Application of Anatomical and Functional Modalities in Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Patients- A Review Article

Sied Kazem Razavi Ratki[1], Amirpasha Amelshahbaz[1], Reza Nafisi-Moghadam[1,]
Naser Hossein Sartipzadeh[2]*

1. MD, Department of Radiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences Yazd, Iran.
2. MD, Department of Cardiology, Afshar Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

*Correspondence:
Naser Hossein Sartipzadeh, MD, Assistant Professor of Cardiology, Department of Cardiology, Afshar Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
Email: razavi822@gmail.com
Tel: (98) 353 525 5011

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Abstract

Cardiovascular disease (CAD) screening in asymptomatic patients with diabetes mellitus is controversial. An exercise stress test is a safe and effective initial testing for Ischemic Heart Disease (IHD) screening. Treadmill stress test is not the best screening method for a particular patient who is not able to exercise, abnormal electrocardiogram (ECG) or positive exercise treadmill test (ETT) and other anatomical or functional studies are recommended to evaluate for the myocardial ischemia. This concept is supported by the high rate prevalence of silent myocardial ischemia, CAD and cardiovascular events rate. Coronary angiography is an expensive and invasive test which is considered as gold standard for diagnosis obstructive CAD and not be used for screening. In this review article we discussed about anatomical modalities (Coronary Artery Calcium Score (CACS)) and nuclear imaging (SPECT) for evaluation of silent ischemia.

Keywords: Cardiovascular disease, Ischemic heart disease, Treadmill test.

Introduction

American Centers for Disease Control and Prevention (CDC) reported approximately 21 million people have diabetes mellitus (DM) in the United States which 15million with and 6 million without diagnosis of diabetes (1). More than 95% of this patients have type 2 diabetes.(1)

Diabetic patients have an increased risk of developing coronary artery disease (CAD) and hard cardiovascular event compared to the non-diabetic people. Prevalence of CAD in diabetic patients was reported about 43% to 53% without considering age and gender.(2,3) Diabetic patients have progressive disease

with decreased survival compared to general population. (4-8)

Mechanism of silent ischemia in diabetes mellitus:

CAD is a main reason of mortality in diabetic patients. (9) It is essential that diabetic patients at risk of cardiovascular disease (CVD) which should be detected as early as possible. Most burden of DM is related to CVD. (8) Atypical angina and silent ischemia are frequently seen in diabetic patients and these manifestations are a major challenge in detection of CAD in patients with DM (10).

About 25% of diabetic patients have evinced of Myocardial infarction in ECG; however 50% of them were asymptomatic. (11) Cardiac autonomic neuropathy is likely related to increased risks of silent myocardial ischemia but predictive value was low. (12)

Increased in vitro platelet activation is coincidence with cardiac autonomic dysfunction which may be associated with myocardial perfusion abnormality and coronary vasculopathy. Suggested that cardiac autonomic dysfunction was most strong predictor for silent ischemia (13). Also male gender, diabetes duration were strong predictors of reversible ischemia. (13)

A smaller amount of diabetic patients with positive myocardial perfusion scan revealed angina during exercise compared to general population (14-15). The prevalence of silent ischemia in patients with diabetes was unclear and studies reported a difference range 21% to 59%. (14-16)

Endothelial dysfunction:

Endothelial dysfunction couldcontributethe pathogenesis of vascular disease in patients with diabetes mellitus .Additionally myocardial perfusion abnormalities in patients without obstructive epicardial CAD are associated with endothelial dysfunction. (17) Trial evidences revealed diabetes mellitus and insulin resistance are associated with endothelial dysfunctions, which could accentuate atherosclerosis process. (18) Also vasodilator response nitric oxide (NO)-mediated vasodilation is impaired in diabetic patients. (19,20)

In Asymptomatic diabetic patients without obstructive epicardial CAD abnormal myocardial perfusion is a common finding which is associated with endothelial dysfunction. (20)

Clinical factors and silent myocardial ischemia:

Numerous studies suggest several clinical factors to predict silent ischemia including:

Traditional risk factors for CAD, micro/macro albuminuria, retinalvasculopathy, HbA1c, BMI, period of diabetes ,C-reactive protein, peripheral neuropathy disease, lipoprotein (a), peripheral arterial disease, and cardiac autonomic dysfunction. (21-25)

The above mentioned predictors can be useful for selection CAD screening tests.

Screening modalities:

When the high-risk diabetic patients were selected, it is important to choose the optimal test to discover Silent myocardial ischemia (SMI) and CAD.

Although resting ECG is suggested annually, due to its low negative predictive value in patients with normal ECG that including major diabetic population, ECG is not recommended to screening silent myocardial ischemiaalone. (26)

Stress test with physical exercise is first choice method for detection of CAD; however it is related to the ability to reach an adequate 85%

of the target heart rate. But in diabetic population exercise capacity was reduced and achieve to maximal heart rate is not ever possible in these patients because of obesity, peripheral vessel disease, peripheral neuropathy and other co-morbidities. (25-26) Third to half of this papulation were not able to reach optimal exercise stress test level .(26) Therefore unable patients were appropriate candida for pharmacologic stress test.

Single Photon Emission Computed Tomography:

Clinical role of Single Photon Emission Computed Tomography (SPECT), as a non-invasive method to evaluation myocardial perfusion is increasing universal, mainly in the screening. Medical stress test with SPECT imaging assesses myocardial ischemia with sensitivity of 91-96% and specificity of 75-82%.

SPECT myocardial perfusion scan is a confirmed nuclear medicine method for detection of myocardial ischemia. gated SPECT is perfusion images which synchronized with ECG and provide information about cardiac function including left ventricular ejection fraction (LVEF), end diastolic and end systolic volumes, regional LV function (wall motion and wall thickening) and diastolic parameter. The data of gated SPECT has incremental prognostic value more than coronary angiography in patients with known or suspected CAD. (27)

The nuclear cardiology advantages are more than clinical findings, Stress and resting ECG, as it defines the severity and extent of ischemic myocardium. Reversible perfusion abnormality in SPECT can describe a silent ischemia in diabetics. (27)

Stress test can be performed with exercise stress test and pharmacologic stress test (dipyridamole, adenosine). The incremental prognostic value of pharmacologic myocardial perfusion imaging (MPI) is comparable with exercise stress test. (28)

SPECT has higher sensitivity and specificity than ECG stress test for detection if myocardial ischemia. Also Sensitivity and specificity of Stress MPI is equal in nondiabetics and diabetics population. (29)

Coronary Artery Calcium Score (CACS):

Some studies suggested strong association between the coronary calcium and theatheromatous plaque burden. (30,31) Valuation of subclinical coronary atherosclerosis with CACS (table 1) make an available chance to identify asymptomatic patients who are high risk (32) Moreover, coronary calcium can predict future coronary events (33,34) .In diabetic patients CACS can be an effective test for detection of silent CAD. Presence of DM may be considered as a CACS indication regardless the risk of CAD. In comparison with non-diabetic population diabetic patients have higher CACS (35) and diabetes was the strongest predictor for a higher CAC score. Additionally CACS was an independent predictor of primary cardiovascular endpoint events such as coronary death, nonfatal MI, coronary revascularization, as well as stork. (36,37)

CACS are associated with obstructive CAD in angiography. CACS of 0 nearly ruled out significant angiographic CAD and suggested that diabetic patients with no visible coronary calcium had excellent survival. There was not detected significantly difference in comparison with non-diabetic population.

Computed Tomographic Angiography:

Table 1. Coronary artery calcium score (CACS)

CAC score agatston unit	Coronary calcification category
0	Absent
1-10	Minimal
11-100	Mild
101-400	Moderate
401-1000	Severe
>1000	Extensive

CT Angiography is a noninvasive technique that used intravenous contrast injection to visualize the contrast-filled coronary vessels. coronary computed tomographic angiography (CCTA) is a non-invasive test that reveals information about CAD lesion location, severity, and characteristics of atherosclerotic plaque.(38)

As shown in asymptomatic diabetic patients, frequency of atherosclerosis was 64% to91.4% and significant CAD were observed in 26% to33.3%. (39-41) and significant CAD is associated with a poorer prognosis and some lesions were located in the Left Main (LM) or proximal LAD artery. Also prognostic role of CCTA in diabetic patients is documented. (42)

About one third of diabetic patient with no symptom had significant CAD on CCTA and who are at high risk for cardiac events. CCTA may have a potential role in identifying patients.Some asymptomatic diabetic patients with zero CACS had significant CAD on CTA (43) which suggest additional value of CCTA more than CACS for the evaluation of CAD in asymptomatic type 2 diabetic population. Also suggested that 10% of diabetic patients with negative CACS had non-calcified plaques on CCTA (44). About 2% of patients with CAC scores < 100 Au revealed evidence of ischemic on MPS. About 20% of patient with CAC scores> 1000 Au showed ischemia on MPS.(45)

All patients with a CAC score between 0 and 10 had normal SPECT and good outcome (figure1). Also 23% positive SPECT was seen in asymptomatic diabetic population that who had a CAC of 101 to 400. Prevalence of silent myocardial ischemia in Patients with CAC more than 400 had a 48% and this number increased in CAC > 1.000. (46) .Although some studies were reported minimal higher sensitivity for CCTA about 50% of patients with positive CCTA had normal MPI which this findings suggest non-flow limiting coronary lesion in CTA without functionally significance. (47)

To use of MPI or CTA for detection of CAD two major questions is considered: first, degree of correlation between CTA and MPI and second, supplementary role of these modalities.

There is frequently a considerable discrepancy between severity of coronary lesion evaluated by CTA and MPI results. MPI and CTA make available complementary anatomical and functional data, which steno tic lesion on anatomical imaging (CCTA or invasive angiography) is not necessarily associated with a hemodynamically significance necessarily.

Also a positive MPI is not necessarily associated with a significant luminal stenosis on anatomical imaging (48-50). An abnormal CTA in the presence of a good coronary flow reserve on MPI is suggestive of subclinical atherosclerosis and aggressive medical therapy should be considered for this cases. (50)

If CTA was used as first non-invasive method to detection of CAD, regarding the CTA findings what type results should be referred to MPI?

Lesions equal or more than 70% in CCTA had hemodynamically significant and abnormal MPI and coronary angiography may be considered as further test regarding the clinical data. CTA lesions less than 50% are associated with normal MPI totally therefore no other testing is suggested. Myocardial perfusion scintigraphy is considered as further testing for lesion 50% to 69% delineated on CCTA (51)

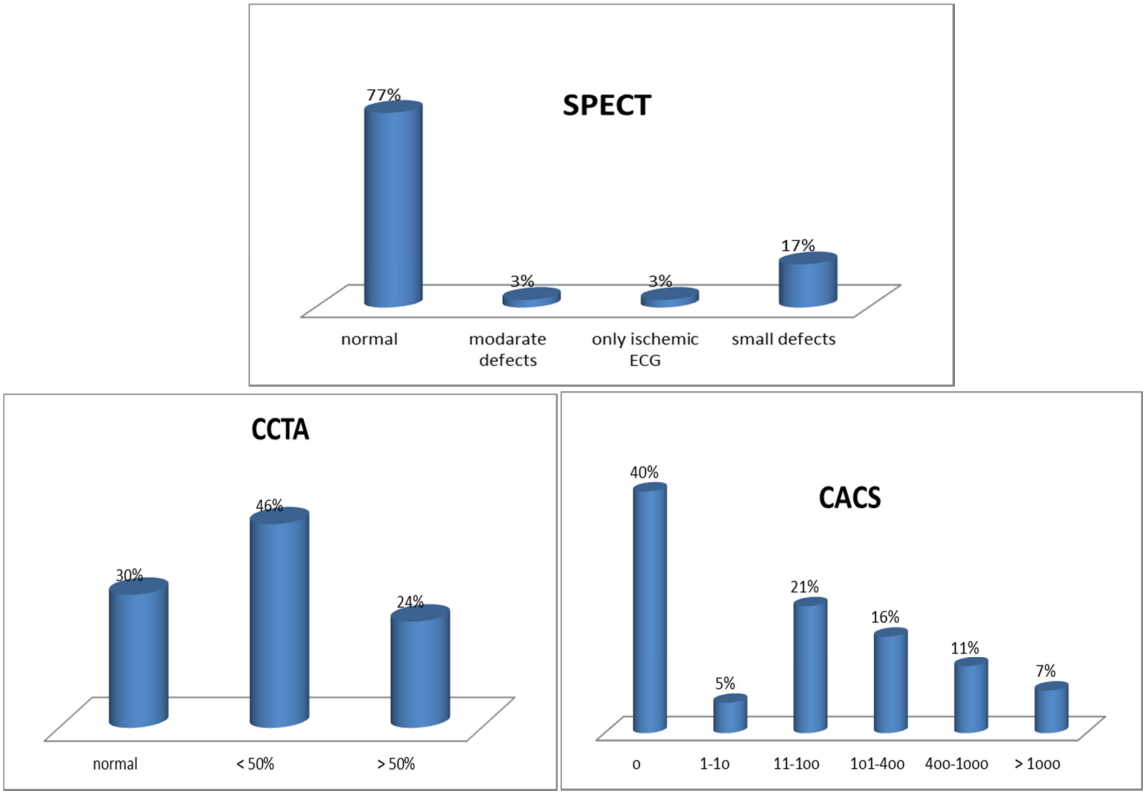

Figure 1. Distribution of findings on SPECT, CAC score and CCTA 2 in asymptomatic diabetic patients. (Source: Scholte AJHA, et al: Different manifestations of coronary artery disease by stress myocardial perfusion imaging, coronary calcium scoring, and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus, J NuclCardiol 15:503-9, 2008.) 54

Difference algoritms suggested for screening of myocardial ischemia in diabetic patients which tow algorism are noticed in this review article. (52,53)

Implication:

Screening in asymptomatic patients with diabetes is controversial. An exercise stress test is a safe and effective initial testing for IHD screening. Treadmill stress test is not the best screen tests for a particular patient who not able to exercise, abnormal ECG or positive ETT and other anatomical or functional studies are recommended to evaluate for the myocardial ischemia. This concept is supported by the high rate prevalence of CAD and cardiovascular events rate.

Coronary angiography is an expensive and invasive test which is considered as gold standard for diagnosis obstructive CAD (figure 2).

Conclusion

Noninvasive imaging modalities are useful in diagnostic and prognostic evaluation of coronary artery disease in diabetic. Although there is not enough evidence that confirmed screening silent ischemia is necessary, some clinical predictors (such as traditional risk factors for CAD, micro/macro albuminuria, retinal vasculopathy, HbA1c, BMI, period of diabetes, C-reactive protein, peripheral neuropathy disease, lipoprotein (a), peripheral arterial disease, and cardiac autonomic dysfunction) can help us to selection appropriate criteria to choice proper screening tests in asymptomatic diabetic patients.

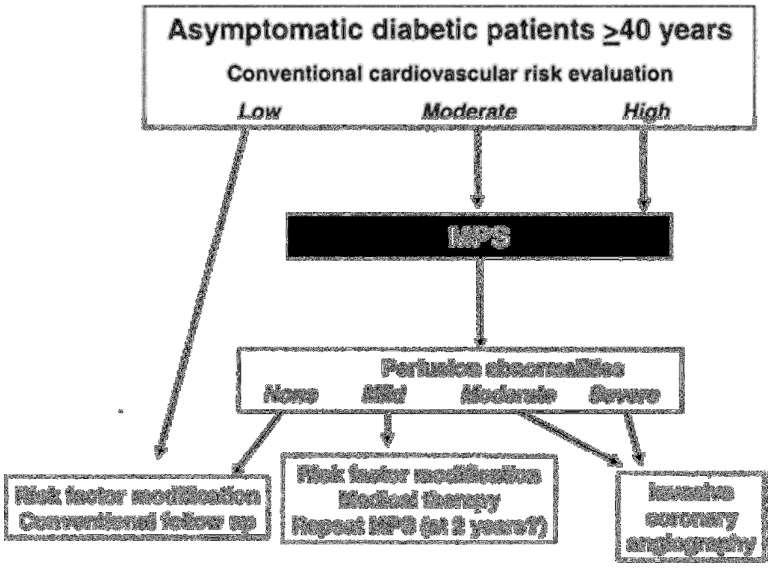

Figure2. Algorithm for Risk Assessment and Management in Asymptomatic Type 2 Diabetic Patients(Adapted with permission from Bax JJ, at al: The potential of myocardial perfusion scintigraphy for risk stratification of asymptomatic patients with type 2 diabetes. Journal of the American College of Cardiology. 2006;48(4):754-60

Fiure2. Algorithm for detection of silent ischemia in Asymptomatic Type 2 Diabetic Patients (source: Peix A. Usefulness of nuclear cardiology techniques for silent ischemia detection in diabetics. MEDICC review. 2013;15(1):33-6.)

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