design, the bed positions are offset from the center of the field of view (where spatial resolution is maximal). The spatial resolution should be known or evaluated to a radial extent at least as large as the radius of a circle circumscribing the 4 bed positions (~4 cm). Additionally, because simultaneously imaging multiple mice typically involves elevated activities within the scanner field of view, it is critical to consider the scanner count rate performance in order to ensure the accuracy of detector dead-time corrections. Attention to scanner count rate performance is particularly important for nonstandard radionuclides, as there will be two considerations in addition to the aforementioned ones. First, many nonstandard positron emitters emit concomitant γ-rays, which may significantly contribute to dead-time counting losses, especially with the elevated activities within the field of view associated with simultaneously imaging multiple mice. Second, prompt γ-coincidences, which occur for radionuclides with γ-emissions within—or downscattering into—the positron annihilation photon energy window (e.g., ^{86}Y, ^{124}I), are amplified when multiple mice are within the scanner field of view. We note that preclinical PET imaging workflows for mice often neglect corrections for attenuation and scatter because of their relatively minor impact for small animals such as mice; however, we recommend these corrections for multiple-mouse imaging because of the increased quantity of attenuating material and the increased likelihood of scatter. Finally, we note that there are no provisions included in our design for animal monitoring or body temperature maintenance, which may be required in, for example, ^{18}F-FDG imaging or extended scanning periods. Provisions for monitoring or temperature control may be added by users but should be evaluated by their Institutional Animal Care and Use Committee before application.

The use of multiple-animal imaging protocols at our institution has greatly streamlined many imaging studies while reducing cost. We greatly value and encourage recent efforts, both commercially aligned and community-contributed, toward development of imaging solutions to increase throughput while maintaining quantitative accuracy.

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

TO THE EDITOR: For efficiently differentiating the pancreas uptake of the dopamine D_2/D_3-receptor agonist ^{11}C-(+)-PHNO (3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol) between healthy controls and patients with type 1 diabetes mellitus (T1DMs), Bini et al. recently compared different methods of quantitative PET imaging. These methods involved tissue-compartment model analyses providing the tracer distribution volume, as well as reference-region approaches, which did and did not require arterial sampling, respectively (*1*). Quantitative parameters were also correlated to clinically relevant measures of β-cell-mass function such as C-peptide, proinsulin, age at diagnosis, and disease duration. The authors reported a reduction in the 20- to 30-min pancreas-to-spleen SUV ratio of 36.2% between healthy controls and T1DMs ($P = 0.03$) and concluded that this ratio could be used to differentiate β-cell mass in healthy controls and T1DMs.

We assume that the study of Bini et al. did not fully take into account the trapping reversibility of ^{11}C-(+)-PHNO in the pancreas of both healthy controls and T1DMs—a characteristic that could, in addition, be helpful for assessing β-cell mass using data acquired beyond 30 min after injection. Trapping reversibility is evidenced in Figure 3 of the paper, in which representative decay-corrected time–activity curves of the pancreas (and spleen) acquired over 120 min clearly do not reach a plateau at late imaging (*1,2*).

First, let us note that trapping reversibility may impair the use of distribution volume, that is, the equilibrium ratio of tissue concentration to plasma concentration, when this ratio is assessed at any time after injection, unlike under irreversible trapping condition (*3*).

Second, Bini et al. acknowledged that the 1-tissue-compartment model does not fit the data for times of more than 60 min (Fig. 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 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 time–activity curve (*4*). Comparison between arterial input function and pancreas SUV (Figs. 1 and 3, respectively) shows that this part is less than 2% at 30 min after injection, thus allowing the fitting of the pancreas (decay-corrected) time–activity curve beyond 30 min after injection with a monoexponentially 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 release rate constant 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 release rate constant obtained from the pancreas time–activity curve monoexponential fitting beyond 30 min after injection could be helpful to differentiate β-cell mass in healthy controls and T1DMs.

To conclude, Bini et al. relevantly emphasized the potential utility of ^{11}C-(+)-PHNO for measuring the β-cell mass in vivo in T1DMs 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 ^{11}C-(+)-PHNO trapping in the pancreas has not been fully exploited. Indeed, without the need for arterial sampling, monoexponential fitting of the pancreas time–activity curve beyond 30 min after injection might be a relevant quantitative method to further differentiate β-cell mass in healthy controls and T1DMs. Finally, we suggest that investigating the possible correlation of the derived amplitude and release rate constant with C-peptide, proinsulin, age at diagnosis, and disease duration might be of interest.

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

REPLY: 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 (3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-9-ol) to assess β-cell mass in healthy controls and type 1 diabetics (*1*). Laffon and Marthan 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 1- or 2-tissue-compartment models (1TC and 2TC, respectively) (*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 model, 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 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 the 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 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 min "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 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 the pancreas and the spleen. Ex vivo animal well counting studies in both pancreas and spleen tissue would need to be performed at multiple time points after 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 min). 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 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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