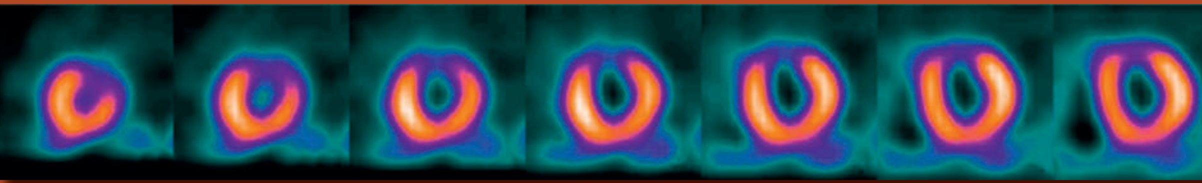

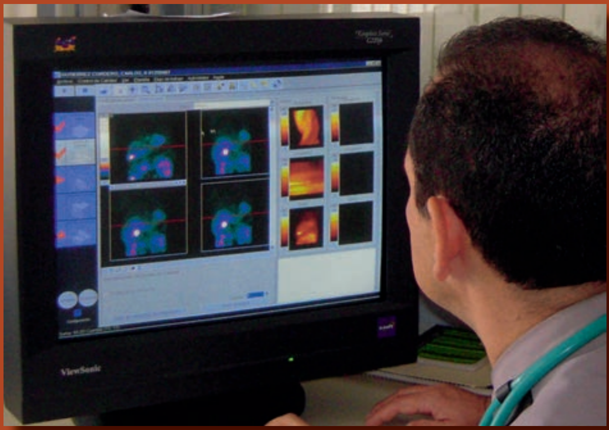

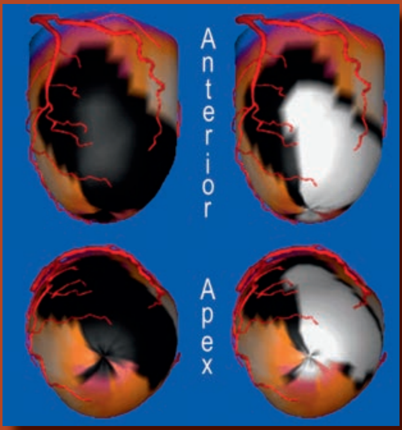

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No. 18

Nuclear Cardiology: Its Role in Cost Effective Care

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NUCLEAR CARDIOLOGY:
ITS ROLE IN COST EFFECTIVE CARE

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NUCLEAR CARDIOLOGY: ITS ROLE IN COST EFFECTIVE CARE

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Marketing and Sales Unit, Publishing Section
International Atomic Energy Agency
Vienna International Centre
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fax: +43 1 2600 29302
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FOREWORD

The incidence and prevalence of cardiovascular diseases (CVDs), of which coronary artery disease (CAD) account for the vast majority of cases, are increasing tremendously in every part of the world, regardless of the level of development. CVDs are now the leading cause of death worldwide, resulting on more than five million deaths per year in the developing world.

A great deal of effort has been devoted to reducing the incidence of severe CAD, as evidenced by the slight decline in morbidity and mortality in developed countries. However, this has not been seen in the developing world. There has also been much emphasis on primary prevention in CAD, and the concept of 'imaging for prevention' has recently been advocated.

The diagnostic and prognostic value of myocardial perfusion imaging (MPI) in CAD is very well established. Nuclear techniques not only provide perfusion and functional data which aid the management decision, they also provide non-perfusion data (for example, lung to heart ratio, transient ischaemic dilation of the left ventricle (TID), right ventricular uptake and myocardial stunning), which can also aid in decision making.

Although MPI has many advantages, it has its limitation in that it cannot detect early stage coronary disease, and may miss detection of multivessel disease, resulting in balanced ischaemia. Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) remains an accepted standard for the detection and quantification of significant myocardial ischaemia and has been shown to be a strong prognostic indicator of the risk for adverse cardiac events. Recently, other techniques, including cardiac computed tomography angiography has been promoted vigorously in the detection of coronary disease. The use of coronary calcium score for the early detection of atherosclerotic disease has been well established and it can provide powerful prognostic information, leading to modifications in the management of CAD, which would not otherwise have been achieved if the early disease remained undetected.

This publication presents a comprehensive overview of CVDs as a public health problem in developing countries, the relative role of nuclear cardiology methods within a scenario of unprecedented technology advances, and the evidence behind appropriateness recommendations. The potential expanding role of non-invasive functional imaging through the transition from diagnosis of obstructive CAD to defining the global burden of CVDs is also discussed, as well as the need for thorough training, education, and quality in nuclear cardiology practice.

This report will be of interest for all medical practitioners involved in the management of CAD, including internists, cardiologists, and nuclear medicine physicians, as well as hospital administrators and health care stakeholders.

The IAEA technical officers responsible for this publication were M. Dondi and F. Mut Bastos of the Division of Human Health.

CONTENTS

1. INTRODUCTION

1.1. BACKGROUND

As reported by the World Health Organization (WHO), cardiovascular diseases (CVDs) are the principal cause of death globally. More people die from CVDs than from any other cause. Almost one third of all deaths are caused by CVDs, mainly by coronary artery disease (CAD). Low and middle income countries are disproportionally affected, since more than 80% of cardiac deaths take place in these countries and occur almost equally in men and women. According to current trends, it is expected that by 2030, more than 23 million people will die from CVDs; CAD and strokes are projected to remain the single leading causes of death. The largest percentage increase of cardiovascular mortality will occur in the eastern Mediterranean and in the Southeast Asian regions.

Individuals can reduce their risk of CVDs by changes in lifestyle, for example by engaging in physical activity, avoiding tobacco use and choosing a healthy diet. However, these preventive measures are often incomplete or insufficient and take time to have a clinical impact, while there are also other risk factors, such as diabetes, which cannot be totally under the patient's control.

Although still the most prevalent of all form of CVD, CAD has declined over the last few decades in developed countries due to the introduction of prevention strategies. Nuclear cardiac imaging has a dominant position within some of these strategies, particularly in secondary prevention. However, it is clearly underutilized in many areas of the world, especially those more affected by CVDs.

1.2. OBJECTIVE

Non-invasive cardiac imaging techniques, in particular stress single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), have a central role in the diagnostic workup and risk assessment of patients with known or suspected CAD, lowering the cost of caring for those patients. The objective of this publication is to discuss the cost effectiveness of non-invasive imaging techniques, and more specifically of MPI. It describes the currently available non-invasive cardiac imaging modalities for the detection of CAD and reviews the strengths and weaknesses of each modality to help optimize the utilization of available techniques focusing on effective patient management.

1.3. SCOPE

This publication presents a comprehensive overview of CVDs as a public health problem in developing countries, the relative role of nuclear cardiology methods within a scenario of unprecedented technology advances, and the evidence behind appropriateness recommendations. The potential expanding role of non-invasive functional imaging through the transition from diagnosis of obstructive CAD to defining the global burden of CVD is also discussed, as well as the need for solid training, education and quality in nuclear cardiology practice.

1.4. STRUCTURE

This report summarizes the epidemiology of CVDs worldwide with emphasis on the increasing prevalence in developing countries; describes the evidence behind the utility of nuclear techniques in common clinical scenarios; reviews the global utilization of the method in various regions of the world; provides support for its cost effective use suitable for developing countries; analyses the opportunities and challenges posed by established or emerging competing modalities; and presents some technical advances potentially enhancing the performance of nuclear cardiology. The central role of nuclear cardiology in preventive care is analysed, leading to expanded clinical applications focused on special populations at risk of cardiac disease and events. Finally, the need for quality nuclear cardiology practice is discussed, including training, education and radiation safety issues.

2. EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES IN DEVELOPING COUNTRIES

2.1. INTRODUCTION

Cardiovascular disease (CVD) refers to a class of diseases that involve the heart and/or blood vessels. While the term technically refers to any disease that affects the cardiovascular system, it is generally used to identify conditions related to atherosclerosis. Atherosclerosis is a process that develops over decades and is silent in a large proportion of cases until an acute and sometimes fatal event (such as a heart attack, sudden death or a stroke) occurs, usually at or after the fourth decade of life.

There is frequently a misconception that cancer kills more people than does CVD, especially breast cancer in women. However, all statistics consistently show the opposite. According to WHO, CVD is the leading cause of mortality in adults worldwide for both men and women, killing a much larger number of persons compared with cancer. It is estimated that currently 17.5 million people die every year due to CVD, which correspond to about 30% of all causes of deaths in the world (Fig. 1). Unfortunately, if this trend continues, by the year 2015 this number will increase to approximate 20 million global deaths per year, of which 7–8.5 million will be people under the age of 70 (Fig. 2). Of major importance is the fact that according to WHO estimates, about 80% of these deaths occur in low to middle income countries (i.e. developing nations) with limited resources to face a problem of this magnitude. The victims of CVD are usually at their peak productive age, which further aggravates the economic situation of these nations.

The fatal consequences of CVD typically affect individuals of middle to more advanced age. However the process of atherosclerosis evolves slowly over decades, beginning during infancy. Awareness regarding potential modifiable factors that contribute to the development of CVD such as obesity, diabetes, sedentary life style, smoking, hypertension, and high lipid values, is extremely important and education about these factors should start during childhood as a way to promote primary prevention.

Although primary prevention is important, it is a slow process and the impact on mortality reduction will only be seen over the middle and long term; this will have limited impact in reducing the epidemic of CVD mortality already being seen throughout the world. However, the course of the disease is potentially modifiable. To produce an impact on mortality today, it is imperative to identify individuals with advanced atherosclerosis (symptomatic or asymptomatic) and

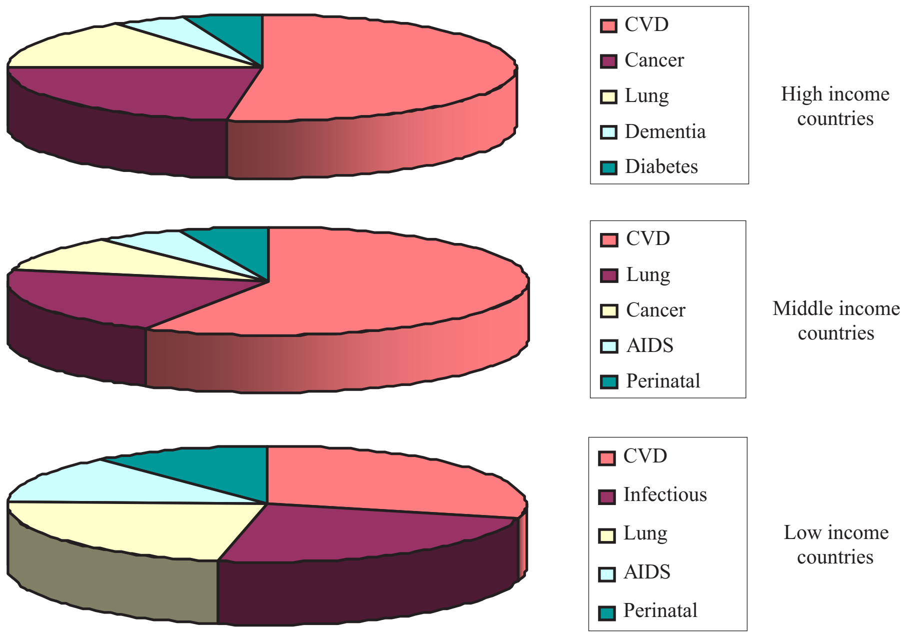

FIG. 1. The five main causes of death in the world. The graphics show the relative weight of specific causes among the five most prevalent. CVD: cardiovascular diseases, including stroke; Cancer: includes the five most prevalent types of cancer for the specific group of countries; Lung: all respiratory diseases including pneumonia, but not tuberculosis; Infectious: includes gastrointestinal infections, tuberculosis and malaria, but excludes other respiratory infections. CVDs are the most single common cause of death among the three categories of countries. (Source: adapted from WHO data (2003); income categorization from the World Bank).

start treatment (medical or interventional) and secondary prevention measures as soon as high risk disease is discovered.

2.2. EPIDEMIC OF OBESITY AND DIABETES IN DEVELOPING COUNTRIES

Diabetes mellitus (DM) is closely linked with the development of atherosclerotic lesions and CVD. In general terms, there are two types of DM, one starting during childhood and adolescence which is related to lack of insulin production, called type 1 DM, and the other occurring in adults and closely linked to obesity and large deposition of adipose tissue around the waist. This is

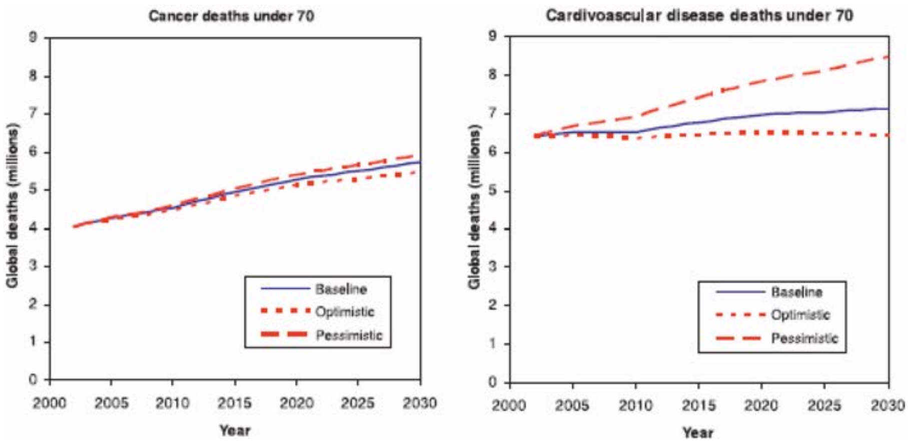

FIG. 2. Current and predicted deaths until 2030 for the population under age 70 due to cancer and CVD under three different scenarios (adapted from WHO data (2003)).

type 2 DM and accounts for 90% of all cases of diabetes. Importantly, it is estimated that 70% of individuals with DM will die because of CVD.

Changes in lifestyle, especially related to high fat and carbohydrates intake and lack of exercise, have been responsible for a rapidly increasing number of DM patients in low and middle income countries. Data from WHO demonstrate that in countries of South-east and South Asia, about 8% of the population has DM. The Diabetes International Federation estimates that, by the year 2025, some Latin American countries like Brazil and Mexico, as well as some Middle Eastern countries like Saudi Arabia, will have between 14% and 20% of their population suffering from DM. These countries are already seeing the consequences of the high incidence of DM, with a progressively increasing number of individuals affected by CVD. From the ten nations with the highest prevalence of diabetes, seven are developing countries (Fig. 3), and the observed increase in incidence is expected to be higher in the developing world (Fig. 4). The alarming statistics also reflect on governmental budgets, which must be oriented to deal with this severe health problem.

One of the major problems with diabetes is the high incidence of 'silent' myocardial ischaemia. This leads to late consultation by the patient, or to the development of chronic heart failure due to the repetition of ischaemic episodes and even myocardial infarction cursing with no symptoms. Early and accurate detection of cardiac complications is thus essential in this group of patients in order to apply secondary preventive measures. A case of a young individual with diabetes and additional cardiovascular risk factors with advanced ischaemic heart

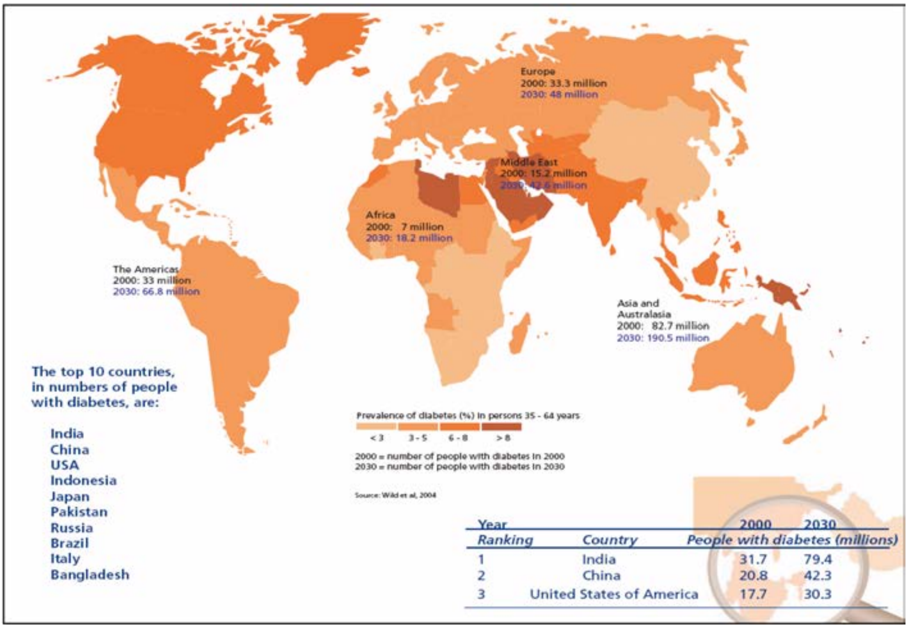

FIG. 3. Prevalence of diabetes in the world in 2000 and projections for 2030. Source: WHO Diabetes Programme (www.who.int/diabetes/en/).

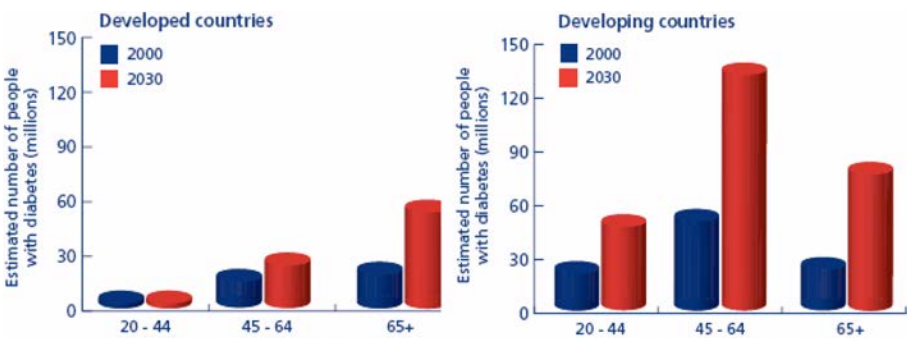

FIG. 4. Estimated number of adults with diabetes in developed and developing countries and projections to 2030 (WHO Diabetes Programme www.who.int/diabetes/actionnow/en/diabprev.pdf).

disease and a few symptoms evaluated with nuclear cardiology is presented in Fig. 5.

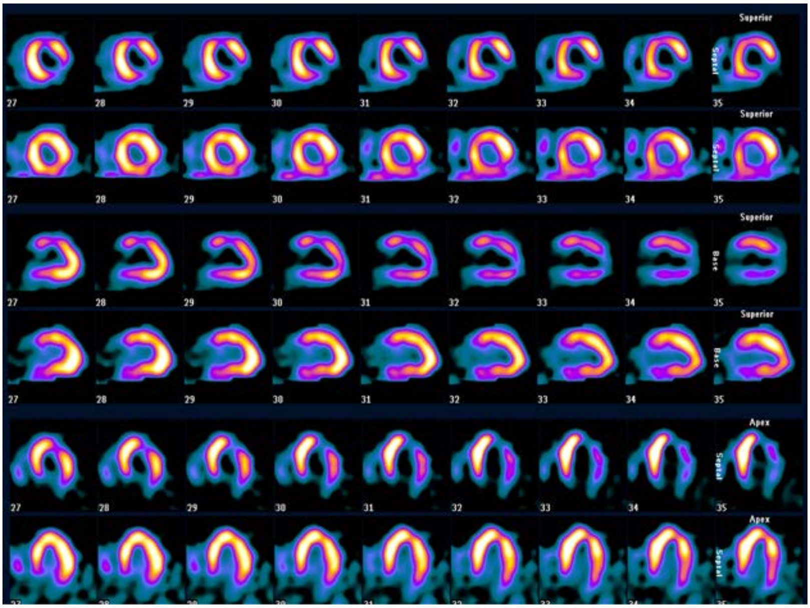

FIG. 5. A 36 year old man with diabetes, obesity, hypertension, and high cholesterol levels who complained of shortness of breath. Despite having no chest pain and a negative exercise electrocardiogram, this patient had nuclear cardiology findings consistent with advanced CAD and high risk of death and/or myocardial infarction (courtesy J. Vitola, Brazil).

2.3. THE AGEING POPULATION

While high mortality rates are seen in young and middle aged adults with DM and CVD in developing nations, some developed and developing countries are also facing a significant problem because of the ageing of their population (Fig. 6). For example, the life expectancy in Japan is 79 years for men and 86 years for women; in Australia and Italy, it is 79 years for men and 84 years for women; in Argentina, it is 72 years for men and 78 years for women; and in Cuba, it is 75 years for men and 79 years for women, to mention a few examples. Since atherosclerosis is a process that progresses throughout life, elderly individuals are more likely to present a higher incidence of the disease and its related complications.

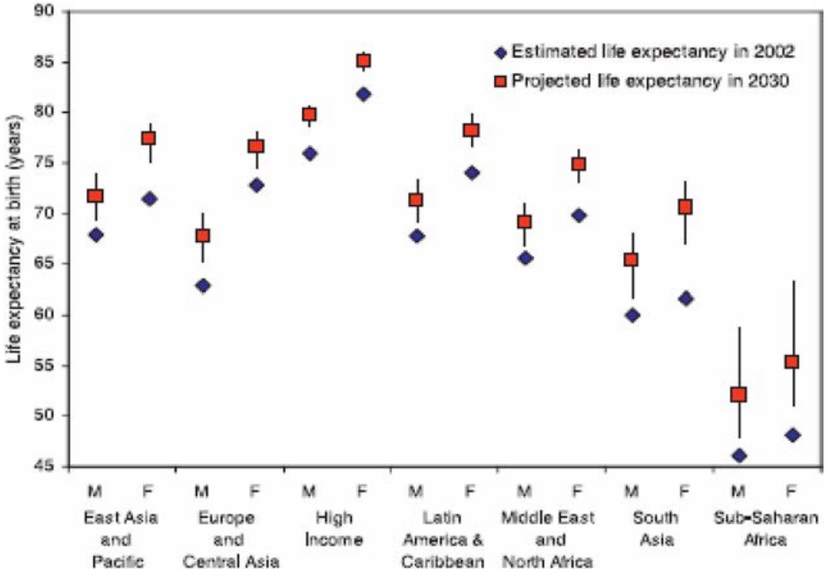

FIG. 6. Projected life expectancy at birth in 2030 compared with 2002 (WHO data (2003)).

Considering the costs related to the management of CVD in the elderly population, as well as the associated co-morbidities, this increasing incidence seen in developed and in low to middle income nations is an extremely important issue with economic implications that physicians, governments and health care providers will need to face.

2.4. IMPORTANCE OF EARLY DETECTION AND TREATMENT

Successful management of cardiac patients depends largely on early detection of pathological conditions, adequate risk stratification which is crucial for treatment planning, and prompt application of therapeutic measures. Currently, there are many techniques and alternatives to diagnose and evaluate CVD, providing different types of information regarding the anatomy and physiology of the heart, particularly for diagnosis, risk stratification and proper management. These different types of information are generally complementary, but occasionally the methods are competitive. Considering the costs involved, optimization of resources through a rational utilization of each diagnostic technique is especially important for low and middle income countries.

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3. NUCLEAR CARDIOLOGY: ONE OF THE MOST ACCEPTED TOOLS FOR THE MANAGEMENT OF PATIENTS WITH CARDIOVASCULAR DISEASE

3.1. INTRODUCTION

Nuclear cardiology is a well established technique to detect CAD and to assess ventricular function, and its role as a non-invasive methodology for the characterization of a variety of cardiac conditions has been extensively evaluated. A radiotracer is injected to the patient and images are obtained using a special instrument (gamma camera). In Canada and the USA, as well as in other developed countries, this is the most commonly used procedure for detecting and determining the severity of CAD. It is sensitive, accurate and cost effective, and gives excellent prognostic information that is not provided by other diagnostic modalities. Nuclear cardiology uses the single photon emission computed tomography (SPECT) imaging method, which provides three dimensional information about the distribution of a radioactive compound in the heart, which was previously administered intravenously at rest or during a stress test.

SPECT MPI is commonly performed with technetium-99m labelled tracers, such as sestamibi and tetrofosmin, or with thallium-201. MPI can detect myocardial ischaemia and viability as well as assess left ventricular (LV) function. The safety of MPI during exercise or pharmacological stress (dipyridamole, adenosine or dobutamine) is comparable to exercise ECG, although the diagnostic yielding is largely superior in terms of both sensitivity and specificity. Substantial evidence from developed and developing countries strongly supports the accuracy and cost effectiveness of MPI for the evaluation and management of patients with suspected or known CAD. The American College of Cardiology/American Heart Association (ACC/AHA), and the European Society of Cardiology (ESC) Guidelines strongly recommend MPI as class I or II indications for the diagnosis and risk stratification of patients with suspected or known CAD. While SPECT MPI is currently the most commonly used technique for the assessment of CAD in many developed nations, it is underutilized or even non-existent in a large proportion of developing countries.

3.2. MYOCARDIAL PERFUSION IMAGING IN STABLE CAD

In a recent meta-analysis of large studies which included the use of thallium-201 and technetium-99m labelled tracers with either exercise or pharmacological stress tests, the average sensitivity for detection of angiographically significant CAD was reported to be 87% and the specificity was 73%. These values are significantly superior to exercise ECG, and are consistent and independent of the subpopulations selected, i.e. women, obese patients, subjects with chronic renal disease and diabetic patients. Moreover, the availability of ECG gated images (gated SPECT) improves the accuracy up to 90%. The accuracy of MPI has been compared with that of stress echocardiography, generally showing MPI to have higher sensitivity and equivalent or slightly lower specificity.

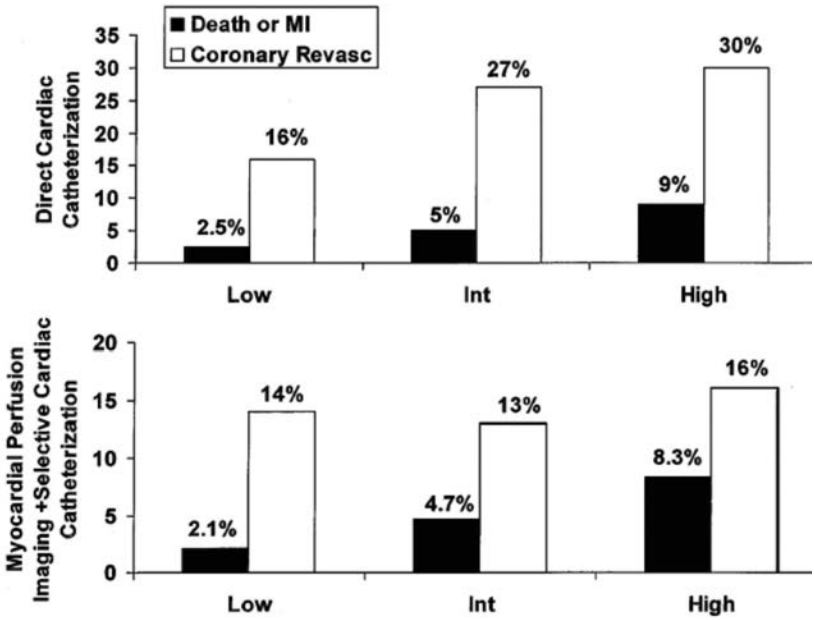
The value of MPI in assessing prognosis in patients with stable CAD has been established in large cohorts of patients with a variety of underlying risk profiles and pathologies. Normal MPI in patients with intermediate to high likelihood of CAD predicts a very low cardiac event rate (<1%/year). In contrast, abnormal MPI in the same populations increases the annualized event rate by up to a factor of 7, and the risk of events is closely related to the extension and severity of perfusion abnormalities. Thus, MPI is superior to ECG, echo, magnetic resonance imaging (MRI), and even contrast coronary angiography for prognosis and risk stratification.

Similarly, it has been demonstrated that diagnostic strategies based on nuclear cardiology rather than direct reference to catheterization are associated with significantly lower rates of cardiac events, especially cardiac revascularization (Fig. 7).

3.3. MYOCARDIAL PERFUSION IMAGING IN ACUTE CORONARY SYNDROMES

Of the approximately six million patients evaluated for chest pain in emergency departments in the USA, only one third will be found to have symptoms of cardiac origin. The role of SPECT MPI as a ‘gatekeeper’ to hospital admission for acute chest pain is well documented. MPI has a high negative predictive accuracy for ruling out acute coronary syndromes and future cardiac events in patients presenting to the emergency room with acute chest pain, non-diagnostic ECG and negative cardiac enzymes. An algorithm for the evaluation of patients with suspected acute coronary syndrome (ACS) is presented in Fig. 13. Following this algorithm, patients with low probability of ACS can be identified and safely discharged, while others will be admitted and undergo further testing or coronary angiography.

Current guidelines also recommend stress MPI after an episode of unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) for risk



	Low	Int	High
Reversible Perfusion Defect	20%	43%	51%
Cardiac Catheterization	16.4%	22.3%	31.3%

FIG. 7. Cardiac event rates (death, MI, revascularization) according to direct catheterization strategy versus myocardial perfusion — first strategy. The latter is most significantly associated with lower revascularization rates (from L.J. Shaw; reprinted with permission).

stratification, especially in patients with a low to intermediate likelihood of cardiac events according to traditional markers of risk. Stress MPI is an option in selected patients after ST-elevation myocardial infarction (STEMI) that might have received thrombolytic therapy but who have not yet undergone coronary angiography in order to determine the extent of ischaemic myocardium and whether revascularization will be beneficial. SPECT MPI with dipyridamole is considered a safe test even early after myocardial infarction, provided no contraindications are present.

3.4. MYOCARDIAL PERFUSION IMAGING BEFORE NON-CARDIAC SURGERY

Surgery is a major stress factor for the heart, especially vascular non-cardiac surgery as well as some non-vascular interventions, and patients with known or non-diagnosed CAD are at risk of cardiac events. Trials of beta blockers in patients undergoing non-cardiac surgery have reported conflicting results. The POISE Trial was a large, randomized controlled group trial of metoprolol versus a placebo in 10 000 patients undergoing non-cardiac surgery, designed to determine the impact of perioperative administration of metoprolol on cardiovascular events during the 30 day post-operative period in at-risk patients undergoing non-cardiac surgery. Results showed that although fewer patients in the metoprolol group had a myocardial infarction, there were more deaths than in the placebo group. Therefore, beta blockers cannot be used in all patients and there is a clear need to identify those who would benefit most from its use.

MPI has received a class I indication for risk stratification of patients undergoing elective non-cardiac surgery. MPI with pharmacological stress is also effective in determining risk in patients with poor exercise capacity undergoing high risk surgery regardless of clinical predictors. Information derived from MPI should be used not only for surgical risk stratification, but also for the subsequent cardiac management of patients after non-cardiac surgery. For high risk patients, myocardial revascularization prior to the planned surgical procedure could be indicated, or special preventive measures could be adopted.

3.5. ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND OTHER NON-PERFUSION PARAMETERS IN CARDIAC DISEASES

Left ventricular (LV) global and regional function can be accurately assessed with radionuclide ventriculography (RNVG) using labelled red blood cells, or gated SPECT MPI. The reproducibility of radionuclide methods is higher than that of other non-invasive imaging modalities, probably with the exception of MRI. The LV ejection fraction (LVEF) is the most powerful predictor for cardiac death in patients with heart failure. The method for evaluating left ventricular performance with radionuclides refers to a true 3-D technology, fully automated, operator independent, with no limitations regarding body size and shape, reliable and reproducible.

At present, there are at least three software packages commercially available worldwide using gated SPECT myocardial perfusion, which despite small systematic differences show good agreement with cine MRI over a wide range of end diastolic volumes (EDV), end systolic volumes (ESV), and LVEF values (Fig. 8). Hence, gated SPECT provides clinically relevant information on cardiac function and volumes with all three algorithms. However, considering the importance of accurate LVEF measurements — especially in borderline values — for therapeutic implications, it should be kept in mind that an interchangeable use of the three algorithms is not advisable for the evaluation of serial changes and

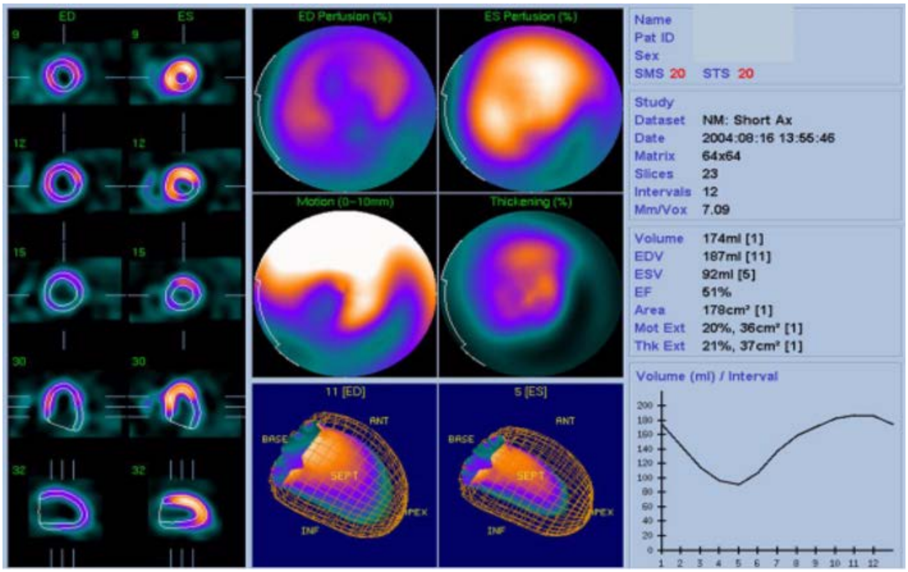


FIG. 8. Example of LV function analysis with gated SPECT. Several parameters can be assessed, including ventricular volumes, LVEF, and regional wall motion and thickness (courtesy S. Bouyoucef, Algeria).

for prognostic conclusions. Regardless of the software used, the method is repeatable over a wide range of values and there is solid scientific evidence that gated SPECT can be considered a reliable technique both in clinical practice and for multicentre research trials.

Since LVEF together with regional wall motion and thickness can be assessed both at rest and in the post-stress period, it is possible to detect transient ischaemic dysfunction when LV contractile function is significantly deteriorated post-stress. This is thought to represent the so-called myocardial stunning phenomenon and represents a sign of poor prognosis, usually reflecting severe and extensive ischaemia. Also, ischaemic transient LV dilation (TID) can be measured, having a similar significance with pulmonary uptake and retention of the radiotracer after stress injection. All three phenomena (change in LVEF, TID and pulmonary uptake) may reflect LV ischaemic dysfunction during stress and are of special diagnostic value when there is balanced ischaemia and no segmental abnormalities are evident in the perfusion images.

The development of a computer algorithm to measure 3-D LV shape index, derived as the ratio of maximum 3-D short and long axis LV dimensions for end systole and end diastole, has been reported. This index can be measured even in patients with large perfusion defects and it represents a promising new 3-D variable derived automatically from gated MPI providing highly repeatable ventricular shape assessment. Preliminary findings suggest that the LV shape index might have clinical implications in patients with congestive heart failure.

To extract the most clinical information from nuclear imaging studies, all functional and morphological parameters should be considered, and quantitative data fully integrated for final analysis and interpretation, provided the quality of acquisition and processing phases are kept within optimal standards.

In cases where only functional (non-perfusion) data are needed for clinical management, the use of RNVG rather than gated SPECT MPI could be more cost effective. SPECT RNVG is also available in most cardiac software packages, permitting a more precise assessment of regional ventricular function. Care is to be taken when comparing results from different equipment, especially if different quantitative software is used which could potentially affect reproducibility.

3.6. ASSESSMENT OF VIABLE AND HIBERNATING MYOCARDIUM IN HEART FAILURE

The concept of myocardial hibernation was introduced to describe a condition of chronic sustained abnormal contraction attributable to long term hypoperfusion in CAD patients in whom revascularization induces the recovery of LV function. In turn, myocardial stunning has been defined as a spontaneously reversible myocardial contractile dysfunction due to an acute ischaemic episode, in the presence of normal resting myocardial blood flow. Differentiation between permanently dysfunctional (fibrotic) myocardium and viable myocardium is important for therapy planning. Nuclear cardiology techniques are able to detect signs of myocardial viability including cell membrane integrity and residual glucose metabolism and are, at present, considered the most sensitive tools to detect viability in comparison to other techniques such as low dose dobutamine echocardiography which explores contractile reserve.

The end points evaluated in several viability studies, designed to analyse the effects of revascularization, include improvement in global and regional LV function, improvement in symptoms and exercise capacity, efficacy in reversing LV remodelling, and prognosis in terms of event-free survival and quality of life. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET is used to define viable myocardium in patients with CAD and severe LV dysfunction, and to guide revascularization decisions. The presence of glucose uptake in a dysfunctional area with impaired perfusion (mismatch pattern) is characteristic of hibernated (viable) myocardium with a potential for functional improvement after revascularization. A meta-analysis of 24 prognostic studies (comprising 3088 patients) that used various

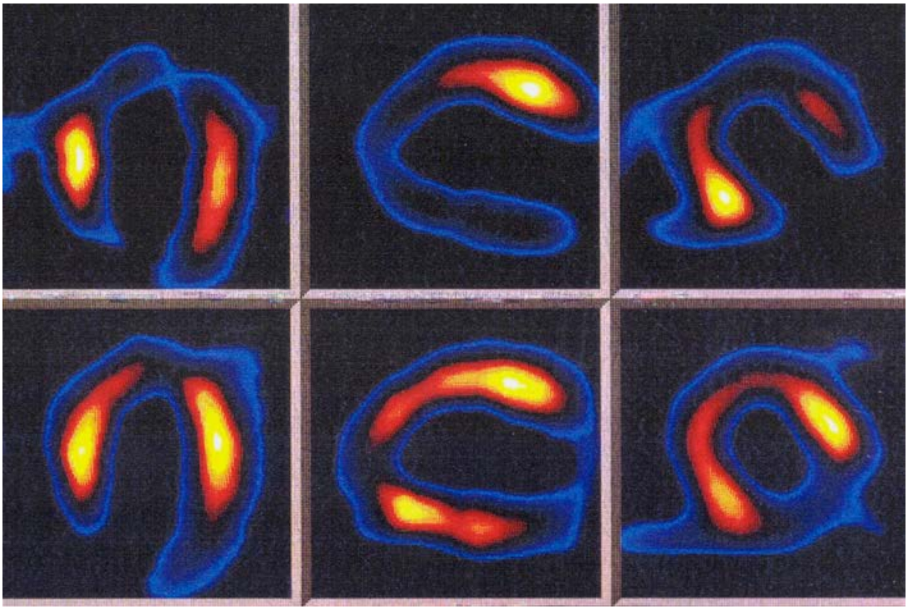


FIG. 9. Viability study with ^{99m}Tc-sestamibi. Upper row: horizontal long axis, vertical long axis and short axis; basal MPI demonstrating large areas of hypoperfusion in the apical, anterior, inferior and posterolateral walls. Bottom row: nitrate enhanced study showing improvement of perfusion in all territories, although less evident in the posterolateral wall where dominant fibrosis is more likely to be present (courtesy F. Mut).

techniques for viability assessment, showed a 3.2% annual death rate in patients who had viable myocardium and who underwent revascularization, compared with a 16% annual death rate in patients who had viable myocardium and were treated medically. Thus, the detection of viable myocardium has a significant impact in patient management.

It has been demonstrated that SPECT strategies using conventional imaging can also be effective for viability evaluation. Sensitivity, specificity, and accuracy of two sequential strategies to predict improvement in LVEF after revascularization using SPECT perfusion tracers have been investigated and compared with FDG, with similar results. In particular, the use of nitrate enhanced MPI with conventional tracers is a simple and inexpensive way to evaluate myocardial viability (Fig. 9). However, there is still lack of data from randomized trials to prove unequivocally that revascularization of dysfunctional but viable myocardium may lead to reverse LV remodelling and confers prognostic benefits in patients with post-ischaemic heart failure.

Recently, it has been documented by using gated SPECT MPI that in patients with LV dyssynchrony the response to cardiac resynchronization therapy

(CRT) is related to the extent of viable myocardium and inversely related to the amount of scar tissue. Moreover, it is suggested that ^{18}F-FDG PET may be used to optimize the selection process for CRT by identifying viable segments, which yields high accuracy for predicting CRT response.

In summary, myocardial viability can be assessed both by SPECT MPI and by myocardial FDG utilization (the latter using the more sophisticated PET technique). Nitrate enhanced MPI protocols are widely available and can be used in developing countries because of its accuracy, convenience and low cost. Patients with ventricular dysfunction but with substantial myocardial viability (hibernated myocardium) will most likely benefit from revascularization through improvement in ventricular function and symptoms. In contrast, patients without evidence of viability will not significantly benefit from revascularization, and the high risk of surgery should be avoided; this approach has been demonstrated to be cost effective. Non-invasive imaging is also recommended for the detection of obstructive CAD in patients with symptomatic LV dysfunction using stress rest SPECT MPI, in order to identify any ischaemic component that could undergo either medical or invasive treatment and improve patient outcome.

3.7. CLINICAL GUIDELINES

A list of recommendations for the use of nuclear cardiology procedures in different clinical settings can be seen in Table 3.1, including management of CAD syndromes under chronic and acute conditions, pre-operative risk assessment, and heart failure. These recommendations have been issued by recognized scientific societies such as the European Society of Cardiology (ESC), the American College of Cardiology (ACC) and the American Heart Association (AHA), and supported by a large and solid body of literature. Similar recommendations from other national and international organizations and institutions can also be found elsewhere. Following these evidence based guidelines, appropriateness criteria for the clinical indication of nuclear cardiology procedures have been prepared and are in use in health systems of several countries throughout the world. However, it should be noted that exact translation of these guidelines into local health systems and institutions may not be totally advisable or applicable due to economic and cultural differences, as well as biological diversity affecting the natural course of cardiac diseases. Nevertheless, the guidelines provide an adequate set of references for clinical practice worldwide. It must be kept in mind that the success of nuclear cardiology for the management of patients with known or suspected CAD relies on its accuracy, safety, and availability which make these techniques very cost effective diagnostic tools.

TABLE 3.1. RECOMMENDATIONS FOR MPI IN PATIENTS WITH SUSPECTED OR KNOWN CAD ACCORDING TO CURRENT CLINICAL GUIDELINES. ESC = EUROPEAN SOCIETY OF CARDIOLOGY; ACC = AMERICAN COLLEGE OF CARDIOLOGY; AHA = AMERICAN HEART ASSOCIATION
(modified from MARCASSA, C., et al., Eur. Heart J. (2008))

Clinical scenario	Recommendation	Issuing body	Class	Level of evidence
Chronic chest pain	Diagnosis of CAD in patients with intermediate pre-test likelihood: unable to exercise, abnormal rest ECG	ESC/ACC/AHA	I	B
Chronic chest pain	Evaluation of CAD in patients with intermediate pre-test likelihood: identification of culprit lesions, assessment of the haemodynamic significance of stenosis, evaluation post-PCI or CABG	ESC/ACC/AHA	I	B
Acute chest pain	Detection of resting ischaemia	ESC/ACC/AHA	IIb IIa	B
	Detection of ischaemia in low to intermediate risk patients after UA/NSTEMI	ESC/ACC/AHA	I	B
	Detection of ischaemia in patients with uncertain diagnosis	ESC/ACC/AHA	I	A
	Assessment of infarct size and myocardium at risk after STEMI	ESC/ACC/AHA	I	B
Pre-operative risk assessment	Risk stratification before elective non-cardiac surgery	ACC/AHA	I	C
Heart failure	Detection of ischaemia and viability assessment	ESC/ACC/AHA	IIa	B
	Diagnosis of CAD	ACC/AHA	IIb	C

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4. USE OF NUCLEAR CARDIOLOGY AROUND THE WORLD

4.1. INTRODUCTION

The use of nuclear cardiology procedures varies widely in different countries and regions of the world. Economic situation, technology availability, human resources development, health system priorities, education and awareness of the benefits of the technique are probably some of the reasons for this disparity.

4.2. ANALYSIS OF AVAILABLE DATA

Unfortunately, there are currently no worldwide reliable statistics on the utilization of nuclear cardiology besides some regional data from developed areas, registered mainly by the corresponding scientific societies. The IAEA has established a mechanism for recording data from developing countries, although this process has been relatively slow due to poor response rate and is far from being completed. It is expected that institutions and departments around the world will understand the importance of participating in this survey and will submit accurate data which will allow to have a more exact picture of the current status of nuclear medicine practice in general, and of nuclear cardiology, in particular.

According to recently gathered data and despite significant variations across countries, it is estimated that in developed nations the utilization of the technique is at least seven times higher than in developing countries (Fig. 10), although among these, there is also large heterogeneity. The reasons for this are multiple, no doubt including economic factors which have a major role to play as well as educational, cultural and political aspects. The characteristics of the health system and the relative availability and dominance of alternative diagnostic procedures are also very important when the rate of utilization of nuclear cardiology for a particular country or region is considered.

However, for any particular region there are significant differences between countries, even in developed areas. For example, utilization of nuclear cardiology is much higher in the USA and Canada as compared with Japan and the European Union (Fig. 11). Although experiencing a rise during the last years, the UK exhibits a utilization rate below the European average despite being one of the most developed countries in the region.

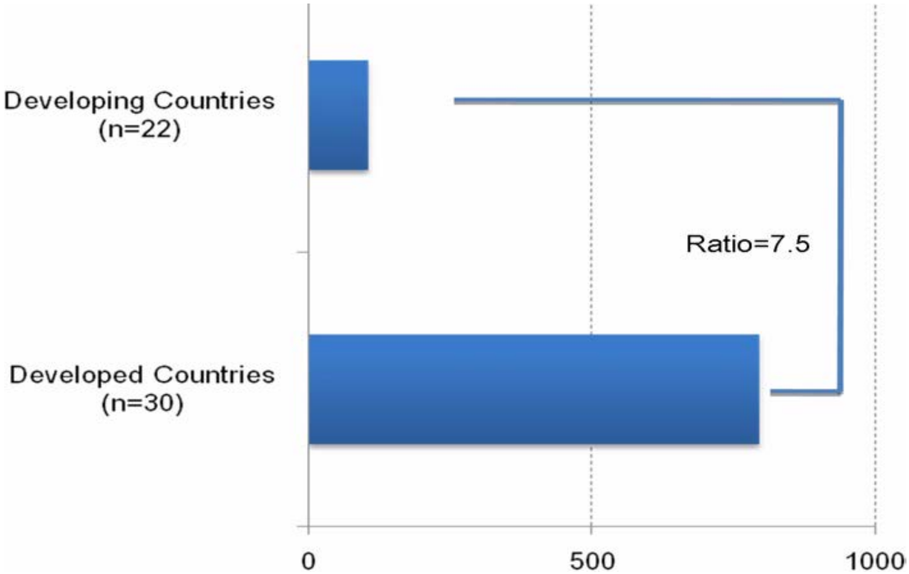

FIG. 10. Nuclear cardiology procedures per 100 000 of the population per year for developing versus developed countries (estimated average, 2007) (source: ASNC, EANM, ALASBIMN. IAEA Technical Meeting, Vienna (May 2008)).

In some countries in Latin America, the utilization is similar to that of developed areas, while in others the technique is almost non-existent. In big countries like Brazil, there are state of the art facilities in some urban areas while on the other hand, large sectors of the population have little or no access to the technology. A similar situation is seen in Asia-Oceania, where clearly the most developed nations present higher utilization rates as compared with poorer countries, with some exceptions such as New Zealand, where provision for nuclear cardiology services is very limited. Again, larger countries like India and China exhibit quite inhomogeneous coverage for nuclear cardiology procedures.

In Africa, nuclear cardiology is rarely utilized due to the existence of very few operative nuclear medicine departments. These are concentrated mainly in South Africa and in the northern part of the continent, with most of the countries having no availability of these services at all. Although the public health situation in Africa is such that it demands many priorities at the same time, the incidence of cardiac disease is high and steadily increasing in most nations. Egypt is the country where nuclear cardiology is more developed, though with a utilization rate below the average in Latin America.

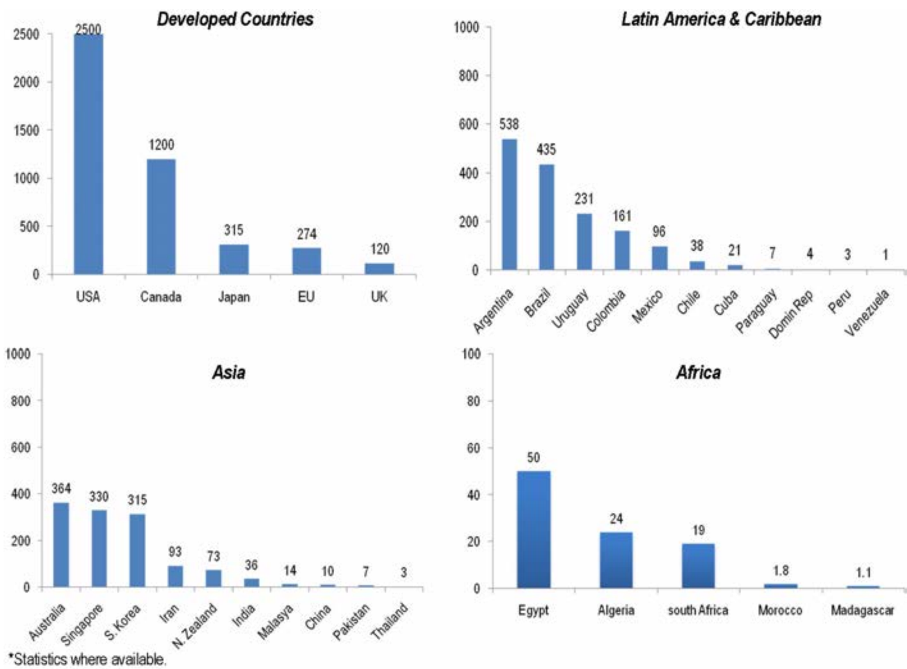

FIG. 11. Nuclear cardiology procedures per million of the population by country in different areas of the world (only countries with available statistics from 2006–2007 are represented). European countries are grouped and averaged under EU (European Union), with the exception of the UK (source: ASNC, EANM, ALASBIMN. IAEA Technical Meeting, Vienna (May 2008)).

Figure 12 shows the global utilization of nuclear cardiology as per a recent estimate, with the blanks reflecting insufficient data or complete absence of nuclear cardiology practice.

4.3. USE OF NUCLEAR CARDIOLOGY VERSUS MORTALITY RATE

Interestingly, there is an inverse relationship between the use of nuclear cardiology and mortality rates in some developed countries where data are available (Fig. 13). In fact, nuclear cardiology procedures have been increasing in number in Japan, Australia, Canada and the USA, while mortality rates (mainly due to CVDs) have been declining. Obviously, the availability of state of the art technologies both for diagnosis and treatment, including the development of new drugs, together with the successful implementation of preventive measures and not only the increasing use of nuclear cardiology or other imaging modalities, are responsible for this observed decrease in mortality.

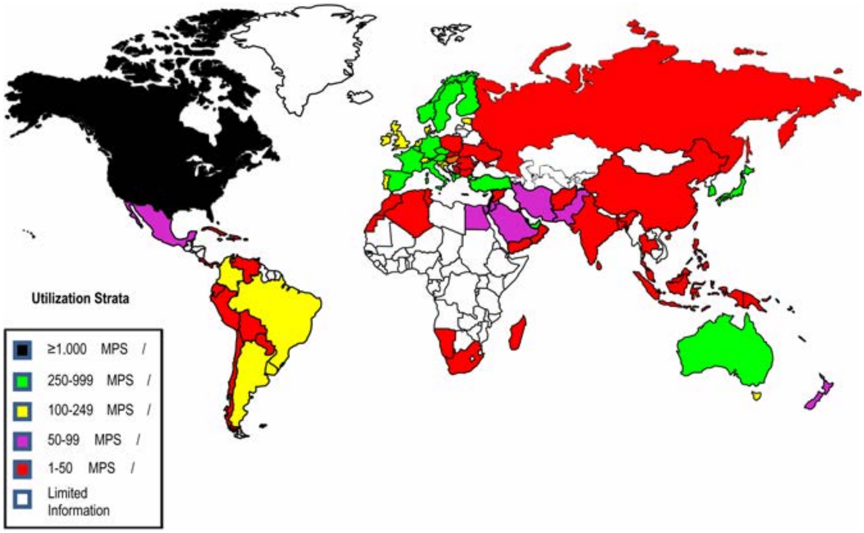

FIG. 12. Estimates of worldwide utilization (per 100 000 of the population) of nuclear cardiology procedures in 2006–2007. Uncoloured areas represent countries with non-existent nuclear cardiology facilities, or unavailability of information (source: IAEA Technical Meeting, Vienna (May 2008)).

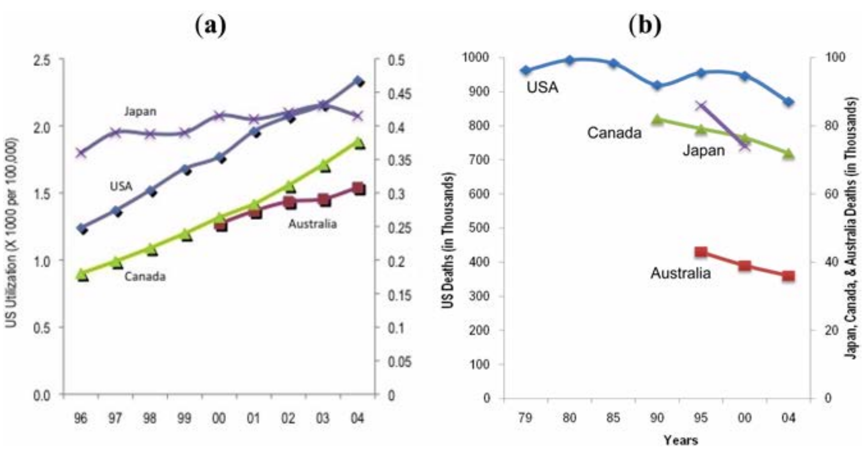

FIG. 13. (a) Utilization of SPECT MPI in selected developed countries over the last decade. (b) Observational evidence of declining cardiovascular mortality, as reported from these same developed countries over the past several decades. Note that for both figures, the USA uses the y-1 axis and Japan, Canada and Australia are plotted on the y-2 axis (source: IAEA Technical Meeting, Vienna (May 2008)).

Nevertheless, from the epidemiological evidence the relationship exists and the role that nuclear cardiology plays in the proper management of cardiac patients is likely to be reflected to some extent in the recent dramatic declines in CVD mortality.

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5. COST EFFECTIVENESS

5.1. INTRODUCTION

Cost effectiveness analysis (CEA) is an analytical approach that integrates the clinical effectiveness of a diagnostic or therapeutic procedure with its economic value. For countries with very limited resources, the calculation of marginal or incremental cost effectiveness provides a rational means to balance health care quality and clinical value in terms of the best outcome at a reasonable economic cost. As an example, SPECT MPI can be evaluated on whether its use is worth the additional cost when compared with other diagnostic modalities. Other definitions of CEA can be considered as well, for example, according to the US Preventive Services Task Force, CEA is defined as an incremental comparison of the cost per life-year saved. In cardiovascular medicine, disease specific CEA has also been defined as the cost per correct disease classification or the cost per event detected. Thus, the global equation that can be applied for any CEA is: Δcost/Δoutcome. In other words, CEA relates the economic resources consumed to the benefits attained.

5.2. COST EFFECTIVENESS IN NUCLEAR CARDIOLOGY

Nuclear cardiology procedures, in particular SPECT MPI, are cost effective in several settings because they represent mostly outpatient investigations of moderate cost, high diagnostic accuracy and low risk. This is an important issue of particular interest to developing countries with an urgent need for optimizing resources distributed to the health area.

In general, SPECT MPI can be considered as a moderately priced diagnostic modality involving lower costs than those for PET, MRI and invasive coronary angiography. However, SPECT costs are still higher than a simple consultation with the cardiologist, a treadmill test, or an echocardiography study. Cardiac SPECT MPI costs can nevertheless be relatively reduced in centres performing high volumes of studies or by sharing fixed costs across non-cardiac procedures, which is commonly the case in general nuclear medicine departments.

Cost differences between modalities are frequently used to decide the test of choice for a particular clinical situation. However, diagnostic costs must also take into account the economic burden involved in the episode of care; not only the direct test costs, but also any induced costs emanating from the procedure result must be considered. For many modalities including SPECT MPI, this would include the false positive and negative results that might define the degree of inefficiency for a diagnostic procedure. One method to quantify the cost 'waste' with SPECT MPI is to examine the diagnostic accuracy through an insight into the common rates of false positive and negative results. According to a recent review, the overall diagnostic sensitivity and specificity are 87% and 73% (n = 19 studies) for exercise, and 89% and 75% (n = 24 studies), respectively, for pharmacological stress SPECT MPI. This means that in nearly 9 out of 10 patients with significant coronary stenosis by coronary arteriography, perfusion abnormality is noted on SPECT MPI. However, nearly 1 in 4 patients has a false positive SPECT MPI result. Most often, these are due to perfusion abnormalities related to endothelial dysfunction in a region with an intermediate coronary stenosis (physiological true positive, but anatomically false positive) or to soft tissue attenuation artefacts in women and in obese patients. With regard to the latter, some improvements have reduced the false positive rate, including attenuation correction algorithms and the use of gated SPECT for assessment of regional wall motion and thickness.

5.3. PATIENTS WITH STABLE ANGINA

In patients with stable angina and intermediate pre-test probability of CAD, it has been shown that a diagnostic strategy guided by SPECT MPI is more cost effective than a more conventional strategy using direct coronary angiography or even CT angiography. A SPECT MPI led management strategy results roughly in 25–40% cost savings compared with direct referral to coronary angiography (Fig. 14), mainly because with the first approach many unnecessary invasive procedures are avoided. Therefore, and contrary to popular opinion, MPI is a cost saving procedure in the overall management of chronic CAD patients.

By reviewing the SPECT MPI literature, some general economic principles can be considered and applied. The technique presents high diagnostic sensitivity so that costly false negative results (e.g., myocardial infarction or death in a patient with normal perfusion) are rare. From the prognostic evidence, a normal myocardial perfusion SPECT MPI is associated with annual rates of cardiac death or myocardial infarction of 0.7% (exercise) to 1.2% (pharmacological stress), the negative predictive value being a particular strength of this modality.

Available prognostic data also lend considerable insight into the value of a positive study. Published studies consistently demonstrate a direct linear relationship between the extent and severity of perfusion abnormalities and clinical outcomes, especially cardiac death and non-fatal myocardial infarction. From this evidence, a close relationship between risk and cost can be easily seen; high risk SPECT MPI results are associated with high cost care, because events

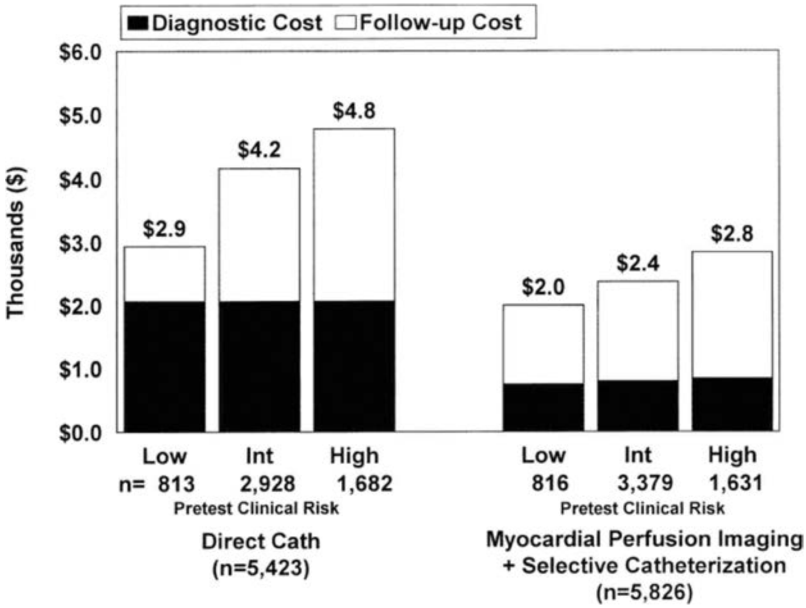

FIG. 14. Cost savings derived from the application of a strategy using selective catheterization according to the result of SPECT MPI. Cost savings are significant both for diagnostic as well as for follow-up phases of patient management (from SHAW, L.J., J. Am. Coll. Cardiol. (1999) (reprinted with permission)).

have direct economic consequences. Additionally, high risk patients also have a greater frequency of significant obstructive coronary disease and require more aggressive therapeutic intervention, leading to even greater costs of care. For the high risk patient, this relationship of risk to expenditures is the result of the more intensive use of diagnostic modalities and interventions aimed at improving life expectancy and quality of life. However, the economic aim of diagnostic strategies is that higher costs of care would be justified if the application of these strategies result in reducing premature morbidity and mortality, being clinically effective and, therefore, cost effective.

Thus, the estimation of risk by SPECT MPI allows the allocation of high cost care resources to those who will receive the most benefit from such care. For the low risk patient, low costs of care are expected for two–three years after SPECT MPI, which would be associated with minimal use of coronary angiography for patients with normal results. For patients with moderate or severely abnormal SPECT MPI results, high cost interventional care is directed to a cohort with more advanced CAD and on those who have the most to gain in terms of life expectancy. Thus, SPECT MPI might be cost effective, even if more costly in absolute terms than other diagnostic modalities, because its performance is significantly better for the identification of risk and for the optimization of patient management, and it is more efficient in guiding the allocation of resources.

5.4. PATIENTS WITH CHEST PAIN AND SUSPECTED ACUTE CORONARY SYNDROMES

There is strong evidence of the cost effectiveness of SPECT MPI in patients with acute chest pain. It is estimated that approximately three million patients presenting at the emergency department (ED) with acute chest pain and whose symptoms are due to non-cardiac conditions, are unnecessarily hospitalized at a high annual cost. Additionally, 4–7% of patients really undergoing an ACS will be inappropriately sent home from the ED, with potential severe consequences thereafter. Because of its ability to identify low risk patients among those presenting with acute chest pain and non-diagnostic ECG, 'resting' acute MPI can be used for excluding acute myocardial infarction (AMI) and ischaemia in this setting. Standard stress–rest imaging can also be used, with the obvious limitations of stress testing in unstable patients but with higher specificity to rule out AMI.

When MPI is introduced into a chest pain workup, rates of hospitalization decline significantly. A report concluded that the use of SPECT MPI to guide admissions resulted in a 29% decrease in the rate of unnecessary hospitalizations and a 6% reduction in inappropriate discharges from the ED. A similar report demonstrated significant cost savings, a lower angiography rate, and a shorter average length of stay for patients initially undergoing MPI when compared with a control population. These results support the high negative predictive value for MPI in ruling out AMI or future adverse cardiac events. Based on these data, the ACC/AHA/ASNC guidelines assign a Class IA indication to the assessment of myocardial risk in possible ACS patients with non-diagnostic ECGs and initial normal serum markers.

In addition to the benefits demonstrated in the emergency setting for acute chest pain, a substantial cost benefit of MPI is also evident in hospitalized patients. A prospective, randomized study assessed differences in hospital costs between conventional strategies and those guided by SPECT MPI, showing that the hospital costs per patient were much lower in the MPI-guided arm than in the conventional arm. In general, studies show a more appropriate triaging in more than 40% of patients, at a marginal added cost. A rational algorithm for the triage of patients with symptoms suggestive of ACS is presented in Fig. 15.

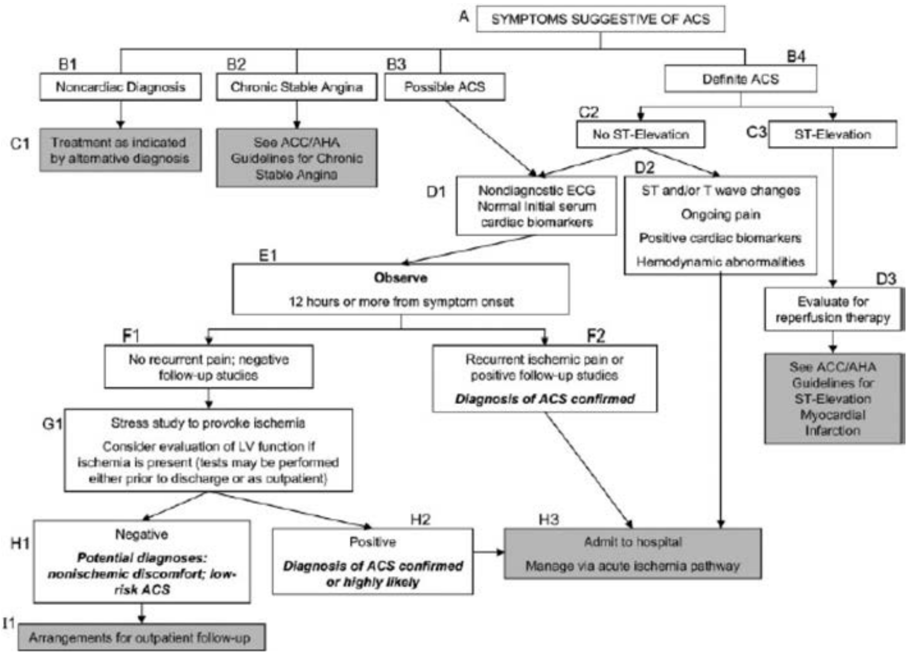

FIG. 15. Algorithm for the management of patients with suspected ACS (reprinted with permission).

5.5. SPECIAL POPULATIONS

Recent studies suggest that SPECT MPI may be particularly cost effective in special subgroups including patients with diabetes, women, and patients with end-stage renal disease. In all these groups, the occurrence of cardiac events is closely related to the severity and extent of perfusion defects in SPECT MPI (Fig. 16). Thus, the procedure can be used for selecting aggressive treatment in patients with high risk, avoiding unnecessary interventions in those with normal or mildly abnormal results. The most important drivers of cost of cardiovascular care in diabetics are based on ischaemic burden and the extent of CAD. Thus, from this evidence, the intensity of resource consumption might be predicted based on the results of SPECT MPI to a greater extent than diabetes itself.

It has been proposed that SPECT MPI could be cost effective for screening CAD in asymptomatic patients with diabetes, given the high prevalence of atherosclerosis in this population. The Detection of Ischemia in Asymtomatic Diabetics (DIAD) study was designed to determine the prevalence and severity of inducible myocardial ischaemia in asymptomatic patients with type 2 diabetes

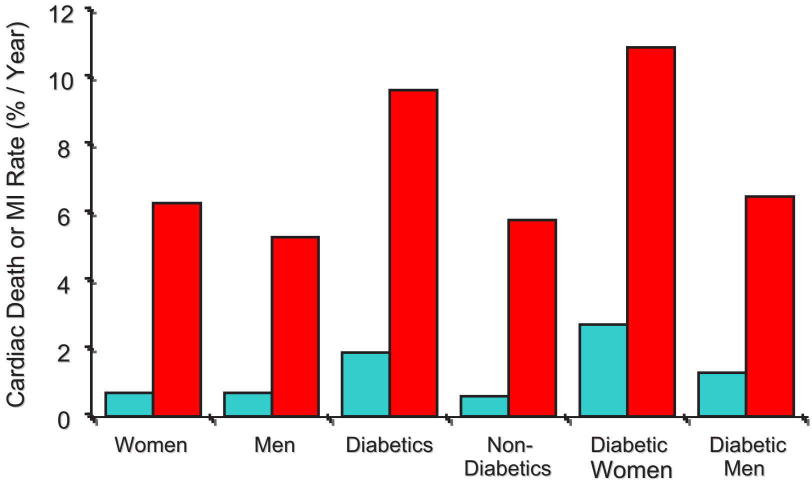

FIG. 16. Risk of cardiac death or myocardial infarction according to the result of SPECT MPI in different subgroups of patients. Green: low risk MPI; red: high risk MPI; p<0.05 between low and high risk (adapted from SHAW, L.J., and ISKANDRIAN, A.E., J. Nucl. Cardiol. (2004)).

using adenosine stress SPECT MPI along with clinical and laboratory predictors of abnormal test results. The initial findings of this study demonstrated that silent myocardial ischaemia is present in 1 in 5 asymptomatic diabetic patients and that 1 in 16 has significant perfusion abnormalities that should warrant further evaluation with coronary angiography. However, in this study population the cardiac event rates were low and were not significantly reduced by SPECT MPI screening for myocardial ischaemia over almost five years. Preliminary results from an ongoing international coordinated research study by the IAEA with a similar approach tend to demonstrate a higher incidence of abnormal perfusion findings as compared with patients with risk factors other than diabetes. Since almost all patients studied are from developing countries, it is possible that poorer control of diabetes due to less availability of health services, medication, or patient education, could be involved as an explanation of these results.

Worldwide, CVD is the largest single cause of death among women, accounting for one third of all deaths. In some countries, even more women than men die every year of CVD, a fact largely unknown to many physicians. The public health impact of CVD in women is not only related to the mortality rate, given that advances in science and medicine allow many women to survive heart disease. For example, in the USA, 38.2 million women (34%) are living with CVD, and the population at risk is even larger. In China, a country with a population of approximately 1.3 billion, the age standardized prevalence rates of dyslipidemia and hypertension in women 35–74 years of age are 53% and 25%,

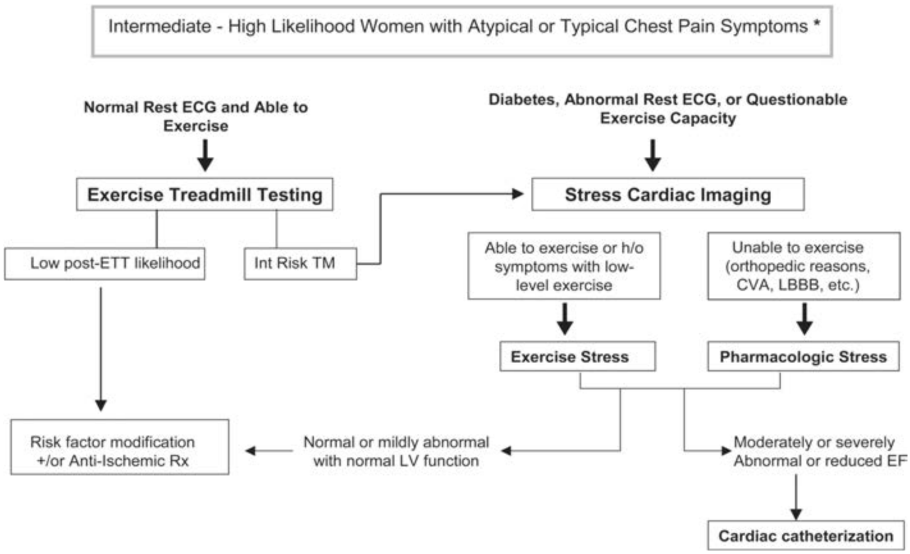

FIG. 17. Algorithm for the management of symptomatic women using stress ECG and MPI (from MIERES, J.H., et al., J. Nucl. Cardiol. (2003) (reprinted with permission)).

respectively, which underscores the enormity of CVD as a global health issue and the need for prevention of risk factors in the first place. As life expectancy continues to increase and economies become more industrialized, the burden of CVD on women and the global economy will continue to increase. As an example for proper utilization, the American Heart Association has published an algorithm for the evaluation of symptomatic women using exercise ECG and SPECT MPI (Fig. 17).

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6. NUCLEAR CARDIOLOGY AND COMPETING MODALITIES FOR THE EVALUATION OF CARDIAC PATIENTS

6.1. INTRODUCTION

Nuclear cardiology has been a mainstay of cardiac assessment in ischaemic heart disease for many decades because of its proven clinical usefulness. However, with the emergence of new technologies, namely cardiac computed tomography, cardiac magnetic resonance and stress echocardiography, the clinical utility of nuclear cardiology procedures has been called into question and the role of the method in the assessment of patients with known or suspected CAD has become an evolving issue. The dynamic nature of technology developments requires an updated evaluation of the relative roles that different methods play in clinical algorithms, with special emphasis in their respective strengths and weakness, and in view of available evidence.

6.2. RESTING ELECTROCARDIOGRAM (ECG)

Since its early description by Einthoven about a century ago, the resting ECG has been proven useful as a screening tool for heart disease. Despite the plethora of more sophisticated modalities available to evaluate the heart, none is so widely performed as a simple resting ECG. It is inexpensive, universally available, can be performed in the physician's office and provides information about heart rhythm, myocardial hypertrophy, conduction system abnormalities, myocardial injury and infarction, and it can eventually demonstrate acute or chronic ischaemic changes in many cases. However, the resting ECG has many well known limitations. For example, approximately half of patients experiencing an ACS (unstable angina or AMI) will have a non-diagnostic resting ECG, thus precluding its clinical utility in such cases.

6.3. EXERCISE STRESS TEST (TREADMILL STRESS TEST)

Guidelines for exercise testing have been published by the American College of Cardiology (ACC) and the American Heart Association. A multitude of parameters derived from this test have been studied and validated over the last four decades. Some useful parameters from the treadmill stress test (TMT) include: total exercise time, the magnitude of increase in blood pressure and heart rate (indicative of cardiac function), the magnitude and morphology of ST segment shifts, the presence of chest pain on exertion and the cardiac rhythm during exercise, among others. In addition, the prognostic information obtained from a TMT is extremely important. Failure to achieve 85% of the age predicted maximum heart rate and a low chronotropic index can predict adverse cardiovascular events. Attempting to obtain some quantitative information from the TMT has led to the development of the Duke Treadmill Score (DTS), which results from a combination of different stress parameters and is widely used for risk stratification.

According to two meta-analyses, the average sensitivity and specificity of TMT for the diagnosis of CAD is restricted at 67% and 72%, respectively. Unfortunately, the TMT also has additional limitations. The exercise ECG is non-interpretable in patients with left bundle branch block (LBBB) and pacemakers. Moreover, some baseline ECG abnormalities will make any additional changes during exercise poorly specific, such as those that may occur in left ventricular hypertrophy (LVH), in the presence of Wolf–Parkinson–White syndrome or prior myocardial infarction, or with the use of some medications such as digitalis. Furthermore, the sensitivity of TMT is decreased when related to a limited capacity to achieve an adequate increment of myocardial oxygen consumption, due either to limited exercise capacity or because of concurrent medical treatment with calcium channel blockers, beta blockers and other drugs.

TMT is less accurate in women than in men. The reported lower specificity may be due to a digoxin-like effect of circulating estrogens, resulting in varying changes in the ST segment which can lead to a higher false positive rate of exercise ECG testing in women.

In summary, the TMT is an effective, proven technique for diagnosis and determination of prognosis in patients with suspected CAD, but its many limitations restrict its utility, requiring the application of alternative or complementary modalities in many patients. TMT is most appropriately indicated for patients with normal resting ECG and adequate exercise tolerance. Available evidence demonstrates that, despite the stratification power of the DTS, SPECT MPI can further subdivide the initial risk groups into post-test low or high risk patients (Fig. 18).

6.4. ECHOCARDIOGRAPHY

Early in its development, resting echocardiography was mainly used to evaluate cardiac structures, measure wall thickness, chamber volumes, heart valves, and global contractility. Technological improvements have permitted the development of new applications. Stress echo was developed in 1979,

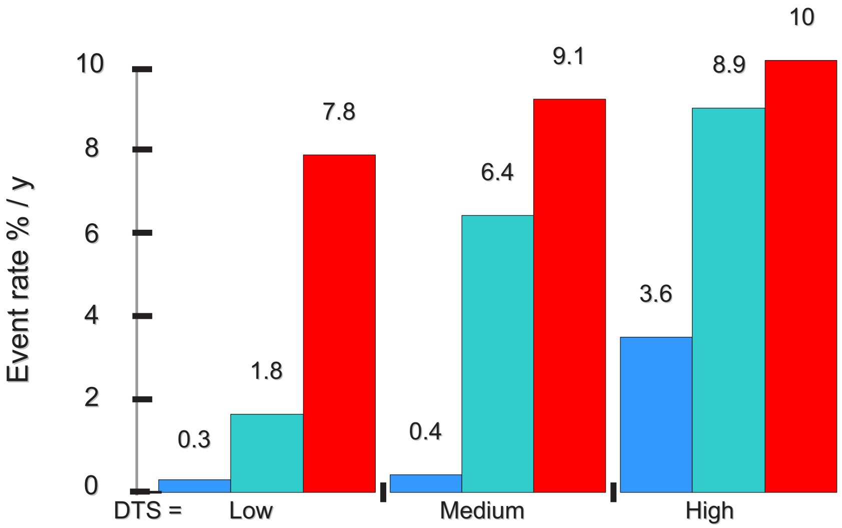

FIG. 18. Cardiac event rate according to the result of SPECT MPI in groups of patients with low, medium and high Duke Treadmill Score. SPECT MPI provides further stratification in all groups. Blue: low risk MPI; green: medium risk MPI; red: high risk MPI (modified from HACHAMOVITCH, R., et al., Circulation (1996)).

predominantly to evaluate patients with multi-vessel CAD who would benefit from CABG, as effective medical therapy and percutaneous intervention had not yet been developed. Stressors, including exercise or dobutamine, have been widely used for ischaemia induction. The occurrence of a transient, stress induced contractile abnormality is a very specific finding for the presence of CAD. The limitations of the test include difficulties in acquiring high quality images in patients with a limited acoustic window, problems defining all the endocardial borders in some cases and dobutamine intolerance. For example, approximately 4–5% of patients will develop complex ventricular arrhythmias during dobutamine infusion, hence the risks inherent to the use of this drug limit its safety profile. Moreover, patients with previous myocardial infarction and extensive scar tissue often have already significant wall motion abnormalities at rest, further posing a challenge for interpretation of new areas of ventricular dysfunction or worsening of pre-existing ones. Patients with previous ventricular dysrhythmia, atrial fibrillation, or concurrent beta-blockade are also poor candidates for dobutamine stress. In addition, the technique is more time consuming for the physician compared with other modalities.

The diagnostic accuracy of the stress echo has been shown to be inferior to nuclear methods for the detection of ischaemic burden. It has been well established that the sensitivity of the technique is lower compared with SPECT

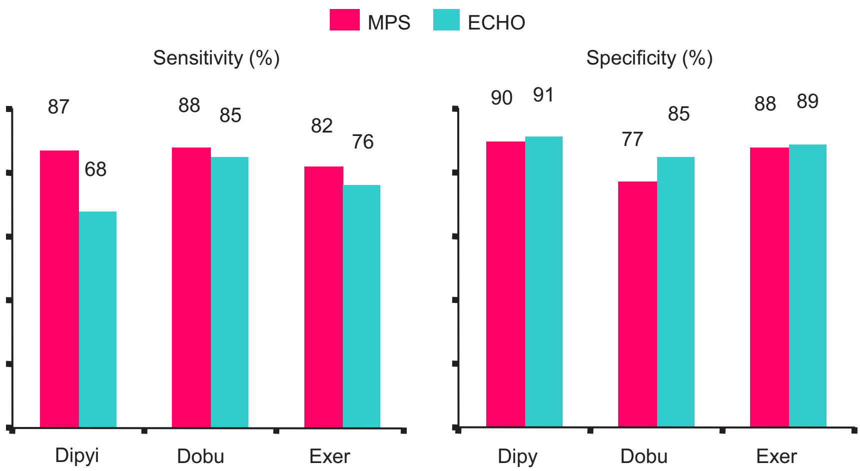

FIG. 19. Diagnostic performance of MPI and echocardiography (ECHO) using different types of stress. MPI is more sensitive, while echocardiography is slightly more specific for the detection of myocardial ischaemia (head to head comparison, n = 1421 patients from 23 studies). Dipy=dipyridamole, Dobu=dobutamine, Exer=exercise (modified from MARCASSA, C., et al., Eur. Heart. J. (2008)).

MPI, independent of the type of stress used (Fig. 19) because echocardiography relies on the detection of wall motion abnormalities during ischaemic episodes, which is further down the ischaemic cascade compared with perfusion abnormalities. This is even more apparent in the diagnosis of single vessel CAD. However, the specificity of stress echocardiography is slightly higher than nuclear methods, as the occurrence of stress induced wall motion abnormalities is almost always related to an ischaemic insult. However, the time window for accurate assessment of wall motion abnormalities is very short, tempered by patient motion and heavy breathing, so high quality echocardiography studies just past peak stress may become very difficult to obtain. Moreover, the incidence of suboptimal or uninterpretable echocardiography scans is known to be greater than with nuclear techniques, and at times stress echocardiography cannot be performed at all because of poor echogenic windows. Nuclear cardiology, on the other hand, is not limited by these issues.

Stress echocardiography suffers from the inability to objectively assess the amount of ischaemia or infarction, so usually the report is only that of a positive or negative scan based on wall motion abnormalities during stress, whereas nuclear perfusion imaging offers a clearly graded assessment of ischaemia which is associated with risk of future events. This gradient of risk has been made more accurate through the use of quantitative software, and eventually allows for a more conservative approach in patients with mild ischaemia. This is in keeping with recent data demonstrating effective long term outcome in these patients using optimal medical therapy only. Dobutamine echocardiography can potentially produce ventricular arrhythmias at the dose necessary to detect ischaemia, and is contraindicated in patients with high blood pressure at rest.

Resting echocardiographic assessment of wall motion abnormalities and myocardial thickness is compromised by hibernation and stunning, which can mimic infarction. Low dose dobutamine echocardiography can be used for the evaluation of viability by exploring the contractile reserve of the myocardial area in question. It has been demonstrated that segments showing preserved contractile function response to dobutamine will most probably recover basal state contractility after revascularization. However, the use of dobutamine enhanced echocardiography in this clinical setting is limited by a lower diagnostic accuracy compared with nuclear cardiology techniques, especially concerning sensitivity.

Myocardial contrast echocardiography has been promoted to improve the accuracy of stress echocardiography by improving wall motion detection. However, the cost of the contrast agent and its availability limits its usefulness and there have been reports on undesirable side effects of contrast materials. In addition, contrast perfusion myocardial imaging has not been shown to be clinically effective.

Another drawback of echocardiography is the subjective nature of interpretation, requiring a very experienced operator for reliable results. This situation has yet to be overcome through the use of standardized software analysis. However, image acquisition is still highly dependent on the skill of the operator, who is expected to obtain reproducible images through an iterative process that involves different patient positioning and placement of the transductor. Thus, although the published diagnostic accuracy approaches that of nuclear techniques in selected academic centres, stress echocardiography has really not come to the forefront of diagnostic ischaemia imaging. In the clinical setting, stress echocardiography is more often performed to rule out significant myocardial ischaemia.

Several points should nevertheless be mentioned in favour of echocardiography. Its wide availability, the lack of added costs, the absence of ionizing radiation, its ability to evaluate cardiac structure including pericardial effusion and valves, and the possibility of ischaemia detection in 'real time' are some advantages over nuclear techniques.

6.5. MAGNETIC RESONANCE IMAGING

Multiple applications for cardiac MRI have been developed during the last decade. Its major advantage over other technologies is its very good spatial resolution, good temporal resolution, high contrast between rapidly flowing blood and cardiac chambers, superior soft tissue contrast, and therefore excellent definition of cardiac structures. These advantageous aspects of MRI can be used to provide: (1) superb 3-D definition of normal and pathological anatomical details, allowing highly accurate measurement of wall thickness, volumes, and mass; and (2) qualitative and quantitative assessment of the function of cardiac chambers and valves, with direct measurement of functional parameters and wall thickening dynamics. Phase contrast imaging can produce Doppler like waveforms, allowing measurement of parameters such as pressure gradients across stenosis or total blood flow through the aorta or pulmonary artery.

Technological developments have permitted progressive improvement in image quality and resolution. Recent MRI studies have demonstrated the possibility of defining thrombus age and monitoring progression or regression of atherosclerotic lesions in experimental animal models. In addition to detailed evaluation of anatomy, dynamic gadolinium contrast enhanced MRI provides the potential to evaluate myocardial perfusion in the resting and pharmacological stress states. However, stress perfusion MRI remains predominantly a research technique. In MR angiography, limited temporal resolution compromises evaluation of coronary anatomy. A major strength of MRI is in delayed gadolinium contrast enhancement, a technique that is able to identify areas of scarring and has demonstrated to be helpful in differentiating scar from hibernating but viable myocardium (Fig. 20). Its clinical use in the setting of myocardial infarction is well established; its superior resolution as compared to echocardiography and nuclear techniques has made it more sensitive for such application, being able to detect both transmural and partial thickness infarcts, something that nuclear methods cannot match at present. For the measure of ventricular function, gated MRI is currently considered the gold standard due to

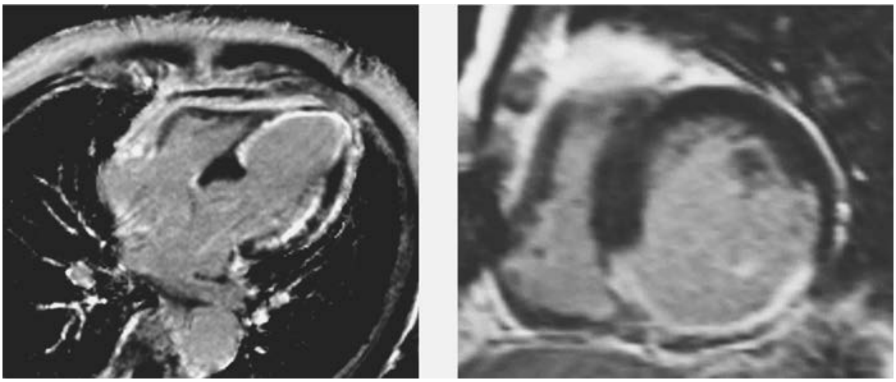

FIG. 20. Horizontal long axis (left) and short axis (right) slices of the heart with contrast enhanced MRI in a patient with MI (courtesy Z.X. He, China).

its excellent spatial resolution allowing very precise border definition of cardiac chambers, and the three dimensional nature of the investigation.

Cardiac MRI is used predominantly in the evaluation of congenital and structural heart disease (e.g. RV dysplasia), allowing accurate imaging of heart structure without the problems of ionizing radiation. This technique is therefore very appealing for imaging in children.

For the evaluation of ischaemic heart disease, challenges for this technique include inability to effectively monitor the patient during pharmacological stress, difficulty in obtaining interpretable, reproducible images of semi-quantitative nature, and a very narrow imaging window of opportunity. Inability to perform MRI during physical stress and the contraindication of its use in patients with metallic devices are also important disadvantages. Moreover, the requirement of expensive equipment and the time necessary to perform a complete viability or perfusion scan, together with its heavy reliance on suitably trained personnel, tempers its rise in popularity for cardiac imaging. Due to the paucity of technology in many countries, the cost and waiting time to perform such scans are still prohibitive. In addition, some hazards associated with the use of gadolinium have recently been emphasized amongst patients with impaired renal function. Despite its magnificent properties, due to a large list of disadvantages cardiac MRI is still not widely used in routine clinical practice and availability in developing countries is quite limited.

6.6. MULTI-SLICE COMPUTED TOMOGRAPHY

The use of cardiac CT has increased greatly all over the world, partly as a result of marketing by the industry and partly because of many advances of this technology over the past few years. Although the CT modality has been introduced decades ago, it had been used mainly for imaging still organs in the body. A key advancement in CT was the development of helical (or spiral) acquisition of multi-slice computed tomography (MSCT) simultaneously. Compared with single slice CT, MSCT permits a larger area to be scanned in a shorter time and in greater detail. However, it was not until the introduction of the 16 detector CT that cardiac imaging really took off although it is nowadays considered that good quality CT coronary angiography can only be achieved with at least 64 slice scanners. With improved spatial resolution and ECG gated acquisition, in addition to high resolution coronary angiography, MSCT can assess cardiac function, congenital structural abnormalities, and perform calcium scoring although the latter was already possible with the use of less sophisticated equipment. While CT assessment of myocardial perfusion and viability with delayed imaging is currently under investigation, it remains a research tool at present.

Cardiac MSCT can provide an accurate delineation of the heart structures, with a resolution superior to that of cardiac MRI, and definitely better than nuclear techniques. Contrast cardiac CT angiography has emerged as an effective technique to perform coronary angiography non-invasively. However, there are many problems with cardiac MSCT that have to be solved before an interpretable image can be produced. These include motion artefacts due to heart rate, patient motion, breathing, contrast effects, heavy calcification, and radiation dose. Several devices and techniques have been developed to overcome motion artefacts, and for new generation faster scanners this is no longer an important issue. Nevertheless, the presence of calcified plaques often makes impossible to establish the degree of arterial stenosis.

In general, it is well accepted that SPECT MPI have better specificity and positive predictive value (PPV) than MSCT for assessing physiologically significant lesions, while MSCT has a better negative predictive value (NPV) and thus is more useful to ‘rule out’ disease. A study conducted to evaluate the functional significance of coronary artery lesions with a hybrid SPECT–MSCT device found that the sensitivity, specificity, PPV, and NPV of MSCT alone were 96%, 63%, 31% and 99%, respectively, as compared with 96%, 95%, 77% and 99%, respectively, for integrated SPECT–MSCT studies.

Although cardiac MSCT has a superior resolution compared to other non-invasive techniques, it still cannot approach the spatial resolution of invasive X ray angiography (0.5 mm versus 0.1 mm). Thus, assessment of the degree of coronary stenosis in CAD can be inaccurate, especially when arteries the size of 2 mm will only have 4 pixels across the lumen, and thus — instead of a continuum of lesion severity — usually only four steps of stenosis (such as mild, moderate, severe, and total occlusion) are reported. Among patients with intermediate stenosis, this step approach to severity categorization sometimes limits the CTA’s ability to aid clinical decision making. Attempts in the CT literature to grade stenosis on a continuum compared with invasive quantitative coronary angiography (QCA) has at the moment demonstrated the inaccuracy of this approach on an individual patient basis, as shown in Fig. 21.

The heavy investment in research by the CT industry has resulted in huge advancements in this technology, with the introduction of dual source CT, 256 and 320 detector MSCT, which are already in clinical use with variable success, as well as the development of high definition CT, with in-plane spatial resolution significantly higher than what is currently achievable. The ability to dose-modulate and also the implementation of prospective versus retrospective gated imaging has resulted in a potential reduction in radiation doses to levels that are now comparable to those of recent nuclear imaging techniques (that is, using state

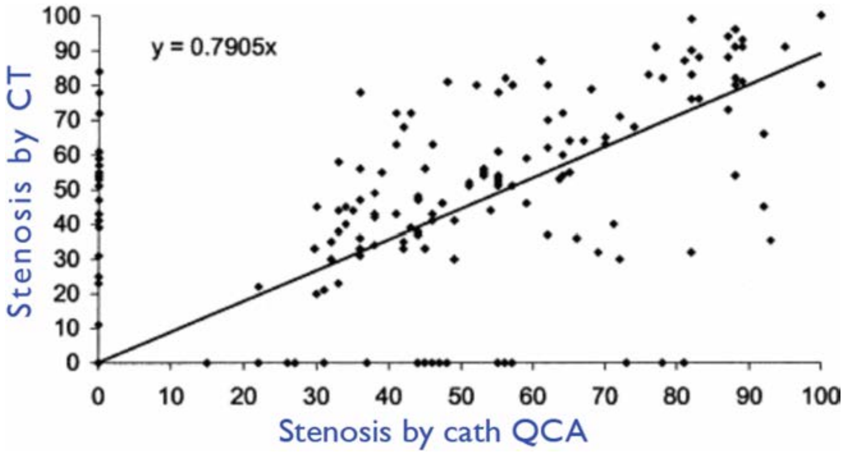

FIG. 21. Correlation of coronary stenosis severity between 64 slice CT angiography and conventional quantitative coronary angiography (QCA) (from LEBER, A.W., et al., J. Am. Coll. Cardiol. (2005) (reprinted with permission)).

of the art equipment and protocols). However, many centres do not use these dose modulation protocols because of the potential for not obtaining optimal diagnostic images. The issue of the possible risk associated to the utilization of iodinated contrast media is also very pertinent in selected patients.

Although there are recent only single centre prognostic data available regarding MSCT, nuclear techniques have a long track record in the evaluation of ischaemia, infarction and prognosis, something that cardiac MSCT still cannot match at present. There is no long term follow-up data on the prognostic significance of different results with cardiac MSCT. In contrast to nuclear studies, MSCT offers no clinically useful physiological information since only anatomic data is provided. Several reports have shown, and is now well established, that physiological parameters provided by SPECT MPI are more important than anatomy for the prediction of future cardiac events.

Furthermore, it is recognized that the use of nuclear techniques for long term follow-up of treatment response in patients with CAD is of critical importance. Advances in optimal medical therapy now allow the physician to treat CAD patients more conservatively with good prognostic outcomes. The gradient of risk supplied by nuclear cardiology studies is helpful in selecting patients for optimal medical therapy as an initial strategy. This same gradient of risk permits the safe monitoring of the effectiveness of medical therapy and the progression of disease, allowing timely revascularization when necessary. Lacking a true physiological evaluation, MSCT is at present unable to provide this assessment. The role for MSCT perfusion is still mainly research and is

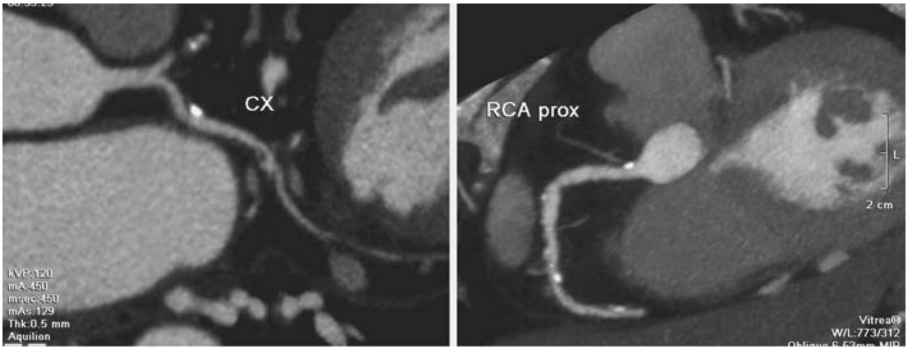

FIG. 22. MSCT angiography showing multiple calcified plaques in all three coronary territories, all assessed to be non-critical. The calcium score was 121 (courtesy F. Keng, Singapore).

hampered by the patient not being able to exercise, and by the need for beta blockers and for the performance of two CT studies.

Both MSCT and electron beam computed tomography (EBCT) permit quantitation of coronary artery calcification using calcium scoring (Fig. 22). The coronary calcium score (CCS) correlates with the extent of coronary atherosclerosis, although only approximately 20% of atherosclerotic plaques are calcified. Therefore, CCS is useful for early detection of coronary atherosclerosis and risk stratification, as outlined in the Expert Consensus Document on EBCT for the diagnosis and prognosis of CAD published by the ACC/AHA. The long term prognostic data for CCS has been robust across different ethnic groups. Similar to CTA, its advantage is in its initial diagnostic capability, rather than in long term monitoring, management of disease progression or therapy response of CAD patients. On the other hand, it has been demonstrated that assessment of perfusion is more important than CCS for prognosis, and cardiac event rate is low when SPECT MPI shows normal or nearly-normal results even in patients with high calcium score.

The CCS and SPECT MPI findings are independent and complementary predictors of short and long term cardiac events. Despite a normal SPECT result, a severe CCS identifies subjects at high long term cardiac risk. After a normal SPECT MPI result, it is useful to perform a CCS in patients who are at intermediate or high clinical risk for coronary artery disease to better define those who will have a high long term risk for adverse cardiac events.

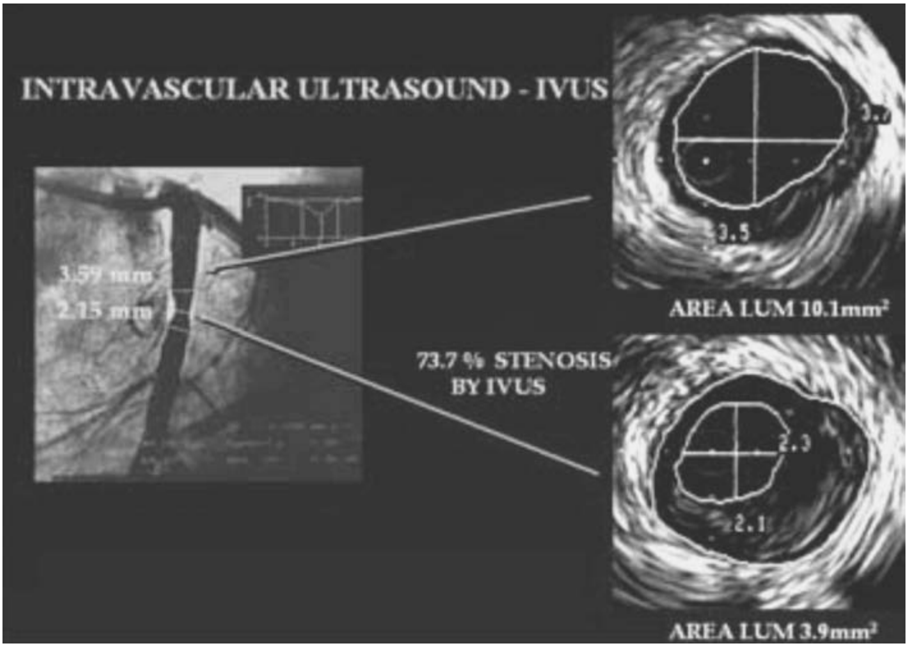

FIG. 23. Coronary angiography showing a stenosis of the left anterior descending (LAD) artery (left) and intravascular ultrasound (IVUS), demonstrating the lumen cross-sectional area with high precision in a normal segment (upper right) and the eccentric character of the lesion (bottom right). Both methods are accurate in providing anatomical detail, but are invasive in nature, requiring arterial catheterization (from VITOLA, J.V., DELBEKE, D., Nuclear Cardiology and Correlative Imaging (reprinted with permission).

6.7. CONTRAST CORONARY ANGIOGRAPHY (CA) AND INTRAVASCULAR ULTRASOUND (IVUS)

Both CA and IVUS are invasive and costly techniques for evaluation of CAD (Fig. 23). The technical advances of non-invasive imaging modalities allow early diagnosis of CAD and CA can be reserved to evaluate the anatomical aspect of lesions and plan therapy. Unfortunately, CA cannot predict the site of a subsequent MI in a patient with mild to moderate CAD, illustrating that lesions detected are not necessarily those that put the patient at risk of adverse cardiac events.

Advances in the technique of coronary intervention over the years have changed the management of patients with CAD, resulting in safer and more effective percutaneous revascularization. Coronary angiography may be inconclusive in some borderline lesions (40–60% obstruction). More precise anatomical evaluation using IVUS and physiological lesion assessment using coronary flow reserve (CFR) or fractional flow reserve (FFR) may be required for adequate therapeutic decisions, before and after percutaneous coronary intervention.

The development of IVUS has permitted exquisite assessment of coronary plaque morphology, helping to differentiate 'hard' stable plaques from 'soft' vulnerable plaques, and more accurate measurement of the stenotic area compared with contrast angiography alone. Moreover, IVUS is now seen as the 'gold standard' for the presence of CAD since it can detect eccentric lesions which do not protrude to the arterial lumen, thus giving a 'normal' result in angiography. However, in addition to the invasive nature of the technique, IVUS is expensive and requires a big amount of expertise to obtain good results.

A rational integration and step-wise use of non-invasive techniques to detect CAD and to determine prognosis, together with invasive approaches (CA and IVUS) to evaluate the detailed anatomical and morphological aspects of lesions constitute state of the art practice of cardiology.

6.8. NUCLEAR CARDIOLOGY

Nuclear medicine procedures allow evaluation of myocardial perfusion, viability and function using SPECT, gated SPECT, PET and RNVG. Nuclear imaging of the heart is a valuable, widely used, non-invasive procedure which reveals important information about cardiac structure and physiology. The indications for cardiac radionuclide imaging have been extensively reviewed and discussed in the Guidelines published by a Task Force of the ACC/AHA, and summarized in Section 2.

Perfusion imaging using SPECT MPI is a nuclear medicine technique extensively used to evaluate myocardial blood flow (MBF). It provides the possibility of assessing coronary flow reserve, detecting ischaemia, and providing risk stratification, including the degree, location and extent to which CAD is affecting regional MBF. The prognostic and diagnostic value of MPI has been well established in the literature over the last three decades. MPI continues to grow, with 3.1 million patients in the USA having undergone the procedure in 1996, 3.7 million in 1997, 4.1 million in 1998, 4.5 million in 1999 and 6 million in 2001. The number of ^{201}Tl administrations remained similar between 1998 and 2001, whereas the number of ^{99m}Tc labelled radiopharmaceutical administrations (especially MIBI) doubled during the same period. At the time of writing, approximately 30% of MPI are being performed using ^{201}Tl alone, 30% using ^{99m}Tc-MIBI alone, 20% using rest ^{201}Tl/stress ^{99m}Tc-MIBI, and 20% using ^{99m}Tc-tetrofosmin, either alone or in combination with ^{201}Tl.

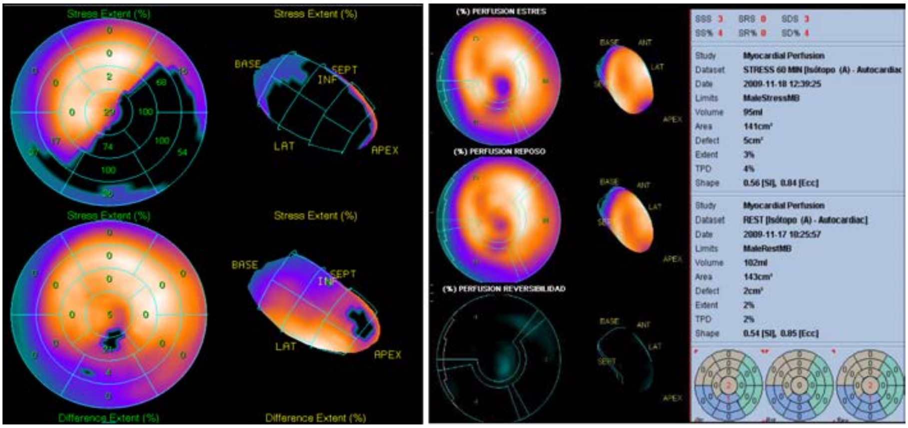

FIG. 24. Quantitative analysis of a SPECT MPI in the same patient before and after therapeutic intervention (left), showing a change from 28% to 2% in total perfusion deficit (TPD). Studies have demonstrated that the degree of remnant ischaemia after therapy is related to future cardiac events (courtesy L. Shaw, USA). On the right, quantitative stress/rest perfusion values from a different patient study. Quantitation is a powerful strength of SPECT MPI, especially for follow-up, assessment of therapy and clinical research (courtesy F. Mut).

The stress tests most commonly used for the evaluation of coronary blood flow reserve include exercise, dipyridamole, adenosine and physical exercise combined with pharmacological stress. All of these are intended to provoke coronary vasodilation so as the moment of tracer injection, flow heterogenity can be readily detected, which is representative of significant CAD. Recent technological developments in nuclear imaging include new solid state detectors for gamma cameras, improved software and hardware for better performance and interpretation of gated SPECT studies, quantitative refinements (Fig. 24), new radiopharmaceuticals, and new vasodilators for pharmacological tests (see below).

Evaluation of ventricular function is critical in many clinical situations, including patients with CAD and valvular diseases. Both global and regional wall motion can be accurately evaluated with planar and SPECT gated blood pool studies or RNVG with labelled red blood cells. In addition, ventricular size, right and left ventricular ejection fractions (RVEF, LVEF) and regurgitation indexes can be calculated. The RNVG technology and other non-perfusion applications in nuclear cardiology have been reviewed and summarized in a report by the task force of the ASNC. Recent technical developments of SPECT technology applied to gated blood pool studies allow more accurate evaluation of ventricular performance, especially right ventricular function and diastolic function.

In general, the choice of one of the tests or methods discussed above to evaluate a specific patient will depend on several factors including: clinical question to be responded, availability of technology, local experience with a given modality and the pre-test probability of disease, as well as patient specific factors such as body habitus and the presence of resting ECG abnormalities.

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7. TECHNOLOGICAL ADVANCES IN NUCLEAR CARDIOLOGY

7.1. INTRODUCTION

Several innovations are on the horizon in the field of nuclear cardiology which will impact the diagnostic accuracy of the technique, as well as imaging time, and cost savings among other advantages including dosimetry issues. These advances will help repositioning the speciality in the new technological scenario and will allow it to compete in a more advantageous way with the fascinating developments exhibited by other modalities.

7.2. DEVELOPMENT OF NEW PHARMACOLOGICAL STRESS AGENTS AND PROTOCOLS

Agents that are specific to only coronary vasodilatation (selective A2A receptors) have been developed and clinically tested. Regadenoson is one of such drugs that was recently approved by the FDA in the USA and is expected to have widespread application in the near future, provided competitive costs can be achieved. This agent can be used as a fixed bolus dose without the need for dose adjustment for patient's weight, body mass index (BMI), renal function, or hepatic function. The performance of this new agent is similar to that of conventional adenosine, but with fewer side effects, such as bronchospasm, and although the cost is currently quite high, it is envisaged that it will soon decrease as commercial competition becomes a reality. Other similar pharmacologic stressors have been also developed and are reaching the commercial phase.

Protocols combining exercise with pharmacological stress are becoming increasingly popular, complementing each other especially in patients unable to achieve sufficient exercise levels. Furthermore, the addition of exercise also increases the clinical tolerance of the pharmacological agent, resulting in reduced incidence of side effects, and the quality of images is also generally improved as compared to pharmacological-only stress, which is associated with high sub-diaphragmatic activity. The availability of different pharmacological agents such as vasodilators and inotropics, together with the validation of these new combined protocols, have widened the spectrum of patients to be stressed, allowing for very precise tailoring of the test according to the condition of the patient and the clinical question to be answered.

7.3. DEVELOPMENT OF NEW TRACERS

Radiopharmaceuticals with improved tracer kinetics that approach the characteristics of ^{15}O-H_2O (the gold standard for myocardial perfusion requiring PET technology) are under investigation. At present, SPECT imaging suffers from the problem of depicting 'relative' myocardial perfusion, in contrast to PET imaging that can provide 'absolute' perfusion data, thus eliminating the possibility of missing balanced ischaemia in which no segmental defects can be identified in spite of a severe global reduction in blood flow. New SPECT tracers under research will possibly enable to quantitate absolute perfusion in the future. Other researchers have been developing tracers that can be imaged immediately following injection instead of waiting 30–40 minutes so as to decrease the waiting time for such scans, thus reducing the total duration of tests for both patient comfort and economic benefits.

New ^{123}I tracers like BMIPP hold the promise of detecting myocardial ischaemia many hours after the patient has recovered from an episode of ischaemic chest pain. This is the so-called 'ischaemic memory', and represents a transient metabolic disruption which is expressed for longer time than the impairment of blood flow to the myocardium. Patients with impaired LV function are at risk of sudden cardiac death. This risk can be assessed with ^{123}I-MIBG, which depicts regional cardiac innervation, allowing for optimally guided therapy for its prevention (Fig. 25). It has been demonstrated that if cardiac innervation is damaged, as reflected by reduced ^{123}I-MIBG uptake in the heart, the patient is at increased risk for heart failure progression, arrhythmic events and cardiac death. A new PET cardiac perfusion tracer and agents for cardiac innervation labelled with ^{18}F are currently under investigation and are expected to be soon released commercially.

Acetate labelled with ^{11}C offers the possibility of studying both myocardial perfusion and metabolism with the same PET tracer. Although PET continues to have marginal utility in nuclear cardiology, widespread availability of the technology and development of new tracers that can be labelled with commonly used positron emitters open a window of opportunity for research and possibly for practical applications in specific clinical scenarios.

Imaging of vulnerable atherosclerotic plaques has already been demonstrated in larger arteries such as the carotids. Development of new tracers that have an affinity for certain elements of vulnerable plaques can help determine which plaques are more likely to rupture, especially in the coronary arteries. These tracers can include various radiolabelled monoclonal antibodies

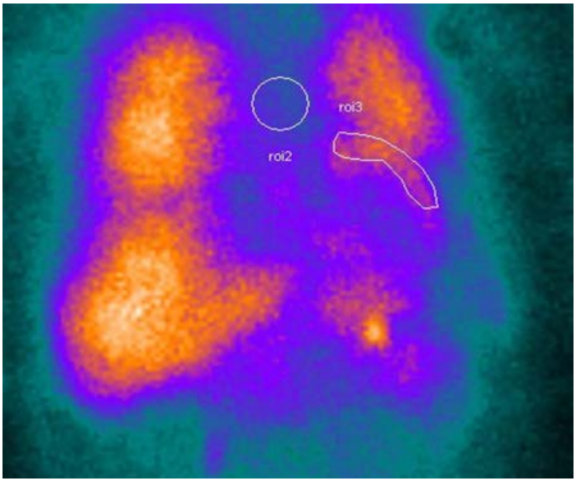

FIG. 25. ^{123}I-MIBG cardiac innervation study. Anterior planar image of the chest and abdomen. Areas of interest are placed on the myocardium and mediastinum to quantitate tracer uptake ratio. This parameter is of prognostic significance in patients with heart failure (courtesy R. Giubbini).

targeting molecular components of atherosclerosis (oxidized LDL, apoptotic cells in necrotic core, thrombus, etc.). Inflammatory imaging using ^{18}F-FDG is also being studied in carotid plaques in both experimental animals and human studies (Fig. 26). Such imaging can be also accomplished with nuclear probes that are small enough to be mounted on coronary catheters and placed within the coronary lumen to pick up radioactivity in plaques and characterize their composition.

Challenges at present include developing of SPECT and PET tracers suitable for such imaging atherosclerotic imaging and also probes that can detect such minute amounts of activity. If this research is successful and can be translated into clinical practice, it will constitute a major breakthrough in cardiovascular clinical imaging. However, there is still a long way to go before this technological advance can be incorporated into routine practice.

Apoptosis imaging utilizing ^{99m}Tc Annexin-V also shows promise in the field of cardiology. The ability to predict the onset of irreversible degeneration of the myocyte is important as it may provide insight into the causes of apoptosis (genetically programmed cell death) and also possibly suggest novel treatments for such causes. Whether Annexin-V can be used to image apoptosis in coronary plaque remains investigational, but preliminary results appear encouraging. Anti-apoptotic therapy can then be monitored accurately to determine their effectiveness. Stem cell therapy for advanced heart failure is well into clinical trials and shows great promise, although data in the literature are still

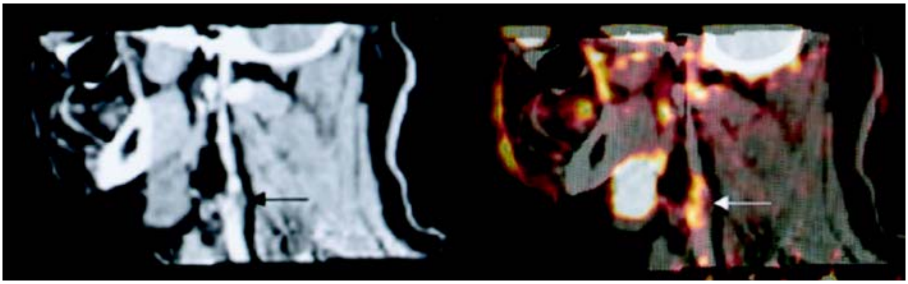

FIG. 26. Carotid plaque (arrow) imaged with ^{18}F-FDG in a patient with a stroke. Left: CT angiography image; right: PET/CT fusion image (modified from Rudd, J.H., et al., Circulation (2002)).

controversial. Similarly, angiogenesis factors have been developed to promote the formation of new blood vessels in areas of the heart with deficient perfusion. SPECT and PET imaging can aid in the monitoring of such therapies as these methods have sufficient resolution to gauge improvement in perfusion and viability after the institution of such novel therapies.

7.4. NEW COMPUTER ALGORITHMS AND TOOLS

New processing algorithms for image reconstruction resulting in half-imaging time are now available. For example, wide beam reconstruction technology is a resolution recovery method based on an accurate modelling of the emission detection process. This modelling is designed to simultaneously suppress noise and improve image resolution, and is optimized specifically for performing short gated SPECT MPI. This technology is still under validation, but if proved successful it will be able to reduce scanning time by about half, with no deterioration in image quality or diagnostic accuracy. The obvious consequence would be an improvement in patient comfort and compliance, and also an increase in the throughput time which would be significant for cost savings, especially in busy nuclear cardiology laboratories.

Fusion of cardiology diagnostic data from different modalities is now gaining interest in the imaging field. All major vendors manufacturing gamma cameras and PET scanners have incorporated fusion software that can accurately co-register DICOM images utilizing nuclear, CT and MR data for the simultaneous assessment of functional and anatomic parameters, without the need for hybrid machines which can be quite costly (see below). However, it must be recognized that, at least in the case of PET, all manufacturers have now incorporated CT into their PET scanners so stand-alone PET has been discontinued. This is not the case for SPECT, although hybrid SPECT/CT machines are gaining widespread utilization.

7.5. NEW GAMMA CAMERA TECHNOLOGY

New semi-erect or upright imaging cameras can decrease the problems of extra-cardiac activity contaminating cardiac imaging (hepatic, gastrointestinal uptake). Semiconductor detectors with much higher sensitivity as compared with conventional detectors are allowing the use of lower doses of radiopharmaceuticals or a decrease in imaging time, or a combination of both, features that are associated with costs reduction and lower radiation to the patient.

The incorporation of these new detectors into novel camera designs also result in images with outstanding spatial resolution and contrast. Some cameras using these detectors permit optimal proximity from the chest wall thus further increasing image resolution (Fig. 27). These cameras also exhibit improved energy resolution for better dual isotope imaging. Since the detector components are reduced in weight and size compared to conventional cameras, lightweight

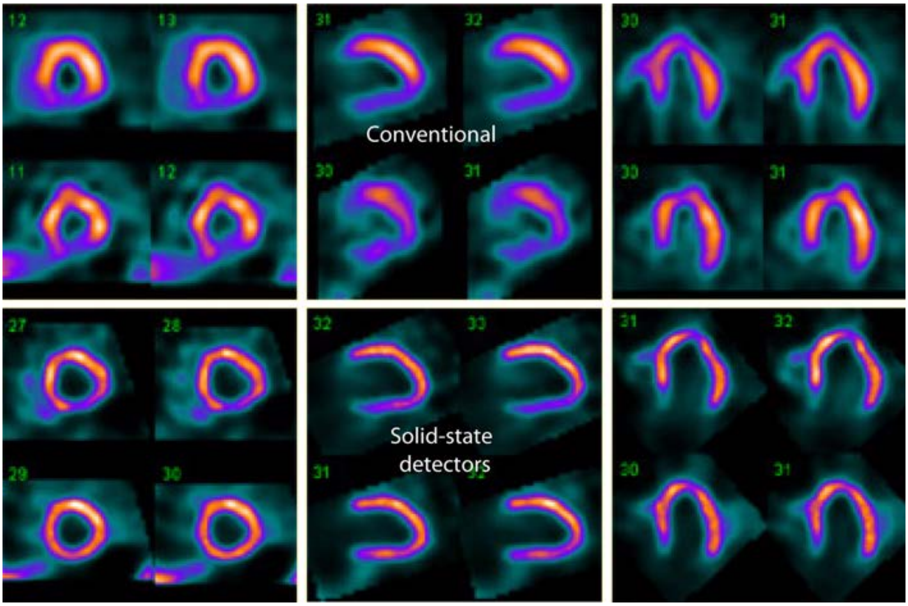

FIG. 27. Myocardial perfusion images using conventional SPECT technology (upper row) and a new dedicated cardiac camera equipped with solid state Cadmium Zinc Telluride (CZT) detectors (bottom row). Studies were performed sequentially on the same patient. The difference in image resolution can be readily appreciated (courtesy B. Hutton and S. Ben-Haim, UCL Hospitals, London, UK).

and compact designs are possible allowing mobility among department and floors, even under emergency conditions in coronary care or intensive care units. Some gantry designs will also allow coupling with CT machines providing the possibility of attenuation correction, calcium scoring, and simultaneous assessment of coronary anatomy.

These cameras are not general purpose instruments, but rather are intended to be used for cardiology studies only, so with the cost still quite significant, the purchase of such equipment would for the moment only be justified for a laboratory with very high cardiac workload or for a large university department.

Physiological cardiac imaging has been the mainstay of imaging for at least 30 years. Renewed and significant industry investment in research and development in nuclear cardiology is required to allow the field to meet its full potential as an essential diagnostic tool in the care of cardiac patients. Such investment is best directed globally to enable talented physicians and scientists throughout the world to focus on bettering the field.

7.6. HYBRID SYSTEMS AND IMAGE FUSION

Multimodality imaging with integrated PET/CT and SPECT/CT systems offer the possibility for simultaneous evaluation of anatomy and function and is one of the most exciting new developments in imaging technology (Fig. 28). Additionally, CT data can be used to correct for attenuation, thus decreasing the number of false positive cases due to attenuation artefacts and increasing the specificity.

SPECT/CT and PET/CT operate on the same basic design principle: the dual modality acquires CT and radionuclide scans by translating the patient from one detector to the other while the patient remains on the table. This allows both images to be taken with consistent scanner geometry and with minimal delay between the two acquisitions. After both sets of images have been acquired and reconstructed, image-registration software fuses the images while accounting for differences in scanner geometry and image format between the two data sets (Fig. 28).

While the principle may be the same, each modality has its specific benefits. One of the major anticipated uses of SPECT/CT is the achievement of better attenuation correction. Apparent perfusion defects occur most often in the anterior wall in women and in the inferior wall in men, and soft tissue attenuation can also shift between resting and stress images. Interpreting these examinations requires clinicians to recognize any attenuation artefacts and allow for them in evaluating the underlying perfusion pattern. With SPECT only, relative perfusion often uncovers only the territory subtended by the most severe coronary stenosis,

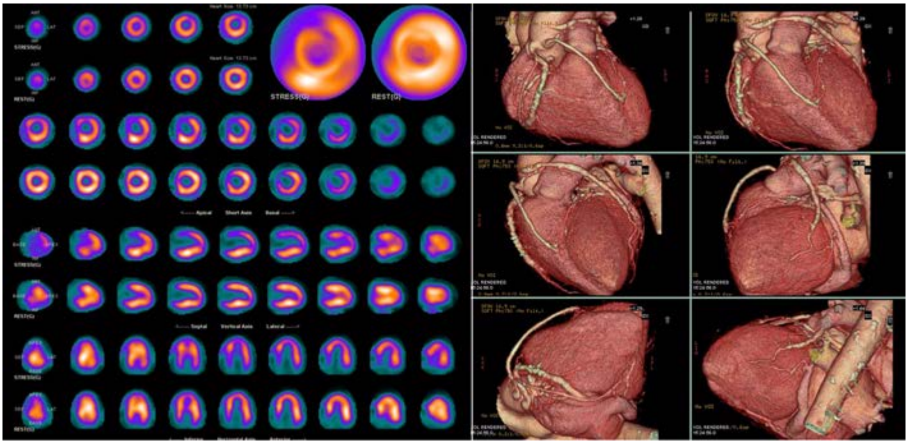

FIG. 28. Multimodality imaging. Stress (adenosine) and rest PET MPI with rubidium-82 (left), and 3-D display of CT angiography (right). Studies were performed sequentially on a PET/CT scanner for a total time of 35 minutes. Full functional and anatomical information can be obtained with such imaging protocol, including stress/rest ventricular function and calcium score (not shown) (courtesy UCL Hospitals, London, UK).

leading to underestimation of the extent of CAD. An additional benefit of SPECT/CT is its ability to quantitate blood flow in an absolute sense, which is important for the better detection of global balanced ischaemia. If a patient has triple vessel disease, there will be reduced flow in all vascular territories. That can look normal because the information is relative, not absolute. Attenuation correction, coupled with scatter correction, can reveal absolute coronary blood flow to diagnose patients better.

Myocardial perfusion PET provides high sensitivity (91%) and specificity (89%) for the diagnosis of obstructive CAD. Quantitative PET provides a non-invasive assessment of MBF and CFR and improves detection of preclinical and multivessel coronary atherosclerosis. Similarly, CT coronary angiography is an accurate means to image the entire continuum of anatomic coronary atherosclerosis from non-obstructive to obstructive CAD. However, not all coronary stenoses are haemodynamically significant and <50% of the patients with obstructive CAD on CT angiography demonstrate stress induced perfusion defects. Stress PET data complement the anatomical information on the CT angiogram by providing instant readings about the ischaemic burden of coronary stenoses. Thus, combined PET/CT may be potentially superior to CT angiography alone for the guiding revascularization decisions. Further, fusion of the PET and CT angiogram images allows identification of the culprit stenosis in patients presenting with chest pain. Finally, the advances in molecular imaging and image fusion may soon make non-invasive detection of vulnerable coronary plaques a clinical reality. In summary, integrated PET/CT is a powerful new non-invasive modality that offers the potential for refined diagnosis and management of the entire spectrum of coronary atherosclerosis.

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8. ROLE OF NUCLEAR CARDIOLOGY IN PREVENTIVE CARE

8.1. INTRODUCTION

Preventive care refers to measures taken to avoid the onset of disease. The term contrasts in method with curative and palliative care, and in scope with public health methods (which work at the level of population health rather than individual health).

Prevention involves a wide range of interrelated programs, actions, and activities. Some preventive measures are sweeping global policy initiatives, such as national and state government actions to reduce health risks by promoting changes in lifestyle, and limiting the exposure to hazardous substances like tobacco. Others are focused efforts of public health professionals and agencies, in order to reduce the incidence (occurrence of new cases) of specific diseases such as heart disease, diabetes, etc., and complications associated with these. The effectiveness of disease prevention programmes depends largely on the extent to which individuals take personal responsibility for their own health by avoiding health risks and by taking positive actions, and by the guidance that alerted physicians can provide to these individuals, especially if they are part of a special at-risk population.

8.2. CLASSIFICATION AND DEFINITIONS

Prevention involves working at three levels to maintain and improve the health of communities. One level, known as primary prevention, is inhibiting the development of disease before it occurs. Secondary prevention, also called 'screening' refers to measures to identify persons with disease before it is symptomatic. Finally, tertiary prevention focuses on people already known to be affected by disease with the attempt to reduce resultant disability and restore functionality.

Primary prevention programmes are developed in response to actual and potential threats to community public health and address specific health problems such as cardiovascular disease, cancer, or infections. Primary prevention of chronic diseases is more challenging than primary prevention of infectious diseases because it requires changing health behaviour. In cardiology, primary prevention measures include actions to protect against the development of cardiac disease, especially CAD, such as quitting smoking, exercising regularly and eating a healthy diet. Primary prevention is the responsibility of public health agencies with the involvement of the community as a whole. Clearly, imaging methods like nuclear cardiology have no role in primary prevention.

The goal of secondary prevention is to identify and detect disease in its earliest stages, before noticeable, when it is most likely to be treated successfully. With early detection and diagnosis, it may be possible either to cure a disease or slow its progression, prevent or minimize complications and limit disability. In cardiology, secondary prevention implies identification of occult CAD in order to establish measures to limit disease progression and avoid complications such as myocardial infarction, need for revascularization, or cardiac death. Secondary prevention should be in the hands of health care personnel and can be conducted by general practitioners with the aid of other professionals when necessary. For example, imaging specialists can have a significant role for detecting disease by studying special subgroups of the general population (i.e. patients with non-diagnostic ECG), or by helping to decide upon equivocal findings of other screening procedures such as exercise tests. In this context, the ultimate goal is to identify those patients with subclinical atherosclerosis who are at risk for near term atherothrombotic events and enable a more personalized management of care.

Tertiary prevention aims to improve the quality of life for people with disease by limiting complications and disabilities, reducing the severity of the condition, and providing rehabilitation. Tertiary prevention efforts have demonstrated that it is possible to slow the natural course of some progressive diseases and prevent or delay many of the complications associated with chronic diseases. In cardiology, typical tertiary prevention measures are the risk stratification of CAD patients in order to select the appropriate treatment, to apply effective treatment, and to evaluate treatment results through follow-up. Thus, unlike primary and secondary prevention, tertiary prevention involves actual treatment for the disease and is conducted by specialists (i.e. cardiologists with the aid of other professionals in related fields such as interventional cardiologists, cardiac surgeons, and imaging specialists). The role of non-invasive imaging in this setting is to risk stratify patients rather than to establish a diagnosis; additional utility is to evaluate the efficacy of therapeutic measures or to restratify patients during follow-up.

A three tiered preventive intervention classification system has been proposed: universal, selective and indicated prevention. Amongst others, this typology has gained favour and is used by many institutions in developed countries like the US Institute of Medicine, the National Institute on Drug Abuse (NIDA) Centre and the European Monitoring Centre for Drugs and Drug Addiction. This classification can be applied to cardiovascular disease as in Table 8.1.

TABLE 8.1. PROPOSED CLASSIFICATION OF PREVENTIVE INTERVENTIONS

Tier	Definition
Universal prevention	Addresses the entire population (national, local community, district) and aim to prevent or delay the occurrence of cardiovascular disease. All individuals, without screening, are provided with information and skills necessary to prevent the problem.
Selective prevention	Focuses on groups whose risk of developing cardiovascular problems is above average and involves a screening process. The subgroups to be screened may be distinguished by characteristics such as age, gender, family history, or predisposing pathology such as hypertension or diabetes.
Indicated prevention	Involves a further screening process, and aims to identify individuals who exhibit early signs of cardiovascular disease or are at special risk among the relative high risk defined by the previous categorization. These could be patients with diabetes and high calcium score, women with early menopause and concurrent risk factors, etc.

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9. EXPANDING CLINICAL APPLICATIONS OF NUCLEAR CARDIOLOGY

9.1. INTRODUCTION

With the introduction of new technologies and the evolving evidence about the role of these methods for risk assessment, CV imaging now includes a more comprehensive evaluation of global atherosclerotic disease burden and vascular function. Today, the CV imaging physician faces an expansion of the risk detection paradigm which approaches his/her categorization more to a vascular physiologist. Like in no other discipline, cardiology imaging now involves the non-invasive assessment of stress and rest ventricular function, coronary anatomy, and myocardial perfusion, sometimes in one single examination.

9.2. BEYOND OBSTRUCTIVE CORONARY STENOSIS

Although risk stratification evidence with SPECT MPI is very robust, undetected risk in patients with non-stenotic, diseased coronary arteries without functional or hemodynamic significance remains a concern. Evidence from serial reports demonstrates that many often mild to moderate stenoses are prone to rupture with ensuing presentation as acute myocardial infarction; thus searching solely for an obstructive stenosis by the application of any testing paradigm will fail to detect a sizeable proportion of at risk patients. This is supported by evidence from recent randomized trials noting that targeted risk reducing medical therapy with anti-ischaemic and anti-atherosclerotic properties can be equally effective as strategies focusing on improving blood flow to the myocardium via percutaneous coronary intervention.

This notion of disease beyond obstructive lesions, although not new for most clinicians, remains poorly understood among a large proportion of physicians who still focus on the anatomy of the lesions rather than on the functional aspects of a vascular disorder. Defining prognostically significant disease as a standard for clinical management now takes into account both anatomical and functional parameters and, in this paradigm, flow limitation features may include an intermediate or severely stenotic lesion but also the presence of endothelial dysfunction (Fig. 29).

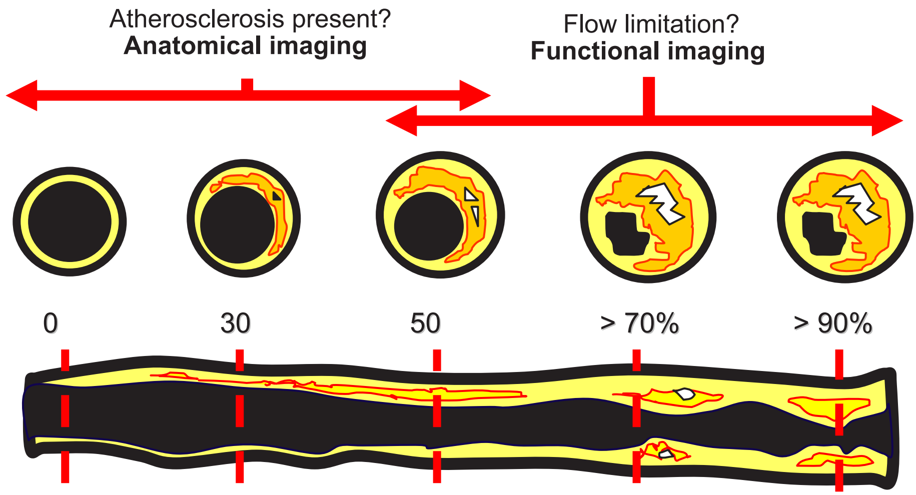

FIG. 29. The imaging paradigm in CAD. Anatomical methods such as CCS, MSCT angiography and IVUS are best suited for depicting the presence of atherosclerotic disease, whereas functional methods like SPECT and PET (and to some degree MRI and echocardiology) can establish the functional significance of the lesions, even if the obstruction is not severe (courtesy F. Keng, Singapore).

9.3. SHORT TERM AND LONG TERM RISK ASSESSMENT

PET and SPECT techniques for measuring myocardial blood flow or perfusion reserve are non-invasive methods to evaluate markers of endothelial function. This expanded testing model, which includes a focus on diagnosis of actually or potentially obstructive CAD as well as atherosclerotic plaque, coincides with parallel research focusing on the importance of lifetime risk of CHD. The medical community and professional organizations like the AHA may eventually expand the interest of risk detection beyond the Framingham risk score (FRS) estimation of ten year risk in order to predict a patient's lifetime risk of CVD. In fact, many patients may be at low risk over a period of ten years, but their lifetime risk of CHD may be significant. For instance, a 50 year old woman would have a low FRS in most cases; however the lifetime risk of incident CAD is 39% for this patient. Instead of being incongruous, this case reflects a vision of near term versus long term disease risk. Therefore, focusing exclusively on short term risk assessment fails to identify the burden of disease in women and other important patient subsets. Clinicians will have to evaluate the impact of each risk assessment by using an integrative approach that considers both short term and long term risk in guiding management decisions.

This concept can be translated to diagnostic modalities regarding short term and long term risk information, focusing on the utility and strength of a particular modality. For the high risk patient, in general, detection of non-obstructive atherosclerosis provides a long term estimation of risk, which may guide the intensity of preventive strategies. On the other hand, the detection of extensive ischaemia by SPECT MPI provides an estimation of elevated short term risk and may guide decisions on the need of immediate revascularization. Given the known power of SPECT MPI in predicting outcomes, what is currently required from these new CV imaging modalities is sound evidence on their ability to provide incremental prognostication through risk markers of plaque morphology or vulnerability and vascular function.

9.4. PRE-CLINICAL EVALUATION OF CARDIAC DISEASE: IMAGING FOR PREVENTION

A logical extension of current testing strategies would need to focus on the detection of non-obstructive atherosclerosis. Moreover, expanded testing algorithms that target 'high risk' yet asymptomatic patients could be another method to further reduce the burden of symptomatic disease and cardiac death. In this expanded testing paradigm, CV imaging would focus on the identification of risk in early or 'preclinical' disease states with ensuing aggressive preventive strategies aimed at further reducing the burden of CV morbid mortality, which falls into the categorization of secondary prevention. This can also be called selective prevention since the purpose is to target special at-risk groups so as to take appropriate measures. Within this vision of testing high risk asymptomatic patients (Fig. 30), the concept of selective imaging for prevention can be

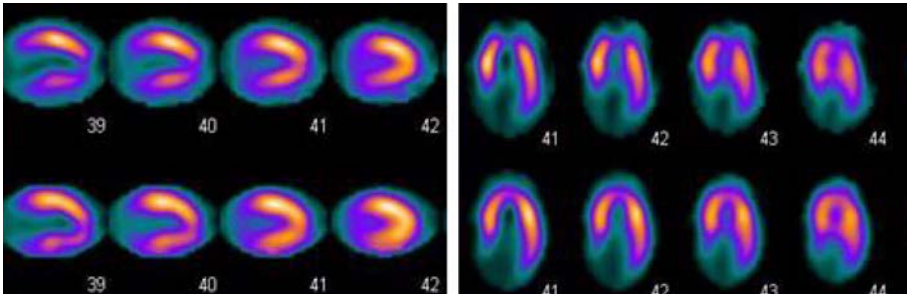

FIG. 30. Vertical long axis (left) and horizontal long axis (right) stress and rest SPECT MPI showing a reversible apical defect consistent with moderate induced ischaemia. The patient was a 37 year old man with no symptoms and normal stress ECG but strong family history of early CAD (courtesy F. Mut).

introduced, where the goal of testing is to target therapeutic intervention with the endpoint of improved patient outcome. The field of CV imaging is then challenged to define the role of various imaging modalities to successfully achieve this goal, and most probably future cardiac imaging research will focus on this preventive cardiology approach.

9.5. DEFINING EFFECTIVE PRE-SYMPTOMATIC RISK ASSESSMENT

The ideal scenario is one in which subclinical disease may be accurately detected and there is an established, effective therapy to treat preclinical or pre-symptomatic atherosclerosis. The success of such an approach requires demonstration of clinical effectiveness and global cost advantages of any imaging strategy in any health care environment with limited resources. The optimal imaging strategy may involve more than one approach or technique for the detection of risk, measurement of global risk, and assessment of the response to lifestyle modifications or medical interventions in terms of risk reduction. Imaging strategies ideally will reduce costs and not impose additional financial weight on the economy of health systems. Testing strategies must target a sufficient level of pre-test risk to ensure incremental value of cost effective imaging while distinguishing this effort from inappropriate or even harmful testing practices in low risk populations. Thus, discussions on test indications and appropriateness should be framed within the context that a clinical test is useful if it: (1) effectively identifies patients at high and low risk of future adverse events; (2) effectively defines targeted treatment strategies that result in decreased future adverse cardiac events for those selected high risk patients; and (3) establishes cost effectiveness, which is that the cost of the test, aggressive treatment for high risk individuals, and savings incurred by non-treatment (or conservative, less aggressive treatment) of low risk individuals result in a cost efficient strategy that at the same time improves patient outcome.

The term ‘pre-symptomatic risk’ stratification can be defined as the evaluation of risk in asymptomatic individuals whose underlying hazard for coronary events exceeds that of other average asymptomatic cohorts. There is available evidence supporting the idea that selected subsets of asymptomatic patients may have CHD event rates, including death or myocardial infarction, that place them in a so-called ‘risk equivalent’ status; that is, their underlying risk is equivalent to a patient with known CAD (which is defined by the US National Cholesterol Education Program as having an annual rate of CV death or non-fatal myocardial infarction of 2% or higher). Although not all of these individuals meet the criteria for initiating aggressive preventive therapies, a sizable portion are likely to present higher underlying atherosclerotic burden with functional vascular impairment and are probably at a high risk of subsequent CV events.

For example, patients with a CAC score of 400 or higher have a high rate of inducible ischaemia and should be referred for stress MPI after their index CAC scan. For diabetic patients, those with a family history of premature CAD, or those with the metabolic syndrome, the threshold for referral to stress MPI is lower, at a CAC score of 100. Overall, approximately one fourth of asymptomatic patients with CAC scores of 400 or greater will have significant MPI ischaemia as compared with nearly half of the higher risk diabetic patients in the same score group. The value of SPECT MPI in this setting has been studied, showing the safety of relying on a normal MPI study to establish a benign prognosis in patients with extensive CAC, provided that effective medical therapy is applied. It was demonstrated that after risk adjustment, there was no difference in four year cardiac event rates in patients with a normal SPECT MPI study and CAC scores of greater than 1000, 400 to 999, or less than 400. This represents a good example of how to apply a diagnostic imaging test to further risk stratify patients with a previous categorization of high risk for cardiac events.

The concept of pre-symptomatic risk assessment focuses on the clinical value of imaging high risk asymptomatic patients. There are a number of high-risk asymptomatic patient cohorts who are probably underserved by CV imaging. The full scope of diagnostic targets and the potential for improved clinical outcomes have yet to be realized but clearly there seems to be room for the expansion of appropriate imaging in order to yield optimal risk detection. The current paradigm for CV imaging that is based on population screening is controversial. Most cardiologists see a selected higher risk patient cohort, with probably already established cardiac disease. This reflects a need to improve the efficiency of testing strategies, considering selected circumstances in which testing of asymptomatic, high FRS patients (e.g. diabetic patients) may be clinically useful and thus be included in appropriateness guidelines.

Clinicians should take care to examine vulnerable low FRS patient subsets whose risk may be underestimated, notably women and younger men. The addition of an imaging test should be considered in appropriate patients with an intermediate FRS. Risk factors that are not included in the FRS should also be used to define candidates for CV imaging risk detection, including patients with a family history of premature CHD or those with the metabolic syndrome. Patients who may also be candidates for CV imaging include those with a higher risk of atherosclerosis, including (a) women with polycystic ovary syndrome (who are considered to be at higher risk for development of diabetes) or early menopause (i.e. <40 years of age); and (b) patients with rheumatoid arthritis, systemic lupus erythematosus, or other autoimmune diseases, since these disorders — more frequent in females — are associated with higher atherosclerotic burden.

Although diabetic patients are classified as CAD risk equivalents, an index risk assessment that includes imaging may serve as a guide to evaluate disease progression. Those patients with longstanding diabetes (i.e. >5 years) or with poorly controlled glycaemia may be reasonable candidates for cardiovascular imaging. Other CAD risk equivalents of value for index risk assessment include peripheral artery disease, cerebrovascular disease, or chronic renal disease. Other notable patient candidates within current testing guidelines include those undergoing preoperative risk detection, as well as those with new-onset atrial fibrillation or LV hypertrophy.

A list of conditions associated with relatively high risk for CAD or cardiac events that could be used for selection of patients for pre-symptomatic risk assessment with cardiac imaging is shown in Table 9.1.

TABLE 9.1. CONDITIONS ASSOCIATED WITH SPECIAL HIGH RISK FOR CAD OR CARDIAC EVENTS

Diabetes >5 years
Diabetes with poorly controlled glycemia
Peripheral artery disease
Cerebrovascular disease
Atrial fibrillation
LV hypertrophy
Autoimmune diseases
Non-cardiac major surgery
Polycystic ovarian syndrome
Early menopause (<40 years)
Chronic renal disease

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10. EDUCATION AND TRAINING IN NUCLEAR CARDIOLOGY

10.1. INTRODUCTION

All the benefits of nuclear cardiology as a cost effective tool to confront the increasing incidence of cardiovascular diseases must be supported by qualified practice. Poor standards of practice are associated with results that are far from those reported in the literature, so just buying a nuclear medicine instrument and obtaining a license for the handling of radioisotopes from the regulatory authorities do not guarantee the delivery of services that will have an impact in the clinical management of cardiac patients. Nuclear cardiology is multidisciplinary in nature, so all members of the imaging team should be properly trained and prepared to produce high quality results with the potential to affect patient management in a reliable and significant way. Training strategies should be well planned and directed towards achieving these objectives, keeping in mind the necessity of harmonization among team members. Finally, education of referring physicians and the public is essential if the benefits of nuclear techniques are to be fully understood and effectively used, including information on potential radiation hazards which have recently been a subject of controversy.

10.2. TRAINING OF PHYSICIANS

Nuclear cardiology is a ‘super specialty’ in which various techniques of nuclear medicine are utilized for diagnostic purposes in cardiology. Only physicians with certification in nuclear medicine or some specific training in this area should be qualified to perform and interpret nuclear medicine studies.

A problem arises in reconciling the views of cardiologists who wish to practice nuclear medicine solely in the form of nuclear cardiology, and nuclear medicine specialists who feel that unless a cardiologist has received full training in nuclear medicine, he or she should not be permitted to practice nuclear cardiology. In the USA, a cardiologist can practice nuclear cardiology after a three month training period in nuclear medicine. In Europe, a cardiologist can only receive certification after a full four years of training in nuclear medicine to practice nuclear cardiology. In many developing countries, however, the practice is not regulated or requires only minimal training in the handling of radioisotopes.

The nuclear medicine community is keen that cardiologists learn nuclear medicine techniques, understand their benefits to patients with cardiac disease and increase the application of these techniques among the population at risk. On the other hand, nuclear cardiology can be regarded as an attractive and competitive element to the nuclear medicine physician. Conversely, the cardiologist sometimes regards the nuclear medicine practitioner undertaking cardiological investigations as having neither adequate training nor the necessary understanding or qualifications to interpret the results appropriately in the light of clinical findings.

Thus, training in nuclear cardiology poses a special challenge since it involves two medical specialities at the same time. A physician can be successfully trained in nuclear cardiology following three different pathways:

(1) Training in nuclear cardiology of a physician having no specific background in neither nuclear medicine or cardiology;
(2) Training in cardiology of a physician coming from nuclear medicine practice;
(3) Training in nuclear medicine of a physician coming from cardiology practice.

While in most countries nuclear cardiology procedures are performed and reported by nuclear medicine physicians with some (if any) specific training in cardiology, in others these procedures are in the hands of cardiologists with variable degrees of training in nuclear medicine. However, in most cases there is no specific training in nuclear cardiology as a subspecialty. On the other hand, stress tests are generally (and should always be) conducted by a cardiologist with specific experience in such procedures. The result of the stress test represents a fundamental portion of the whole procedure, strongly influencing the interpretation of the nuclear scan. Hence, the practice of nuclear cardiology is a synergic activity where the nuclear physician and the cardiologist must act together to achieve an optimal outcome. Alternatively, a physician coming from one of the two fields should be cross-trained in the other specialty to become proficient in the practice of nuclear cardiology.

The continuous growth of nuclear cardiology has been possible under any of the abovementioned scenarios; however it must be kept in mind that nuclear cardiology is one of several applications of nuclear medicine and, as such, it should be under the control or supervision of a practitioner with solid training in nuclear techniques. It should be also noted that nuclear cardiology is multidisciplinary, involving other medical professionals such as radiopharmacists, technologists, physicists, and nurses, who must act in harmony within a well regulated, quality managed environment.

Appropriate performance and interpretation of nuclear cardiology studies requires knowledge of the principles of nuclear medicine, cardiac physiology, pharmacology and stress testing. It is important that the cardiology trainee become proficient with the basic principles of radioisotope preparation, as well as radiopharmaceutical administration and gamma camera instrumentation, and principles of image development. Further, there should be a national standardized approach to the training of individuals.

Two levels of proficiency in nuclear cardiology may be acquired during a general cardiology training programme. Basic knowledge would be achieved through a two month training period, obtained consecutively or spread through the programme period. Advanced training to allow interpretation and performance of studies in an established facility would be obtained over an additional period. Training should take place in an active laboratory at a university teaching centre or university approved and/or affiliated institution, ideally performing a sufficient number of studies per year, with state of the art equipment and directed by a cardiologist with advanced level expertise in nuclear cardiology, or by a nuclear medicine physician with comparable nuclear cardiology training.

The American College of Cardiology has divided the training of fellows in nuclear cardiology into three levels:

- Level 1 (General): Makes the trainee conversant with the field of nuclear cardiology for application in general clinical management of cardiovascular patients (recommended training time: two months).
- Level 2 (Specialized): Provides the trainee with special expertise to practice clinical nuclear cardiology (recommended training time: between four and six months).
- Level 3 (Advanced 3): Provides advanced training sufficient to pursue an academic career or direct a nuclear cardiology laboratory (recommended training time: one year).

Training in nuclear cardiology at all levels should provide an understanding of the indications for specific nuclear cardiology tests, the safe use of radionuclides, radiopharmaceutical concepts, the basics of instrumentation and image processing, methods of quality control, image interpretation, integration of risk factors, clinical symptoms, and stress testing, and the appropriate application of the resultant diagnostic information for clinical management. Training in nuclear cardiology is best acquired in academic approved training programsme in cardiology, nuclear medicine, or radiology. If these programmes are not in place, it would be desirable to have them established provided there is a sufficient real or potential demand in the country for nuclear cardiology procedures. Laboratory training in radiation safety and radioisotope handling may be provided by qualified physicians, scientists or senior technologists on a non-academic basis when such a programme is not available as part of the clinical training programme.

10.3. TRAINING OF TECHNOLOGISTS

The nuclear medicine technologist plays a critical role in the routine practice of nuclear cardiology since the quality of work and care taken during study execution determines the ultimate diagnostic capability of the test being performed. In many countries, the importance of training technologists has been poorly understood and, consequently, the professional development of this group has lagged behind. As a result, there are many technologists working in nuclear medicine who have had little or no formal training. Both the availability and the role of technologists vary considerably from country to country. The adoption of a basic level of training for technologists should be encouraged and the establishment of sustainable formal training programmes in each country is highly desirable.

The nuclear cardiology technologist's primary role is to perform diagnostic studies, frequently working in a general nuclear medicine service or department. This involves understanding the overall procedure and taking responsibility for all aspects of the study, except for clinical interpretation. The range of responsibility varies in different countries with an overlap between other professional groups (e.g. nurses, scientists, radiopharmacists), depending on resources. Technologists are also likely to have responsibilities in management, teaching and research. Although they may often have only a very specific, repetitive duty to perform, they usually take on overall responsibility for the study execution. Involvement in the whole procedure and awareness of the outcome is important, providing not only better appreciation of quality assurance but also improved job satisfaction.

In most developing countries, the lack of structured training has resulted in the recruitment of a broad range of individuals from elementary school leavers to science graduates to work as nuclear medicine technologists. It has been suggested that the minimum level of education should be a school higher certificate (equivalent to the entry level for tertiary education). In many countries, technologists enter the field after completion of a tertiary course in a different medical imaging or laboratory speciality. While lacking any formal nuclear medicine component, these courses provide useful background knowledge, but will require additional training in relevant oriented subjects. Full time academic courses in nuclear medicine technology, as offered in some countries, tend to include a range of subjects that broaden the education of students (e.g. business management and behavioural science) rather than being merely vocationally based. Distance assisted training programmes with on-site practical training have been successfully used with support from the IAEA in many developing countries. In any case, what needs to be recognized is that in order to fulfil their role, technologists require a reasonable solid educational background and multidisciplinary expertise.

10.4. TRAINING OF NURSES

The role that nurses play in patient care is just as important in nuclear cardiology as in any other clinical practice. Ideally, nurses should serve in diagnostic nuclear medicine sections and be present during nuclear cardiology stress testing. A nurse is the first interface with the nursing ward of inpatients and should be able to inject patients with radiopharmaceuticals (e.g. for rest studies) after training in intravenous injection and having received appropriate information on radiation protection and handling of radionuclides. Nurse professionals are expected to provide significant input to any quality management programme and to interact actively with other staff members, as well as to be involved in basic training to other members of personnel on fundamentals of patient care both for routine and emergency situations.

10.5. TRAINING IN MEDICAL PHYSICS

Nuclear medicine remains a highly technical field that not only uses advanced instrumentation but also applies quantitative techniques. Also, the direct use of unsealed sources of radiation calls for particular attention to radiation safety. As in the case of the radiopharmacist, a medical physicist is not necessarily required on a full time basis in small nuclear medicine departments or nuclear cardiology laboratories, but should be available for consultation. Since the medical physicist’s role is largely advisory and supervisory, the number of medical physicists working in the field is generally small. It is therefore difficult to justify the development of training courses in medical physics in most countries. Where medical physics is established as an academic specialty, there are well developed post-graduate courses, suitable for general training.

As in the case of other nuclear medicine professionals, the role of the medical physicist varies from country to country, depending to some extent on the stage of development of nuclear medicine practice and the local regulations. There is an overlap of duties with other professionals and sometimes the distinction between the medical physicist and the technologist is hard to define.

In any event, these two professionals should work closely in many areas such as quality control of instruments, image processing and data management.

10.6. TRAINING IN RADIOPHARMACY

Radiopharmacy is an essential and integrated activity in all nuclear medicine facilities. Although expertise is essential for preparation of radiopharmaceuticals, the process is not always managed or performed by a pharmacist, a feature desirable but rarely achievable. However, standards of practice need to be consistently high, irrespective of the background of staff performing the process.

Training should be adapted to the background and level of expertise of the trainees in order to ensure that they have the necessary grounding in these aspects of radiopharmacy relevant to their intended role. The person managing the preparation of radiopharmaceuticals needs to demonstrate a thorough knowledge of all areas of the specialty. In addition, training in radiopharmacy should be a separate, required section or subject for the nuclear physician, the technologist and other professional and technical staff.

10.7. TRAINING IN CARDIAC PET AND HYBRID TECHNIQUES

Cardiac PET and PET/CT imaging of positron emitting radionuclides are part of nuclear cardiology. Since an increasing number of nuclear laboratories have access to both conventional SPECT and PET imaging, training guidelines for PET imaging in cardiology are appropriate. Training in this specific technology can be integrated with programmes directed to conventional nuclear cardiology; however, it should include those aspects that are unique or specific to imaging using positron emitting radionuclides. Depending on the desired level of expertise, training in cardiac PET should incorporate knowledge of substrate metabolism in the normal and diseased heart; knowledge of positron emitting tracers for blood flow, metabolism and neuronal activity, medical cyclotrons, radioisotope production, and radiotracer synthesis; and principles of tracer kinetics and their in vivo application for the non-invasive measurements of regional, metabolic and functional processes. The training should also include the physics of positron decay, aspects of imaging instrumentation specific to the imaging of positron emitters and the use of CT (since hybrid instruments are now the rule), production of radiopharmaceutical agents, quality control, handling of ultra-short life radioisotopes, appropriate radiation protection and safety, and regulatory aspects.

Hybrid imaging devices combining PET or SPECT with CT are playing an increasing role in the field of cardiac imaging. Currently, all commercial PET scanners are offered as PET/CT devices, and SPECT/CT instruments are available from most manufacturers. As these devices are becoming more widely disseminated, there is also a need for training guidelines for fellows, residents and nuclear cardiologists or for nuclear physicians already in practice. The applications of hybrid imaging in cardiology include the use of CT scanning to provide reliable and precise attenuation correction of SPECT or PET images, and to assess coronary calcium as a marker of coronary atherosclerosis. Even these applications of hybrid imaging will require additional training beyond that required for CT alone. With contrast injection, high resolution CT coronary angiography can be performed and combined with rest/stress assessments of myocardial perfusion provided by PET or SPECT, allowing almost simultaneous functional assessment of the anatomical findings. The specific aspects of the training required should include the physics of hybrid systems, CT attenuation correction, principles and application of CT coronary calcium assessment, and principles and application of CT coronary angiography.

10.8. EDUCATION OF REFERRING PHYSICIANS

Clinical indications and benefits of nuclear cardiology are not fully understood by many clinicians, thus hampering the application of useful tools for patient management which is associated with suboptimal therapeutic decisions and clinical outcomes. Figure 31 depicts an example of the situation in a representative developing country, clearly showing lack of information about nuclear cardiology among cardiology practitioners.

Observational data from other countries demonstrate a similar scenario, which results in under-utilization of nuclear cardiology beyond economic considerations. Efforts should be made to disseminate evidence based information to professionals following outreaching strategies that should be developed according to the local cultural, socioeconomic, and professional environment. Usually, the integration of nuclear cardiology into pre- and post-degree academic curriculums, the creation of nuclear cardiology committees within scientific cardiology societies, the inclusion of lectures or symposia in clinical cardiology meetings, and other educational activities such case discussion sessions have been successful strategies in many countries.

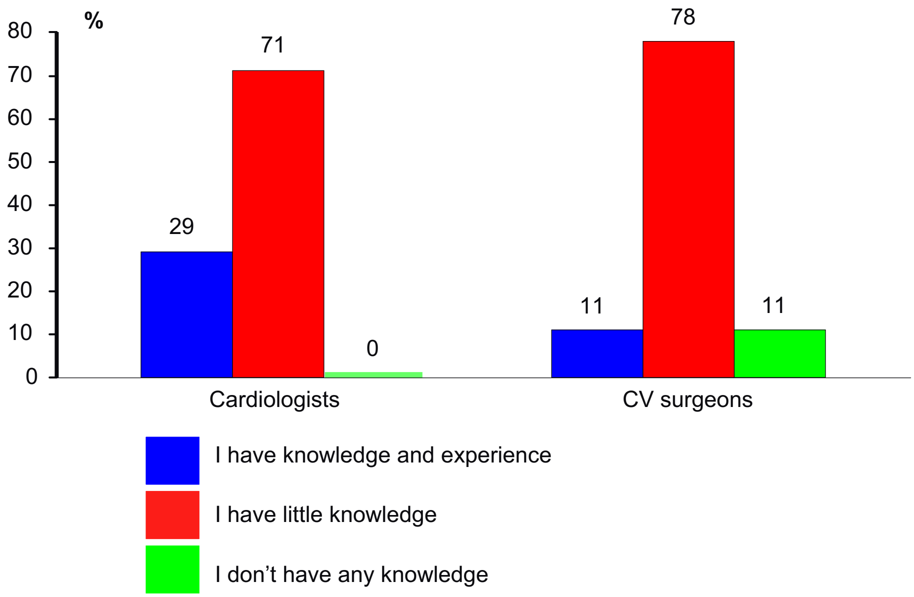

FIG. 31. Results of a survey performed in a developing country exploring the level of knowledge about nuclear cardiology among clinical cardiologists and cardiac surgeons. Despite its availability in the country, only 29% and 11% of the respective specialists recognized having sufficient knowledge of the technique (courtesy A. Peix, Cuba).

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11. RADIATION SAFETY AND CARDIAC IMAGING

11.1. INTRODUCTION

Radiation safety is always an issue in nuclear medicine. The IAEA recognizes this problem and the fact that the nuclear cardiology community has tried to reduce the amount of radiation the patient undergoing such procedures receives, following the ALARA (as low as reasonably achievable) principle. This implies that reasonable radiation exposure is justified for medical diagnostic applications. In this context, justification of an examination means that a physician has reached the conclusion that an individual patient needs the procedure and that the benefits of performing the procedure significantly outweigh any risks that may be incurred by applying it. For procedures that require exposure to ionizing radiation, the risks include the associated short and long term risks, and justification must consider all alternative methods available, either not requiring radiation exposure or involving a comparative reduced dose.

11.2. APPROPRIATE USE OF CARDIAC DIAGNOSTIC PROCEDURES INVOLVING RADIATION EXPOSURE

In the last decade, appropriateness has become the guiding principle and the key to define the essentiality of any health care intervention, from the introduction of new drugs or new treatment modalities, to the implementation of new diagnostic procedures. Basically, such health care interventions might be deemed appropriate when their efficacy has already been proved for defined clinical indications and the balance between benefits and unwanted side effects is definitely in favour of benefits[1].

Public concern about the safety of imaging procedures using ionizing radiation has been raised by reports reaching the general public, and this may have led to some amount of fear among patients that could potentially affect the utilization of techniques that have been extensively proven to benefit patient management, outweighing the risks when properly applied.

[1] Appropriate use implies assessing the evidence of improved diagnostic performance (higher sensitivity and specificity) compared with other current techniques; that the information derived from the procedure influences clinical practice; that the information from the procedure has a plausible impact on the patient's outcome, either through adoption of more effective therapeutic strategies or non-adoption of ineffective or harmful practices.

As published in a recent ASNC Information Statement, radiation risk to both the patient and to imaging personnel from medical imaging procedures involving the use of ionizing radiation is a matter of concern and controversy among the diagnostic imaging community. With the increased utilization of MSCT imaging, both stand-alone and in conjunction with PET and SPECT, radiation risk has received significant attention both scientifically and in the mass media. Several studies are reporting significant increased risk to the patient receiving low ionizing radiation from CT and nuclear studies, raising questions regarding the appropriateness of these techniques for radiation safety. With new technological developments and the increased availability of hybrid scanners, the combination of SPECT MPI and MSCT for CAD evaluation is very appealing since it would overcome the shortcomings of each technique, allowing comprehensive functional and anatomical assessment. However, the practicability of this approach has been hampered by the fact that the total radiation burden can be as high as 40 mSv. This also applies for PET–CT protocols for which the dose could be even higher, especially with the use of rubidium-82 as a perfusion agent. Patient radiation exposure estimates for typical nuclear medicine and other cardiac imaging studies using ionizing radiation in 2007 are shown in Fig. 32.

For diagnostic procedures, radiation concerns focus mainly on long term theoretical patient risk; however, the immediate and long term benefits of potentially life saving tests should also be emphasized and considered in the

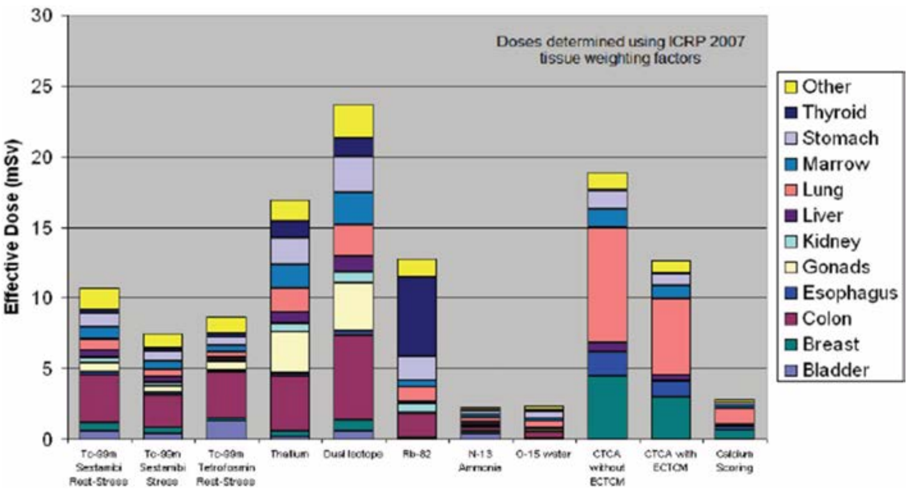

FIG. 32. Radiation exposure (as effective dose in mSv) from different imaging procedures and protocols used in cardiac imaging (from EINSTEIN, A.J., et al., Circulation 2007 (reprinted with permission)).

risk–benefit equation. Thus, the risk of such nuclear procedures to the patient should be balanced against the risk of not performing a well indicated procedure in such patients. Since CVD is the leading cause of death worldwide, this would eventually deny the immediate benefits of life saving treatments to potentially high risk patients.

11.3. OPTIMIZING RADIATION EXPOSURE FROM DIAGNOSTIC PROCEDURES

The International Commission on Radiological Protection (ICRP) has suggested that dose limits recommended for the general public and occupationally exposed workers should not be applied to medical exposure. This is based on the ethical fact that the exposed individual (i.e. the patient) will derive benefit from the procedure, provided it has been properly justified; this approach has been adopted worldwide. Nevertheless, medical procedures involving radiation exposure are subject to the requirement for optimization. Various tools, such as diagnostic reference levels and dose constraints, are useful in this regard and may be used as a guide to good practice. Following published appropriateness or referral criteria or related algorithms and protocols designed to guide the use of the most appropriate examination for specific clinical situations is also a useful way not only for cost effective care, but also for reducing unnecessary radiation. Since these tools also have limitations, they should be considered as guides and not be given the status of a legal or required standard of practice.

The nuclear medicine community has continued to address ALARA by adopting measures which include minimizing the dose required for the scan, in part using new processing algorithms and new gamma camera designs, performing separate day protocols, and reducing the utilization of protocols requiring thallium injection, which is an isotope delivering a much higher dose of radiation than ^{99m}Tc. Unfortunately, the shortage of ^{99m}Tc due to problems with ^{99}Mo production worldwide has obliged a return to the use of thallium, which was being progressively abandoned. It is expected that this situation will be resolved in the mid-term by the incorporation of new reactors to the medical isotopes production chain. New, rapid algorithms promoting the avoidance of rest perfusion studies when the stress study is normal, although controversial, can further limit radiation burden and are being successfully applied in many laboratories. Overall, such measures have the potential to effectively decrease radiation exposure from nuclear studies by about 1/10 to 1/5 compared with previous estimates (Fig. 33). A recently published ASNC Information Statement

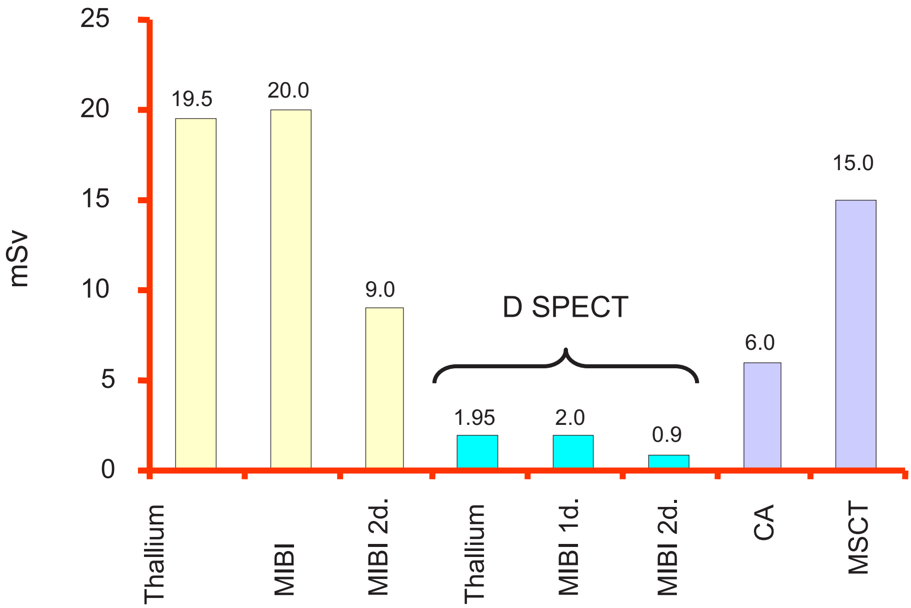

FIG. 33. Estimated decrease in effective radiation dose by the use of a new high sensitivity gamma camera (D-SPECT), resulting in 1/10 reduction as compared to the use of conventional nuclear medicine technology. (MIBI 1 d. = ^{99m}Tc-sestamibi SPECT using one day protocol; MIBI 2 d. = ^{99m}Tc-sestamibi SPECT using a two day protocol; CA = conventional coronary angiography; MSCT = multi-slice CT using conventional protocol; D SPECT = new camera design)

includes an updated set of recommendations for reducing radiation exposure in MPI.

11.4. NEW DEVELOPMENTS IN NUCLEAR MEDICINE TECHNOLOGY FOR CARDIAC STUDIES

In the last few years, major advancements have had impact on the nuclear medicine practice, in particular in the field of cardiology. Those advancements targeted the reduction of the scanning time and administered radiation dose to patients while improving the overall image quality, thus allowing a more confident and efficient diagnosis of CVDs and improving the departments workflow. The new technology combines new detector materials such as cadmium–zinc–telluride (CdZnTe, or CZT), the use of focused pinhole collimation, 3-D reconstruction, and data acquisition models. The new high speed system is characterized by an increase in count sensitivity, with excellent linear correlation between the amounts of perfusion abnormality at stress and rest detected by the new camera compared to the conventional system, with an estimated decrease in effective radiation dose by the use of the new high sensitivity gamma camera, resulting in 1/10 reduction as compared to the use of conventional nuclear medicine technology. The scanning time is reduced to a four minute stress/two minute rest acquisitions with the high speed camera providing images with improved resolution and, when compared to the conventional SPECT MPI, similar amount of perfusion abnormality.

Additionally, using the latest MSCT technical refinements like prospective triggering can further ensure safer cardiology multi-imaging practice optimizing benefits to the patient and minimizing concern about radiation dose among health personnel and the general public.

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12. CONCLUSIONS

Cardiovascular diseases are on the rise all over the world, and thus the nuclear cardiology area should respond to the challenge with innovations that can be easily put in practice, especially in developing countries. Nuclear cardiology has the unique ability to 'predict the future' in people at risk of CAD, non-fatal cardiac events and sudden death. Radionuclide methods can accurately identify patients who do not have significant CAD, thus requiring only continued preventive measures. Conversely, patients identified as having milder forms of disease can be safely treated with intensive medical therapy without interventions, while patients with more severe ischaemia can be referred directly to revascularization procedures such as percutaneous intervention or coronary bypass surgery.

Following revascularization, or after instauration of optimized medical therapy, nuclear techniques continue to provide crucial diagnostic and prognostic information over the remainder of the patient's life. This approach to patient management has been proved to be cost effective and suitable for emerging economies as well as for developed countries. Under-utilization of these techniques should be confronted by the dissemination of evidence based information supporting applications in a wide variety of clinical scenarios.

Special training requirements should be considered since the specialty has contact points between major disciplines such as nuclear medicine, cardiology, and radiology. Cross-education of professionals already trained in their respective fields should be necessary, including physicians, technologists, and other allied professionals. Curriculum details have been proposed by several institutions and organizations, and each country should set its own training programmes according to local regulations, needs and available resources.

Dosimetry issues are of major concern in modern medical imaging involving ionizing radiation. Radiation exposure from diagnostic procedures can be minimized by following established appropriateness criteria for tests and by using state of the art protocols and technology.

High quality practice of nuclear cardiology is essential to provide significant aid in patient management and to respond to increasing demands of cost effectiveness in medical care. The concept of imaging for prevention can include nuclear cardiology procedures, giving an opportunity for new clinical applications in special target populations, for which tailored diagnosis and treatment may result in improved quality of life and survival.

CONTRIBUTORS TO DRAFTING AND REVIEW

Allam, A.	Mohandessin, Egypt
Allman, K.	Royal Prince Alfred Hospital, Australia
Better, N.	Royal Melbourne Hospital, Australia
Bouyoucef, S.E.	Centre Hospitalo Universitare, Algeria
Dondi, M.	International Atomic Energy Agency
Ellmann, A.	Tygerberg Hospital, Stellenbosch University, South Africa
Giubbini, R.	Universita degli Studi di Brescia, Italy
He, Z.X.	Fu Wai Hospital, China
Keng, F.	National Heart Centre, Singapore
Kiess, M.	St. Paul’s Hospital, Canada
Lee, B.-N.	Kuala Lumpur Hospital, Malaysia
Mut, F.	International Atomic Energy Agency
Orellana, P.	Pontificia Universidad Católica de Chile, Chile
Peix, A.	Institute of Cardiology and Cardiovascular Surgery, Cuba
Sambuceti, G.	University of Genoa, Italy
Shaw, L.	Emory University School of Medicine, United States of America
Sritara, C.	Mahidol University, Thailand
Thomas, G.	Mission Internal Medical Group, United States of America
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This publication presents an overview of cardiovascular diseases as a public health problem in developing countries, the role of nuclear cardiology within a scenario of unprecedented technology advances and the evidence behind appropriateness recommendations. The potential expanding role of non-invasive functional imaging through the transition from diagnosis of obstructive coronary artery disease to defining the global burden of cardiovascular diseases is also discussed, as well as the need for training, education and quality in nuclear cardiology practice.

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