made our best to discuss the problem in the paper. The use of dexamethasone (DXM) suppression is considered to circumvent the confounding effect of CYP11B1 uptake. However, the effect of DXM on CYP11B2 uptake has not been studied except for the 7 (13%) subjects with bilateral PA in our study and in six (15%) subjects with unilateral PA by Burton *et al.* (3). In addition to cortisol, aldosterone is also regulated by ACTH. It's not clear to what extent the activity of CYP11B2 in PA patients with various subtypes is suppressible by DXM. Literature demonstrates the effect of DXM suppression test (DST) on aldosterone levels (4). In patients with an aldosterone-producing adenoma (APA), 1 mg DST decreased 08:00 h

aldosterone concentrations from 36.1 to 19.9 ng/L (–45%) and 21.8 to 16.7 ng/L (–23%) in patients with and without *KCNJ5*-mutations, respectively (5). In another study, patients with APA presented with suppressed aldosterone levels by 50% with 1 mg DST (6). Previous data (7, 8) and a recent elegant paper by St-Jean *et al.* (9) reported even larger variations in aldosterone suppression when high-dose DST was applied (also used in the pilot studies by Burton *et al.* (3) and O'Shea *et al.* (10)). St-Jean *et al.* (9) found the median (IQR) relative suppression of aldosterone to be –72% (–44 to –76%) in bilateral hyperplasia and –47% (+2 to –67%) in APA. Our conclusion is that neither approach, the use of nor refraining from DXM pretreatment, is ideal. Only tracers that are more selective for CYP11B2 can improve the accuracy of isotope imaging methods in PA.

Crimi *et al.* (1) note that our study used an acquisition protocol, which differs from that used by Burton *et al.* (4) and O'Shea *et al.* (10). However, previous studies by the nuclear medicine specialists in our group show that a plateau activity is reached in approximately 10 min and tracer kinetics of ^{11}C -metomidate remain rather stable in both normal adrenals and adrenal adenomas upto

40 min (11). Therefore, the acquisition protocol is unlikely to explain the differences in the results.

Our interpretation is that the differences in patient selection remain a major determinant of the variations in outcomes because Burton *et al.* (3) performed PET studies on selected patients based on anatomical findings and the study by O'Shea *et al.* (10) presented a retrospective case series. Our study defined a pre-specified protocol to include all carefully verified PA patients who were eligible for adrenal surgery and thus required lateralization studies (2). Of these patients, 14 (25%) had no identifiable adrenal tumors in CT.

The criteria for surgery vs medical therapy has been debated (12, 13). Our threshold for lateralization index (LI) in cosyntropin-stimulated AVS was 4 according to the guidance by Funder *et al.* (14) which led to a significant proportion (62%) of the patients being operated. Furthermore, the results of adrenalectomy are well characterized by immunohistochemistry and by clinical/biochemical cure. We identified four subjects with an LI of 3–3.4 in our study. All had contralateral suppression index > 1 (1.54–2.36). Of these, two had low SUV_{max}-ratios (1.00 and 1.07) and the values in 2 others were 1.54 and 1.53, that is, above the cut point suggested by the ROC. None of these subjects had a single anatomical adrenal adenoma. Our comparison between the methods for lateralization would not have been different if the AVS threshold had been less strict, however, the cure rate after adrenalectomy could have been lower.

Disappointingly, ¹¹C-MTO PET-CT did not achieve the expected impact of reliable identification of PA lateralization in our prospective patient cohort. However, we eagerly wait for improved technologies for non-invasive diagnostics of PA lateralization.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

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