52 *Recent Advances in Diagnosis of Coronary Artery Disease in Diabetes*

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Abstract: With better control of infective and metabolic complications, diabetes has emerged as a cardiovascular disease. The ATP III recognizes it as a CHD equivalent and the American Diabetes Association has categorized it as a cardiovascular disease. Unlike microvascular disease, which gets clicked with onset of diabetes, macrovascular disease, particularly coronary artery disease (CAD) predates the diagnosis of diabetes by several years. The mortality of diabetic infarct is very high compared to a nondiabetic infarct. The diagnosis of CAD in diabetic should be made at the earliest preferably in prediabetic state to minimize the high morbidity and mortality associated with it. The diagnosis of CAD with stable plaques with hemodynamically stenosis is simple but documentation of vulnerable plaque, the dangerous subset of CAD with high propensity to develop an acute coronary syndrome, still poses a very challenging problem.

INTRODUCTION

With better control of infective and metabolic complications, diabetes has emerged as a cardiovascular disease (CVD). About 75% of diabetics succumb to a cardiovascular disease and of this a major chunk, almost to the tune of 75% is contributed by coronary artery disease (CAD), the remaining 25% by cerebrovascular disease and peripheral vascular disease. CAD is the leading cause of death in diabetics. It accounts for 40% of death in diabetics during 40s and this mounts to 50% in the sixth decade. Above the age of 65 years, 70% of diabetics die of CAD. Diabetes has been categorized as CHD risk equivalent by National Education Cholesterol Program Expert Panel (NECP) on Detection, Evaluation and Treatment of High Blood Cholesterol in adults (Adult Treatment Panel III) thereby implying that the 10 year CHD risk in diabetes is > 20%. The ADA has also recognized diabetes as a cardiovascular disease. The risk of development of acute myocardial infarction in a diabetic patient over a 7 year period is same as if a nondiabetic patient had already sustained a myocardial infarction.

Screening for CHD at the time of diagnosis of diabetes is too late because the development of CAD predates the diagnosis of diabetes by several years. Attempts should therefore be made to screen and target CAD in prediabetic state.

CORONARY ARTERY DISEASE IN DIABETICS EXITS IN 2 FORMS

Stable Plaque

These plaques are usually hemodynamically significant and often present as provocable myocardial ischemia, symptomatic or silent and are easily detectable by diagnostic modalities (Table 52.1).

Vulnerable Plaque

They are small soft plaque and are not **hemodynamically** significant. They are therefore asymptomatic. They are rich in lipids, have high macrophage density, less smooth muscle cells and thin fibrous cap, with high propensity for rupture with superimposed thrombus formation resulting in acute coronary occlusion and acute coronary syndrome (ACS). Most distressing is the fact that once acute myocardial infarction develops in a diabetic, the mortality is very high as shown by the Finmonica study. The study showed that the mortality at the end of one year in diabetic infarcts was 53.1% (pre-hospital 28.6%, in-hospital 28 days—15.4 and one year post hospital 9.1%) in male 35.9% (pre-hospital 22.1%, in-hospital 9.6% and 1st year post-hospital 4.2%) and in female compared to non diabetic infarct mortality of 34.7% in male and 23.7% in females. Therefore it is of prime in importance to diagnose vulnerable plaque, the precursor of AMI in diabetic patients so that plaque can be passivated with drugs and probability of AMI is future can be minimized.

DETECTION OF CORONARY STENOSIS

This can be done in two ways:

a. Direct visualization of coronary stenosis.
b. Inferring coronary stenosis by demonstrating myocardial ischemia/diminished perfusion.

Direct visualization of coronary stenosis. The various modalities utilized for this are as follows:

i. *Catheter coronary angiography:* This undoubtedly remains the gold standard for luminal assessment of coronary arteries. However it has limitations that it shows 2 dimensional silhouette of a three-dimensional structure and does not visualizes subliminal pathology.
ii. *CT angiography:* This shows coronary arteries like catheter angiography but in a non-invasive way. However it cannot accurately measure stenosis with heavy calcified plaque burdens. It is useful in post-CABG patient to judge patency of grafts[1-3] and also in post- coronary stenting patients to detect restenosis.
iii. If the patient is likely to require a revascularization procedure catheter angiography is preferred but if only exclusion of CAD is the aim, CT angiography may be preferable.
iv. *MR coronary angiography:*[4] The clinical role of MR coronary angiography still needs to be established and is not ready to compete with coronary angiography.

Tests inferring coronary stenosis by demonstrating myocardial ischemia/decreased perfusion. A panoply of test like stress ECG, stress echo including pharmacological stress echo, stress thallium and upcoming myocardial contrast echocardiography (MCE) are used for indirectly inferring coronary stenosis by demonstrating myocardial ischemia/decreased perfusion. Stress electrocardiography is most widely practiced but has limitations that the sensitivity in single vessel disease in 33%, two vessel disease 66% and three vessel disease 95%. It has limitations in patients with pre- existing ECG abnormalities like ventricular hypertrophies, bundle branch block, WPW syndrome, patients on drugs like digoxin, females etc. Stress echocardiography[5-8] particularly stress dobutamine has a sensitivity and specificity comparable to stress thallium. It has the dual advantage of assessing both ischemia as well as viability. Stress thallium has a high sensitivity and specificity but is not widely available. MCE[9,10] is fast emerging as a modality to judge myocardial perfusion and viability. The ease and rapidity with which it gives informations right at the bed side in CCU, it is likely to find a permanent place in CCUs.

Other Tests

Electron beam tomography (EBCT). EBCT with ECG triggering has been gold standard for detecting and qualifying coronary artery calcifications (CAC) for more than 10 years.[11,12] While CAC score correlate well with the total atherosclerotic burden[13,14] and strongly predict future events,[15,16] the amount of CAC does not correlate well with the stenosis severity of a given lesion.[17]

Carotid intima media thickness (CIMT). Although the modality is used to evaluate carotid atherosclerosis, it has very good correlation with CAD.[18-21] It can be used as a very simple test to screen for CAD in prediabetics and asymptomatic diabetics. A cut off point of 1.1 mm is usually taken to define carotid atherosclerosis. The CIMT has also consistence association with severity of CAD and future coronary events. Interestingly diabetics not only develop increased carotid IMT earlier but also have higher values than non-diabetics.[22]

MODALITIES TO EVALUATE PLAQUE MORPHOLOGY AND DETECT VULNERABLE PLAQUE (VP)

A panoply of modalities are being tried to detect VP (Table 52.1) but only vascular MRI has emerged as the most widely acceptable non-invasive modality to diagnose and evaluate VP, the dangerous subset of CAD. Most of the other modalities outlined in Table 52.1 are still in the process of development.

Vascular MRI

Currently this has emerged as the modality of choice for evaluation of VP.[23-27] It has the added advantage of being non-invasive. However it is still not available for general use. All the four components of plaque, i.e. fat, collagen, calcium and thrombus can be identified and the effect of pharmacological interventions is under evaluation by Valentine Fuster, et al.

Intravascular Ultrasound (IVUS)

This furnishes an insight into the composition of he plaque' Lipid deposition which is an important feature of VP appear as echolucent and can be detected with a sensitivity of 78-95% and a specificity of 60%[28,29]. However, the main limitation is its invasiveness and cost.

Intravascular Thermography[30,31]

The VP are metabolically active and hot because of increased macrophage density. The thermistor used during intravascular thermography has a temperature accuracy of 0.05ºC. Hot plaques are prone for rupture and development of ACS.

Angioscopy

This allows direct visualization of plaque surface and intraluminal structures. Angioscopic visualization of plaque rupture and thrombus is associated with an adverse outcome.[32] Yellow plaques compared to white plaques on angioscopy are more often associated with development of ACS in future.[33]

Neverthless angioscopy is difficult to perform, invasive and only a limited part of vessel can be visualized. Most importantly, the vessel has to be occluded and the remaining blood has to be flushed out with saline to visualize vessel wall and this may cause ischemia. Information on the plaque extent into vessel wall is not provided by angioscopy.

Radiofrequency Tissue Characterization and Virtual Histology[34]

Virtual histology images are created using this technique yielding information regarding volumetric composition.

Intravascular Elastography

This new technique was introduced to measure the mechanical properties of tissue using ultrasound elastography.[35] The underlying principle is that when tissue is deformed, the rate of

deformation is related to the local mechanical properties. Measurement of local plaque deformation (strain) is obtained with ultrasound.

Near infrared Spectroscopy

Near-infrared (NIR) spectroscopy obtains information on the chemical components of the coronary vessel wall. NIR spectroscopy molecular vibrational transitions measured in the NIR region (750-2500 Nm) give qualitative and quantitative results on plaque composition. NIR spectroscopy sensitivity and specificity for histological features of plaque vulnerability were 90 percent and 93 percent for lipid pool, 77 percent and 93 percent for thin cap, and 84 percent and 89 percent for inflammatory cells.[36] A differentiation between vulnerable and non-vulnerable carotid plaques could be achieved *ex vivo*.[37] Future studies will address the questions whether NIR spectroscopy is feasible in vivo.

Optical Coherence Tomography (OCT)[38-42]

This can provide images with ultrahigh resolutions. The technique involve measuring the intensity of backreflected light, like IVUS measures acoustic waves.

Despite all these advances, the documentation of VP is still a very challenging problem.

Thus, for decreasing the morbidity and mortality of CVD in diabetics, the disease must be picked up early, preferably in the prediabetic state and preventive and therapeutic strategies initiated at the earliest to favorably change the course of the disease.

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