What can be and what cannot be accomplished with PET to detect and characterize atherosclerotic plaques

Abass Alavi, MD, PhD, DSc,[a] Thomas J. Werner, MSc,[a] and Poul Flemming Høilund-Carlsen, MD, DMSci, Prof (Hon)[b]

[a] Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA
[b] Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark

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The introduction of FDG as a radiotracer for imaging brain function in normal and disease states has led to the survival of PET as a viable and thriving imaging modality over the past 4 decades.[1,2] Furthermore, a great deal of effort has been made to expand the domain of this extraordinary technology by utilizing an array of radiotracers intended to assess many malignant and benign disorders.[3] As such, new tracers have been introduced primarily by relying upon the in vitro and pre-clinical animal data without realizing their relevance or feasibility in the in vivo settings. These attempts have been made without realizing the limitations of this technology in addressing the requirements to meet the many challenges that we face for conducting in vivo imaging studies. Over the years, the adoption of some unjustified concepts has resulted in performing a large number of human studies, and consequently, unfounded claims have been made about the role of certain PET tracers for both research and clinical purposes. Therefore, it is quite timely to clarify these misconceptions and define what can and cannot be accomplished with PET imaging, temper unrealistic expectations in the future, and utilize the limited available resources more effectively for research and clinical indications.

Reprint requests: Abass Alavi, MD, PhD, DSc, Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104; *abass.alavi@uphs.upenn.edu*
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In spite of substantial improvements made during the past few decades in generating images with high resolution and great detail, PET remains a gross scanning technique. While the original PET instruments provided images with spatial resolution on the order of 1.5 cm or higher,[4,5] current machines are designed to generate scans with superb spatial resolutions in the range of 5-10 mm in phantoms and in human studies.[6] These advances have been made by increasing the number of detectors and developing sophisticated reconstruction algorithms that have overcome many of the shortcomings of the earlier generation of PET machines.[6] This trend has been particularly impressive in imaging the brain and animals where small structures in the range of a few mm's can be visualized by modern instruments.[7,8] Despite the ability to target specific biological processes and generate high contrast images with PET, this imaging modality will fail to portray details at the cellular and molecular levels if the intended tracer is not taken up by a relatively large mass of cells or other structural targets. As such, extrapolating what is achievable at the in vitro settings as well as on the autoradiographic imaging approaches to human studies will be too simplistic and flawed. Based on experience gained over the years, it has been realized that detection of biological activities at the molecular level requires a large mass of targets that are clumped together in a volume that exceeds several mm^3 (realistically more than 1 cm^3) to be visualized by PET imaging.[9] Furthermore, the degree of tracer uptake in such sizable volumes has to be substantial and significantly higher than the background activity levels in order to achieve a detectable contrast. Therefore, efforts made to detect and visualize target volumes that are very small (a few cubic millimeters) in size and have relatively low levels of uptake of the intended compound have and will fail based on this proven logic.

Unfortunately, these facts, which are well established and documented in the scientific literature by well-designed research studies, have been overlooked by some groups and this has resulted in conducting research studies that have generated questionable results.

Misleading scientific communications have appeared in the literature over the years in which issues associated with the spatial resolution of PET and the related partial volume effect have been completely ignored. These include attempts that have been made to image pancreatic islets, plaques, and tangles in the brains of patients with cognitive impairment, bacteria, and atherosclerosis (in major and coronary arteries).

In this editorial, we will particularly focus on challenges that we face in detecting and characterizing atherosclerotic plaques in the arteries. Over the past decade, a relatively large number of scientific communications have been published about visualizing inflammation and calcification in both large arteries and the coronaries in humans. By now, it is well established that inflammatory cells are highly glycolytic, and therefore, administered FDG is taken up by the activated macrophages in the plaques.[10] Similarly, 18F-Sodium Fluoride (NaF) is taken up at the sites of calcification and ossification due to physicochemical exchange of 18-F ion with hydroxyl group in hydroxyapatite deposited at such locations.[11,12] It is a fact that atherosclerotic plaques even in the large arteries are no more than few millimeters in width even in the advanced stages of the disease, and therefore, cannot be visualized in vivo with acceptable sensitivity because of the limitations of PET as described above. Furthermore, arterial wall motion related to cardiac cycle deteriorates the spatial resolution of PET beyond the inherent limitations of this imaging modality. This limitation becomes a main source of concern when PET is employed in an attempt to detect and visualize inflammation and calcification in the coronary arteries. These vessels are very small in size (no more than a few millimeters even at their origin) and cannot be readily detected by an imaging system that has very poor spatial resolution and requires scanning for an extended period of time (several minutes or longer).

The main confounding issue in examining coronary arteries relates to combined cardiac and respiratory motions during data acquisition over several minutes. These combined physiologic movements make it almost impossible to assess uptakes of the intended tracers (including FDG and NaF) at the targeted sites. While cardiac and respiratory gating has been proposed as a potential solution for overcoming these undesirable phenomena, the success of such approaches is questionable at best, since they are unable to overcome the complexities that are posed by these undesirable physiological functions. Particularly, issues related to respiratory cycle are very complicated and cannot be readily overcome by adopting gating approaches described in the literature.[13] In contrast to cardiac cycle, which is regular in nature, respiratory motion is very irregular and varies considerably from breath to breath and therefore, attempts to improve spatial resolution of PET for imaging pulmonary or cardiac disorders have been unsatisfactory. The combination of respiratory motion with cardiac contractions makes it almost impossible to measure precise levels of tracer concentration in coronary arteries. Based on the limitations enumerated, the reports in the literature about imaging of the coronary arteries to detect atherosclerosis with either FDG or NaF have to be viewed with great caution. This is also applicable to other tracers that have been tested for this purpose.

Marchesseau et al's article, ''Hybrid PET/CT and PET/MRI imaging of vulnerable coronary plaque and myocardial scar tissue in acute myocardial infarction'' refers to certain publications from the literature to legitimize the results reported in this communication.[14-16] Unfortunately, as noted above, the validity of existing data in the literature is questionable at best. Therefore, such comparisons further complicate the ongoing debate about utilizing these techniques in future research and the clinical applications of PET in cardiac disorders.

In recent years, several research projects have been conducted to measure hypoxia, cell proliferation, angiogenesis, and other pathologies in both major arteries as well as in the heart.[17-19] In spite of relative successes of FDG in detecting macrophages in the plaques in the major arteries, which contain abundant numbers of these inflammatory cells, the possibility of detecting plaques as well as their consequent complications with these tracers in the arteries is almost none.[20-23] Therefore, such attempts should be abandoned in the future. Similarly, efforts are being made to visualize certain biological phenomena (angiogenesis, cell proliferation, hypoxia, and other pathological processes) around myocardial infarction in both animal models and human beings are impossible tasks. Furthermore, irregular cardiac cycle, which is a common complication of myocardium infarction, along with respiratory motion further complicates such research initiatives.[24] Also, the volume of the target tissues to be imaged is extremely small and beyond the spatial resolution of PET imaging as described above.

Additionally, attempts to use certain tracers to detect thrombosis in vulnerable coronary arteries are somewhat naïve and misconceived. It is known that immediately after arterial thrombosis or embolism, blood flow through the affected vessel will cease. This would mean that the administered tracers will not be

able to reach the surface of the clot and visualize the thrombus. In order to detect clots by molecular imaging techniques, there must be an ongoing clot formation while appropriate PET tracers are circulating in the blood and are incorporated into the body of thrombosis. In other words, successful results with this approach will require active clot formation and constant incorporation of the injected compound into the clot at the site. This approach has been successful in detecting clots in the venous system and excellent results have been reported in the literature by employing a variety of radiotracers by both conventional and PET imaging techniques.[25,26] Therefore, considering the arterial nature of the coronary artery clots, the physical limitations of PET in such domains, and the timing for imaging these clots, it will be nearly impossible to detect clots in patients with myocardial infarction.

Some of the difficulties that have been enumerated above about visualizing subtle uptake of PET compounds can be overcome by resorting to quantifying global uptake of tracers in various organs and structures.[27-42] We should mention that in major arteries, such as the aorta, partial volume correction following accurate measurement of wall thickness may allow detection of inflammation or calcification to some extent.[24] However, this technique is of limited value in assessing small vessels such as coronary arteries and other novel approaches should be adopted for this purpose. The concept of PET-based global measurement was introduced in the early 1990s, which provided a means to separate patients with AD from controls with higher accuracy compared with conventional regional assessment.[43] This concept has been tested extensively in several research studies with excellent results.[29,31,32,34-37,39-42] By adopting this novel analysis scheme, we are able to detect evidence for disease activity in its early states, while subtle focal abnormalities are of limited value.[38] For example, we have employed this methodology in detecting uptakes of FDG and NaF in atherosclerotic plaques with high sensitivity.[21,44-49] Specifically, we have validated measurements of global coronary artery calcification with NaF-PET in animals and human studies.[12,50] Similarly, we have used this approach in detecting inflammation in many other organs including the liver, heart, lungs, and bowel as well as disease activity in various malignancies.[32,34-36,39] Therefore, we believe some of the shortcomings of conventional methods for detecting and quantifying radiotracer uptake can be overcome by resorting to global assessment approaches in the future.

Disclosure

The authors declare that they have no conflict of interest.

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