Evaluation of Coronary Artery Disease

RD Lele

In this issue of JAPI there are two articles on the evaluation of suspected or known coronary artery disease: comparison of stress ECG and stress myocardial perfusion imaging (MPI), and adenosine stress MPI. This is a good opportunity to review the subject of evaluation of Coronary Artery Disease (CAD). The views expressed are based on my personal experience of 25 years in nuclear cardiology and an extensive review of world literature over the last 30 years, including proceedings of the 6th International Conference on Nuclear Cardiology in Florence (April 27 - 30, 2003), which represents a cumulative experience of 10,000 patients in 17 different countries worldwide. Coronary artery disease has assumed epidemic proportion in India, affecting all socioeconomic groups; it is more extensive and severe in Indians and occurs 10 years earlier than in the rest of the world population. Hence the cost-effectiveness and cost-benefit ratio of tests employed for the early detection of CAD, risk stratification for management planning, and follow-up of medical therapy as well as aggressive revascularization therapy, assume great importance, not only for the patients and clinicians but also for hospital administrators, insurance companies and third party health care providers and health care policy planners.

**History and Physical Examination**

An important objective of history and physical examination (PE) is to acquire information that can be used to estimate the probability of the presence of CAD. Assessment of symptoms - quality of pain and duration, location and radiation, precipitating and relieving factors and associated symptoms taken together with the risk factor profile of the individual patient - age, sex, family history, smoking, hypertension, hyperlipidemia, diabetes mellitus stress level etc. and certain changes in the rest ECG strengthen the predictability about the presence or absence of CAD.

The number of patients subjected to tests done for CAD are inversely proportional to the time taken by the clinicians for this primary evaluation - a crucial point to remember in this era of cost-conscious practice of medicine.

History taking remains the richest source of information in this evaluation. A typical history of precordial pain aggravated by exertion and relieved by rest has a high degree of sensitivity, specificity and positive predictive value for the diagnosis of ischaemia, the commonest cause of which is atherosclerotic coronary artery disease (CAD). Ischemia due to demand-supply discrepancy can also occur in conditions with left ventricular hypertrophy: hypertension, severe aortic valve disease, hypertrophic cardiomyopathy etc. quite independent of CAD.

It is important to recognize that angina means “tightening”, not pain - pressing, squeezing, strangling, constricting, bursting, burning, weight in the centre of the chest, are many adjectives which indicate ischaemia. The anginal threshold is lower in the morning than at other times in the day; activities that cause angina in the morning do not do so later in the day. When the threshold for angina is quite variable, defies any pattern or is prominent at rest, the possibility of coronary spasm should be considered.

A chest pain that lasts for only a few seconds, or that lasts for all 24 hours, is not ischemic. If the pain or discomfort can be reproduced by direct pressure, it usually indicates chest wall as the origin, not the heart. True ischaemic pain does not permit localization to a small area less than 3 cm. in diameter.

Chest pain accompanied by palpitation may be due to acute myocardial ischemia precipitated by a tachyarrhythmia.

Prolonged severe chest pain or discomfort with profuse sweating, extreme fatigue or nausea and vomiting should be a matter of great concern, signifying acute myocardial infarction (or less commonly acute pulmonary embolism or aortic dissection).

Anginal “equivalent” such as dyspnoea, faintness, fatigue and eructations, are common, particularly in the elderly. A history of abnormal exertional dyspnoea may be an early indicator of CAD even in the absence of angina or ECG evidence of ischaemia.

Chest discomfort that is atypical for angina pectoris is more common in women than in men. How much of it is due to microvascular and vasospastic coronary artery disease and how much due to non-ischaemic causes is not easy to determine by history alone. Women with epicardial coronary artery lesions more often report chest discomfort at rest, during sleep or during mental stress than in men. It is very easy to dismiss it as non-cardiac and deny them further confirmatory testing. This happens all the time in all parts of the world.

Hon. Chief Physician and Director of Nuclear Medicine, Jaslok Hospital and Research Centre, Mumbai. Hon. Director of Nuclear Medicine and RIA, Lilavati Hospital and Research Centre, Mumbai. Emeritus Professor of Medicine for life and Ex-Dean, Grant Medical College and Sir JJ Hospitals, Mumbai. Dean (Academic) All India Institute of Diabetes, Mumbai.
In taking history it is useful to determine whether the patient has symptoms or complications caused by atherosclerosis of other vascular beds eg. intermittent claudication, transient ischaemic attacks or stroke; and palpate all peripheral pulses during PE.

Pain due to esophageal spasm has many of the features of, and may be difficult to differentiate from angina pectoris. The difficulty is compounded by the frequent coexistence of these two common conditions, by the observation that esophageal reflux lowers the threshold for angina, and by the observation that esophageal spasm can be precipitated by ergonovine and relieved by nitroglycerine.

History has its limitations when symptoms are absent.

**Silent Ischemia And Silent Myocardial Infarct**

Clinicians have to face the enigma of silent ischemia - an uncoupling of ischaemia and angina. 24 hrs. Holter ECG monitoring led for the first time to the detection of silent ischaemia.1 Deanfield JE et al2 analyzed ST segment changes during ambulatory ECG monitoring in normal subjects and in patients with angina pectoris.

The mechanism and prognostic importance of silent ischaemia have been the subject of considerable interest for over 30 years. Cohn1 has categorized three types of silent myocardial ischaemia:

**Type I**: least common; occurs in totally asymptomatic patients with obstructive CAD which may be severe. They do not experience angina at any time even during acute myocardial infarction.

**Type II**: Occurs in patients with documented previous acute myocardial infarction - due to ischaemic sympathetic denervation.

**Type III**: Occurs in patients who also experience the usual chronic stable angina, unstable angina and Prinzmetal angina. Some ischaemic episodes are associated with angina, while others are not.

The extensive use of ambulatory ECG monitoring led to the greater appreciation of the high frequency of type III silent ischaemia.3 Eighty five percent of ambulant ischaemic episodes are silent and 66% of anginal episodes were unaccompanied by ST segment depression,4 indicative of the enigmatic uncoupling of angina and ischaemic ECG changes.

In silent ischaemia, 60 - 70% were preceded by increase in heart rate (HR) and blood pressure (BP). The circadian variations in HR and BP also paralleled the increase in silent ischaemic events.5 The prognosis of myocardial ischaemia is not affected by the presence or absence of concomitant angina.6

Between 20 - 60% of non-fatal acute myocardial infarcts are not recognized by the patient; of these about half are truly silent, with the patient unable to recall any symptoms whatsoever. Silent infarcts occur more commonly in patients without antecedent angina pectoris and in patients with diabetes and hypertension. Ten years’ experience with gated MPI has impressed me about the frequent occurrence (20%) of silent infarcts.

Other modalities of investigation have also detected silent ischaemia such as radionuclide ventriculography (RNV), ambulatory RNV with vest and echocardiography. Transient LV dilation and LV systolic dysfunction have been documented in silent ischaemia. Review of literature indicates silent myocardial ischaemia to be more prevalent during mental stress than during physical exercise.

**Ischaemia Induced By Mental Stress**

John Hunter, the famous British surgeon who had angina pectoris, was aware of the effect of mental stress when he said: “My life is in the hands of any rascal who chooses to provoke me.” Effects of anger on LVEF in CAD were documented by Ironson G et al.8 Sudden cardiac death has been triggered by an earthquake.9

More often, mental stress-induced ischaemia is silent. Deanfield et al10 was the first to document silent myocardial ischaemia during mental stress. Several other reports documented induction of silent ischaemia during mental stress.11,12,13 Mental stress-induced ischaemia has been reproduced in the laboratory and has been compared with ambulatory ischaemia during daily life along with haemodynamic features.14 Laboratory protocols involving mental stress (arithmetic problems, speech assignments) have been used along with exercise RNV and vest.

Several studies have been done for detection and reproducibility of mental stress-induced myocardial ischaemia with Tc-MIBI SPECT in normal and CAD populations.15 Comparison of physical and mental stress in the same patients showed that of the 19 patients who showed exercise-induced perfusion defects, 16 (84%) showed the same changes during mental stress. None of the 21 normal control subjects showed any defects during physical and mental stress. It is important to note that mental stress can induce silent ischaemia more frequently than physical stress in the same patient.17 There is concordance and discordance between ECG changes during physical and mental stress in the same patients with CAD. In one study ECG abnormalities were seen in 15/24 patients with CAD during physical exercise but none during mental arithmetic. Chest pain was experienced by five patient during exercise but by none during mental stress. Jain et al18 discussed the prognostic implications of mental-stress-induced silent ischaemia and LV dysfunction in stable angina patients. Thirty patients with stable angina pectoris and reversible defects on MPI underwent continuous ambulatory LV function monitoring with VEST. Mental stress was induced by mental arithmetic. 15/30 developed transient LV dysfunction. At 2 years follow-up 10/15 (67%) with mental stress-induced LV dysfunction developed cardiac events compared with 4/15 (27%) with no mental stress-induced LV dysfunction. Mental stress may be a Trigger for adverse cardiac events. RNV studies during
mental stress have shown decreased LVEF and stress MPI have shown reversible perfusion defects in 20 patients with stable CAD.17

**REST AND STRESS ECG**

ECG is the most commonly available and most commonly performed test in clinical practice, and continues to be the procedure of first choice for the evaluation of chest pain, dizziness, syncope and unexplained sweating with fatigue. A normal resting ECG does not exclude ischaemia or even acute infarct - some times ECG changes evolve slowly over 24 hours. Pathological Q wave may be absent even in known previous infarction and depressed LV function. Conduction disturbances eg. LBBB or WPW may mask the diagnosis of infarct. On the other hand Q waves, ST segment elevation or depression, tall T waves and deep, inverted T waves can occur in a variety of non-coronary settings. A variety of factors such as digitalis, estrogens, hypokalaemia, hyperventilation and ventricular hypertrophy can mimic subendocardial ischaemia. Interpretation of ECG is improved by obtaining clinical information about the patient, unfortunately most ECGs are read without this information. Further, availability of previous ECGs can improve the clinical value of the current ECG and its proper interpretation for example bundle branch block in the setting of acute infarction. Errors in ECG interpretation are common and can lead to clinical mismanagement including failure to detect and triage acute myocardial ischaemia and other life-threatening situations. Physicians who practice in small towns and peripheral remote areas can now avail of the facility of telemedicine and get expert on-line advice from centres like the Escort Heart Hospital in New Delhi.

Various kinds of stress are used in testing for the presence of CAD. These tests work best when the apriori probability is between 40 -50 %. These tests are listed in Table 1.

**Limitations of exercise ECG**

For the detection of CAD both the sensitivity and specificity of exercise ECG testing is suboptimal compared to coronary arteriography. A meta-analysis of 147 published papers in the literature reveal a mean sensitivity of 68% and specificity of 77%.18

In the presence of baseline ECG abnormalities exercise - induced ST segment depression may be non-specific for ischaemia. The sensitivity for the detection of single vessel disease with stress ECG alone is 50 -55%. Hence wherever facilities are available Exercise ECG should be combined with gated MPI SPECT. For example in patients with a > 85% likelihood of CAD on exercise ECG alone, a normal MPI has shown absence of cardiac events during follow-up.19 The sensitivity for detection of triple vessel disease with stress ECG with stress MPI is 95 - 100%. This is the group of patients which benefits most from CABG.

When there is discordance between ECG changes and MPI during adenosine stress test, it is important not to ignore significant ECG ischemic changes even with normal MPI. A follow-up study has shown a high cardiac event rate (10% over 3 years) in such patients, similar to that observed in patients with severely abnormal perfusion images.20 Abnormal MPI images require the presence of heterogeneity of flow. Under conditions of global myocardial ischemia (transmyocardial or more likely subendocardial), myocardial flow is diffusely abnormal with no regional differences in flow and tracer uptake. An additional clue for this global flow abnormality is transient LV dilation seen in MPI even in the absence of perfusion defects.

Studies have shown with quantitative PET perfusion the phenomenon of “balanced ischaemia and diffusely decreased coronary flow reserve (CFR) causing a falsely “normal” perfusion scan with SPECT. Similarly diffuse coronary artery disease can give the appearance of a normal angiogram.

**BEYOND CORONARY ARTERIOGRAPHY**

Over 40 years since its introduction coronary arteriography, combined with left ventriculography has remained the gold standard for the detection of CAD and for management decisions based on the extent and severity of the anatomical stenoses. Over a period of time, questions started being raised, “Does visual interpretation of the coronary arteriograms predict the physiological importance of anatomical stenosis?”.21 The concept of coronary flow reserve (CFR) as a physiological measure of stenosis severity was developed.22 The fundamental limitations of coronary arteriography and its poor correlation with functional stenosis severity in terms of blood flow obstruction were well recognized.23 The haemodynamic effects of serial stenoses are also difficult to assess from arteriograms. There is poor correlation between severity of stenoses and their propensity to cause MI, unstable angina or sudden coronary death. 15-30% of patients with symptoms of unstable angina have no

<table>
<thead>
<tr>
<th>Table 1 : Modes Cardiac Stress Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
</tr>
<tr>
<td>Dynamic exercise (isotonic) HR / BP double product</td>
</tr>
<tr>
<td>Hand grip (isometric) less sensitive mode</td>
</tr>
<tr>
<td>Cold pressor test (CPT) : mimics mental stress</td>
</tr>
<tr>
<td>Pharmacologic</td>
</tr>
<tr>
<td>Inotropic : Dobutamine, arbutamine infusion</td>
</tr>
<tr>
<td>Chronotropic : Inf. atroline added to dobutamine</td>
</tr>
<tr>
<td>Combination</td>
</tr>
<tr>
<td>Physical exercise ( low level ) with adenosine to reduce</td>
</tr>
<tr>
<td>unpleasant side effects of adenosine and reduced dose of adenosine.</td>
</tr>
<tr>
<td>Mental stress</td>
</tr>
<tr>
<td>Arithmatic, speaking assignments : In the laboratory, or</td>
</tr>
<tr>
<td>Continuous monitoring with Holter ECG or Vest ( LVEF ).</td>
</tr>
</tbody>
</table>

JAPI • VOL. 51 • JUNE 2003 553
significant coronary stenosis on angiography (especially women and non-white population). They have impaired coronary flow reserve due to microvascular endothelial dysfunction.24

It is now well appreciated that stenoses of less than 50 percent have major prognostic implications because these lesions most commonly lead to plaque rupture and acute infarct. Outward (positive) remodeling of the vessel wall due to lesions may not restrict blood flow, and yet may form the most important site for acute coronary syndromes.

IVUS (intravascular ultrasound) has enhanced our understanding of coronary atherosclerosis. IVUS commonly detects occult disease in angiographically normal sites. In ambiguous lesions, IVUS permits lesion quantification particularly for the left main, especially identification of atheromas at risk of rupture. The vulnerable plaque has a thin fibrous cap and large lipid core accompanied by positive (outward) remodelling. The extent and severity of disease by angiography and IVUS are frequently discordant. New and emerging applications of IVUS continue to evolve, particularly in atherosclerosis progression - regression trials.25

IVUS studies have indicated new dimension in arterial remodelling. Positive remodelling seems to be significantly more prevalent in the unstable angina group. While negative remodelling is more commonly associated with stable angina.

CORONARY SPASM AND CORONARY VASOCONSTRICTION: ANGINA WITH NORMAL ARTERIOGRAM

Maseri 26 has discussed the features of (1) segmental coronary spasm (affecting a small segment of the epicardial coronary arteries) causing occlusion and flow interruption and ischaemia: variant or Prinzmetal angina with ST elevation on ECG : it can be reproduced with ergonovine challenge; (2) diffuse coronary vasoconstriction in response to stimuli that normally cause vasodilation (e.g. intra-coronary acetylcholine). This is due to endothelial dysfunction.

The vasomotor range is estimated as the difference between maximum dilatation (nitroglycerine, nitroprusside or papavarine) and maximal constriction (ergonovine). In normal epicardial vessels ergonovine causes mild diffuse vasoconstriction not more than 20-30% reduction on diameter. It never causes ST elevation and induces ischaemia in a very few patients (4%) with chronic stable angina.

In some patients with variant angina hand grip exercise can induce coronary spasm with a delay of about 30 seconds and cold pressor test (CPT) with a delay of about a minute, suggesting a neural trigger, probably activation of alpha adrenergic receptors coronary spasm can also be induced by increasing the arterial pH to 7.65 to 7.70 by hyperventilation.

Cannon28 and Egashira et al29 provided evidence for impaired dilatation of resistance coronary arteries contributing to ischaemia during times of increased demand, in patients with chest pain and normal coronary arteriogram (syndrome X).

Constrictor substances have been recently identified that can cause severe myocardial ischaemia at low doses in normal coronary vessels. Neuropeptide Y, a neurotransmitter abundantly present in adrenergic nerves, and particularly around small coronary arteries and arterioles in animal hearts, induced severe myocardial ischaemia in patients with angiographically normal coronary arteries. Endothelin, a peptide normally produced by endothelial cells causes massive ischaemia in dogs, predominantly by causing small vessel constriction with no change in epicardial coronary arteries.30 Severe endothelial dysfunction in the absence of obstructive coronary artery disease is associated with increased cardiac events.

ENDOTHELIAL DYSFUNCTION - MICROVASCULAR ANGINA

The release of endothelium - derived relaxing factors (nitric oxide, prostacyclin, EDHF) has been shown experimentally to be of pivotal importance for the maintenance of coronary blood flow during increased demand. In humans with coronary atherosclerosis, endothelial vasodilator dysfunction is not confined only to epicardial conductance vessels but may also extend into the coronary resistance vessels and microcirculation.

Endothelial dysfunction is well recognized in atherosclerosis, hypertension, diabetes mellitus and dilated cardiomyopathy. Reduction in maximal coronary flow reserve (normally five times the resting flow) due to microvascular disease causes a reduction in perfusion during increased demand, quite independent of the presence or absence of associated epicardial coronary stenosis.31 Endothelial dysfunction in coronary vasculature is associated with coronary flow reduction in patients with early atherosclerosis.32 Early detection of abnormal coronary flow reserve in asymptomatic men at high risk for CAD has been possible using PET.33

Coronary endothelial dysfunction in women with chest pain is associated with a polymorphism in the angiotensin II type 1 receptor (AT1R).34 This leads to greater vasoconstrictive response.

Dysregulation of coronary microvascular reactivity in asymptomatic patients with type 2 diabetes mellitus has been demonstrated (Momose et al).35 In a study of 46 patients (36 males and 10 females) myocardial blood flow (MBF) was quantitated at baseline, in response to cold pressor test (CPT) and during adenosine-induced vasodilation, with N-13 ammonia PET. The relation to glycaemic control, control of lipid levels and serum markers of endothelial inflammation were also investigated (von Willebrand factor, thrombomodulin). None of the patients was treated with insulin and none had symptoms of cardiac disease. Decreased MBF during CPT was observed in 16/46 patients while 30/
46 demonstrated increased MBF, expressed as ml/min/g.

CPT is thought to be a sympathetic stimulus which normally results in coronary vasodilation via predominant endothelial α2 receptor-mediated nitric oxide production. In dysfunctional endothelium there is a paradoxical vasconstriction similar to that seen on intra-coronary acetylcholine injection.36

Advanced glycation end-products (AGEs) and their receptors on the endothelium contribute to the endothelial dysfunction.37 Impairment of endothelium-dependent vasodilation in type 2 DM has been also shown by invasive coronary Doppler wire studies as well as by non-invasive method.

Patients with “mild” coronary artery lesions can have severe endothelial dysfunction. Long term follow-up of 157 patients showed more cardiac events (42/157) in those with endothelial dysfunction.38

**ATTEMPTS TO IMPROVE ENDOTHELIAL FUNCTION**

Modification of cardiovascular risk factors that contribute to endothelial dysfunction improve patient outcomes disproportionately to the regression in the anatomic atherosclerotic lesions.39 Lipid lowering and plaque regression can prevent plaque rupture and clinical events. Clearly, mechanisms other than regression of the atherosclerotic stenosis are operating resulting in the improvement; stabilization of the vulnerable plaque, enhancement of endothelial function, reduced thrombotic potential and reduced inflammatory response.

Aggressive cholesterol lowering is able to reduce reversible perfusion defects demonstrated by dipyridamole stress imaging. Statin therapy improves myocardial flow reserve independent of the stenosis severity in the related vessels.40

Nitrates, apart from decreasing the preload and after load of the left ventricle, also alleviate the decreased coronary flow reserve caused by endothelial dysfunction.41 Newer selective β1 adrenoreceptor antagonists such as Nabilol inhibit endothelin-1 liberation and increase the availability of NO.42 Long term L-arginine supplementation improves small vessel coronary endothelial function in humans.43 Exercise training increases regional myocardial blood flow and CFR in patients following myocardial infarction, as a result of improved vasodilation.

Clearly our emphasis must shift from a “stenosis-oriented” approach to a “physiologically-oriented” molecular, integrative and clinical approach.

**NEED FOR SELF INTROSPECTION BY INTERVENTIONISTS**

Prof DS Gambhir, President of the Cardiological Society of India has stressed the need for self introspection by interventional cardiologists. (CSI News letter March 2003). “The availability of superior technology to make PTCA highly safe and successful with long term results comparable to surgery, and the financial returns and glamour involved with these procedures have also resulted in pilferage of this state of the art technology in the hands of physicians and cardiologists who did not receive any formal training to perform these procedures. Several unethical practices have gradually creeped into the medical system to entice the referring physicians. As a result, patients are advised to undergo interventions with or without justifiable indications, some times in the hands of aspiring and trainee interventionists. The outcome is unsatisfactory result, requiring repeat procedures in some cases. If these trends are allowed to flourish unchecked, it may tarnish not only the image of this innovative technology but also erode the credibility of our profession. There is no substitute for self-assessment and introspection. It is therefore time for all of us to pause for a moment and act according to our conscience without jeopardising the patient’s safety.”

Dean Ornish in his book “Reversing Heart Disease” has said : “The insurance company will pay at least $ 30,000 for a CABG, at least $ 7500 for a balloon angioplasty, but only $ 150 if a doctor spends the same amount of time and effort teaching a heart patient about nutrition, exercise and stress-coping. If someone spends the same amount of time teaching a well person how to stay healthy, the insurance company will pay nothing at all. It is not surprising that doctors spend time doing what is reimbursed.”

In the larger interest of society our emphasis and efforts should be on prevention through lifestyle modification beginning from childhood. A vegetarian diet (low in fat; calories and sodium, high in fibre, potassium and antioxidants); regular physical exercise and weight control (especially at the waist); abstinance from smoking and controlling mental stress. The aim of Yoga is to attain “Sthitapradnya awastha” - a state of mental equanimity - the most precious prescription for health.

**REFERENCES**

8. Schlant RC. Prognosis of individuals with silent ischaemia. In
Kelleman and Braunwald (Eds) silent myocardial ischaemia - a critical appraisal. 1990, p. 137.


34. Pauly DF, et al. (Abstract of AHA meeting "Molecular, integrative and clinical approaches to myocardial ischaemia. 2001 seatle WA120.


41. Parker JO. Nitrates and angina pectoris. Am J Cardiol 1993;72:3C.
