Silent Ischemia in People With Diabetes: A Condition That Must Be Heard

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Angina pectoris has long been considered the cardinal symptom of myocardial ischemia. However, it is now known that angina pectoris may be a poor indicator for myocardial ischemia, particularly in patients with diabetes. Despite the recent advances in our understanding of the complex pathophysiology of coronary artery disease (CAD), the recognition of diabetic patients with asymptomatic and yet significant CAD remains difficult. CAD in diabetic patients poses diagnostic and therapeutic challenges for clinicians, especially when patients are asymptomatic during episodes of myocardial ischemia.

In diabetic patients, cardiovascular disease remains the leading cause of death, and myocardial infarctions tend to be more extensive and have a poorer survival rate than in age-, weight-, and sex-matched individuals without diabetes. The medical cost associated with diabetes is staggering, amounting to about $100 billion annually, with vascular complications accounting for the majority of this expenditure.

Definition
“Silent ischemia” refers to the presence of objective findings suggestive of myocardial ischemia that is not associated with angina or anginal equivalent symptoms. Such objective evidence includes exercise testing or ambulatory monitoring demonstrating electrocardiographic changes, nuclear imaging studies demonstrating myocardial perfusion defects, or regional wall motion abnormalities illustrated by echocardiography.

Episodes of silent ischemia can occur with minimal or no physical activity and have been demonstrated in some individuals with stressors as mild as engaging in mental arithmetic. Diabetes, hypertension, previous myocardial infarction, surgical revascularization, and advanced age are all putative risk factors for silent ischemia, although many affected individuals do not have any apparent contributor.

Epidemiology
In the Framingham Study, which was based on 34 years of follow-up of more than 5,000 subjects, about one-fourth of the patients who experienced a heart attack had unrecognized events. Unrecognized infarctions consisted of silent myocardial infarctions and atypical myocardial infarctions. The latter are myocardial infarctions that are accompanied by some symptoms that neither physician nor patient recognize as manifestations of a heart attack.

Proposed Mechanism for Perception of Myocardial Ischemia
In order to understand the potential mechanisms of silent ischemia, one must first understand the process by which myocardial ischemia translates into angina. The perception of angina begins with excitation of free nerve endings in the myocardium. Mechanical and chemical factors can cause electrochemical firing. Ischemia-induced changes in the tone of the ventricular wall may provide mechanical stimulation. In addition, chemicals released from the myocytes in response to hypoxia may also account for nerve stimulation.

These impulses propagate along the cardiac sympathetic nervous system to the thoracic sympathetic ganglia and to the dorsal horn spinal neurons. They reach the thalamus traveling on the spinothalamic tract and are then carried by the thalamocortical tract to the cerebral cortex, where they are perceived as discomfort.

Mechanism of Silent Ischemia
Impaired symptom perception contributes to the lack of recognition of painful stimuli. For angina, this may occur at different levels. Potential reasons may include a higher pain threshold, an excess of endogenous endorphins, and a generalized defective perception of painful stimuli. Episodes of silent ischemia may represent less severe or shorter events than those associated with angina pectoris. In diabetic patients, it is suspected that partial or complete autonomic denervation may contribute to the prevalence of silent ischemia.
Silent ischemia is associated with a circadian pattern, and many events occur in the morning. This may be because of an increased myocardial oxygen demand caused by elevated heart rate and blood pressure, higher catecholamine concentrations, increased coronary vasmotor tone, greater platelet aggregation response, and dampened intrinsic fibrinolytic process.

**Diagnosis of CAD in Diabetic Patients**

Because of the prevalence of CAD in the diabetic population and its overwhelming burden of early mortality, careful evaluation of coronary heart disease (CHD) risk is crucial. Unfortunately, there is little in the way of clinical trial evidence to suggest ideal screening strategies. It must be remembered that the outcomes studies that have validated invasive cardiovascular approaches for the treatment of CHD largely document their benefit for the relief of symptoms and, in more selected situations, improvement in survival (e.g., left main coronary disease) in symptomatic patients.

The American Diabetes Association (ADA) position statement “Standards of Medical Care for Patients With Diabetes Mellitus” states that “emphasis should be placed on reducing cardiovascular risk factors when possible, and clinicians should be alert for signs of atherosclerosis.” It further suggests that a critical component of comprehensive diabetes management is comprehensive cardiovascular risk management including:

- Targeting blood pressure to a goal of <130/80 mmHg, employing regimens based on angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, and diuretics;
- Lowering LDL cholesterol to <100 mg/dl as the primary lipid goal of therapy for adults, using statins as first-line pharmacological therapy;
- Lowering triglycerides to <150 mg/dl and raising HDL cholesterol to >40 mg/dl in men and >50 mg/dl in women as secondary lipid goals;
- Using aspirin therapy (75–325 mg/day) in all adult patients with diabetes and macrovascular disease and considering aspirin therapy for primary prevention in those >40 years old; and
- Advising patients not to smoke and including smoking cessation counseling and other forms of treatment as a routine component of care for smokers.

Indeed, with the recent elevation of diabetes to that of a coronary risk equivalent, it is now appropriate to treat all patients with diabetes as if they have known CAD from the standpoint of risk factor management.

Routine cardiac stress testing in asymptomatic diabetic patients is not currently recommended. Because CHD in diabetes can begin in the third and fourth decade of life, screening for coronary disease in high-risk populations should begin around the age of 30 years and certainly by the age of 40 years. The ADA recommends that an ECG be part of the initial evaluation of adult patients with diabetes. It further suggests cardiac stress testing in a variety of clinical situations in which clinicians are concerned about ongoing CAD.

Cardiac stress tests should be performed in diabetic patients with angina or anginal equivalent symptoms, including dyspnea, lightheadedness, fatigue, or gastrointestinal symptoms if these symptoms seem to be associated with exertion or stress and particularly if they are relieved by rest. Patients with a resting ECG suggestive of ischemia or infarction and patients with known peripheral or carotid occlusive disease should undergo stress testing independent of previous or ongoing symptoms. In addition, asymptomatic patients with diabetes and two or more cardiovascular risk factors should undergo stress testing. These risk factors include:

- Total cholesterol ≥240 mg/dl, LDL ≥160 mg/dl, or HDL ≤35 mg/dl;
- Blood pressure >140/90 mmHg;
- Smoking;
- Family history of premature CAD; and
- Microalbuminuria or proteinuria.

Arguably, patients with controlled CAD risk factors are at increased risk of CAD and perhaps should be included among those screened because of multiple risk factors. Although there is inadequate data to confirm that cardiac autonomic neuropathy is an independent risk factor for coronary disease, the ADA does recommend considering stress testing in patients >35 years old with a >25-year history of diabetes and definitive evidence of cardiac autonomic neuropathy. Finally, stress testing could be of value in patients >35 years old who have been sedentary and plan to initiate a vigorous program of exercise, to identify those at risk for adverse events and aid in planning an appropriate exercise program. Table 1 summarizes indications for stress testing in diabetic patients.

In addition to the traditional tests to assess cardiac risk, there are emerging new nontraditional risk factors for CAD such as B-type natriuretic peptide (BNP) and C-reactive protein (CRP). BNP is released mainly from the left ventricle (LV) in response to ventricular volume expansion and has been shown to correlate well to the degree of LV dysfunction. Recent studies have shown that it is an effective screening tool in diabetic patients suspected of LV dysfunction. CRP is a marker of cardiac inflammation, which is also becoming an important factor when assessing cardiac risk.

Neither of these markers is used routinely at this time; however, they are

### Table 1. Indications for Cardiac Stress Testing in Patients With Diabetes

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<th>Indications</th>
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<tr>
<td>• Typical or atypical cardiac symptoms</td>
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<td>• Resting ECG changes suggestive of ischemia or infarction</td>
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<td>• Peripheral vascular disease or carotid occlusive arterial disease</td>
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<td>• Multiple cardiovascular risk factors</td>
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<td>• Special consideration for patients planning a vigorous program of exercise and those with cardiac autonomic neuropathy</td>
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used by clinicians who feel comfortable interpreting the results and when the traditional markers are equivocal or nondiagnostic.

In lower-risk patients, such as a 40-year-old with minimal risk factors who is planning to start a vigorous exercise program, routine treadmill exercise testing has sufficient sensitivity to be adequate. In higher-risk patients, such as a patient with multiple risk factors and Q waves on a resting ECG, combined stress testing with imaging procedures should be employed because they provide greater sensitivity and specificity as well as an indication of the extent of involvement and ventricular function.

One cannot assume, however, that patients with negative test results do not have coronary disease. It is now recognized that >80% of myocardial infarction occurs in segments of vessels that are <70% occluded and that the vast majority of people with diabetes do have significant coronary artery involvement with the atherosclerotic process. In patients with documented silent ischemia, cardiac testing should probably be repeated every 1–2 years.

Exercise treadmill testing, perfusion scintigraphy, and stress echocardiography are available for clinicians to screen diabetic patients for CAD. The diagnostic and prognostic values of these various methods of stress testing have not been thoroughly studied in the diabetic population; their usefulness has been extrapolated from studies performed in the general population.

Diabetic patients with a normal ECG and who are capable of exercising to reach at least 85% of maximal heart rate adjusted for their age should undergo exercise testing. Exercise treadmill testing offers not only diagnostic but also prognostic information. Patients with good exercise capacity who are able to reach Stage IV of the Bruce Protocol have better survival rates. Conditions that preclude performing an exercise treadmill test include malignant arrhythmias, severe aortic stenosis, acute cardiopulmonary event, and severe hypertension. Hypertrophic cardiomyopathy serves as a relative contraindication. Furthermore, the usefulness of an exercise treadmill test is compromised when left-bundle branch block, ST segment depression, or pacemaker are present at baseline because test results cannot be accurately interpreted. Several studies have also suggested that the exercise treadmill test may not be as reliable when evaluating women.

Myocardial imaging techniques, echocardiography, and nuclear myocardial perfusion imaging are alternative modalities for diagnosing CAD. Furthermore, determining LV function provides prognostic information. Conventionally, these imaging techniques are used in conjunction with pharmacological agents, although cardiac stress may also be achieved by exercise during these imaging techniques.

Cardiac stress is traditionally achieved via dipyridamole and adenosine during nuclear myocardial perfusion techniques and dobutamine during echocardiography. By stimulating β-1 receptors in the heart, dobutamine increases heart rate and contractility and, therefore, myocardial oxygen demand. On the other hand, adenosine and dipyridamole cause smooth muscle relaxation and vasodilation of coronary arteries. Stenosis in the coronary vessels causes shunting of blood flow away from the affected blood vessel. During nuclear medicine testing, this change in distribution of blood flow can be visualized using radiolabeled substances such as thallium, technetium, or their derivatives (Sestamibi). Adenosine and dipyridamole are contraindicated in patients with active asthma or chronic obstructive pulmonary disease.

Prognosis
CAD is a major cause of morbidity and mortality in the diabetic population; it is the cause of death in at least 70% of all diabetic patients. Diabetic patients with myocardial infarction have higher rates of congestive heart failure, cardiogenic shock, and cardiac arrest.

The impact of silent ischemia in diabetic patients is concerning because many diabetic patients may not seek medical attention, and, as a result, the diagnosis and treatment may be delayed. Silent ischemia also carries prognostic implications in survivors of myocardial infarction. Patients with evidence of exercise-induced ischemia in stress studies after sustaining myocardial infarction are at risk for recurrent myocardial infarctions and cardiac death.

The proper detection of diabetic patients with silent ischemia will result in a more rapid initiation of appropriate treatment. In turn, early administration of appropriate therapy will result in favorable prognostic outcomes.

Management
Several questions remain unresolved regarding proper treatment of silent ischemia. The management of diabetic patients with CAD requires a multidisciplinary approach. As discussed above, management of blood pressure and lipids, smoking cessation, and routine use of aspirin are indicated for all patients with diabetes but arguably will have an even greater impact on morbidity and mortality in patients with ongoing ischemia. When aspirin is not tolerated, other anti-platelet agents should be considered, such as clopidogrel (Plavix). Considered below are interventions beyond those routinely suggested in diabetes that may improve outcomes in patients with ischemic heart disease.

Glycemic control is the cornerstone for treating and preventing diabetic microvascular complications such as retinopathy and nephropathy. However, improved glycemic control may also help to lower rates of macrovascular complications such as cardiovascular events. Appropriate glycemic control includes medical nutrition therapy/meal planning, exercise, and pharmacotherapy as needed.

β-blockers are arguably the most effective class of anti-anginal medications and are a cornerstone of therapy in suppressing silent ischemia. This class of
medications has a favorable effect on myocardial oxygen demand by reducing blood pressure and heart rate. β-blockers reduce the duration and frequency of silent ischemic episodes more than do other classes of anti-anginal drugs.

Clinicians have been reluctant to use β-blockers in diabetic patients because of the potential dampening symptoms of hypoglycemia or worsening of glycemic control. However, cardioselective β-blockers should be considered in all diabetic patients with CAD. β-blockers are associated with prognostic benefits including fewer cardiovascular complications, subsequent infarctions, and deaths, particularly in patients with diabetes.

ACE inhibitors are known to reduce infarct size, limit myocardial remodeling, and reduce mortality. In diabetic patients, they are also the treatment of choice for proteinuria and hypertension. Proteinuria, in turn, is an indicator for diabetic nephropathy and possibly for advanced atherosclerosis and cardiovascular disease. Recent studies suggest that ARBs carry similar benefits.

Calcium-channel blockers (CCBs) are also effective pharmacotherapy. Similar to the β-blockers, CCBs reduce the duration and frequency of silent ischemia. This class of medications may be prescribed when the maximal effect of β-blockers has been achieved or when β-blockers are contraindicated or not tolerated.

Nitrates may be used in oral or transdermal routes with β-blockers when desirable suppression of silent ischemia is not achieved with β-blockers alone. The effect of chronic usage of nitrates is limited by tolerance. This limitation can be overcome by allowing an 8- to 10-hour nitrate-free period daily.

Treatment of psychological and emotional issues is also important because psychological stressors may also contribute to precipitating silent ischemia. Recognizing and treating depression is of critical importance. Proper management of such stressors may indeed reduce myocardial ischemia. This may require individual or group counseling and the involvement of patients’ family members and friends.

Revascularization as a means of therapy for silent ischemia is not well supported. Coronary revascularization may be achieved surgically via coronary artery bypass graft (CABG) or percutaneously via percutaneous coronary intervention (PCI). Recent advances and improvements in surgical and percutaneous techniques have allowed physicians to reperfuse and revascularize the coronary arteries of diabetic patients at lower morbidity and mortality rates. Therefore, CABG and PCI should be considered in high-risk patients who display ongoing myocardial ischemia despite an adequate trial of pharmacotherapy.

Summary
Angina pectoris is an insensitive indicator for myocardial ischemia, particularly in patients with diabetes. Cardiovascular disease remains the leading cause of death in patients with diabetes. The impact of silent ischemia in patients with diabetes is concerning because patients may not seek medical attention and, therefore, may not be evaluated, diagnosed, or treated in a timely manner.

It has been estimated that at least one-fourth of patients with diabetes who experience a heart attack have unrecognized silent or atypical events that are accompanied by symptoms that neither physicians nor patients recognize as manifestations of a heart attack.

Autonomic nervous system dysfunction is believed to be the primary underlying mechanism for impaired recognition of ischemia in diabetic patients. Asymptomatic patients with diabetes who have two or more cardiovascular risk factors are at intermediate risk for CAD. ADA recommendations include cardiac stress testing for these patients, as well as for those with proteinuria and microalbuminuria, peripheral vascular disease, carotid occlusive disease, or abnormal ECG, and for those who have been sedentary and are about to start an exercise program.

Myocardial imaging techniques, echocardiography, and nuclear myocardial perfusion imaging are alternative and more sensitive methods of testing than resting ECG for diagnosing CAD in people with diabetes.

Glucose, lipid, and blood pressure control and aspirin therapy are the cornerstones of diabetes therapy. In patients with ischemic heart disease, additional attention to these factors, with greater emphasis on the use of β-blockers, ACE inhibitors, ARBs, nitrates, and CCBs, is essential. Revascularization therapy has also been proven to be more effective than percutaneous transluminal coronary angioplasty and should be considered in high-risk patients who sustain myocardial ischemia despite pharmacotherapy.

REFERENCES
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