The tools are ready, are we?

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Received Jul 5, 2017; accepted Jul 5, 2017
doi:10.1007/s12350-017-1032-7

See related article, 543–556

In this issue of the *Journal of Nuclear Cardiology*, Lee and colleagues elegantly review the recent advances in the instrumentations for nuclear cardiac imaging.[1] Solid-state radiation detectors incorporating cadmium zinc telluride (CZT) become the detector of choice for dedicated cardiac imaging systems. CZT single-photon emission computed tomography (SPECT) has improved image quality and shortened acquisition time of myocardial perfusion imaging (MPI) thanks to its direct energy conversion mechanism, narrow energy resolution, and pixelated nature of electrical circuit. The measurement of absolute myocardial blood flow (MBF) as well as coronary flow reserve (CFR) using CZT SPECT is now under active investigation and is showing clinical feasibility. Multimodality imaging systems which hybridized SPECT and positron emission tomography (PET) with CT widened clinical application of cardiac imaging studies. Quantitative SPECT/CT provides additive information of coronary calcium burden, attenuation correction for both visual and quantitative assessment of myocardial perfusion, and enables quantification of myocardial blood flow and flow reserve. Cardiac PET is also an active progress. Adoption of silicon photomultipliers (SiPMs) leads to enhancements in image quality and count rates. The application of accurate time-of-flight (TOF) information reduced emission-transmission mismatch artifacts. Information of the extracted coronary arteries from CT angiography allows non-linear motion correction of PET plaque images. Replacement of photomultiplier tubes with semiconductor photosensors such as the avalanche photodiode (APD) and SiPM has made it possible to integrate PET with magnetic resonance (MR). PET/MR system is now clinically available in hybrid as well as parallel camera structure.

The recently introduced nuclear cardiac imaging tools are ready to provide more information in better quality than ever before. It is fair to question whether we are ready to apply these tools in clinical fields. There are challenges to overcome before we can use the state-of-the-art imaging tools.

MEASUREMENT OF MBF AND CFR

Several studies showed clinical feasibility of measuring MBF and CFR by dynamic image acquisition using Tc-99m sestamibi and CZT SPECT/CT cameras.[2,3] It does not directly mean that it can be accepted as a clinical tool in daily practice. Measuring MBF and CFR by cardiac PET is a mature technology but is not widely used in clinics. Several obstacles are noted.[4] First of all, resting MBF is variable according to hemodynamic and metabolic changes. MBF and CFR cannot differentiate epicardial obstructive and microvascular diseases or provide anatomical localization of coronary obstruction. The complex interplay among different MBF parameters has not been fully unveiled. Different MBF parameters stand for different coronary pathophysiologies, and are not interchangeable.[5] For example, a relative MBF ratio namely relative flow reserve (RFR) could be more suitable for the diagnosis of focal significant coronary stenosis in need of percutaneous

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J Nucl Cardiol 2019;26:557–60.
1071-3581/$34.00

coronary intervention (PCI).[6,7] By contrast, low CFR indicates the presence of diffuse atherosclerosis, for which bypass surgery may be more beneficial than is PCI.[8]

Additional critical weakness of measuring MBF using Tc-99m-labeled tracers is its low extraction fraction. By the first human study comparing MBF data from dynamic CZT acquisition with data from PET Nkoulou et al.[9] showed that median MBF at rest was comparable between CZT and PET, whereas it was significantly lower at stress in CZT than PET. This resulted in median myocardial flow reserve values of 1.32 by CZT, which is very low as compared to the usual cutoff value of 2.0 by many PET-based studies. They concluded that the estimation of absolute MBF index values by CZT SPECT MPI is technically feasible, although hyperemic values are significantly lower than from PET. Using correction factors to solve the problem makes another problem. Multiplying correction factor can increase the noise and make MBF and CFR values unreliable. Lee et al.[1] also noted that the extraction fraction of Tc-99m myocardial perfusion imaging agents is far lower than that of PET tracers, and the mitigation of the lower extraction fraction by means of K1 uptake rate and MBF relationship amplify the random error of MBF measurement.

CLINICAL ROLES OF MULTIMODALITY IMAGING

Multimodality imaging does not mean multiple imaging modalities in series. Rather, this involves the extraction of additional information not capable of being derived from any single image. From this perspectives, multimodality imaging has frequently been defined as combining morphological and functional images with or without fusion, SPECT/CT, PET/CT, and PET/MR. The information of coronary calcium burden and coronary vascular anatomy can be additionally given by CT and combined to SPECT or PET MPI data, making more comprehensive understanding of myocardial perfusion in regards to coronary plaque characters possible.[6,10,11] Clinicians are getting additional information on coronary plaques from additional invasive technologies including intravascular ultrasound, optic coherence tomography as well as near infrared imaging. It is a challenge to nuclear cardiologists how to provide comprehensive characterization of coronary plaques before the patient undergoes invasive coronary studies.

MR has advantages of the higher soft tissue contrast without using ionizing radiation. PET/MR is suited to image myocardial inflammatory process in various clinical conditions. Hanneman et al.[12] showed that PET/MR detected FDG uptake in cardiac sarcoidosis and myocarditis in 90% patients, while PET/CT was successful in 60%. The possible reasons for the difference are a longer duration of the PET acquisition with PET/MR, and superior PET detectors in the newer PET/MR scanner. Adding information on the myocardial inflammation and edema using T2-weighted MR imaging and fibrosis using late gadolinium enhancement (LGE) further intensifies the accuracy of PET/MR in the diagnosis of myocardial inflammatory diseases.[13] Myocardial inflammation can also result from acute myocardial infarction (AMI) as a healing process. Detecting intense inflammation early after AMI which may promote adverse remodeling has an important clinical implication to guide therapy. PET/MR is a perfect tool for the myocardial viability assessment as it gives information on FDG uptake as well as LGE. In a study which simultaneously assessed FDG uptake and LGE using a hybrid PET/MR system, Rischpler et al.[14] showed that the established PET and MR 'viability' parameters prior to revascularization therapy predict accurately the regional outcome of wall motion after AMI.

PET/MR, the most recently introduced state-of-the-art imaging technique has also limitations. Many patients with pacemakers, mechanical valves, or implantable cardioverter defibrillators cannot be studied by MR because of electromagnetic fields. Indirect attenuation correction and long imaging time often make it difficult to measure MBF by PET/MR. We are waiting for further improvement of the technology to use for more patients.

Given the multiple modalities available, selecting the optimal combination for proper multimodality imaging in the clinical setting can be challenging. Weissman et al.[15] discussed the opportunities and challenges of multimodality imaging in the management of cardiovascular disease. To summarize the challenges as follows: (1) rapid development and technologic advances, (2) expert developing only one modality and neglecting other modalities, (3) modality-specific training programs, and (4) non-medical factors (availability, cost, ownership, education, personal bias). The first and fourth challenges are considered inevitable environmental factors for nuclear cardiology practitioners, while the second and third challenges can be overcome. Efforts to solve these problems in the cardiovascular field require expert training. The Core Cardiology Training Symposium (COCATS) Task Force 4 suggested appropriate training guidelines in the era of multimodality imaging. According to the guidelines,[16] level I (basic) competency is required for all non-invasive imaging modalities (echo, nuclear imaging, coronary CT, cardiac MR) within 7 months. Level II or III (advanced) competency can be achieved by selected fellows. Further training in

addition to standard 3-year cardiovascular fellowship is required when there are more than two modalities. Training of physicians to select, interpret, and guide treatment is the first step to make multimodality imaging useful, in accordance with the technological advances. However, training for multimodality imaging is necessary but not sufficient. Additionally, clinical management of cardiovascular diseases should be conducted in a multidisciplinary team approach, as recommended by the European Society of Cardiology in the management of infective of endocarditis (Endocarditis Team; Class IIa, LOE B).[17] In the current situation, different imaging experts of separate modalities should take part in the selection of studies, diagnosis, treatment decision, discussion of concordant and/or discordant image findings, along with clinicians. If multimodality imaging successfully settles into the cardiovascular training in the future, the participating doctors will be more aware of other modalities and benefits from integrating multimodality imaging, so that the workflow may be more effective and comprehensive.

RADIATION DOSE REDUCTION

The ionizing radiation exposure to the U.S. population from medical procedures has increased six-fold since the early 1980s.[18] More than 10% of the entire U.S. population radiation burden was related to MPI.[19] Half of all nuclear medicine procedures and quarter of all X-ray studies worldwide are performed in U.S. which has 5% of world population.[20] Representative effective dose values of Tl-201 stress/rest study is the highest (25 mSv) followed by Tc-99m sestamibi one-day stress/rest (10 mSv) and N-13 ammonia stress/rest (3 mSv).[21] Introduction of high-sensitivity CZT-based system has opened the possibility of very low radiation dose associated with SPECT myocardial perfusion studies. The MultIcenter nucLear Low-dose Imaging at a milliSIEVERT (MILLISIEVERT) study have demonstrated that the radiation dose can be reduced to a range of 1 to 2 mSv with the same or superior image quality.[22]

According to observations that increasing percentage of rest-stress studies are normal and that outcomes of normal rest-stress and stress-only studies are identical, a stress-only procedure is preferred for many patients in current guidelines.[23] Adopting the stress-only procedure with high efficiency CZT SPECT camera which gives effective dose of 1 mSv can significantly reduce the radiation exposure to the U.S. population. Most current PET scanners use hardware and software modes of high-resolution, low-dose imaging. An effective spatial resolution of as low as 2 mm and effective radiation dose as low as less than 1 mSv can be achieved with time-of-flight, high-definition iterative reconstruction, and motion-frozen imaging, stress-only PET MPI in 3D mode. Many patients undergoing PET MPI have severe coronary artery disease and need comprehensive evaluation of coronary vascular dysfunction. CFR is a powerful prognostic marker which cannot be estimated by stress-only imaging. One option is the measurement of stress MBF with low-dose CT coronary angiography and calcium scoring, which can identify significant coronary artery disease that may warrant aggressive medical therapy.[24] Low-dose CT coronary angiographies can now be achieved with a radiation dose below 1 mSv by use of automated exposure control, electrocardiographically controlled tube modulation, and reduced tube voltage.[25]

CONCLUSION

Last decade we witnessed a rapid development of nuclear cardiology tools. The state-of-the-art tools are being more prepared and introduced for clinical uses in cardiovascular diseases. We may be unprepared to use them properly. There are tasks to make more evidence for proper use of each modality alone or combined. Many biomarkers including MBF, FDG uptake, as well as CT and MR parameters need to be validated in various clinical settings. Innovative physician training and multidisciplinary team approach in cardiovascular diseases are also expected.

Acknowledgements

This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1D1A3B01006631).

Disclosures

Sang-Geon Cho, Zeenat Jabin and Changho Lee declare no conflicts of interest. Henry Hee-Seung Bom has research grant from the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1D1A3B01006631).

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