The Current State of Cardiac PET for Perfusion Imaging: How It Developed and Where We Are

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Beginning with studies in the 1970s using N-13 ammonia\(^1\) and rubidium-82 (Rb-82),\(^4\) the clinical utility of cardiac positron emission tomographic (PET) perfusion imaging in patients with known or suspected coronary artery disease (CAD) has been appreciated. While single photon emission tomographic (SPECT) using thallium-201 (Tl-201), technetium-99m (Tc-99m) sestamibi and Tc-99m-tetrofosmin has dominated the field of myocardial perfusion imaging (MPI), having demonstrated robust diagnostic and prognostic utility,\(^5,6\) from PET’s development its advantages have been understood.\(^7\)

PET is distinct from SPECT in technical aspects and in the tracers available for use.\(^7\) As PET events are measured by coincidence detection of two 511-keV annihilation photons emitted simultaneously at an \(\sim 180^\circ\) angle, physical collimation is unnecessary, allowing detection of a larger percentage of counts compared with SPECT, thus a higher signal to noise ratio improving image quality and spatial resolution. In addition, for PET attenuation correction is routinely applied with a transmission line source, or more recently by computed tomography (CT) with most current commercial cameras being hybrid PET-CT machines.\(^10\)

With respect to radiotracers, positron emitting nuclides are generally of lower atomic number, atoms such as carbon-11, nitrogen-13, and oxygen-15, and thus more easily incorporated into biologically active compounds useful for physiological studies. As PET tracers generally have shorter half-lives than SPECT tracers, study protocols are faster and more convenient. Finally, with PET patient radiation exposure is lower, typically 2-5.4 mSv for a Rb-82 study and 4-6 mSv for an N-13 ammonia study, compared with \(\sim 11\) mSv for a typical Tc-99m sestamibi one-day study.\(^11,12\)

In the 1980s-1990s, several studies demonstrated superior CAD diagnostic accuracy for PET (sensitivity 91 percent, specificity 90 percent, accuracy 92 percent) compared with SPECT (sensitivity 86 percent, specificity 65 percent, accuracy 78 percent).\(^8,13-17\) While these mean values were derived mostly from different patient cohorts, a noteworthy study by Go et al.\(^16\) compared, in the same 132 patients, the diagnostic effectiveness of Rb-82 PET versus Tl-201 SPECT, finding that PET had superior diagnostic accuracy (92 percent vs. 78 percent for SPECT) with higher image quality and increased interpretive confidence.

Despite such evidence of PET’s potentially superior value, its clinical development was stunted due to limited availability (at just a few research centers). (Continued on page 2. See Cardiac PET)
PET was considered expensive and, until 1995, reimbursement was lacking for portable generator-produced Rb-82 (more feasible for most than on-site cyclotron required N-13 ammonia). Availability of user-friendly software for image processing and display was limited. To a large extent, CMS approvals from 1998 to 2005 of Medicare PET reimbursement for malignancies was the key factor increasing the availability of PET cameras, thereby spurring advocacy for reimbursement of cardiac procedures and motivating the undertaking of the necessary technological advancements and supportive investigative studies.

In 2006, after a clinical study gap of about a decade, Bateman et al. compared the diagnostic accuracy of pharmacologic stress Tc-99m-sestamibi SPECT with Rb-82 PET MPI in separate 112-patient cohorts, matched by gender, body mass index, and presence and extent of CAD, who underwent PET or SPECT. PET image quality and interpretive certainty were higher, and accuracy was better for men and women, and for obese and non-obese patients, with improved detection of multi-vessel CAD.

A large meta-analysis of 15 PET (1344 patients) and eight SPECT (1755 patients) studies assessing the accuracy of Rb-82 PET was performed by McArdle et al. As in the table, PET’s diagnostic accuracy was superior to that of SPECT. Soon after, an 11,862 patient meta-analysis in the table, PET’s diagnostic accuracy was superior to SPECT. However, because of the high accuracy of F-18-flurpiridaz for identifying CAD at a regional cyclotron and delivery in unit doses to imaging centers. The shorter positron range produces images with improved resolution. Finally, the extraction fraction of F-18-flurpiridaz is 94 percent without significant roll-off at higher flows, compared with roll-off and extraction fractions of 82 percent for N-13 ammonia and 42 percent for Rb-82.

In a multicenter 143-patient Phase II study, compared with SPECT a higher percentage of F-18-flurpiridaz images were rated excellent or good with improved diagnostic certainty, and there were improved sensitivities and specificities for identifying CAD. A Phase III trial confirmed the high accuracy of F-18-flurpiridaz for identifying CAD with a higher sensitivity than for SPECT. However, because of the inability to meet the non-inferiority specificity threshold, attributed to an under-diagnosis of CAD by SPECT, another Phase III study is planned.

While diagnostic accuracy is important, an imaging test’s utility is increasingly judged on its ability to direct “appropriate and targeted therapies that improve symptom burden and long-term outcomes … [that] are not offset by high upfront procedural and induced costs …” An important aspect of guiding patient management is effective risk stratification. Similar to what has been demonstrated for SPECT, the prognostic power of cardiac PET is found to be consistently strong.

The first reported study, performed by Marwick et al. in 685 patients who underwent Rb-82 PET, found a yearly mortality rate of 0.9 percent in patients with normal images, compared with 4.3 percent for those with abnormal images. A subsequent study of 367 lower risk patients by Yoshinaga et al. reported the annual hard event (cardiac death and myocardial infarction) to be 0.4 percent for patients with normal images, compared with 2.3 percent for patients with mildly abnormal images and 7.0 percent for patients with moderate to severe abnormalities.

The largest undertaking to date is a multicenter registry of 7061 patients who underwent Rb-82 PET, showing cardiac death rates of 0.8 percent over a 22-month median for patients with normal studies, with a graded increase related to the degree of image abnormality up to 9.7 percent for patients with ≥20 percent abnormal myocardium at stress (p<0.0001). Further supporting the utility of PET MPI, the percent of ischemic and scarred myocardium improved classification of

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Twin Study: Genetics and Environment Affect Different Regions of the Brain

A recent study, reported in the March issue of The Journal of Nuclear Medicine, found evidence that genetic influence on cerebral glucose metabolism played a major role in the bilateral parietal lobes and the left temporal lobe of the human brain, while environmental influences after birth dominated in other regions.

Twins have long been the subject of studies in the quest to determine the influences of nature vs. nurture. An earlier study, published in the journal Nature Genetics in May 2015, examined more than half a century of research collected on 14.5 million pairs of twins and concluded that the nature versus nurture debate is a draw; both have nearly identical influences on a person’s traits and diseases. But we still didn’t know specifically how nature and environment can affect our brains.

Now, researchers at Osaka University Graduate School of Medicine in Japan have begun to focus in on just that. In their study of 40 monozygotic (identical) and 18 dizygotic (fraternal) twin pairs, ages 30 or older, they used positron emission tomography (PET) scans with the radiopharmaceutical 2-deoxy-2-F-18-fluoro-D-glucose (FDG) targeting regional cerebral glucose metabolism. Eighteen control pairs matched genetically unrelated individuals of the same age and gender as the twins in the study.

Jun Hatazawa, MD, PhD, corresponding author of the study, explains, “Glucose is an essential fuel for brain energy metabolism as well as oxygen. Functional activation of neurons is normally associated with increases in the local cerebral glucose utilization and blood flow.”

They evaluated the F-18 FDG uptake in each cerebral lobe for the identical and fraternal twins as well as the controls. By comparing differences, they could estimate the genetic and environmental contributions.

Hatazawa notes that previous studies have revealed strong genetic influence on the volume of frontal gray matter, whereas this study shows that frontal glucose metabolism is preferentially influenced by environmental factors. Knowing which areas of the brain are more influenced by the environment will help with understanding particular neurological and psychiatric disorders.

He states, “The frontal lobes of monozygotic twins are anatomically identical, but they are metabolically and functionally different under environmental influences. This twin-imaging research can be applied to amyloid imaging in Alzheimer’s disease and neurotransmitter-receptor imaging in psychiatric disorders where genetic, epigenetic and environmental influences remain unknown. In future twin studies, we may be able to identify specific environmental risk factors.”

Authors of the article “Genetic and Environmental Influences on Regional Brain Uptake of 2-deoxy-2-18F-fluoro-D-glucose: a PET Study in Monozygotic and Dizygotic Twins” include Shinichiro Watanabe, Hiroki Kato, Eku Shimosegawa, and Jun Hatazawa of Osaka University Graduate School of Medicine. This study was supported by KAKENHI grants-in-aid S 24229008 and C 26462204 for scientific research. It was also supported in part by the Osaka Medical Research Foundation for Intractable Disease.

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cardiac death risk by 12 percent beyond clinical modeling parameters.29

An additional variable that is uniquely useful for PET is the difference between the post-stress and rest gated image LVEF. For a stress SPECT study, imaging is performed about an hour after stress, with the post-stress gated LVEF therefore more a reflection of the resting EF; for PET, the stress imaging is performed during or quickly after stress, when the effects of the stress agent are still present. Dobbala et al.30 reported that in healthy subjects the post-stress PET gated EF is normally higher than the rest EF, with the absence of this LVEF reserve (and especially a decrease in LVEF) frequently indicative of multi-vessel disease despite a normal or low risk perfusion pattern. A case of impaired LVEF reserve is shown in the Figure. Absence of LVEF reserve has been shown to increase the likelihood of cardiac events and death.31

Nevertheless, despite the aforementioned advantages, PET is still hindered by known deficiencies of conventional MPI. Current image interpretive methodology assesses relative differences in regional myocardial tracer uptake, determining tracer uptake heterogeneity in reference to normal patients, with ischemia manifest as reduced heterogeneity on rest compared with stress images.

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Current interpretive techniques do not well detect balanced ischemia from multi-vessel disease, leading to frequent underestimation of disease extent or, in some cases, missing disease entirely. In addition, endothelial dysfunction, and diffuse epicardial and microvascular disease may not be appreciated. The increased counts measured with PET provide the means to overcome these deficiencies by accurate measurements of dynamic count changes during tracer administration, thereby allowing determination of true quantitative myocardial blood flow (MBF) parameters.

As well described in a recent review by deKemp et al., quantitative flow values are derived by relating tracer concentration in arterial (myocardial cavity) blood to that in myocardial tissue, correcting for tracer extraction fraction. Parameters obtained include absolute myocardial blood flow in ml/g/min and the ratio of stress to rest blood flow, i.e., myocardial blood flow reserve (MBFR) (also referred for as coronary flow reserve, CFR). A MBFR below a particular threshold (ranging from about 1.5 to 2.0 in published studies) has been shown to enhance detection of multi-vessel CAD beyond conventional MPI interpretative methods, and improve risk stratification, with correct risk reclassification in one study as high as 34.8 percent.

Normal-appearing perfusion images, along with a satisfactory MBFR, increase confidence of adequate stress and high assurance that the risk of an event is extremely low. At the same time, among patients considered at low risk because of minimal to no perfusion abnormalities seen visually or detected by conventional summed stress scores, there is a subgroup of patient with abnormal MBFRs who are at increased risk for cardiac events, including death.

Such hidden risk appears especially the case in patients with diabetes as, even in the absence of known CAD, those with impaired MBFR have a death rate comparable to non-diabetic patients with CAD. Enhanced risk stratification by MBF measurements may, in part, represent overcoming missed obstructive epicardial coronary disease in the setting of balanced ischemia, but may also detect diffuse non-obstructive epicardial and microvascular disease, with endothelial dysfunction that predispose an individual to adverse outcomes. A recent study by Taqueti et al. found that PET MBF measurements predict adverse outcomes better than the extent of anatomic disease on invasive coronary angiography, and may better select patients who would benefit from bypass surgery.

While further investigation and standardization of quantitative MBF is needed, including dealing with variability related to age, gender, vasodilator and tracer used, and analytic software (as well as how to interpret the findings...}

**PET in the News**

The international literature on PET, PET/CT and PET/MR continues to grow at a pace that challenges both researchers and clinicians. The media has recognized the value of these modalities and regularly features advances in research and technology in the news. In each issue, the PET CoE Newsletter presents a tomographic slice of the breadth of PET media coverage that appears in publications around the world. Additional news articles can be found online at www.snmmi.org under “MI: Making a Difference.”

- Powerful PET probe shows potential for improving cancer treatment
  Health Imaging

- FDG-PET/CT Accurate in Diagnosing Breast Cancer Recurrence
  Cancer Therapy Advisor

- PET Scan After Two Cycles Guides Therapy For Hodgkin Lymphoma
  Clinical Oncology News

- Scientists image amyloid buildups of language dementia
  UPI

- 3-month PET/CT helps track oropharyngeal cancer
  Aunt Minnie

- Early diagnosis, staging of Alzheimer’s disease seen in PET scans
  UPI

- Predicting liver tumor recurrence with immediate post-ablation FDG PET/CT
  Molecular Imaging

- PET/CT Plus MRI May Aid Salvage Radiotherapy for Nodal Recurrent PCa
  Renal and Urology News

- PET/MR enterography offers potential in Crohn’s disease
  Aunt Minnie

- Novel PET tracer could aid detection of tau deposits
  Aunt Minnie

- New imaging test detects prostate cancer much better than any other tests in use today
  News-Medical
in various clinical scenarios). MBF measurements could potentially change the way CAD is approached and managed. It has been well demonstrated that percent coronary stenosis on arteriography, the parameter by which revascularization and medical management decisions are customarily made, is poorly related to functional severity. It has also been demonstrated that basing revascularization decisions on anatomic epicardial artery narrowing does not improve patient outcome and may lead to an inferior patient outcome compared with using physiologic measurements.

While the functional significance of discrete arterial narrowings seen at coronary angiography can be assessed by invasive measurements of fractional flow reserve (FFR), PET assessment of MBF provides a more comprehensive determination of the severity of disease throughout the coronary vasculature. In addition to potentially improving guidance for referral to invasive revascularization, one would expect an accurate quantitative assessment to better assess patient response to medical treatments and lifestyle changes compared with conventional PET interpretative techniques. It is hoped that further investigations, development of more convenient tracers, and wider clinical experience will provide the impetus for expanding the use of cardiac PET, ultimately improving outcome and well-being of patients with known or suspected CAD.

REFERENCES

**Prostate Cancer Continued from page 5.**


**President’s Report. Continued from page 1.**

“Practical PET/CT,” which will discuss a potpourri of topics related to contemporary issues routinely faced by all of us when reading PET/CT on a daily basis. I’d also like to invite you to attend the PET Center of Excellence business meeting, which will be held on Sunday, June 12, from 11:30 AM to 1 PM. As always, your ideas and suggestions are welcome!