



Futility of attempts to detect and quantify beta cells by PET imaging in the pancreas: why it is time to abandon the approach

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Abstract

In this commentary, we describe the limitations of positron emission tomography (PET) in visualising and characterising beta cell mass in the native pancreas in healthy individuals and those diagnosed with diabetes. Imaging with PET requires a large mass of targeted cells or other structures in the range of approximately 8–10 cm³. Since islets occupy only 1% of the pancreatic volume and are dispersed throughout the organ, it is our view that uptake of PET tracers, including [¹⁸F]fluoropropyl-(+)-dihydrotetrabenazine, in islets cannot be successfully detected by current imaging modalities. Therefore, we dispute the feasibility of PET imaging for the detection of loss of beta cells in the native pancreas in individuals with diabetes. However, we believe this novel approach can be successfully employed to visualise beta cell mass in individuals with hyperinsulinism and transplanted islets.

Keywords Beta cell mass · Imaging in diabetes · Limitations of PET · Partial volume effect · PET quantification

Abbreviations

BCM	Beta cell mass
CT	Computerised tomography
¹⁸ F-FP-(+)-DTBZ	[¹⁸ F]fluoropropyl-(+)-dihydrotetrabenazine
HOV	Healthy obese volunteer
PET	Positron emission tomography

Introduction

In spite of the great success of positron emission tomography (PET) for research and clinical applications over the past four decades, it has certain limitations that have to be taken into consideration for optimal use of this powerful technology in the future. Although PET is quite sensitive in examining organ function and characterising pathological states, this modality suffers from limited spatial resolution for visualising subtle

sources of abnormality in many organs, particularly those residing in the abdomen [1–4]. While the spatial resolution of PET is 4–5 mm in phantoms imaged in stationary mode, the ability of PET to detect uptake sites in the human body is substantially suboptimal and is in the range of 8–10 mm. Furthermore, the degree of contrast between the sites of tracer uptake and the background activity has to be significant to be visible by external imaging techniques. Realistically, attempts for successful imaging of either normal or abnormal structures require target tissues with large volumes and substantial uptake of the intended tracer for positive results. Therefore, efforts to image targets that are dispersed within high background activity sites will fail, as has been demonstrated ever since this technology was introduced to medicine in the 1970s [5]. In spite of the significant advances that have been made to generate images with relatively high spatial resolution, this serious limitation of PET cannot be overcome due to the basic physical principles that dictate its *in vivo* imaging capabilities in either human or animal settings.

Recently, we have published several editorials to make the community aware of the issues that we face in applying PET in several important domains [6, 7]. In particular, we have been very critical of approaches that utilise PET to detect normal structures or lesions that are very small in size and dispersed in organs with significant non-specific background activity. These include detecting plaques (amyloid) and

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tangles (tau) in the brain of individuals with suspected Alzheimer's disease, where the volume of these structures is only a small fraction (less than 1%) of the grey matter and the degree of uptake of the intended compounds is minimal [8]. Similarly, the detection of bacteria at an infected site is challenging because of the small volume of the microorganisms and their rapid phagocytosis by leucocytes (the latter preventing exposure of the bacteria to the administered compound). We are also concerned about detecting atherosclerotic plaques as focal abnormalities, particularly in the coronary arteries, and, therefore, have questioned the validity of published data in the literature [9].

PET for pancreatic beta cell mass imaging

Detection of the islets in the native pancreas in healthy individuals and those with diabetes also poses significant challenges and it is our view that it is impossible to visualise and characterise islet cell function and structure with PET, at least for the foreseeable future, despite what has been portrayed in the literature [10–15]. In a major review article, we have described many unjustified claims made about the feasibility of PET imaging to detect islet cells in the native pancreas [16]. In this review, we also describe, in detail, the issues that need to be resolved in several domains before adopting PET imaging as a viable option to detect and characterise beta cells in the native pancreas of individuals with diabetes. The following topics, which we believe are relevant to this complicated imaging procedure, are described: (1) biological obstacles and challenges that we face for beta cell imaging with PET in the pancreas; (2) loss of pancreatic volume in type 1 and type 2 diabetes, as well as in animal models of these disorders; (3) the necessity of achieving optimal contrast between target tissue and background activity; (4) anomalous uptake of beta cell radiotracers in health and disease following single blockade studies and residual uptake in those with diabetes; and (5) unfavourable observations of autoradiographic results [14].

Extensive scientific evidence for the issues discussed in this review clearly indicates that these insurmountable obstacles will prevent in vivo imaging of beta cells in health and disease. A major reason for this unjustified attempt is the small volume of islets in the pancreas (1–2% of the entire pancreatic volume). Furthermore, the degree of uptake of various tracers that have been proposed for this purpose is similar to that of the acinar tissue surrounding the islets [17]. This is due to non-specific binding of these radiotracers based on autoradiographic data. Furthermore, it is well known that the volume of the pancreas in individuals with type 1 or type 2 diabetes is substantially smaller than that of healthy individuals and this further affects the accuracy of beta cell quantification by PET [16]. It is well established that PET measurements in structures that are smaller than 3–4 cm in diameter are

underestimated due to partial volume effect [3]. Therefore, the lower values of tracer uptake reported in participants with diabetes are partly related to significant pancreatic atrophy in this population. In addition, respiratory motion plays a role in underestimation of measured values in individuals with diabetes and, based on published data in the literature, gating of this physiological movement cannot accurately correct for this major source of measurement error [18].

As a recent example, the study reported by Cline et al in this issue of *Diabetologia* [19] describes the use of PET imaging with [^{18}F]fluoropropyl-(+)-dihydrotrabenazine (^{18}F -FP-(+)-DTBZ) for assessing the correlation of beta cell mass (BCM) and its function in individuals with impaired glucose tolerance (prediabetes) or type 2 diabetes and age-BMI-matched healthy obese volunteers (HOV). In doing so, the authors aimed to test the hypothesis that a loss of BCM contributes to impaired insulin secretion in humans with type 2 diabetes. These investigators performed dynamic imaging of the upper abdomen over 4 h and calculated standard uptake value ratio (SUVR) in various segments of the pancreas by using the spleen as a reference source for non-specific binding of the compound. The data appeared reproducible and correlated well with beta cell function for the whole pancreas and its various segments. The authors reported a large spread of ^{18}F -FP-(+)-DTBZ binding and uptake variables in the pancreas of the HOV and participants with prediabetes overlapping with the type 2 diabetes participants.

Unfortunately, the data described by Cline et al suffer from the deficiencies that we have described in the literature over the years [19]. The authors fail to discuss how the volume and the function of beta cells in the pancreas were measured. Structural imaging techniques, such as computerised tomography (CT) and MRI (as used in the study by Cline et al) have limited spatial resolution for this purpose. Therefore, validation of the data generated from this research would have required microscopic examination of the excised pancreas from those who had undergone PET imaging. To enable this, perhaps patients undergoing pancreatectomy (e.g. for cancer or other disorders) could be used in future research for validating the methodologies adopted. At this junction, and without direct comparison between imaging and microscopic results, we are dealing with speculative interpretation of the ongoing research studies in this discipline. Therefore, the validity of the results generated by this method is questionable.

The authors have discussed the issue of non-specific binding, which is a main source of error in the quantification of uptake of PET tracers by beta cells. They indicate that by using splenic uptake as a reference region, they have overcome the serious issue of non-specific binding in the pancreas [19]. However, we must point out that non-specific uptake of these compounds is primarily confined to the acinar tissue of the pancreas and the metabolic activity of these cells is completely different from that of the spleen, which is related to the bone

marrow and lymphatic system. Therefore, the approach adopted is unjustified for this purpose. Furthermore, the authors have referred to respiratory gating as a means to overcome pancreatic motion caused by respiration, and this also is another source of concern. It is known that correction for respiratory motion is very complicated due to irregular movement of the diaphragm during PET data acquisition over several minutes. Finally, the images that the investigators have provided of the healthy pancreas clearly demonstrate significant non-specific uptake of the compound in the entire pancreas and cannot be related to beta cells alone since they occupy only 1% of this organ.

Other investigators have also raised serious concerns about the feasibility of visualising pancreatic islets and quantifying their function using this approach. In particular, Sweet et al, who were among the first to investigate the role of PET in this domain, have stated that the approach is very challenging and unrealistic at this time [20]. Based on their estimates, tracers that have been proposed to visualise beta cells in the native pancreas have to achieve a contrast ratio of 1000:1 compared with the surrounding acinar tissues [20]. This cannot be accomplished with any of the compounds that have been tested for visualising islets to date.

We would like to note that the study by Cline et al [19] is just one example of many in the literature that have used PET imaging to quantify beta cell mass [13–15, 21–26] and we have expressed our views on these studies in the form of several letters to the editor [27, 28]. We hope that by continuing to communicate our views on this subject (which are shared by others [20, 29, 30]) to the scientific community, we will soon abandon the unjustified use of PET imaging in the native pancreas in diabetes research and improve the validity of future research in this domain.

Conclusion

It is our belief that the idea of imaging islets in the native pancreas with PET is unjustified and should be abandoned at this time. However, PET imaging of a substantial volume of transplanted islets (in the range of 8–10 mm³) as a clump in locations with low background activity is currently an available option for visualising beta cells and monitoring the course of this form of treatment in patients with type 1 and type 2 diabetes [31]. In addition, we have been very supportive of adopting this powerful technology for detecting sources of hyperinsulinism in newborns for both surgical and medical interventions [32]. As such, PET-based diagnosis of this serious disorder has been accepted for optimal management of the affected population. With this in mind, prospective attempts to visualise islets in the native pancreas by PET imaging should be reconsidered. Therefore, future research

efforts should focus on imaging transplanted islets and not the beta cells in the native pancreas.

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

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