Can We Really Justify the Treatment of Silent Ischemia in 1992? No!

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Summary. Since the advent of ambulatory ST-segment monitoring, it has been established that silent ischemia is common in patients with various coronary artery disease syndromes, and such silent episodes represent up to 80% of all ischemic episodes. It appears to be associated with an adverse prognosis when compared with similarly characterized patients without silent ischemia during daily life. Silent ischemia does not, however, bother the patients, by virtue of the fact that it is silent, and therefore treatment of such ischemia must be justified by an improved outlook for the patient, rather than symptom relief. There is no direct evidence to date that silent ischemia is associated with acute myocardial infarction or sudden cardiac death in a cause-and-effect relationship, or that reduction or eradication of silent ischemia will lead to an improved prognosis for the patient; indeed, we have been unable to demonstrate any significant improvement in outlook when using the various antianginal/antiischemic agents at our disposal. Until we can demonstrate a benefit to the patient by detecting and treating silent ischemia, we should not waste large resources attempting to eradicate something whose significance we do not understand.

In medical media terms, silent ischemia is a relatively new disease, although it has been apparent for many decades that coronary events, whether ischemia, infarction, or sudden cardiac death, could occur in the absence of symptoms. The increasing availability of ambulatory ST-segment monitoring devices has made the study of ischemic activity during the daily activities of both asymptomatic individuals and those with known coronary disease a relatively easy exercise, and it is now well recognized that in those with coronary disease there are frequent transient alterations in the ST segment during daily life, the majority of such changes occurring in the absence of symptoms. These observations have led, quite naturally, to the assumption that such, predominantly silent, ischemic episodes may lead to the end points of coronary disease, both acute myocardial infarction and sudden cardiac death, and the questions have been raised as to a) whether we should attempt to actively identify silent ischemia in coronary populations and b) whether we should attempt to treat all ischemic episodes, and not just try to improve patient symptomatology.

In this paper we have discussed the frequency of silent ischemia in coronary populations; have highlighted the evidence to suggest that we might actively attempt to identify and treat those with silent ischemia, both in coronary and in asymptomatic populations; and have discussed why we should not attempt to treat silent ischemia at this time.

How Frequent is Silent Ischemia?

Many studies have been published in recent years to assess the frequency and characteristics of silent myocardial ischemia, and over the past few years a general consensus as to its prevalence has been reached, particularly in those subgroups with coronary artery disease. In the late 1970s and early 1980s, when ambulatory ST-segment monitoring was becoming available for research purposes, a few units published work on the frequency of silent ischemia in patients with stable coronary artery disease [1-4]. In small studies of highly selected patients (positive exercise test at relatively low workloads) [3,4], the authors reported that patients with stable coronary artery disease had frequent episodes of silent ischemia during their daily lives, and extrapolation of the findings of these studies led to the conclusion that up to 80% of all angina patients had frequent daily episodes of silent ischemia [5]. The popular press was soon to refer to the "phenomenon" as the silent killer. Many more recent studies have included patients who were not selected for study on the basis of prior documentation of ischemia, and in these it appears that approximately 40-50% of patients with coronary artery disease and stable angina who are not receiving routine antianginal therapy at the time of study [6] have evidence of silent ischemia during their daily lives. In those studies that looked at the frequency of silent ischemia in patients with stable angina who were receiving standard anti-
anginal therapy at the time of study (including those studied while awaiting elective coronary artery bypass surgery because of restrictive symptoms of angina), the figure of 30–40% who have transient episodes of silent ischemia seems representative [7–9]. In those studies where the prognostic significance of silent myocardial ischemia in patients with stable angina was being assessed, and where patients chosen for study had exercise tests positive at low workloads [10,11], 53% of those studied off therapy [10] had evidence of silent ischemia (despite a mean time to ischemia of 3.4 minutes on exercise testing), and 43% of those studied on therapy [11] had evidence of silent ischemia (mean time to ischemia of 3.3 minutes on exercise testing).

In the setting of the postmyocardial infarction situation, reports suggest that 30–45% of patients have silent ischemia on ambulatory ST-segment monitoring, whether that monitoring is performed in the early predischARGE state [12,13] or late following such events [14]. The many studies published that have looked at silent ischemia in the setting of unstable angina have reported a variable frequency of silent ischemia of 10–50%, depending on whether patients were selected for inclusion in such studies on the basis of having an abnormal resting electrocardiogram at presentation or not [15–18].

**Evidence to Suggest that We Should Attempt to Identify and Treat Silent Ischemia**

Most of the studies that have looked at the prognostic implications of silent myocardial ischemia have been published in the past 4 years, and almost all have studied relatively small numbers of stable angina, postinfarction, or survived sudden death patients. Assey et al. [19] reported that patients with exercise-induced silent myocardial ischemia were more likely to have a subsequent myocardial infarction than those without, and Sharma and colleagues [20] noted that in survivors of out-of-hospital ventricular fibrillation, subsequent exercise testing revealed a significant number with silent ischemia. The implications of both these studies were that silent ischemic episodes might lead to these end points of coronary disease.

In two prognostic studies in stable angina patients [10,11], it has been reported that transient episodes of predominantly silent ischemia detected by ambulatory ST-segment monitoring are of independent prognostic significance, above and beyond that information gleaned from formal exercise testing. In a study by Rocco et al. [10], 86 patients with stable angina underwent ambulatory ST-segment monitoring and exercise testing off therapy and were then followed for a year while on standard medical therapy. During the 12-month follow-up period, 21 events were recorded (death, myocardial infarction, unstable angina, revascularization) in 15 patients, 20 of which occurred in the group of 49 patients with transient ischemia detected on ambulatory ST-segment monitoring (it is noteworthy that the mean time to ischemia on exercise testing in these 49 patients was less than 3 minutes). In a more recent publication by Deedwania and Carbajal [11], 107 patients with stable angina were followed for a mean of 23 months on standard medical therapy following ambulatory ST-segment monitoring and exercise testing. In the follow-up period there were 19 reported deaths (18% of study population), 16 of which were deemed cardiac in origin. Eleven of the 16 deaths occurred in those 45 patients with silent ischemia during ambulatory ST-segment monitoring (mean time to ischemia on exercise testing 3.3 minutes in those with evidence of ambulatory ischemia). These two studies suggested that silent ischemia on ambulatory ST-segment monitoring is of independent prognostic and considerable adverse significance in patients with stable coronary artery disease.

Three studies have assessed the prognostic significance of silent ischemia detected on ambulatory ST-segment monitoring in patients in the short [12,13] and long term [14] following acute myocardial infarction, and all have suggested that the presence of silent ischemia is of adverse prognostic significance. Gottlieb et al. [12] have demonstrated that in high-risk patients following myocardial infarction, ambulatory ST-segment monitoring prior to discharge from hospital helps in identifying a subgroup of patients at increased risk of death in the short term, and Ouyang and colleagues [13] have confirmed these findings in uncomplicated myocardial infarction patients. In a study of 224 patients (many of whom were completely asymptomatic) who underwent ambulatory ST-segment monitoring at a mean of 2 years following acute myocardial infarction, Tzivoni et al. [14] have reported that the presence of silent ischemia detected on ambulatory monitoring predicted an adverse outcome when compared to patients without such electrocardiographic changes. In this study there was, however, no significant difference between those groups with and without transient ischemia in terms of the hard end points of coronary disease, acute myocardial infarction, and cardiac death.

Many studies looking at the prognostic significance of transient, and predominantly silent, myocardial ischemia have been published in recent times to show that silent ischemia is of adverse prognostic significance in the setting of unstable angina [15–17,21]. In two studies by Gottlieb et al. [15,21], they reported that not only are silent ischemia episodes common in the setting of unstable angina, even after stabilization of symptoms [15], but there is a significant excess of acute myocardial infarction and death in those with silent ischemia when compared to those without it for up to 2 years following the index admission [21].

A few studies have been published to assess the prognostic significance of silent ischemia following