Functional imaging by ^{11}C -metomidate PET: a really useless technique for primary aldosteronism subtyping?

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Dear Editor,

Soinio *et al.* (1) recently compared the diagnostic accuracy of ^{11}C -metomidate PET (^{11}C -MTO-PET) and cosyntropin-stimulated adrenal venous sampling (AVS) for the subtyping of patients with primary aldosteronism (PA), who were diagnosed according to the 2008 Endocrine Society guidelines (2). Metomidate, the methyl ester of 1-[(1R)-1phenylethyl]-1H-imidazol-5-carboxylic acid, inhibits both steroid-11-beta-hydroxylase (CYP11B1) and aldosterone-synthase (CYP11B2) in human adrenocortical tissues with similar IC₅₀ (0.24 vs 0.6 nM) (3). Because of this poor selectivity, the compound was not further considered as a therapeutic tool to decrease high plasma aldosterone in humans. However, it was pursued for functional imaging based on promising results in pilot studies (4, 5).

Soinio *et al.* concluded that ^{11}C -MTO-PET offered no diagnostic usefulness in PA patients. In our view, this conclusion needs to be taken with great caution owing to a number of concerns that can be raised concerning their study.

First, notwithstanding the poor selectivity for CYP11B2, they performed ^{11}C -MTO-PET without prior suppression of background uptake of the radiotracer in the glucocorticoid-producing zona fasciculata of the normally functioning adrenocortical tissue adjacent to an aldosterone-producing adenoma (APA) by means of dexamethasone administration (5). This is, in our view, of key importance in order to avoid excess background radiotracer uptake inasmuch as ^{11}C -MTO binds also to CYP11B1, which is widely expressed in the adrenocortical tissue (6). Accordingly, in previous studies on ^{11}C -MTO-PET, which highlighted its potential for functional imaging

of PA, dexamethasone suppression was systematically administered (4, 5). The lack of background suppression could explain the low SUV_{max}-ratio cutoff of 1.16 identified by Soinio *et al.* (1) in their ROC curve analysis, as compared to the 1.25 found by Burton (5) and used by O'Shea (4).

Therefore, the negative results of Soinio *et al.* (1) are somehow expected and by no means contradict previous positive studies (4, 5). Considering this bias in their study design, the authors repeated seven PET examinations (13% of the whole population) after dexamethasone suppression using a protocol identical to that used in the previous studies by Burton (5) and used by O'Shea (4). However, this further testing was undertaken only in patients with no lateralization at AVS in whom an increased uptake in one of the adrenal glands could be expected to be highly unlikely.

Secondly, although the radiotracer activity used by Soinio *et al.* was presumably similar to that used by O'Shea *et al.* and Burton *et al.*, the PET images acquisition protocol differed markedly. Soinio *et al.* performed a 20 min acquisition starting 15 min after the radiotracer injection, while O'Shea *et al.* and Burton *et al.* performed dynamic acquisitions to select the time frame that warranted the best SUV values. Burton suggested to start the acquisition of PET images 35 min after tracer injection and to acquire data for 10 min and O'Shea replicated the same protocol. Therefore, the acquisition protocol used by Soinio *et al.* is markedly different from previous literature and does not take into account kinetic dynamic properties of the tracer. Moreover, cosyntropin was shown to confound or even invert the lateralization in about 24%

of patients (7) and therefore the results obtained by AVS could have been biased in a certain number of patients causing a misclassification of PA subtype.

Finally, in these studies (1, 4, 5) the lateralization index (LI) used thus far was ≥ 4 . In the AVIS-2 Selectivity study (8) adoption of less restrictive cutoffs was associated with similarly good clinical outcomes. Thus, it is quite likely that all these studies selected patients with the most florid phenotype of unilateral PA, which likely led to overestimating the diagnostic accuracy of ^{11}C -MTO-PET functional imaging.

In summary, functional imaging of PA with ^{11}C -MTO-PET certainly has some limitations and negative studies are equally important as positive studies to obtain a balanced view of its diagnostic usefulness. However, it seems premature to draw definitive conclusions based on protocols that failed to meet basic methodological requirements.

Declaration of interest

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

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