



## Physiological Assessment of Myocardial Perfusion Using Nuclear Cardiology Would Enhance Coronary Artery Disease Patient Care – Which Imaging Modality Is Best for Evaluation of Myocardial Ischemia? (SPECT-Side) –

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Nuclear cardiology has played an important role in both diagnosis and risk assessments of coronary artery disease since early 1970. Among the non-invasive diagnostic tests, the great advantage of nuclear imaging is that this technique can obtain physiological information, such as myocardial perfusion, which is difficult to obtain by other techniques. When patients have inducible myocardial ischemia and sufficient viable myocardium, coronary revascularization treatment should be performed. Both stress myocardial perfusion imaging (MPI) and viability imaging provide important information. Another important aspect of stress perfusion imaging is that normal stress perfusion is associated with low risk for future cardiac events. Therefore, stress MPI plays an important role in the selection of an invasive therapeutic regime and also in avoiding unnecessary invasive procedures. As is the case for other imaging techniques, there have been many technical and instrumental developments in recent years in nuclear cardiology imaging, including new single-photon-emission computed tomography tracers, new pharmacological stress agents, a new generation of  $\gamma$  camera, and positron emission tomography. This review will address the advantages of nuclear cardiology in the clinical setting and recent developments in nuclear cardiology. (*Circ J* 2011; **75**: 713–723)

**Key Words:** Blood flow; Myocardial ischemia; Prognosis; Tomography

Nuclear imaging has played an important role in the diagnosis of coronary artery disease (CAD) since early 1970.<sup>1</sup> Following the injection of radioisotopes under rest and stress conditions, myocardial perfusion imaging (MPI) can detect the extent and severity of myocardial ischemia. Risk assessment using myocardial perfusion single-photon-emission computed tomography (SPECT) is now well established, based on large numbers of well-designed studies.<sup>1–4</sup> Myocardial perfusion SPECT can accurately predict cardiac events and can be used to determine the level of risk in patients from low to high applicability in determining low to high risk for future cardiac events, especially in patients with intermediate likelihood of having CAD. This capability greatly contributes to clinical decision making and patient care.

Nuclear imaging does not require contrast agents, and the use of technetium-labeled radioisotopes or positron emission tomography (PET) tracers causes limited radiation expo-

sure.<sup>5–7</sup> Thus, most patients are able to have this test even if they have other disease, such as renal dysfunction.<sup>8</sup> There are other advantages of nuclear imaging. Recent technological advances, such as PET, molecular imaging including metabolic information, semiconductor SPECT, and new stress agents, have contributed to reducing the data acquisition time and enhancing diagnostic accuracy.<sup>1,9</sup> These new developments make nuclear imaging even more effective in detecting myocardial ischemia, and hence patient care.

### Use of Nuclear Cardiology in CAD Patient Care

In stable CAD patients, percutaneous coronary intervention (PCI) improves angina symptoms but does not reduce the risk of cardiac events in the general population.<sup>10</sup> However, PCI provides a survival benefit in patients with moderate to severe ischemia and in patients with ischemia reduction after PCI.<sup>11,12</sup> This fact suggests that physiological assessment of

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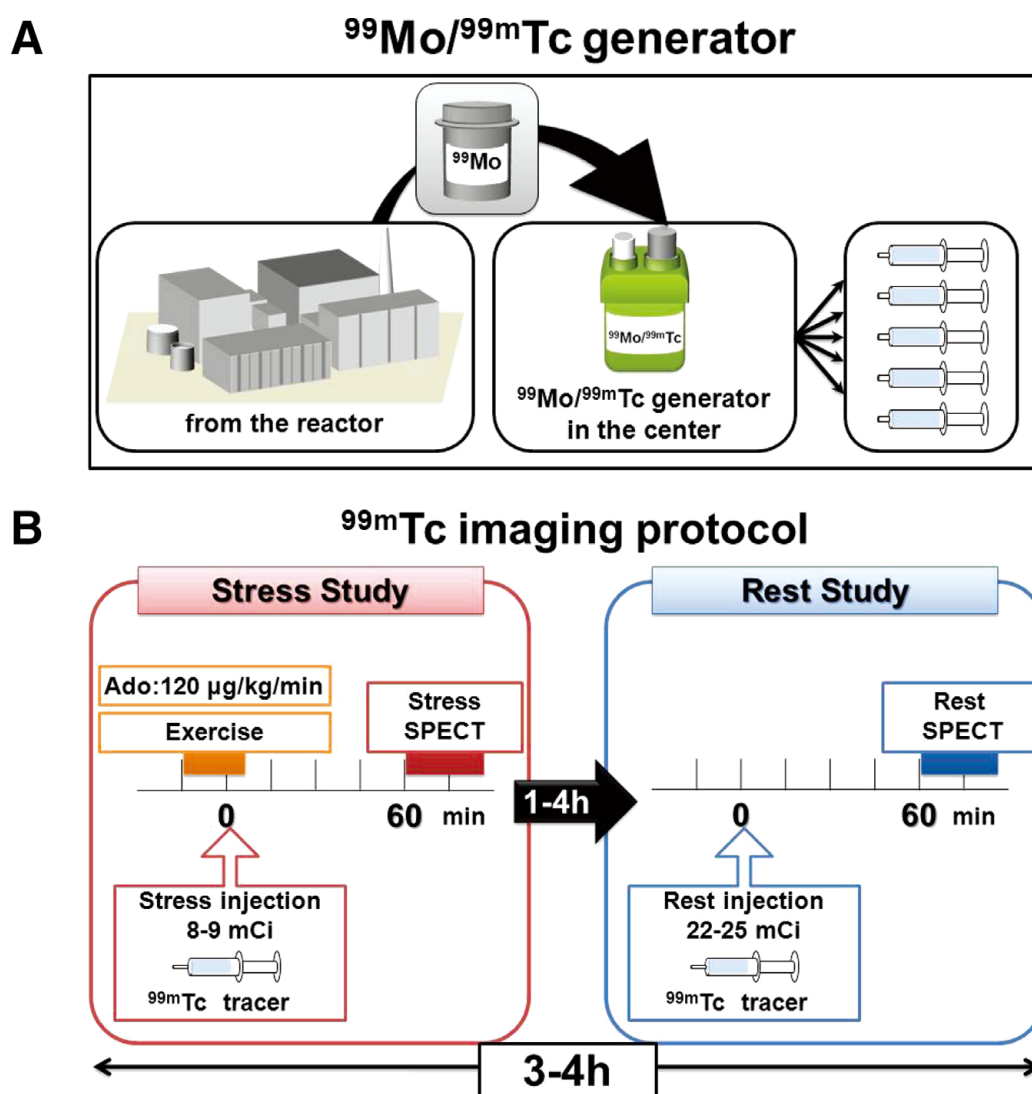
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**Table 1. Common Myocardial Blood Flow Tracers**

Tracer	PET/SPECT	Tracer production	Half-life	Scan time (min)	Positron energy (MeV)	Radiation dosage (m)*Sv
Technetium-99m sestamibi/tetrofosmin	SPECT	Generator	6 h	12–15 (dual head camera)	–	1-day: stress-rest. Sestamibi/tetrofosmin 12/10.6 (40 mCi) 2-day: stress-rest. Sestamibi 17.5 (30 mCi+30 mCi) 25.1 (4 mCi)
Thallium-201	SPECT	Cyclotron	72.9 h	12–15 (dual head camera)		
Rubidium-82	PET	Generator	76 s	6–10	3.15	16 (90 mCi)
Oxygen-15 water	PET	Cyclotron	110 s	6–10	1.72	2.5 (60 mCi)
Nitrogen-13 ammonia	PET	Cyclotron	9.97 min	2–4	1.19	2.4 (30 mCi)
F-18 FBnTP	PET	Cyclotron	110 min	12–15 (dual head camera)	0.63	Not available

\*Radiation dose is based on the total dose of standard rest/stress perfusion study.

CI, curie; SPECT, single-photon-emission computed tomography; PET, positron emission tomography.



**Figure 1.** (A)  $^{99\text{m}}\text{Tc}$  myocardial perfusion tracers can be obtained from a  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator. (B) Imaging protocol of exercise/pharmacological stress  $^{99\text{m}}\text{Tc}$  myocardial perfusion imaging. Mo, molybdenum; SPECT, single-photon-emission computed tomography; Tc, technetium.

**Table 2. Stress Protocols**

Stress protocol	Indications	Contraindications
Exercise	Able to exercise Moderate pretest risk likelihood	Unstable angina Congestive heart failure Major vascular disease
Pharmacological stress	Unable to exercise	Advanced atrioventricular block
Vasodilator	Rest ECG abnormality	Uncontrolled asthma or COPD
Adenosine	LBBB	
Dipyridamole	Paced rhythm	
ATP		
Dobutamine	Asthma, COPD	Unstable angina Congestive heart failure Major vascular disease

COPD, chronic obstructive lung disease; LBBB, left bundle branch block.

coronary arterial stenosis severity is a more critical component in the management of patients with CAD than are morphological approaches.<sup>13</sup> In fact, specific angiographic features of coronary stenosis are a major indication for revascularization in stable CAD. At the same time, 2 other important indications are significant inducible myocardial ischemia and the existence of enough viable myocardium.<sup>13</sup>

### Radiopharmaceuticals and Stress Protocols: Multiple Choices for Nuclear Imaging

#### Radiopharmaceuticals

In general, radiopharmaceuticals for diagnostic imaging are designed not to have specific pharmacological effects themselves. Thus, radiotracers do not have specific side-effects other than minimal radiation exposure. Thus, it is possible to use nuclear imaging tests for almost all patients.

Thallium-201 (<sup>201</sup>Tl) was the first myocardial perfusion tracer for SPECT imaging introduced in the 1970s<sup>14</sup> and was the only perfusion tracer available in the clinical setting until the 1990s. When <sup>201</sup>Tl debuted, it had a significant impact on clinical practice, such that some cardiologists may still think that nuclear cardiology means <sup>201</sup>Tl MPI. However, like other cardiac imaging techniques, nuclear cardiology has some relatively new agents, such as technetium-99m (<sup>99m</sup>Tc) labeled perfusion tracers (Table 1). Currently, we have 2 options for a myocardial perfusion tracer in the clinical setting.<sup>15</sup>

**<sup>201</sup>Tl** The initial myocardial uptake of <sup>201</sup>Tl early after injection is associated with regional myocardial blood flow. <sup>201</sup>Tl is transported into the myocyte cell membrane by the <sup>201</sup>Tl concentration level. <sup>201</sup>Tl wash-out is faster from normal myocardium than from segments with lower <sup>201</sup>Tl activity (ie, ischemic segments). The redistribution images are considered to be rest images.

**<sup>99m</sup>Tc-Labeled Perfusion Tracers** As with other technological developments, <sup>99m</sup>Tc-labeled perfusion tracers (sestamibi and tetrofosmin) overcome the disadvantages of <sup>201</sup>Tl. <sup>99m</sup>Tc-labeled tracers have a higher photon energy peak of 140 keV, which is suitable for  $\gamma$  camera imaging. <sup>99m</sup>Tc has a short physical half-life, 6 h, which is associated with lower radiation exposure. Thus, it is possible to increase a given tracer dose to up to 10–15 times the amount of <sup>201</sup>Tl (Table 1), contributing to better image quality and improved diagnostic accuracy.<sup>16</sup> Because <sup>99m</sup>Tc (parent compound is <sup>99m</sup>Mo) is generator-produced and the powdered agent is readily available, this tracer is always available (Figure 1A). Therefore, once a generator has been obtained, perfusion imaging can

be available whenever it is required. This is another advantage of <sup>99m</sup>Tc-labeled perfusion tracers.<sup>17</sup>

The initial uptake is directly related to regional myocardial blood flow. <sup>99m</sup>Tc-labeled perfusion tracers are transported across the myocyte membrane with passive diffusion and bind to mitochondria.<sup>18</sup> Unlike <sup>201</sup>Tl, clearance of <sup>99m</sup>Tc-labeled perfusion tracers from myocytes is slow, so the amount of redistribution is low. Given this low tracer redistribution, two separate injections of <sup>99m</sup>Tc-labeled perfusion tracers are required, one during exercise/pharmacological stress and one at rest (Figure 1B) for the assessment of reversibility (ie, myocardial ischemia).

#### Stress Protocols

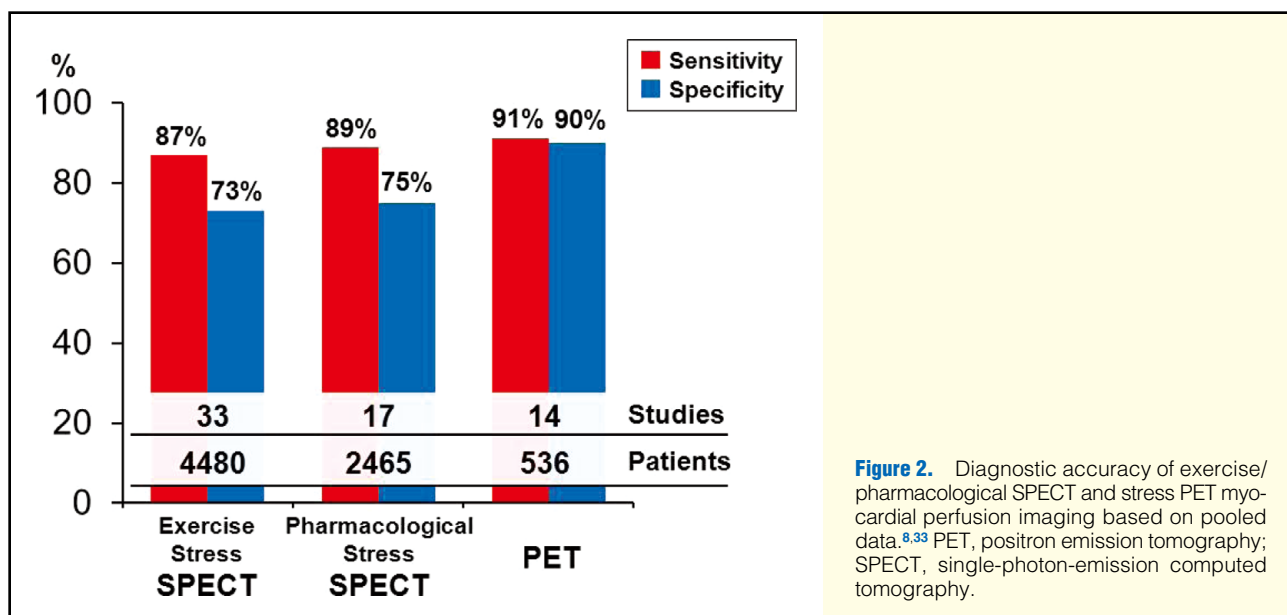
One of the great advantage of nuclear cardiology imaging is that there are plenty of stress protocols available for various clinical settings (Table 2).

**Exercise Stress** This is commonly performed in SPECT MPI. Exercise stress is particularly beneficial for patients with exertional symptoms. Exercise stress can evaluate the relationship between the symptoms induced during stress and the location, extent, and severity of abnormal perfusion defects.<sup>8</sup> Exercise stress also provides information such as functional capacity and stress-induced ECG changes in addition to the MPI information.

Exercise stress is the preferred stress protocol. However, there are many patients who cannot perform an optimal level of exercise or who are not suitable for exercise. As the population ages, and given the presence of comorbid diseases such as peripheral vascular disease and diabetes, there are increasing numbers of patients referred for stress tests who are unable to exercise.

In fact, the American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology (ACC/AHA/ASNC) guidelines suggest that pharmacological stress is suitable for patients who are unable to exercise or who have an abnormal rest ECG, left bundle branch block or paced rhythm.<sup>8</sup>

**Pharmacological Stress** This is an alternative protocol (Table 2). There are 2 types of pharmacological stress agents: coronary artery vasodilator agents, such as adenosine, adenosine triphosphate, and dipyridamole, and inotropic agents such as dobutamine. In clinical practice, the most widely used pharmacological agents are the vasodilators. Adenosine induces maximal vasodilatation in resistance vessels and does not increase myocardial oxygen consumption. Thus, vasodilator agents are considered to be very safe for most patients



including those with major vascular disease. There are some minor common side-effects, such as flushing, atypical chest pain, and dyspnea. However, given the very short half-life of adenosine (<10s), most of these effects resolve in a very short time. Dipyridamole also has similar minor side-effects, although dipyridamole lasts longer (15–25 min), and aminophylline (125–250mg IV) is sometimes required to treat its side-effects.

In the clinical setting of an aging population, we may have patients with asthma or chronic obstructive lung disease. Originally there was absolute contraindication for vasodilator agents for these patients, but given recent developments in the treatment of these obstructive lung diseases, most of the patients referred for stress tests are under control.<sup>17</sup> Thus, updated ASNC guidelines suggest that vasodilator stress can be used if patient's symptoms are adequately controlled.<sup>17</sup>

As addressed here, combined exercise stress and MPI provide excellent information on symptoms, ECG changes and myocardial perfusion defects. An alternative approach using pharmacological stress may be used for most patients who are unable to exercise or for whom exercise is not suitable. Again, given the aging population, having a variety of choices of stress protocols should be considered highly beneficial.

### Image Interpretation

In standard practice, myocardial perfusion images during stress and rest are compared to detect the existence, extent, and severity of stress-induced myocardial perfusion defects. These perfusion defects can be categorized as myocardial ischemia, reversible perfusion defect, myocardial injury, fixed perfusion defect, and so-called infarction in patients with CAD. As the next step, the relationship between the coronary arteries and defect areas would be evaluated.

### Diagnosis of CAD Using Nuclear Imaging

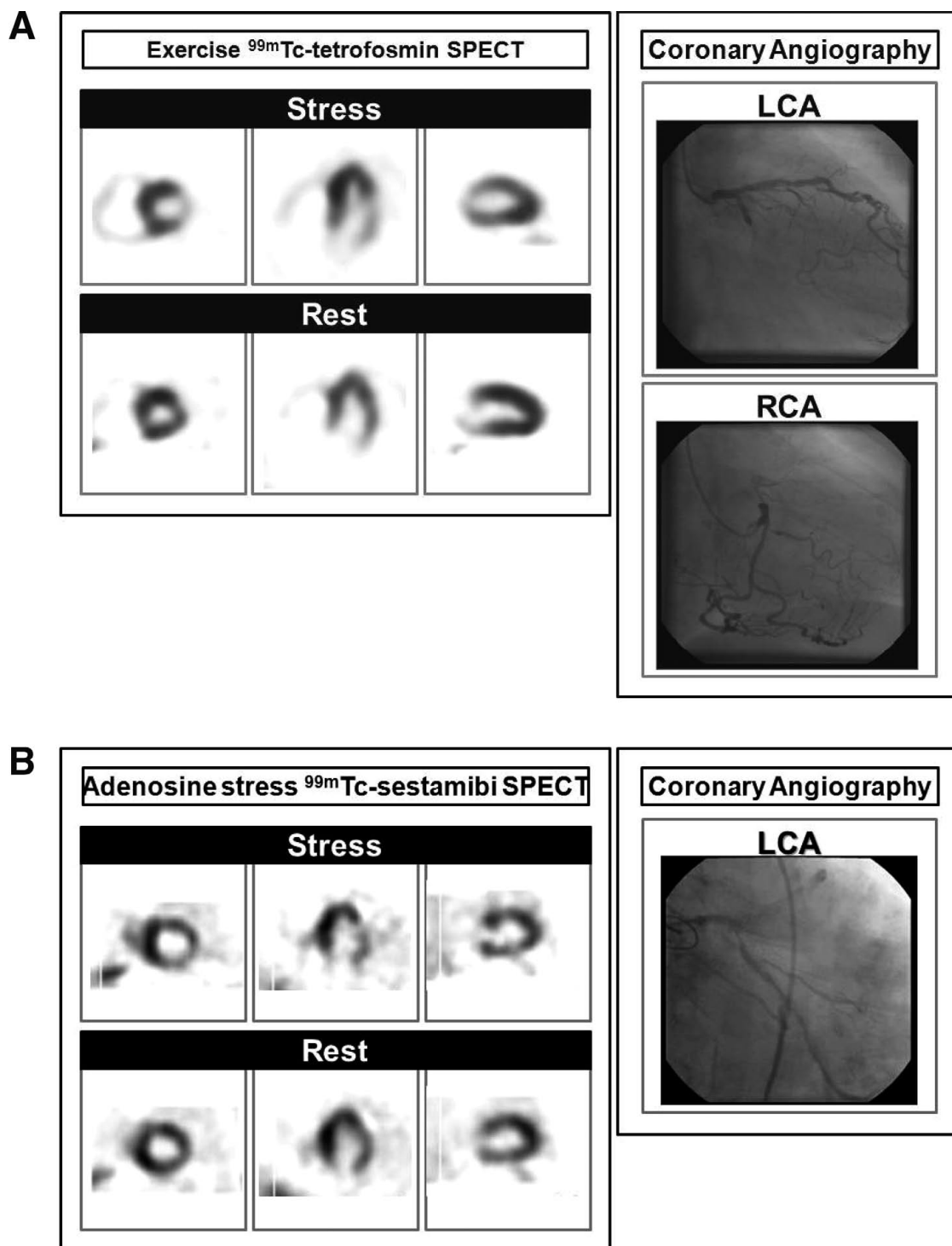
Pooled data from 33 published studies with 4,480 patients showed that sensitivity to detect CAD was 87% (range 71–97%) and specificity to rule out CAD was 73% (36–100%) for exercise MPI (Figure 2).<sup>8</sup> Recent meta-analysis with 8,964 patients also reported similar diagnostic accuracy; the mean

sensitivity was 86% and specificity was 74% (Figure 2).<sup>19</sup> Looking further at diagnostic accuracy in each coronary arterial territory, the sensitivity for the left anterior descending (LAD) territory tended to be higher than that for other territories (LAD 80%, left circumflex (LCX) 70%, right coronary artery (RCA) 60%). On the other hand, there was similar specificity among the 3 coronary arterial territories (LAD 77%, LCX 76%, and RCA 79%).

Both sensitivity and specificity were relatively good. However, there was lower specificity due to soft tissue attenuation artifacts, including diaphragm, breast, and lateral fat pads. Incorporating ECG-gated imaging of regional function can improve specificity. In the case of normal wall thickening in the fixed perfusion defect area, this area should be considered as normal rather than one of myocardial injury (ie, infarction). Combined ECG-gated sestamibi SPECT imaging and perfusion imaging improves the specificity compared to standard perfusion imaging alone in women (92% vs. 84%).<sup>16</sup> Thus, ECG-gated SPECT MPI can reduce the false-positive rate and improve specificity.

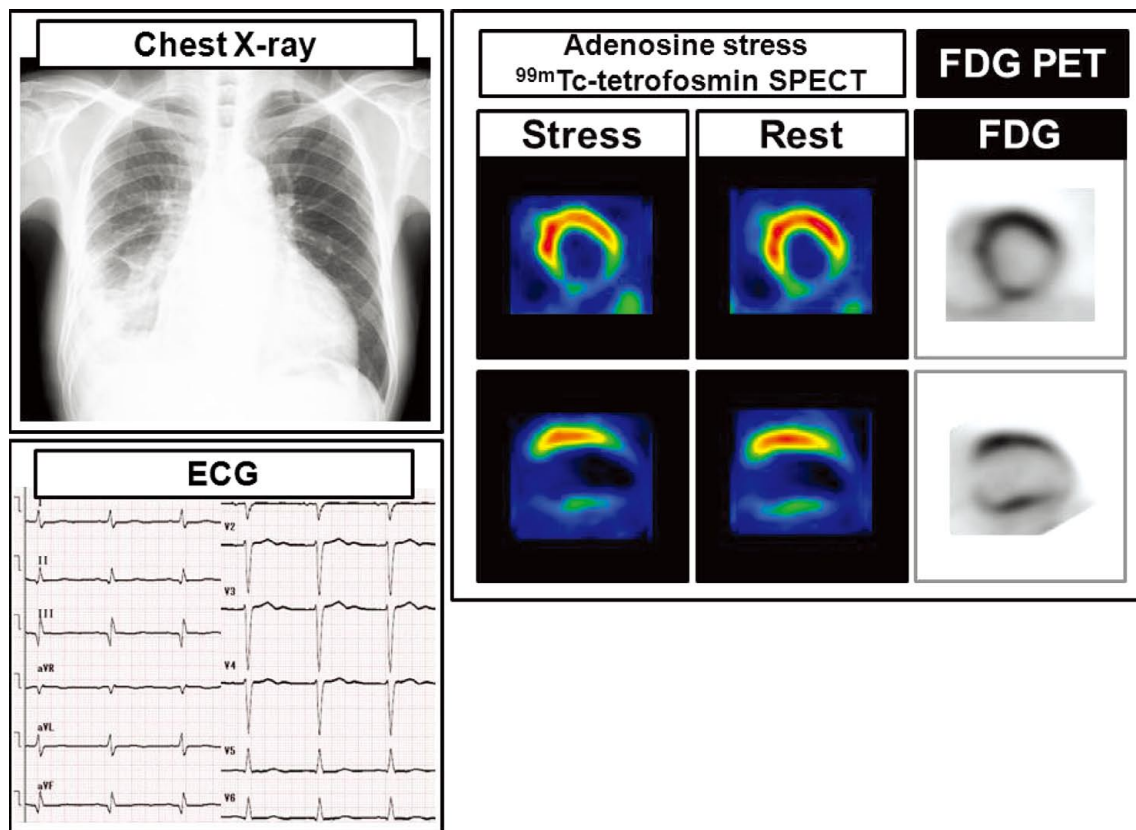
As previously addressed, pharmacological stress is widely used with SPECT MPI. The diagnostic accuracy was essentially similar to exercise stress MPI. The overall sensitivity and specificity using vasodilator stress was 89% and 75%, respectively, based on 17 studies with 2,465 patients.<sup>8</sup> Kim et al<sup>20</sup> conducted a meta-analysis of data from 82 studies. Adenosine stress MPI had higher sensitivity (90%) and relatively good specificity (75%); dipyridamole stress MPI showed similar sensitivity and specificity to adenosine stress MPI (89% and 65%). O'Keefe et al summarized the published data for dobutamine stress MPI: sensitivity was 91% and specificity was 86% for CAD detection.<sup>21</sup>

Both exercise and pharmacological stress MPI show good sensitivity for the detection of CAD and relatively good specificity for ruling out CAD. Integration of ECG-gated imaging with perfusion imaging improves sensitivity, an approach that is currently routine in clinical practise. Thus, stress MPI now has good diagnostic accuracy for detecting CAD. In addition, there have been many technical developments that may contribute to improving diagnostic accuracy. Some of the recent developments will be addressed later.



**Figure 3.** (A) Representative images from a 67-year-old woman with exertional chest pain. Her pretest risk likelihood of coronary artery disease was intermediate. Exercise stress  $^{99m}\text{Tc}$  myocardial perfusion imaging (MPI) showed a reversible perfusion defect in lateral wall, indicating moderate ischemia in the left circumflex artery (LCX) territory. Coronary angiography showed LCX occlusion. (B) Representative images from a 76-year-old man who had undergone previous coronary artery bypass grafting (CABG) for the left anterior descending and right coronary arteries (LCA and RCA). He had exertional chest pain for 8 years after CABG. Pharmacological stress  $^{99m}\text{Tc}$  MPI showed reversible perfusion defect in inferolateral wall, indicating moderate ischemia in the LCX territory. Coronary angiography showed LCX stenosis. SPECT, single-photon-emission computed tomography; Tc, technetium.





**Figure 4.** Representative images from a 74-year-old man with an old myocardial infarction, diabetes and renal failure. He was admitted due to congestive heart failure. He had 3-vessel disease. Pharmacological stress  $^{99m}\text{Tc}$  myocardial perfusion imaging showed a fixed perfusion defect inferior to the apex, indicating previous myocardial injury in the left anterior descending and right coronary arterial territories.  $^{18}\text{F}$  FDG images showed an inferior perfusion/metabolism mismatch, indicating viable myocardium in the RCA territory. FDG, fluorodeoxyglucose; Tc, technetium.

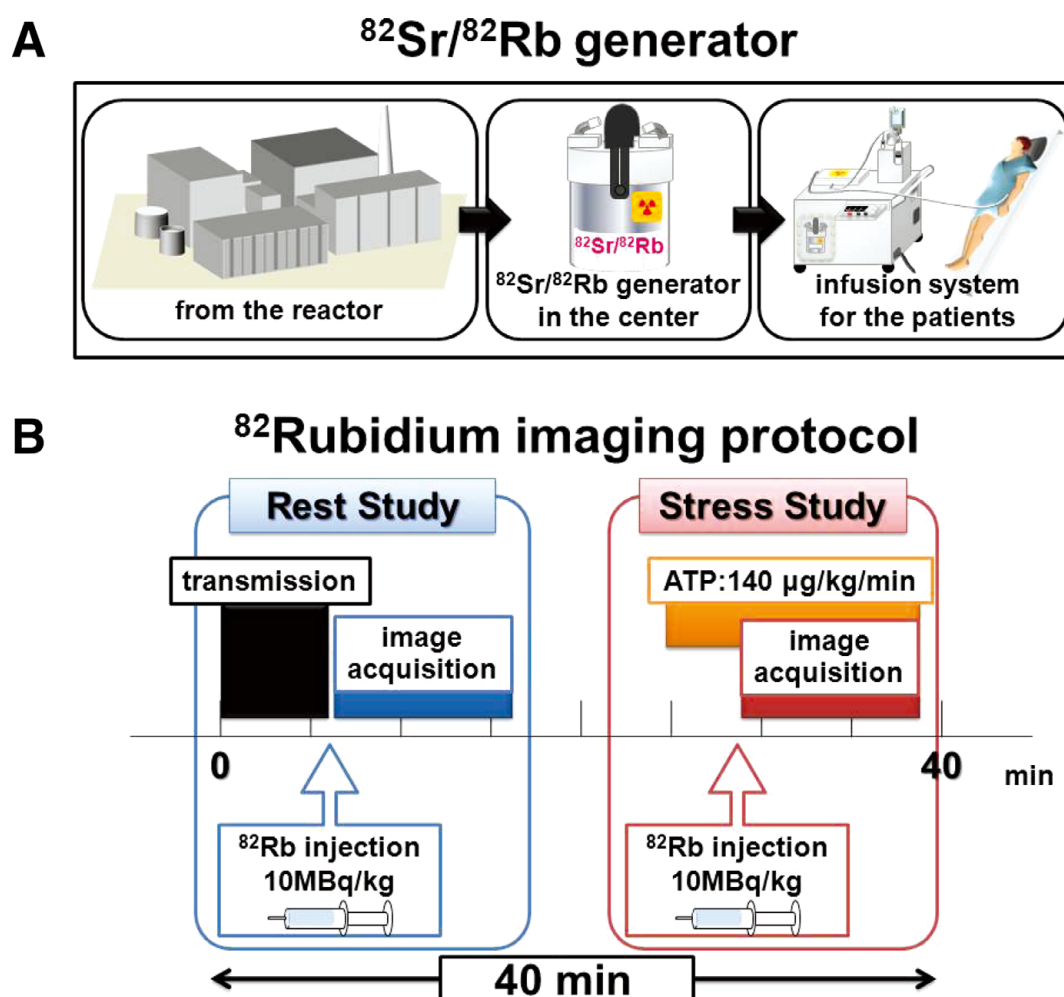
### Risk Assessment of CAD Using Nuclear Imaging

As addressed in the previous section, nuclear imaging has high diagnostic accuracy for detecting CAD. Another important role for diagnostic imaging is risk prediction for future cardiac events or risk stratification in patients with known or suspected CAD. The prognostic value of exercise and pharmacological stress MPI has been established by thousands of patients in numerous clinical studies.<sup>1</sup> One of the main goals of stress perfusion imaging is to determine which patients have a higher risk for cardiac death and fatal myocardial infarction (MI), and which have low risk for any cardiac events. Patients whose scans reveal a high risk can be considered for prompt invasive therapeutic strategies. In contrast, patients with low risk can avoid unnecessary invasive procedures.

Iskander and Iskandrian<sup>3</sup> analyzed 14 previous studies with 12,360 patients that had looked at the prognostic value of stress  $^{99m}\text{Tc}$  sestamibi perfusion SPECT. Patients with normal stress perfusion had a significantly lower annual hard event rate (0.6%/year), whereas patients with abnormal stress perfusion defects had a higher annual hard cardiac event rate (7.4%/year). Berman et al applied semiquantitative visual analysis for image interpretation and divided the patients into 4 groups: normal, mild, moderate, and severe.<sup>2</sup> There have been some modifications, but this approach is now considered to be standard.<sup>8</sup> Hachamovitch et al reported that patients

with intermediate risk based on their Duke Treadmill Score and normal stress  $^{99m}\text{Tc}$  sestamibi perfusion SPECT had a low hard cardiac event rate (0.4%/year with 2,200 patients).<sup>4</sup> As expected, patients with an intermediate Duke Treadmill Score and high-risk stress SPECT had a higher major cardiac event ratio (8.9%/year).

The important aspect of these studies is that the cardiac event ratio of a normal stress perfusion scan is quite low (<1%/year). In clinical practice, many cardiologists may be concerned about borderline cases using diagnostic tests, including SPECT MPI, or mild to moderate coronary arterial stenosis on coronary angiography (CAG) or computed tomography (CT) angiography. The definition of normal stress perfusion is a summed stress score from 0 to 4.<sup>4,8,22–24</sup> This includes a completely normal stress scan to very mild stress perfusion defects. In the case of patients with angina symptoms, we may have difficulty determining whether we should perform further invasive tests or invasive treatments. However, such borderline cases do not need further evaluation based on these data. One of the great features of stress perfusion SPECT is its excellent negative predictive value for low mortality and fatal MI in patients with a normal stress scan, as evidenced by many well-designed studies. This feature should greatly contribute to decision making in clinical practice.



**Figure 5.** (A)  $^{82}\text{Rb}$  PET myocardial perfusion tracers can be obtained from a  $^{82}\text{Sr}/^{82}\text{Rb}$  generator. Because of its very short half-life (76 s),  $^{82}\text{Rb}$  usually is administered to the patient using an automated infuser. (B) Imaging protocol of pharmacological stress  $^{82}\text{Rb}$  PET myocardial perfusion imaging. PET, positron emission tomography; Sr, strontium.

### Which Patients Benefit From Nuclear Cardiology Imaging?

Exercise or pharmacological stress MPI has good diagnostic accuracy and established prognostic value. Thus, nuclear imaging is highly valuable in general. However, there are some specific populations who especially benefit from nuclear imaging.

Considering the pretest likelihood of CAD, patients with a stable condition and intermediate risk have good indications for stress MPI (Figure 3A). The Duke Treadmill Score has proven valuable in predicting future cardiac events, but there remains uncertainty of cardiac event risk especially in patients with intermediate risk according to their Duke Treadmill Score. As previously addressed, stress MPI can determine the cardiac event risk in this population<sup>4</sup> and so these patients may benefit from stress MPI.

The variability in the relationship between anatomical coronary stenosis and coronary flow reserve is well recognized.<sup>25</sup> In the case of intermediate stenosis (25–75%) shown by CAG, the appropriate choice of treatment strategy is uncertain.

Nuclear imaging is especially useful for these patients.<sup>26</sup> Even for significant coronary stenosis, normal stress perfusion is associated with a low risk for future cardiac events.<sup>27</sup> Moreover, Hachamovitch et al reported that patients with a small area of ischemia did not have survival benefits from revascularization as compared with medical therapy.<sup>11</sup> Therefore, stress MPI plays an important role in deciding on treatment strategies when patients have intermediate coronary stenosis (25–70%).<sup>8,28</sup>

Patients undergo revascularization. Shaw et al reported reduced ischemic regions were associated with cardiovascular event risk reduction.<sup>12</sup> For patients with angina symptoms, nuclear imaging can evaluate whether a symptom may be associated with the appearance of new regions or the appearance of restenosis (Figure 3B).<sup>8</sup> Nuclear imaging is also useful for risk assessment in these populations. Like other previous studies, normal stress perfusion studies were associated with low risk of future cardiac events in patients who had prior revascularization.

**Table 3. Radiation Dosage of Selected Exposures**

	Total body effective dose (mSv)
<b>Diagnostic tests</b>	
Chest X-ray	0.08
Barium contrast gastrointestinal radiographic examination	2.3
Computed tomography: 64-slice multidetector CTA without ECG pulsing	
Male	9.6–15.2
Female	13.5–21.4
<b>Environmental</b>	
Average Japanese background radiation	2 mSv/year
Air travel	0.01/1,000 miles

CTA, computed tomography angiography.

### Myocardial Viability Assessment: <sup>18</sup>F Fluorodeoxyglucose (FDG) PET Is the “Gold Standard”

As previously addressed, 2 important indications for revascularization are significant inducible myocardial ischemia and enough viable myocardium. Detecting myocardial viability is essential when considering revascularization in patients with left ventricular (LV) dysfunction due to CAD.<sup>29</sup> Thus, these therapeutic strategies increase the demand for an accurate, sensitive, and physiological diagnostic approach.<sup>9,29</sup>

Free fatty acid is the main energy source in the normal myocardium, responsible for up to 90% of myocardial oxygen consumption. Fatty acid metabolism turns to glucose metabolism in dysfunctional but viable myocardium.<sup>29,30</sup> Therefore, it is very feasible to evaluate myocardial viability using glucose analog imaging. <sup>18</sup>F FDG is a glucose analog used to evaluate myocardial glucose utilization. Among several imaging techniques, <sup>18</sup>F FDG PET is considered the “gold standard” or at least the “best standard” for the evaluation of myocardial viability.

The first step in detecting viable myocardium in patients with LV dysfunction and CAD should be stress/rest perfusion imaging. In the case of a fixed perfusion defect, <sup>18</sup>F FDG PET would be the next test (Figure 4).<sup>8,29</sup> The preserved <sup>18</sup>F FDG uptake and perfusion defect represent viable myocardium, the so-called hibernating myocardium (Figure 5). This is a type of hot spot imaging. Beanlands et al conducted a systematic review of a total of 1,047 patients with a LV ejection fraction (EF) <40% in studies published after 2001 and the mean sensitivity for LVEF improvements was 90% and specificity was 61%.<sup>31</sup> Schinkel et al<sup>32</sup> conducted a further comprehensive systematic review of viability studies using several imaging techniques such as FDG PET, other nuclear imaging, dobutamine stress echocardiography, and cardiac magnetic resonance imaging (CMR). Among several imaging techniques, FDG PET showed the highest sensitivity ( $P<0.05$  vs. other tests). In contrast, dobutamine stress echocardiography had the highest specificity. In a randomized clinical trial, Beanlands et al reported a trend for outcome benefits using FDG PET.<sup>33</sup>

### Radiation Exposure: Is It High in Nuclear Cardiology?

Among the several diagnostic tests, cardiac imaging tends to have higher radiation because of the higher radio sensitivity in the lungs and breasts of women.

People in general are concerned with high radiation expo-

sure from nuclear imaging. The first-generation myocardial perfusion tracer, <sup>201</sup>Tl, has a relatively higher total body effective dose than do other common tracers used in diagnostic imaging because of its long half-life (72.9 h) (Table 1).<sup>6</sup> The <sup>99m</sup>Tc-labeled myocardial perfusion tracers are associated with lower radiation doses (between 10.6 and 12 mSv) because of their short half-life (6 h). This radiation dose is similar to that of other standard diagnostic imaging. The lifetime risk of fatal cancer from 0.01 Sv (10 mSv) radiation exposure from CT is calculated to be 1 in 2,000.<sup>34</sup> The same report also stated that the lifetime risk of fatal cancer is 1 in 5 in the general population (Table 3).

Recently, new SPECT cameras have been developed, which have highly sensitive crystal material, such as sodium iodine crystals, and use an advanced reconstruction algorithm. These technical advances make it possible to reduce injection doses and thus reduce radiation exposure by approximately 50%.

Another way to reduce radiation exposure is by using myocardial PET. The effective radiation dose is associated with the distance from the radioactive source, the time of exposure, and the shield from radiation sources. Exposure duration is very important for patients undergoing nuclear imaging. PET tracers have very short half-lives. Thus, PET perfusion studies can reduce patient dosimetry, especially in obese patients. Newly developed hybrid PET/CT scanners have a 3-dimensional data-acquisition mode, which has very high sensitivity and requires a much lower injection dose (usually less than 50%).<sup>5</sup>

We should give careful consideration to radiation exposure when deciding which test is best for a patient. New tracers and technical improvements have contributed to reductions in radiation exposure in nuclear cardiology. Although we still need to exercise caution, these developments can increase the use of nuclear cardiology in the clinical setting.

### Overcoming Technical Disadvantages: Recent Technical Developments

#### New SPECT Cameras: Possibility of Reduced Data-Acquisition Time

The introduction of 2-head  $\gamma$  cameras has contributed to reducing data-acquisition times. However, standard SPECT acquisition usually still requires 12–15 min in each study. Recently, alternative SPECT camera systems have been developed, such as semiconductor detectors or solid-state detectors.

In solid-state detectors,  $\gamma$  rays are detected by semiconductor materials. The collected electron charge is used to determine the location and energy of the  $\gamma$  rays. This detector has an improved count sensitivity and provides higher energy



resolution and spatial resolution.<sup>35</sup> This high sensitivity to  $\gamma$  rays makes it possible to reduce data-acquisition time while improving image quality. A clinical trial is under way and clinical use is expected shortly.

### PET Myocardial Perfusion Imaging: Reduced Study Time and Improved Diagnostic Accuracy

Current SPECT MPI protocols require 3–4 h for stress and rest imaging, which is one of its limitations in the clinical setting. Another possible approach to reducing the test time is to use PET MPI. Current PET tracers have a short half-life, ranging from 76 s with  $^{82}\text{Rb}$  or 110 s with oxygen-15-labeled water to 9.97 min with nitrogen-13 ammonia (Table 1).<sup>9,36</sup> After 5 times the duration of the half-life, the effects of the tracers have usually disappeared, and the next scan can be started. Among the PET perfusion tracers,  $^{82}\text{Rb}$  has the shortest half-life, so is suitable for repeated and sequential perfusion studies, usually at 10-min intervals.<sup>22</sup> In our institution, the total rest and stress  $^{82}\text{Rb}$  PET MPI requires 40 min (Figure 5B).<sup>36</sup> It is expected that the use of new pharmacological stress agents will mean a shorter total study time.

**Access to PET MPI** There may be some concern with the accessibility of PET MPI because most of the tracers require an on-site cyclotron due to their short physical half-life. On the bright side,  $^{82}\text{Rb}$  is a generator-produced PET MPI tracer produced from a strontium-82/rubidium-82 ( $^{82}\text{Sr}/^{82}\text{Rb}$ ) (parent/daughter) generator (Figure 5A), which does not require a cyclotron and can be used in larger populations.<sup>37</sup> More than 1,000 PET or PET/CT scanners have been installed in the United States (US), and there are nearly 200 PET centers in Japan.<sup>36</sup> The US Food and Drug Administration (FDA) approved  $^{82}\text{Rb}$  for clinical use in 1989, and US Medicare reimbursement began in 1995. Recently, some cardiovascular centers in Japan and Europe have begun  $^{82}\text{Rb}$  studies.<sup>38</sup> Thus, PET MPI using  $^{82}\text{Rb}$  could be widely available shortly.

**Which Patients Benefit Most From PET MPI?** PET MPI has excellent diagnostic accuracy in patients with CAD. The mean sensitivity and specificity of PET MPI are 90% (83–100%) and 87% (73–100%), respectively, based on a systematic review of 14 studies and 1,460 patients.<sup>31</sup> Three studies using PET/CT scanners showed a similar sensitivity of 87.8% and a higher specificity of 95.7%.<sup>36</sup> PET MPI uses tissue attenuation correction, which contributes to good image quality. Thus, PET MPI has good diagnostic accuracy. Recent PET/CT hybrid scanners have newer imaging crystals, such as lutetium oxyorthosilicate, and new-generation electronics, which may further contribute to improved diagnostic accuracy.

As well as SPECT MPI, PET MPI has prognostic value. Yoshinaga et al reported that normal stress imaging was associated with a low hard cardiac event ratio (0.4%/year) and that patients with abnormal stress perfusion had higher major cardiac events (2.3% and 7.0% for mild and moderate to severe, respectively) using  $^{82}\text{Rb}$  PET MPI.<sup>22</sup> A study with a much larger sample was conducted by Lertsburapa et al, who reported that integration of stress perfusion defects and LV function during pharmacological stress enhanced risk stratification in 1,441 patients.<sup>37</sup>

Recent data clearly show that PET MPI has excellent diagnostic accuracy and prognostic value, but let's return to the question of which patients benefit from using PET MPI.

Although SPECT MPI and exercise stress ECG have good diagnostic accuracy, these approaches sometimes have either false-positive or false-negative results. Bateman et al com-

pared the diagnostic accuracy of  $^{82}\text{Rb}$  PET and  $^{99\text{m}}\text{Tc}$  sestamibi SPECT MPI. Using a 50% threshold of coronary artery stenosis, the diagnostic accuracy was higher for  $^{82}\text{Rb}$  PET than for  $^{99\text{m}}\text{Tc}$  sestamibi SPECT ( $P=0.002$ ). One important finding of that study was that PET MPI has higher diagnostic confidence compared to SPECT MPI.<sup>39</sup> Yoshinaga et al reported that  $^{82}\text{Rb}$  PET MPI could be used to make risk assessments in patients who had non-diagnostic findings with SPECT MPI.<sup>22</sup> In fact, ACC/AHA/ASNC guidelines suggest that PET MPI is useful when patients have equivocal results from other diagnostic tests.<sup>8</sup>

Another population that presents a significant challenge for cardiac imaging is obese patients. The prevalence of obesity (body mass index  $>30$ ) has dramatically increased, with over 20% of the US adult population being reported as obese. Sampson et al reported that  $^{82}\text{Rb}$  PET MPI was equally sensitive in detecting CAD in patients who were obese or non-obese (sensitivity: 100% vs. 87%).<sup>40</sup> In obese patients, the annual total cardiac event rate was 11.1% with an abnormal stress scan and 1.5% with a normal scan using  $^{82}\text{Rb}$  ( $P<0.001$ ).<sup>22</sup> Based on these studies, PET MPI should be useful for diagnosis and risk assessment in obese patients.

## Conclusions

Nuclear cardiology imaging has excellent diagnostic accuracy for myocardial ischemia and viable myocardium. MPI has excellent prognostic value in patients with known or suspected CAD. With an aging population, patients are more vulnerable because of coexisting disease. However, nuclear cardiology can be applied to almost all such patients with no contraindication. Therefore, nuclear cardiology imaging should return to the main stream of non-invasive cardiac imaging in order to enhance patient care.

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### Authors' Comments on the MRI-Side Authors

We read with great interest the paper by Dr Cheung et al on the evaluation of myocardial ischemia using cardiac magnetic resonance imaging (CMR).<sup>41</sup> CMR is an attractive imaging modality because it can provide both anatomical and physiological information with high spatial resolution.

As Dr Cheung et al have addressed, CMR has high diagnostic accuracy, similar to other non-invasive diagnostic tests. However, given the novelty of the technique for cardiac use, there is as yet limited data on the CMR findings and its predictive value for future cardiac events. Thus, the prognostic value of CMR has not been established. Myocardial perfusion studies using CMR do not involve radiation exposure but do require a contrast medium. Given the increase in the aging population, more patients with coronary artery disease have coexisting disease, and an accompanying increase in the number of patients with a contraindication to contrast medium may also be expected. In addition, when a myocardial perfusion study is performed under pharmacological stress to assess myocardial ischemia, such stress needs to be induced within the limited space of a table in the magnetic resonance imaging (MRI) room. In addition, because of the high magnetic power associated with MRI, bringing a 12-lead ECG machine into the room may not be feasible, which presents a possible limitation to CMR perfusion studies, along with the risk to patients who may experience myocardial ischemia during pharmacological stress. Nuclear imaging does expose patients to radiation, but, as addressed by us, the total radiation dose has been recently reduced. In addition, it is quite feasible to do radionuclide imaging of exercise stress or pharmacological stress in a separate room. Since the radiopharmaceutical is trapped within the myocardial cell for a short period after the stress test, stress myocardial perfusion imaging may be performed while the patient is at rest after a stress test. CMR could be made available in many cardiovascular centers, but the standard scan protocol still needs to be established and should reduce sequential acquisition time.

For these reasons, nuclear cardiology, single-photon-emission computed tomography and positron emission tomography remain the major non-invasive imaging tests for detecting myocardial ischemia and for making risk assessments in the clinical setting.