Nuclear Medicine and Molecular Imaging (2021) 55:151–161
https://doi.org/10.1007/s13139-021-00702-w

REVIEW

KSNM60 in Cardiology: Regrowth After a Long Pause

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Received: 1 March 2021 / Revised: 9 May 2021 / Accepted: 25 May 2021 / Published online: 8 June 2021

Abstract

The Korean Society of Nuclear Medicine (KSNM) is celebrating its 60th anniversary in honor of the nuclear medicine professionals who have dedicated their efforts towards research, academics, and the more comprehensive clinical applications and uses of nuclear imaging modalities. Nuclear cardiology in Korea was at its prime time in the 1990s, but its growth was interrupted by a long pause. Despite the academic and practical challenges, nuclear cardiology in Korea now meets the second leap, attributed to the growth in molecular imaging tailored for many non-coronary diseases and the genuine values of nuclear myocardial perfusion imaging. In this review, we describe the trends, achievements, challenges, and perspectives of nuclear cardiology throughout the 60-year history of the KSNM.

Keywords Myocardial perfusion imaging · Coronary artery disease · Single-photon emission computed tomography · Positron emission tomography · Korea · Nuclear medicine

Introduction

Among the fields of nuclear medicine, nuclear cardiology is a field that blossomed relatively late. Despite this, myocardial perfusion single-photon emission tomography (SPECT) has become a significant part of nuclear medicine since the 1990s. In recent years, the capability of nuclear cardiology has been expanded in new diseases through the quantitative analysis of myocardial blood flow (MBF) by positron emission tomography (PET), the development of new radiotracers, and molecular imaging in non-coronary diseases. In commemoration of the 60th anniversary of the Korean Society of Nuclear Medicine (KSNM), we would like to describe the process of change and the achievements of nuclear cardiology and its future challenges and opportunities that will allow it to flourish.

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Achievements in Nuclear Cardiology

Major Events of Nuclear Cardiology in Korea

Nuclear cardiology began in Korea with the planar first-pass angiocardiography through the installation of the first single-head gamma cameras in 1969 [1]. In the earlier times, the majority of radioisotopes used in the medical fields consisted of I-131 and Au-198 colloid. Therefore, nuclear cardiology radiotracers were used as I-131-labeled forms (e.g., I-131 macroaggregated albumin, I-131 human serum albumin [RIHSA or RISA]) [2]. Such early radionuclides were mostly imported from abroad until domestic reactor production grew up to a competent level in 1970s [3]. Also, Tc-99 m generator had not been available until it was first imported in 1979 [4]. Tl-201 myocardial perfusion study was introduced in 1983 [5] and gained popularity as the prevalence of ischemia heart disease increased. However, Tl-201 was very expensive in the beginning before its domestic production became possible around 1986 [1]. In the 1980s and

1990s, various stress protocols and myocardial perfusion radiotracers were introduced with the exercise stress being introduced first, followed by the dipyridamole and adenosine stress protocols. Exercise stress was the most common stress testing, while dipyridamole infusion was used only in patients who could not exercise [1]. However, the majority of stress testing in Korea is currently based on the adenosine stress protocol. Tc-99 m methoxyisobutyl isonitrile (MIBI), N-13 ammonia, O-15 water, and Rb-82 were first used in the 1990s. Tc-99 m tetrofosmin was the last of myocardial perfusion tracers that entered clinical use in Korea, being introduced in 1999. Tc-99 m MIBI has been more commonly used than Tc-99 m tetrofosmin in Korea.

In response to these developments, the first academic organization, the Korean Study Group on Nuclear Cardiology (KSNC) was established in 2002 [4] and has since evolved into a multidisciplinary organization, now named Korean Study Group for Cardiovascular Imaging (KCI) under the Korean Society of Cardiology. This new organization includes radiologists, cardiologists, and nuclear medicine physicians. However, the KSNC remains independent of the KCI, holding annual nuclear cardiology seminars and symposia under the administration of the KSNM.

The Korean national insurance has covered myocardial perfusion SPECT since its inception in the early 1990s. In 2020, the reimbursement criteria were re-defined for its use in preoperative risk assessment: it is covered by the national insurance for patients undergoing intermediate-to-high-risk surgery. Viability testing using F-18 fluorodeoxyglucose (FDG) for the evaluation and post-treatment follow-up of ischemic heart disease was first reimbursed in 2006. Through the several amendments to the national insurance coverage of oncologic FDG PET, it is still being covered by the national insurance program. In contrast, N-13 ammonia PET has not achieved national insurance coverage and was officially listed as a non-reimbursable item in 2015.

The major events in the history of nuclear cardiology in Korea are summarized in Table 1.

Statistical Data

The use of nuclear cardiology studies increased in the 1990s but was followed by a plateau of 10 years in the 2000s. Despite the robust principles of myocardial perfusion imaging (MPI), its utilization in Korea declined in clinical fields due to multifactorial reasons including clinical preferences, incompetencies in nuclear medicine practices, economic issues (camera occupation, relatively affordable invasive coronary angiography, etc.), and other competitive modalities. However, the number of MPI began to increase in the early 2010s. Although the increase is modest relative to the 1990s, the total number of nuclear cardiology studies reached over 100,000 in 2019, with the majority (> 80,000) focusing on myocardial perfusion SPECT (Fig. 1).

The first abstract presented at the KSNM scientific meeting was entitled "Measurement of cardiac output with RISA" by Suh et al. (1967) [6], while the first research paper was entitled "A comparative study of the cardiac output measurement with RIHSA and ^{131}I-hippuran" by Lee et al. (1970) [7]. Many studies concentrated on CAD in the late 1980s to the early 2000s parallel to the introduction of stress testing protocols and myocardial perfusion radiotracers: 78% (76/97) of KSNM abstracts investigated CAD until 2005. However, taking advantage of molecular imaging developments, many radiotracers have become clinically available and highlighted, leading to an increase in non-CAD studies. During the last 15 years, 37% of the KSNM abstracts and 43% of nuclear cardiology research papers were related to non-coronary diseases (Fig. 2). The major academic achievements of Korean investigators are reviewed in the following section.

Academic Achievements

CAD

CAD remains the most investigated disease entity in the history of nuclear cardiology in Korea. In addition to the earliest studies that analyzed planar imaging-based blood pool scans, the SPECT imaging technique had already been used since the introduction of MPI in Korea [14]. During this period, MPI research sought to define and understand various imaging findings on tomographic orientation [14–18]. In addition, different radiotracers [19] and stress protocols [20, 21] were compared, introduced within a relatively short period (Table 1). Both perfusion and non-perfusion information (e.g., wall motion and volume parameters on gated images) were analyzed, which are still considered clinically important.

Since the 2000s, Korean investigators have been elevating their research competencies globally as several studies using Tl-201 myocardial perfusion SPECT were published in international journals. They found that the more marked perfusion defects on Tl-201 myocardial perfusion SPECT were associated with increased left ventricular remodeling [22] and typical angina [23]. Furthermore, Chun et al. [24] found that the size of the perfusion defect may be less extensive in the adenosine-5′-triphosphate stress test than in the adenosine stress, underestimating the hemodynamic significance of CAD. In 2009, a multicenter study investigating patients from five domestic institutions [25] compared the diagnostic performances of standalone myocardial perfusion SPECT and hybrid SPECT/computed tomography angiography (CTA) images. They found that the latter showed significantly improved diagnostic

Table 1 Major events in history of Korean nuclear cardiology

Events	Time
Academic	
First abstract at KSNM (Suh et al. "Measurement of cardiac output with RISA [6]")	1967
First research paper (Lee et al. "A comparative study of the cardiac output measurement with RIHSA and ^{131}I-hippuran [7]")	1970
Korean Study Group on Nuclear Cardiology established	2002 [4]
Equipments	
Gamma cameras	1969 [1]
First SPECT camera	1980 [4]
Multi-headed SPECT camera	1991 [4]
PET cameras	1994 [4]
CZT SPECT camera	2015
Imaging studies	
Single-pass cardiac study	1971 [4]
Dynamic heart study	1979 [4]
Tl-201 MPI	1983 [5]
Exercise stress MPI	1984 [8]
Dipyridamole stress MPI	1985 [9]
Tc-99 m MIBI MPI	1988*
Adenosine stress MPI	1991 [10]
PET MPI	
Rb-82	1994 [11]
N-13 ammonia	1997 [12]
O-15 water	1998 [13]
Tc-99 m tetrofosmin MPI	1999**
Insurance	
Coverage for FDG viability testing in ischemic heart disease	2006
N-13 ammonia PET officially listed as a non-reimbursable item	2015
Coverage for preoperative myocardial perfusion SPECT in intermediate-to-high-risk surgeries	2020

KSNM Korean Society of Nuclear Medicine; *RI(H)SA* radioiodinated human serum albumin; *MIBI* methylisobutylisonitrile; *FDG* fluorodeoxyglucose; *CZT* cadmium-zinc-telluride; *MPI* myocardial perfusion imaging; *SPECT* single-photon emission computed tomography; *PET* positron emission tomography

*From the annual KSNM online survey database

**Based on consultation to the import permit issued by the Korean Food and Drug Administration and consultation to the importing company

accuracy, leading to changes in the diagnosis in 37.5% of the cases. Despite being the first multicenter study of the history of nuclear cardiology in Korea, it remains as one of the leading studies in the era of multimodality imaging. Relatively large-scale studies were performed in 2010s regarding the treatment decision making in CAD, demonstrating the genuine values of MPI. Accordingly, MPI could significantly improve patients' prognosis as the initial test for the evaluation of stable CAD [26] and as the guide for revascularization in multivessel CAD [27]. Studies in the late 2010s highlighted the prognostic value of phase analysis using myocardial perfusion SPECT [28] and MBF quantification using cadmium-zinc-telluride SPECT camera [29], further expanding the use of myocardial perfusion SPECT in various CAD scenarios.

Myocardial perfusion PET studies were already performed in the mid-1990s. During this period, the radiotracers available included O-15 water, N-13 ammonia, and even Rb-82, which is now widely used in the USA [11]. MBF quantification using PET was investigated [13, 30, 31], and novel F-18-labeled radiotracers were also tested to overcome the shortcomings of the Rb-82 generator [32]. Despite active research with state-of-the-art techniques on myocardial perfusion PET, its use did not translate to daily clinical practice. Although the exact introduction of myocardial perfusion PET in clinical practice in Korea is unclear, the first official

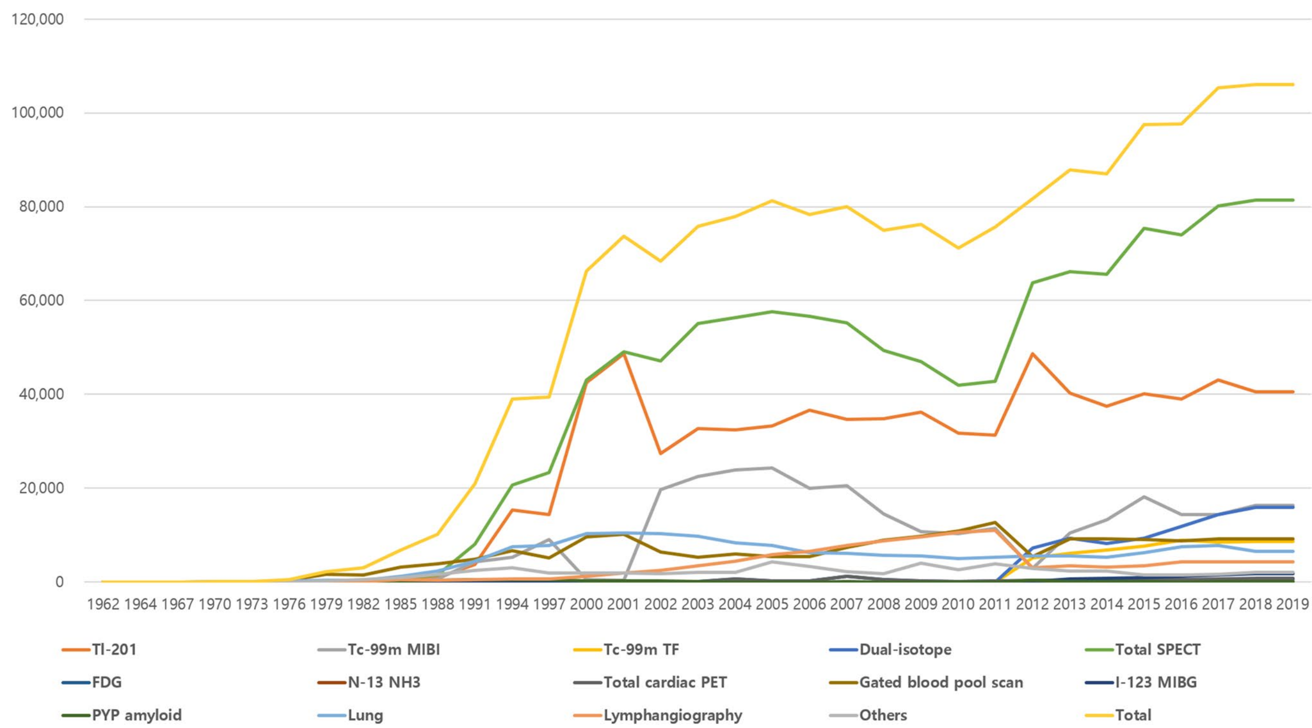

Fig. 1 Trends in nuclear cardiovascular imaging studies in Korea*. The total number of studies shows a rapid increase from 1980 to 2000, followed by a 10-year plateau. Beginning in 2011, an increase in the number of studies is seen mainly due to Tl-201 and dual-isotope SPECT. *Data are from the annual KSNM online survey database. KSNM, Korean Society of Nuclear Medicine; MIBI, methylisobutylisonitrile; TF, tetrofosmin; SPECT, single-photon emission computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; MIBG, metaiodobenzylguanidine; PYP, pyrophosphate

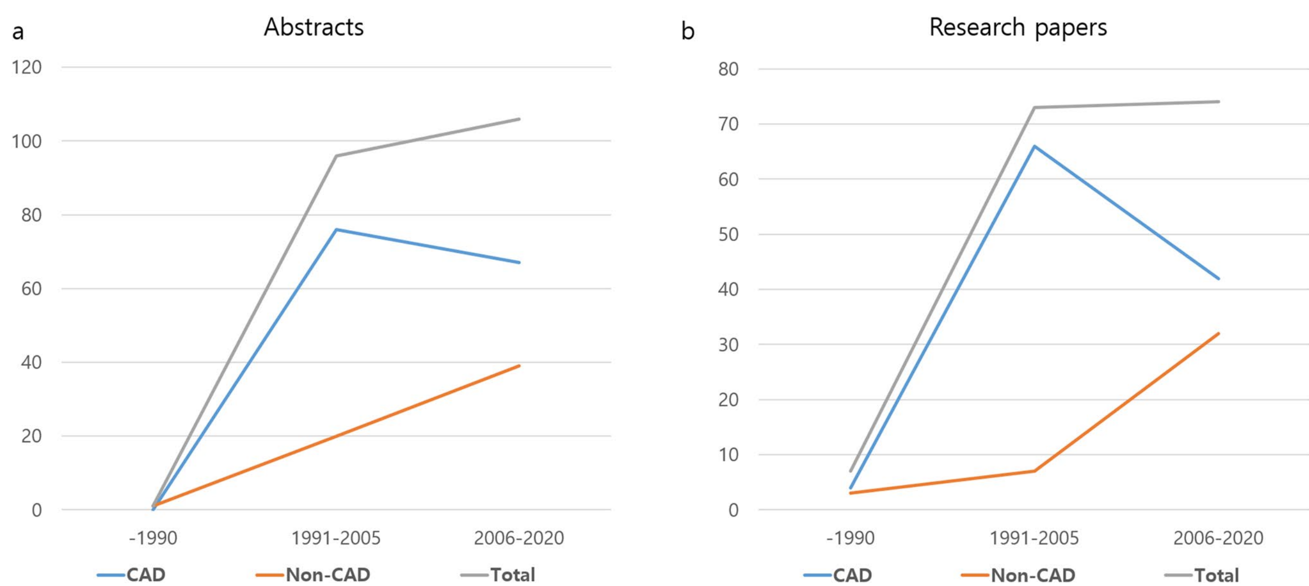

Fig. 2 Trends in nuclear cardiology research by Korean investigators according to disease entities.* The number of abstracts presented at KSNM scientific meetings (**a**) and the research papers published by Korean investigators (**b**) is presented in 15-year intervals. The initial rapid increase in nuclear cardiology research mainly focused on coronary artery disease until 1990. However, the proportion of studies on non-coronary diseases has consistently grown, reaching 37% of abstracts and 43% in research papers. *Data are based on KSNM archive of the Korean Journal of Nuclear Medicine, Springer online archive of Nuclear Medicine and Molecular Imaging, online reference search with specified keywords (and their combinations) including "myocardium," "heart," "cardiac," "nuclear medicine," and "Korea", and provided references from the authors

statistics of N-13 ammonia PET studies (research purposes) appeared in 2013, and the other PET radiotracers are still clinically unavailable. Even N-13 ammonia PET was not available for clinical use until it was listed as a non-reimbursed item in 2015. This took over 20 years from the first installation of cyclotron in 1984 and PET cameras in 1994. In terms of cost-effectiveness, myocardial perfusion PET is considered to be inferior to oncologic FDG PET which has received national insurance coverage since 2006. In addition, the short half-life and the need for an on-site cyclotron (or Rb-82 generator) could not match the widely available myocardial perfusion SPECT.

Nevertheless, many fundamental studies on the clinical application of myocardial perfusion PET have been conducted by Korean investigators. Choi et al. [33] established a compartment model for MBF quantification using N-13 ammonia PET. Moreover, the mathematical modeling for O-15 water PET was developed and improved by Korean investigators [34–38] (Fig. 3). These outstanding advances have been implemented in clinical and/or research software packages as part of the technical standards for myocardial perfusion PET image analyses.

Novel F-18-labeled radiotracers were actively developed throughout the 2010s. Representatively, the triphenylphosphonium cation, a mitochondrial voltage sensor, provided a chemical motive to develop a series of myocardial perfusion PET radiotracers [39–45] to overcome the short half-lives of the currently available PET radiotracers. Regarding that the first F-18-labeled radiotracer F-18 flurpiridaz has recently shown promising results in phase-III clinical trial in the USA [46], the novel radiotracers developed by Korean investigators are also expected to help bring myocardial perfusion PET into clinics, regardless of the availability of an on-site cyclotron. The PET-measured MBF parameters were clinically evaluated in the late 2010s. Based on the comparisons with diameter stenosis and fractional flow reserve, relative flow reserve (the ratio of MBF measured in the area of interest to that measured in the reference area) was found to correlate better with the severity of a focal stenosis [47, 48]. A meta-analysis performed by two Korean institutions [49] also found that relative flow reserve was the most specific MBF parameter for diagnosing significant coronary stenosis, while hyperemic MBF was the most sensitive. The inherent lack of anatomical information for PET has recently raised the need for more lesion-specific MBF measurements. An international prospective trial with the participation of three Korean institutions is evaluating the value of lesion-specific MBF measurement using hybrid imaging [50].

Non-CAD

Active investigations have not been limited to CAD but have also covered many non-coronary cardiovascular disorders. Earlier nuclear cardiology imaging modalities included single-pass radionuclide cardiac angiography and gated blood pool scan. Using single-pass radionuclide cardiac angiography, congenital cardiopulmonary shunt was accurately detected: preoperative shunt detection rate reached 95.4% and postoperative imaging could detect remnant shunts in 5.1% [1]. For valvular heart diseases, gated blood pool scan was used to measure both ventricular volumetric parameters [51, 52].

Cardiomyopathies were studied using various nuclear imaging modalities. Cardiac sympathetic innervation imaging with I-123 meta-iodobenzylguanidine (MIBG) scintigraphy was used to evaluate patients with different cardiomyopathies in 1993 [53]. Prediction of functional improvement of dilated cardiomyopathy after medical treatment with

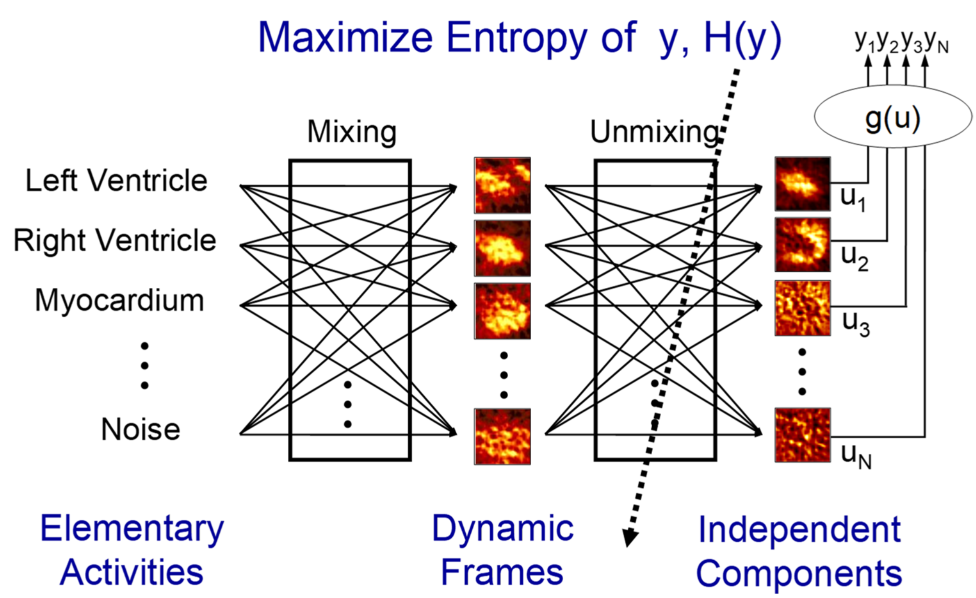

Fig. 3 Blind source separation in O-15 water PET*. Using independent component analysis, Lee et al. defined regions of interest for cardiac structures on O-15 water PET images, eliminating the need for arterial blood sampling or additional radiation exposure from carbon monoxide blood volume scanning. Reprinted from Lee et al. [36] with permission. **This research was originally published in JNM. Lee et al. Blind separation of cardiac components and extraction of input function from H215O dynamic myocardial PET using independent component analysis. J Nucl Med. 2001;42:938–43. © SNMMI*

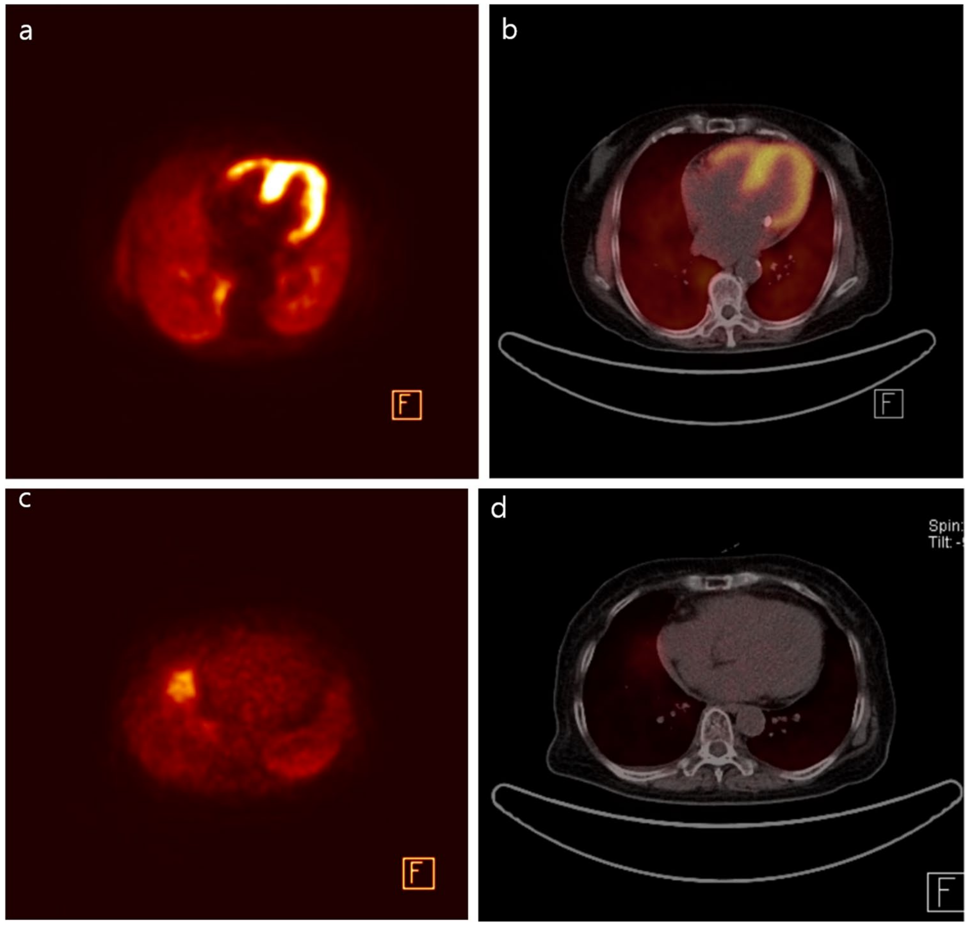

Fig. 4 C-11 PiB PET in cardiac amyloidosis. A 75-year-old woman with renal amyloidosis showing strong myocardial uptake on cardiac screening with C-11 PiB PET (**a**, **b**). The myocardial SUV was 11.5, and endomyocardial biopsy revealed cardiac involvement in light chain amyloidosis. In contrast, a 70-year-old woman with underlying multiple myeloma did not show significant myocardial uptake on C-11 PiB PET (**c**–**d**). The myocardial SUV was 1.7, and endomyocardial biopsy did not reveal any evidence of amyloidosis involvement on Congo red staining. SUV, standardized uptake value; PiB, Pittsburgh compound B

I-123 MIBG scintigraphy [54] preceded the ADMIRE-HF trial [55], a large prospective trial in the USA, by 9 years. Because of the difficulty of diagnosis and subtyping in clinical practice, Lee et al. [56] evaluated the value of C-11 Pittsburgh compound B (PiB) to diagnose the light chain (AL) subtype of cardiac amyloidosis (Fig. 4). In addition to its original purpose of detecting cerebral amyloid deposition (e.g., Alzheimer's dementia), C-11 PiB could visualize cardiac amyloidosis and differentiate chemotherapy-naïve patients from those with previous chemotherapy and normal controls. This study demonstrated the genuine value of Alzheimer's PET radiotracers in diagnosing cardiac amyloidosis. Now, PET positive findings using these compounds are currently considered as one of the imaging criteria for diagnosing cardiac amyloidosis [57]. Furthermore, Korean investigators also conducted a meta-analysis and proved excellent performance of PET imaging in the diagnosis of cardiac amyloidosis [58]. Bone scintigraphy is another effective nuclear imaging modality in the visualization of cardiac amyloidosis caused by transthyretin amyloid (ATTR) deposition [59]. A prospective study by KSNM investigators analyzed 21 patients with systemic amyloidosis, 16 of whom having cardiac involvement, and found differential intensity of abnormal organ uptake for ATTR vs. AL amyloidosis (ATTR > AL). Also, additional SPECT imaging could determine the actual intensity of equivocal cardiac uptake on planar imaging in more than half of the patients with cardiac involvement. Cancer therapeutics-related cardiac dysfunction (CTRCD) is another type of cardiomyopathy gaining clinical relevance. The availability of oncologic FDG PET after completion of chemotherapy and/or radiotherapy in Korea has allowed researchers to evaluate myocardial FDG uptake in the management of CTRCD. Their findings revealed that right ventricular FDG uptake was predictive of CTRCD after chemotherapy, with or without radiotherapy, for breast cancer [60]. In addition, increased myocardial FDG uptake was associated with a higher cardiac irradiation dose [61]. With the improvements in cancer survival, more patients affected by CTRCD will need appropriate diagnostic tools. Studies by Korean investigators can shed light on the role of nuclear imaging in the management of CTRCD.

The first nuclear medicine research on atherosclerosis looked at the therapeutic application of the radioisotope Ho-166. In 2003, a Ho-166-coated, beta-emitting balloon showed inhibiting effect on porcine coronary stent restenosis [62]. The clinical application of radioactive balloon was also promising. Local radiation using intravascular balloon filled with Re-188 brought significant enlargement in vessel lumen and external elastic membrane of the coronary arteries [63, 64], showing favorable prognosis [65, 66]. Although radioactive balloons and stents were extensively tested from the late 1990s to the early 2000s, evolving generations of drug-eluting stents have become the mainstay of percutaneous coronary intervention, limiting the clinical applications of radioactive balloons/stents. Subsequent studies on nuclear imaging have concentrated on the atherosclerotic activity of large vessels using FDG PET, which is unaffected by the partial-volume effect and physiologic myocardial uptake, making it less challenging to visualize the small coronary branches. FDG uptake of the large vessels (e.g., aorta or carotid arteries) could reflect cardiovascular risks [67–69] and predict future coronary calcification [70] and the occurrence of ischemic stroke in cancer patients [71]. Recently, serial PET scans showed pathophysiological links between atherosclerotic activity, psychological stress, macrophage hematopoiesis, and acute myocardial infarction [72]. FDG uptake in the spleen, bone marrow, or visceral fat was also associated with acute cardiovascular events [73, 74]. More recent studies utilized F-18 NaF to visualize atherosclerotic plaques in the coronary arteries. Positive F-18 NaF uptake was associated with adverse plaque characteristics on intravascular ultrasound and optical coherence tomography, including higher plaque burden, positive remodeling, higher maximum lipid arc, and more frequent microvessels [75]. Interestingly, compared to 1-h image, 3-h images were superior in terms of target-to-background contrast and plaque activity visualization [76]. F-18 NaF PET was also used for measuring the calcification activity of the descending thoracic aorta, showing significant associations with cardiovascular risk factors in patients with CAD [77]. However, plaque uptake of FDG and F-18 NaF was prevalent among the carotid arteries with insignificant difference between either culprit or non-culprit carotids [78].

The capability of FDG PET to detect cardiovascular inflammatory/infectious diseases has also been studied due to its ability to visualize active inflammation in acute myocardial infarction [79] and pericarditis [80, 81]. In particular, the treatment response prediction using FDG PET is expected to play an important role in deciding whether surgical or medical treatment is more appropriate in constrictive pericarditis [80]. A new radiotracer, Ga-68 mannosylated human serum albumin, has also proved its value in visualizing inflammation in pulmonary hypertension [82].

F-18 glycoprotein (GP)-1 is a thrombus imaging radiotracer that targets GP IIb/IIIa which is the key factor in platelet aggregation [83], first synthesized in 2017. Two phase-1 trials on its use for venous thromboembolism and acute arterial thrombosis were conducted in Korea [84, 85], and the results were promising for both indications, highlighting the role of PET imaging in thrombotic diseases which had mostly been occupied by CTA. Furthermore, Tc-99m-labeled nanoparticles that can deliver and visualize angiogenic peptides in hindlimb and myocardial ischemia models have also shown the application of nuclear medicine techniques in treating peripheral artery disease [86–88].

In relation to patient safety, radiation dose reduction is another important issue in nuclear cardiology. As such, Korea has actively participated in the international collaborations led by the International Atomic Energy Agency Nuclear Cardiology Protocol Study [89–91]. The data from the Asian region indicate that adherence to the best practices in patients' radiation exposure is not satisfactory because of the low rate of stress-only imaging and weight-based dosing [89]. Therefore, the role of the KSNM in establishing individualized protocols and dosing is becoming more important as a leading country in the nuclear cardiology of the Asian region.

Summary and Perspectives

The introduction of planar first-pass angiocardiography studies using single-head gamma cameras in the 1970s ushered in nuclear cardiology in Korea. Furthermore, the use of MPI initially with Tl-201 was introduced in the 1980s, later with Tc-99 m-labeled tracers, led to an explosive growth of nuclear medicine in the 1990s. Of note, Korean nuclear medicine physicians did not experience planar MPI as SPECT cameras were introduced during the height of the former's popularity in the early 1990s. Although PET perfusion tracers, such as O-15 water and N-13 ammonia, and very rarely Rb-82, have been utilized since the beginning of nuclear cardiology in Korea, PET MPI has not gained popularity until now. Adenosine infusion is the preferred majority of stress tests in Korea. The history of nuclear cardiology tests has had three phases: rapid growth in the 1990s, a plateau in the 2000s, and slow regrowth in the 2010s.

The application of nuclear cardiology to diseases other than CAD has been gaining traction in Korea. Infectious and inflammatory diseases, such as infective endocarditis, myocarditis, and pericarditis, are common indications of nuclear cardiology studies. Meanwhile, cardiomyopathies due to infiltrative etiologies are more novel indications of both SPECT and PET studies. A similar trend has been observed in research activities. Korean investigators are developing novel radiotracers for new applications in nuclear cardiology. The KSNC is the heart of nuclear cardiology research and education in the Korean nuclear medicine community.

Nuclear cardiology is expected to attract more research interest from younger Korean nuclear medicine professionals.

Author Contribution Sang-Geon Cho and Eun Jung Kong: historical data collection and analyses, primary writing.

Won Jun Kang, Jin Chul Paeng, Hee-Seung Henry Bom, and Ihnho Cho: data review and approval, critical manuscript revisions.

Funding This work was supported by a grant (NRF-2016R1D1A3B01006631) from the Basic Science Research Program of the National Research Foundation (NRF) funded by the Ministry of Education, Republic of Korea.

Availability of Data and Materials.

The statistical data in our manuscript will not be shared as they are securely administrated by the Korean Society of Nuclear Medicine (KSNM).

Declarations

Conflict of Interest Hee-Seung Henry Bom received research funding from the NRF, funded by the Ministry of Education, Republic of Korea. Sang-Geon Cho, Eun Jung Kong, Won Jun Kang, Jin Chul Paeng, and Ihnho Cho declare that they have no competing interests.

Ethics Approval and Consent to Participate This work does not contain any studies with human participants or animals performed by any of the authors.

Consent for Publication Not applicable.

References

1. Koh CS. The historical background and current status of nuclear cardiology in Korea. Korean J Nucl Med. 1986;20:1–7.
2. Lee M. The present status of nuclear medicine in Korea. Korean J Nucl Med. 1968;2:9–14.
3. Koh CS. Development history and current status of nuclear medicine in Korea. Korean J Nucl Med. 1979;13:1–5.
4. Korean Society of Nuclear Medicine. The 50-year history of the Korean Society of Nuclear Medicine. 2011. https://www.ksnm.or.kr/member/50th.pdf. Accessed 4 June 2021.
5. Lee M, Koh CS. Nuclear medicine application in Seoul National University Hospital: 1964–1986. Korean J Nucl Med. 1988;22:1–14.
6. Suh HJ, Lee JK, Lee M. Measurement of cardiac output with RISA. Korean J Nucl Med. 1967;1:S106.
7. Lee AK, Kil KS, Park JY, Kim DS, Kim JI, Koh CS. A comparative study of the cardiac output measurement with RIHSA and ^{131}I-hippuran. Korean J Nucl Med. 1970;4:73–6.
8. Chung NS, Cho SY, Jang YS, Park KS, Shim WH, Lee WK. Comparative study on stress electrocardiography and thallium-201 stress myocardial scintigraphic imaging in coronary artery disease. Korean Circ J. 1986;16:27–36.
9. Woo Y, Baek Y, Kim E, Lee H, Kim J, Lee H, et al. Dipyridamole thallium-201 myocardial scan. Korean J Nucl Med. 1986;20:128.
10. Lee SC, Lee BR, Chae SC, Jun JE, Park WH, Lee J, et al. Diagnostic value of Tc-99m MIBI myocardial perfusion scintigraphy during maximal coronary artery dilation with adenosine in coronary artery disease. Korean Circ J. 1992;22:956–67.
11. Jeong JM, Chung JK, Lee DS, Kwark CE, Lee KH, Lee MC, et al. Preparation of ^{82}Sr/^{82}Rb generator and positron emission tomographic image of normal volunteer. Korean J Nucl Med. 1994;28:326–30.
12. Kim BT, Kim SE, Kim JY, Choi Y, Lee KH, Choe YS, et al. A refined method for quantification of myocardial blood flow using N-13 ammonia and dynamic PET. Korean J Nucl Med. 1997;31:73–82.
13. Koh CS, Lee MC, Chung JK, Lee DS, Jeong JM, Shin SA, et al. The heterogeneity of flow distribution and partition coefficient in ^{15}O–H_2O myocardium positron emission tomography. Korean J Nucl Med. 1998;32:32–49.
14. Koh EM, Lee KH, Um JH, Kim MA, Oh BH, Park YB, et al. Myocardial SPECT imaging of post-infarction ventricular aneurysm. Korean J Nucl Med. 1989;23:19–25.
15. Kim SE, Nam GB, Choi CW, Choi KJ, Lee DS, Sohn DW, et al. Quantitative analysis of thallium-201 myocardial tomograms. Korean J Nucl Med. 1991;25:165–76.
16. Lee JT, Lee KB, Heo J, Iskandrian AS. Variations in the size of the ischemic myocardium due to differences in the normal file. Korean J Nucl Med. 1992;26:49–57.
17. Lee MC, Chung JK, Lee YW, Seo JD, Park YB, Lee DS, et al. Comparison between myocardial perfusion and function in rest state in coronary artery disease - dipyridamole ^{99m}Tc-MIBI SPECT and rest gated blood pool scan. Korean J Nucl Med. 1992;26:265–73.
18. Kim KW, Kim DY, Park MJ, Choi TY, Kang HS, Choue CW, et al. Clinical characteristics and findings of ^{99m}Tc-MIBI heart SPECT in patients with acute myocardial infarction with normal coronary arteriography. Korean J Nucl Med. 1993;27:65–70.
19. Kim JY, Bom HS, Park JH, Ahn Y, Jeong MH, Cho JG, et al. Comparison of ^{99m}Tc-MIBI myocardial uptake at rest with reinjection and 24-hour after reinjection images of ^{201}Tl. Korean J Nucl Med. 1992;26:274–9.
20. Lee KB, Lee JT, Park WH, Chung BC, Choi CI, Jun JE, et al. Adenosine ^{99m}Tc-MIBI scintigraphy in the diagnosis of coronary artery disease: comparison with exercise ^{99m} Tc-MIBI scintigraphy. Korean J Nucl Med. 1992;26:72–81.
21. Lee KB, Lee JT, Chung BC, Chae SC, Kwak DS, Choi JI, et al. Myocardial uptake and clearance of thallium-201 in normal subjects: a comparison between pharmacologic stress with intravenous adenosine. Korean J Nucl Med. 1993;27:35–50.
22. Choi JY, Moon DH, Lee CW, Shin JW, Park SW, Hong MK, et al. Prediction of left ventricular dilatation with thallium-201 SPET imaging after primary angioplasty in patients with acute myocardial infarction. Eur J Nucl Med. 2002;29:728–34.
23. Lee SJ, Lee KH, Park SM, Lee EJ, Chung HW, Cho YS, et al. Myocardial perfusion defects and coronary risk factors in symptomatic and asymptomatic elderly women. Int J Cardiovasc Imaging. 2008;24:277–81.
24. Chun KA, Lee J, Lee SW, Ahn BC, Ha JH, Cho IH, et al. Direct comparison of adenosine and adenosine 5’-triphosphate as pharmacologic stress agents in conjunction with Tl-201 SPECT: hemodynamic response, myocardial tracer uptake, and size of perfusion defects in the same subjects. J Nucl Cardiol. 2006;13:621–8.
25. Kong EJ, Cho IH, Kang WJ, Kim SM, Won KS, Lim ST, et al. Added value of 3D cardiac SPECT/CTA fusion imaging in patients with reversible perfusion defect on myocardial perfusion SPECT. Nucl Med Mol Imaging. 2009;43:513–8.
26. Park GM, Kim YH, Yun SC, Ahn JM, Choi HI, Roh JH, et al. Anatomic or functional evaluation as an initial test for stable coronary artery disease: a propensity score analysis. J Nucl Med. 2016;57:1364–9.
27. Kim YH, Ahn JM, Park DW, Song HG, Lee JY, Kim WJ, et al. Impact of ischemia-guided revascularization with myocardial

perfusion imaging for patients with multivessel coronary disease. J Am Coll Cardiol. 2012;60:181–90.
28. Cho SG, Jabin Z, Park KS, Kim J, Kang SR, Kwon SY, et al. Clinical values of left ventricular mechanical dyssynchrony assessment by gated myocardial perfusion SPECT in patients with acute myocardial infarction and multivessel disease. Eur J Nucl Med Mol Imaging. 2017;44:259–66.
29. Han S, Kim YH, Ahn JM, Kang SJ, Oh JS, Shin E, et al. Feasibility of dynamic stress ^{201}Tl/rest ^{99m}Tc-tetrofosmin single photon emission computed tomography for quantification of myocardial perfusion reserve in patients with stable coronary artery disease. Eur J Nucl Med Mol Imaging. 2018;45:2173–80.
30. Koh CS, Lee MC, Chung JK, Lee DS, Seo JD, Jeong JM, et al. A study on the estimation of regional myocardial blood flow in experimental canine model with coronary thrombosis using Rb-82 dynamic myocardial positron emission tomography. Korean J Nucl Med. 1995;29:48–53.
31. Kim SE, Kim JY, Choi Y, Lee KH, Choe YS, Kim JH, et al. Quantification of myocardial blood flow using dynamic N-13 ammonia PET and factor analysis. Korean J Nucl Med. 1999;33:327–37.
32. Yu KH. Synthesis and ^{18}F labelling organic ammonium salts to new cardiac flow tracer for PET and their biodistribution. Korean J Nucl Med. 1994;28:326–30.
33. Choi Y, Huang SC, Hawkins RA, Kim JY, Kim BT, Hoh CK, et al. Quantification of myocardial blood flow using N-13-ammonia and PET: comparison of tracer models. J Nucl Med. 1999;40:1045–55.
34. Ahn JY, Lee DS, Lee JS, Kim SK, Cheon GJ, Yeo JS, et al. Quantification of regional myocardial blood flow using dynamic ($H_2{}^{15}O$ PET and factor analysis. J Nucl Med. 2001;42:782–7.
35. Lee JS, Lee DS, Ahn JY, Yeo JS, Cheon GJ, Kim SK, et al. Generation of parametric image of regional myocardial blood flow using $H_2{}^{15}O$ dynamic PET and a linear least-squares method. J Nucl Med. 2005;46:1687–95.
36. Lee JS, Lee DS, Ahn JY, Cheon GJ, Kim SK, Yeo JS, et al. Blind separation of cardiac components and extraction of input function from $H_2{}^{15}O$ dynamic myocardial PET using independent component analysis. J Nucl Med. 2001;42:938–43.
37. Lee JS, Lee DS, Ahn JY, Cheon GJ, Kim SK, Yeo JS, et al. Parametric image of myocardial blood flow generated from dynamic $H_2{}^{15}O$ PET using factor analysis and cluster analysis. Med Biol Eng Comput. 2005;43:678–85.
38. Lee BI, Lee JS, Lee DS, Choi SJ. Myocardial blood flow quantification in dynamic PET: an ensemble ICA approach. 2005. http://mlg.postech.ac.kr/static/publications/inter_conf/2005/icann05_bilee.pdf. Accessed 4 June 2021.
39. Kim DY, Kim HJ, Yu KH, Min JJ. Synthesis of [^{18}F]-labeled (6-fluorohexyl)triphenylphosphonium cation as a potential agent for myocardial imaging using positron emission tomography. Bioconjugate Chem. 2012;23:431–7.
40. Kim DY, Kim HJ, Yu KH, Min JJ. Synthesis of [^{18}F]-labeled (2-(2-fluoroethoxy)ethyl)tris(4-methoxyphenyl)phosphonium cation as a potential agent for positron emission tomography myocardial imaging. Nucl Med Biol. 2012;39:1093–8.
41. Kim DY, Kim HJ, Yu KH, Min JJ. Synthesis of [^{18}F]-labeled (2-(2-fluoroethoxy)ethyl)triphenylphosphonium cation as a potential agent for myocardial imaging using positron emission tomography. Bioorg Med Chem Lett. 2012;22:319–22.
42. Kim DY, Kim HS, Jang HY, Kim JH, Bom HS, Min JJ. Comparison of the cardiac microPET images obtained using [F-18]FPTP and [N-13]NH_3 in rat myocardial infarction models. ACS Med Chem Lett. 2014;5:1124–8.
43. Kim DY, Kim HS, Min JJ. Radiosynthesis and evaluation of ^{18}F-labeled aliphatic phosphonium cations as a myocardial imaging agent for positron emission tomography. Nucl Med Commun. 2015;36:747–54.
44. Kim DY, Kim HS, Min JJ. Comparison of ^{18}F-labeled fluoroalkylphosphonium cations with ^{13}N-NH_3 for PET myocardial perfusion imaging. J Nucl Med. 2015;56:1581–6.
45. Kim DY, Min JJ. Synthesis and evaluation of ^{18}F-labeled fluoroalkyl triphenylphosphonium salts as mitochondrial voltage sensors in PET myocardial imaging. Methods Mol Biol. 2015;1265:59–72.
46. Maddahi J, Lazewatsky J, Udelson JE, Berman DS, Beanlands RSB, Heller GV, et al. Phase-III clinical trial of fluorine-18 flurpiridaz positron emission tomography for evaluation of coronary artery aisease. J Am Coll Cardiol. 2020;76:391–401.
47. Lee JM, Kim CH, Koo BK, Hwang D, Park J, Zhang J, et al. Integrated myocardial perfusion imaging diagnostics improve detection of functionally significant coronary artery stenosis by ^{13}N-ammonia positron emission tomography. Circ Cardiovasc Imaging. 2016;9:e004768.
48. Cho SG, Park KS, Kim J, Kang SR, Song HC, Kim JH, et al. Coronary flow reserve and relative flow reserve measured by N-13 ammonia PET for characterization of coronary artery disease. Ann Nucl Med. 2017;31:144–52.
49. Cho SG, Lee SJ, Na MH, Choi YY, Bom HHS. Comparison of diagnostic accuracy of PET-derived myocardial blood flow parameters: a meta-analysis. J Nucl Cardiol. 2020;27:1955–66.
50. AlBadri A, Piccinelli M, Cho SG, Lee JM, Jaber W, De Cecco CN, et al. Rationale and design of the quantification of myocardial blood flow using dynamic PET/CTA-fused imagery (DEMYSTIFY) to determine physiological significance of specific coronary lesions. J Nucl Cardiol. 2020;27:1030–9.
51. Shin S, Chung J, Lee M, Cho B, Seo J, Lee Y, et al. Measurement of the left ventricular regurgitation by gated cardiac blood pool scan: before and after valvular replacement surgery. Korean J Nucl Med. 1982;16:29–36.
52. Sohn I, Shin S, Lee M, Seo J, Koh C, Lee M. Right ventricular ejection fraction measured with gated cardiac blood pool scan in mitral valve diseases. Korean J Med Assoc. 1983;26:151–5.
53. Lee DY, Lee JD, Kim SJ, Park CY, Cho SY, Ham JK, et al. Evaluation of sympathetic innervation in cardiomyopathy with ^{123}I - MIBG. Korean J Nucl Med. 1993;27:195–202.
54. Choi JY, Lee KH, Hong KP, Kim BT, Seo JD, Lee WR, et al. Iodine-123 MIBG imaging before treatment of heart failure with carvedilol to predict improvement of left ventricular function and exercise capacity. J Nucl Cardiol. 2001;8:4–9.
55. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. J Am Coll Cardiol. 2010;55:2212–21.
56. Lee SP, Lee ES, Choi H, Im HJ, Koh Y, Lee MH, et al. ^{11}C-Pittsburgh B PET imaging in cardiac amyloidosis. JACC Cardiovasc Imaging. 2015;8:50–9.
57. Dorbala S, Ando Y, Bokhari S, Dispenzieri, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 2 of 2-Diagnostic criteria and appropriate utilization. J Nucl Cardiol. 2020;27:659–73.
58. Kim YJ, Ha S, Kim Y-I. Cardiac amyloidosis imaging with amyloid positron emission tomography: a systematic review and meta-analysis. J Nucl Cardiol. 2020;27(1):123–32. https://doi.org/10.1007/s12350-018-1365-x.

59. Paeng JC, Choi JY. Nuclear Imaging for cardiac amyloidosis: bone scan, SPECT/CT, and amyloid-targeting PET. Nucl Med Mol Imaging. 2021;55:61–70.
60. Kim J, Cho SG, Kang SR, Yoo SW, Kwon SY, Min JJ, et al. Association between FDG uptake in the right ventricular myocardium and cancer therapy-induced cardiotoxicity. J Nucl Cardiol. 2020;27:2154–63.
61. Jo IY, Lee JW, Kim WC, Min CK, Kim ES, Yeo SG, et al. Relationship between changes in myocardial F-18 fluorodeoxyglucose uptake and radiation dose after adjuvant three-dimensional conformal radiotherapy in patients with breast cancer. J Clin Med. 2020. https://doi.org/10.3390/jcm9030666.
62. Kim W, Jeong MH, Park OY, Rhew JY, Bom HS, Choi SJ, et al. Effects of beta-radiation using a holmium-166 coated balloon on neointimal hyperplasia in a porcine coronary stent restenosis model. Circ J. 2003;67:625–9.
63. Hong MK, Park SW, Moon DH, Oh SJ, Lee CW, Kim YH, et al. Intravascular ultrasound analysis of nonstented adjacent segments in diffuse in-stent restenosis treated with radiation therapy with a rhenium-188-filled balloon. Catheter Cardiovasc Interv. 2003;58:428–33.
64. Koo BK, Lee MM, Oh S, Chae IH, Kim HS, Sohn DW, et al. Effects of beta-radiation with a ^{188}rhenium-filled balloon catheter system on non-stented adjacent coronary artery segments. Int J Cardiol. 2004;96:73–7.
65. Park S-W, Hong M-K, Moon DH, Oh SJ, Lee CW, Kim J-J, et al. Treatment of diffuse in-stent restenosis with rotational atherectomy followed by radiation therapy with a rhenium-188–mercaptoacetyltriglycine-filled balloon. J Am Coll Cardiol. 2001;38(3):631–7.
66. Lee SW, Park SW, Hong MK, Kim YH, Lee JH, Park JH, et al. Long-term outcomes after treatment of diffuse in-stent restenosis with rotational atherectomy followed by beta-radiation therapy with a ^{188}Re-MAG$_3$-filled balloon. Int J Cardiol. 2005;99:201–5.
67. Noh TS, Moon SH, Cho YS, Hong SP, Lee EJ, Choi JY, et al. Relation of carotid artery ^{18}F-FDG uptake to C-reactive protein and Framingham risk score in a large cohort of asymptomatic adults. J Nucl Med. 2013;54:2070–6.
68. Moon SH, Cho YS, Noh TS, Choi JY, Kim BT, Lee KH. Carotid FDG uptake improves prediction of future cardiovascular events in asymptomatic individuals. JACC Cardiovasc Imaging. 2015;8:949–56.
69. Lee SJ, On YK, Lee EJ, Choi JY, Kim BT, Lee KH. Reversal of vascular ^{18}F-FDG uptake with plasma high-density lipoprotein elevation by atherogenic risk reduction. J Nucl Med. 2008;49:1277–82.
70. Cho SG, Park KS, Kim J, Kang SR, Kwon SY, Seon HJ, et al. Prediction of coronary artery calcium progression by FDG uptake of large arteries in asymptomatic individuals. Eur J Nucl Med Mol Imaging. 2017;44:129–40.
71. Kim J, Choi KH, Song HC, Kim JT, Park MS, Cho KH. ^{18}F-FDG PET/CT imaging factors that predict ischaemic stroke in cancer patients. Eur J Nucl Med Mol Imaging. 2016;43:2228–35.
72. Kang DO, Eo JS, Park EJ, Nam HS, Song JW, Park YH, et al. Stress-associated neurobiological activity is linked with acute plaque instability via enhanced macrophage activity: a prospective serial 18F-FDG-PET/CT imaging assessment. Eur Heart J. 2021. https://doi.org/10.1093/eurheartj/ehaa1095.
73. Kim EJ, Kim S, Kang DO, Seo HS. Metabolic activity of the spleen and bone marrow in patients with acute myocardial infarction evaluated by ^{18}F-fluorodeoxyglucose positron emission tomograpic imaging. Circ Cardiovasc Imaging. 2014;7:454–60.
74. Pahk K, Kim EJ, Joung C, Seo HS, Kim S. Association of glucose uptake of visceral fat and acute myocardial infarction: a pilot ^{18}F-FDG PET/CT study. Cardiovasc Diabetol. 2020;19:145.
75. Lee JM, Bang JI, Koo BK, Hwang D, Park J, Zhang J, et al. Clinical relevance of ^{18}F-sodium fluoride positron-emission tomography in noninvasive identification of high-risk plaque in patients with coronary artery disease. Circ Cardiovasc Imaging. 2017;10:e006704.
76. Kwiecinski J, Berman DS, Lee SE, Dey D, Cadet S, Lassen ML, et al. Three-hour delayed imaging improves assessment of coronary ^{18}F-sodium fluoride PET. J Nucl Med. 2019;60:530–5.
77. Ryoo HG, Paeng JC, Koo BK, Cheon GJ, Lee DS, Kang KW. Clinical implication of ^{18}F-NaF PET/computed tomography indexes of aortic calcification in coronary artery disease patients: correlations with cardiovascular risk factors. Nucl Med Commun. 2020;41:58–64.
78. Kim JM, Lee ES, Park KY, Seok JW, Kwon OS. Comparison of [^{18}F]-FDG and [^{18}F]-NaF positron emission tomography on culprit carotid atherosclerosis: a prospective study. JACC Cardiovasc Imaging. 2019;12:370–2.
79. Lee WW, Marinelli B, van der Laan AM, Sena BF, Gorbatov R, Leuschner F, et al. PET/MRI of inflammation in myocardial infarction. J Am Coll Cardiol. 2012;59:153–63.
80. Chang SA, Choi JY, Kim EK, Hyun SH, Jang SY, Choi JO, et al. [^{18}F]Fluorodeoxyglucose PET/CT predicts response to steroid therapy in constrictive pericarditis. J Am Coll Cardiol. 2017;69:750–2.
81. Hyeon CW, Yi HK, Kim EK, Park SJ, Lee SC, Park SW, et al. The role of ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography in the differential diagnosis of pericardial disease. Sci Rep. 2020;10:21524.
82. Park JB, Suh M, Park JY, Park JK, Kim YI, Kim H, et al. Assessment of inflammation in pulmonary artery hypertension by Ga-68-mannosylated human serum albumin. Am J Respir Crit Care Med. 2020;201:95–106.
83. Lohrke J, Siebeneicher H, Berger M, Reinhardt M, Berndt M, Mueller A, et al. ^{18}F-GP1, a novel PET tracer designed for high-sensitivity, low-background detection of thrombi. J Nucl Med. 2017;58:1094–9.
84. Kim C, Lee JS, Han Y, Chae SY, Jin S, Sung C, et al. Glycoprotein IIb/IIIa receptor imaging with ^{18}F-GP1 positron emission tomography for acute venous thromboembolism: an open-label, non-randomized, first-in-human phase 1 study. J Nucl Med. 2019;60:244–9.
85. Chae SY, Kwon TW, Jin S, Kwon SU, Sung C, Oh SJ, et al. A phase 1, first-in-human study of ^{18}F-GP1 positron emission tomography for imaging acute arterial thrombosis. EJNMMI Res. 2019. https://doi.org/10.1186/s13550-018-0471-8.
86. Lee TK, Hwang H, Na KS, Kwon J, Jeong HS, Oh PS, et al. Effect of angiogenesis induced by consecutive intramuscular injections of vascular endothelial growth factor in a hindlimb ischemic mouse model. Nucl Med Mol Imaging. 2014;48:225–9.
87. Lee TK, Lee CM, Hwang H, Jeong HS, Oh PS, Kwon J, et al. Scintigraphic evaluation of therapeutic angiogenesis induced by VEGF-loaded chitosan nanoparticles in a rodent model of hindlimb ischemia. Macromol Res. 2015;23:531–6.
88. Hwang H, Kwon J, Oh PS, Lee TK, Na KS, Lee CM, et al. Peptide-loaded nanoparticles and radionuclide imaging for individualized treatment of myocardial ischemia. Radiology. 2014;273:160–7.
89. Einstein AJ, Pascual TNB, Mercuri M, Karthikeyan G, Vitola JV, Mahmarian JJ, et al. Current worldwide nuclear cardiology practices and radiation exposure: results from the 65 country IAEA

Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS). Eur Heart J. 2015;36:1689–96.
90. Hirschfeld CB, Dondi M, Pascual TNB, Mercuri M, Vitola JV, Karthikeyan G, et al. Worldwide diagnostic reference levels for single-photon emission computed tomography myocardial perfusion imaging: findings from INCAPS. JACC Cardiovasc Imaging. 2020. https://doi.org/10.1016/j.jcmg.2020.06.029.
91. Hirschfeld CB, Mercuri M, Pascual TNB, Karthikeyan G, Vitola JV, Mahmarian JJ, et al. Worldwide variation in the use of nuclear cardiology camera technology, reconstruction software, and imaging protocols. JACC Cardiovasc Imaging. 2021. https://doi.org/10.1016/j.jcmg.2020.11.011.