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Reply LTE: ^{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:

We would like to address several assumptions recently posited by Laffon and Marthan, in their letter to the editor that was prompted by our recently published study examining the use of ^{11}C-(+)-PHNO to assess beta cell mass in healthy controls and type 1 diabetics(*1*). Laffon, et al, put forth several contentions as the basis for use of their method to exploit 'trapping reversibility' of ^{11}C-(+)-PHNO; we have significant concerns with their viewpoint.

The first statement in question is that we did not exploit the reversible nature of ^{11}C-(+)-PHNO. In fact, our method depends explicitly on the reversible binding nature of this tracer. For reversible radioligands, the uptake is conventionally described by either one- or two-tissue compartment models (1TC, 2TC)(*2*). For 1TC models, the rate constants K_1 and k_2 describe the kinetics in and out of the tissue from plasma, respectively. For a 2TC, there are additional rate constants, k_3 and k_4, defining the rate of receptor binding and disassociation, respectively. The 1TC and 2TC models, were both assessed as the gold-standard in our recent publication, with the use of a metabolite-corrected arterial input function to estimate the distribution volume (V_T), the ratio of the radioligand concentrations in the target tissue to that in plasma at equilibrium (e.g., $V_T = K_1/k_2$ for 1TC). V_T cannot be estimated reliably unless the tracer clearance constant (k_2 for the 1TC) is large enough so that there is significant clearance from the target organ during the imaging period. Thus, our modeling *explicitly does take into account reversibility* of ^{11}C-(+)-PHNO. Laffon and Marthan go on to suggest that a monoexponential fit should be applied to the

tail portion of the time-activity curve (TAC) yielding the parameter k_B. If the plasma activity was truly 0, then this parameter would be equal to k_2 in our 1TC model. However, although the ratio of blood to tissue activity is low, it is not 0, and is consistent with the model estimate of V_T of 20-30 mL/cm^3. The fact that the time activity curves out to 120 minutes 'do not reach a plateau at late imaging' is fully consistent with the reversible model we used.

We also consider it important to address the issue of radiolabeled metabolites, especially in the context of imaging outside of a functioning blood-brain barrier. Given the low parent fraction in the plasma (<20%), extra caution must be taken to minimize the effects of radiolabeled metabolites in both pancreas and spleen. Ex vivo animal well counting studies in both pancreas and spleen tissue would need to be performed at multiple time points post injection of ^{11}C-(+)-PHNO to determine the amount of radiolabeled metabolites present in both organs. As we stated in the original publication, our group previously demonstrated radiolabeled metabolites may be accumulating in the pancreas and spleen at similar levels, as was seen in a previous study with ^{18}F-FP-(+)-DTBZ(*3*), however, this has yet to be proven with ^{11}C-(+)-PHNO, and is technically challenging given the shorter half-life of this tracer (~20 minutes). This uncertainty of radiolabeled metabolites encouraged us to develop quantitative measures based on early time points (e.g., 30 min).

To conclude, 1TC and 2TC compartment modeling intrinsically exploits the reversible nature of radioligands. Such reversible tracers are preferred for quantitative assays of protein targets in the molecular imaging field(*2*).

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