T
erapeutic decisions in patients with coronary artery disease are frequently based on the severity of chest pain despite the lack of correlation between severity of symptoms and prognosis. There are many circumstances in which objective evidence for myocardial ischemia is present but symptoms are absent. Episodes of so-called “silent myocardial ischemia” are very frequent in some patients with other manifestations of coronary heart disease; for example, patients with angina have no symptoms in 70 to 80 percent of all recorded ischemic episodes. While the overall incidence, spontaneous variability, and relationship of symptomatic to asymptomatic ischemia are largely unknown, this condition is being increasingly recognized. The purpose of this review is to discuss the clinical aspects of silent ischemia and the rationale for treatment (Fig 1). This information can be used to develop a strategy to help the clinician deal with this problem.

Natural History of Silent Ischemia

Our understanding of the natural history of silent ischemic episodes is poorly understood. As silent ischemia is asymptomatic, the major issue is how silent ischemia relates to prognosis and long-term outcome. The natural history of ischemic heart disease is highly variable in terms of frequency of symptoms, severity, and event rates; and possibly the presence, frequency, and magnitude of silent ischemic episodes accounts for this. It is probable that the natural history is related to severity of coronary narrowings, alterations in myocardial oxygen demands, the extent of left ventricular dysfunction, and the presence of other medical problems.

Large numbers of patients with documented silent myocardial ischemia have not been followed for long periods of time to allow for precise description of the natural history of this problem. In completely asymptomatic subjects, the time sequence for evolution of silent ischemia into symptomatic ischemia is not known. Data such as those from McHenry et al derived from exercise testing suggest that silent ischemia will frequently evolve into symptomatic ischemia, perhaps indicating that development of symptoms represents a later phase of the disease process. Whether all patients go through this asymptomatic phase is unknown. The group of patients in the asymptomatic stage of development of their ischemic syndrome perhaps have a different prognosis than the very large group of patients with symptoms who also have silent ischemia at other times. What seems clear is that ischemia, whether silent or symptomatic, at whatever stage, renders individuals at much higher risk for cardiac events than the population at large. Anything that can improve this risk has potential benefit as the events that occur, myocardial infarction and death, are clearly important enough to attempt to modify their occurrence. Since silent ischemia appears more common than symptomatic ischemia, any treatment directed at eliminating ischemia to reduce risk must be directed at both silent and symptomatic ischemia. Various treatments have been used but primarily in patients with symptoms also. No data on treatment are available in a large number of patients with no overt manifestations of ischemic heart disease and silent ischemic episodes. To take the opposite point of view, i.e., that silent ischemia can but should not be treated, requires proof of the hypothesis that silent ischemia is a “benign form” of ischemia. There are no data to support this point of view.

Detection and Follow-Up

Exercise testing has been used by many clinicians to monitor effects of various forms of anti-ischemia treatment, with the idea that transient ischemia is caused generally by increases in myocardial oxygen demand. The exercise test is an excellent tool for assessing risk in large groups of patients who present with symptoms. Indeed, many types of anti-anginal therapy have

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been assessed using this method. Whether end points currently used to gauge exercise response are valid or appropriate for patients with silent ischemia during daily life is unknown. However, beside allowing only a limited monitoring period, exercise testing has other limitations in assessing patients with symptomatic coronary artery disease, let alone silent ischemic events. The artificial nature of the exercise laboratory does not allow for accurate assessment under all physiologic circumstances (ie, it may alter autonomic tone, etc) and may not be relevant to the mechanism responsible for angina occurring in daily life.

Myocardial ischemia may be caused by events other than those that only reflect an increase in determinants of myocardial oxygen demand, thus limiting any type of monitoring that responds only to those parameters. Different patients may respond differently to different types of stress, such as cold stimulation and mental arithmetic. Thus, various patterns of ischemia occurring during life are probably not accurately reflected only by exercise testing.

Because of the limitations of exercise testing, the ambulatory electrocardiogram has recently been used for assessing silent ischemic events. Advantages of this technique are multiple and include (1) a longer monitoring period, (2) observation during both normal and abnormal physiologic stimuli (ie, circadian rhythm, cigarette smoking, etc), allowing maximal effect on the coronary vasculature, (3) removal of stress and subsequent changes in autonomic tone of the exercise laboratory, (4) measurement of frequency, duration, magnitude, and morphology of ST-segment shifts, (5) identification of natural triggering mechanisms and events in any given patient, and (6) provision of a simple tool for follow-up. A substantial body of information is available regarding the relative sensitivity and specificity of ambulatory electrocardiographic monitoring for silent ischemic events, as well as its application to patients with ischemia.3,5

Other methods for detecting transient ischemic episodes exist but have limited potential for following ambulatory patients. Various investigators have used radionuclide techniques, including radionuclide angiography, thallium perfusion scanning, the nuclear probe, and positron emission tomography, with reasonable sensitivity and specificity; however, because of
the intermittent nature of silent ischemia and the variability of stressors known to produce it, these techniques offer little capability for quantifying episodes and are thus ill-designed for follow-up. In addition, the considerable expense and exposure to radiation limit their frequent use.

**TREATMENT**

Despite the fact that the natural history of silent ischemia still remains to be adequately defined and methods for detection and follow-up are not optimal, various insights can be gained through review of attempts to treat patients with silent ischemia as part of their problem. The literature that is available is all on studies of patients over a relatively short time using various methods for detection and follow-up and a variety of medications and interventions primarily in patients with other manifestations of ischemic heart disease.4

**Modification of Risk Factors**

There is evidence from the Multiple Risk Factor Intervention Trial6 that modification of risk factors alone is associated with a decrease in death rate from coronary artery disease in patients with silent ischemia. In this study, there were over 12,000 asymptomatic middle-aged men at high risk for coronary heart disease assigned to either usual community care (UC) or special intervention (SI) for vigorous modification of risk factors (eg, hypertension, cigarette smoking, and hypercholesterolemia). Of these subjects, 12.7 percent of the SI group and 12.2 percent of the UC group had ST-segment depression by exercise test, suggesting myocardial ischemia. In the SI group with a positive exercise test for silent ischemia, the seven-year death rate from coronary heart disease was 2.2/1,000 men; however, in the UC group with a positive exercise test, the seven-year death rate from coronary heart disease was 51.8/1,000 men, a 57 percent difference (p = 0.007). These results strongly suggest that modification of risk factors alone can have a major benefit on prognosis in patients with silent ischemia.

**Pharmacologic Agents**

All studies using a wide variety of pharmacologic agents have been reported in patients with symptomatic and asymptomatic ischemia. We have reviewed these studies in detail elsewhere.4

**Conventional Anti-Anginal Agents**

Various studies have been performed using β-adrenergic blocking agents to treat silent ischemic episodes. Atenolol, propranolol, practolol, and the combined α-adrenergic and β-adrenergic blocking agent, labetalol, all seem to be effective. There is some evidence that propranolol may not be beneficial in patients with variant angina, but this is not true in all patients tested. Variant angina with transient ST-segment elevation represents a subset of patients with ischemic heart disease that perhaps has a different mechanism for ischemia. Exaggerated vasomotion probably plays a bigger part in variant ischemic episodes than in other patients with ischemia.

Obviously, there are differences between β-adrenergic blockers in terms of selectivity, intrinsic sympathomimetic activity, and concomitant α-adrenergic blockade. There are no studies which compare drugs with these different properties to allow an accurate assessment of which β-adrenergic blocker is best in any individual patient. Except for pindolol, there are data to suggest that many β-adrenergic blocking agents are effective. Whether this relates to the intrinsic sympathomimetic activity present in pindolol is unknown.

There are data to suggest that nifedipine,6 verapamil,7 and nicardipine8 are also effective in relieving episodes of silent ischemia in patients with either effort-dependent or rest angina. As with β-adrenergic blockers, it is not known which calcium antagonist is most effective. As these drugs are so dissimilar in chemical structure, clinical activity, pharmacokinetics, and mode of action, data on comparisons should be very helpful when available.

Schang and Pepine8 showed nitroglycerin administered hourly to be effective in reducing episodes of asymptomatic ischemia in patients with effort-induced angina. It has also been shown that silent as well as symptomatic ischemia in unstable patients can be controlled with intravenous administration of dinitrate for brief periods in the cardiac care unit.

Shell8 recently suggested that patients who remained symptomatic receiving β-adrenergic blockers and sublingual nitroglycerin had reduction of both symptomatic and asymptomatic ischemic episodes with addition of transdermal nitroglycerin. In addition, the duration of these ischemic episodes decreased from 110 to 21 min/24 hr.

Combinations of nifedipine and propranolol have been shown to decrease silent ischemic episodes in uncontrolled and controlled studies. This suggests that the mechanism responsible for silent ischemic episodes is complex and related to factors that are favorably affected by both calcium and β-adrenergic blockade.

**Other Pharmacologic Agents**

Medication other than conventional anti-anginal agents has potential use for treatment of silent ischemia, although scant data are available. On theoretic grounds, aspirin and other thromboxane-inhibiting agents, as well as prostacyclin, may be useful if transient local coronary arterial platelet aggregation...
occurs or if platelet-mediated changes in vascular reactivity play a role in the pathogenesis of this problem.

There is preliminary evidence that aspirin, despite its potential role in reducing the frequency of myocardial infarction and sudden death in unstable angina and in patients after myocardial infarction, may not be helpful in the prevention of silent ischemia in patients with coronary spasm. Chierchia et al. also found prostacyclin ineffective for ischemic episodes in patients with variant angina.

Fox et al. studied effects of ticlopidine in ten patients with coronary artery disease and asymptomatic and symptomatic ischemic episodes. Ticlopidine is an inhibitor of platelet aggregation which is apparently unrelated to prostaglandin metabolism. These investigators found an improvement during therapy with ticlopidine (7.5 vs 21 episodes per four days for ticlopidine vs placebo), which was most pronounced in those episodes without an increase in heart rate. These results suggest some role for platelet aggregation in the pathogenesis of ischemic episodes, but exactly what this role is remains unclear.

**CORONARY REvascularization**

There has been considerable controversy regarding coronary bypass surgery, and while it is clear that this procedure improves symptoms and increases life expectancy in certain subsets of patients, little has been written and even less agreed upon about coronary surgery in patients without symptoms. No study exists that evaluates a large number of asymptomatic patients with definite ischemia who undergo operation in a prospective randomized fashion strictly prophylactically to improve life expectancy or prevent events. Available literature provides a heterogeneous group of patients with few or no symptoms related to coronary artery disease who underwent surgery for various reasons. In addition, detection and measurement of silent ischemia has not had wide acceptance in the past, which also limits available data. Nevertheless, available data lend insight into the issue of bypass surgery in patients with coronary artery disease and silent ischemia.

Grondin et al. reported an uncontrolled retrospective experience in 55 patients who had severe coronary artery disease and underwent coronary artery bypass surgery, 16 of whom never had angina, with minimal symptoms in the others. In their entire group followed for a mean of 69.2 months, there were four late deaths and seven late myocardial infarctions, in addition to two perioperative myocardial infarctions. Of the 51 late survivors, only 60.8 percent (31) were free of angina, and it is not clear what happened to those with silent disease. There were no data in this group regarding the presence of silent ischemia, but there is little in this study to support prophylactic coronary bypass.

Norris et al. studied 205 men with recent recurrent myocardial infarction, 100 of whom had either minimal symptoms or were asymptomatic. Of these 100 patients, 50 were randomly assigned to coronary artery bypass surgery and 50 to nonsurgical therapy. At a mean follow-up time of 4.5 years, six patients (12 percent) assigned to surgery died, five from a cardiac cause. Likewise, in the nonsurgical group, five patients (10 percent) died, all from a cardiac cause. Despite an inherent bias in selection, this study does not provide support for coronary artery bypass grafting in patients with minimal or no symptoms despite severe coronary disease.

Hammermeister et al., in discussing the Seattle Heart Watch data for survival in patients with coronary artery disease, reported the effect of surgical treatment on survival in patients with minimal or no symptoms. There were 227 patients (65 NYHA class I) treated medically and 392 (49 NYHA class I) treated surgically in a nonrandom fashion. Over the course of a five-year follow-up period, there seemed to be a tendency (p = 0.069) toward better survival with surgery, but this was largely in patients with three-vessel disease. In addition, in patients with three-vessel disease and an ejection fraction between 31 and 50 percent, there was improvement with surgical therapy, although the numbers are small. Again, no attempt was made to measure ischemia not related to angina, but it can be assumed based on other studies, that this was present.

The most extensive data available on effects of coronary artery bypass surgery on patients with either minimal symptoms or no symptoms after a myocardial infarction come from the CASS study. In that study, it was reported that coronary artery bypass surgery in the group as a whole does not prolong life or prevent myocardial infarction. A benefit only applies to those with three-vessel disease and depression of left ventricular function. Our ability to use these data to extrapolate to patients with silent ischemia is limited because parameters of silent ischemia were neither measured nor followed, and purely asymptomatic patients were not separated. Furthermore, all those with moderate or severe symptoms were excluded. In addition, no data exist for coronary angioplasty in silent ischemia. It seems appropriate to conclude that the precise role of procedures for revascularization in the management of patients with silent myocardial ischemia remains to be defined.

**Recommendations for Therapy**

Our rationale and recommendations for treatment of silent myocardial ischemia assume an accurate diagnosis of coronary artery disease and objective evidence for myocardial ischemia. An algorithm for
diagnosis and treatment is presented in Figure 1. Currently, we do not know if patients with silent ischemia need long-term therapy, but risks of withholding treatment in this type of patient are likewise unknown. It is possible that silent ischemic episodes contribute to hundreds of thousands of sudden cardiac deaths and myocardial infarctions each year. Development of ischemic cardiomyopathy without definite infarction could possibly relate to silent ischemia. All available studies indicate that silent episodes are at least as common, if not more common, than symptomatic episodes and are present in most patients with ischemic heart disease studied. On this basis and the variable largely unknown natural history, it is our opinion that silent ischemia should be treated as aggressively as symptomatic ischemia until additional data are available.

The most rational way to treat this type of patient is to begin with a baseline of the frequency and magnitude of ischemia with an ambulatory ECG. Forty-eight to 72 hours under normal daily circumstances are probably adequate, but how long a recording period is necessary or how often recordings should be repeated is not known. Once this baseline is established, attempts should be made to modify risk factors such as high blood pressure, high levels of cholesterol, or smoking. Obvious triggering events (such as mental stress, cold, exposure to other specific activity, etc.), as identified from the electrocardiographic record, should be eliminated. The next step is adding medical therapy, beginning with nitrates and either a calcium antagonist or β-adrenergic blocker. It is not known what specific therapy is ideal, but it is reasonable to use the same logic as with symptomatic ischemia where combination therapy seems most beneficial. This is probably even more true in patients with silent ischemia because of differing provoking mechanisms for episodes. More aggressive treatment with angioplasty or coronary bypass surgery remains controversial, even in symptomatic patients, and has not been clarified in the treatment of silent ischemia; however, treatment should be aimed at eliminating all ischemic episodes, so if medical therapy is not successful, revascularization options should probably be considered.

Whether these recommendations are proven to be beneficial and appropriate for the population with ischemic heart disease as a whole remains to be determined. We recognize that these recommendations are aggressive and based on lack of direct data from prospective trials. If silent ischemia either spontaneously resolved or terminated in angina, little would be gained from detection and treatment of silent ischemia. Ischemia is broader in scope than to be simply equated with angina. Every ischemic episode has several possible outcomes; it can remain silent and terminate spontaneously or result in either a silent infarction or sudden death. On the other hand, the silent episode can evolve to a painful phase where it may also terminate spontaneously or with myocardial infarction or death. Presumably, the prognosis of every patient with silent ischemic episodes is related to the magnitude of ischemia, the size of the region at risk and residual ventricular function. Given that ischemic heart disease is naturally progressive, it seems appropriate to attempt to modify or prevent most, if not all ischemic episodes that are detected. With that in mind, as a clinician, one must choose which therapy is appropriate at any point in time in patients with coronary artery disease.

CONCLUSIONS

The role of asymptomatic ischemia in patients with coronary heart disease is just now beginning to be recognized and understood. Before we can adequately evaluate the effect of various types of treatment on the prognosis in these patients, an optimal tool for detection and follow-up needs to be developed and used. At present, the ambulatory ECG seems to be the best tool for achieving this, but refinements are clearly needed. Effects of various types of therapy on prognosis need to be assessed using large populations of patients in a prospective fashion using an objective method. Optimal therapy will evolve as our knowledge of this problem increases. Until then, we believe that it is appropriate to treat silent ischemia using principles employed to manage painful ischemia.

REFERENCES

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