

## DEBATE ARTICLES: WHICH IMAGING IS THE BEST FOR DETECTING CAD ?— REVIEW ARTICLE

# Nuclear Medicine is the Best Approach for Detecting Coronary Artery Disease: From JSNC 2016 Evening Seminar

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### Abstract

Diagnostic modalities including SPECT and CT are both useful for detecting coronary artery disease. Physiological and anatomical approaches are two sides of same coin. In a twist of irony, increasing of CT angiography and decreasing of SPECT field in Japan would be associated with inappropriate coronary interventions in terms of American appropriate use criteria of coronary interventions. Quantification of perfusion abnormality and myocardial flow reserve using dedicated CZT gamma camera would make it possible to identify the patients, in whom interventions may improve the long-term prognosis. Recent publication reported that initial non-invasive diagnostic modalities (SPECT or CT) did not affect patients' outcome. Medical economical approach should be taken into account for the selection of those two modalities in future.

**Keywords:** CT, CZT, Myocardial flow reserve, Semiconductor gamma camera, SPECT

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**S**tress myocardial perfusion single-photon emission computed tomography (SPECT) is one of the well-known diagnostic modalities in detecting coronary artery disease (CAD). Coronary CT angiography (CCTA) is also widely used for the detection of coronary luminal narrowing using a contrast medium. According to The Japanese Registry Of All cardiac and vascular Diseases (JROAD) annual report 2015, about four hundred and forty thousand CCTA were performed in 2015, and are increasing in the last five years (1). Conversely, the numbers of myocardial perfusion SPECT imaging (MPI) in Japan is decreasing in recent history. Interestingly, Inohara et al. reported that temporal trends in non-invasive test and frequency of inappropriate rating of percutaneous coronary intervention (PCI) (2). The manuscript investigated that inappropriate PCIs in stable ischemic CAD increased in parallel with the utilization of CCTA according to appropriate use criteria 2009 in US (3). We would like to clarify the usefulness of MPI in clinical settings from recent publication and the evening seminar of JSNC 2016 in Tsu.

### Quantification of MPI

MPI provides many technical indices including myocardial perfusion and cardiac functions, in which are strongly associated with future major adverse cardiac events (MACE). Summed stress score (SSS) from the summation of visual scoring using American heart association 17-segment model and ejection fraction derived from Quantitative gated SPECT (QGS) software are the major powerful predictor of MACE (4, 5). In addition, recent clinical guideline recommends to prove  $\geq 10\%$  of stress induced ischemia or jeopardized myocardium in the cases of stable PCIs, which is expressed in summed difference score (SDS) (6, 7). Survival benefit with the measurement of stress induced ischemia on MPI was reported in 2003 by Hachamovitch et al. This concept was followed by Shaw in the nuclear sub-analysis of COURAGE, and proved that  $\geq 5\%$  of ischemic reduction led the improvement of outcomes (8). Recently the 12-year follow-up of COURAGE trial was documented (9). Additional prognostic information was available from 53% of the original population. Therapeutic outcomes achieved by PCI plus

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**Fig. 1** GE Discovery NM530c (left, from GE home page), Spectrum Dynamics D-SPECT (right).

optimal medical therapy or optimal medical therapy alone showed almost same survival outcome up to 15-year follow-up. Actually, approximately 4%/year mortality (death) was reported.

By association, less than 5% of improvement on ischemia may not change patients' long term outcome in a Japanese population. A single-center retrospective analysis by Hori et al. reported that the statistically significant difference on survival from MACE between <5% and  $\geq$ 5% stress induced ischemia group (10). This is very justifiable, but less than 5% of myocardial ischemia will not create more than 5% of ischemic reduction by PCIs.

In addition, automated software including quantitative perfusion software (QPS) and QGS made it possible to have "few seconds processing" from the reconstructed image (11, 12). Less time-consuming analysis to measure ischemic perfusion deficits on MPI would be a favorable choice in a daily busy clinical situation. This would be a productive point in comparison to stress CT or MRI perfusion imaging, in which engages relatively a longer time for processing.

### Patient centered imaging

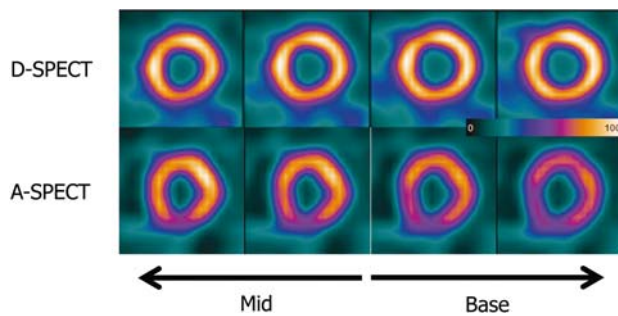
American Society of Nuclear Cardiology (ASNC) adheres to patient centered imaging (P.C.I.) concept (13). This concept includes practical recommendations based on a custom-made imaging with higher medical safety, lower radiation exposure, lower medical cost, higher quality imaging and appropriate use criteria (AUC) for choosing multi-imaging modalities (14). The concept of AUC contributes the standardization of cardiac imaging beyond the control of clinical guidelines by a consensus of experts' opinion (15). Those important points on AUC were also longtime concerns in a "conventional gamma camera generation". Increase of unfavorable PCIs might cause an incomplete reimbursement on Diagnosis Procedure Combination (DPC) system in future.

### Semiconductor gamma camera

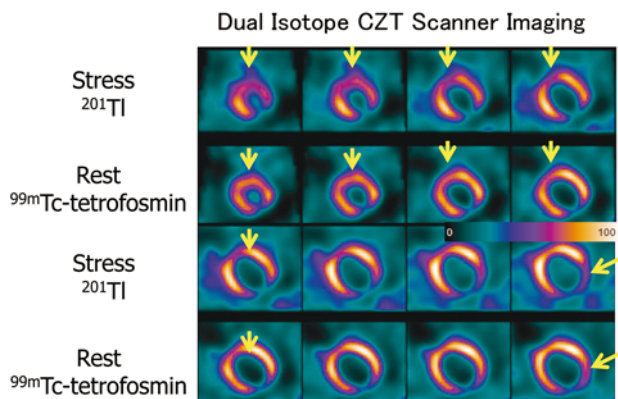
To accomplish appropriate P.C.I., dedicated semiconductor detector gamma camera would become a breakthrough on MPI (16, 17). This gamma camera mounts cadmium-zinc-telluride (CZT) detector which allows  $10\times$  sensitivity,  $2\times$  spatial resolution and high energy-spectrum resolution in comparison to NaI crystal on a conventional type gamma camera. There are two types of collimator of CZT detector gamma camera, pin-hole (GE, Discovery NM530c) or parallel-hole (Spectrum Dynamics, D-SPECT) collimators (Fig. 1) (18). Comparison of mid to basal short-axis images between D-SPECT and Anger type gamma camera (A-SPECT: GE, Discovery NM 630) on one-day  $^{99m}\text{Tc}$  protocol is depicted in Fig. 2. D-SPECT shows less attenuated images especially in the inferior walls. Recently Makita et al. developed a high-speed MPI protocol using low-dose rest  $^{99m}\text{Tc}$ -tetrofosmin ( $<185\text{MBq}$ ) and adenosine stress  $^{201}\text{Tl}$  ( $<75\text{MBq}$ ) in Fig. 3 (19). Higher energy-spectrum resolution between  $^{99m}\text{Tc}$  and  $^{201}\text{Tl}$  on CZT detectors made it possible to perform a simultaneous acquisition ( $<10\text{min}$ ) of different two isotopes. Time reduction and patient throughput on scans are one of the major factors in terms of P.C.I. Typical images of simultaneous acquisition dual-isotope SPECT protocol were depicted in Fig. 4. It clearly showed the presence of myocardial ischemia in the anterior to anteroseptum and the lateral wall of the left ventricle.

### Coronary flow reserve

Coronary flow reserve (CFR) derived from PET imaging revealed its prognostic value predicting mortality independently from SSS (20). Unfortunately clinical utility of cardiac PET imaging using  $^{13}\text{N}$ -Ammonia or  $^{15}\text{O}$ -water would be a little bit limited in Japan due to an installation of cyclotron. Recently the relationship between fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) using invasive stress



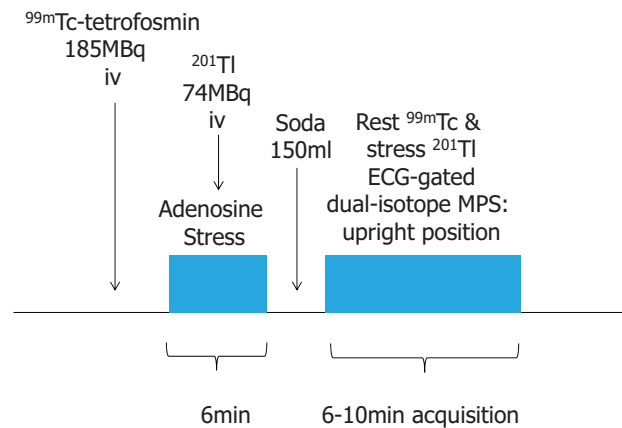
**Fig. 2** Comparison of mid to basal short-axis images between D-SPECT (upper line) and A-SPECT (lower line) on one-day  $^{99m}\text{Tc}$  protocol.



**Fig. 4** Simultaneous acquisition of rest  $^{99m}\text{Tc}$  and stress  $^{201}\text{Tl}$  protocol using CZT scanner, myocardial ischemia is present in the anterior and lateral wall.

catheter procedure was documented. They reported that discordance with a normal FFR ( $>0.8$ ) and abnormal CFVR ( $<2.0$ ) is associated with long-term MACE in comparison to intermediate stenosis in which FFR and CFVR are correspondently normal (21). Moreover, global CFR would affect therapeutic decision making to the patients who need coronary revascularization. Patients who had a coronary artery bypass graft surgery with impaired CFR ( $<1.6$ ) might have a good prognosis in comparison to the person in whom had PCI (22). Impaired CFR is resulted from diffuse CAD or triple vessel disease, which might cause incomplete revascularization. Global CFR is associated with outcomes independently of an angiographic stenosis, and changes the impact of revascularization (22).

Ten times higher sensitivity of photon-counts and list-mode acquisition on dedicated CZT gamma camera permitted to perform dynamic-flow acquisition protocol which could calculate myocardial flow reserve (MFR) (23, 24). Blood-pool time-activity curves which used as input functions in a 2-compartment kinetic model.  $K_1$  values ( $^{99m}\text{Tc}$ -sestamibi uptake) were calculated for the stress and rest images, and  $K_2$  values ( $^{99m}\text{Tc}$ -sestamibi washout) were set to zero. MFR was calculated as the ratio of the stress and rest  $K_1$  values. They



**Fig. 3** Simultaneous acquisition of dual-isotope imaging using CZT scanner.

found that MPR index showed a stepwise reduction with increasing extent of obstructive CAD. Triple-vessel disease or left main truncus disease in the left coronary artery is well known as balanced reduction of myocardial flow, and would be recognized as a point of weakness in MPI. Dynamic flow imaging using CZT detectors might allow reducing false negative cases in common clinical settings.

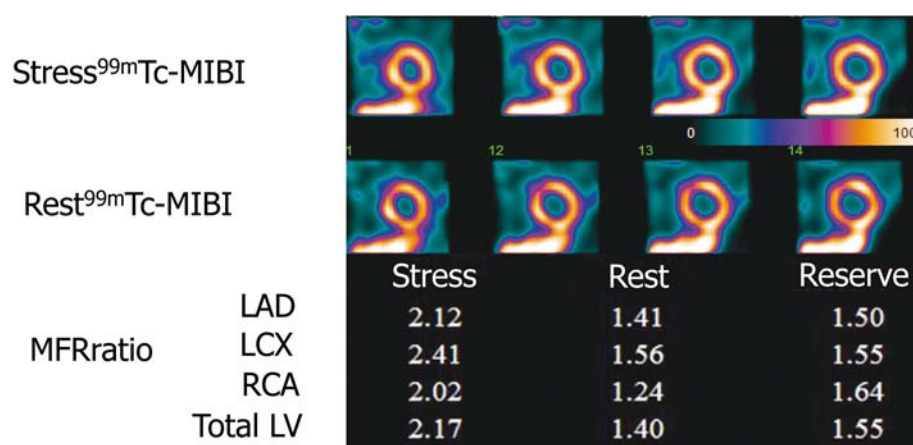
A 60-year old male who has significant stenoses in the main truncus of left coronary artery and ostium of the right coronary artery by CCTA referred to the hospital. His conventional MPI showed nearly normal perfusion (Fig. 5, upper and middle line), but dynamic flow imaging successfully calculated MFR ratio as follows, left anterior descending coronary artery; 1.50, left circumflex coronary artery; 1.55, right coronary artery; 1.64, respectively (Fig. 5, lower line). This case clearly suggests that the impaired MFR in patients with triple-vessel disease, in which would be missed. Unfortunately the cut-off point of MFR ratio is not decided yet in the project of D-SPECT user's group, the reason is that the project needs many dynamic flow cases for measuring the normal range of MFR ratio.

### Initial diagnostic modality

Recent publication regarding choice of initial diagnostic modalities (CCTA or MPI, treadmill test and stress echo) showed that there was no statistical difference ( $p=0.75$ ) of clinical outcome (death, myocardial infarction, unstable angina and complication with therapeutic procedure) between CCTA first group and functional test group (25, 26). Another important point in this manuscript suggests the cost effectiveness of choosing diagnostic modalities. To find out the cost effectiveness in the diagnostic modalities, further investigations are important in a prospective cohort (27, 28).

### Conclusions

MPI is a conventional but new diagnostic modality adding



**Fig. 5** Stress  $^{99m}\text{Tc}$  image (Upper line), rest  $^{99m}\text{Tc}$  image (middle line) using CZT scanner, MFR ratio in each coronary vessel and total LV (lower line).

amazing image quality and dynamic flow imaging into regular clinical situation. Clinical evidence and prevalence of CZT gamma camera would be a hope in this field.

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#### Conflicts of interest

None.

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