Introduction

Various new imaging modalities provide multiple options with which to clinically diagnose coronary artery disease (CAD). Among such modalities, the major indications for nuclear cardiology remain the diagnosis of myocardial perfusion including stress-induced ischemia and infarction. However, coronary CT angiography is more suitable for visualizing the coronary anatomy of patients with mild to intermediate risk, and nuclear cardiology is more appropriate for detecting stress-induced ischemia among patients with intermediate-to-severe risk. Solid-state SPECT cameras equipped with cadmium-zinc-telluride detectors enable dynamic data acquisition and generate information about myocardial flow reserve, which might offer a new perspective of multi-vessel diseases and the microcirculation. Artificial intelligence is emerging as a possible new strategy for identifying ischemia. The applications of $^{123}$I-labeled non-perfusion tracers have expanded in Japan. For example, $^{123}$I-BMIPP can visualize ischemic memory, help determine the prognosis of patients with chronic kidney disease or those on hemodialysis, and it has also recently proved useful for diagnosing triglyceride cardiomyoscopy. Although $^{123}$I-MIBG is indicated for heart failure, model-based approaches to differentially predicting causes of cardiac death are under investigation. Other applications include $^{99m}$Tc-pyrophosphate imaging of transthyretin cardiac amyloidosis and $^{18}$F-FDG for cardiac sarcoidosis. Among all multimodal imaging modalities, nuclear cardiology continues to be tracer-based and reflect myocardial perfusion, flow reserve and molecular imaging.

KEY WORDS: artificial intelligence, coronary computed-tomography angiography, fatty acid imaging, innervation imaging, myocardial perfusion imaging

A major achievement in nuclear cardiology has been the identification of ischemia, and multimodal imaging of coronary artery disease has been pivotal in this process. X-ray computed tomography (CT) is an imaging modality that can reveal information about coronary artery stenosis. Thus, the number of studies has rapidly increased in Japan, where CT is widely available in clinical practice. However, coronary CT angiography is more suitable for visualizing the coronary anatomy of patients with mild to intermediate risk, and nuclear cardiology is more appropriate for detecting stress-induced ischemia among patients with intermediate-to-severe risk. Solid-state SPECT cameras equipped with cadmium-zinc-telluride detectors enable dynamic data acquisition and generate information about myocardial flow reserve, which might offer a new perspective of multi-vessel diseases and the microcirculation. Artificial intelligence is emerging as a possible new strategy for identifying ischemia. The applications of $^{123}$I-labeled non-perfusion tracers have expanded in Japan. For example, $^{123}$I-BMIPP can visualize ischemic memory, help determine the prognosis of patients with chronic kidney disease or those on hemodialysis, and it has also recently proved useful for diagnosing triglyceride cardiomyoscopy. Although $^{123}$I-MIBG is indicated for heart failure, model-based approaches to differentially predicting causes of cardiac death are under investigation. Other applications include $^{99m}$Tc-pyrophosphate imaging of transthyretin cardiac amyloidosis and $^{18}$F-FDG for cardiac sarcoidosis. Among all multimodal imaging modalities, nuclear cardiology continues to be tracer-based and reflect myocardial perfusion, flow reserve and molecular imaging.

KEY WORDS: artificial intelligence, coronary computed-tomography angiography, fatty acid imaging, innervation imaging, myocardial perfusion imaging
From perfusion-defect quantitation to flow reserve

Evaluating stress-induced ischemia has been a major target of nuclear cardiology\(^6,\) and functional testing to assess ischemia is critical for patients with stable CAD\(^5\). Since an intermediate degree of coronary artery stenosis, for example, 50–75% stenosis does not necessarily result in a peripheral decrease in perfusion, this could be underestimated by myocardial perfusion imaging (MPI). This discrepancy can be rationalized as follows. The straightforward explanation is that ischemia is absent because of preserved flow reserve, which is related to the severity, duration, and morphology of coronary artery stenosis, and collateral circulation. Only the most severe stenosis or culprit lesion of ischemia might be identified in multi-vessel disease, and a balanced reduction in coronary flow can obscure a regional decrease in myocardial flow. From the viewpoint of radiopharmaceuticals such as \(^99m\)Tc-methoxyisobutylisonitrile (MIBI) and tetrofosmin, the relationship between tracer count in the myocardium and true blood flow is not linear under high flow, while adenosine-induced stress increases resting myocardial perfusion 3–5-fold. Although easy quantitation of ischemia using summed defect scores has been an advantage of nuclear cardiology, and various software programs have become popular over the past two decades\(^8,\) the threshold of 10% ischemia was created from a prognostic study to determine the causes of severe cardiac events\(^11\). However, the \%ischemia of clinical percutaneous coronary interventions (PCI) to resolve patient symptoms might be < 10%. In fact, a 5% reduction in ischemia due to PCI had favorable prognostic effects in the COURAGE trial substudy\(^12\) and the J-ACCESS investigations\(^13,\)\(^14\).

A new approach to achieving more quantitative myocardial flow reserve values using dynamic SPECT is useful\(^15,\)\(^16\). Dynamic data acquisition at 3 seconds per frame is required for 1 minute during initial transit, and at present, only the CZT camera can achieve this. Rest and adenosine-stress images take one hour to acquire from the moment of the \(^99m\)Tc-MIBI intravenous injection. Since the calculation uses compartment or retention models, input function is measured on the left ventricular cavity and the output on the myocardium. In multivessel diseases that might manifest balanced ischemia, reduced MFR can be revealed in stenotic coronary territories. Fig. 1 shows an example of a dynamic D-SPECT study of patient before undergoing coronary artery bypass graft surgery.

The reliability of perfusion and flow reserve has been assessed. The WATERDAY study estimated MBF and MFR by dynamic SPECT using a CZT camera in patients with stable CAD, and compared the results with those of \(^15\)O-water PET and FFR\(^17\). Correlations were reasonable if ischemia was considered when PET and CZT-SPECT respectively identified MFR < 2 and 2.1. This provides good diagnostic value for detecting impaired MFR and abnormal FFR. Although some issues require resolution such as adjustments of appropriate retention models and the linearity of \(^99m\)Tc tracers, how and when SPECT-based MFR values should be clinically applied requires further investigation.

Quantifying ischemia with MPI: A new viewpoint

Although visual assessment of perfusion is the basis for interpreting SPECT images, quantitative values have been routinely incorporated into interpretations in nuclear cardiology. Semi-quantitative perfusion defect scores have been included in the most popular software programs in the USA and Europe\(^8,\)\(^10\) and Japan\(^8,\)\(^10\) since the 1990s. These programs use standard normal databases for defect scoring, but persistent minor differences are specific to each program. Normal databases including all radiopharmaceuticals for perfusion and \(^123\)I tracers are available from the Japanese Society of Nuclear Medicine\(^20\). Standardizing measured results using universal standards is an advantage of nuclear cardiology.

To avoid underestimating stress-induced ischemia, the integration of various parameters that support ischemia might be helpful. The first step is to find a region of hypoperfusion that can be supported by the segmental values (%). Since a slight change in counts might be overlooked, additional parameters have been introduced. Post-stress dysfunction includes transient ischemic ventricular dilation and reduced left ventricular ejection fraction (LVEF), which are sometimes associated with multivessel diseases. Transient ischemic dilation is considered as subendocardial ischemia in addition to actual dilation of the left ventricular cavity. Regional wall motion abnormalities can be visualized as post-stress stunning when ischemia develops during stress, or
even when ischemic count reduction is not obvious. Dyssynchrony or heterogeneity of contraction timing, and post-ischemic regional dyssynchrony have recently been identified using phase analysis\(^ {21, 22}\). Although these individual parameters might not be diagnostic, the integrated understanding of various aspects of parameters might help to avoid overlooking ischemia that exists, but remains hidden due to the absence of decreased myocardial counts. Fig. 2 shows several aspects of ischemia found in various parameters.

Artificial intelligence: Clinical applications

Although artificial intelligence has become popular, its value to nuclear cardiology and clinical decision-making is just emerging. Along with the increasing complexity of diagnostic imaging cardiologists, radiologists, and nuclear medicine physicians must constantly expand their knowledge base\(^ {23, 24}\). Therefore, if artificial intelligence could integrate clinical information, suggest diagnoses and guide possible treatment strategies, it would certainly aid physicians dealing with complicated clinical challenges. Artificial intelligence has not yet reached this stage, but detecting ischemia and infarction by interpreting images has become feasible, and artificial neural network-based software has been developed in Europe and Japan for this purpose\(^ {23, 25}\). CardioREPO (Fujifilm Toyama Chemical, Japan; Collaboration of EXINI Diagnostics, Sweden) was created by training the neural network on data from 1,001 patients with suspected CAD. The training procedures included candidate regions of ischemia and infarction. The neural network used these patients as teachers, and “truth” was determined by nuclear cardiology specialists analyzing >5,000 possible candidate regions. Features for ischemia and infarction were determined from stress, rest and subtracted images, and the training also included sex, regional count, shape, location, wall motion, and other possible features. As noted above, ischemia is not simply a reduction in regional counts, and composite findings could be used for a final judgement of abnormalities. The results of neural networks are expressed as probabilities that are displayed on maps and in three-dimensions. This approach is quite different from statistical analysis.

After validation with a new group of patients with CAD, the diagnostic accuracy was better for the neural network than statis-
tical analysis: receiver-operating characteristics analysis showed an area under the curve of 0.90–0.98: 0.90 before PCI, and 0.98 in patients with old myocardial infarction. The detectability was comparable to expert interpretation, as far as extant abnormalities were judged. Since expert readers use more clinical information from patients, physicians should apply integrated judgement. However, artificial intelligence might provide a useful second opinion to support or rule out abnormalities in borderline or ambiguous situations. Software could also be applied for beginners in nuclear cardiology and technologists who are not familiar with nuclear cardiology imaging. Artificial intelligence also predicts 5-year all-cause mortality in patients undergoing CCTA more precisely than either clinical or CCTA metrics alone, indicating the superiority of machine learning.

Fatty acid imaging with $^{123}\text{I}$: Not only ischemic memory

The tracer, $^{123}\text{I}$-BMIPP, has been applied to ischemic memory imaging, especially during the acute and subacute phases of myocardial ischemia, and the early stages of myocardial damage. Myocardial perfusion can be preserved despite metabolic damage, and this results in a perfusion-fatty acid metabolic mismatch that can arise in pathophysiological conditions other than ischemia. Cardiac sarcoidosis, primary and secondary cardiomyopathies, Takotsubo syndrome, and chronic kidney disease or dialysis are examples of mismatch defects determined by $^{123}\text{I}$-BMIPP findings and they are associated with specific patterns. The JCS guidelines for $^{123}\text{I}$-BMIPP include the results of the multicenter B-SAFE study of patients on hemodialysis.

When $^{123}\text{I}$-BMIPP defect scores were calculated as myocardial perfusion defects, all-cause death and cardiac death rates were 18.5% and 6.8%, respectively. The incidence of severe cardiac events including cardiac, cerebrovascular and other vascular-related death was significantly higher among patients with defect scores ≥ 4 (slight or more) or ≥ 9 (moderate or more).
The J-ACCESS-3 multicenter study included patients with chronic kidney disease who were followed up for 3 years after undergoing stress MPI. Cardiac events, including cardiac death, sudden death, non-fatal myocardial infarction and hospitalization due to heart failure, developed in 60 (11%) of 529 patients32,33, and 46 (77%) were admitted to hospitals with heart failure. The J-ACCESS risk model to predict major cardiac events showed that patients with estimated glomerular filtration rates (eGFR) of < 15 L/min/1.73 m² were at significantly higher risk regardless of other risk values34. Both 123I-BMIPP and J-ACCESS 3 studies found higher risk profiles in patients with chronic kidney disease, typically those on hemodialysis. Thus, patients with clinical manifestations such as chest symptoms, electrographic abnormalities, wall motion abnormalities, and hypotension during hemodialysis might be indicated for readily-applied 123I-BMIPP imaging that does not require stress tests.

Another recent application of 123I-BMIPP is triglyceride deposit cardiomyosculopathy (TGCV), which was identified in Japan during 200835, and characterized by the deposition of triglyceride rather than cholesterol atherosclerosis. The diagnostic criteria were revised this year35,36, and essential items include a decreased washout rate (< 10%) determined by myocardial 123I-BMIPP SPECT, or myocardial triglyceride deposition determined by biopsy, CT or magnetic resonance spectroscopy. Since the established cause of TGCV is a genetic deficiency of adipose triglyceride lipase, 123I-BMIPP has played a key role in the diagnosis of TGCV in patients with diffuse narrowing of coronary arteries and reduced LVEF (< 40%). Early and delayed SPECT imaging findings confirmed a washout rate of < 10% as characteristic of TGCV.

Innervation imaging using 123I-MIBG: A new approach to heart failure

The risk stratification and prognostic evaluation of patients with heart failure are major indications for 123I-MIBG. Large-scale studies in the USA, Europe and Japan have unanimously confirmed that the average count ratio of the heart: mediastinum (H/M) can predict the progression of heart failure, cardiac death, sudden cardiac death, and possibly arrhythmic events37–39. The H/M ratio can be simply calculated using an anterior planar image by setting regions of interest on the heart and mediastinum. We recently created a multivariate logistic model that included age, sex, LVEF, New York Heart Association functional class and 123I-MIBG H/M ratio, to estimate risk for two- and five-year cardiac mortality based on a cohort of 1,322 patients40. The actual and estimated mortality rates were in good agreement when estimated risk was validated with a new patient cohort41.

We further developed a machine-learning based risk model that included 13 variables to differentiate death due to heart failure from fatal arrhythmic events (including sudden cardiac death and appropriate therapy by implantable cardioverter defibrillator)42. Since causes of arrhythmic events are multifactorial and not predictable from a single variable, complicated estimation using artificial intelligence might function in the risk-stratification of patients with heart failure. A risk strategy for heart failure treatment could be adopted; for example, cardiac devices are beneficial for patients at high risk, whereas appropriate medical therapy benefits those at low-risk. Further prospective studies are required to confirm the effectiveness of such strategies. Innervation imaging combined with left ventricular dysynchrony determined by gated myocardial perfusion imaging are related to lethal cardiac events in patients with heart failure and reduced LVEF43.

Cardiac amyloidosis with bone-imaging radiopharmaceuticals

The American Society of Nuclear Medicine (ASNC) and the Japan Circulation Society have emphasized the relevance of 99mTc-pyrophosphate (PYP) to diagnosing cardiac amyloidosis, and a brochure describing practice points is available from ASNC44,45. Cardiac amyloidosis has been assessed using 99mTc-PYP since the 1980s, but with low diagnostic accuracy. However, the role of 99mTc-PYP has been greatly enhanced by the discovery that 99mTc-PYP accumulation is specific for the amyloid transthyretin (ATTR), but not for the amyloid immunoglobulin light-chain (AL) type, and the approval of treatment for cardiac amyloidosis. Bone imaging agents such as 99mTc-hydroxymethylene diphosphonate (HMDP) and -3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) have also been applied. Cardiac activity is still quantified based on planar anterior imaging at 1 or 3 h, and a heart-to-contralateral lung ratio of 1.5 as the diagnostic threshold. Since a diagnosis of ATTR amyloidosis is often delayed or missed, several clues such as heart failure with preserved ejection fraction, discordance between QRS voltage and wall thickness, association with carpal tunnel syndrome, and autonomic nervous system dysfunction, might be good indications for further tests including 99mTc-PYP. Also included are apical sparing of echographic strain imaging, arrhythmias such as atrial fibrillation or other conduction abnormalities, and aortic stenosis, notably with a low-flow, low-gradient profile. Fig. 3 shows a man aged in his 80s with wild-type ATTR. SPECT-CT imaging can conveniently localize 99mTc-PYP uptake by the myocardium. Non-invasive tests of type for amyloid light-chain (AL) amyloidosis and ATTR can be practical for patients who need further tests for documented gene mutations.
FDG imaging for cardiac sarcoidosis as a key role in the guidelines

Metabolically active lesions in cardiac sarcoidosis have been identified using $^{18}$F-FDG PET, and the diagnostic guidelines were updated during 2016. While multimodal imaging methods are applicable to diagnosing the involvement of cardiac sarcoidosis, the most popular imaging strategies are presently echo cardiography to visualize septal thickening, wall motion abnormalities, and positive FDG accumulation in the heart, and MR imaging with delayed contrast enhancement. The Japanese Society of Nuclear Cardiology has summarized guidelines for appropriate preparation of carbohydrate restriction, and ≥12, and preferably 18 hours of fasting is considered necessary. To avoid physiological cardiac activity, abnormal $^{18}$F-FDG accumulation is defined as focal and focal-on-diffuse. Although appropriate histological findings are required for a definitive diagnosis, the JCS guidelines define a clinical diagnosis as epithelioid granulomas in organs other than the heart, with clinical findings strongly suggestive of cardiac involvement, or clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis, and at least two of the five characteristic laboratory findings of sarcoidosis and clinical findings strongly suggestive of cardiac involvement. The J-CASP multicenter registry is ongoing, and over 200 patients are currently being analyzed to determine the diagnostic and prognostic utility of $^{18}$F-FDG based on updated JCS guidelines. $^{18}$F-FDG accumulates in active lesion of cardiac sarcoidosis and effective steroid therapy can significantly reduce activity (Fig. 4). Although the diagnostic ability of $^{18}$F-FDG is established, its relevance to steroid tapering and prognostic evaluation requires further validation.

Trends in non-invasive imaging for ischemia

X-ray CT and SPECT imaging have become standard approaches in the era of multimodal imaging. Negative predictive values for serious cardiac events are considered low in both methods, and appropriate medications or follow-up can be indicated. On the other hand, high-risk patients can be indicated for CAG, and more active medical therapy and/or coronary revascularization will be selected depending degree of ischemia. Patients with confirmed myocardial ischemia and typical chest pain are generally indicated for coronary intervention. However, the practice of initial CCTA and PCI based only on stenosis is discouraged, and confirmation of ischemia has been included as an indication for PCI by the Ministry of Health and Labor in Japan since 2018. The ischemia-based approach is also supported by values for FFR measured during CAG, as well as instantaneous wave-free and resting full-cycle ratios without the need for pharmacological coronary dilation might play a more practical role. The initial results of the ISCHEMIA trial of patients with moderate or severe ischemia who were randomized to invasive and conservative strategies showed comparable event rates regarding all-cause death, cardiovascular death, and composite events including non-fatal myocardial infarction and unstable angina. Since the patients were randomized after ischemia was proven, the findings do not imply that non-invasive imaging for ischemia is unnecessary. A Japanese multicenter study recently showed that a 5% reduction in ischemia exerted favorable effects on the occurrence of subsequent cardiac events. At present, whether revascularization reduces death and other car-

Fig. 3 Patient with ATTR wild-type amyloidosis. Heart-to-contralateral lung (H/CL) ratio is >1.50 (A), which is ATTR amyloidosis threshold, and $^{99m}$Tc-pyrophosphate (PYP) accumulation is obvious in the myocardium (B).
diovascular outcomes is uncertain; a systematic meta-analysis associated routine revascularization with a lower risk of nonprocedural myocardial infarction and unstable angina with greater freedom from angina, but not with improved survival over 4.5 years compared with an initial medical approach. Thus, baseline studies of ischemia and risk estimation in patients with stable ischemic heart disease are still needed, and symptomatic patients will benefit more if indications are determined by the consensus of cardiologists and patients, which will include an improved quality of life and better prognoses for patients.

Lastly, technology is developing for calculating CT-based FFR in addition to diagnosing coronary stenosis, and estimated FFR values are comparable to those measured during CAG. Since complicated features such as the morphology of stenosis, the location of coronary intervention or stent deployment, and collateral circulation might affect final flow reserve, further evidence of diagnostic and prognostic value is required. With respect to estimating myocardial flow reserve, FFR provides information about coronary arteries, whereas myocardial perfusion SPECT provides information about myocardial perfusion reserve including the whole heart and microcirculation. Although several methodologies can provide similar information, the key is not to select only one optimal method, but to understand the advantages and disadvantages of each method in clinical practice and improve the quality of life of patients. Complementary roles and appropriate applications should be investigated according to the specific needs of individual patients.

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Conflict of interest

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Fig. 4 Patient with cardiac sarcoidosis.
Upper and lower panels show maximum intensity projection and 18F-FDG-PET fusion images, respectively. Patient had atrioventricular block and pacemaker implantation, then was diagnosed with cardiac sarcoidosis (A). One-year after steroid therapy (B) cardiac FDG uptake is markedly reduced. Two years later, although accumulation was not found in the myocardium, mediastinal lymph-node activity has relapsed (C) despite continuing steroid therapy.
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