

Early Non-Invasive Detection of CAD

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INTRODUCTION

CAD is the leading cause of death worldwide. Its first and the only symptom may be a fatal myocardial infarction. Plaque build-up starts at an early age, long before the fatal event. Early detection offers the greatest chance of slowing or even abating the disease process, before it progresses. In fact, early diagnosis is critical in saving many lives.

NON-INVASIVE METHODS

Clinical examination and biochemical tests

The early detection of CAD begins with a meticulous clinical examination and identification of the conventional risk factors like high stress lifestyle, smoking, obesity, physical inactivity, hypercholesterolemia and other dyslipidemias, hypertension, diabetes. New biochemical markers, such as C-reactive protein, lipoprotein(a) [L_p(a)], and homocysteine, have been shown to increase the likelihood of further cardiovascular events,¹⁻³ especially in patients with hypercholesterolemia, but no consensus has been reached regarding routine measurement of these markers, and measuring them is not generally recommended.⁴

ECG

A 12-lead ECG is the gold standard initial non-invasive screening test for a patient of chest pain. As per ACC / AHA guidelines, the most important aim in emergency room is early evaluation of a suspected case of CAD by ECG especially in acute presentation and to plan the treatment schedule including thrombolysis after deciding the type of acute coronary syndrome (ACS). ACC/ AHA guidelines also recommended ECGs for people of any age in occupations with high cardiovascular demands or whose cardiovascular status might affect the well being of many other people (e.g. pilots, bus or truck drivers, railroad engineers).⁵ In the presence of acute chest pain the cardiac markers like CPK, CPK-MB, Troponin T or I and myoglobin etc. may help in diagnosing CAD especially when ECG is normal. Of these troponin levels are more sensitive and specific and can detect even small infarct leading to necrosis.

Exercise ECG Testing

According to ACC / AHA guidelines it is considered appropriate for the diagnosis of obstructive CAD in adult patients (including those with complete RBBB or <1mm of resting ST depression) with an intermediate pretest probability of CAD based on

gender, age and symptoms.⁶ Various exercise protocols include Bruce's, modified Bruce's protocol, Naughton, Weber, ACIP (asymptomatic cardiac ischaemia pilot trial), mACIP and Ramp protocols. Duke treadmill score calculates the risk and annual mortality as follows:-

$$\text{Score} = \text{exercise time} - (5 \times \text{ST deviation}) - (4 \times \text{treadmill angina index})$$

Angina index

0 = no angina

1 = non-limiting angina

2 = exercise limiting angina

Total score	Risk group	Annual mortality
≥ 5	Low	0.25%
-10 to +4	Intermediate	1.25%
≤ -11	High	5.25%

Exercise parameters associated with an adverse prognosis and multivessel CAD are;

- Duration of symptom limiting exercise < 6 METs
- Failure to increase systolic BP ≥ 120mm Hg or a sustained decrease ≥ 10mm Hg, or below rest levels, during progressive exercise.
- ST segment depression ≥ 2mm, downsloping ST segment starting at < 6 METs, involving ≥ 5 leads, persisting ≥ 5 minutes into recovery.
- Exercise-induced ST segment elevation.
- Angina pectoris at low exercise workloads.
- Reproducible sustained (>30 second) or symptomatic VT.

Exercise ECG testing is associated with false positive test in the following conditions-cardioactive drugs (digitalis, quinidine), abnormal serum potassium levels, resting abnormalities of ST and T wave, intraventricular conduction disturbances. It is associated with false negative test in circumflex coronary artery obstruction since the posterior portion of the heart which this vessel supplies is not well represented on the surface 12-lead ECG. Its sensitivity is 68% and specificity is 77%.⁸

Advantages of ECG stress testing are low cost, high sensitivity in three vessel or left main CAD, provides useful prognostic information (e.g. ischaemia at low workload). Limitations include suboptimal sensitivity, low detection rate of single vessel disease, poor specificity in premenopausal women, need to achieve ≥ 85%

of maximal heart rate for maximizing accuracy. It is not of much value in preexisting LBBB, LVH, WPW syndrome, non-specific abnormalities of ST and T wave, MVP syndrome and artificial pacemaker rhythm.

ECHOCARDIOGRAPHY

Echocardiography helps in CAD detection by showing regional wall motion abnormality (RWMA), wall thickening abnormalities, evidence of dyskinetic area, decrease in ejection fraction and increase in end-systolic volume with stress.

Stress Echocardiography

The form of cardiovascular stress include exercise with treadmill^{9,10} and bicycle ergometry.^{11,12} For patients incapable of physical exercise pharmacological stress can be used in the form of vasodilators like Dipyridamole (0.142mg / kg / min over 4 minute), Adenosine (maximum 140 microgram / kg / min) or inotropes like Dobutamine (5 microgram / kg / min to a max. of 40 microgram / kg / min or till 85% of THR is achieved). Dobutamine can be safely used in patients with asthma in whom dipyridamole and adenosine are contraindicated. Atropine increases the accuracy of dobutamine stress echocardiography in patients with inadequate heart rate responses, especially those taking beta-blockers and those in whom second degree heart block develops at higher atrial rates.

Advantages of stress echocardiography are that it directly visualizes the ischaemia-induced systolic wall motion abnormality which occurs well before ECG changes or angina develops and can assess ventricular function, viability and complications at the same time. It is highly sensitive and specific than exercise ECG. Its specificity is higher than that of myocardial perfusion imaging (88% vs 78%). The technique is portable, no highly sophisticated instrumentation is required and the cost is relatively low.

Its limitations are decreased sensitivity for detection of single-vessel disease or mild stenosis with post-exercise imaging, infarct zone ischaemia less well detected, highly operator-dependent for image analysis, poor acoustic window in some patients (e.g. COPD).

High risk finding on stress echocardiography are multiple reversible wall motion abnormalities, severity and extent of these abnormalities, severe reversible cavity dilatation, left ventricular systolic dysfunction at rest. Its sensitivity is 78% and specificity is 88%.

Contrast Echocardiography

Ultrasound reflects all of the structures with different acoustic properties. Thus, a tissue fluid interface is a more potent reflector of ultrasound than the interior of a solid structure. Even more potent reflector of ultrasound is a gas / fluid interface, such as can be created by microcavitations or bubbles. Various contrast agents used are agitated saline, microbubbles based on albumin,¹³ perfluorocarbon agents.¹⁴ Contrast echocardiography is rapidly evolving field in non-invasive testing for the diagnosis and assessment of CAD.¹⁵

Advantages of contrast echocardiography are microcirculatory integrity as well as systolic thickening evaluation, better estimation of extent and viability than functional assessment alone, precise delineation of the area of necrosis, good spatial resolution permitting endocardial versus epicardial perfusion.

Its limitations include difficult windows in 30% of patients, attenuation problems and scant clinical data available.

Ergonovine Stress Echocardiography to Detect Coronary Vasospasm¹⁶

Ergonovine provocation testing by monitoring left ventricular RWMA on 2D-ECHO is a highly feasible and accurate test. It is used for the early diagnosis of coronary vasospastic angina even before the development of chest pain or ECG changes. It is highly sensitive even with the single vessel spasm. This stress test is not affected by hyperventilation, tachycardia and excessive chest wall movement.

STRESS SPECT MYOCARDIAL PERFUSION IMAGING

Stress in this testing can be provided with exercise or in those not able to exercise it can be done with vasodilator agents like dipyridamole, adenosine or inotropes like dobutamine. Radionuclides like thallium-201 [²⁰¹Tl] or technetium 99m [^{99m}Tc] based perfusion tracer are used.¹⁷ Radionuclide is injected intravenously at peak exercise and the patient is encouraged to exercise for another 30-40 sec. Acquisition of stress images is performed several minutes later, when the patient is at rest. A separate image is obtained at rest to compare stress images with rest images.

Image interpretation

Normal image is homogeneous uptake of the radiopharmaceutical throughout the myocardium. Defect is a localized myocardial area with relatively less radiotracer uptake than normal. Reversible defect is a defect present on the initial stress images and no longer present or present to a lesser degree on resting or delayed images. This pattern indicates myocardial ischemia. Improvement over time on ²⁰¹Tl imaging is referred to as "redistribution". Fixed defect is a defect that is unchanged and present on both exercise and rest (delayed) images. This pattern generally indicates infarction or scar tissue.

Advantages of stress SPECT perfusion imaging in CAD diagnosis as opposed to exercise ECG (in patients with LBBB, an electronically paced ventricular rhythm, >1mm ST segment depression at rest, patient with unequivocal treadmill exercise electrocardiogram) include assessment of systolic thickening, global LV ejection fraction accurately measured, simultaneous evaluation of perfusion and function with gated SPECT, viability and ischaemia simultaneously assessed, higher sensitivity and specificity than exercise ECG, high specificity with ^{99m}Tc-labelled agents, quantitative image analysis.

Limitations of stress SPECT imaging are reduced spatial resolution and sensitivity in comparison to PET, less quantitative than PET, area of attenuation (e.g. inferior wall on ^{99m}Tc-sestamibi scans) misinterpreted as non-viability, cannot differentiate endocardial from epicardial viability which is best assessed with contrast

ECHO, no absolute measurement of blood flow (measures relative blood flow) and lower specificity than dobutamine echocardiography.

Criteria for high risk findings on myocardial perfusion imaging

Multiple perfusion defects (total plus reversible defects) in more than one vascular supply region (e.g. defects in coronary supply regions of the left anterior descending and left circumflex vessels), large and severe perfusion defects (high semiquantitative defect score), increased lung thallium -201 uptake reflecting exercise-induced left ventricular dysfunction, post-exercise left ventricular cavity dilatation and left ventricular dysfunction on gated SPECT. Its sensitivity is 89% and specificity is 76%.

RADIONUCLIDE ANGIOGRAPHY

First pass radionuclide angiography and equilibrium gated blood pool radionuclide angiography are nuclear cardiology techniques that use a gamma camera and ECG gating for determining the changes in radioactivity in the left and right ventricular chambers over the cardiac cycle by generating time-activity curves. Quantitative ejection fraction measurement from both the right and left ventricles are highly accurate. Ventricular and pulmonary blood volumes and regional ventricular wall motion can also be assessed.

Ambulatory monitoring- Further application of the technique of equilibrium angiocardiology relates to the use of miniaturized equipment suitable for monitoring patients during routine activities. An instrument called VEST allows the monitoring overall several hours following blood pool labeling. It again uses the basic principles of ERNA (equilibrium radionuclide angiogram). The device is worn by the patients, so they are fully ambulatory. Radionuclide and ECG data are stored on tape in a manner comparable to the use of Holter monitor for arrhythmia detection. Off-line analysis provides trended data concerning ventricular function. This instrument has been validated and standardized in several laboratories and is ready for broader clinical application. A second generation device with significant technical improvement has been recently available. Initial studies suggest a potential major role for this device in the assessment of silent myocardial ischemia and mental stress.¹⁸

POSITRON EMISSION TOMOGRAPHY (PET)

Positron emitting radionuclides are characterized by excess positive charge. The positron travels a few mm in tissue when it encounters an electron, annihilation occurs which leads to simultaneous emission of two very high energy photons in opposite directions. These can then be imaged by a series of detectors placed in a ring around the patient. The very high energy photons result in far less scatter and attenuation than the conventional nuclear cardiology techniques.

Radiopharmaceuticals involved require a cyclotron for production and generally have short half-lives. PET is considered by many to be the standard of reference for the non-invasive detection of myocardial viability by nuclear cardiology techniques because PET imaging can simultaneously assess myocardial perfusion and metabolism.¹⁹ Nitrogen-13-labelled ammonia is the most often

used perfusion tracer (measures absolute regional blood flow), and fluorine-18-labelled fluorodeoxyglucose (FDG) is the metabolic tracer for glucose utilization. Increased fluorodeoxyglucose uptake in regions of decreased perfusion (termed glucose/blood flow mismatch) indicated the presence of ischaemic myocardium that has preferentially shifted its metabolic substrate towards glucose rather than fatty acid and lactate. Preserved myocardial oxygen consumption estimated by carbon¹¹ (¹¹C) –acetate PET imaging is found in myocardial regions that are hibernating. ¹¹C-acetate PET imaging is an alternative to FDG-PET imaging for detection of viability.

Limitations - PET has lower specificity than dobutamine echocardiography or MRI, it cannot separate endocardial from epicardial viability as assessed by contrast ECHO. Also, it is costly and has limited availability.

Sensitivity - 72%, Specificity- 89%

ELECTRON BEAM (CINE, ULTRAFAST) CT-SCAN [EBCT]

EBCT has emerged as a highly sensitive method for detecting coronary calcification. Calcium score is a good marker of the total coronary atherosclerotic burden.²⁰ The absence of calcium on CT imaging is predictive of the absence of significant atherosclerotic disease in older persons²⁰ but it is possible for younger people (man < 45 years, women < 55 years) to have obstructive CAD and hence a risk for further cardiac events in the absence of detectable calcification or with a low calcium score.²¹

Although coronary calcification is a highly sensitive finding in patients who have CAD but specificity of this finding for identifying patients with obstructive CAD is very low.²²

ACC/AHA²² concluded that whereas the technique is highly predictive for the presence of atherosclerosis, the degree of atherosclerosis cannot be predicted and the prognostic importance has not been established. It was not recommended for routine screening of patients.²²

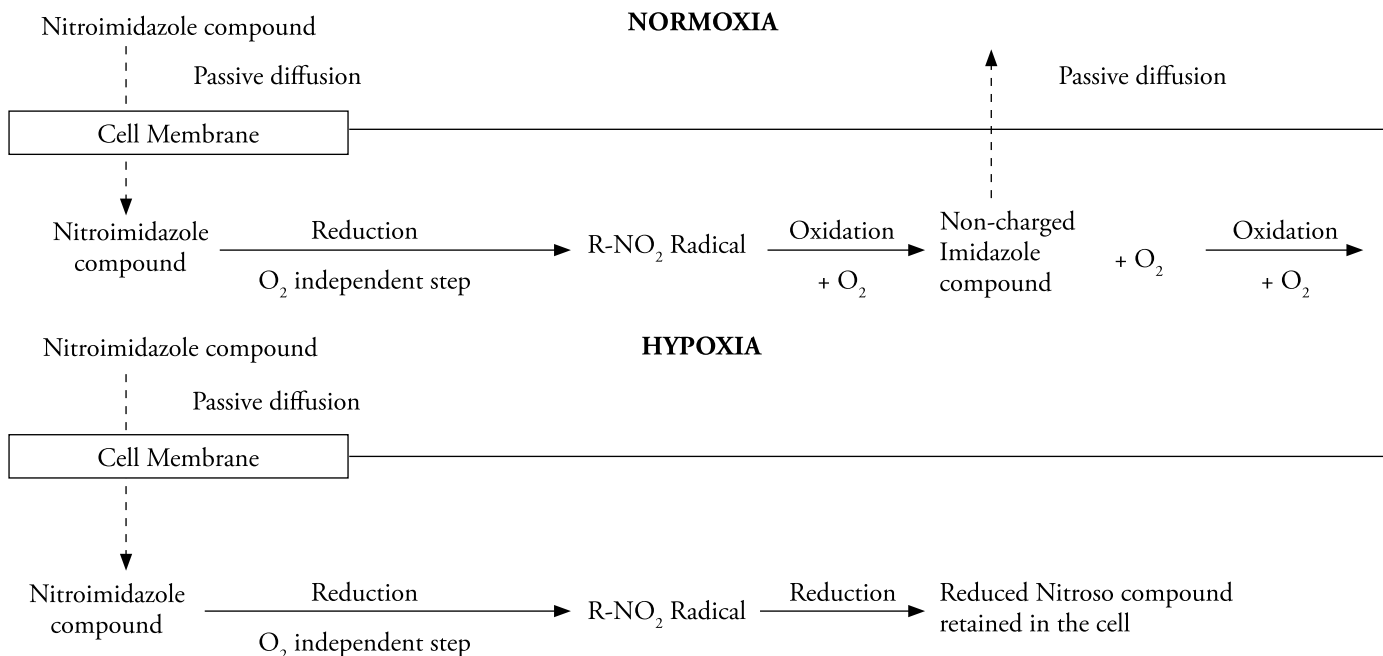
MAGNETIC RESONANCE IMAGING

MRI provides three dimensional information with high resolution anatomical detail in any desired imaging plane. It can accurately assess regional and global LV function. Myocardial tagging permits analysis of subendocardial, midwall and subepicardial function. High speed MRI permits perfusion imaging.

Limitations are lack of portability, need to correct for cardiac and respiratory motion, claustrophobia in some patients and patients with pacemakers are to be excluded.

Dobutamine MRI

It separately evaluates inotropic reserve in endocardium with tagging. The measurement of wall thickness is more accurately done than with transesophageal echocardiography. It provides better image quality than echocardiography for assessment of contractile reserve and simultaneously assesses perfusion using contrast enhancement. It has a good sensitivity and specificity for viability detection with good imaging windows in all patients.



Limitations are higher cost than echocardiography and less sensitive than nuclear techniques but may be more specific. Sensitivity - 89%, Specificity - 94%.

The role of MRI in evaluation of CAD is still in the early stages.

Magnetic resonance coronary angiography

Provides visualization of the origin and proximal course of the major coronary arteries and can demonstrate stenosis of coronary arteries and coronary blood flow. It is still under developmental stage.

SPECIAL NON-INVASIVE TECHNIQUE

Fatty acid imaging²³⁻²⁵

68% of ATP is produced within the myocardium under aerobic conditions is derived from fatty acid (FA) oxidation. Fatty acid imaging is based on the imaging of the myocardium on radiolabeled FA uptake to assess myocardial metabolism and viability. Radiolabeled fatty acids used for imaging are ¹²³I labeled straight chain FA and ¹²³I labeled branched chain FA.

¹²³I labeled straight chain FA undergo rapid beta-oxidation and are then released from the myocardium with rapid turnover rate. Rapid washout presents difficulties with respect to high quality SPECT imaging because of low count statistics. ¹²³I labeled branched chain FA e.g. BMIPP, because of chemical manipulation of their structure are metabolically trapped within the myocardium and thus provide excellent image quality. BMIPP is currently the most widely used FA imaging agent which provides information concerning metabolism that is independent of perfusion. In vasospastic angina delayed imaging with BMIPP may provide a memory image of a previously occurring ischaemic event that has protracted metabolic consequences. Significant work has been done particularly in Japan, with the use of BMIPP in the setting of CAD.

Myocardial Imaging with Hypoxia Markers²⁶

It is a new approach to the assessment of myocardial ischaemia and viability. Two ^{99m}Tc-labelled nitroimidazole^{27,28} compounds e.g. BMS-181321, ^{99m}Tc-HL91 are being used. The nitroimidazoles are believed to diffuse passively across the cell membrane. Once in the cytoplasm of the myocardial cell, nitro reduction occurs with the formation of an R-NO₂ radical ion, which is an oxygen-independent step. In the presence of normoxia, the radical interacts with oxygen to yield superoxide and non-charged nitroimidazole. The free radical anion formation is then reversed in the presence of oxygen. The non-charged compound diffuses back out of the cell. Under hypoxic conditions, the radical anion is reduced further and yields a nitroso compound. The reduced metabolites of the nitroimidazole have lower permeability and are retained within the hypoxic cell. Areas of hypoxia are visualized as zones of increased radionuclide uptake. Agents also appear to have a threshold level of hypoxemia below which retention will be demonstrated.²⁹ This new class of compounds present potential excitement for studying ischaemia and regional hypoxia.

A PERSPECTIVE OF THE FUTURE OF CARDIAC IMAGING

The future appears bright for further progress in technology and clinical application of non-invasive imaging techniques. With respect to nuclear cardiology, the development of transmission-emission SPECT instrumentation will provide attenuation and scatter correction leading to fewer imaging artifacts and enhanced specificity for CAD detection. New radiopharmaceuticals on the horizon will allow molecular imaging of gene expression by using reporter gene/ reporter probe systems to image the expression of endogenous and exogenous genes. Imaging of the various stages of the atherosclerotic process in the vascular wall is also potentially feasible in imaging sites of apoptosis. With respect to contrast ECHO, progress in microbubble contrast agents and imaging technology to enhance the microbubble signal

to noise ratio will enable assessment of myocardial perfusion and viability with intravenous injection of contrast. Imaging of coronary plaque by MRI and spectroscopic techniques may allow differentiation between stable and unstable plaque, which could be a great contribution to the evaluation of patients with asymptomatic CAD. Finally, phosphorus-31 nuclear magnetic resonance spectroscopy, which can directly measure high energy phosphates in the myocardium, may prove useful for non-invasively identifying metabolic evidence of stress-induced ischemia.³⁰

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