PET-based imaging to detect and characterize cardiovascular disorders: Unavoidable path for the foreseeable future

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Received Aug 24, 2017; accepted Aug 24, 2017

doi:10.1007/s12350-017-1062-1

The discovery of x-ray by Roentgen in 1895 started a major revolution in medicine which has continued to the 20th and 21st centuries with accelerated pace over the past 5 decades. Due to minimal contrast between abnormal sites and the background *noted on planar radiography*, efforts have been made to overcome this deficiency by administering high-density preparations orally or intravenously for certain indications. The concept of focused collimation introduced by Casen in the 1950s led to the invention of rectilinear scanners to image radiolabeled tracers. A decade later, Anger started a new era in medical imaging by inventing his scintillation camera as we know today.¹ Planar images generated by this approach also suffered from suboptimal contrast between the sites of abnormality and the background activity. In spite of a great desire to employ tomographic imaging in medicine, this concept did not become a reality until David Kuhl at the University of Pennsylvania (Penn) designed and built several radiotracer-based instruments in the '60s and '70s.² This research initiative was based on detecting single gamma rays from multiple projections and reconstructing tomographic images by the back-projection approach. In 1971, Hounsfield performed the first tomographic images of the brain with x-rays which revolutionized the field.³ This technology (x-ray computed tomography (XCT)) was initially used to detect brain diseases and

disorders until the mid-to-late '70s when whole-body assessment with XCT became a standard modality in medical imaging. This technology has improved substantially over years and current instruments can scan organs of the entire body with high resolution and great speed. Iodinated contrast agents are routinely administered for improving sensitivity and specificity of this technique in spite of their significant side effects. Also, in recent years, concerns have been raised about the high radiation doses associated with modern spiral XCT machines.

Initial radiotracer-based tomographic images were acquired by specialized instruments that focused on assessing brain disorders.^{4,5} The concept of tomographic imaging by using an Anger camera was introduced by investigators at the University of Michigan and Berkeley, which led to adopting emission tomography as a powerful modality in the practice of medicine.^{6,7} Currently, single-photon emission computed tomography (SPECT) is the workhorse of the specialty around the world. Unfortunately, SPECT imaging has suffered from the lack of progress in synthesizing novel tracers for research and clinical purposes. In general, attempts to label available radionuclides such as technetium and iodine to biologically important compounds have been disappointing.

In the early '70s, the lack of prospects for introducing novel radiotracers for SPECT led investigators at Penn to explore the possibility of labeling positron emitters to biologically important compounds for molecular assessment of disease activity in various organs including central nervous system (CNS) disorders.⁸ This effort eventually resulted in synthesizing 18F-fluorodeoxyglucose (FDG), which was successfully administered in August of 1976 to two human beings.⁹

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J Nucl Cardiol 2018;25:203–7.

1071-3581/\$34.00

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In parallel with these developments, instrumentation for imaging positron emitters had been substantially improved by investigators at Washington University led by Ter-Pogossian et al.¹⁰ Research and clinical applications of FDG and other PET tracers along with advances made in PET instrumentation have enormously strengthened the field of molecular imaging.

The introduction of Magnetic Resonance Imaging (MRI) in the 1970s further enhanced the role of imaging in medicine.¹¹ Although initially claims were made about its ability to detect disease at the molecular level, currently MRI remains as a structural imaging technique. MRI agents with potential for molecular imaging have proven to be toxic and have been abandoned for many applications.^{12,13}

The introduction of PET/CT by investigators at the University of Pittsburgh in the late 1990s provided a paradigm shift in medical imaging and has allowed co-registration of structural images provided by CT and molecular images generated by PET for both research and clinical purposes.¹⁴ This has rejuvenated the field of molecular imaging with PET. Since 2001 when the first commercial PET/CT units were introduced to the market, PET/CT imaging has become the workhorse of modern nuclear medicine laboratories. The main compound currently being used for PET/CT imaging is FDG, which is employed primarily for the management of patients with a variety of malignancies.¹⁵ The introduction of PET/CT has led to combining CT with SPECT and this has further enhanced the role of SPECT in assessing certain diseases with conventional radiopharmaceuticals. The introduction of PET/MRI over the past decade has opened up a new domain for molecular imaging and its role is being investigated at this time.¹⁶ It is expected that this modality will play a role in three major domains and include disorders of the brain, cardiovascular system, and musculoskeletal (MSK) structures. The main challenge for PET/MRI is suboptimal attenuation correction to emitted gamma rays for generating high-quality images of deep structures and quantification of tracer concentrations in normal and disease sites.

The experience gained over the past century has revealed that structural imaging is quite insensitive in the detection of disease in its early stages and also in the assessment of response following therapeutic interventions. Over the years, this initially led to adopting certain physiologic measurements and imaging with various available approaches (Figure 1). Measurements of blood flow to the brain and the heart as markers for cerebral and cardiac dysfunction have been extensively explored during the past 5 decades.¹⁷ Cerebral blood flow measurement was primarily adopted for research purposes and its clinical significance has been uncertain all along.

In contrast, imaging of coronary artery perfusion for detection of atherosclerosis has become the workhorse of functional imaging in cardiology since the 1980s. Currently, as noted in the companion editorials, perfusion imaging particularly with technetium-labeled compounds is the most common imaging methodology adopted for the detection of coronary artery disease. This approach is primarily based on imaging with SPECT which is widely available around the world. As clearly stated by both groups, there are advantages and disadvantages to continuing with SPECT and perfusion imaging as we explore other possibilities for managing patients with cardiac disorders with potentially more powerful imaging modalities. Perfusion imaging with PET has gained some recognition during the past decade because of the availability of the rubidium generators, which provides high-resolution imaging of cardiac blood flow within a short period of imaging. Furthermore, radiation exposure is substantiated higher with SPECT than with PET.

We have to emphasize that PET imaging is substantially superior to SPECT with regard to its potential to detect and quantify numerous metabolic parameters in cardiovascular disorders.¹⁸ Over the past 4 decades, we have realized that the potential for preparing potent positron emitting tracers is enormous and overshadows what is achievable with SPECT tracers. Particularly, it has been shown that PET allows not only imaging and quantifying blood flow to the myocardium, but also allows for assessment of disease at the molecular level

Figure 1. This figure graphically portrays the probable sequence of biological events as they relate to many disorders. Functional changes refer to physiological alterations such as blood flow and organ motility. This pattern is particularly relevant to the assessment of atherosclerosis in the coronary arteries as well as other organ arteries. As such, molecular imaging with PET may provide early evidence of the disease process.

Figure 2. The graphic data shown above reveal the correlation between age and evidence for inflammation (FDG) and calcification (NaF) in healthy subjects (A, C) and subjects with high risk for atherosclerosis (B, D). Based on these molecular data, NaF-PET imaging appears to be more sensitive in detecting evidence for atherosclerosis in the arch of the aorta than FDG-PET scanning.

in many settings.¹⁹ The number of tracers that can be used for molecular imaging is limitless and has the potential to completely revolutionize the field of cardiovascular imaging in the future.

Furthermore, the spatial resolution of PET far exceeds that of SPECT imaging. The spatial resolution of PET is at least 2-3 times higher than that of SPECT, and therefore PET generates images with greater detail in the cardiovascular structures. Perfusion imaging allows detecting abnormalities that are due to substantial narrowing of the coronary arteries, and therefore it has a relatively high sensitivity for assessing the disease that is somewhat advanced. This is particularly true when proximal arteries are narrowed, resulting in under-perfusion of the relatively large territories supplied by these vessels. This would mean that abnormalities that are peripherally located may not be readily detectable by perfusion imaging alone. There is evidence that coronary artery disease commonly involves small vessels without involving proximal arteries. Based on this logic, there is a dire need for detecting atherosclerosis when it

is subtle in nature and has not resulted in significant physiologic changes that can be detected by blood flow measurements alone. Therefore, imaging techniques that are able to detect disease process at the molecular level will become essential as a future trend in cardiac imaging for coronary disease and many maladies of the cardiovascular system. Therefore, it is our belief that PET will become the modality of choice for assessing cardiac abnormalities in the foreseeable future. By the time the disease is detectable by physiological imaging, the process is likely to be irreversible and may require invasive intervention.

Since most cardiovascular disorders are diffuse in nature, global measurements may play an essential role for accurate diagnosis of the underlying pathological states in their early stages. Detection of focal abnormalities by PET or SPECT, particularly in the coronary arteries, is very challenging because of two major motions: cardiac and respiratory cycles.^{20,21} Therefore, global assessment of disease process appears an important path as we explore the role of molecular imaging in

cardiovascular disorders.²² Particularly, this logical scheme has been quite successful in quantifying cardiac and arterial calcification with NaF-PET imaging (Alavi-Carlsen Calcification Score).

We would like to emphasize that focusing on coronary artery disease assessment alone will overlook and underestimate the presence of atherosclerosis elsewhere, particularly in the carotid arteries with its devastating consequences.²³⁻²⁵ Therefore, examining the whole body for atherosclerosis may provide the means for detecting the extent of disease burden beyond the heart. Imaging with PET provides a practical means for this purpose and cannot be matched by any other existing imaging modalities today. An example of this type of approach is to detect and quantify calcification in the plaques of the entire cardiovascular system (coronary arteries, in the aorta, and carotid arteries) by Sodium Fluoride (NaF)-PET imaging (Figure 2). With the recent advances being made in PET instrumentation, this relatively simple approach is expected to revolutionize management of patients with atherosclerosis.²⁶⁻²⁸ This sets the tone for more advances to be made in the near future.

Therefore, we believe that the future of cardiovascular imaging is going to heavily depend on PET/CT and possibly PET/MRI and this will completely replace other imaging techniques such as SPECT in the next decade or two. Arguments about availability of PET for routine purposes and the costs of performing PET may not be relevant. When we are dealing with a common, treatable, yet potentially fatal disease such as atherosclerosis, these arguments may not be valid because of the high cost effectiveness of this modality. Therefore, we would encourage our colleagues to embrace PET as the future imaging modality for assessing cardiovascular disorders

Disclosure

Authors declare that they have no conflict of interest.

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