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Nuclear Cardiology in Asia

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Nuclear cardiology for patients with ischemic heart disease and cardiac failure is expanding in Asia, although quite heterogeneously. In Asia, Israel showed the highest utilization with more than 1000 scans/100,000 inhabitants a year followed by Korea, Japan, UAE, Turkey, Australia (250-999 scans/100,000). Saudi Arabia, Kuwait, Jordan, Lebanon, Iran, and Pakistan practiced 60-99 scans/100,000. Most of South East Asian countries, China, India, and Bangladesh practiced 1-50 scans/100,000 per year. Countries in Central Asia, Mongolia, Vietnam, Cambodia, Lao, Myanmar, Nepal, and Bhutan showed limited use or no nuclear cardiology practice. Myocardial perfusion imaging (MPI) in Asia was characterized by more frequent use of ^{201}Tl, less use of weight-based ^{99m}Tc dosing, and a trend toward a lower rate of stress-only imaging. Accordingly, the effective dose in nuclear cardiology practices was higher than those of the rest of the world. ^{99}Mo-^{99m}Tc generators are available in most countries, relying mainly on the global supply chain because there is little supply chain beyond countries within the region. In practice, the threshold values of left ventricular ejection fraction, end-systolic volume, and end-diastolic volume between normal and pathologic states were set based on the regional normal database in China and Japan because these values were dependent on age, gender, and body weight. The purpose of the MPI SPECT study was to evaluate myocardial ischemia in symptomatic patients with chest pain, effects of percutaneous coronary intervention and coronary artery bypass-graft, and cardiac function in patients with chronic heart failure. The ability of ^{99m}Tc-based MPI for predicting hard cardiac events was confirmed in Asian inhabitants with low risk of ischemic heart disease. Human resource development of nuclear medicine professional and public awareness of nuclear medicine is key issues to promote nuclear cardiology in Asia. International organizations such as the International Atomic Energy Agency and academic organizations in the region such as Asia Oceania Federation of Nuclear Medicine and Biology, Asia Regional Cooperative Council for Nuclear Medicine, East Asia Nuclear Medicine Association, and Arab Society of Nuclear Medicine have an important role in addition to national Societies of Nuclear Medicine in each country and region.
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Introduction

Nuclear cardiology is extensively used for the diagnosis of ischemic heart disease and cardiac failure, the decision of therapy strategy, the evaluation of therapy effects, and predicting severe cardiac events.[1,2,3] It is now expanding in Asia, although quite heterogeneously.[4] The International Atomic Energy Agency (IAEA) conducted world-wide survey of nuclear cardiology practice including Asia.[5-7] The reports described radiation exposure and best practice for myocardial perfusion imaging (MPI) in selected centers in the region. Here, the current status of nuclear cardiology practice in Asian countries was widely surveyed by including China and India where approximately 3 billion inhabitants live, and the problems were extracted. Several trials to overcome those and to promote nuclear cardiology are presented.

Ischemic Heart disease in Asia

Based on the WHO measures of member states,[8] mean age-related death rate by all causes in Asia was quite heterogeneous

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among countries and regions between 349.3 (Japan) and 1978.2 (Afghanistan) per 100,000 inhabitants (Table 1). The age-standardized death rate (ASDR) by ischemic heart disease was low in East Asia, Israel, and Sri Lanka whereas high in Central Asia, moderately high in South Asia (except Sri Lanka), and moderate in West Asia (except Israel) and South East Asia. Mean ratio of ASDR $_{\text{ischemic heart disease}}$ to ASDR $_{\text{all causes}}$ was 0.292 in Central Asia, 0.205 in West Asia, 0.170 in South Asia, 0.143 in South East Asia, and 0.092 in East Asia (WHO website).

Nuclear Medicine Centers and Facilities in Asia

Distribution of nuclear medicine centers (NMC) are heterogeneous among countries and regions (Table 2). There are more than 2226 hospitals and centers where nuclear medicine practice of diagnostic imaging and radionuclide therapy is performed. The number of NMC per 1,000,000 habitants are highest in Japan followed by Lebanon, Israel, Kuwait, Korea, and Turkey. Although the most advanced imaging technology such as SPECT/CT and PET/CT has already been introduced in most countries in Asia, an accessibility to nuclear medicine practices is still limited. As previously noted, this is not solely related to economic power.[9] For example, in South East Asia, Philippine, and Vietnam showed much more availability of NMC than Indonesia and Myanmar in spite of lower gross domestic product per inhabitant (4681 USD for Philippines and 4012 USD in Vietnam vs 5214 USD in Indonesia and 6265 USD in Myanmar). Government-level awareness of clinical values of nuclear medicine practice and human resource development of nuclear medicine professionals are critical factors other than economics. The IAEA Technical Corporation (TC) Program is effectively working to promote

Table 1 Age-Standardized Death Rate Per 100,000 by Ischemic Heart Disease in Selected Countries and Regions

Regions	Male	Female	Persons	All Cause	CHD/All Causes
West Asia					
Israel	63.2	33	46.4	391.7	0.118
UAE	118.3	60.1	94.5	517.4	0.183
Turkey	178.8	136	157.1	673.4	0.233
Saudi Arabia	239.8	105.6	180.6	797.3	0.227
Jordan	217.6	106.2	162.5	873	0.186
Kuwait	121.8	89.8	109.6	479.6	0.229
Oman	241	102.5	181.9	709.2	0.256
Yemen	280	200.6	238.5	1130.5	0.211
South Asia					
Iran	222.4	165.5	194.5	771.4	0.252
Pakistan	255.8	187.1	222.9	1189.7	0.187
Bangladesh	232.6	176	203.7	1137.3	0.179
India	211.9	121.6	165.8	1146.6	0.145
Sri Lanka	115.8	58.4	84.5	935.5	0.090
Afganistan	399.3	255.7	328.6	1978.2	0.166
Central Asia					
Kazakhstan	462.1	266.4	346.5	1236.4	0.280
Uzbekistan	381.5	275.4	323.2	985.7	0.328
Turkmenistan	496.8	334.5	405.1	1256.4	0.322
Kyrgyzstan	401.6	302.1	349.4	1110.9	0.315
Tajikistan	213.8	213.1	213.7	988.4	0.216
South East Asia					
Philippines	148.8	96.5	121.6	885.2	0.137
Thailand	103.7	72	87.1	934.7	0.093
Malaysia	175	104.6	138.7	762.4	0.182
Indonesia	190.2	116.7	150.8	961.1	0.156
Singapore	109.9	57.9	82.4	400.1	0.206
Vietnam	131	98.7	112.5	795.6	0.141
Cambodia	175	96.4	128.8	1291.4	0.100
Lao	226.2	167.8	194.3	1253.5	0.155
Myanmar	197.1	137.2	164.7	1474.9	0.112
East Asia					
Japan	43.8	20.2	31.2	349.3	0.089
Korea	43.5	27.5	35.7	435.8	0.082
China	84.5	74.4	79.7	731.4	0.109
Mongolia	115.7	43.3	75.7	879.9	0.086

This Table is created based on the World Health Organization: Global status report on noncommunicable disease. Geneva, Switzerland, World Health Organization, 2010. Available at: http://whqlibdoc.who.int/publications/2011/9789240686458_eng.pdf. (reference 9)

Table 2 Number of Nuclear Medicine Centers and Facilities in Selected Countries and Regions

Region	Population	Number of NM Centers	Per 1,000,000	Number of SPECT/CT	Number of PET/CT
West Asia					
UAE	9,270,000	13	1.40	3	4
Israel	8,800,000	40	4.5	26	9
Jordan	9,500,000	14	1.47	0	6
Lebanon	5,000,000	27	5.40	1	10
Saudi Arabia	33,840,000	41	1.21	34	13
Qatar	2,570,000	2	0.78	1	1
Syria	17,950,000	4	0.22	2	2
Turkey	75,620,000	240	3.17	12	122
Yemen	27,580,000	4	0.15	0	0
Oman	2,590,000	2	0.77	2	2
Kuwait	3,250,000	12	3.69	6	6
South Asia					
Pakistan	193,200,000	50	0.26	5	6
Iran	79,000,000	155	1.96	6	6
Sri Lanka	21,670,000	1	0.05	1	1
Bangladesh	165,642,000	20	0.12	3	3
Iraq	32,960,000	6	0.18	0	0
India	1,324,000,000	175 (450)	0.13	70	222
South East Asia					
Malaysia	31,200,000	15	0.48	10	16
Philippines	103,000,000	30	0.29	8	4
Myanmar	52,900,000	4	0.08	4	1
Thailand	69,126,000	23	0.33	18	11
Indonesia	261,000,000	14	0.05	12	4
Vietnam	92,700,000	20	0.21	4	6
Singapore	5,600,000	9	1.61	7	12
East Asia					
China	1380,000,000	800	0.58	215	270
Korea	51,250,000	163	3.18	46	169
Japan	127,000,000	1260	9.94	164	412

The data collected by SNMMI Nuclear Medicine Global Initiative directed by Dr Andrew Scott were integrated in this table with courtesy. The data were also collected by the survey of nuclear medicine practice in Asia and Oceania in the 12th Asia Oceania Congress of Nuclear Medicine and Biology held in Yokohama on October 5-7, 2017 chaired by Dr Tomio Inoue.

nuclear medicine in Asia. In recent years, the Vietnamese government has decided to build domestic capacity in generating radioisotopes such as ^{201}Tl, ^{67}Ga, ^{18}F, ^{11}C for diagnostic applications by establishing 2 cyclotrons and PET centers, with the primary funding by the government and, expertise, human resource development, support equipment supplied by the IAEA TC project. In Thailand, the IAEA TC project assisted in the installation of PET-CT, cyclotron, and radiopharmaceutical production facilities. Recently, Indonesia Nuclear Expo 2019 was held on September 2-7 where the application of nuclear science and technology, nuclear medicine, and human resources development in Indonesia was presented in front of the government officers and industrial and medical equipment stakeholders. In Myanmar, the first PET/CT Center was installed in Yangon General Hospital in 2017 under the support of the IAEA. At the same time, the first International Scientific Workshop was launched by the Myanmar Society of Nuclear Medicine. Increasing awareness of public, health strategy planner, stakeholders, and academia is important to initiate nuclear medicine practice in Asia.

Availability of Radiopharmaceuticals for Nuclear Cardiology

In the MPI SPECT/CT, ^{99m}Tc-labeled radiopharmaceuticals and ^{201}TlCl are used. Several countries have an ability of nuclear reactor-based production of ^{99}Mo for domestic distribution (China, India, and Bangladesh). Most of Asian countries rely on the international supply chain of ^{99}Mo. ^{99}Mo-^{99m}Tc generator is available in all the countries where nuclear cardiology practice is performed. In China, Iraq, Myanmar, and Sri Lanka, ^{201}TlCl is not available. The MPI SPECT/CT is conducted by use of ^{99m}Tc-methoxyisobutylisonitrile (MIBI) or ^{99m}Tc-tetrofosmin (TF) in these countries. ^{123}I availability is limited. ^{123}I-meta-iodobenzylguanidine (MIBG) is used in Iran, Israel, Jordan, Lebanon, Saudi Arabia, Syria, Turkey, China, Korea, and Japan.

Shifting from ^{201}TlCl to technetium-based MPI is a trend worldwide to reduce radiation exposure in patients and to improve image quality of MPI.[10] An important concern, however, is a risk of ^{99}Mo supply in Asia. Availability of ^{99}Mo and

Table 3 Best Practices of Nuclear Cardiology

	West Asia *n* = 17	South Asia *n* = 16	South East Asia *n* = 20	East Asia *n* = 16	All of Asia *n* = 69	Rest of World *n* = 239	*P* Value
Avoid thallium stress	71%	81	65	88	75	96	$<$0.001
Avoid dual isotope	94%	88	100	88	93	98	$<$0.05
Avoid too much technetium	100%	94	90	88	93	83	0.054
Avoid too much thallium	94%	100	100	100	99	100	
Perform stress-only	53%	25	15	0	23	32	
Use camera-based dose-reduction strategy	59%	69	75	75	70	66	
Weight-based dosing for technetium	24%	6.3	15	0	12	33	$<$0.001
Avoid shine through dosing	35%	31	45	38	38	46	

This table is a duplication of Table 2 in the reference 6 by Pascual TBN, et al with modification.

^{99m}Tc is a critical issue for reliable clinical practice of nuclear cardiology. In recent years, most of Asian countries experienced a shortage of ^{99}Mo supply, and the ^{99m}Tc-based MPI SPECT was influenced. In Indonesia and Korea, nuclear reactor-based production of ^{99}Mo is planned. In Japan, several trials are going on for mass production of ^{99}Mo and ^{99m}Tc by accelerator. Until sufficient and stable supply of ^{99}Mo and ^{99m}Tc is realized, the longer physical half-life of ^{201}Tl (73 hours) would have some merits in spite of lower image quality and larger radiation dose.

Nuclear Cardiology in Asia

The IAEA Technical Meeting Panel reported worldwide utilization (per 100,000 of the population) of nuclear cardiology procedures (mostly MPI).[9] In Asia, Israel showed the highest utilization with more than 1000 scans/100,000 individuals a year followed by Korea, Japan, UAE, Turkey, Australia (250-999 scans/100,000). Saud Arabia, Kuwait, Jordan, Lebanon, Iran, Pakistan practiced 60-99 scans/100,000. Most of South East Asian countries, China, India, and Bangladesh practiced 1-50 scans/100,000 per year. Central Asia, Mongolia, Vietnam, Cambodia, Lao, Myanmar, Nepal, and Bhutan showed limited use or no nuclear cardiology practice.

The IAEA Nuclear Cardiology Protocols Cross-Sectional Study evaluated the quality of nuclear cardiology practice in selected centers in Asia in relation to radiation exposure and best practice for MPI.[6] Total of 308 centers participated the survey, and 69 centers were from Asia (Korea, India, Philippine, Israel, Saudi Arabia, Turkey, Indonesia, Kuwait, China, Singapore, Vietnam, Bangladesh, Iran, Japan, Pakistan, Sri Lanka, and UAE), and the remaining 239 centers were from the rest of the world. The best practice was categorized as follows: (1) Avoidance of ^{201}Tl stress SPECT; (2) Avoidance of dual isotope imaging; (3) Avoidance of too much ^{99m}Tc; (4) Avoidance of too much ^{201}Tl; (5) Performance of stress only imaging; (6) Use of camera-based dose-reduction strategies; (7) Use of weight-based dosing for ^{99m}Tc; (8) Avoidance of inappropriate dosing that can lead to “shine-through” artefact. The survey revealed that radiation dose of MPI in Asia is higher than in the rest of the world. This was due to more frequent use of ^{201}TlCl, less use of weight-based dosing, and less use of stress-only imaging (if stress images are normal, subsequent rest imaging can be omitted). In East Asia, no participant centers performed stress-only protocol and weight-based dosing for ^{99m}Tc (Table 3). This is partly related to the fact that the syringe-type ^{201}Tl and ^{99m}Tc solution kits with fixed radioactivity are delivered to hospitals by centralized radiopharmacy of companies.

Regional Status of Nuclear Cardiology in Selected Countries

China

In China, about 2,100,000 examinations of single photon imaging were performed annually in 2018, and examinations of nuclear cardiology accounted for about 5% in them, which has been stable for years.[11] However, it is underused very much compared with more than 700,000 percutaneous coronary intervention (PCIs) annually in 2017.[12]

The most examinations of nuclear cardiology were performed with SPECT and SPECT/CT, and few with PET/CT. Eight solid state Cadmium Zinc Telluride SPECT (including 4 GE NM530c and 4 D-SPECT) have been installed in the hospital since 2016. The total number of single photon equipment (including SPECT, SPECT/CT) is 828 according to the survey provided by Chinese Society of Nuclear Medicine.[13] Single photon nuclear cardiology practices mainly consist of MPI, including stress/rest, rest-only studies, and a very small amount of other items, such as gated equilibrium blood pool imaging.

^{201}Tl and ^{123}I are not available now in China, including its labeled compound, such as ^{123}I-b-methyl-p-iodophenyl-pentadecanoic acid and $^{123/131}$I-MIBG. ^{99m}Tc-MIBI and ^{99m}Tc-TF are available commercially, and most examinations of nuclear cardiology were performed with ^{99m}Tc-MIBI. Both symptom limited exercise stress tests and 85% of maximal age-predicted heart rate stress tests are used in China. Now, adenosine is the only pharmaceutical for pharmaceutical stress test. The clinical trial for regadenoson is undergoing for Food and Drug Administration approval. Several hospitals have started some new types of single photon cardiac imaging, such as ^{99m}Tc-PYP cardiac amyloidosis, which has a very good diagnostic efficiency for ATTR cardiac amyloidosis.

For cardiac PET clinical application, it mainly consists of evaluation of myocardial cell viability with ^{18}F-FDG and accounted for only 0.9% (4597cases) among total numbers of PET/CT examinations (522,854 cases) in 2018.[14] For positron perfusion agents, ^{13}N-ammonia is used and measurement of coronary flow reserve using PET/CT is also in the initial stage in China. Rubidium-82 is not available in the market. On the other side, vasculitis, cardiac sarcoidosis, and inflammation imaging of cardiovascular implanting using PET/CT are paid much attention as a new direction for cardiovascular positron imaging in recent years. Although a few PET/MR have been used clinically, little information related to cardiac practices is reported till now.

For better use and providing useful information to the clinic, the standardized report writing of radionuclide myocardial imaging was issued by Chinese Society of Nuclear Medicine in 2018.[14] In order to precisely quantifying the extent and severity of decreased myocardial perfusion, multicenter study on normal Chinese population reference database for SPECT-MPI started under the leadership of Professor Yaming Li, which filled up the domestic blank of this field, and he also organized expert consensus on key points of imaging technique and process with single photon MPI (in print). Under the leadership of Prof. Sijin Li, a guideline for the clinical use of myocardial radionuclide imaging has been published in the Chinese journal of Cardiology in 2019, whose purpose is to promote and guide the clinical use of myocardial radionuclide imaging (Society of Nuclear Medicine of Chinese Medical Association, Society of Cardiology of Chinese Medical Association, 2018).

In a word, problems and challenges of nuclear cardiology in China go hand in hand for the current state, but also leave a very huge potential for promoting practices of nuclear cardiology in the future.

India

The prevalence of coronary artery disease (CAD) in India is increasing with 14.5% of total death. The risk factors are dyslipidemia, smoking, hypertension, diabetes mellitus, abdominal obesity, psycho social stress, unhealthy diet, and inactivity. There are approximately 450 NMC, where 60,000 MPI examinations are conducted every year. ^{201}TlCl, ^{99m}Tc-MIBI, and ^{99m}Tc-TF are available. Since the national populations are 1.4 billion, approximately 43 MPI studies per 100,000 inhabitants are conducted every year. In contrast to high incidence of CAD, the MPI is underutilized in India.[15,16]

In the major urban cities, although cardiac MRI, CT, angiography suites, electrophysiology studies, angioplasty, and bypass facilities are well established, the MPI scans are not growing as compared to CT and conventional angiography in CAD. One of the reasons is limited education of nuclear cardiology to nuclear medicine physicians and cardiologists. For nuclear medicine physician, nuclear cardiology training is a part of the training in general nuclear medicine. For cardiologist, training programs in cardiology offer little nuclear medicine procedures. The practicing cardiologists are often not fully familiar with the value of nuclear cardiac imaging. These lack of education/training profoundly influences underutilization of MPI by cardiologists. The cost of the study is additional problem. The average cost to patients of MPI with a ^{99m}Tc-based agent is approximately $180 (compared to the average monthly middle-class income of about $500).

Japan

Subcommittee on Survey on Nuclear Medicine Practice in Japan, Medical Science and Pharmaceutical Committee, Japan Radioisotope Association performs a nationwide survey of in vivo nuclear medicine practice every 5 years since 1982.[17] In 2017, total of 231,129 examinations of MPI imaging was conducted. The aim of the study was an evaluation of cardiac function and residual ischemia after myocardial infarction and/or PCI. Although SPECT MPI is a gate keeper examination before PCI and coronary artery bypass-graft in United States, only 27% of PCI patients had MPI SPECT in Japan. Thallium use is decreasing from 78.6% in 1997 to 55.6% in 2017. Stress MPI was increasing from 81.0% to 88.8% of total MPI because of increasing needs to confirm myocardial ischemia before PCI or coronary artery bypass-graft. Stress MPI employed exercise-loading (23.7%) or drug-loading (dipyridamole or adenosine triphosphate, 64.2%). Use of drug-loading is increasing because of increasing senile patients who had a difficulty of appropriate exercise-loading. Percentage of ECG-gated MPI was increased from 59.5% in 2012 to 77% in 2017.

^{123}I-b-methyl-p-iodophenyl-pentadecanoic acid cardiac SPECT are conducted to evaluate myocardial fatty acid metabolism which is sensitive to metabolic shift from fatty acid to glucose in the early stage of myocardial ischemia (18,335 studies in 2017). ^{123}I-MIBG is available to examine denervation of sympathetic nerve which is vulnerable to ischemia (12,335 studies in 2017). ^{123}I-MIBG cardiac study was used to diagnose Parkinson's disease related pathology (32,871 studies in 2017).

The number of SPECT/CT is increasing from 153 in 2012 to 314 in 2017. The SPECT/CT has several merits not only for fusion imaging but for accurate attenuation correction. Semiconductor SPECT dedicated to cardiac imaging was installed in 18 Centers. Because of better energy resolution, spatial resolution, sensitivity, and noise equivalent counts than Ange-type camera, it improves a quality of nuclear cardiology practice and contributes to reduction of radiation dose.

Use of PET/CT for nuclear cardiology is limited. ^{18}FDG PET/CT was used to detect metabolic viability of myocardium and sarcoidosis. ^{13}N-NH_3 was used in patients with severe chronic heart failure to evaluate myocardial blood flow quantitatively before and after regeneration therapy with myocardial sheets. PET/MR was installed in 8 centers mainly for oncology. The advantage of PET/MR in nuclear cardiology remains uncovered.

Pakistan

Pakistan has over 50 NMC, 19 of these are funded by the Pakistan Atomic Energy Commission (PAEC). Centers can be stand-alone general nuclear medicine facilities, with cardiology as one of the many services provided. This is the usual model adopted by the PAEC. Some NMC can be part of a specialty hospital. The most common specialty hospital with a nuclear medicine section is a cardiology hospital that usually has its own catheter lab, cardiac CT, and MR in addition to nuclear medicine. Most centers use SPECT cameras though 1 center in Karachi, interestingly a general stand-alone facility, has a dedicated solid state Cadmium Zinc Telluride cardiac camera.

There is central procurement of radionuclides (generator and other) for the PAEC centers although individual sourcing remains a possibility depending upon local preferences. After a few initial years of using ^{201}TlCl, most centers have shifted to ^{99m}Tc-MIBI scans because of logistic and economic reasons. Only 1 center in Karachi currently does ^{201}TlCl imaging. Exact figures are difficult to come by because of the absence of centralized record keeping but the accumulated numbers of total studies of cardiac NM including MPI and MUGA are 33,500 for 2016, 35,100 for 2017, and 38,000 for 2018. Of these numbers 1 center in Lahore performs about 50 MPI procedures per day (around 15,000/year). While most centers use fixed dose, weight-related optimization is common since unit doses are not delivered and most centers formulate their own radiopharmaceutical with cold kits and ^{99m}TcO4 from generators. Many centers use single day protocol but a 2-day protocol with stress done first remains in vogue in about half of the cases. If an adequately done stress is normal, the study protocol stands concluded. More than 90% of cardiac tests involve perfusion studies with MUGA numbers only slowly improving especially for oncotherapy workups. About 100 cardiac PET scans are also done annually. There are only 4 PET scanners in the country. Some centers have actually noted a decline in their numbers from 1190 in 2011 to 450 in 2018 probably due to more accessibility to cardiac catheter study which appears to be the preferred test among cardiologists.

Predictability of Cardiac Event by MPI SPECT in East Asian Inhabitants

Nuclear medicine guidelines in the United States[18] and Japan [19] have approved prognostic evaluation with MPI SPECT. Because Asian background in the prevalence of CAD, associated condition of diabetes mellitus, hypertension, and hyperlipidemia, and food preference and lifestyle might significantly differ from that in the rest of the world, the values of nuclear cardiology has to be confirmed in Asian inhabitants. For this purpose, the Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated SPECT (J-ACCESS investigation) was conducted.[20]

A total of 4629 consecutive patients were registered at 117 hospitals. A 3-year follow-up after the MPI SPECT was done in 4406 patients. Stress and rest SPECT studies with ^{99m}Tc-TF were performed using a 1-day protocol. Mean dose of the initial stress study and the second rest study was 305 MBq and 709 MBq, respectively. The stress study was done by exercise (68%) or with dipyridamole (14.7%) or adenosine triphosphate (13.8%). The ECG-gated studies were performed. Quantitative gated MPI SPECT data were analyzed using QGS software. The parameters of ejection fraction (EF%), end-diastole volume (EDV, mL), and end-systolic volume (ESV, mL) were calculated.

Perfusion defect scoring was performed by visual inspection. The SPECT images were divided into 20 segments. In each segment, the uptake of ^{99m}Tc-TF was scored as follows; 0, normal; 1, mildly reduced; 2, moderately reduced (50% uptake of the maximum); 3, severely reduced; 4, no uptake. Summed stress scores (SSS) and rest scores (SRS) were calculated based on the stress and rest findings. The summed difference score (SDS) was defined as the difference between SSS and SRS. The severity of myocardial perfusion defects was defined with 4 grades; normal, SDS $<$ 3; mildly abnormal, 4 $<$ SDS $<$ 8; moderately abnormal, 9 $<$ SDS $<$ 13; Severely abnormal, SDS = 14 or more. During the 3-year follow-up, major cardiac events were defined as cardiac death, nonfatal myocardial infarction, and hospitalization due to severe heart failure.

In this population, 57 cardiac deaths (1.3%), 37 nonfatal myocardial infarctions (0.8%), and 93 severe heart failures (2.1%) were found during the 3-year follow-up period (Table 4). The incidence of cardiac death and nonfatal myocardial infarction in the current study was much lower than that of the United States (3.0% and 2.3%, respectively). When the threshold LVEF at rest was set 45%, cardiac death and nonfatal myocardial infarction rate was significantly higher in patients with LVEF at rest less than 45% (16.55%) than in those with LVEF at rest of 45% or more (2.94%). Similarly, cardiac death and nonfatal myocardial infarction rate was significantly higher in patients with ESV at rest more than 60 mL in men and 40 mL in women. In this population, a multivariate model analysis revealed that significant predictors for major cardiac events (cardiac death, nonfatal myocardial infarction, and severe heart failure requiring hospitalization) were age, association of diabetes mellitus, ESV at rest, and LVEF at rest both in men and women. Those for hard cardiac events (cardiac death and nonfatal myocardial infarction) were age, ESV, and LVEF. The J-ACCESS study proved that the ^{99m}Tc-based MPI SPECT is useful for risk stratification for patients living in countries with low incidence of ischemic heart disease.

Normal Values of QGS and Other Parameters

Since Asian people have different genetic and/or nutritional background from those of Western people, normal values such as polar maps and QGS parameters should be established differently from current global standard. There were considerable differences in these parameters between East-Asian (Japanese) and Western people. For example, mean

Table 4 Characteristics of Patients With and Without Hard Cardiac Events (Cardiac Death and Nonfatal Myocardial Infarction)

Variate	Hard Events (*n* = 96)	No Hard Events (*n* = 3935)	*P* Value
Age (y)	69.69 ± 8.74	65.76 ± 10.07	<0.0001
Male gender (*n*/total, %)	77.10%	63.70%	0.0095
Typical chest pain (n/total, %)	53.10%	46.00%	0.2004
Body mass index (kg/m^2)	22.43 ± 3.22	23.72 ± 3.21	<0.0001
History of myocardial infarction (*n*/total, %)	47.40%	28.90%	<0.0001
Diabetes mellitus (*n*/total, %)	53.10%	28.50%	<0.0001
Hypertension (*n*/total, %)	63.50%	54.70%	0.1051
Hyperlipidemia (*n*/total, %)	42.10%	47.30%	0.3716
Family history of coronary artery disease (*n*/total, %)	12.50%	11.80%	0.9943
Current smoking (*n*/total, %)	24.40%	16.10%	0.0635
Ischemia during stress ECG (*n*/total, %)	50.00%	49.10%	1
Summed stress scores (SSS)	15.23 ± 16.17	8.51 ± 11.08	<0.0001
Summed rest scores (SRS)	13.54 ± 14.91	7.11 ± 10.44	<0.0001
Summed difference score (SDS)	1.69 ± 3.91	1.44 ± 3.75	0.5491
Left ventricular ejection fraction at rest (LVEF, %)	51.23 ± 16.95	62.18 ± 13.38	<0.0001
End-diastolic volume at rest (EDV, mL)	112.97 ± 59.98	84.05 ± 34.90	<0.0001
End-systolic Volume at rest (ESV, mL)	63.4 ± 55.02	35.17 ± 27.74	<0.0001

This table is a duplication of Table 2 in the reference number 20 by Nishimura T, et al.

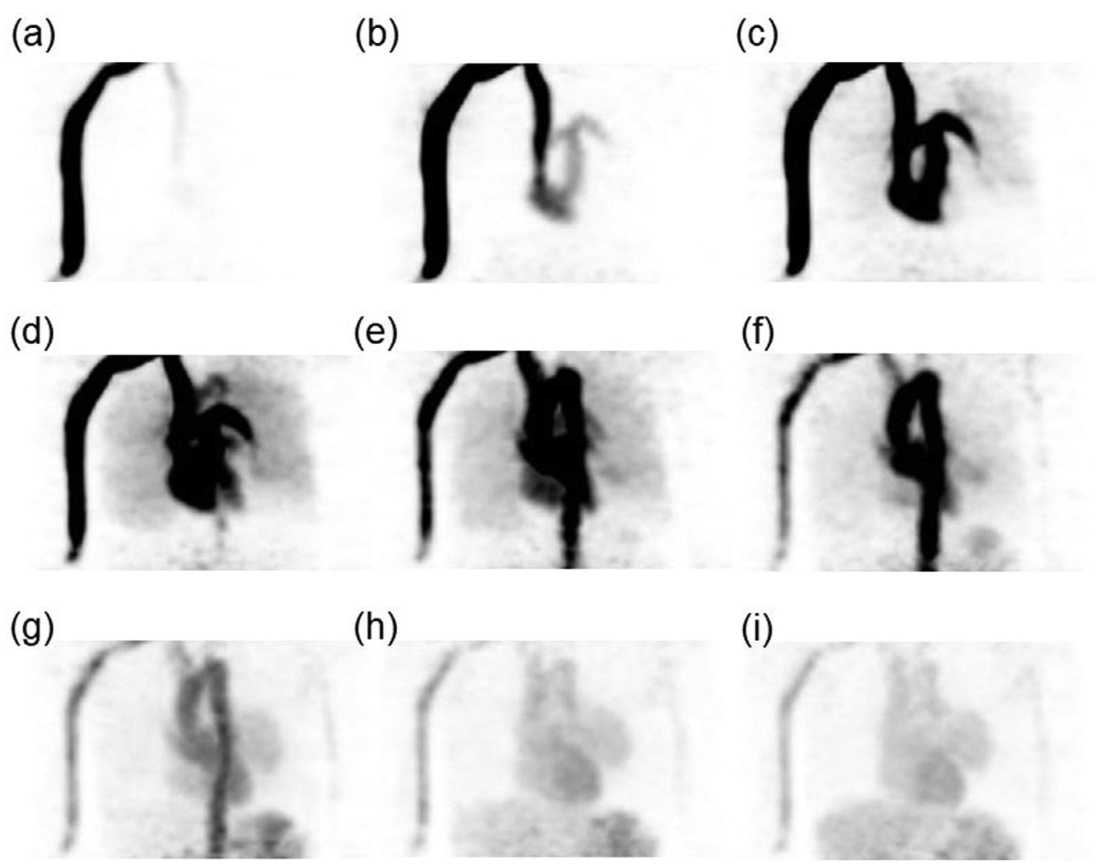

Figure 1 $H_2{}^{15}O$ PET angiography. Immediately after intravenous bolus injection of $H_2{}^{15}O$, radioactivity from chest was acquired by list mode count collection in a patient with left lung cancer with PET-CT having 28-cm-axial length detectors. MIP Images were reconstructed every 2 seconds. Serial images demonstrated $H_2{}^{15}O$ in brachial and subclavial veins (1), right atrium and ventricle (2), roght and left trunks of pulmonary artery (3), pulmonary vessels and left atrium and ventricle (4), ascending artery, aortic arch, and descending artery (5). Tissue radioactivity corresponding to tissue blood flow in myocardium and lung cancer is visible in the late phase images (7-9).

LVEF in normal women was 74% in Japanese,[21,22] and was 67%, 67%, and 66% in 3 previous literatures from United States[23,24] and Europe.[25] Lower normal limit (mean-2 SD) of LVEF was 56% in Japanese, and 49%, 51%, and 48% in the literature from United States and Europe. When the threshold value based on the United States[23,24] and European studies[25] is applied, a number of patients with LVEF ranging from 50% to 56% is misdiagnosed as having normal LVEF. In addition, even within Asia, there were significant difference in patients' body weight among regions (63.7 kg in East Asia vs 80.2kg in West Asia).[6] Since the LVEF, ESV, and EDV is dependent on age, gender, and body weight, the threshold values between normal and pathologic state of QGS parameters should be set according to regional normal database (Table 4).

In small hearts, underestimation of the true volume of left ventricle occurs. The effect is higher for ESV volume than for EDV, which results in higher LVEF in women and children.

Research Activities

There are several research activities in Asia. ^{123}I-MIBG cardiac SPECT is used for differential diagnosis of dementia. Cholinergic innervation in myocardium was evaluated by ^{11}C-labeled acetylcholinesterase inhibitor Donepezil for studying parasympathetic innervation (Fig. 1).[26] Regeneration therapy by means of myocardial tissue sheet was evaluated by ^{13}N-NH3 PET and ^{15}O water PET study. PET angiography after bolus injection of H215O is utilized for evaluation of pulmonary and myocardial perfusion in a single study (Fig. 2).[27]

Education and/orTraining for Nuclear Cardiology

Education and/or training platform for development of human resources of nuclear medicine professionals is essential to promote Nuclear Cardiology in Asia. In the region, training and/or education platform is still limited as shown in Table 5.[28]

The IAEA have continuously supported implementation of nuclear medicine in Asia by funding for initial imaging facilities, cyclotrons, and human resource development. Recently, IAEA published Training Curriculum for Nuclear Medicine Physicians under the responsibility of Drs D. Paez. T. Pascual, and F. Giammarile of the Division of Health.[29] The IAEA launched the IAEA-Eleven Universities Consortium of Japan

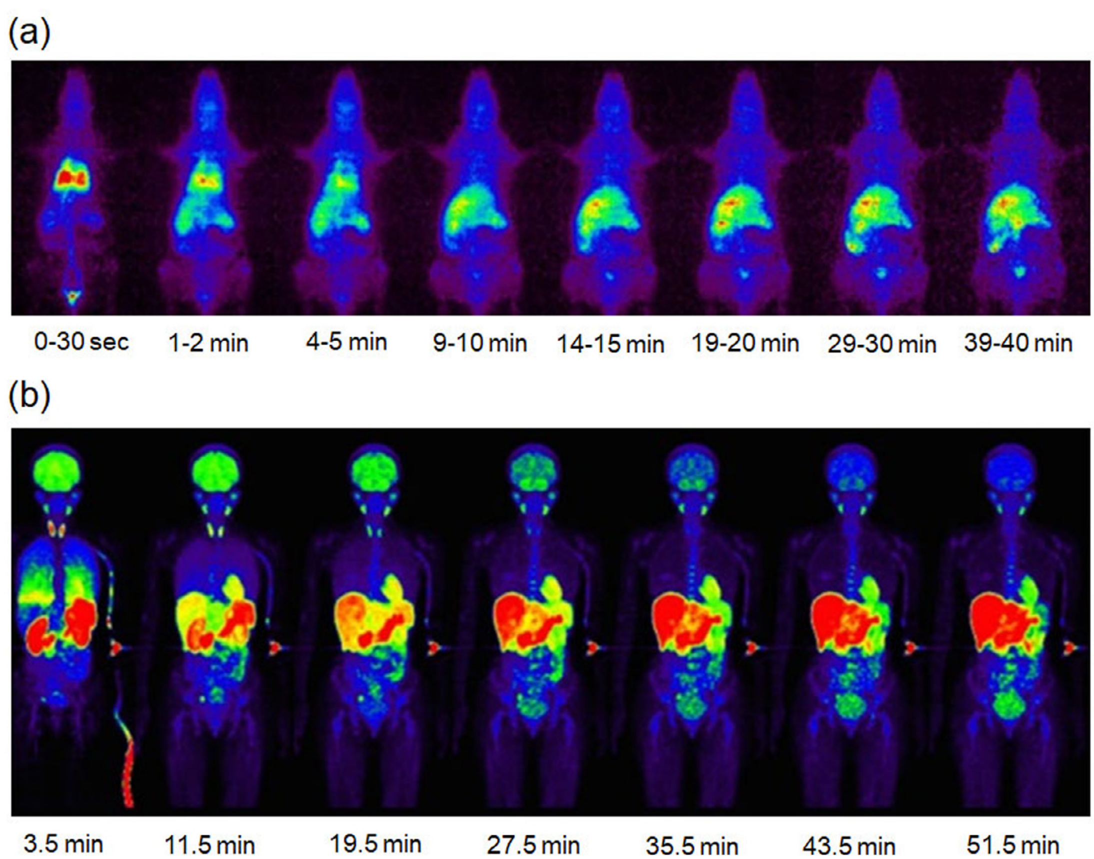

Figure 2 Imaging parasympathetic innervation on myocardium. Serial coronal images were acquired by means of PET-CT after intravenous injection of ^{11}C-labeled Donepezil hydrochloride, an acetylcholine esterase inhibitor which is prescribed to patients with Alzheimer's disease. Note an elevated accumulation of the ligand in myocardium rather than a target organ of brain.

Table 5 Education and Training Platform in Selected Country/Region

Number	PAK	MAL	PHI	KOR	SRL	BGD	JPN	THA	IRA	MYA	IND	CPR	VIE	UAE	MON	TWI	INS
Nuclear medicine physician	150	30	80	323	5	40	2650	40	320	10	500	6000	40	20	5	171	31
Nuclear medicine physician graduating every year	10	10	3	24	0	5	50	5	6	2	30	200	4	0	0	6	3
Education/training center	15	4	6	24	0	1	500	5	3	1	20	80	3	0	0	35	1
Practicing nuclear medicine physician	50	15	30	163	5	20	1267	23	126	5	175	800	20	10	1	49	14

BGD, Bangladeshi; CPR, China; IND, India; INS, IndonesiaIRA, Iran; JPN, Japan; KOR, Korea; MAL, Malaysia; MON, Mongolia; PAK, Pakistan; PHI, Philippine; SRL, Sri Lanka; THA, Thailand; TWI, Taiwan; UAE, United Arab Emirates; VIE, Vietnam.

for an education training platform of human resource development of nuclear medicine. The first Workshop was held in Tokyo in August 2019 followed by the second Workshop in Sapporo in September 2019 by focusing on nuclear cardiology. The Asia Oceania Nuclear Medicine Board headed by Dr Durre Sabih of Multan Institute of Nuclear Medicine and Radiology, Pakistan, started an accreditation system for nuclear medicine specialist since 2014 under the guide of EANM experts (Drs Ariane Boubaker and Trond Bogsrud). The AOFNMB published an official journal Asia Oceania Journal of Nuclear Medicine and Biology under the editorship of Dr Seyed Rasoul Zakavi of Mashhad University, Iran.

Summary

Nuclear cardiology remains underdeveloped in most of Asian countries. Awareness of value of nuclear cardiology in referring doctors, governments, and public level is important. Human resource development of nuclear medicine professional is a key issue to develop and to maintain nuclear cardiology in Asia. Although incidence of ischemic heart event is much lower in East Asia, MPI studies proved predictive values of fatal cardiac events even in such inhabitants. There are several trials to establish normal database of QGS parameters in Asia to improve accuracy and value of the study. Limited and unstable supply of ^{99}Mo is major concern to promote ^{99m}Tc-based MPI. International collaboration based on the activities of the IAEA and regional nuclear medicine societies such as AOFNMB, ARSNM, ARCCNM, and EANMA has important roles.

References

1. Beaglehole R, Bonita R, Horton R, et al: Priority actions for the noncommunicable disease crisis. Lancet 377:1438-1447, 2011
2. Boutayeb A: The double burden of communicable and non-communicable diseases in developing countries. Trans R Soc Trop Med Hyg 100:191-199, 2006
3. Lopez AD, Mathers CD, Ezzati M, et al: Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. Lancet 367:1747-1757, 2006
4. Padhy AK, Dondi M: Themantic planning: The role of the International Atomic Agency in promoting education, medical research, and technology transfer among nuclear medicine communities of the developing world. Semin Nucl Med 38:S2-S4, 2009
5. Vilota JV, Shaw LJ, Allam AH, et al: Assessing the need for nuclear cardiology and other advanced cardiac imaging in the developing world. J Nucl Cardiol 16:956-961, 2009
6. Pascual TNB, Mercuri M, El-Haj N, et al: Nuclear cardiology practice in Asia: Analysis of radiation exposure and best practice for myocardial perfusion imaging-result from the IAEA Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS)- Cir J2017; 81: 501-510
7. Paez D, Becic T, Bhonsle U, et al: Current status of nuclear medicine practice in the middle east. Semin Nucl Med 46:265-272, 2016
8. World Health Organization: Global status report on non-communicable disease. Geneva, Switzerland, World Health Organization, 2010. Available at: http://whqlibdoc.who.int/publications/2011/9789240686458_eng.pdf.
9. Bom HS, Chung JK, Lee MC: A decade of the Asian regional cooperative council for nuclear medicine: A path to reduce heterogeneity of nuclear medicine practice in Asia. World J Nucl Med 10:113-114, 2011

10. Einstein AJ, Weiner SD, Bernheim A, et al: Multiple testing, cumulative radiation dose, and clinical indications in patients undergoing myocardial perfusion imaging. JAMA 304:2137-2144, 2010
11. Chinese Society of Nuclear Medicine: A brief report on the results of the national survey of nuclear medicine in 2018. Chin J Nucl Med Mol Imaging 38:813-814, 2018
12. Shengshou H, GAO Runlin G, Lisheng L, et al: Summary of the 2018 report on cardiovascular diseases in China. Chin Circul J 34:209-220, 2019
13. Society of Nuclear Medicine of Chinese Medical Association: Society of cardiology of Chinese Medical Association. Guideline for the clinical use of myocardial radionuclide imaging. Chin J Cardiol 47:519-527, 2019
14. Writing Committee of Chinese Society of Nuclear Medicine for the 2018 Expert Consensus for Standardized Report Writing of Radionuclide Myocardial Imaging: 2018 expert consensus for standardized report writing of radionuclide myocardial imaging. Chin J Nucl Med Mol Imaging 38:805-809, 2018
15. Lele VR: Challenges and opportunities of nuclear cardiology in India. Ann Nucl Cardiol 3:183-185, 2017
16. Lele VR, Soman Prem: Nuclear cardiology in India and the developing world: Opportunities. . .and challenges! J Nucl Cardiol 16:348-350, 2007
17. Nishiyama Y, Kinuya S, Kato T, et al: Nuclear medicine practice in Japan: A report of the eighth nationwide survey in 2017. Ann Nucl Med 33:725-732, 2019
18. Klocke FJ, Baird MG, Lorell BH, et al: ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation 108:1404-1418, 2003
19. Tamaki N: Guidelines for clinical use of cardiac nuclear medicine (JCS 2005). Circ J 69(Suppl. IV):1125-1202, 2005
20. Nishimura T, Nakajima K, Kusuoka H, et al: Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. Eur J Nucl Med Mol Imaging 35:319-328, 2008
21. Nakajima K, Kusuoka H, Nishimura S, et al: Normal limits of ejection fraction and volumes determined by gated SPECT in clinically normal patients without cardiac events: A study based on the J-ACCESS database. Eur J Nucl Med Mol Imaging 34:1088-1096, 2007
22. Nakajima K, Matsumoto N, Kasai T, et al: Normal values and standardization of parameters in nuclear cardiology: Japanese Society of Nuclear Medicine working group database. Ann Nucl Med 30:188-199, 2016
23. Rozanski A, Nichols K, Yao SS, et al: Development and application of normal limits for left ventricular ejection fraction and volume measurements from 99mTc-sestamibi myocardial perfusion gated SPECT. J Nucl Med 41:1445-1450, 2000
24. Ababneh AA, Sciacca RR, Kim B, et al: Normal limits for left ventricular ejection fraction and volumes estimated with gated myocardial perfusion imaging in patients with normal exercise test results: Influence of tracer, gender, and acquisition camera. J Nucl Cardiol 7:661-668, 2000
25. De Bondt P, Van de Wiele C, De Sutter J, et al: Age-and gender-specific differences in left ventricular cardiac function and volumes determined by gated SPECT. Eur J Nucl Med 28:620-624, 2001
26. Mochida K, Shimosegawa E, Kanai Y, et al: Whole-body distribution of donepezil as an acetylcholinesterase inhibitor after oral administration in normal human subjects: A ^{11}C-donepezil PET Study. Asia Ocean J Nucl Med Biol 1:3-9, 2017
27. Matsunaga K, Yanagawa M, Otsuka T, et al: Quantitative pulmonary blood flow measurement using $^{15}O\text{-}H_2O$ PET with and without tissue fraction correction: A comparison study. Eur J Nucl Med Mol Imaging Res 7:102, 2017. https://doi.org/10.1186/s13550-017-0350-8
28. Durr-e-Sabih: The Asian Nuclear Medicine Board (ANMB); why do we need it? Asia Ocean J Nucl Med Biol 1:1-3, 2013
29. Training Curriculum for Nuclear Medicine Physicians. IAEA TECDOC SERIES IAEA-TECDOC-1883, International Atomic Energy Agency, Vienna, ISBN 978-92-0-160219-0 ISSN 1011-4289