EDITORIAL COMMENT
Silent Ischemia Predicts Poor Outcome in High-Risk Healthy Men*
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Myocardial ischemia is well established as a reliable predictor of physiologically significant coronary artery disease (CAD) (1,2). During the past two decades, a large number of epidemiologic studies and prospective observational data have demonstrated that the presence of myocardial ischemia is associated with adverse outcomes in asymptomatic individuals as well as those with established CAD (3–22). The results of these reports emphasizing the prognostic significance of myocardial ischemia in asymptomatic individuals have led the American Heart Association and the American College of Sports Medicine to recommend that apparently healthy men ages ≥45 years and women ≥55 years (even those without known cardiovascular risk factors) should undergo a maximal exercise treadmill test before engaging in a vigorous exercise program (23).

However, the issue of routine screening of apparently healthy individuals for myocardial ischemia continues to be a controversial issue and a topic of constant debate. This issue is further compounded by the fact that, frequently, myocardial ischemia detected by ST-segment depression during stress testing in healthy individuals is not associated with chest pain. Because of the absence of symptoms, it has been suggested that the ST-segment changes without associated chest pain during stress testing in asymptomatic subjects do not necessarily reflect ischemic changes and could be a false-positive finding. Such confusion and questions have arisen largely because stress testing has been occasionally used inappropriately in individuals with a low pretest likelihood of CAD. However, when used in evaluating appropriate individuals (those at high risk of developing CAD), exercise-induced ST-segment depression can identify the subgroup with increased risk of future coronary events and cardiac death.

The study by Laukkanen et al. (24) in this issue of the Journal emphasizes this point by showing that exercise-induced silent ischemia (SI), which was predominantly silent, was associated with adverse outcome largely in the apparently healthy individuals who were at high risk of developing CAD owing to the presence of one of the three conventional coronary risk factors (24). These findings reported by Laukkanen et al. (24) raise several important questions: 1) Should all healthy middle-aged individuals with coronary risk factors undergo exercise testing to identify the future risk of cardiac events? If so, which ones are likely to benefit the most from such testing? 2) Can these results be generalized to individuals with other emerging and newer coronary risk factors? 3) Perhaps the most difficult and clinically relevant question would be: What should be done in those with an abnormal test? Should the individuals with exercise-induced ischemia be subjected to further testing, including coronary angiography? And if further testing is to be performed, how would it alter the management of such asymptomatic individuals? These are all clinically relevant and important questions that must be addressed.

THE PRESENT STUDY
The report by Laukkanen et al. (24) describes the importance of exercise-induced silent myocardial ischemia in a large cohort of middle-aged Finnish men with no prior coronary heart disease (CHD) who participated in the Kupio Ischemia Heart Disease Risk Factor Study. Of the 1,769 men who had complete interpretable electrocardiographic (ECG) data obtained during a maximal symptom-limited exercise test on the bicycle ergometer, 189 (10.7%) had SI during exercise and 54 (3.1%) had ischemia during the postexercise recovery period. The comparison of baseline characteristics demonstrated that subjects with SI had higher serum cholesterol, higher systolic blood pressure, higher maximal heart rate and lower maximal oxygen uptake (24).

The main results of the study (24) demonstrated that SI during exercise predicted higher risk of acute coronary events and CHD death predominantly in those subjects with one of the three major coronary risk factors, which include smoking, hypercholesterolemia and hypertension. Although several previous studies have demonstrated similar prognostic data in association with exercise-induced myocardial ischemia, the Laukkanen et al. (24) study has several unique features that deserve attention. First, it is important to note that, unlike the previous reports on this subject, patients who developed chest pain during the baseline exercise test were excluded from the present study, making this perhaps the first and best-published report regarding the prognostic importance of SI during exercise testing in apparently healthy individuals. Although the absolute risk of coronary events and cardiac death during the follow-up was low in the present study, it is important to note that even after adjustment for conventional risk factors, men with SI during exercise had significantly increased relative

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risk of acute coronary events and CHD death (24). Another interesting finding in the study was the fact that even SI detected during the postexercise recovery phase was associated with adverse clinical outcome, emphasizing the importance of close ECG monitoring in the recovery phase.

Despite all the interesting findings reported by Laukkanen et al. in the present study (24), several critical questions remain. First, the investigators have not provided any information regarding the importance of multiple risk factors in the individual with SI. It is generally well accepted that the presence of two or more major risk factors, such as hypertension, hypercholesterolemia, diabetes and smoking, carries not just an additive but a multiplicative risk of future cardiac events. Because many individuals in clinical practice present with multiple risk factors, it would have been interesting to learn from the present study if patients with multiple risk factors had a higher incidence of SI and subsequent cardiac events. Although the investigators have only emphasized the interaction of SI with smoking, hypercholesterolemia and hypertension in their study, the question remains about the prognostic significance of SI in individuals with low high-density lipoprotein (HDL) cholesterol, which is reported as a strong predictor of acute coronary events in the present study. This is particularly important because isolated low HDL cholesterol is present in a significant proportion of men with CHD, and the overall prevalence of this risk factor is rising with the increasing incidence of type II diabetes in the world.

It is also interesting to note that, in the present study, high body-mass index (BMI) was also a strong predictor of CHD death, raising the possibility that many of these men with high BMI might have had dysmetabolic profile and insulin-resistant state, shown to be associated with increased cardiovascular risk (25). Although it is understood that the present study was begun in 1984 and, as such, it could not have incorporated the evaluation of the newer emerging risk factors such as the inflammatory markers like C-reactive protein (CRP), the question remains whether the presence of SI would have similar or different association with CRP for future risk of cardiac events. Finally, it is important to note that the data presented in this study are largely limited to middle-aged men and might not necessarily be applicable to other subjects such as the elderly and women. Despite these limitations, the present study by Laukkanen et al. (24) does provide strong evidence in support of SI as an important marker of adverse outcome in apparently healthy middle-aged men with one or more conventional risk factors.

PREVIOUS STUDIES

Several previous studies have evaluated the prognostic significance of myocardial ischemia during exercise testing in asymptomatic individuals (4–19). Most of these studies have consistently demonstrated that myocardial ischemia diagnosed by exercise-induced ST-segment depression is associated with subsequent poor outcome (4–19). The Seattle Heart Watch study was probably one of the earliest and best investigations in this field (4,5). In this prospective community study of >4,000 healthy subjects initiated in 1971, Bruce et al. (4,5) showed that the annualized risk of cardiac death increased fivefold in individuals with any conventional risk factors and the presence of ≥2 exercise test predictors that included ≥1-mm ST-segment depression, chest pain during exercise, limited exercise capacity and maximum achieved heart rate ≤90% of predicted.

In another study by McHenry et al. (8) of 916 apparently healthy middle-aged (27 to 35 years) men, abnormal exercise test findings were associated with a nearly eightfold increase in the risk of cardiac events. The interaction of conventional risk factors with exercise test findings was also studied in the Multiple Risk Factor Interventional Trial (MRFIT), the Lipid Research Clinic (LRC) mortality follow-up study and the LRC Coronary Primary Prevention Trial (LRC–CPPT) (10–12). In the MRFIT study, 12,422 healthy middle-aged men participated in exercise treadmill test evaluation (10). During the seven-year follow-up, an almost fourfold increase occurred in CHD mortality (10). Similar data have been reported from the two LRC studies (11,12). In the LRC mortality follow-up study, the abnormal exercise test response was associated with a nearly 10-fold increase in the risk of cumulative mortality in men with increased cholesterol during the 8-year follow-up (11). In the LRC–CPPT, there was nearly a fivefold increase in mortality in those with an ischemic response during the treadmill exercise test (12).

In an attempt to evaluate the independent prognostic value of ST-segment changes, Giagnoni et al. (9) performed bicycle exercise tests in 10,723 subjects free of heart disease and hypertension. Of these, 135 subjects had ≥1-mm ST-segment depression. During the 6-year median follow-up period, when compared to controls, the individuals with ischemic ST-segment changes during exercise had a fivefold greater risk of coronary events. In a recent study, Katzel et al. (19) had specifically evaluated the role of exercise-induced SI in 170 healthy, sedentary middle-aged and older men. Of these, 37 men (22%) had exercise-induced SI during treadmill testing. During the 7-year follow-up, 17 of 37 men (46%) with SI had a significant cardiac event compared to only 14 of 133 men (11%) without SI (19).

Although these previous studies had shown that abnormal exercise test findings in apparently healthy subjects were associated with adverse outcome, it was not established whether the poor outcome was directly associated with the presence of myocardial ischemia or other abnormalities such as poor functional capacity (4–16). Furthermore, these studies did not specifically evaluate the role of SI because, unlike the present study by Laukkanen et al. (24) patients with chest pain were included. Also, none of these studies provided information regarding the significance of ST changes during the recovery phase. Additionally, the cardiac
events often included soft end points such as the development of anginal symptoms during the follow-up period. Based on the results of these previous studies, as well as the present study by Laukkanen et al. (24), it is quite evident that exercise-induced myocardial ischemia in healthy subjects is associated with subsequent adverse outcome.

**SILENT OR SYMPTOMATIC ISCHEMIA: DOES IT REALLY MATTER?**

Although in the past considerable emphasis was placed on anginal symptoms, the data from a number of studies have now shown that the absence of pain should not be considered as a sign of insignificant disease or benign prognosis (20–22). Several studies have evaluated the relative prognostic value of silent versus painful ischemia (20–22,26). Results of these studies have shown that the presence or absence of anginal pain during exercise testing does not alter the subsequent risk of death that is primarily related to the presence of myocardial ischemia (21,22,26). In a recent study, the functional significance of silent versus symptomatic ischemia during exercise testing was examined by comparing the perfusion abnormalities on thallium-201 single-photon emission computed tomography (27). The findings of the study revealed that, in the population with a high likelihood of CAD, chest pain tends to lose its apparent value as a clinical test parameter, and there was little difference in the magnitude of perfusion abnormalities between those with silent and symptomatic ischemia (27). Previous studies in victims of sudden cardiac death and survivors of cardiac arrest have also shown that there is no significant difference in the extent of CAD in those with a prior history of angina versus those with no symptoms (28,29). Based on these data, it is becoming increasingly apparent that it is the presence of myocardial ischemia (regardless of the associated symptoms) that determines the subsequent prognosis (20).

**MECHANISMS RESPONSIBLE FOR ADVERSE IMPACT OF SI IN ASYMPTOMATIC SUBJECTS**

The precise mechanism by which SI leads to adverse outcomes in otherwise healthy subjects is not known. There are several potential explanations. Clearly, it is well accepted that the presence of ischemia during exercise testing identifies individuals with significant CAD. Although ischemia is generally produced by a flow-limiting stenotic lesion, the process of atherosclerosis is generalized; therefore, it is quite conceivable there are multiple atherosclerotic plaques in various stages of progression. Indeed, some of these plaques might have a large lipid core with an abundance of inflammatory cells, which makes the plaques susceptible to rupture and thrombosis, thereby increasing the risk of acute coronary events. The other possibility is that SI can lead to life-threatening ventricular arrhythmias, especially in individuals who may have arrhythmic substrate such as hypertensive patients with left ventricular hypertrophy or those with left ventricular dysfunction.

Finally, repeated episodes of SI can have important pathophysiologic consequences such as depletion of energy stores, cell death, subendocardial necrosis and areas of patchy myocardial fibrosis (30,31). Over time these processes can lead to progressive left ventricular dysfunction. Future studies should evaluate the specific pathophysiologic consequences of SI in humans to understand better the mechanism(s) responsible for adverse prognosis.

**CLINICAL IMPLICATIONS AND FUTURE DIRECTION**

The findings described in the study by Laukkanen et al. (24) raise several important clinical questions such as who should be tested, what should be done for those with abnormal findings and ways to improve the clinical outcome in the high-risk subset. Clearly, it is neither feasible nor advisable to screen every middle-aged man for myocardial ischemia. As previously emphasized and based on the results of the present study, it would seem prudent to recommend the screening exercise stress test only for high-risk healthy subjects such as those with 2 coronary risk factors. Such a strategy would not only avoid unnecessary testing in low-risk individuals but also reduce the risk of false-positive findings. The next question is obviously what to do for those with evidence of SI detected during exercise testing. It is generally recommended that the presence of myocardial ischemia detected by ECG changes during exercise testing should be confirmed by an imaging study, such as myocardial perfusion scintigraphy or a stress echocardiography study, depending on the local expertise. Previous reports have shown that such an imaging study is not only helpful in confirming the presence of myocardial ischemia and diagnosis of CAD but also provides additional prognostic information. In general, coronary angiography should be reserved for those with findings suggestive of high-risk CAD on the imaging study. A good deal of caution and restraint is, however, required to avoid unnecessary procedures that might not only be expensive and inappropriate but also have the potential for harm.

The final obvious question concerns what can be done to alter the adverse prognosis associated with SI in apparently healthy subjects. The most important action in this regard would be directed toward aggressive risk-factor modification, including smoking cessation measures, control of blood pressure in hypertensive subjects and lipid-lowering therapy in those with hypercholesterolemia. Although, in general, the benefits of such risk factor modification strategies are well established, little information is available regarding the specific effects of such therapies in high-risk healthy subjects with SI. Future studies should evaluate the impact of various therapeutic strategies on the clinical outcome in asymptomatic patients with SI.
REFERENCES


