Clinical and scientific value in the pursuit of quantification of beta cells in the pancreas by PET imaging

Gary W. Cline¹ · Timothy J. McCarthy² · Richard E. Carson¹ · Roberto A. Calle²

Received: 30 July 2018 / Accepted: 1 August 2018 / Published online: 22 August 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Keywords Beta cell · Diabetes · Pancreas · PET imaging · Positron emission tomography · Vesicular monoamine transporter type 2 · VMAT2

Abbreviations

[¹⁸ F]-FP-(+)-DTBZ	[¹⁸ F]fluoropropyl-(+)-dihydrotetrabenazine
PET	Positron emission tomography
SPECT	Single photon emission computed tomography

To the Editor: The commentary by Alavi and Werner [1] mentioning our recent paper [2] concludes that ‘it is impossible to visualise and characterise islet cell function and structure with [positron emission tomography] PET’. First, and perhaps it is a matter of misunderstanding, we are not attempting to ‘visualise and characterise islet cell function and structure with PET’. Our objective is limited to determining clinically relevant changes in pancreatic beta cell mass and, in our studies, PET is neither used to visualise islet cell function nor structure. Rather, our use of PET provides an integrated measure of the number of beta cells present in a defined volume of the pancreas. That is, we are measuring beta cell density within the pancreas, which we conclude is clearly an achievable goal even in the face of the biological and technical concerns raised again by Alavi and colleagues, as discussed below:

1. Dispersal of islets throughout the pancreas and relative volume of islets

Dr. Alavi has previously raised the concern that PET cannot be used to determine beta cell

mass due to the small volume of beta cells within the pancreas and their dispersal throughout the pancreas [1, 3]. We believe that these issues were exceptionally well addressed by Ichise and Harris in a 2011 response [4] to a previous letter to the Editor from Alavi and colleagues [3]. In that response, quantitative imaging of vesicular monoamine transporter type 2 (VMAT2) in beta cells was compared with the measurement of neuroreceptors and transporters in the striatum [4]. Like pancreatic beta cells, dopaminergic terminals occupy a small fraction of the volume of the striatum. Nevertheless, for over 30 years, PET imaging has succeeded to easily image these targets [5]. Further, with the development of higher affinity ligands, which produce a higher contrast, PET has evolved to measure dopamine receptors in cortical regions [6], where the density of dopaminergic terminals (per unit volume) is much lower. Thus, there is clear evidence from 30 years of PET imaging that specific imaging signals representing specific protein targets can be achieved with ligands with appropriately high affinity.

- Spatial resolution and partial volume effects** It is well known that PET has finite resolution, based on the finite detector size and post-reconstruction filtering. In our study, we minimised these effects in several ways: (1) by using a high-resolution scanner; (2) by using point-spread function reconstruction to minimise the partial volume effect; and (3) by using thin regions-of-interest to minimise resolution effects (see ESM Fig. 1 in [2]).
- Motion correction** In PET scans, respiratory and bulk body motion can degrade PET images. In our work, we performed dynamic body motion correction to eliminate the latter issue. With regard to respiratory motion correction, while not applied in our study [2], we and others are developing novel methods for event-by-event respiratory motion correction using external devices or with data-

✉ Gary W. Cline
gary.cline@yale.edu

¹ Yale University, 801 Howard Avenue, PO Box 208048, New Haven, CT 06520, USA

² Pfizer Worldwide R&D, Cambridge, MA, USA

driven techniques [7–9]. These methods will become critical for accurate quantification using dynamic PET in the body.

4. **Loss of pancreatic volume** Volume loss clearly affects all PET quantification methods, so combined measurement of volume loss using anatomical imaging with functional/pharmacological loss using PET is essential. For example, in type 1 diabetes, the effective assessment of beta cell loss might best be summarised using the combined loss of volume and beta cells per unit volume [10]. However, in our work in type 2 diabetes mellitus, the loss of volume was not statistically significant and is not likely to explain the correlations found between PET measurements and disease-specific indices (see Fig. 4 in [2]).
5. **Optimal contrast** With regard to the analysis that deduced that a radioligand contrast ratio of 1000:1 is needed to visualise beta cells in the native pancreas [11], we believe that a more appropriate question is: what degree of change in beta cell mass can be detected given achievable test–retest variability and measured radioligand specificity? In other words, this is a question of signal:noise ratio. In knowing the test–retest coefficient of variation, one can calculate the change in beta cell mass needed to be detectable by PET for a radioligand of known specificity. With a test–retest variability of <10%, which has been obtained by us and others [2, 12], a ~25% change in beta cell mass would be detectable using a radioligand with a specificity of ~35:1, while a ~15% change in beta cell mass would be detectable for a radioligand with a specificity of ~100:1, such as [^{18}F]fluoropropyl-(+)-dihydrotetrabenazine (^{18}F -FP-(+)-DTBZ). The clinical value of PET imaging of beta cell mass is not in determining absolute amounts, which are highly variable in both healthy people and those with diabetes [13–15], but in detecting changes in beta cell mass in response to disease progression or therapeutic intervention. We conclude that measuring longitudinal changes in beta cell mass is currently achievable with the proven test–retest variability and the specificity of existing PET and single photon emission computed tomography (SPECT) radioligands.
6. **Non-specific binding** With all PET and SPECT imaging agents that bind to molecular targets, the signal not only consists of specific binding to the target, but also non-specific binding to surrounding tissue. We have clearly recognised the importance of defining an accurate reference region and have utilised several independent strategies, including blocking studies and displacement studies in animal models [16–18]. More specifically, we use PET studies of the inactive enantiomer of ^{18}F -FP-DTBZ to develop and validate a suitable reference method to correct for non-specific binding in the pancreatic tissue [16, 17]. Thus, our use of the spleen as the reference tissue [2] is not based on

speculation but has been validated in both nonhuman primates and humans.

Yes, there are hurdles to overcome in achieving the goal of using PET and SPECT imaging (and magnetic resonance imaging) as viable research and clinical tools to assess changes in beta cell mass that may occur with type 1 and type 2 diabetes. Faced with these challenges, one could declare the hurdles as insurmountable and declare the task futile, as Alavi and Werner propose [1]. Alternatively, one can take the more productive and forward-looking approach, as we and other independent research teams are doing [12, 14, 19–23], and develop solutions. We have many reasons to take this optimistic approach. Looking back over the 40 year history of PET imaging, there has been huge improvement in PET scanner performance (from single-slice machines with a resolution of ~2 cm to whole body systems with time-of-flight and resolutions better than 5 mm) and constant development of highly specific and sensitive radiopharmaceuticals. In light of this amazing scientific progress, imaging of beta cells with PET is by no means a ‘futile’ endeavour.

Funding The work [2] discussed in this response was supported by the Yale-Pfizer Bioimaging Research Alliance and National Institutes of Health (NIH) grant 1S10OD010322-01. This publication was also made possible by Clinical and Translational Science Award Grant Number UL1 TR000142 from the National Center for Advancing Translational Sciences (NCATS), a component of the NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement All authors were responsible for drafting the article and revising it critically for important intellectual content. All authors approved the version to be published.

References

1. Alavi A, Werner TJ (2018) Futility of attempts to detect and quantify beta cells by PET imaging in the pancreas: why it is time to abandon the approach. *Diabetologia*. <https://doi.org/10.1007/s00125-018-4676-1>
2. Cline GW, Naganawa M, Chen L et al (2018) Decreased VMAT2 in the pancreas of humans with type 2 diabetes mellitus measured in vivo by PET imaging. *Diabetologia*. <https://doi.org/10.1007/s00125-018-4624-0>
3. Kwee TC, Basu S, Saboury B, Torigian DA, Naji A, Alavi A (2011) Beta-cell imaging: opportunities and limitations. *J Nucl Med* 52:493
4. Ichise M, Harris PE (2011) Reply: beta-cell imaging: opportunities and limitations. *J Nucl Med* 52:493–495
5. Farde L, Hall H, Ehrin E, Sedvall G (1986) Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. *Science* 231:258–261
6. Slifstein M, van de Giessen E, Van Snellenberg J et al (2015) Deficits in prefrontal cortical and extrastriatal dopamine release in

- schizophrenia: a positron emission tomographic functional magnetic resonance imaging study. *JAMA Psychiatry* 72:316–324
7. Chan C, Onofrey J, Jian Y et al (2018) Non-rigid event-by-event continuous respiratory motion compensated list-mode reconstruction for PET. *IEEE Trans Med Imaging* 37:504–515
 8. Lu Y, Fontaine K, Mulnix T et al (2018) Respiratory motion compensation for PET/CT with motion information derived from matched attenuation corrected gated PET data. *J Nucl Med*. <https://doi.org/10.2967/jnumed.117.203000>
 9. Ren S, Jin X, Chan C et al (2017) Data-driven event-by-event respiratory motion correction using TOF PET list-mode centroid of distribution. *Phys Med Biol* 62:4741–4755
 10. Normandin MD, Petersen KF, Ding YS et al (2012) In vivo imaging of endogenous pancreatic beta-cell mass in healthy and type 1 diabetic subjects using [^{18}F]FP-(+)-DTBZ and PET. *J Nucl Med* 53: 908–916
 11. Sweet IR, Cook DL, Lernmark A, Greenbaum CJ, Krohn KA (2004) Non-invasive imaging of beta cell mass: a quantitative analysis. *Diabetes Technol Ther* 6:652–659
 12. Freeby MJ, Kringas P, Goland RS et al (2016) Cross-sectional and test-retest characterization of PET with [^{18}F]FP-(+)-DTBZ for beta cell mass estimates in diabetes. *Mol Imaging Biol* 18:292–301
 13. Wang X, Misawa R, Zielinski MC et al (2013) Regional differences in islet distribution in the human pancreas—preferential beta-cell loss in the head region in patients with type 2 diabetes. *PLoS One* 8: e67454
 14. Carlbom L, Espes D, Lubberink M et al (2017) [^{11}C]5-Hydroxytryptophan PET for assessment of islet mass during progression of type 2 diabetes. *Diabetes* 66:1286–1292
 15. Saisho Y, Butler AE, Manesso E, Elashoff D, Rizza RA, Butler PC (2013) β -Cell mass and turnover in humans: effects of obesity and aging. *Diabetes Care* 36:111–117
 16. Naganawa M, Lim K, Nabulsi NB et al (2018) Evaluation of pancreatic VMAT2 binding with active and inactive enantiomers of [^{18}F]FP-DTBZ in healthy subjects and patients with type 1 diabetes. *Mol Imaging Biol*. <https://doi.org/10.1007/s11307-018-1170-6>
 17. Naganawa M, Lin SF, Lim K et al (2016) Evaluation of pancreatic VMAT2 binding with active and inactive enantiomers of [^{18}F]FP-DTBZ in baboons. *Nucl Med Biol* 43:743–751
 18. Singhal T, Ding YS, Weinzimmer D et al (2011) Pancreatic beta cell mass PET imaging and quantification with [^{11}C] DTBZ and [^{18}F]FP-(+)-DTBZ in rodent models of diabetes. *Mol Imaging Biol* 13:973–984
 19. Eriksson O, Laughlin M, Brom M et al (2016) In vivo imaging of beta cells with radiotracers: state of the art, prospects and recommendations for development and use. *Diabetologia* 59:1340–1349
 20. Gotthardt M, Eizirik DL, Cnop M, Brom M (2014) Beta cell imaging - a key tool in optimized diabetes prevention and treatment. *Trends Endocrinol Metab* 25:375–377
 21. Brom M, Woliner-van der Weg W, Joosten L et al (2014) Non-invasive quantification of the beta cell mass by SPECT with ^{111}In -labelled exendin. *Diabetologia* 57:950–959
 22. Goland R, Freeby M, Parsey R et al (2009) ^{11}C -dihydrotetabenazine PET of the pancreas in subjects with long-standing type 1 diabetes and in healthy controls. *J Nucl Med* 50:382–389
 23. Harris PE, Farwell MD, Ichise M (2013) PET quantification of pancreatic VMAT 2 binding using (+) and (−) enantiomers of [^{18}F]FP-DTBZ in baboons. *Nucl Med Biol* 40:60–64