REVIEW ARTICLE

Novel Cardiac SPECT Technology with Semiconductor Detectors: Emerging Trends and Future Perspective

Masao Miyagawa, MD, PhD[1)], Yoshiko Nishiyama, MD, PhD[1)], Rami Tashiro, MD, PhD[1)], Hayato Ishimura RT[1)], Yasuyuki Takahashi, PhD[2)], Teruhito Mochizuki, MD, PhD[1)]

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Abstract

Recently, two vendors have introduced novel SPECT scanners with solid-state semiconductor detectors: Discovery NM530c (D530c) and D-SPECT utilizing the same cadmium zinc-telluride (CZT) detectors, with a different combination of high-sensitivity multi-pinhole or parallel-hole collimator which focuses on the myocardium. The physical performance is dramatically higher than that of conventional Anger cameras, however, 2 CZT cameras are inherently different. Spatial resolution and contrast-to-noise ratio are better with the D530c, whereas detection sensitivity is higher with the D-SPECT. Although ^{99m}Tc-labeled myocardial perfusion tracers might not be ideal, estimation of absolute myocardial blood flow or coronary flow reserve using dynamic CZT SPECT is of great interest and a challenging subject.

Keywords: Myocardial perfusion imaging, Cadmium zinc telluride, Cardiac SPECT, Coronary flow reserve, Effective dose, Dynamic imaging

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Over the past 40 years, radionuclide myocardial perfusion imaging (MPI) has become a major tool in the noninvasive evaluation of coronary artery disease (CAD). Whereas in 1990, fewer than 3 million nuclear cardiology studies were performed in the USA, the overall procedural utilization for stress MPI reached its height in 2006 with over 10 million studies and Medicare payment over 1 billion dollars (1). After the dramatic increase at a rate of often greater than 20% per year (2), however, a reduction in MPI use had begun in 2007 which continued through 2011 and declined by 51%. These reductions could not only be explained by increasing use of alternative modalities such as coronary CT angiography but there were several concerns about its overutilization. The National Council on Radiation Protection and Measurements reported that a 6-fold increase in ionizing radiation exposure to the U. S. population from medical procedures since the early 1980s (3), in particular finding that 10.5% of the entire radiation burden was related to MPI (4).

Owing to these considerations, professional societies have developed appropriate use criteria for MPI in order to lower its radiation dose and costs (5-7). Correspondingly, vendors have developed dedicated cardiac SPECT scanners with solid-state semiconductor detectors, primarily to address the concerns about radiation dose and long imaging time. In this review, we will focus on the latest advances in MPI procedures which ought to be able to maximize the value of state-of-art cardiac SPECT scanners with semiconductor detectors in the current era demanding reduced costs, examination time, and radiation exposure.

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1）Masao Miyagawa, Yoshiko Nishiyama, Rami Tashiro, Hayato Ishimura, Teruhito Mochizuki
Department of Radiology, Ehime University Graduate School of Medicine, Shitsukawa, Toon-city, Ehime, Japan, 791-0295
E-mail: miyagawa@m.ehime-u.ac.jp

2）Yasuyuki Takahashi
Department of Nuclear Medicine Technology, Gunma Prefectural College of Health Sciences.

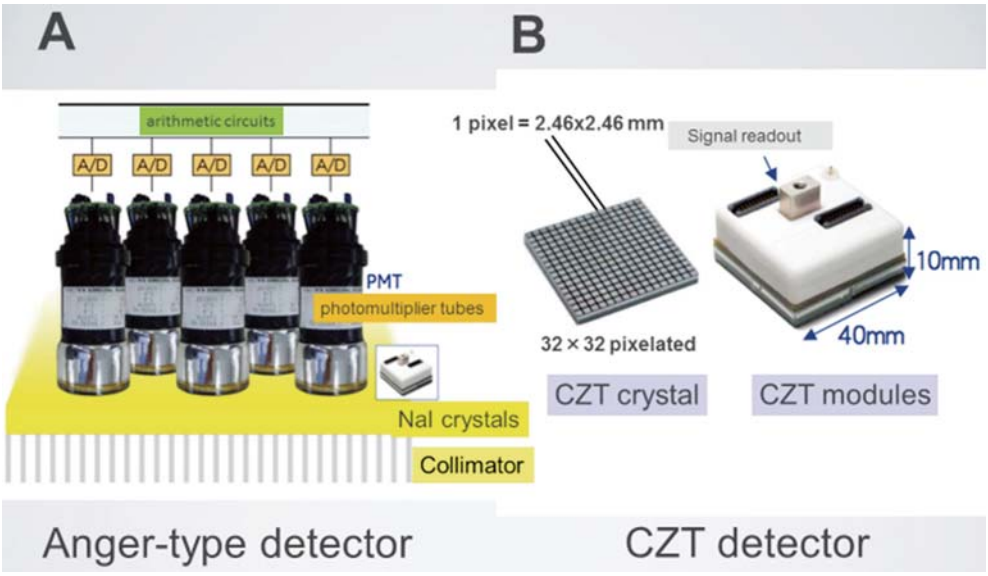

Fig. 1 Comparison of 2 different ditectors
A: A 4×4 cm CZT detector module has a compact size as compared to the combination of NaI crystals with photomultiplier tubes of the conventional Anger camera.
B: Each detector contained 32×32 pixelated CZT elements（1024 elements with thickness of 2.46×2.46×5 mm）. CZT＝Cadmium Zinc Telluride, NaI＝sodium iodide

Fig. 2 An ultra-fast cardiac SPECT camera（Discovery NM530c）
A gantry that is similar to a conventional cardiac SPECT camera, with a different detector assembly that is completely stationary during acquisition.

Technological advantages of cardiac SPECT with semiconductor detectors

Conventional SPECT is typically performed using an Anger scintillation camera, which is based on a design advanced by Berkeley electrical engineer Hal Anger in 1957（8）. Typically, each scintillation camera is equipped with parallel-hole high-resolution collimators. Since collimation is necessary to acquire the projection views, less than 0.02% of the photons emitted from the heart are collected（9）. As a result, acquisition times of 15-20 min are required for myocardial SPECT studies.

Recently, two vendors have introduced novel scanners: Discovery NM530c:（D530c）; GE Healthcare and D-SPECT; Spectrum Dynamics utilizing the same cadmium zinc-telluride（CZT）detectors（Fig. 1）, with a different combination of high-sensitivity multi-pinhole（Fig. 2-4）or parallel-hole collimator which focuses on the myocardium（10,11）. More than 300 of

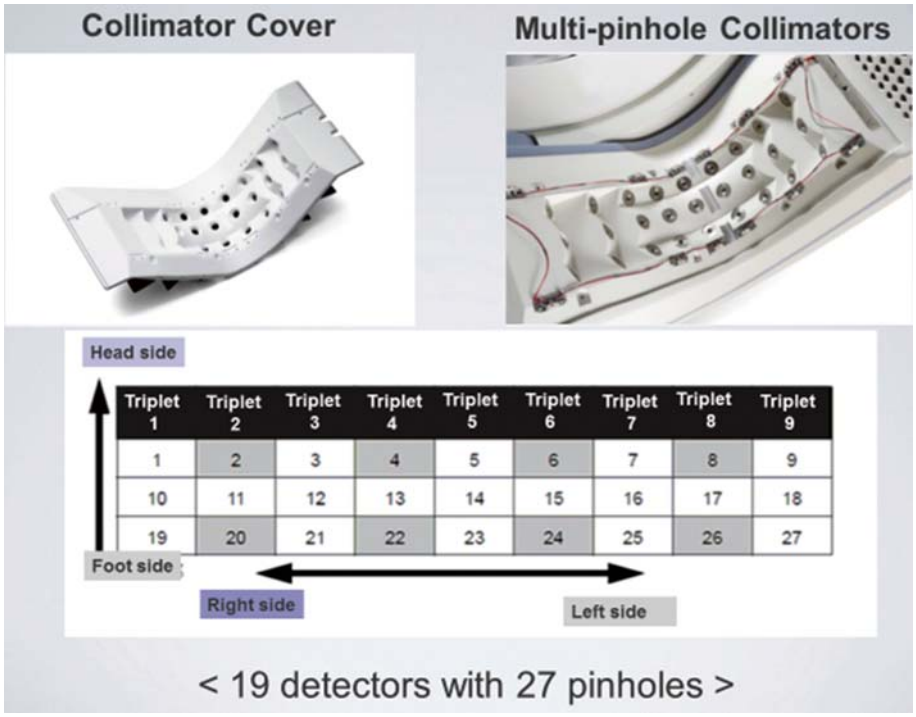

Fig. 3 Multi-pinhole Collimators
There are 9 triplets with 27 pinholes. Nineteen CZT detectors are allocated to the pinhole numbers of 1, 3, 5, 7, 9-19, 21, 23, 25, 27, respectively. There are no CZT detector in the pinholes which are shown as 10 gray areas.

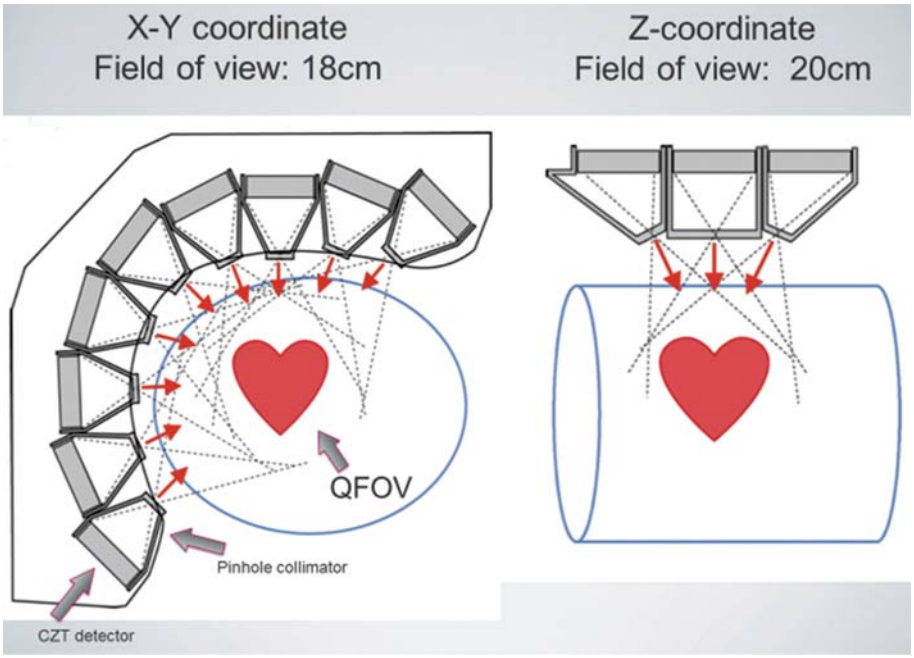

Fig. 4 A curved array of solid-state CZT detectors with optimal geometry
The detector heads are directed to the heart and the region around it. The target volume for high quality imaging is called quality field of view (QFOV) which is approximately a sphere of 18 cm diameter

such cardiac CZT SPECT scanners are currently available in the world, and the number is increasing by more than 100 per year.

We conducted a comparative study using ^{99m}Tc line-source phantoms with and without photon scattering caused by water in the cylinder (12). D530c had a higher spatial resolution than did the conventional Anger camera with a NaI scintillation crystal and a

Table 1 FWHM by three ^{99m}Tc line sources

	Without water	With water
D530c		
Central	3.00	6.64
Tangential	3.48	5.03
Radial	1.73	3.88
Infinia		
Central	11.05	15.48
Tangential	12.63	16.28
Radial	8.17	15.61

unit; mm

dual-detector (Infinia; GE Healthcare). The measured FWHM values are summarized in Table 1. We also found that a D530c has better energy resolution compared to Infinia, which is as narrow as 5%. Therefore, energy window width could be narrowed enough to be feasible for performing dual radioisotope simultaneous SPECT with ^{99m}Tc-tetrofosmin and ^{123}I-BMIPP (13). Moreover, the high sensitivity of D530c allows for a shorter acquisition time, actually, 5 min is sufficient for QGS in the clinical setting. Although CZT detectors are higher in cost, they have been shown to provide an 8- to 10-fold increase in sensitivity, coupled with a 2-fold improvement in spatial resolution, and higher energy resolution enabling a significant reduction in imaging time and dose of isotopes, and a dual radionuclide simultaneous SPECT with ^{99m}Tc and ^{123}I(10, 11). Imbert et al. also conducted analyses of phantom and human SPECT images, comparing the D530c and D-SPECT CZT cameras with Anger cameras and reported that the physical performance of CZT cameras is dramatically higher than that of Anger cameras, however, 2 CZT cameras are inherently different. Spatial resolution and contrast-to-noise ratio are better with the Discovery NM 530c, whereas detection sensitivity is markedly higher with the D-SPECT (14).

Optimal imaging protocol for CZT SPECT

Reduction in injection dose of radiopharmaceuticals

The introduction of CZT cameras has opened the possibility of reducing radiation dose of SPECT MPI. Oddstig et al (15). reported that they performed a 1-day ^{99m}Tc-tetrofosmin stress-rest protocol using D530c in 150 patients who were divided into three subgroups (50 patients in each group) with 4, 3, and 2.5 MBq/kg body weight of administered activity in the stress MPI, respectively. The total effective dose (stress and rest) decreased from 9.3 mSv in the 4 MBq/kg group to 5.8 mSv in the 2.5 MBq/kg group. The image acquisition times for 2.5 MBq/kg were 8 and 5 minutes (stress and rest, respectively) compared to 15 minutes for each when using conventional SPECT. The average image quality for the stress and the rest showed no statistically significant difference among the 4, 3, and 2.5 MBq/kg groups. Starting the MPS protocol with examination at stress and analyzing the stress images before deciding of the need for rest examination (that is to say "stress only protocol") reduce the effective dose. The effective dose was no more than 1.4 mSv for a patient receiving 2.5 MBq/kg, who underwent the stress only protocol. A protocol for CZT SPECT in our institution is shown in Fig. 5. The total effective radiation dose ranged 3.4 to 6.7 mSv. Novel CZT technology can considerably decrease the effective dose and acquisition time for MPI with preserved high image quality.

Stress only protocol

A strategy of the stress only protocol has reduced the effective dose and offered higher laboratory throughput. Duvall et al. reported that over 4,000 patients with more than 50% undergoing the stress only protocol successfully in an Emergency Department Chest Pain Unit. The return rate for rest imaging in the group of the stress only protocol was very low at 5% (16). There are technical matters for abnormal stress images such as soft tissue attenuation or patient motion. The return rate for rest imaging without attenuation correction and QGS analysis has been reported to be more than 50%, which would limit the benefit of performing a stress only protocol.

As an alternative to attenuation correction, accuracy could also be improved with images which were obtained by using supine-prone (Fig. 5) or supine-upright positions (17,18). Goto et al. reported that 322 consecutive Japanese patients with a high pretest probability of CAD, experienced a 1-day ^{99m}Tc-tetrofosmin stress and rest MPI by the D530c camera, and also coronary angiography (19). Of 124 patients with inferolateral perfusion defect on supine stress imaging, immediately thereafter, 63 (51%) were judged to be normal on prone imaging. They found that the overall return rate for rest imaging was 19% with combined stress supine and prone imaging, which was lower than 39% with the supine imaging alone in detection of inferolateral CAD. Consequently, the majority of patients (97%) with normal supine and prone imaging did not have angiography-confirmed CAD. In a similar study with 748 patients who had significantly larger body mass indexes than the Japanese population,

Ann Nucl Cardiol 2015；1（1）：18-26

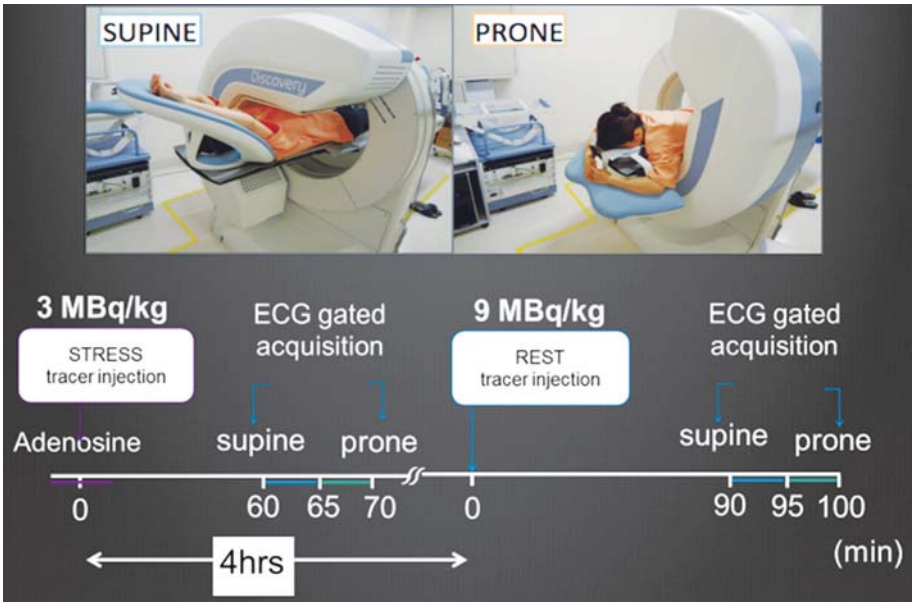

Fig. 5 Imaging protocol of our institution for CZT SPECT
We adopt a stress/rest one-day protocol with ^{99m}Tc-perfusion radiotracers. Supine and prone positionings are routinely performed. The total effective dose ranged 3.4 to 6.7 mSv. The stress-only protocol can be performed with the effective dose averaging 1 mSv.

Worden et al.（20）demonstrated that the return rate for rest imaging was 23% with a "second look" prone stress imaging, which was lower than 64% with the supine imaging alone.

More recently, Einstein et al.（21）also performed the stress-first MPI using supine and prone positions by the D530c camera in patients with chest pain. They demonstrated that in patients who did not have a high pretest probability, stress-only imaging could be performed in more than two thirds of patients with an effective dose averaging 1 mSv. An excellent prognosis was found with only 4% of the patients presenting again to the hospital within 3 months, and no death or acute coronary syndrome at 1 year.

Imaging obese patients

Obesity may often affect the quality of conventional MPI, mainly because of decreasing test specificity by diaphragm attenuation or extra-cardiac radionuclide activity. Attenuation correction has been found to improve diagnostic accuracy. The CZT cameras were expected to offer improved image quality even in obese patients. However, Fiechter et al（22）. reported poor diagnostic quality in severely obese patients with body mass index（BMI）greater than 40 kg/m^2. In those patients, image quality was non-diagnostic in 81%, which decreased to 55% after CT-based attenuation correction. They also realized that repositioning of the patients resulted in improved image quality. They concluded the poor quality may be due to the difficult positioning of such severely obese patients in the limited field-of-view of D530c. The volume which shows the intersection of the 19 views from each pinhole is named the quality field of view（QFOV）. It is a sphere with a diameter of 18 cm in which the heart needs to be positioned correctly（Fig. 4）. For most of all patients in our daily routine, whose BMI are smaller than 40 kg/m^2, such concern does not exist（Fig. 6）. However, this limitation might be critical in morbidly obese patients. And moreover, accurate positioning of the patient's heart within the center of the QFOV is very important for the D530c camera to avoid positioning related artifact（23）.

Attempts to estimate of coronary flow reserve using CZT SPECT

Fractional flow reserve（FFR）has become the standard method to assess ischemic heart disease in the catheterization laboratory after the demonstration that decision-making based on FFR results in better patient outcomes than angiography-guided revascularization（24）. At present, coronary flow reserve（CFR）has been mostly replaced by FFR primarily due to its technical simplicity in the catheterization lab. In contrast, in the noninvasive field, quantification of PET-derived CFR is an emerging index used for improving both the diagnosis and risk stratification in patients with suspected CAD. And with the increased use, reliable evidences have been suggested that CFR is a powerful independent predictor of cardiac events and mortality

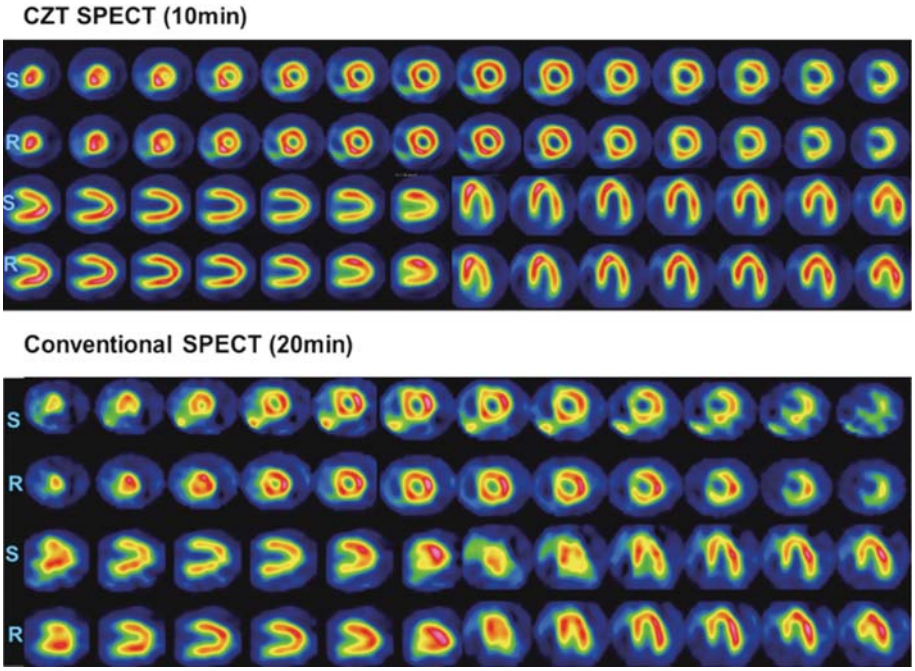

Fig. 6 Myocardial perfusion imaging of an obese patient（10 min acquisition with D530c and 20 min acquisition with Infinia）

A female patient in her 60's with chest pain, whose body weight is 93 kg（body mass index; 35.3 kg/m^2） underwent with ^{99m}Tc-tetrofosmin CZT SPECT imaging with D530c（upper panel）, immediately followed by a conventional camera（lower panel）. There are some perfusion defects probably due to attenuation artifacts in the images by a conventional camera, but no such defects are found in those by D530c. S=stress, R＝rest

(25-29).

While at the same time, some studies have reported that using first-pass planar scintigraphy in humans (30-34) or dynamic SPECT in animals (35), providing evidences that the estimates of CFR can be also derived from conventional SPECT MPI. Although fair agreements have been noted between CFR estimated by SPECT and PET or intracoronary Doppler flow studies, they also highlighted the limitations of conventional gamma camera for the dynamic data collection during rapidly changing radiotracer concentrations (36).

The CZT cameras provide higher temporal and spatial resolution. Dynamic SPECT imaging during the first pass of a tracer was attained with use of these cameras. From the list data, time activity curves (TAC) would be generated for the left ventricular cavity (input function) and for myocardial tissue (output function) during stress and rest. Ben-Haim et al. (37) firstly reported the feasibility of dynamic ^{99m}Tc-MIBI SPECT and quantitation of global and regional CFRs using the D-SPECT. They calculated CFR index as the ratio of the stress and rest K1 values. Global CFR index was higher in patients with normal MPI than in patients with abnormal MPI. The CFR index was lower in territories supplied by stenosed coronary arteries than in non-stenosed arteries. In Fig. 7, TACs by dynamic ^{99m}Tc-tetrofosmin SPECT using the D530c in our laboratory during pharmacologic stress and rest are shown. Novel software is currently under development in our institution (38).

Most recently, Wells et al. applied the D530c to a study with a pig model for quantitation of absolute myocardial blood flow (MBF) using common perfusion tracers as ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin, and ^{201}thallium (39). Dynamic images were reconstructed with CT-based attenuation correction and energy window-based scatter correction, then processed with kinetic analysis using a 1-tissue compartment model to obtain the uptake rate constant K1 as a function of microsphere MBF. Converting K1 back to MBF using the measured extraction fractions produced accurate values and good correlations with microsphere MBF. They have demonstrated that dynamic SPECT by the CZT camera may be feasible to estimate of absolute MBF.

Advantages and disadvantages of the measurement of CFR with SPECT

At the current moment, PET plays a major role in accurate estimation of MBF or CFR. However, it has limited value for routine clinical studies because of its higher cost and more complicated procedures, including the production of short-half-lived positron tracers by

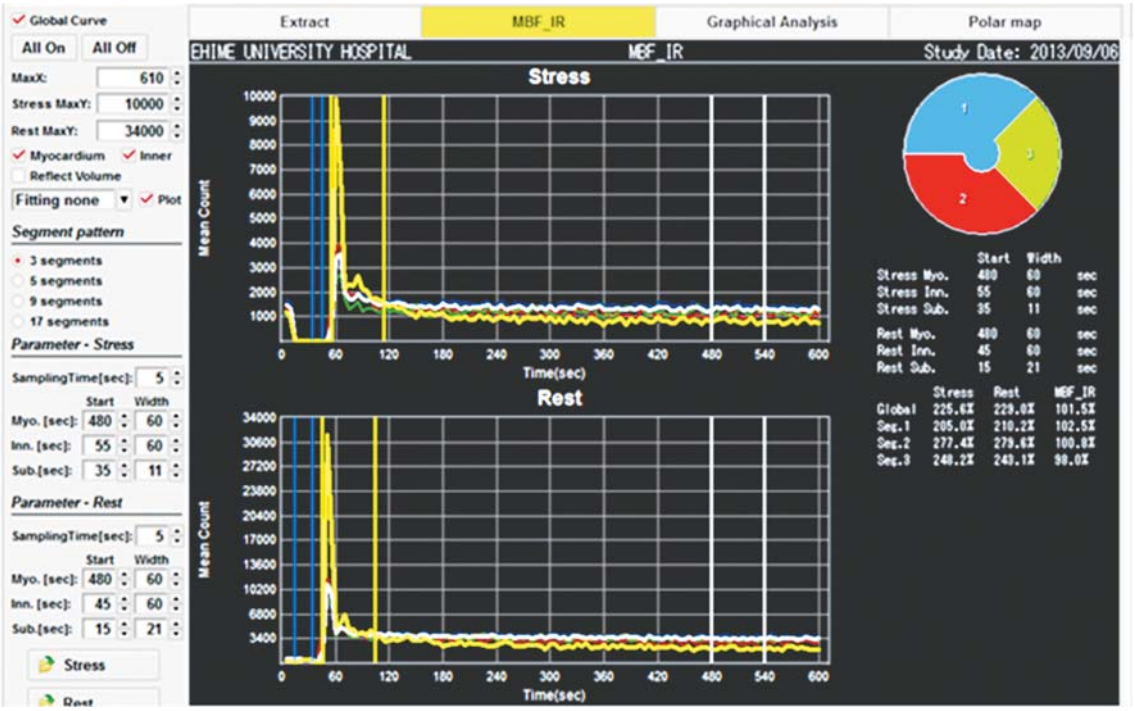

Fig. 7 Time activity curves（TAC）with ^{99m}Tc-tetrofosmin by dynamic SPECT during ATP stress and at rest
Dynamic acquisition data with list-mode were transferred to a workstation for analysis using our original software. It allows the automatic definition of a volume of interest（VOI）for the blood pool in the left ventricle and the left ventricular myocardium. The VOI-related TAC can be extracted by averaging the signal intensity in the VOI in each time frame, then, expressed in counts per mm^3/sec. Global TAC was fitted to a 2-compartment kinetic model with input functions which was served by the blood pool curves.

in-house cyclotrons. Therefore, the advantage of SPECT-measured technique utilizing common ^{99m}technetium perfusion tracers, is that it would increase the utility of CFR measurement in the clinical setting with a much smaller financial cost.

On the other hand, the disadvantage of quantifying CFR with SPECT may be underestimation of the CFR value, compared to that with PET. The reasons for this underestimation could be mainly due to the limited extraction of ^{99m}technetium perfusion tracers at high flow rates, at which the extraction of the tracer becomes limited by membrane transport（36）.

Conclusions and future directions

Now is the time to move to a new paradigm of CZT SPECT technology. We need to explore patient centered, radiation exposure controlled, and appropriately-designed protocols which do not sacrifice image quality or diagnostic accuracy of the new modality. Although ^{99m}Tc-labeled radiotracers might not be ideal flow agents, estimation of absolute MBF or CFR using dynamic CZT SPECT is challenging and of great interest. This technology will hold great promise if the several issues can be solved through future studies.

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Conflicts of Interest

None

Reprint requsts and correspondence：
Masao Miyagawa,
Department of Radiology, Ehime University Graduate School of Medicine, Shitsukawa, Toon-city, Ehime, Japan, 791-0295
E-mail：miyagawa@m.ehime-u.ac.jp

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