Silent myocardial ischemia (SMI) is defined as the presence of objective evidence of myocardial ischemia in the absence of chest discomfort or other anginal equivalents. Most silent ischemic episodes occur during minimal or no physical exertion. The exact reasons for the development of angina during some episodes of myocardial ischemia and the absence of symptoms during other episodes are not known. Some mechanisms include inability to reach pain threshold during an episode of ischemia, lesser severity and shorter duration of ischemic episodes, presence of higher threshold for pain, generalized defective perception of painful stimuli and presence of a defective anginal warning system. Coronary artery disease (CAD) is the major cause of morbidity and mortality in patients with diabetes. CAD is usually more advanced at the time of diagnosis and has unfavorable prognosis in diabetic patients. Later diagnosis of CAD may be explained by the presence of SMI, which is more frequent in patients with diabetes (probably because of diabetic neuropathy). The prevalence of SMI is 10%-20% in diabetic patients versus 1%-4% in nondiabetic patients. Exercise treadmill test (ETT) and ambulatory (Holter) monitoring are the most readily available and frequently used tests to identify SMI in clinical practice. The exact reason for unfavorable prognosis associated with SMI is not known. It is possible that repeated episodes of SMI could lead to progressive fibrosis and development of left ventricular dysfunction, and to life-threatening arrhythmias, especially in patients with an electrical substrate for arrhythmias. SMI is associated with an increase in coronary risk that may be reversible with appropriate therapy.

Silent myocardial ischemia (SMI) is defined as the presence of objective evidence of myocardial ischemia in the absence of chest discomfort or other anginal equivalents. Patients with silent ischemia have been stratified by Cohn into three categories (1). Type I silent ischemia is the least common form that occurs in fully asymptomatic patients with obstructive coronary artery disease (CAD). These patients do not experience angina at any time. They probably have defective anginal warning system. Type II silent
ischemia occurs in patients with documented previous myocardial infarction. Type III silent ischemia, much more frequent, occurs in patients with the usual forms of chronic stable angina, unstable angina and Prinzmetal’s angina. These patients exhibit some episodes of ischemia that are associated with chest discomfort and some episodes that are not (silent, asymptomatic ischemia). The ‘total ischemic burden’ in these patients refers to the total period of ischemia, both symptomatic and asymptomatic.

Anginal pain is a poor indicator and underestimates the frequency of significant cardiac ischemia (2). Most silent ischemic episodes occur during minimal or no physical exertion. Silent ischemia is associated with an increase in coronary risk that may be reversible with appropriate therapy. Sudden death is the initial manifestation of coronary disease in 18% of coronary events (3), and more than one-half of sudden deaths occur without a prior history of coronary heart disease (CHD) (4).

EPIDEMIOLOGY AND PATHOGENESIS

The epidemiology of silent ischemia can be viewed from the standpoint of those who are asymptomatic (no history of CHD) and those who are symptomatic (patients with a history of myocardial infarction or angina pectoris).

Asymptomatic patients

The prevalence of asymptomatic but significant coronary disease in the general population can be estimated from data of screening studies and studies evaluating autopsy findings in people not known to having had coronary disease. Between 2 and 4 percent of apparently healthy asymptomatic middle-aged man have a significant coronary disease. The prevalence may be up to 10 percent in asymptomatic men with 2 or more coronary risk factors (smoking, obesity, family history of heart disease, age over 45, diabetes, hypertension, and hypercholesterolemia). The data on women are inconclusive because of a higher incidence of false positive electrocardiograms.

The risk of silent ischemia is increased substantially in patients with diabetes, particularly if they have other risk factors.

Symptomatic patients

A review of available data suggests that 15%-30% of acute myocardial infarction (MI) survivors have silent ischemia (5,6). The largest number of patients at risk of silent ischemia are those with stable angina (the prevalence of silent ischemia is 25%-50% and up to 70%-80% of ischemic episodes are silent (7,8). Atherosclerotic coronary artery disease is the most common underlying cause responsible for myocardial ischemia.

Two observations are interesting. First, conventional or intensive antianginal drug therapy aimed at symptom control does not eliminate silent ischemic episodes (9,16). Second, patients with silent ischemia detected during Holter monitoring have more advanced CHD with frequent evidence of multivessel disease (10).

The exact reasons for the development of angina during some episodes of myocardial ischemia and the absence of symptoms during other episodes are not known. Some mechanisms include:

1) inability to reach pain threshold during an episode of ischemia,
2) lesser severity and shorter duration of ischemic episodes,
3) presence of higher threshold for pain,
4) generalized defective perception of painful stimuli,
5) presence of a defective anginal warning system,
6) higher beta-endorphin levels (11,12), and
7) higher production of anti-inflammatory cytokines which block pain transmission pathways and increase the threshold for nerve activation. Autonomic neuropathy involving cardiac afferent nerves in diabetes mellitus might account for the higher incidence of silent ischemia in diabetics (13).

The exact mechanism that plays a role in silent ischemia is dependent upon a variety of factors such as age, ethnic background, presence of diabetes or other
cause of autonomic neuropathy, prior MI, prior coronary artery bypass graft (CABG), use of certain drugs, etc.

Myocardial ischemia occurs when there is an imbalance between myocardial oxygen supply and demand. Myocardial oxygen demand is dependent upon heart rate, myocardial contractibility, afterload (systolic blood pressure) and ventricular wall tension (preload). For clinical purposes, heart rate, systolic blood pressure and calculated double product (HR x systolic BP) are the most important determinants of myocardial oxygen demand.

Atherosclerotic coronary disease is the most common underlying cause responsible for myocardial ischemia (even in early stages before the lesion becomes occlusive). Changes in vasomotor tone (vasospasm) may also play a role. When atherosclerosis produces critical stenotic lesion (50%-70% luminal narrowing), there is a threshold point beyond which an increase in myocardial oxygen demand may result in myocardial ischemia (ischemic threshold). The ischemic threshold varies from patient to patient and can even change in a given patient based upon a variety of factors (e.g., time of the day, level of mental stress, physical activities and neurohormonal status).

The pathophysiological mechanisms responsible for the genesis of silent myocardial ischemia remain unresolved. It has been suggested that primary reduction in coronary blood flow plays a dominant role; most silent ischemic episodes occur during minimal or no physical activity (13,14,16) and ambulatory monitoring studies have shown relatively small increases in the heart rate immediately preceding silent ischemic episodes, which is in contrast to the prominent increases during exercise testing (14,15). Other reports suggest that increased myocardial oxygen demand for any cause plays a major role in the pathogenesis of silent ischemia (16,17). The majority of patients who experience silent myocardial ischemia during daily life have evidence of inducible ischemia during exercise test that is primarily due to an increase in myocardial demand (15,16). Several factors, such as mental stress and intrinsic physiologic changes due to circadian rhythm, are associated with significant hemodynamic changes that raise myocardial oxygen demand (24). Associated with mental stress induced myocardial ischemia are wall motion abnormalities, which can be prevented by atenolol therapy (as the result of lower rate-pressure product) and by nifedipine (coronary vasoconstriction and decrease in myocardial blood flow also occur).

Most episodes of silent ischemia are preceded by an increase in oxygen demand (only 20%-30% are due to reduced coronary flow secondary to vasospasm or other factors) (18). Silent myocardial ischemia has a bimodal distribution, with a peak between 6.00 a.m. and noon. It may be related to one or more physiological changes (15,23) such as increased heart rate and blood pressure, elevated catecholamine levels, elevated coronary vasomotor tone, enhanced platelet aggregation, and decreased intrinsic fibrinolytic activity. Asymptomatic nocturnal ST segment changes are almost invariably an indicator of two- or three-vessel CAD or the left main coronary artery stenosis.

**SILENT ISCHEMIA AND DIABETES MELLITUS**

Coronary artery disease is the major cause of morbidity and mortality in patients with diabetes (19,20). More than half of all diabetic patients die from coronary artery insufficiency (21,22). CAD is usually more advanced at the time of diagnosis and has unfavorable prognosis in diabetic patients (23,24). Later diagnosis of CAD may be explained by the presence of SMI. Angiographically proved SMI is more frequent in patients with diabetes than in nondiabetic patients (probably because of diabetic neuropathy). SMI has a prevalence between 10% and 20% in diabetic patients versus 1% to 4% in nondiabetic patients (25,26). Traditional and emerging cardiac risk factors have not been associated with abnormal stress tests, although cardiac autonomic dysfunction was found to be a strong predictor of ischemia.

Scognamiglio et al. (27) performed detection of coronary disease in asymptomatic patients with type 2 diabetes mellitus. They found that two risk groups (≥2 vs. 0 or 1 risk factors) had equivalent rates of an
abnormal stress test (60%) and of significant coronary disease on angiography (65%). The patients with ≥2 risk factors had more severe coronary disease with significant higher rates of three-vessel disease (33% vs. 8%), diffuse disease (55% vs. 18%) and vessel occlusion (31% vs. 4%). Janand-Delenne et al. (28) performed a 1-year study to estimate the prevalence of SMI in type 1 and 2 diabetic patients and to define the high-risk diabetic population by systematically testing patients with no symptoms of CAD. The results showed that SMI with significant lesions occurred in 20.9% of type 2 diabetic male patients who were completely asymptomatic for CAD. They recommend routine screening for male patients in whom the duration of type 2 diabetes is more than 10 years or even less when more than one cardiovascular risk factor are present.

The Detection of silent myocardial Ischemia in Asymptomatic Diabetics (DIAD) study (29) was designed to determine the prevalence of inducible myocardial ischemia in asymptomatic patients with type 2 diabetes using adenosine-stress single-photon emission-computed tomography (SPECT) myocardial perfusion imaging as well as clinical and laboratory predictors of abnormal test results. A total of 22% of patients had silent ischemia. The strongest predictors for abnormal tests were abnormal Valsalva (lower Valsalva heart rate ratio), male sex and diabetes duration. Selecting only the patients who met the American Diabetes Association guidelines (those who have two or more additional CAD risk factors), they would have failed to identify 41% of patients with silent ischemia. Traditional cardiac risk factors or inflammatory and prothrombotic markers were not associated with abnormal stress tests, although cardiac autonomic dysfunction was a strong predictor of ischemia.

Autonomic neuropathy is a serious and common complication of diabetes. About 20% of asymptomatic diabetic patients have abnormal cardiovascular autonomic function (30,31). The risk of cardiovascular autonomic neuropathy depends on the duration of diabetes and the degree of glycemic control. The main consequences are dysfunctional heart rate control, abnormal vascular dynamics and cardiac denervation, which have become clinically overt as exercise intolerance (32), orthostatic hypotension (33), intraoperative cardiovascular lability and SMI. Cardiovascular autonomic neuropathy may provoke ischemic episodes by upsetting the balance between myocardial supply and demand. Instead of typical angina, patients often complain of shortness of breath, diaphoresis or profound fatigue. Silent ischemia delays treatment of acute coronary events and makes it more difficult to monitor anti-ischemic treatment or determine whether restenosis has occurred after coronary intervention.

It is presently recommended that baseline determination of cardiovascular autonomic function be performed upon diagnosis in type 2 diabetes and within 5 years of diagnosis in type 1 diabetes, followed by yearly repeated tests (34).

**DIAGNOSIS**

No single diagnostic test is ideal in screening patients for asymptomatic CHD. Due to the relatively low pretest likelihood of the disease, the predictive accuracy of any screening test is low and generally requires confirmation by further testing (35).

Exercise ECG testing has been widely used in screening for asymptomatic CHD. Although an abnormal ECG response predicts a high risk of subsequent coronary and cardiac death in patients with known CHD (36-38), it has a low predictive value in subjects without known disease.

Exercise treadmill test (ETT) and ambulatory (Holter) monitoring are the most readily available and frequently used tests to identify silent ischemia in clinical practice.

**Exercise testing**

Exercise testing is the most suitable laboratory diagnostic test to document SMI in asymptomatic individuals (i.e. patients with no history of CHD) and in those with a history of CHD or exertional angina.
Conventional ST segment analysis during the test is moderately sensitive in detecting CHD. It has low specificity because of an unacceptably high rate (10%-35%) of false positive responses (asymptomatic persons and women) (39). The diagnosis of myocardial ischemia by ETT in asymptomatic persons must be confirmed by radionuclide imaging techniques (e.g., thallium perfusion scintigraphy or exercise ventriculography) before the subject is labeled as having silent ischemia (40).

Holter monitoring

Holter monitoring is the second most frequently used diagnostic test for silent ischemia. The advantage is providing long-term ECG recording of ischemic and arrhythmic events while patients are engaged in routine daily activities out of hospital (41). Episodes of transient ischemia during Holter monitoring are diagnosed by the sequence of ECG changes that include a flat or downsloping ST depression of at least 1 mm, with gradual onset and offset that lasts at least one minute (42). One potential limitation to the use of outpatient Holter monitoring is the marked day to day variability in frequency and duration of ST depression and ischemic episodes (43). The ST depression recorded during Holter monitoring and other simultaneous objective evidence of ischemia by perfusion scintigraphy, radionuclide cardioangiography and hemodynamic monitoring show an excellent correlation.

Exercise test remains the preferred diagnostic modality for initial identification of patients with silent ischemia. Only a small fraction of patients with negative finding on exercise testing will demonstrate evidence of ischemia on Holter monitoring.

Nuclear and echocardiographic imaging studies

Nuclear imaging tests such as stress thallium scintigraphy or exercise radionuclide ventriculography are recommended for the evaluation of silent ischemia in patients who have an abnormal baseline ECG (e.g., left ventricular hypertrophy or stain, bundle branch block, preexcitation syndrome) or those who receive drugs that produce repolarization changes (digoxin, phenothiazines). Pharmacological stress tests with dipyridamole or adenosine plus thallium scintigraphy or dobutamine stress echocardiography can be used in those patients who are unable to ambulate or exercise (e.g., due to advanced peripheral vascular disease) (Table 1).

| Table 1. Diagnostic modalities for detection and evaluation of silent myocardial ischemia |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Exercise treadmill test          | Continuous ECG (Holter) monitoring |
| Exercise myocardial perfusion scintigraphy |
| Radionuclide angiocardiography   |
| Pharmacological stress scintigraphy |
| Hemodynamic monitoring          |

PROGNOSIS AND THERAPY

Episodes of myocardial ischemia, regardless of whether they are symptomatic or asymptomatic, are of prognostic importance in patients with CAD. As such, myocardial ischemia, as opposed to symptoms alone, has been identified as a valid therapeutic target. In asymptomatic patients, the presence of exercise-induced ST segment depression has been shown to predict a four- to fivefold increase in cardiac mortality (30).

The Lipid Research Clinics Coronary Primary Prevention Trial (asymptomatic hypercholesterolemic men) and the Multiple Risk Factor Intervention Trial (MRFIT) (asymptomatic middle-aged men with two or more coronary risk factors) found significant association between exercise test-induced silent ischemia and mortality (6,7). A study by Laukkanen et al. also demonstrated the relationship between CHD risk in patients with silent ischemia and coronary risk factors; exercise-induced silent ischemia was associated with an increase in mortality and the risk of any acute coronary event was 5.9- and 3-fold in those who smoked; 3.8- and 1.9-fold in hypercholesterolemic subjects; and 4.7- and 2.2-fold in hypertensive patients (44). These associations were weaker and not significant in men without these risk factors.
factors. The Heart and Soul study suggested the presence of ischemia rather than that of angina to determine the outcome (45). In the Psychophysio:logical Investigations of Myocardial Ischemia study, the presence of mental stress-induced ischemia, as established by new or worsened wall motion abnormalities on radionuclide imaging, significantly predicted death during an average follow-up of 5.2 years (46).

The exact reason for the adverse prognosis associated with silent ischemia is not known. It is possible that repeated episodes of silent ischemia could lead to progressive fibrosis and the development of left ventricular dysfunction, and to life-threatening arrhythmias, especially in patients with an electrical substrate for arrhythmias.

**Treatment without revascularization**

Pharmacological agents that reduce or abolish episodes of symptomatic ischemia, i.e. nitrates, beta-blockers and calcium antagonists, also reduce or abolish episodes of silent ischemia.

As increased myocardial oxygen demand appears to be the primary reason for the development of silent ischemia, beta-blockers and heart rate reducing calcium channel blockers are the first choice. Combination therapy is necessary when monotherapy with beta-blockers does not effectively suppress silent ischemia. One of the most favored combinations is a long acting beta-blocker and long acting nitrate preparation. The elimination of ST segment depression on Holter monitoring is frequently used to evaluate the effect of this therapy, but the marked variability in the number and duration of ischemic episodes as detected with this technique may confound the accurate assessment of prescribed therapy (13).

Two studies with mental stress management showed that a program of stress management reduced the frequency of ischemic events, particularly among patients with a higher frequency of ischemic episodes (≥4/hour) (47), and had a significantly lower number of coronary events at two years (48).

Hyperlipidemia is associated with endothelial dysfunction, which promotes the development of atherosclerosis and can also cause unopposed vasoconstriction or established coronary stenoses, thereby triggering silent or overt ischemia. A study with lovastatin (49) showed that after six months of therapy there was a significant reduction in the number of episodes of ST segment depression and abolished ST segment depression in a higher percentage of patients (65% vs. 10% in the placebo group).

**Treatment with revascularization**

There are limited data evaluating the efficacy of coronary revascularization in the treatment of silent ischemia. However, the data available suggest that revascularization may improve patient outcomes. The NIH-sponsored Asymptomatic Cardiac Ischemia Pilot (ACIP) study (50,51) illustrated that CABG more effectively suppressed ischemia than PTCA (both on ambulatory ECG and on ETT); that mortality after one and two years was lower in patients undergoing revascularization compared to those with Holter guided therapy or medical therapy guided by relief of angina; and that the rates of combined end points of death, myocardial infarction or recurrent hospitalization at one and two years were lower in patients undergoing revascularization compared with those undergoing either form of medical therapy.

**CONCLUSION**

Silent myocardial ischemia is defined as the presence of objective evidence of myocardial ischemia in the absence of chest discomfort or other anginal equivalents. Most silent ischemic episodes occur during minimal or no physical exertion. SMI is associated with an increase in coronary risk that may be reversible with appropriate therapy. The risk of silent ischemia is increased substantially in patients with diabetes, particularly if they have other risk factors. Exercise treadmill test (ETT) and ambulatory (Holter) monitoring are the most readily available and frequently used tests to identify silent ischemia in clinical practice. Therapy for asymptomatic episode is equal as for the symptomatic one.
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