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Review Article

Nuclear Cardiology in Japan —A Historical Review Based on Personal Experiences—

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Practice of nuclear medicine (NM) in Japan started in 1950 when radioisotopes (RIs) were imported from the U.S.A. and Japan Radioisotope Association (JRIA) launched with the purpose for bulk buying and distribution of RIs to each user. The author has experienced the nuclear medicine practices since its dawn to present. The purpose of this historical review is to follow tracks of nuclear cardiology in Japan as seen by the author. The nation-wide survey of nuclear medicine practice in Japan which was conducted by a subcommittee of JRIA tells us numbers of examinations, instruments and radiopharmaceuticals used for cardiac imaging and their temporal changes. The author describes his experiences with cardiac imaging in NM and its chronological changes in accordance with developments of imaging devices and radiopharmaceuticals used. The author believes the new developments in instrumentations and radiopharmaceuticals together with multi-disciplinary cooperation will facilitate nuclear cardiology and contribute to welfare of patients.

Key Words: myocardial perfusion imaging (MPI), scintigraphy, cardiac SPECT, cardiac PET, [^{201}Tl] thallium chloride (TlCl)

1. Introduction

The author had opportunities to give presentations in the 61st and 62nd Annual Meeting of the Japanese Society of Nuclear Medicine (Jpn. SNM) in 2021 and 2022 (the latter as a combined program with 34th Japanese Society of Nuclear Medicine Technologists) on historical reviews on nuclear cardiology and the dawn of nuclear medicine in Japan, respectively. This review article is based on those presentations made in Japanese language with the purpose to address to wider audience who may be interested in how nuclear cardiology has developed in Japan. The review is based on personal experiences of the author which covers nearly half a century from the dawn of nuclear medicine (NM) in Japan to early 21st century, that is from 1965 to 2011, when the 10th International Congress of Nuclear Cardiology (ICNC 10) a biennial meeting since 1993 was held in Amsterdam, the Netherlands. This was the last international meeting of nuclear cardiology in which the author participated. People cannot precisely predict what will happen in future. There are always unpredicted events to happen in future to come. Each person on the other hand knows what happened in the past to him or to her, which is a personal history. The author expects that younger people may learn somethings useful for the future prospect from historical events which were experienced by the author.

2. Nuclear Cardiology in Japan: A Historical Review

2･1 The Japanese Society of Nuclear Medicine: how it began

The import of RIs to Japan was started in 1950. The first cargo received was a gift by the US Academy of Philosophical Society to Prof. Yoshio Nishina, a world-famous nuclear physicist who had built cyclotrons in Japan.

JRIA was established in 1950 with the purpose of bulk buying the RIs and their distribution to users.[1]

In 1961 the 1st conference of nuclear medicine study group was held, which was organized by a clinical subgroup of Nuclear Medicine Section of JRIA. The 4th conference held in 1964 was reorganized and renamed as the 4th Annual Meeting of Jpn. SNM.

An epoch-making event in the history of NM was the 1st World Congress of Nuclear Medicine and Biology (WCNMB) held in Tokyo and Kyoto in 1974 with Prof. Hideo Ueda of the University of Tokyo as president. Dr. Henry N. Wagner, Jr. Prof. of Nuclear Medicine at Johns Hopkins Hospital wrote in his book entitled personal history of nuclear medicine[2] that "The Japanese had taken a great risk financially in holding the first congress." Fortunately, the meeting was a great success. The WCNMB has been held every 4 years in a different country in a different continent.[3] In September 2022 the 13th Congress was held for the 2nd time in Kyoto, Japan with Prof. Seigo Kinuya of Kanazawa University as president.

Founding of the Asia Oceania Federation of Nuclear Medicine and Biology was proposed by Prof. Hideo Ueda, and was established during the 1st WCNMB. The 1st Asia Oceania Congress of Nuclear Medicine and Biology (AOCNMB) was held in 1976 in Sydney, Australia. The AOCNMB has been held mostly every 4 years thereafter.

2･2 Changes of diseases spectrum in Japan

Life styles of Japanese people changed dramatically through the World War II (1941–1945) and the post-war periods (1945–1970). In short, having overcome food shortage during the war and immediate post-war period (1945–1950) the life styles in overall and particularly in urban areas in Japan had rapidly changed toward Euro-American style in parallel with the economic growth of 1960's. The changes of disease spectrum have followed the life style changes. During 1950's and 1960's valvular diseases as sequalae of rheumatic fever and syphilis were dominant cardiac diseases as well as congenital heart diseases. Among strokes, brain hemorrhages were more frequent than cerebral infarctions. The first leading cause of deaths in 1960 was cerebrovascular diseases followed by malignant neoplasms (2nd) and the 3rd heart diseases (excluding hypertensive diseases). In 1981 malignant neoplasms exceeded cerebrovascular diseases and was ranked as the 1st leading cause of deaths. In 1985 the heart diseases exceeded cerebrovascular diseases and was ranked as the 2nd leading cause of deaths. The heart diseases have kept the rank and increased to be doubled by 2022 accounting for 14.9% of all deaths. Malignant neoplasms accounts for 26.5% of all deaths in 2022.[4] In the USA on the contrary heart diseases have been ranked as the first leading cause of death and accounts for 20.1% of all deaths in 2021.[5] Although continuously increased in the past 60 years, the incidence of coronary heart disease in Japan is low as compared with the incidence in the USA.

2･3 Cardiac imaging in nuclear medicine

Subcommittee of JRIA on survey of nuclear medicine practice in Japan has couducted a nationwide survey every 5 years since 1982. Questionnaires are sent to all nuclear medicine facilities asking the numbers and category of examinations as well as the kind and dose of the radiopharmaceuticals used

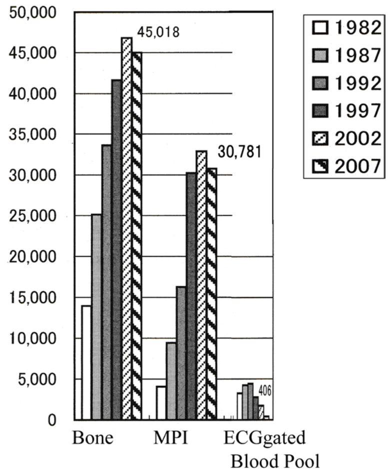

Fig. 1 Numbers of examinations performed in a month of June based on 6th nation-wide survey (Cited from ref. 6 with permission).

during the 30 days of June. The recovery rates of the questionnaires have been over 90%. Numbers of each examination per year and per day are estimated based on the numbers in the month of June.

The numbers of myocardial perfusion imaging (MPI) reported in the sixth survey[6, 7] is shown in Fig. 1. The numbers of MPI dramatically increased during the period from 1982 to 2002, when numbers of MPI reached over 30,000 per months. The numbers of MPI have gradually decreased after 2002. In 2022 the numbers were 24,070 per month.[8, 9]

2･4 Instruments used

2･4･1 Rectilinear scanner

In the 1960's rectilinear (scintillation) scanners and [^{131}I]-labelled radiopharmaceuticals were used for imaging in NM.[10]

The rectilinear scanner was invented by Benedict Cassen in 1951. It was commercialized for clinical use in 1960's and 1970's. A rectilinear scanner consisted of a scintillation detector (a 3-to 5-inch-diameter, 2- to 3- inch thick sodium iodide (NaI) crystal) with a multi-hole focusing collimator, a mechanical system that moved the detector over a patient, a gamma-ray spectrometer, and an image recording system. As the detector moved back and forth in a line across the patient, a metal pen followed over a carbon copy paper making a image of dots in earlier system. This dot recorder system was soon replaced by a photo recorder in that a light source moves over a photographic film. The darkening of the paper or film reflected the count rate at each detector position.[10]

2･4･2 Gamma camera

A camera type imaging devise invented by Paul Anger in 1954 was commercialized as gamma (or scintillation) cameras. An Anger-type gamma camera with wide field of view (typically 19 inches in diameter) and thin NaI scintillator (typically 0.5 inches) became available together with ^{99m}Tc with short half-life of 6 hs and relatively low gamma energy of 140 keV, which made it possible to take dynamic images of ^{99m}Tc-albumin moving in the heart (Fig. 2).

The Anger-type gamma cameras replaced rectilinear scanners in clinical settings of NM by early 1970's.

2･4･3 Single photon emission computed tomography (SPECT)

Tomographic images of nuclear medicine were reconstructed using multiple images taken by a gamma camera rotating around the body (Fig. 3). Clinical use of a single photon emission computed tomography (SPECT) was prevailed since middle of 1980's, which facilitated MPI SPECT taken at rest and after exercise or pharmacological stress. The myocardial viability was evaluated comparing stress and rest MPI. [^{99m}Tc]-labelled radiopharmaceuticals such as methoky isobutyl lisonitrile (MIBI) and tetrofosmin became available in early 1990's. Gated myocardial perfusion SPECT made it possible to calculate the left ventricular cavity volume and derives the global ejection fraction from the end-diastolic and end-systolic volume. The development of a completely

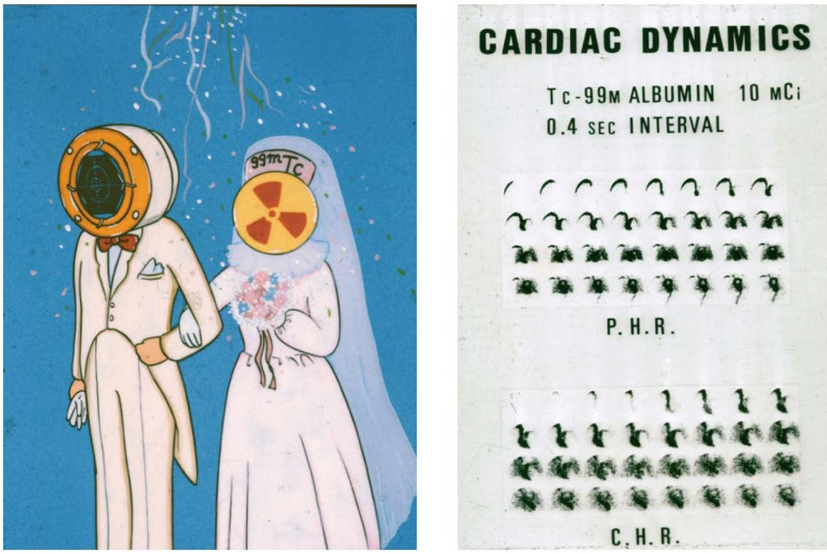

Fig. 2 Happy wedding of scintillation-camera and ^{99m}Tc (left) enabled dynamic imaging of the heart (right) (Color online).

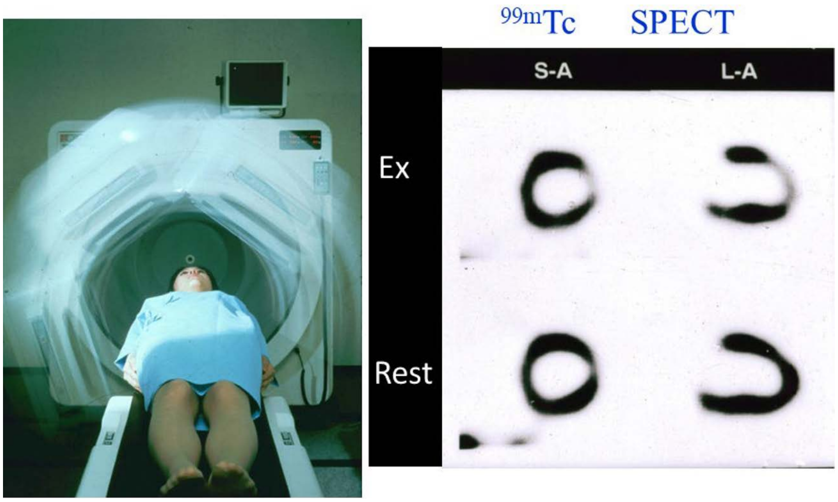

Fig. 3 Clinical use of SPECT (left) prevailed in 1980's making short axis(S–A) and long axis(L–A) tomography of myocardial perfusion images in excise (Ex) and rest conditions (right) (Color online).

automatic algorithm in 1995 enabled automatic quantification of ejection fraction.[11] The technique is called quantitative gated SPECT (QGS) in that myocardial perfusion and ventricular functions are evaluated simultaneously, which has been widely used in nuclear medicine practice.

In Japan nuclear cardiology boomed in clinical practice and research during 1995 and 2005 to the extent that nearly a half of presentations in the Annual Meeting of Jpn. SNM were occupied by nuclear cardiology related themes.

American Society of Nuclear Cardiology launched in 1992. The 1st International Conference of Nuclear Cardiology (ICNIC) was held in April 1993 in Canne, France. The conference has been held every 2 years mostly in Europe. The Japanese Society of

Nuclear Cardiology was organized in 1998 in cooperation of Jpn. SNM and Japan Circulatory Society. The 34th Annual Meeting was held in June 2024. ^{201}TlCl remains as the major radiopharmaceuticals used for MPI in Japan, although [^{99m}Tc]-laberlled pharmaceuticals have been increased gradually as is shown in Fig. 4.

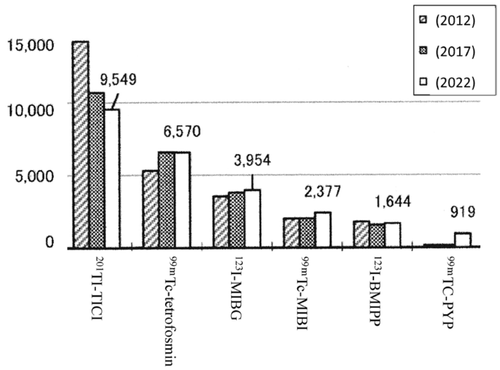

Fig. 4 Radiopharmaceuticals used for cardiac imaging based on 9th nation-wide survey (cited from ref. 8).

2･4･4 Positron emission tomography (PET)

In Japan, the first PET center was started in 1979 at National Institute of Radiological Sciences (NIRS) in Chiba. The first home-made PET named Positologica I was made in cooperation of NIRS and Hitachi Ltd. and was used to take brain images[10].

Clinical PET centers were started in Kyoto University Hospital in 1982 followed by Kyushu University Hospital and Gunma University Hospital in 1983[9]. The 1st whole body PET was installed in Kyoto University Hospital in 1985. [^{13}N]-NH_3 has been used for myocardial perfusion PET imaging.

3. Imaging of the Heart: Personal Experiences

3･1 Scintigraphy, imaging at the dawn of NM in 1960's

Representative organ scintigrams taken in 1960's. are illustrated in Fig. 5. [^{131}I]-sodium iodide was used for thyroid imaging which revealed functioning adenoma as a hot nodule or an area of increased

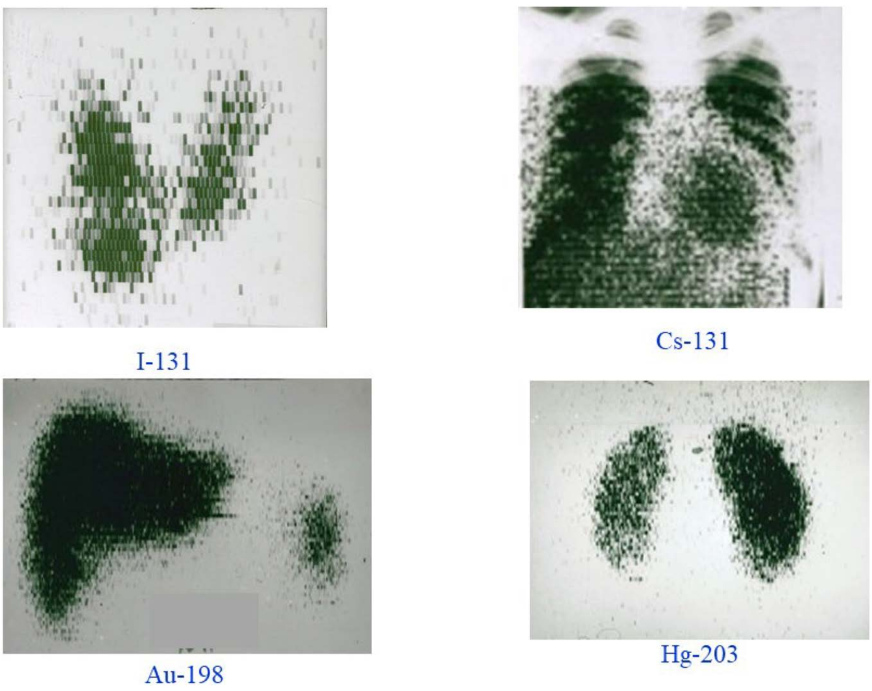

Fig. 5 Scintigrams in 1960's using various radioisotopes (Color online).

radioactivity. ^{131}CsCl was used for myocardial imaging, ^{198}Au colloids for liver imaging, ^{203}Hg neohydrin for kidney imaging and so on.

3･2 Blood pool scintigraphy for detection of pericardial effusion

For cardiac patients, blood pool scintigrams were taken using ^{131}I-human serum albumin (radio iodinated serum albumin: RISA), and a little later using ^{99m}Tc-Albumin. The blood pool images combined with chest X-ray images reveal pericardial effusion as a halo of absent radioactivity surrounding cardiac blood pool (Fig. 6).

3･3 Application of computer in early 1970's

With rapid development of computer science and its application in late 1960's to early 1970's ECG gated blood pool analysis became available for routine clinical use. The left ventricular wall motion was visualized and the ejection fraction was measured to diagnose heart failures.

3･4 ^{201}Tl MPI saved NM from CT impact in early 1970's

The invention of the computed axial tomography or CT by Hounsfield in early 1970's revolutionized body imaging and diagnostic radiology. The introduction of CT delivered an almost fatal blow to clinical practices of nuclear medicine, as brain scintigrams, the most clinically useful nuclear medicine procedure at that time, were rapidly replaced by CT. The so-called CT impact made the future of nuclear medicine gloomy, which was rescued by the emergence of nuclear cardiology in early 1970's, particularly by myocardial perfusion imaging (MPI) using ^{201}TlCl (Fig. 7).

3･5 Visualization of acute myocardial infarction with ^{99m}Tc-pyrophospate (PYP)

^{99m}Tc-PYP was used to visualize acute myocardial infarction. Ryo et al. tried hard to perform ^{99m}Tc-PYP scintigrams as early as possible after heart attack. They reported total of 30 patients in whom acute infarction was visualized using ^{99m}Tc-PYP[12] (Fig. 8).

3･6 Expert system (artificial intelligence) in 1980's

In 1985 the author launched Department of Nuclear Medicine in Gunma University which was the 3rd independent nuclear medicine department approved in national universities. Daily practice of NM and clinical research ware performed in cooperation with cardiologists, radiologists, endocrinologists, neurologists as well as private companies dealing with radiological equipment. One of the cooperative projects with private company was development of expert system (artificial intelligence in present day

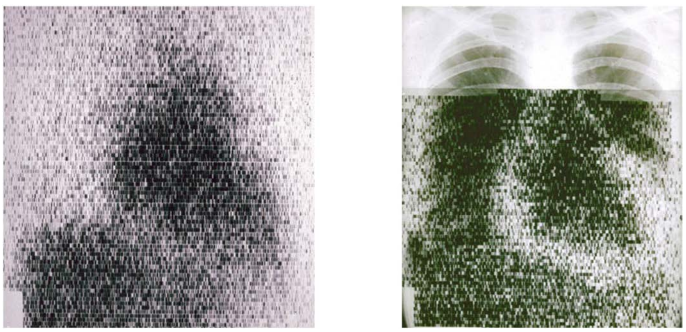

Fig. 6 Blood pool scintigraphy using RISA (^{131}I-Human Serum Albumin) (left) and ^{99m}Tc-Alubumin overlapped on X-ray photo showing cold halo surrounding the hot blood poon in a patient with pericardial effusion (right) (Color online).

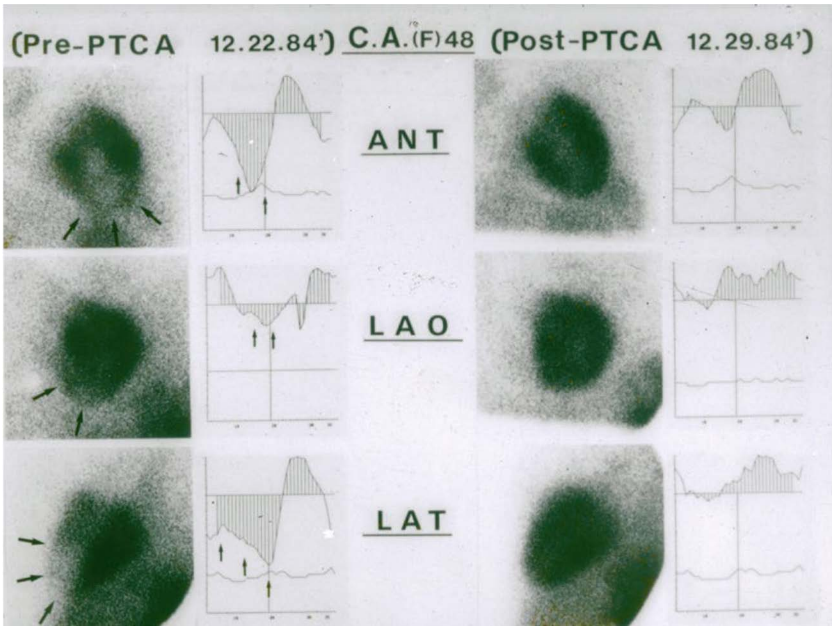

Fig. 7 Planar myocardial perfusion images (MPI) in a patient with acute myocardial infarction revealing perfusion defects (arrows) (left). After treatment by percutaneous transluminal coronary angioplasty (PTCA) showing disappearance of perfusion defect (right) (Color online).

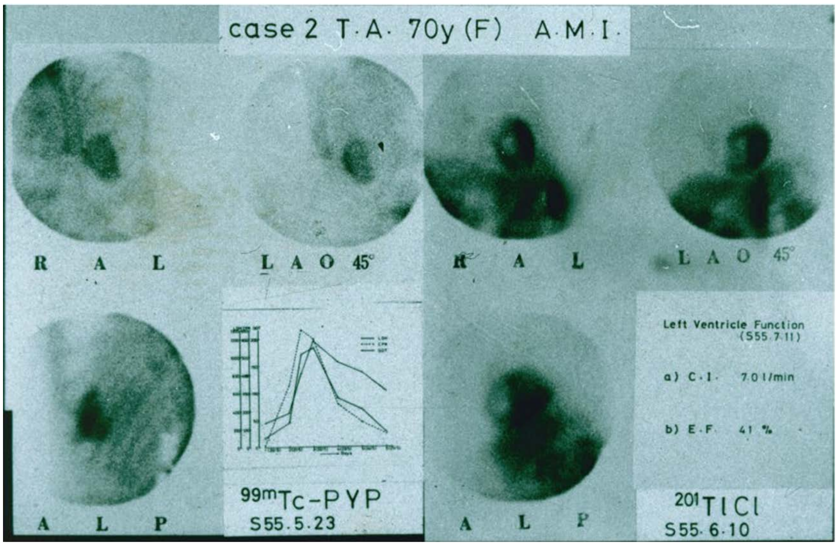

Fig. 8 Visualization of acute myocardial infarction accumulating ^{99m}Tc-pyrophsopate (PYP) (left). MPI using ^{201}TlCl showing focal defect due to acute myocardial infarction (right) (Color online).

terminology) for exercise myocardial SPECT. The two-dimensional polar (bull's eye) display of ^{201}Tl myocardial SPECT was transferred from image processor to the data base of patient managements (PM) system. When inference request is made, the feature extraction program extracts information on localization, extent and severity of focal defects comparing count-rates pixel by pixel with reference obtained from normal controls. The inference engine is activated to determine presence of focal defects utilizing diagnostic rules in the knowledge base. The results are sent back to PM system and reported with probability of assurance. The reported results agreed well with the decision made by experienced nuclear medicine physicians and cardiologists. The system was judged useful to provide physicians with complementary and supportive information applicable to decision making and reporting.[13)]

3･7 Cardiac PET with $^{13}NH_3$ and ^{18}FDG

A whole-body PET with small cyclotron was installed in 1988 in the University of Tokyo Hospital where the author was assigned in 1990 to chair department of radiology. Myocardial perfusion PET images were taken using $^{13}NH_3$. An internist, I. Yokoyama cooperated with radiologists to analyze myocardial flow reserve (MFR) in patients with non-insulin-dependent (type II) diabetes mellitus (NIDDM). They found MFR during dipyridamole loading was significantly lower in patients with NIDDM than in control subjects[14)]. They subsequently studied myocardial flow mechanisms in NIDDM using PET and $^{13}NH_3$ and ^{18}FDG[15–17)].

Integration of myocardial flow reserve and QGS improves risk stratification of patients with coronary artery diseases and contributes to patient management by indicating the need for angiography[18)].

3･8 MDCT impact on nuclear cardiology

With the development of multi detector CT (MDCT) loaded with more than 64 detector arrays the cardiac applications of the new technology have increased. The sub-second scanning time with wider scan coverage made it possible to visualize coronary vessels noninvasively after intravenous injection of a contrast agent. In the 10th ICNC held in 2011 in Amsterdam, the Netherlands a session was organized to discuss pros and cons of MPI vs. MDCT. Heated arguments were made over the future of MPI. The arguments reminded the author of CT impact on nuclear medicine in early 1970's. Actually, numbers of MPI have apparently decreased in Japan after 2007.[7)]

4. Conclusion

The radioactive tracer technology was invented by George de Hevesy in 1913. The technology was applied to human independently by H. Blumgart and S. Wise in late 1920's[19)] to measure circulation time between one arm to the other, which was the beginning of NM. The circulatory physiology was studied in human using radioactive tracers since the early stage of NM. The author has observed the progress of nuclear cardiology in Japan from its dawn to present. The road for NM has not been a smooth one as was shown in CT and MDCT impacts. The coordinated developments of instruments and radiopharmaceuticals promoted nuclear cardiology like the two wheels of a vehicle. Cooperative efforts of physicians, technologists and other specialists in related fields should promote nuclear cardiology in the future.

Nuclear cardiology will continue to be facilitated by the images of function combined with images of structures. New developments of radiopharmaceuticals and instrumentation should be watched carefully to be applied in the study of cardiac diseases.

Conflict of interest

The author has no conflict of interest to declair.

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要　旨

日本の心臓核医学
—個人の経験に基づく歴史的総説—

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本総説の目的は，日本での心臓核医学の軌跡を筆者の経験に基づいて辿ることである。全国核医診療実態調査が日本の心臓核学診療の実態と経年的変化を記録している。過去約60年間日本の核医学の歩みを見てきた筆者の体験に基づいて，この間の心臓核医学画像の変遷と進歩を記録し，装置と放射性医薬品の進歩と多分野の専門家の協働が今後の心臓核医学の発展を推進することを示したい。

2024年 7月31日　受付
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