Practicing Nuclear Cardiology in Emerging Economies

How to overcome challenges to the practice of nuclear cardiology in emerging economies

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Non Communicable Diseases
In developing countries

• Cardiovascular disease (CVD), cancer, chronic respiratory disease and diabetes
  - Contribute most to the global NCD burden
  - are mainly responsible for the rapidly rising NCD morbidity and mortality trends in low- and middle-income countries

• Furthermore, cost-effective interventions that can be implemented in low-resource settings are available to prevent and control these four major NCDs

WHO 2012
Comparison of leading causes of death over the past decade, 2000 and 2011

- Ischaemic heart disease
- Stroke
- Lower respiratory infections
- COPD
- Diarrhoeal diseases
- HIV/AIDS
- Trachea bronchus lunc...
- Prematurity
- Diabetes mellitus
- Road injury
- Tuberculosis

WHO 2012
The 10 leading causes of death in the world by percentage:

- Prematurity: 48.2%
- Trachea bronchus, lung cancers: 11.2%
- Stroke: 10.6%
- Road injury: 6.7%
- HIV/AIDS: 5.8%
- COPD: 4.7%
- Diarrhoeal diseases: 3%
- Ischaemic heart disease: 2.7%
- Diabetes mellitus: 2.6%
- Lower respiratory infections: 2.2%
- Other causes: 1.9%
WHO Member States are classified according to the World Bank income categories for the year 2011 (World Bank list of economies, July 2012).
WHO Member States are classified according to the World Bank income categories for the year 2011 (World Bank list of economies, July 2012).

![Top 10 causes of death in high income countries]

- Ischaemic heart disease: 119 deaths per 100,000 population
- Stroke: 69 deaths per 100,000 population
- Trachea bronchus, lun...: 51 deaths per 100,000 population
- Alzheimer disease and ...: 48 deaths per 100,000 population
- COPD: 32 deaths per 100,000 population
- Lower respiratory infections: 32 deaths per 100,000 population
- Colon rectum cancers: 27 deaths per 100,000 population
- Diabetes mellitus: 21 deaths per 100,000 population
- Hypertensive heart disease: 20 deaths per 100,000 population
- Breast cancer: 16 deaths per 100,000 population
Framingham risk score

- The Framingham risk score is a multivariable risk function that predicts 10-year risk of developing cardiovascular disease events (coronary heart disease, stroke, peripheral artery disease or heart failure).
- The sex-specific scores incorporate age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetic status.
- A score below 10% is considered low, 10%-20% intermediate, and >20% high 10-year risk of cardiovascular events.

Methods for Risks classification

• **Diamond Forrester score**
  
  The probability of having significant CAD could be calculated using the Diamond Forrester model.
  
  This model takes into account age, sex, and type of chest pain, which was classified as typical, atypical or non-anginal.
  
  The commonly used classification cut-offs of 30% and 70% were used.
  
  Consequently, a score below 30% was considered low, 30%-70% intermediate and >70% high risk of having significant CAD.

Methods for Risks Classification

**PROCAM risk score**

- PROCAM participants were followed up for acute coronary events (myocardial infarction, sudden cardiac death) for 10 years.
- The calibrated risk score included: age, LDL cholesterol, smoking, HDL cholesterol, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus, and triglycerides.
- A score below 10% is considered low, 10%-20% intermediate, and >20% high 10-year risk of coronary events.

**SCORE risk score**

- The SCORE predicts 10-year risk on fatal cardiovascular disease resulted in a model which included gender, age, systolic blood pressure, total cholesterol, and smoking. A score of 0%-4% was considered low, 5%-9% intermediate, and ≥10% high risk of cardiovascular death in 10 years.
APPROPRIATENESS CLASSIFICATION of Patients by category

- Appropriate: 71%
- Uncertain: 15%
- Inappropriate: 14%

Large Number of CV Events in Individuals not at High Risk

Proportion in each risk category
NHANES 1999-2002

76%
13%
11%

Estimated Number of CV Events

High Risk
Int Risk
Low Risk

10-year CHD Events (Millions)

Ajani UA et al, JACC 2006;48:1177
Treatment modalities for CAD

• Modifications of risk factors (prevention, stabilisation, regression)
• Medical treatment - drugs (e.g. cholesterol lowering medications, beta-blockers, nitroglycerin, calcium antagonists, etc.);
• Percutaneous coronary intervention (PCI), (balloon and stent)
• Coronary artery bypass grafting (CABG, Cabbage)
Outputs of Revascularisation (8)

- 79.6% with a significant chi-squared statistic ($\chi^2=147$, $p<0.0001$)
- 23.0% with a marginally significant chi-squared statistic ($\chi^2=1.43$, $p=0.23$)
Desiderio Favarato and All: Relative Cost Comparison of Treatments for Coronary Artery Disease: The First Year Follow-Up of MASS II Study *Circulation*. 2003; 108: II-21-II-23
Challenge

• Budget for Health: Big difference between Developed and developing countries PCI and CABG
• Waiting list, prioritization of patients
• Need for Optimization of the use of financial resources in developing countries
• Screening, modifications of risk factors and optimization of the use of medical treatment
Coronary angiography (ICA)

- The gold standard for the visualization of the coronary arteries and detection of coronary artery stenosis is invasive coronary angiography (ICA).

- However, ICA cannot be used as a gold standard for detecting myocardial ischemia which is an expression of a flow limiting stenosis.

- The criterion for a significant stenosis is usually set at ≥50% obstruction in at least one major coronary artery. Often, the decision to revascularize a territory of the myocardium is based on the presence of an optical impression of luminal stenosis.

- However, the cost, risk, and invasive nature of coronary angiography render a reliable non-invasive method, with the ability to provide a better assessment of which vessel with obstruction needs intervention, very desirable.
Normal Coronary Angiogram
Non invasives
Modalities

Calcium score

<table>
<thead>
<tr>
<th>MPI</th>
<th>Large reversible perfusion defect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multiple perfusion defects</td>
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<tr>
<td></td>
<td>SDS ≥ 15</td>
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<tr>
<td></td>
<td>Poststress TID</td>
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<td></td>
<td>Poststress RV uptake</td>
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<td></td>
<td>Poststress lung uptake</td>
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<tr>
<td></td>
<td>Abnormal poststress LVEF</td>
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</table>

| Stress ECHO | Poststress global LV impairment    |
|            | Diastolic dysfunction              |
|            | Poststress LV cavity dilatation    |
|            | Mitral regurgitation               |

| Cardiac CT  | Left main stenosis ≥ 50%           |
|            | 3 vessel disease                   |
|            | 2 vessel disease including proximal LAD |

| Cardiac MR  | SDS ≥ 7                           |
|            | Presence of late gadolinium enhance and reversible perfusion defects |

| Exercise Treadmill Testing (ETT) | Duke score ≤ -11 |
|                                 | (ST-segment depression, exercise time and symptoms) |
|                                 | Time to onset of ST-segment depression |
|                                 | ST-segment elevation |
|                                 | Time to resolution of ST-segment depression |
|                                 | Exercise induced ventricular arrhythmias |

CAD = coronary artery disease, MPI = myocardial perfusion imaging, SDS = sum difference score (sum stress score - sum rest score), TID = transient ischemic dilatation, RV = right ventricle, LVEF = left ventricular ejection fraction, ECHO = echocardiography, LAD = left anterior descending artery
Criteria required for a good screening test

• Provides an accurate determination of the likelihood that an asymptomatic person has the condition (accuracy)
• Reproducible results (reliability)
• Detect individuals where early treatment intervention is likely to have a beneficial impact
• Should provide incremental value to risk predicted by office-based risk assessment

Redberg and Vogel et al., 34th Bethesda Conf. JACC 2003; 41: 1855-1917
Incremental Prognostic Value

Pretest Likelihood

Incremental Value

No Incremental Value

Exercise Time
ST-seg Δ
Symptoms
BP
Age

+ TEST
Test for detecting CAD in patients

Patterson et al. JACC 1989
SPECT/MPI

• Well established technique for diagnosis, prognosis and contributing for finding appropriate therapeutic strategy
Ischemic Cascade

Systolic wall motion imaging

Perfusion imaging

angina
ECG changes
systolic dysfunction
diastolic dysfunction
hypoperfusion

Time from onset of ischemia
The ischemic Cascade

- Chest pain
- Global dysfunction
- Wall motion abnormality
- Perfusion heterogeneity

STRESS TIME

O2 DEMAND
Myocardial ischemia

Physiopathology

Blood Flow

% Stenosis

Ischemic windows
Coronary blood flow (ml/g per min) vs. Percentage of coronary stenosis.

Gould et al. Am J Cardiol 1974;33:87
Ischemia

Perfusion ml.g\(^{-1}\).min\(^{-1}\)

Degree of stenosis

Courbes de Gould

Perfusion flow
Coronary reserve flow

- Dipyridamole

- Apex

- Base

Perfusion ml.g⁻¹.min⁻¹

Decrease of the coronary reserve flow

Stenosis

4

1

0%  50%  100%
Stress techniques

• To produce coronary vasodilation, several stress modalities can be applied in nuclear cardiology, including:
  
  • Exercise,
  • Vasodilators: Dipyridamole, Adenosine, Regadenosan (Asthma, COPD)
  • exercise combined with vasodilators,
  • Dobutamine (Asthma, COPD)
Monitoring
ECG
AP
O2
Emergency
drugs
ECG 12 channels
Emergency
call
Monitoring
ECG
Exercise stress

- Graded exercise stress is usually performed with a treadmill or bicycle ergometer with continuous patient monitoring.
- All stress procedures must be supervised by a qualified health care professional and performed in accordance with the guidelines.
- Reach 85% of maximum predicted heart rate for injecting of radiopharmaceuticals.
- Stress ECG findings constitute very good complement for SPECT/MPI.
Exercise ECG for Diagnosis of CAD

- Meta-analysis of 147 consecutive studies involving 24,074 patients
Exercise Stress ECG for Diagnosis of CAD
When shifting to the pharmacological Stress

- Inability to exercise: severe pulmonary disease, arthritis, amputation, or neurologic disease
- Left bundle branch block (LBBB) or pacemaker
- Failure to achieve 85% maximum predicted heart rate (MPHR, see below) in the absence of typical angina or ischemic ST segment depression.
Ce tableau constitue un des clichés du coffret de diapositives qui accompagnent le film « STRUCTURE de la MATIERE », 16 mm en couleurs (le film et les diapositives sont prêtés gratuitement par l'Office National des Universités, 96, bd Raspail, PARIS 7e - Tél. 222.46.44). Ce tableau existe en panneau mural (77 × 120 cm); il est distribué par la Librairie de Documentation Scientifique, 29, rue du Mont Thabor, PARIS 1er - Tél. 749.30.36.
Radiopharmaceuticals:
Extraction Fraction

Myocardial Blood Flow

Tracers

- Thallium 201(+): Reference tracer for MP, similar biologic behaviour than potassium, rapid clearance, high extraction efficiency (4% of the total injected activity) by myocardial cells
- Thallium 201(-): Low photon energy (attenuation), a long life (limited injected activity and dosimetry), restricted availability (cyclotron product) and expense
- Thallium 201 has a rapid redistribution, images should be acquired immediately after IV injection
- Myocardial distribution of Thallium reflects coronary blood flow and normal cellular metabolism immediately after its injection, either during stress or rest
Tracers

- **$^{99m}$Tc-MIBI(+):** $^{99m}$Tc Methoxy Isobutyl Isonitrile is a lipophilic agent, rapid clearance, diffuses into the myocytes, associated with mitochondria, better retention in myocyte, physical properties of technetium 99m
- **$^{99m}$Tc-MIBI(+):** Insignificant redistribution, Link between injection and immediate imaging is broken, first pass study and gated ventricular function
- **$^{99m}$Tc-MIBI(-):** Two separate injections, important delay between them, important hepatobiliary uptake
- Myocardium distribution of $^{99m}$Tc-MIBI reflects blood flow and normal cellular metabolism after its injection, either during stress or rest
"The strengths of MPI with Tc labelled perfusion tracers"

1. Intrinsically 3D
2. Real evaluation (measure?) of perfusion
3. Easy quantitation
4. Simultaneous evaluation of perfusion and LV function
5. Standardized and reproducible
6. High sensitivity for CAD (Ischemia)
7. Diagnostic accuracy and prognostic value demonstrated by a large body of literature
8. Widely available
9. Easy managed
10. Limited costs
11. Low radiation exposure
Traceurs Tc - preparation of patient

Tetrofosmine
- Easy to prepare
- Better clearance
- Early images possible

Sestamibi
- Heating and boiling
- Better myocardial uptake
- Parathyroid and oncology
SPECT MPI

SPECT Myocardial perfusion imaging Study can measure:

- Perfusion and function of the left ventricle
- Pulmonary Uptake of the Radiotracer
- Ischemic Dilation of the left ventricle
- Scoring abnormalities: SSS, SRS, SDS

Each of these measurements are unique, reproducible and have prognostic impact
Functional Imaging:
ECG-Gated Myocardial SPECT

- Acquired during perfusion imaging
- 3-dimensional volumetric measure
  - LVEF
  - LVEDV/LVESV
  - Wall motion and thickening
- Completely objective
- Proven to be accurate and precise
Echantillonnage
8 images / R-R
Echantillonnage
16 images / R-R
Sum of images
Systolic thicknessing

Gated SPECT

Gating process - Functional assessment
ventricular wall motion
ES and ED ventricular volumes
LV ejection fraction
  normal = 64% +/- 12%
Myocardial Perfusion Scintigraphy: Assessment of Diagnosis, Prognosis, and Treatment Response of Cardiovascular Risk.

Diagnosis, Prognosis, and Response to Therapy

- Suspected Coronary artery disease
- Known stable coronary artery disease
- Prior to non-cardiac surgery
- Before and after cardiac revascularization
Myocardial Perfusion Scintigraphy: Assessment of Diagnosis, Prognosis, and Treatment
Response of Cardiovascular Risk

Diagnosis, Prognosis, and Response to Therapy Special populations (women, diabetics)

- Evaluation of acute chest pain syndromes
- Myocardial infarction
- Screening: Multiple risk factors, Family history
- Response to medical therapy
Populations Who Benefit from SPECT MPI

- Diagnostic and prognostic chest pain evaluation
- Angina
- Atypical Angina
- Atypical Chest Pain
- Non-cardiac Chest Pain
- Peri-operative risk of non-cardiac surgery
- Diagnostic and prognostic evaluation of ACS
- Emergency Department
- In Hospital
Populations Who Benefit from SPECT MPI

- Hemodynamic/prognostic assessment of known CAD
- High risk asymptomatic populations
- Diabetes, Metabolic syndrome, insulin resistance syndrome
- Family history of sibling with coronary event
- Mediastinal radiation
- Multiple coronary risk factor
- Monitoring effectiveness of surgical and percutaneous revascularization
- Monitoring effectiveness of “medical revascularization”
Diagnosis and assessment of CAD

SPECT MPI Study for the clinician

• Indications: when ECG-testing not conclusive, patients with intermediate risk, CTA findings

• Expected answers:
  - does the patient need to go to the cathlab?
  - Does the coronary stenosis is inducing ischemia at stress?
  - Severity of this ischemia? Prognosis?

• SPECT MPI sensitive (87%-92%), high negative predictive value for major adverse cardiac events (MACE)
SSS (Summed Stress Score) Long term (6 years) Prognosis of SPECT MPI of Patients in Relation to Perfusion Defects after Physical Exercise
Normal Myocardial Perfusion
Transient ischemic dilation of the LV
TID
Gated Images

- Gated images are made possible by ECG-gated SPECT

- Physicians can now access cardiac function:
  - Wall motion – does the LV contract uniformly?
  - Ejection Fraction – does the LV pump out enough blood to the body?
NEW HARDWARE FOR OPTIMIZED MPS IMAGING

• Faster imaging times due to:
  - increased sensitivity and by
  - eliminating the need to position the patient’s arms above the head by imaging in an upright or reclining position,
  - patient comfort is dramatically improved.
  - As a consequence of faster imaging times and more comfortable patient positioning

• Additional benefit of reducing patient motion during a scan.

• Low activity of radiopharmaceuticals and reduction of irradiation to the patients
CZT cristal

- This system uses pixilated CZT detector arrays mounted in 9 vertical columns and placed in a 90° gantry geometry.
- While CZT detectors are higher in cost, they have advantages of superior energy resolution (by a factor of approximately 1.7 at 140 keV).
- Compact size as compared to the combination of NaI(Tl) with photomultiplier tubes of the conventional Anger camera.
- With D-SPECT, each detector column is fixed in a mechanical mounting, and the data acquisition is performed by rotating these multiple columns in synchrony.
- The photons from a given location are detected at multiple angles by multiple columns as the fields of view of the detectors are swept through the region of interest.
## PET Perfusion Agents

### Diffusible tracers

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Form</th>
<th>Half-life</th>
<th>MeV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubidium-82 ($^{82}$Rb)</td>
<td>Chloride</td>
<td>75 sec</td>
<td>3.15</td>
</tr>
<tr>
<td>Nitrogen-13 ($^{13}$N)</td>
<td>Ammonia</td>
<td>10 min</td>
<td>1.19</td>
</tr>
<tr>
<td>O-15 ($^{15}$O)</td>
<td>Water</td>
<td>110 sec</td>
<td>1.72</td>
</tr>
<tr>
<td>Copper-62 ($^{62}$Cu)</td>
<td>PTSM</td>
<td>9.8 min</td>
<td>2.94</td>
</tr>
<tr>
<td>Potassium-38 ($^{38}$K)</td>
<td>Chloride</td>
<td>7.6 min</td>
<td>2.70</td>
</tr>
<tr>
<td>Carbon-11 ($^{11}$C)</td>
<td>Butanol</td>
<td>20 min</td>
<td>0.96</td>
</tr>
</tbody>
</table>

PTSM, pyruvaldehyde methylthiosemicarbazone
Rb-82 Infusion System
2D vs 3D Gated Rb-82 PET

Knesaurek. BMC Nucl Med 2007;7:4

16 normal volunteers had resting Rb-82 on a BGO PET camera

Low dose (20 mCi) 3D acquisition compared to high dose (60 mCi) 2D acquisition
Abnormal Rb-82 perfusion study
Abnormal N-13 perfusion study

72 year old man with peripheral vascular disease.

Coronary arteriography:
• LAD: 60% ostial and 80% mid vessel stenoses
• LCX: 90% proximal stenosis and occluded OM
• RCA: 90% ostial stenosis
SPECT/PET

• SPECT
  - Numbers of SPECT cameras >> PET Cameras
  - Well validated in predicting diagnosis
  - Less expensive to acquire and to maintain
  - Isotope are less expensive

• PET
  - 2-4 times more expensive to acquire and to maintain
  - Likely more accurate to predict the degree of CAD
  - Attenuation correction inherent
  - Great potential to measure coronary flow and viability
Challenges

• Integrating and understanding all other modalities: Training in Cardiac Imaging?

• Patients: Reduction of the irradiation and non appropriate/non decisive investigations
10,377 asymptomatic individuals, risk factors undergoing EBCT, follow-up 5 years

All Cause Death (%) vs Calcium Score

- <10: 1.0%
- 11-100: 2.6%
- 101-400: 3.8%
- 401-1000: 6.2%
- >1000: 12.3%

Shaw et al. Radiology 2003
CTA

• Very good tool which needs to have well defined indications

• BUT misuse could lead
  - to increase the cost of management of CAD
  - to increase irradiation burden to the patients
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>RV contrast uptake</th>
<th>LV contrast uptake</th>
<th>Myocardial contrast uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stress-Perfusion</strong></td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td><strong>Rest-Perfusion</strong></td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td><strong>Viability and coronary angiography</strong></td>
<td>![Image]</td>
<td>![Image]</td>
<td></td>
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</tbody>
</table>
Evaluation of CAD (Coronary artery disease) with cardiac MRI

<table>
<thead>
<tr>
<th>CMR imaging technique</th>
<th>Morphological correlates</th>
<th>Clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine imaging</td>
<td>contractile function</td>
<td>LV function</td>
</tr>
<tr>
<td>Rest/stress (LDD)</td>
<td></td>
<td>ischemia / viability</td>
</tr>
<tr>
<td>T2/weighted</td>
<td>myocardial oedema</td>
<td>tissue at risk</td>
</tr>
<tr>
<td>First pass perfusion rest/stress</td>
<td>regional myocardial blood flow</td>
<td>inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>myocardial ischemia</td>
</tr>
<tr>
<td>Early Gadolinum enhancement</td>
<td>microvascular integrity</td>
<td>No reflow</td>
</tr>
<tr>
<td>Late Gadolinium Enhancement</td>
<td>Myocardial necrosis / fibrosis</td>
<td>MVO</td>
</tr>
<tr>
<td></td>
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<td>Infarct size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viability</td>
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Nuclear cardiology in Developing countries

- Two-thirds of scintigraphies were used to perform bone, thyroid, and renal scans.

- Cardiovascular applications account for the highest percentage of all nuclear medicine procedures performed in the United States.

- NC Ranked in fourth place in 2010 with 12%–13% of the overall nuclear medicine practice in the developing world.
Practice of Nuclear cardiology

• Availability of the SPECT/MPI: Irregular, inadequate facilities, shortage of radio isotopes, Long waiting list

• Awareness of Clinicians

• Low number of patients, no local impact on the management of CAD
Challenges

• Education and training of human resources
  A- Physicians
  B- Technologists
• Better collaboration with cardiologists
• Availability of radiopharmaceuticals: Weekly basis
• QC of radiopharmaceuticals and SPECT gamma camera
• Stress room: Cardiologist, Monitoring
Challenges

• Increasing allocated time of SPECT Cameras to nuclear cardiology: Great clinical value
• Increase number of patients to induce local impact in management of CAD
• Decrease the number of non diagnostic scans
• Complete report
• Contribution to the reduction of the irradiation in Cardiac imaging