Nuclear Cardiology: its Role in Cost-effective Care
FOREWORD

Nowadays, due to the multiple techniques available to manage cardiovascular diseases, clinicians face the challenge of choosing the appropriate technique(s) for each clinical setting. To do so, they must be knowledgeable of the relative utility of each method. Basically, non-invasive tests should provide accurate, reliable and reproducible information, as well as incremental prognostic value to the risk predicted by clinical assessment.

Currently, there are well-established modalities with a long proven track record in the assessment of patients with suspected or known coronary artery disease (CAD), but they are not meant to replace coronary angiography. However, if such noninvasive imaging techniques are used to their full potential, they should be able to better identify those groups of patients who will benefit from more invasive approaches and limit the number of unnecessary diagnostic invasive procedures.

The near future holds major developments in the field of cardiac imaging. The pace of these advances will be influenced by the overall economic environment. Specifically, imaging of sub clinical coronary lesions is a field with significant growth potential and important clinical implications. Plaque composition is probably the major determinant of the future occurrence of acute coronary syndrome rather than the severity of stenosis or plaque size. In this respect, functional imaging modalities, can reliably estimate a patient's prognosis and improve the stratification of patients into different risk levels. Further work in this field may allow earlier detection of patients at higher risk of subsequent cardiac events and, thus, provide a paradigm shift in noninvasive imaging of CAD from the current approach.

This review aims to determine the role of the various investigation techniques in the management of coronary artery disease and their resource implications, and should help determine future service provision, accepting that we are in a period of significant technological change and it is the result of a Technical Meeting held in Vienna in May 2007, followed by a Consultant Meeting in August 2008.

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CONTENTS

1. INTRODUCTION ............................................................................................................ 4
  1.1. Background information ..................................................................................... 4
  1.2. Objective ............................................................................................................. 4
  1.3. Scope .................................................................................................................. 4
  1.4. Structure .............................................................................................................. 4

2. EPIDEMIOLOGY OF CARDIOVASCULAR DISEASES IN DEVELOPING COUNTRIES .............................................................. 5
  2.1. Introduction ........................................................................................................ 5
  2.2. Epidemics of obesity and diabetes in developing countries ............................... 6
  2.3. The ageing population ........................................................................................ 8
  2.4. Importance of early detection and treatment ...................................................... 9

3. NUCLEAR CARDIOLOGY: ONE OF THE MOST ACCEPTED TOOLS FOR MANAGEMENT OF PATIENTS WITH CVD ......................... 9
  3.1. Introduction ........................................................................................................ 9
  3.2. Myocardial perfusion scintigraphy in stable CAD ............................................. 9
  3.3. Myocardial perfusion scintigraphy in acute coronary syndromes ................. 10
  3.4. Myocardial perfusion scintigraphy before non-cardiac surgery ....................... 11
  3.5. Assessment of left ventricular function and other non-perfusion parameters in cardiac diseases ......................................................... 11
  3.6. Assessment of viable and hibernating myocardium in heart failure ............... 12
  3.7. Clinical guidelines ............................................................................................ 13

4. NUCLEAR CARDIOLOGY UTILIZATION THROUGHOUT THE WORLD .......... 14
  4.1. Introduction ...................................................................................................... 14
  4.2. Analysis of available data ................................................................................. 14
  4.3. Utilization of nuclear cardiology vs. mortality rate .......................................... 16

5. COST-EFFECTIVENESS .............................................................................................. 17
  5.1. Introduction ...................................................................................................... 17
  5.2. Cost-effectiveness in nuclear cardiology .......................................................... 17
  5.3. Patients with stable angina ............................................................................... 18
  5.4. Patients with chest pain and suspected acute coronary syndromes ............... 19
  5.5. Special populations ........................................................................................... 20

6. NUCLEAR CARDIOLOGY AND COMPETING MODALITIES FOR THE EVALUATION OF CARDIAC PATIENTS ................................................................. 22
  6.1. Introduction ...................................................................................................... 22
  6.2. The resting electrocardiogram (ECG) .............................................................. 22
  6.3. The exercise stress test (treadmill stress test, TMT) ........................................ 22
  6.4. Echocardiography ............................................................................................. 23
  6.5. Magnetic Resonance Imaging (MRI) ............................................................... 25
  6.6. Multi-slice Computed Tomography (MSCT) ................................................... 26
  6.7. Contrast coronary angiography (CA) and intravascular ultrasound (IVUS) ...... 28
6.8. Nuclear Cardiology

7. TECHNOLOGICAL ADVANCES IN NUCLEAR CARDIOLOGY
   7.1. Introduction
   7.2. Development of new pharmacologic stress agents and protocols
   7.3. Development of new tracers
   7.4. New computer algorithms and tools
   7.5. New gamma-camera technology
   7.6. Hybrid systems and image fusion

8. THE ROLE OF NUCLEAR CARDIOLOGY IN PREVENTIVE CARE
   8.1. Introduction
   8.2. Classification and definitions

9. EXPANDING CLINICAL APPLICATIONS OF NUCLEAR CARDIOLOGY
   9.1. Introduction
   9.2. Beyond obstructive coronary stenosis
   9.3. Short-term and long-term risk assessment
   9.4. Pre-clinical evaluation of cardiac disease: imaging for prevention
   9.5. Defining effective pre-symptomatic risk assessment

10. EDUCATION AND TRAINING IN NUCLEAR CARDIOLOGY
    10.1. Introduction
    10.2. Training of physicians
    10.3. Training of technologists
    10.4. Training of nurses
    10.5. Training in medical physics
    10.6. Training in radiopharmacy
    10.7. Training in cardiac PET and hybrid techniques
    10.8. Education of referring physicians

11. RADIATION SAFETY
    11.1. Introduction
    11.2. Concerns about diagnostic radiation exposure
    11.3. Optimizing radiation exposure from diagnostic procedures

12. CONCLUSIONS
1. INTRODUCTION

1.1. Background information

As reported by the World Health Organization, cardiovascular diseases (CVDs) are the number one cause of death globally: more people die annually from CVDs than from any other cause. An estimated 17.1 million people died from CVDs in 2004, representing 29% of all global deaths. Of these deaths, an estimated 7.2 million were due to coronary heart disease and 5.7 million were due to stroke. Low- and middle-income countries are disproportionally affected: 82% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women.

By 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. These are projected to remain the single leading causes of death. The largest percentage increase will occur in the Eastern Mediterranean Region. The largest increase in number of deaths will occur in the South-East Asia Region. Heart disease and stroke can be prevented through healthy diet, regular physical activity and avoiding tobacco smoke. Individuals can reduce their risk of CVDs by engaging in regular physical activity, avoiding tobacco use and second-hand tobacco smoke, choosing a diet rich in fruit and vegetables and avoiding foods that are high in fat, sugar and salt, and maintaining a healthy body weight.

Of all forms of CVDs, coronary artery disease is the most prevalent although it has declined over the last few decades due to the introduction of primary and secondary prevention strategies.

1.2. Objective

Non invasive cardiac imaging techniques, and in particular stress myocardial perfusion single photon emission computed tomography (MPS), have a central role in the diagnostic workup and risk assessment of patients with known or suspected coronary artery disease (CAD), lowering the cost of caring those patients.

The objective of this publication is to discuss the cost-effectiveness of non-invasive imaging techniques, and more specifically of MPS. It describes the currently available noninvasive cardiac imaging modalities for the detection of CAD and reviews strengths and weaknesses of each modality.

1.3. Scope

1.4. Structure
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 than CVD, especially breast cancer in women, however all statistics consistently show the opposite. According to the World Health Organization (WHO), CVD is the leading cause of mortality in adults worldwide for both men and women, killing a much larger number of persons compared to 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 is continued, by year 2015 this number will be increased 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 following WHO estimations, about 80% of these deaths occur in low to mid income countries (developing nations) with limited resources to face a problem of this magnitude. Affected victims of CVD are usually at their peak productive age, which further aggravates the economic situation of these nations.

Figure 1. The five main causes of death in the world. The graphics show the relative weight of specific causes among the five more 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, not tuberculosis; Infectious = includes gastrointestinal infections, tuberculosis, and malaria, excludes other respiratory infections. CVD are the most single common cause of death through the three categories of countries (adapted from WHO Report, 2003; income categorization according to World Bank standards).
The fatal consequences of CVD typically will affect individuals of mid to more advanced age, however the process of atherosclerosis evolves slowly over decades, beginning still 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.

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

Although primary prevention is important, it is a slow process and the impact on mortality reduction will only be seen at mid - long term, while this will have limited impact on 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 readily identify individuals with advanced atherosclerosis (symptomatic or asymptomatic) and to start treatment (medical or interventional) and secondary prevention measures as soon as high risk disease is discovered.

2.2. Epidemics of obesity and diabetes in developing countries

Diabetes mellitus (DM) is closely linked with 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 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, specially related to high fat and carbohydrates intake and lack of exercise, have been responsible for a rapid increasing number of DM patients in low- and mid-income countries. Data from the WHO demonstrates that in countries of Southeast 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 East countries like Saudi Arabia will have between 14% and 20% of their population suffering from DM. These countries are already seeing the consequences of high incidence of DM, with 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.

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

Figure 4. Estimated number of adults with diabetes in developed and developing countries and projection towards 2030. Source: WHO Diabetes Programme (www.who.int/diabetes/actionnow/en/diabprev.pdf).

One of the major problems with diabetes is the high incidence of silent myocardial ischemia. This fact leads to late consultation by the patient, or to the development of chronic heart failure due to the repetition of ischemic 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 ischemic heart disease and few symptoms evaluated with nuclear cardiology is presented in figure 5.

Figure 5. Thirty-six year old man with diabetes, obesity, hypertension, and high cholesterol levels who complained from shortness of breath. Despite having no chest pain and a negative exercise electrocardiogram, this patient had nuclear cardiology findings consistent with advanced coronary artery disease and high risk for death and/or myocardial infarction (courtesy J. Vitola, Brazil).

2.3. The ageing population

While high mortality rates are seeing in young and middle-aged adults with DM and CVD in developing nations, some developed as well as 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 (y) for men and 86 y for women, in Australia and Italy 79 y for men and 84 y for women, in Argentina 72 y for men and 78 y for women, and in Cuba 75 y for men and 79 y for women, just 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.
Figure 6. Projected life expectancy at birth in 2030 compared with 2002 (WHO Report, 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 mid-income nations is an extremely important issue including economical implications that physicians, governments and healthcare providers in general will need to face.

2.4. Importance of early detection and treatment

Successful management of cardiac patients largely depends on early detection of pathologic 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 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 mid-income countries.

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

3.1. Introduction

Nuclear Cardiology is a well established technique to detect coronary artery disease (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 the US and Canada, 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 so-called emission tomography imaging method (single-photon emission computed tomography or SPECT) which renders 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 myocardial perfusion scintigraphy (MPS) is commonly performed with technetium-99m-labelled tracers, such as sestamibi and tetrofosmin, or with thallium-201. MPS can detect myocardial ischemia and viability as well as assess left ventricular function. The safety of MPS during exercise or pharmacological stress (dipyridamole, adenosine or dobutamine) is comparable to exercise ECG, although the diagnostic yielding is largely superior both in terms of sensitivity and specificity. Substantial evidence from developed and developing countries strongly supports the accuracy and cost-effectiveness of MPS 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 MPS as class I or II indications for the diagnosis and risk-stratification of patients with suspected or known CAD (table I). While SPECT MPS is currently the most commonly used technique for the assessment of CAD in many developed nations, it is underutilized or even nonexistent in a large proportion of developing countries.

3.2. Myocardial perfusion scintigraphy 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, consistent and independent of sub-populations 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 MPS has been compared with that of stress echocardiography, generally showing MPS to have higher sensitivity and equivalent or slightly lower specificity.

The value of MPS 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 MPS in patients with intermediate to high likelihood of CAD predicts a very low cardiac event rate (<1%/year). In contrast, abnormal MPS 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. In this way, MPS is superior to ECG, echo, 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).

Figure 7. Cardiac event rates (death, MI, revascularization) according to direct catheterization strategy vs. myocardial perfusion-first strategy. The latter is most significantly associated with lower revascularization rates. From: Shaw LJ, J Am Coll Cardiol 1999 (reprinted with permission).

3.3. Myocardial perfusion scintigraphy in acute coronary syndromes

Of the approximately 6 million patients evaluated for chest pain in emergency departments in the United States, only one third will be found to have symptoms of cardiac origin. The role of SPECT MPS as a ‘gatekeeper’ to hospital admission for acute chest pain is well documented. MPS 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 Figure 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 MPS after an episode of unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) for risk stratification, especially in patients with a low to intermediate likelihood of cardiac events according to traditional markers of risk. Stress MPS is currently recommended in patients after ST-segment elevation myocardial infarction that might have received thrombolytic therapy but who have not yet undergone coronary angiography in order to determine the extent of ischemic myocardium and whether revascularization will be beneficial. SPECT MPS with dipyridamole is considered a safe test even early after myocardial infarction, provided no complications are present.

### 3.4. Myocardial perfusion scintigraphy 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. MPS has received a class I indication for risk stratification of patients undergoing elective non-cardiac surgery. MPS 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 MPS 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 (red blood cells labelling) or gated SPECT MPS. The reproducibility of radionuclide methods is higher than that of other noninvasive imaging modalities, probably with the exception of MRI. Left ventricular ejection fraction 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 magnetic resonance imaging over a wide range of end diastolic volumes (EDV), end systolic volumes (ESV), and LV ejection fraction (LVEF) values (figure 8). Hence, gated SPECT provides clinically relevant information on cardiac function and volumes with all 3 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 3 algorithms is not advisable for the evaluation of serial changes and 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 ischemic 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 ischemia. Also, transient LV dilatation (TID) can be measured, having a similar signification together with pulmonary uptake and retention of the radiotracer after stress injection. All three phenomena reflect LV ischemic dysfunction during stress and are of special diagnostic value when there is balanced ischemia and no segmental abnormalities are evident in the perfusion images.

The development of a computer algorithm to measure 3-dimensional LV shape index, derived as the ratio of maximum 3D 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 3D variable derived automatically from gated myocardial perfusion scintigraphy providing highly repeatable ventricular shape assessment. Preliminary findings suggest that left ventricular shape index might have clinical implications in patients with congestive heart failure.

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

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 ischemic 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 endpoints evaluated in several viability studies, designed to analyze 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. F-18-fluorodeoxyglucose (FDG) positron emission tomography (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 3,088 patients) that used various 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 MPS with conventional tracers is a simple and inexpensive way to evaluate myocardial viability (figure 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-ischemic heart failure.

Recently, it has been documented by using gated SPECT MPS 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 18F-FDG PET may be used to optimize the selection process for CRT by identifying viable segments, which yields high accuracy for predicting CRT response.

Figure 9. Viability study with 99mTc-sestamibi. Upper row: horizontal long axis, vertical long axis and short axis; basal MPS 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, Uruguay).

In summary, myocardial viability can be assessed both by SPECT MPS and by myocardial FDG utilization (the latter using the more sophisticated PET technique). Nitrate-enhanced MPS 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 MPS, in order to identify any ischemic 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 I below, 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 I. Recommendations for MPS 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).

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Recommendation</th>
<th>Issuing body</th>
<th>Class</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>Chronic chest pain</td>
<td>Diagnosis of CAD in patients with intermediate pre-test likelihood: unable to exercise, abnormal rest ECG</td>
<td>ESC/ACC/AHA</td>
<td>I</td>
<td>B</td>
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<tr>
<td>Chronic chest pain</td>
<td>Evaluation of CAD in patients with intermediate pre-test likelihood: identification of culprit lesions, assessment of hemodynamic significance of stenosis, evaluation post-PCI or CABG</td>
<td>ESC/ACC/AHA</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Acute chest pain</td>
<td>Detection of resting ischemia Detection of ischemia in low to intermediate risk patients after UA/NSTEMI Detection of ischemia in patients with uncertain diagnosis Assessment of infarct size and myocardium at risk after STEMI</td>
<td>ESC/ACC/AHA ESC/ACC/AHA ESC/ACC/AHA ESC/ACC/AHA</td>
<td>IIb IIa I I</td>
<td>B A B C</td>
</tr>
<tr>
<td>Pre-operative risk assessment</td>
<td>Risk stratification before elective non-cardiac surgery</td>
<td>ACC/AHA</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Detection of ischemia and viability assessment Diagnosis of CAD</td>
<td>ESC/ACC/AHA ACC/AHA</td>
<td>Ila Iib</td>
<td>B C</td>
</tr>
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4. NUCLEAR CARDIOLOGY UTILIZATION THROUGHOUT THE WORLD

4.1. Introduction

Utilization of nuclear cardiology procedures varies widely considering the different countries and regions of the world. Economic situation, technology availability, human resources development, health systems priorities, education and awareness of the benefits of the technique are probably some of the reasons behind this disparity.

4.2. Analysis of available data

Unfortunately, to date there are no worldwide reliable statistics on the utilization of nuclear cardiology besides some regional data from developed areas mainly registered 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 respond 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 7 times higher than in developing countries (fig. 10), although among these, there is also large heterogeneity. The reasons for this are probably multiple, with 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.

Figure 10. Nuclear cardiology procedures per 100,000 of population per year for developing vs. developed countries (estimated average, 2007). Source: ASNC, EANM, ALASBIMN. IAEA Technical Meeting, Vienna, Austria, May 2008.

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 US and Canada as compared to Japan and the European Union (fig. 11). Although experiencing a raise 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.

Figure 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, Austria, May 2008.

In some countries of Latin America, the utilization is similar to that of developed areas while in others the technique is almost inexistent. 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 to poorer countries, with some exceptions like New Zealand where provision of 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, incidence of cardiac disease is high and steadily increasing in most nations. Egypt is the country where nuclear cardiology is more developed, however still with a utilization rate below the average in Latin America.

The coloured map in figure 12 depicts the global utilization of nuclear cardiology as per a recent estimate, with some blanks reflecting insufficient data or complete absence of nuclear cardiology practice.

![Utilization Strata](image_url)

Figure 12. Estimates of worldwide utilization (per 100,000 of the population) of nuclear cardiology procedures in 2006-2007. Uncolored areas represent countries with nonexistent nuclear cardiology facilities, or unavailability of information. Source: IAEA Technical Meeting, Vienna, Austria, May 2008.

### 4.3. Utilization of nuclear cardiology vs. mortality rate

Interestingly, there is an inverse relationship between the utilization of nuclear cardiology and mortality rates in some developed countries from where data is available (fig. 13). In fact, nuclear cardiology procedures have been increasing in number in Japan, Australia, Canada and the US, while mortality rates (mainly due to cardiovascular diseases) 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 utilization of nuclear cardiology or other imaging modalities are responsible for this observed decrease in mortality.

![Figure 13](image.png)

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

Nevertheless, from the epidemiologic 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 cardiovascular disease mortality.

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 MPS 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 Taskforce, 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: $\Delta \text{cost} / \Delta \text{outcome}$. 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 MPS 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 MPS can be considered as a moderately priced diagnostic modality involving lower costs than those for positron emission tomography (PET), magnetic resonance imaging (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 MPS costs can nevertheless be relatively reduced in centers performing high volumes of studies or by sharing fixed costs across noncardiac 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 MPS, 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 MPS 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 pharmacologic stress SPECT MPS. This means that in nearly 9 out of 10 patients with significant coronary stenosis by coronary arteriography, perfusion abnormality is noted on SPECT MPS. However, nearly 1 in 4 patients has a false-positive SPECT MPS 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 artifacts 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 MPS is more cost-effective than a more conventional strategy using direct coronary angiography or even CT angiography. A SPECT MPS-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 extended popular opinion, MPS is a cost-saving procedure in the overall management of chronic CAD patients.
Figure 14. Cost savings derived from the application of a strategy using selective catheterization according to the result of SPECT MPS. Cost savings are significant both for diagnostic as well as for follow-up phases of patient management. From: Shaw LJ, J Am Coll Cardiol 1999 (reprinted with permission).

By reviewing the SPECT MPS literature some general economic principles can be considered and applied. The technique presents high diagnostic sensitivity so that costly false-negative results (eg, myocardial infarction or death in a patient with normal perfusion) are rare. From the prognostic evidence, a normal myocardial perfusion SPECT MPS is associated with annual rates of cardiac death or myocardial infarction of 0.7% (exercise) to 1.2% (pharmacologic stress), being the negative predictive value 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 MPS results are associated with high-cost care, because events 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 MPS 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 2-3 years after SPECT MPS which would be associated with minimal use of coronary angiography for patients with normal results. For patients with moderate or severely abnormal SPECT MPS 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 MPS 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 more efficient in guiding the allocation of resources.

5.4. Patients with chest pain and suspected acute coronary syndromes

There is also strong evidence on cost-effectiveness of SPECT MPS in patients with acute chest pain. It is estimated that approximately 3 million patients presenting at the emergency department with acute chest pain and whose symptoms are due to non-cardiac conditions, are unnecessarily hospitalized at a high annual cost. Additionally, 4% to 7% of patients really undergoing an acute coronary syndrome will be inappropriately sent home from the emergency room, with potential severe consequences thereafter. Because of its ability to identify low-risk individuals among those patients presenting with acute chest pain and non-diagnostic ECG, resting SPECT MPS can be used for excluding acute infarction and ischemia in this setting.

When SPECT imaging is introduced into a chest-pain workup, rates of hospitalization decline significantly. A report concluded that the use of SPECT MPS 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 SPECT MPS when compared with a control population. These results support the high negative predictive value for SPECT MPS in ruling out acute myocardial infarction 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 acute coronary syndrome 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 perfusion imaging is also evident in hospitalized patients. A prospective, randomized study assessed differences in hospital costs between conventional strategies and those guided by SPECT MPS, showing that the hospital costs per patient were much lower in the perfusion imaging-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 acute coronary syndrome (ACS) is presented in figure 15 below.

![Figure 15. Algorithm for the management of patients with suspected ACS (reprinted with permission).](image)

**5.5. Special populations**

Recent studies suggest that SPECT MPS 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 MPS (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 ischemic burden and the extent of CAD. Thus, from this evidence, the intensity of resource consumption might be predicted based on the results of SPECT MPS to a greater extent than diabetes itself.

It has been proposed that SPECT MPS could be cost-effective for screening CAD in asymptomatic patients with diabetes, given the high prevalence of atherosclerosis in this population. The DIAD study was designed to determine the prevalence and severity of inducible myocardial ischemia in asymptomatic patients with type 2 diabetes using adenosine-stress SPECT MPS along with clinical and laboratory predictors of abnormal test results. The initial findings of this study demonstrated that
silent myocardial ischemia 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 MPS screening for myocardial ischemia over almost 5 years. Preliminary results from an ongoing international coordinated research study from the IAEA with a similar approach tend to demonstrate a higher incidence of abnormal perfusion findings as compared to 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.

![Figure 16. Risk of cardiac death or myocardial infarction according to the result of SPECT MPS in different subgroups of patients. Green = low risk MPS; red = high risk MPS; p<0.05 between low and high risk (adapted from Shaw & Iskandrian, J Nuc Cardiol 2004).](image)

Worldwide, cardiovascular disease 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 by 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 United States, 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 to 74 years of age are 53% and 25%, 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 MPS (fig. 17).
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 ischemic 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. The 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, still 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 ischemic changes in many cases. However, the resting ECG has many well-known limitations. For example, approximately half of patients experiencing an acute coronary syndrome (unstable angina or acute myocardial infarction) will have a non-diagnostic resting ECG, thus precluding its clinical utility in those cases.

6.3. The exercise stress test (treadmill stress test, TMT)

Guidelines for exercise testing have been published by the American College of Cardiology (ACC) and the American Heart Association (AHA). A multitude of parameters derived from this test have been studied and validated over the last four decades. Some useful parameters from the 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 MI, 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 channels 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 MPS can further subdivide the initial risk groups into post-test low or high risk patients (fig. 18).

Figure 18. Cardiac event rate according to the result of SPECT MPS in groups of patients with low, medium and high Duke Treadmill Score (DTS). SPECT MPS provides further stratification in all groups: blue = low risk MPS; green = medium risk MPS; red = high risk MPS (modified from Hachamovitch et al Circulation 1996).

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, 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 ischemia 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 risks inherent to the use of this drug limit its safety profile. Moreover, patients with previous MI 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 to other modalities.

The diagnostic accuracy of the stress echo has been shown to be inferior to nuclear methods for detection of ischemic burden. It has been well established that the sensitivity of the technique is lower compared to SPECT MPS, independent of the type of stress used (fig. 19), because echo relies on the detection of wall motion abnormalities during ischemic episodes, which is further down the ischemic cascade compared to perfusion abnormalities. This is even more apparent in the diagnosis of single vessel CAD. However, the specificity of stress echo is slightly higher than nuclear methods, as the occurrence of stress-induced wall motion abnormalities is almost always related to an ischemic 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 echo studies just past peak stress may become very difficult to obtain. Moreover, the incidence of suboptimal or uninterpretable echo scans is known to be greater than with nuclear techniques, and at times stress echo cannot be performed at all because of poor echogenic windows. Nuclear cardiology, on the other hand, is not limited by these issues.

Stress echo suffers from the inability to objectively assess the amount of ischemia 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 ischemia 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 ischemia. 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 ischemia, and is contraindicated 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 echo in this clinical setting is limited by a lower diagnostic accuracy compared to nuclear cardiology techniques, especially concerning sensitivity.

Figure 19. Diagnostic performance of myocardial perfusion studies (MPS) and echocardiography (ECHO) using different types of stress. MPS are more sensitive while ECHO is slightly more specific for the detection of myocardial ischemia (head-to-head comparison, n = 1421 patients from 23
This Publication is currently under review so it should be considered as a draft version of the final publication which is not available yet on the IAEA publications site.

Myocardial contrast echocardiography has been promoted to improve the accuracy of stress echo 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 skills of the operator, who is expected to obtain reproducible images through an iterative process that involves different patient positioning and placement of the transducer. Thus, although the published diagnostic accuracy approaches that of nuclear techniques in selected academic centres, stress echo has really not come to the forefront of diagnostic ischemia imaging. In the clinical setting, stress echo is more often performed to rule out significant myocardial ischemia.

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 ischemia detection in ‘real time’ are advantages over nuclear techniques.

6.5. Magnetic Resonance Imaging (MRI)

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 three-dimensional definition of normal and pathologic anatomic 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 and 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 pharmacologic 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 echo and nuclear imaging techniques has made it more sensitive for such application, being able to detect both transmural and partial-thickness infarcts, something that nuclear techniques cannot match at present. For the measure of ventricular function, gated MRI is currently considered the gold standard due to 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 ischemic heart disease, challenges for this technique include inability to effectively monitor the patient during pharmacologic 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 (MSCT)

Cardiac CT has blossomed all over the world, partly as a result of marketing by the industry and partly because of excellent advancement of this technology over the past few years. Although the CT modality has been introduced decades ago, it had been mainly used for imaging still organs in the body. A key advancement in CT was the development of helical (or spiral) acquisition of multiple tomographic slices (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 afford 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 artifacts due to heart-rate, patient motion, breathing, contrast effects, heavy calcification, and radiation dose. Several devices and techniques have been developed to overcome motion artifacts, 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.
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 vs 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 4 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 to invasive quantitative coronary angiography (QCA) has to the moment demonstrated the inaccuracy of this approach on an individual patient basis, as shown in figure 21.

![Figure 21. Correlation of coronary stenosis severity between 64-slice CT angiography and conventional quantitative coronary angiography (QCA). From: Leber AW et al J Am Coll Cardiol 2005 (reprinted with permission).](image)

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 & 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-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 single-centre prognostic data available regarding MSCT, nuclear techniques have a long track record in evaluation of ischemia, 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 information is provided. Several reports have shown, and is now well established, that physiological data provided by SPECT MPS is 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 allows to safely monitor effectiveness of medical therapy and progression of disease, permitting timely revascularization when necessary. Lacking a true physiological evaluation, MSCT is at present unable to provide this assessment.
Both MSCT and electron beam computed tomography (EBCT) permit quantitation of coronary artery calcification using coronary calcium scoring (fig. 22). The calcium score correlates with the extent of coronary atherosclerosis, although only approximately 20% of atherosclerotic plaques are calcified. Therefore, coronary calcium scoring 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 coronary calcium scoring 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 and therapy response of CAD patients. On the other hand, it has been demonstrated that assessment of perfusion is more important than calcium scoring for prognosis, and cardiac event rate is low when SPECT MPS shows normal or nearly-normal results even in patients with high calcium score.

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. 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 to 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.
Figure 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 anatomic detail but are invasive in nature, requiring arterial catheterization. From: Vitola JV, Delbeke D: Nuclear Cardiology and Correlative Imaging, Springer Verlag 2004, New York (reprinted with permission).

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 radionuclide ventriculography (RVG). 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 above in section 2.

Perfusion imaging using SPECT MPS is a nuclear medicine technique extensively used to evaluate myocardial blood flow (MBF). It provides the possibility of assessing coronary flow reserve, detecting ischemia, and providing risk stratification, including the degree, location and extent to which CAD is affecting regional MBF. The prognostic and diagnostic value of MPS has been well established in the literature over the last three decades. MPS continue to grow with 3.1 million patients in the United States 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-labeled radiopharmaceutical administrations (especially MIBI) doubled during the same period. At the time of this writing, approximately 30% of MPS are 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.

The stress tests most commonly used for evaluation of coronary blood flow reserve include exercise, dipyridamole, adenosine, and physical exercise combined with pharmacologic stress. All of these are intended to provoke coronary vasodilation so as the moment of tracer injection, flow heterogeneity 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 (figure 24), new radiopharmaceuticals, and new vasodilators for pharmacologic tests (see below).
Figure 24. Quantitative analysis of a SPECT MPS 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 ischemia after therapy is related to future cardiac events (figure courtesy L. Shaw, USA). On the right, quantitative stress/rest perfusion values from a different patient study. Quantitation is a powerful strength of SPECT MPS especially for follow-up, assessment of therapy, and clinical research (figure courtesy F. Mut, Uruguay).

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 radionuclide ventriculography (RVG) with labelled red blood cells. In addition, ventricular size, right and left ventricular ejection fractions (RVEF, LVEF) and regurgitation indexes can be calculated. The RVG 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 the 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 pretest probability of disease, as well as patient-specific factors such as body habitus and the presence of resting ECG abnormalities.

7. TECHNOLOGICAL ADVANCES IN NUCLEAR CARDIOLOGY

7.1. Introduction

Several innovations are in 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 even including dosimetry issues. These advances will help repositioning the specialty 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 pharmacologic 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 US 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. 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 presently 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 pharmacologic 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 pharmacologic agent, resulting in reduced incidence of side effects, and the quality of images is also generally improved as compared to pharmacologic-only stress which is associated with high sub-diaphragmatic activity. The availability of different pharmacologic agents such as vasodilators and inotropics, together with the validation of these new combined protocols have widened the spectrum of patients to be stressed, now
allowing for a 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$_2$O (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 ischemia 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 (MIBG, BMIPP) hold the promise of detecting myocardial ischemia many hours after the patient has recovered from an episode of ischemic chest pain. This is the so-called “ischemic 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 perfusion tracer for cardiac innervation labelled with $^{18}$F is under investigation that is more easily distributable and available to institutions without onsite cyclotrons which are needed to produce $^{123}$I.

Acetate labelled with $^{11}$C offers the possibility of studying both myocardial perfusion and metabolism with the same PET tracer. Although PET remains 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.

Figure 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, Italy).

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 radio-labelled monoclonal antibodies 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.

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

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 show great promise, although data in the literature is still 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, the 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 MPS. 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 through-put 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 to 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). Semi-conductor detectors with much higher sensitivity as compared to 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 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 are rather intended to be used for cardiology studies only, so being the cost still quite significant, purchasing of such equipment would for the moment be only justified for a laboratory with very high cardiac workload or for a large university department.

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

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 artifacts 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 artifacts 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, 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 ischemia. 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 a high sensitivity (91%) and specificity (89%) for the diagnosis of obstructive CAD. Quantitative PET provides a noninvasive assessment of myocardial blood flow and coronary flow reserve 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 nonobstructive to obstructive CAD. However, not all coronary stenoses are hemodynamically significant and ~50% of the patients with obstructive CAD on CT angiography demonstrate stress induced perfusion defects. Stress PET data complement the anatomic information on the CT angiogram by providing instant readings about the ischemic 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 noninvasive detection of vulnerable coronary plaques a clinical reality. In summary, integrated PET/CT is a powerful new noninvasive modality that offers the potential for refined diagnosis and management of the entire spectrum of coronary atherosclerosis.
Figure 28. Multimodality imaging. Stress (adenosine) and rest PET MPS with rubidium-82 (left), and 3D display of CT angiography (right). Studies were performed sequentially on a PET/CT scanner, for a total time of 35 minutes. Full functional and anatomic information can be obtained with such imaging protocol, including stress/rest ventricular function and calcium score (not shown). Courtesy UCL Hospitals, London, UK.

8. THE 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 programs largely depends on the extent to which individuals take personal responsibility for their own health by avoiding health risks and by taking positive actions.

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 focus on people already known to be affected by disease with the attempt to reduce resultant disability and restore functionality.

Primary prevention programs 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 behaviors. In cardiology, primary prevention measures includes actions to protect against the development of cardiac disease, especially CAD, such as quitting smoking, exercise regularly and eating 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 MI, 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 identifying disease by studying special subgroups of the general population (ie, patients with non-diagnostic ECG), or by helping to decide upon equivocal findings of other screening procedures such as exercise tests.

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 (ie, 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 re-stratify 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 U.S. Institute of Medicine, the NIDA and the European Monitoring Centre for Drugs and Drug Addiction. This classification can be applied to cardiovascular disease as in table 2.

Table 2. Proposed classification of preventive interventions.

<table>
<thead>
<tr>
<th>Tier</th>
<th>Definition</th>
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<tr>
<td>Universal prevention</td>
<td>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.</td>
</tr>
<tr>
<td>Selective prevention</td>
<td>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.</td>
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<tr>
<td>Indicated prevention</td>
<td>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.</td>
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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 MPS 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-ischemic 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, still 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 anatomic 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).

Figure 29. The imaging paradigm in CAD. Anatomic 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 echo) 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 noninvasive methods by which 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 coronary heart disease. The medical community and professional organizations like the American
Heart Association (AHA) may eventually expand the interest of risk detection beyond the Framingham risk score (FRS) estimation of 10-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 10 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 ischemia by SPECT MPS provides an estimation of elevated short-term risk and may guide decisions on the need of immediate revascularization. Given the known power of SPECT MPS 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 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.

Figure 30. Vertical long axis (left) and horizontal long axis (rights) stress and rest SPECT MPS showing a reversible apical defect consistent with moderate induced ischemia. The patient was a 37-year old man with no symptoms and normal stress ECG but heavy family history of early CAD.
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. Available evidence supports the idea that selected subsets of asymptomatic patients may have CHD event rates, including death or MI, 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 National Cholesterol Education Program as having an annual rate of CV death or nonfatal MI of 2% or higher). A list of CAD risk-equivalent patient subsets is detailed in Table 1. Although not all of these individuals meet the criteria for initiating aggressive preventive therapies, a sizeable portion of them 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 high-risk CAC score of 400 or higher have a high rate of inducible ischemia and should be referred for stress MPS 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 MPS 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 MPS ischemia as compared with nearly half of the higher-risk diabetic patients in the same score group. The value of SPECT MPS in this setting has been studied, showing the safety of relying on a normal MPS 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 4-year cardiac event rates in patients with a normal SPECT MPS study and CAC scores of greater than 1000, 400 to 999, or less than 400. This represents a good example on 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 is 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 (eg, 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 long-standing diabetes (i.e. >5 years) or with poorly controlled glycemia 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 left ventricular 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 found in table 3.

<table>
<thead>
<tr>
<th>Table 3. Conditions associated with special high risk for CAD or cardiac events.</th>
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<tbody>
<tr>
<td>Diabetes &gt;5 years</td>
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<tr>
<td>Diabetes with poorly controlled glycemia</td>
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<td>Peripheral artery disease</td>
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<td>Cerebrovascular disease</td>
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<td>Atrial fibrillation</td>
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<td>Left ventricular hypertrophy</td>
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<td>Autoimmune diseases</td>
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<tr>
<td>Non-cardiac major surgery</td>
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<tr>
<td>Polycystic ovarian syndrome</td>
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<tr>
<td>Early menopause (&lt;40 years)</td>
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<td>Chronic renal disease</td>
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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 getting a license for 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 multi-disciplinary 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 United States, a cardiologist can practice nuclear cardiology after a three-month training period in nuclear medicine. In Europe, a cardiologist can only receive certification after full four-year training in nuclear medicine to practice nuclear cardiology. In many developing countries, however, the practice is not regulated or requires only minimal training in 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 neither having 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 sub-specialty. 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 multi-disciplinary, involving other medical professionals such as radiopharmacists, technologists, physicists, and nurses, which must act in harmonization 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 program. Basic knowledge would be achieved through a two-month training period, obtained consecutively or spread through the program 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 (ACC) has divided the training of fellows in nuclear cardiology into three levels:

- General (Level 1): Makes trainee conversant with the field of nuclear cardiology for application in general clinical management of cardiovascular patients (recommended training time: 2 months).
- Specialized (Level 2): Provides trainee with special expertise to practice clinical nuclear cardiology (recommended training time: 4 to 6 months).
- Advanced (Level 3): Provides advanced training sufficient to pursue an academic career or direct a nuclear cardiology laboratory (recommended training time: 1 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, 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 programs in cardiology, nuclear medicine, or radiology. Where these programs 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 in a non-academic basis when such a program is not available as part of the clinical training program.

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 programs 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 programs 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 multi-disciplinary 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 program 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 radio-pharmacy 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 to programs 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 noninvasive 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, also is the need for training guidelines for fellows, residents and nuclear cardiologists or 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 anatomic findings. The specific aspects of the training required for 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 30 depicts an example of the situation in a representative developing country, clearly showing lack of information about nuclear cardiology among cardiology practitioners.
Figure 30. 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 a sufficient knowledge about the technique (courtesy A. Peix, Cuba).

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 outreach strategies that should be developed according to the local cultural, socio-economic, and professional environment. Usually, the integration of nuclear cardiology into pre-and post-degree academic curricula, 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.

11. RADIATION SAFETY

11.1. Introduction

Radiation safety is always an issue in the realms of nuclear medicine. The IAEA recognizes this problem in its entirety and the fact that the nuclear cardiology community has strived to reduce the amount of radiation the patient undergoing such procedures receive, 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 exam 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 ionising 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. Concerns about diagnostic radiation exposure

It should be recognized, however, that public concern about the safety of imaging procedures using ionizing radiation have been raised by reports reaching the general public without a strong supporting body of evidence. This has 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 with no demonstrated collateral damage. 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 public media. Several studies are reporting significant increased risk to the patient receiving low ionizing radiation from CT and nuclear studies, raising questions on the appropriateness of these techniques regarding radiation safety. With new technological developments and the increased availability of hybrid scanners, the combination of SPECT MPS and MSCT for CAD evaluation is very appealing since it would overcome the shortcomings of each technique allowing comprehensive functional and anatomic assessment. However, the practicability of this approach has been hampered by the fact that 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 figure 31.

Risk data is sometimes presented in ‘cancer units’ which has generated concern among patients, referring physicians, and diagnostic imaging professionals. The expression of radiation dose in units of cancer risk is misleading for a number of reasons. First, radiation dosimetry values for radiopharmaceuticals are in general subject to considerable uncertainty, as they are based on limited biokinetic data (taken from a small number of patients or from animal data) and are derived for ‘reference’ (median) individuals (adult males, females, etc.). Doses to individual patients have significant variability due to the stochastic nature of radiation dosimetry. Secondly, while average dosimetry or cancer risk values can be expressed for a population, the absolute, incremental cancer risk value for any given individual from a given radiation exposure (e.g. due to a specific diagnostic procedure) may not be derived from these population models. Furthermore, the confidence limits for the dose and risk estimates are not defined, and thus individual risk values should not be reported as a deterministic value with known confidence limits.

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 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.

Figure 31. Radiation exposure (as effective dose in mSv) from different imaging procedures and protocols used in cardiac imaging. From Einstein AJ et al. Circulation 2007 (reprinted with permission).

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 to a return to the use of thallium which was being progressively abandoned. It is expected that this situation 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 decreased radiation exposure from nuclear studies by about 1/10 to 1/5 compared to previous estimates (fig. 32).

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.

Figure 32. Estimated decrease in effective radiation dose by the use of a new high-sensitivity gammacamera (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 2-day protocol; CA = conventional coronary angiography; MSCT = multi-slice CT using conventional protocol; D SPECT = new camera design. Data from the literature compiled by F. Mut, Uruguay.
12. CONCLUSIONS

CAD is on the rise all over the world, and thus nuclear cardiology 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 and sudden death. Radionuclide methods can accurately identify patients who do not have significant CAD, thus requiring only continued preventive measures. Conversely, patients identified to have milder forms of disease can be safely treated with intensive medical therapy without interventions, while patients with more severe ischemia can be referred directly to percutaneous intervention or bypass surgery. Following revascularization or after instauration of optimized medical therapy, nuclear techniques continue to provide vital 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 two major disciplines such as nuclear medicine and cardiology. Cross-education of professionals already trained in their respective fields should be necessary, including physicians, technologists, and other allied professionals. Curricula details have been proposed by several institutions and organizations, and each country should set its own training programs according to local regulations, needs, and available resources.

BIBLIOGRAPHY


BELLER, G.A., BONOW, R.O., FUSTER, V.; American College of Cardiology Foundation; American Heart Association; American College of Physicians Task Force on Clinical Competence


Global Cardiovascular Infobase.  www.cvdinfobase.ca.


Heart Disease and Stroke Statistics—2008 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee
http://circ.ahajournals.org/cgi/reprint/circulationaha.107.187998


Prevention of Disease - Primary Prevention, Secondary Prevention, Tertiary Prevention, Prevention Research And Goals http://www.libraryindex.com/pages/50/Prevention-Disease.html#ixzz0owwZEjoT


