Table of Contents
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Articles

Silent Myocardial Ischemia in Patients With Diabetes Mellitus

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Introduction

It is well established that coronary artery disease is a major complication of diabetes mellitus, representing the ultimate cause of death in more than half of all patients with this disease.[1] Clinicopathological correlations, as well as several angiographic studies, suggest that diabetic patients have more extensive atherosclerotic disease, affecting the coronary arteries in particular.[2,3,4,5,6] Furthermore, myocardial infarction in diabetic patients usually is more extensive and more severe than in nondiabetic patients.[7,8,9] The long-term survival rate after acute myocardial infarction among diabetic patients is also lower than that among nondiabetic patients.[10] In fact, the 5-year survival rates for diabetic patients after the first major coronary event have been found to be 38% and only 25% for those with subsequent events, compared with the corresponding figures in nondiabetic patients of 75% and 50%, respectively.[7,8] Recently, patients with diabetes mellitus and multivessel coronary disease were found to have a significantly higher mortality rate with PTCA than with CABG.[11] In fact, on September 21, 1995, the National Heart, Lung, and Blood Institute released a clinical alert to US physicians regarding the 5-year mortality results of patients with diabetes mellitus in BARI.[11] BARI includes 1829 patients with multivessel coronary artery disease who were randomly assigned to either CABG or PTCA. In this study, the review of available 5-year mortality data demonstrated that patients with diabetes who were on insulin or oral therapy have a 35% mortality rate with PTCA compared with the 19% mortality rate with CABG.[11] Diabetic patients also have a higher rate of infarction and a greater need for additional revascularization procedures, probably because of early restenosis and late progression of coronary disease.[12] In this regard, further studies should be performed to assess whether or not stent implantation will improve the mortality rate after multivessel PTCA in diabetic patients.

Chest pain is certainly the predominant symptom of ischemic heart disease and the one most commonly used to establish the type and the efficacy of treatment. However, several studies suggest that many individuals with severe coronary artery lesions do not have angina pectoris.[13,14,15,16] In these patients, episodes of transitory myocardial ischemia may be "silent," although abnormal asymptomatic ST changes may be recorded during AECG monitoring.[14,15,16] The silent ischemic events considerably outnumber the symptomatic ones,[15] and it is generally accepted that nearly 75% of the transient ischemic episodes recorded during AECG monitoring are asymptomatic in patients with stable angina pectoris.[14,15,16,17]

Numerous studies have demonstrated that the presence of silent ischemia during exercise testing or AECG monitoring predicts adverse clinical outcome and poor survival.[18,19,20] During 2 years of follow-up, there was a threefold increase in cardiac deaths in patients with silent ischemia during AECG monitoring compared with those without silent ischemia (24% versus 8%).[19]

In addition, Deedwania and Carbajal[19] also showed that silent ischemia during AECG monitoring was an independent predictor of mortality, and the clinical variables, exercise parameters, and angiographic extent of coronary artery disease did not provide additional prognostic information.

Several other studies demonstrate that, despite control of anginal symptoms with antianginal drugs, more than 40% of patients with stable angina continue to have ECG evidence of myocardial ischemia on AECG monitoring during ordinary daily activities.[19] [20] [21] [22] [23] The presence of silent myocardial ischemia in this otherwise stable population predicts poor survival and helps to identify the high-risk coronary disease patients. Because most clinicians prescribe and titrate antianginal drugs for control of symptoms, silent ischemia during daily life can remain unrecognized unless ECG monitoring is performed.[19]

Evidence accumulated in recent years demonstrated that asymptomatic myocardial infarction or asymptomatic myocardial ischemia occurs more frequently in diabetic patients.[9] [24] [25] [26] [27] In fact, the Framingham study reported that in diabetic patients, the incidence of painless myocardial infarction was higher than that in nondiabetic patients.[9] [24] Other studies also demonstrated that in diabetic patients, the incidence of painless myocardial infarction is higher than in nondiabetic patients.[25] [28] [29]

The reported higher incidence of painless myocardial infarction stimulated many studies that used AECG monitoring and exercise stress testing to evaluate the presence of asymptomatic episodes of myocardial ischemia. In fact, some evidence suggests that diabetic patients may have a high incidence of transient silent ST changes during Holter monitoring.[26] [30]

In a well-controlled patient population, Nesto and associates[27] also demonstrated that only 28% of the diabetic patients with positive thallium scintigraphy experienced angina pectoris during the treadmill test compared with 68% of nondiabetic patients.

There could be several explanations for the different patterns of symptoms in patients with diabetes mellitus, including different thresholds of pain sensitivity, psychological denial, or the presence of autonomic neuropathy leading to sensory denervation. The latter seems to be more likely in diabetic patients, because autonomic neuropathy is a common feature of diabetes, and abnormalities of the autonomic nerve fibers were demonstrated histologically in diabetic patients who died after painless myocardial infarction.[31] Furthermore, diabetic patients with silent myocardial ischemia show evidence of diffuse abnormalities in *m*-iodobenzylguanidine imaging, suggesting that abnormalities of pain perception may be linked to sympathetic denervation.[32]

The relevant incidence of autonomic dysfunction in diabetic patients is also suggested by the absence of a peak incidence of myocardial ischemia in the morning hours.[30] Finally, diabetic patients with or without signs of autonomic neuropathy have a decreased vagal activity (and hence a relatively higher sympathetic activity) during night hours and at the same time of the day during which a higher frequency of cardiovascular accidents has been reported.[33]

The interesting study of Caracciolo and associates[34] in this issue of *Circulation* reporting results of the ACIP Study states that the percentages of patients without angina during ETT were similar in the diabetic and nondiabetic groups. Similarly, the percentages of patients with only asymptomatic ST-segment depression during the 48-hour AECG monitoring were similar in the diabetic and nondiabetic groups. Although multivessel disease was more frequent in the diabetic group (87% versus 74%, P=.01), total ischemic time per 24 hours, ischemic time per episode, and maximum depth of ST-segment depression were lower in the diabetic group.

However, in the ACIP Study, patients were eligible for inclusion if they had at least one episode of asymptomatic ischemia during 48-hour AECG monitoring. In the ACIP Study, patients who required background medication for control of their angina could continue to take either atenolol or diltiazem SR. A clinical history of hypertension was present more frequently in the diabetic group (55%) than the nondiabetic group (35%). Caracciolo and associates found that only 6% of patients with diabetes mellitus had painful episodes of ST changes during AECG monitoring (compared with 12% of nondiabetic patients); the percentages of patients with asymptomatic episodes were similar in the diabetic and nondiabetic groups (94% versus 88%, P=NS).

The ACIP diabetic group had less measurable ambulatory ischemia (even though coronary disease was more extensive and diffuse in the diabetic group), and the times to onset of 1-mm ST-segment depression and angina during the ETT were similar between the diabetic and nondiabetic groups.

However, caution should be used in applying the ACIP data to a general population of diabetic patients. First, during screening for ACIP, ≈36% of patients with an ischemic response during AECG monitoring were ineligible for ACIP. In addition, several other considerations should be taken into account in interpreting the ACIP data. In fact, diabetic patients represent a heterogeneous group with different patterns of coronary artery disease and different prognoses. Unfortunately, in the retrospective study by Caracciolo and associates, the characteristics of the diabetic patients (duration of the disease, type of therapy, etc) were not reported. More importantly, diabetic patients with hypertension, previous myocardial infarction, hypercholesterolemia, different medical therapy (nitrates, Ca^{2+} antagonists, ß-blockers, etc), and history of smoking should not be pooled together.

In the ACIP Study, patients were eligible for inclusion if they had objective evidence of stress-related ischemia during an exercise treadmill test, had at least one episode of asymptomatic ischemia, and had one or more stenoses with ≥50% reduction in lumen diameter in a major epicardial vessel suitable for revascularization.

It is of interest to note that in the ACIP Study, ß-adrenergic blocking agents were used more frequently in nondiabetic than in diabetic patients (46% versus 32%, $P<.02$). This is an important point, since Stone and associates[35] demonstrated that ß-blockers markedly reduce the number of episodes of asymptomatic ischemia during AECG monitoring, and the pivotal role of heart rate on myocardial ischemia is well known.[36] In the ACIP Study, diabetic patients had a significantly higher basal heart rate and systolic blood pressure compared with nondiabetic patients; the time from cardiac catheterization to study enrollment was almost twice as long in the diabetic group than in the nondiabetic group, and nondiabetic patients were more frequently male.

Another important consideration concerns the statistical analysis of the ACIP data. It is evident that the sample sizes between nondiabetic (n=481) and diabetic (n=77) patients are unbalanced. For instance, if the number of diabetic patients is arbitrarily increased fourfold to 308 (assuming that the percentage of asymptomatic episodes of ST changes will remain unchanged at 94% versus 88%), the difference becomes statistically significant when the Fisher exact test or the χ^2 test is used.

In conclusion, it is well established that patients with diabetes mellitus have a greater morbidity and mortality from cardiovascular disease than nondiabetic patients. Diabetes is also a strong independent risk factor for the development of atherosclerosis and predisposes to the development of other known risk factors, such as hyperlipidemia and hypertension.

However, from the clinical standpoint, further studies should be performed to prospectively evaluate the frequency and duration of silent ischemic events in a larger number of well-characterized diabetic patients compared with well-matched nondiabetic patients. It will also be of great interest for clinicians to determine whether the presence of residual silent ischemia documented during daily life constitutes an independent predictor of cardiac death in diabetic patients.

Selected Abbreviations and Acronyms

ACIP =Asymptomatic Cardiac Ischemia Pilot

AECG=ambulatory ECG

BARI =Bypass Angioplasty Revascularization Investigation

CABG=coronary artery bypass graft surgery

ETT =exercise treadmill testing

PTCA=percutaneous transluminal coronary angioplasty

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