Silent Myocardial Ischemia: an Update

Mady Moriel MD and Dan Tzivoni MD

Department of Cardiology, Jesselson Heart Center, Shaare Zedek Medical Center, Jerusalem, Israel

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Silent myocardial ischemia has been known for several decades but attracted attention only in the mid-seventies. During the last 25 years, hundreds of studies have been published on this subject.

Silent myocardial ischemia is defined as ischemic electrocardiographic changes detected either during exercise testing or continuous ambulatory monitoring, without accompanying anginal symptoms. Stern and Tzivoni [1,2] established the correlation between SMI and significant coronary artery disease, and demonstrated that patients with silent ischemic episodes had similar extent of CAD as patients with symptomatic episodes. In the Reykjavik cohort study, which evaluated the prevalence of silent ST-changes in 9,139 men without overt CAD, silent ST-changes were strongly influenced by age, increasing from 2% at age 40 to 30% at age 80 [3]. Frequent episodes of SMI during daily activities lasting from a few minutes to several hours were observed in more than 40% of patients with stable angina [4–6]. Most ischemic episodes during daily activities are associated with a mild to moderate increase in heart rate [7,8]. Yet ischemic threshold during daily ischemic episodes (heart rate at onset of ischemia) is significantly lower than that during exercise testing. The difference of 15–30 beats/minute indicates that increased coronary tone, which is responsible for the reduced threshold, plays an important role in the induction of daily ischemia [6,9]. The heart rate at the onset of symptomatic and silent episodes is similar [2,10]. While exercise-induced ischemia occurs at a relatively fixed threshold, daily ischemia occurs at a variable threshold [11]. This variable threshold of ischemia in the same individual probably indicates a different degree of coronary tone. The hemodynamic changes related to silent and ischemic episodes are also similar: increase in pulmonary artery diastolic pressures, increase in left ventricular diastolic pressure, and a slight decrease in left ventricular ejection fraction [12].

Benhorin et al. [9] described circadian variations in the distribution of ischemic episodes with two daily peaks, one during the morning which was related to increase in heart rate and myocardial oxygen demand, and a second smaller peak during the late afternoon. They reported that the ischemic threshold was higher during the morning ischemic episodes and was lowest at night. This lower threshold at night was attributed to a dynamic increase in coronary tone.

The lack of symptoms during ischemia might be due to less severe ischemia compared to symptomatic ischemia, altered pain threshold, autonomic neuropathy as present in diabetic patients, and increased endorphin levels [13]. Mulcahy et al. [14] demonstrated, in their study of 148 stable CAD patients who were followed for 1–5 years, that recurrent silent ischemic episodes do not lead to deterioration in left ventricular systolic function.

Prognostic significance of SMI in patients with stable CAD

Oancholy and co-workers [15] examined the prognostic predictors in 521 patients with angiographic evidence of CAD who underwent exercise Tl-201 SPECT imaging. Patients' outcome was related to the extent of myocardium at risk, rather than the presence or absence of symptoms during exercise. Marcassa and colleagues [16] revealed that in 300 patients with established CAD who performed exercise myocardial perfusion study with Tc-Sestamibi, the ischemic burden is greater with painful than with silent myocardial infarction.

Several studies established the correlation between ischemic episodes during 24 hour ambulatory monitoring and future cardiac events. Quyyumi et al. [17] studied 116 low risk CAD patients utilizing 24 hour ambulatory monitoring, who were followed for 29±13 months. Although SMI was frequent during daily life (39% of the patients had transient episodes of ST depression during 48 hours of monitoring), its presence failed to predict future cardiac events. However, different results were found by Tzivoni and co-workers [18] who studied 56 patients with stable CAD and positive stress tests. Of these, 77% had ischemic episodes during daily activities, and patients with ischemic episodes had higher rates of death and infarction during the 2 year follow-up. In the Atenolol Silent Ischemia Study (ASIST) [19], 306 asymptomatic or minimally symptomatic patients with known daily life SMI were randomized to receive atenolol or placebo. At 4 weeks, the most powerful univariate and multivariate event-free survival was the

SMI = silent myocardial ischemia
CAD = coronary artery disease

absence of ischemia on ambulatory monitoring [19]. In the Asymptomatic Cardiac Ischemia Pilot Study (ACIP) [20], at one year follow-up about one-quarter of the patients with stable CAD who had ischemia on ambulatory ECG and exercise test had died, suffered myocardial infarction or required hospitalization for myocardial ischemia.

SMI in patients after acute coronary syndromes

Several studies have examined the prognostic significance of SMI after acute coronary syndromes. Gottlieb and team [21] studied the prognostic significance of myocardial ischemia as assessed by two-lead continuous electrocardiographic monitoring in 103 high risk post-infarction patients. Thirty of the patients had a median of five ischemic episodes per day, and median total duration of 157 minutes. Only one-third reported angina during hospitalization; 28 of the 30 had silent ischemic episodes. Thirty percent of the patients with ischemic episodes died at one year compared to 11% of the patients without episodes. Cox analysis revealed that ischemic changes during continuous ECG monitoring was a predictor of mortality in these patients [21].

Tzivoni et al. [22] studied 224 low risk post-infarction patients using Holter monitoring and exercise testing. Daily ischemic episodes occurred in 33% of the patients, of whom 51% had adverse cardiac events within 28 months of follow-up (cardiac death, myocardial infarction, unstable angina or revascularization), whereas the event rate was 12% in patients without daily ischemia. The event rate was similar among patients with silent or symptomatic ischemia. In the RISC study the prognostic value of SMI during symptom-limited pre-discharge exercise test was evaluated in 740 men with unstable angina or non-Q myocardial infarction [23]. Among the 51% of patients with ST-depression during exercise 18% suffered cardiac death or myocardial infarction at 1 year, compared to 9% of patients who did not have an ischemic response during exercise ($P<0.01$), without any prognostic value to the presence or absence of pain [23]. Gill et al. [24] performed 48 hour ambulatory ECG on 406 patients 5–7 days after acute myocardial infarction and detected ischemia in 23% of them. Mortality at one year was 11.6% in those with ambulatory ischemia compared to 3.9% in patients without ischemia; however, logistic regression analysis suggested that no test result provided prognostic information beyond the clinical variables. The presence of ambulatory ischemia was predictive for re-infarction and hospitalization for unstable angina [24].

In the Multicenter Myocardial Ischemia Study [25], 936 stable patients after myocardial infarction or unstable angina were prescribed rest, ambulatory and exercise ECG, and stress Tl-201 imaging 1–6 months after hospitalization, and were followed for a mean period of 23 months. The patients with SMI (n=378) demonstrated less severe and extensive reversible defects on stress Tl-201 imaging, longer exercise duration, longer time to ST-depression, and less frequent ST-segment depression during ambulatory monitoring. Patients with SMI had a significantly lower frequency of subsequent cardiac events, which included death, myocardial infarction or unstable angina [25]. Similar results were found by Koyanagi et al. [26] in their study of 229 patients who performed exercise Tl-201 SPECT 4.5 weeks after myocardial infarction. Exercise-induced myocardial ischemia occurred in 48% of patients, and 32% had SMI. Although the prevalence of multi-vessel coronary artery disease was similar between patients with silent and symptomatic ischemia, the size of reversible myocardial ischemia was larger in patients with symptomatic compared to patients with SMI (21.3±3 vs. 13.2±1.9% of left ventricle, $P<0.05$). The incidence of reversible ischemia remote from the infarct area was higher in the symptomatic patients (30% vs. 17%, $P<0.01$).

A recent study by Bigi and colleagues [27] revealed that among 407 consecutive patients recovering from acute myocardial infarction, painful ischemia during exercise ECG identified a high risk group for adverse cardiac events (death, myocardial infarction, unstable angina or coronary revascularization), whereas dobutamine stress echocardiography was not predictive of outcome, either with painful or silent myocardial infarction. Recently Lotze et al. [28] studied 126 patients post-acute myocardial infarction who were treated with thrombolysis and early transluminal coronary angioplasty. All patients had 24 hour ambulatory ECG and were followed for 3 years; 10% of them had SMI. The subset of patients with both SMI and left ventricular ejection fraction <40% was at a higher risk for cardiac death [28].

SMI, ventricular arrhythmia and sudden death

Gomes et al. [29], who studied the role of SMI and the arrhythmic substrate in the genesis of sudden cardiac death, found that in 14 patients who had episodes of ventricular tachycardia or fibrillation while wearing 24 hour ECG monitoring, SMI preceded the arrhythmia only in 2 patients (14%). Parthenakis and colleagues [30] studied the incidence of ventricular arrhythmia during SMI in 45 patients with angiographically proven CAD who underwent 72 hours of ambulatory ECG. A total of 225 ischemic episodes were recorded of which 88% were silent and 7.1% of them were associated with ventricular arrhythmias. Stern et al. [31] demonstrated that 27% of ischemic episodes are related to increased ventricular ectopy. It seems that silent myocardial ischemia is related to ventricular arrhythmia only in a small percentage of cases, and it is possible that the duration of the ischemic episodes is related to ventricular arrhythmia [31]. Whitaker and Sheps [32] assessed the prevalence and type of ischemia in 24 survivors of cardiac arrest not associated with acute myocardial infarction. They found that 67% of these patients had exercise-induced myocardial ischemia, of whom only 6% were symptomatic. They

ECG = electrocardiography

concluded that survivors of cardiac arrest have a high prevalence of exercise-induced ischemia, mostly silent.

Pre-operative SMI

Fleisher et al. [33] studied the prognostic significance of pre-operative SMI in 67 patients undergoing vascular surgery and 79 patients undergoing non-vascular surgery. The presence of pre-operative SMI was a predictor of morbid cardiac events in both groups, whereas the absence of SMI predicted an excellent outcome in patients undergoing non-vascular surgery. However, it was less effective in predicting uneventful outcome in the vascular surgery patients.

SMI after percutaneous coronary intervention and coronary bypass surgery

Using Tl-201 scintigraphy in 490 consecutive patients 6 months after successful coronary angioplasty, Pfisterer and team [34] found that 28% had Tl-201 ischemia, of whom 60% were asymptomatic. Tl-201 ischemia was associated with significant stenosis in 97%, whereas 74% of these patients had negative exercise ECG. The degree of restenosis was similar in the patients with symptomatic or silent myocardial infarction. Silent and symptomatic ischemia predicted an increased risk for ischemic events, but not for death [34]. The prevalence and prognostic significance of SMI after bypass surgery was studied in 174 patients of the Coronary Artery Surgery Study (CASS) who performed exercise testing before and 6 months after the operation [35]. Although the frequency of symptomatic ischemia decreased significantly (52% vs. 6%, $P<0.001$), the prevalence of SMI did not change (30 vs. 29%). Survival at 12 years after surgery based on the results of the postoperative exercise test was significantly better for patients without ischemia (80%) than patients with SMI (68%) or symptomatic ischemia (45%) [35]. In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study [36], 262 CAD patients with stress-induced and daily life ischemia were randomized to receive early revascularization (170 patients) after coronary angiography (within 4 weeks), or delayed symptom-driven approach (92 patients). At 1 year follow-up the most important predictor for event-free outcome (death, myocardial infarction, revascularization) was attempted revascularization, whereas none of the clinical or other test results predicted outcome [36].

SMI in diabetic patients

Coronary artery disease is more frequent in diabetic patients and their prognosis is worse, hence early diagnosis of CAD is extremely important in this group of patients. SMI is known to be frequent in diabetic patients. To determine the prevalence of silent myocardial ischemia in diabetic patients, the Milan Study on Atherosclerosis and Diabetes (MiSAD) investigated 925 non-insulin-dependent diabetic patients unknown to suffer from CAD [37]. These patients performed exercise tests, and if abnormal, underwent Tl-201 scintigraphy. The prevalence of SMI as assessed by exercise ECG was 12.1%. Adopting the more strict criteria where both exercise ECG and Tl-201 were positive for ischemia, the prevalence of silent ischemia was 6.4% [37].

Treatment of SMI

Recurrent ischemia may have a deleterious effect on myocardial function and is related to cardiac events. Several studies investigated the effects of calcium-channel blockers, beta-blockers, and their combination on the daily episodes of myocardial ischemia. The Canadian Multicenter Diltiazem Study Group investigated the effect of sustained-release diltiazem 180 mg twice daily vs. placebo in 60 CAD patients [38]. Diltiazem significantly reduced the frequency and total duration of silent ischemic episodes [38]. Tzivoni et al. [39] compared the effect of mibefradil with amlodipine in suppressing exercise-induced and daily SMI in 309 patients. Both mibefradil and amlodipine reduced the number of ischemic episodes [39]. In the Atenolol Silent Ischemia Study, the effect of 100 mg atenolol vs. placebo on daily life SMI in 106 asymptomatic or minimally symptomatic CAD patients was investigated [19]. After 4 weeks, the number and duration of ischemic episodes were significantly lower in the treatment group and were associated with reduced risk for adverse outcome. In the Angina and Silent Ischemia Study (ASIS) [7], propranolol therapy significantly reduced baseline heart rate, the frequency and duration of heart rate increase compared with placebo, diltiazem or nifedipine. Propranolol reduced the proportion of heart rate-related ischemic episodes, whereas nifedipine was more effective in reducing the minority of episodes that were not associated with increased heart rate [7]. In the Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) [40], the effect of amlodipine, atenolol and their combination on ischemia during treadmill testing and 48 hours ambulatory monitoring was examined. Ischemia during treadmill testing was better suppressed by amlodipine, whereas daily ischemia was better suppressed by atenolol. The combination was more effective than either single drug in both settings [40]. Similar results were obtained by the ASIST study [19], which revealed that atenolol treatment reduced daily life ischemia and was associated with reduced risk for cardiac events. However, the results of the ACIP trial suggested that revascularization is preferred to medical therapy: the mortality rate of 192 patients randomized to revascularization was 1.1% at 2 years compared to 6.6% of the patients with angina-guided therapy and 4.4% of the 183 patients with ischemia-guided therapy ($P<0.02$) [20].

Conclusions

Silent myocardial ischemia is frequent in patients with stable and unstable CAD. Although there are conflicting reports regarding the prognostic implications of SMI, it seems that patients with SMI have a worse prognosis than patients free of ischemia. The SMI patients probably have more extensive and more active disease. The prognosis is determined by the

amount of myocardial ischemia and not by the mode of its presentation. In this group of patients, aggressive treatment of myocardial ischemia – silent or symptomatic – is related to improved prognosis.

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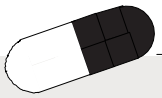
Correspondence: Dr. M. Moriel, Dept. of Cardiology, Jesselson Heart Center, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel. Phone: (972-2) 655-5974/5, Fax: (972-2) 655-5437, email: cardio@szmc.org.il

Give me but one firm spot on which to stand, and I will move the earth.

Archimedes, Greek mathematician (287–212 BC), on the action of a lever

Capsule



Origins of HIV

Molecular clock analyses are used to predict when lineages branch off (split) from a common ancestor in the evolutionary tree. These analyses use the age of known or previously estimated branching events to calculate the correlation between time and molecular divergence in particular genes. This correlation is then used to calculate the date of past evolutionary splits. Different models assume that the rate of change is constant through time and across lineages, or that it varies among lineages at branching events, or that it varies in any part of the evolutionary tree. By analyzing the molecular divergence of the env gene (encoding gp 160) and applying a model of constant change. Korber et al. calculated a best estimate for the date when the last common ancestor of the HIV-I M group came into existence. Their molecular clock analysis provided a date of 1931, with a 95% confidence interval of 1915 to 1941. Analysis of another gene (*gag*) or application of another model (rates allowed to change at splitting events) gave similar results with somewhat broader confidence intervals. However, all analyses included the span of 1916 to 1941 in the 95% confidence interval of the respective estimates. Furthermore, testing a known HIV-l group M isolate from 1959 gave an accurate estimate for the date of its origin, indicating that the assumptions of the method are reasonable.

What does establishing a date in the early 1930s for the last common ancestor tell us about the origins of the HIV-l M group and of the AIDS pandemic it caused? As Korber et al. note, the date of the last common ancestor only identifies when this viral lineage began to diversify; it does not identify when the virus was transmitted from chimpanzees to humans. One could envisage at least three hypotheses to explain the date of this transmission event. The virus could have been transmitted to humans in the 1800s or early 1900s perhaps through the hunting of chimpanzees for food. It then would have remained isolated in a small, local human population until about 1930, when it began spreading to other human populations and to diversify (Transmission Early hypothesis). In this case, socioeconomic and political changes in Africa could account for the increasing spread of the virus in humans. A second possibility is that the virus was transmitted from chimpanzees to humans around 1930, and immediately began to spread and diversify in human populations (Transmission Causes Epidemic hypothesis). A third possibility is that multiple strains of SIV were transmitted from chimpanzees to humans at about the same time in the 1940s or 1950s (Parallel Late Transmission hypothesis). It has been suggested that parallel transmission could have occurred through contamination of poliovirus vaccines with multiple SIVs. Poliovirus was cultured in chimpanzee kidney cells, and oral polio vaccines were administered in Central Africa between 1957 and 1960. However, this mechanism of transmission seems highly unlikely given the small number of chimpanzee kidneys used for preparing oral polio vaccines, the rarity of SIV infections in chimpanzee populations, and the lack of known strains of SIVcpz (the strain that infects chimpanzees) in the cluster of M-group viruses.

Of the three hypotheses, the data of Korber et al. best support the Transmission Early one, but they do not rule out the other two.

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