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^{11}C-(+)-PHNO Trapping Reversibility for Quantitative PET Imaging of Beta-Cell-Mass in Patients with Type-1 Diabetes

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TO THE EDITOR:

For efficiently differentiating the pancreas uptake of the dopamine D2/D3-receptor agonist ^{11}C-(+)-PHNO between healthy controls (HC) and Type-1 diabetes mellitus (T1DM) individuals, Bini et al. recently compared different methods of quantitative PET imaging. These methods involved tissue-compartment model analyses providing the tracer distribution volume (V_T), as well as reference-region approaches, which did or did not require arterial sampling, respectively (*1*). Quantitative parameters were also correlated to clinically relevant measures of beta-cell-mass (BCM) function such as C-peptide, proinsulin, age-at-diagnosis and disease duration. The authors reported a reduction in the 20-30min pancreas/spleen SUV ratio (SUVR-1) of -36.2% between HC and T1DM ($p = 0.03$), and concluded that SUVR-1 could be used to differentiate BCM in HC and T1DM subjects.

We assume that Bini et al.'s study does not take into account the trapping reversibility of ^{11}C-(+)-PHNO in the pancreas of both HC and T1DM subjects, that could, in addition, be helpful to assess BCM by using data acquired beyond 30min post-injection (p.i.). This assumption is evidenced in the Figure 3 of the paper with representative decay-corrected time-activity curves (TAC) of pancreas (and spleen) acquired over 120min that, clearly, do not reach a plateau at late imaging *(1,2)*.

First, let us note that trapping reversibility may impair the use of V_T, i.e., the equilibrium ratio of tissue to plasma concentration, since van den Hoff et al. have previously shown that this ratio, also called tumor-to-blood standard-uptake ratio (SUR) in cancer patients, is strongly correlated to Patlak's uptake rate constant (Ki) under the condition of irreversible trapping *(3)*.

Second, Bini et al. acknowledged that the one-tissue-compartment model does not fit the data for t > 60min (Figure 3)*(1)*. In this connection, we have recently indicated that a previously published method can then be applied to any tracer for assessing its release rate constant (k_B) from tissue back to blood at late imaging, that is, when the part of free tracer in blood and interstitial volume plus, possibly, the part of radiolabeled metabolites, have become negligible in the tissue TAC *(4)*. Comparison between arterial-IF and pancreas SUV (Figure 1 and Figure 3, respectively) shows that this part is less than 2% at 30min p.i., thus allowing the fitting of the pancreas (decay-corrected) TAC beyond 30min p.i. with a mono-exponentially decaying function (GraphPad Prism software, version 5.00) writing: $y = 37.54 \times \exp(-0.02621 \times t)$, where $0.02621 min^{-1}$ (SD = 0.00055) is the k_B estimate for ^{11}C-(+)-PHNO release from pancreas back to blood (amplitude-SD = 1.14; R = 0.998; data extracted with the WebPlotDigitizer software). We therefore suggest that the amplitude and k_B value obtained from the pancreas-TAC mono-exponential fitting beyond 30min p.i. could be helpful to differentiate BCM in HC and T1DM subjects.

To conclude, Bini et al relevantly emphasized the potential utility of ^{11}C-(+)-PHNO for measuring the BCM *in vivo* in T1DM patients, and, hence, the need for a reliable PET quantitative method to assess disease progression and efficacy of therapies, in combination with functional measures. We suggest that the significant reversibility of the ^{11}C-(+)-PHNO trapping in pancreas has not been fully exploited. We indeed indicate that, without the need for an arterial sampling, mono-exponential fitting of the pancreas TAC beyond 30min p.i. might be a relevant quantitative method to further differentiate BCM in HC and T1DM individuals. Finally, we suggest that investigating the possible correlation of the derived amplitude and k_B values with C-peptide, proinsulin, age-at-diagnosis and disease duration, might be of interest.

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