Silent Myocardial Ischemia

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Although much progress has been made in reducing mortality from ischemic cardiovascular disease, this condition remains the leading cause of death throughout the world. This might in part be due to the fact that over half of patients have a catastrophic event (heart attack or sudden death) as their initial manifestation of coronary disease. Contributing to this statistic is the observation that the majority of myocardial ischemic episodes are silent, indicating an inability or failure to sense ischemic damage or stress on the heart. This review examines the clinical characteristics of silent myocardial ischemia, and explores mechanisms involved in the generation of angina pectoris. Possible mechanisms for the more common manifestation of injurious reductions in coronary flow; namely, silent ischemia, are also explored. A new theory for the mechanism of silent ischemia is proposed. Finally, the prognostic importance of silent ischemia and potential future directions for research are discussed. (Circ J 2009; 73: 785–797)

Key Words: Angina; Ischemia; Ischemic heart disease; Myocardial infarction

It is widely known that cardiovascular disease (heart disease and stroke) is the most frequent cause of death not only in the western world but also worldwide (Figure 1), where it causes a staggering 44% of all deaths. This sobering statistic is coupled with the fact that medical advances have been responsible for large reductions in cardiovascular mortality in Japan2 and in the USA3. Thus, despite a marked improvement in treatment, cardiovascular events continue to kill more people than any other cause. The reason for this apparent paradox is not known, but might stem from the fact that the bulk of our therapies target symptomatic coronary and cerebrovascular disease, which occurs late in the disease process.

Curiously the initial presenting symptoms of coronary and cerebrovascular disease are often catastrophic and typically occur when the atherosclerotic process is well-advanced.4 It is estimated that the first manifestation of coronary artery disease (CAD) in 60–70% of patients is either sudden death or myocardial infarction, whereas only a minority present first with angina or other symptoms of reversible ischemia5. The reason for the onset of symptoms late in the disease process is not known but could be related to an impairment in, or inadequate fidelity of the cardiac sensory mechanism responsible for signaling myocardial ischemia. This paper will review evidence for such a reduction in cardiac sensing of ischemia, termed silent myocardial ischemia.

Definition and Prevalence

Silent myocardial ischemia is defined as objective evidence for ischemia without symptoms related to that ischemia. This is a subset of patients with silent coronary disease who often do not have any associated ischemia. Although silent ischemia could occur during any imbalance between myocardial oxygen delivery and supply (eg, LVH, aortic stenosis, microvascular disease) the term is typically applied to patients with evidence of conduit coronary disease manifest by atherosclerosis or spasm.

Silent ischemia can be manifested in several ways. It can be classified as purely silent, as is the case in a substantial percentage of myocardial infarctions in the Framingham study6,7 (Figure 2), or in patients following myocardial infarction who show silent ischemia on a positive stress-imaging study. This latter group is at particularly high risk for cardiovascular events8,9. However, the majority of subjects present with mixed ischemia, some episodes silent and some symptomatic.

Silent ischemia occurs in a broad spectrum of patients with coronary disease. It has been extrapolated from studies in asymptomatic men that silent ischemia occurs in approximately 2–4% of the general adult population10. However, this prevalence must be tempered by the fact that most large screenings of this nature were done in military enrollees and might include sample bias. In diverse groups of patients with stable angina roughly half have evidence of silent ischemia,

The Burden of Diseases


<table>
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<tr>
<th>Cause of Death</th>
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<tr>
<td>Cardiovascular Disease</td>
<td>7.2 million</td>
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<td>Stroke and other cerebrovascular disease</td>
<td>5.7 million</td>
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<td>Lower Respiratory Infections</td>
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<td>Tuberculosis</td>
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<td>Road Traffic Accidents</td>
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<td>Prematurity and Low Birth Weight</td>
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Figure 1. Top 10 causes of death world-wide, according to World Health Organization.
whereas three-quarters of all episodes of ischemia are silent. Patients with chronic renal failure appear particularly disposed to silent ischemia. In patients following myocardial infarction, 80–100% manifest silent ischemic episodes. In patients with unstable angina, upwards of 90% have evidence of silent ischemia whereas in patients with sudden death, almost all are observed to have periods of silent myocardial ischemia. In one study, Sharma et al. performed Holter monitor evaluation for silent ischemia on 19 survivors of a sudden death episode. Upon careful history, only 8 of the 19 had ever had chest pain or angina-like symptoms. However, all 19 showed evidence of ischemia on Holter. Farb et al. evaluated symptoms in 48 survivors of witnessed sudden cardiac death. Only 37% had related symptoms (chest pain or abdominal pain). Sixty-three percent had only silent ischemia in the time previous to the episode. There is a tendency for patients with more frequent or severe ischemia to have greater numbers of silent ischemic episodes, although not all studies confirm this.

In the typical patient with angina pectoris, the frequency of silent ischemia is high, accounting for three-quarters of all ischemic episodes. This has been confirmed in several studies including one where over 2,300 episodes of ST segment depressions were evaluated. Thus, a patient reporting angina 4 times a day, is likely to be having 16 episodes of ischemia during that same time period, the majority of which are asymptomatic. The clinical manifestations of myocardial ischemia represent only the ‘tip of the iceberg’.

Silent ischemia differs from classic angina-associated ischemia in several ways. First, classical angina pectoris occurs during exertion at higher heart rates. Silent ischemia is more likely to occur during periods of low activity including rest and sleep with onset at lower heart rates. Second, while painful ischemia typically lasts only a few
minutes, silent myocardial ischemia can occur for minutes to over an hour (Figure 4). A diurnal pattern to the occurrence of silent ischemia has been described in patients off therapy. This circadian pattern shows a rise in the incidence of silent episodes in the morning, with a nadir occurring in the pre-waking hours, similar to the pattern observed with stable angina pectoris, cardiac death and non-fatal myocardial infarction. This is consistent with a common mechanism for silent ischemia and cardiac events, a relationship that is described in more detail below.

Diagnosis of Silent Ischemia

By definition symptoms of ischemia are absent in this condition. It is important for the examiner to take a careful history because angina might be manifested by atypical chest discomfort, dyspnea, diaphoresis, nausea, and other non-specific symptoms, which must be absent for the diagnosis of silent ischemia. The documentation of ischemia is critical in the absence of symptoms. This becomes difficult because symptoms typically occur late in the ischemic process. Following the onset of myocardial ischemia, a reproducible sequence of events is typically elicited (Figure 5) with the earliest manifestation being a reduction in relaxation followed by reduced myocardial contraction, both within 10s. Only later are hemodynamic and electrocardiographic changes observed. Angina, if it occurs at all, is a late phenomenon, often arising a minute or more after the onset of ischemia.

Several methods have been used to detect silent ischemia, each with strengths and weaknesses. Most commonly used is the stress test. Either treadmill testing alone or in combination with nuclear imaging or echocardiography can detect silent ischemia. The advantage of these diagnostic approaches is the vast clinical experience, but they suffer from the fact that they monitor for ischemia only over a short period of time (min) and during stress. For these reasons they might miss the more typical episodes of silent ischemia which occur more primarily during non-exertional activities. Other diagnostic modalities include invasive myocardial hemodynamics during cardiac catheterization, dobutamine echocardiography, and positron emission tomography.

The most commonly ordered test for diagnosing silent ischemia is the Holter monitor. Using a frequency modulated monitoring system that has sufficient fidelity to assess changes in ST segment height, evidence for ischemia can be obtained during ambulatory dual lead monitoring. The advantages of this system include little need for patient skill.
or participation, the ability to record events over a longer period of time, and ability to monitor for ischemia during routine daily activities. Disadvantages include the large variability in numbers of ischemic episodes from day to day, the non-specificity of ST changes on the ECG, and the need for more extensive recording time, with sensitivity of the test being maximal after 72 h of monitoring. A variety of conditions can cause ST segment depression that mimics myocardial ischemia (Table 1). In addition to myocardial ischemia, let ventricular hypertrophy, digitalis, hyperventilation, mitral valve prolapse, and other conditions can elicit ST segment depression during electrocardiographic monitoring. However, the accuracy of the Holter monitor is greatly increased when the diagnosis of silent myocardial ischemia is limited to the following conditions:
(1) at least 0.5 mm ST segment depression
(2) duration of ST segment depression >60 s
(3) reversibility of ST segment depression.
Using these criteria, the Holter monitor is more than 95% specific for myocardial ischemia and has become the method of choice for detecting silent ischemia in the ambulatory setting. Other ambulatory monitoring devices have also been useful but typically are more cumbersome and expensive. For example, the VEST device can assess ventricular ejection fraction with the theoretical advantage of being able to detect myocardial ischemic episodes that are too short to register on Holter devices (Figure 5). This device has been shown clinically to be beneficial in identifying patients with silent ischemia.

Mechanism of Cardiac Pain

It is helpful to understand the less common symptom of myocardial ischemia; namely, angina pectoris, in order to better understand the more commonly observed manifestation, silent ischemia. In evolutionary timelines, myocardial ischemia is a recent phenomenon, and our ability to adapt might be limited. Alberto Malliani summarized this conundrum nicely when he said ‘it is hard to understand the biological strategy and hence development of a system providing the wild animal with hundreds of fibers exclusively designed for signaling unlikely coronary emergencies’, suggesting that incomplete development of such a system might be responsible for silent myocardial ischemia.

Cardiac sensation is conducted primarily through sympathetic afferent A-delta and unmyelinated C fibers projecting through the dorsal root ganglia to the first 6 thoracic spinal segments. Secondary projections target the thalamus and reticular formation in the brain. Vagal afferent fibers also conduct some cardiac sensory fibers although vagal afferent stimulation can modulate sympathetic sensory stimulation with a reduction in associated spinthalamic tract activity. A variety of mechanical and chemical stimuli can activate cardiac sensory neurons in the spinal cord. However, the response to chemical stimuli appear more consistent with that of nociception because: (1) they involve primarily C and A-delta fibers, the primary fiber type activated by myocardial ischemia in the cat and (2) they are silent at baseline and recruited only during application of chemical agents and with high threshold input. Whether a specific nociceptor exists in the heart is unclear, as some investigations show evidence for sensory fibers selective for pain whereas others suggest that pain receptors also mediate responses to other stimuli. It is possible that both mechanical and chemical stimuli act in concert to evoke the full nociceptive cardiac response.

The stimulus for cardiac pain has been examined previously. Inflammation is a common means of activating sensory pain fibers throughout the body. Indeed, patients with pericarditis often have related chest pain, although different in character from angina. However, many patients with a marked cardiac inflammation due to active myocarditis or endocarditis have no sensory cardiac manifestations. Mechanical stimuli are also responsible for sensory perception in many tissues. Ischemia-induced dyskinesis in a segment of the left ventricular wall could elicit a sensory stimulus. Mechanical perturbations of myocardial motion, including premature contractions and hypercontractile states might be also associated with cardiac sensation but this is easily distinguished from the pain associated with myocardial ischemia. If inflammation or mechanical stimuli participate in the mechanism of angina pectoris it is more likely that they facilitate rather than mediate cardiac pain.

The most prominent theory regarding cardiac pain postulates that chemical factors released in response to ischemia stimulate cardiac afferent pain fibers. A variety of candidate chemical agents have been implicated as a stimulus for angina pectoris during ischemia. Bradykinin when applied to the cardiac surface produces a significant increase in cardiac afferent nerve activity including activation of spinthalamic tract neurons. Application of bradykinin, as part of a mixture of agents, to the surface of the heart elicits a pseudoadaptive response in rats suggestive of pain; however, when infused intracoronary into conscious dogs, Pagani et al observed hemodynamic effects but no evidence of pain. Gutterman et al showed that the afferent neural response to epicardial application of bradykinin is an increase in afferent nerve activity, but the pattern of the increased activity differed from that observed during brief periods of myocardial ischemia, suggesting that bradykinin release does not fully explain cardiac pain sensation. Similar afferent neural responses can be observed with acetylcholine, substance P, serotonin, histamine, lowering pH, adenosine, and potassium ions. Data from animals suggests that these diverse stimuli might be acting through the same common pathway to excite acid-sensing ion channel 3 (ASIC3) during ischemia.

Adenosine has also been postulated as the mediator of...
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Cardiac pain. It is a common clinical observation that patients with or without coronary disease who receive intravenous injections of adenosine or dipyridamole, which increases cardiac adenosine levels, often relate symptoms consistent with angina pectoris, without electrocardiographic manifestations of ischemia. The adenosine hypothesis of cardiac pain was tested in a clinical study. Sylven et al administered increasing bolus doses of adenosine intravenously to healthy volunteers. All participants experienced a dose-dependent chest pain of angina quality, often with radiation characteristic of angina. Aminophylline, an inhibitor of adenosine receptors reduced the pain significantly. Dipyridamole also increased pain intensity. Similar findings were made by Crea et al suggesting that adenosine is an important mediator of cardiac pain in humans, although not all studies confirm this finding.

There are several common features of visceral pain sensation that extend to cardiac sensory fibers as well. First is a prominent tachyphylaxis to repeat application of nociceptive stimuli. Thus, cardiac application of bradykinin elicits a prominent hemodynamic and cardiac sensory response that diminishes if the stimulus is repeated within 20 min. This could be a contributing mechanism for silent myocardial ischemia. Second, there is heterogeneity in the afferent neural response to nociceptive stimuli. Not all spinothalamic tract neurons with mechanical sensory fields in the area of cardiac stimulation respond to the nociceptive stimuli. A variety of responses are observed consisting of increases, decreases or no change in activity. The net response is complex and might not be easily measured by recordings from individual neurons. Third, there is prominent convergence of sensory pain signals from visceral organs. Cardiac afferents project to the same spinothalamic tract neurons as esophageal, lung, gastric, and gall bladder afferents. This might contribute to the well known clinical difficulty in localizing visceral pain, and could mask the diagnosis of myocardial ischemia in some patients. Finally, afferents from other organs might modulate cardiac pain perception.

For example, bladder distension reduces cardiac afferent activity in response to nociceptive stimuli. Thus, integrity of the sensory system of other organs can modulate cardiac pain sensation. Each of these factors might influence the magnitude and even presence of angina pectoris.

Mechanism of Silent Myocardial Ischemia

While much progress has been made in understanding the mechanism of cardiac pain sensation (angina pectoris), the mechanism of the more common symptom of myocardial ischemia; namely, silent ischemia is not known. A variety of theories have been proposed but each has deficiencies and none fully explains the phenomenon. Nevertheless, it is useful to review these theories because each might contribute under certain circumstances.

One of the first theories of silent ischemia was the intensity theory which postulates that more intense or more prolonged episodes of myocardial ischemia elicit pain, whereas less intense or shorter episodes are silent. This theory has been tested in several ways. Support for the intensity theory comes from a study in subjects with CAD and no previous infarction. The size of each patient's myocardial ischemic zone was assessed by echocardiography during exercise stress testing, during which 58 of 89 participants developed painful ischemia. New wall motion abnormalities, poorer exercise performance, and a larger number of ischemic segments were noted in participants with painful compared to those with painless ischemia, supporting the intensity hypothesis. Evaluating ambulatory ischemic ST segment changes in patients with stable CAD, Taki et al found that silent ischemic episodes were of less duration and magnitude than painful ones. However, not all studies arrive at the same conclusion.

Deanfield and colleagues examined 1,934 episodes of myocardial ischemia during ambulatory monitoring in patients with stable angina and stratified them by the degree of ST segment elevation. Twenty-eight percent of episodes...
associated with 1 mm ST segment depression were painful, the remainder silent. Only 32% of episodes with 2 mm of ST segment depression were painful and 36% of those with 3 mm depression were associated with pain. Although more severe ischemia was associated with a greater likelihood of pain, even episodes with the most severe ST segment depression (3 mm) were predominantly silent. In a separate study by Kohya et al, severity of ischemia did not correlate with symptoms. In fact, comparison of symptomatic to silent episodes of ischemia showed that the former were more often of shorter duration and lower magnitude.

Perhaps the strongest evidence against the intensity theory derives from the Framingham study. During follow-up of over 5,000 participants, the 10 year incidence of unrecognized, or silent, myocardial infarction was 28% in men and 35% in women. Thus, approximately a third of all myocardial infarctions were silent. These numbers likely underestimate the true incidence because Framingham participants are better informed to detect symptoms of CAD and myocardial infarction and are less likely to under-report such symptoms compared to most other groups. The implications for the intensity theory are profound because it is difficult to imagine a greater stimulus for pain than ischemic tissue necrosis.

Ischemia duration is a putative differentiating factor determining if the ischemia will be painful or silent. As mentioned above, Cecchi and coworkers used ambulatory monitoring to examine the relationship between duration and symptoms of ischemia in 39 patients with exertional angina. Analysis of the 15 patients who had both silent ischemia and painful ischemia, revealed longer durations of ischemia in those with symptoms. However, for any given activity studied, there were more silent than painful episodes of ischemia during that activity (Figure 4). Silent ischemia tended to be more prominent during relatively sedentary activities. Thus, no consistent correlation between intensity or duration of pain related to the presence or absence of symptoms.

A popular theory for the etiology of silent ischemia is that pain perception is impaired in this condition. Droste and Roskamm examined this theory in 42 patients with CAD, 22 of whom had symptomatic ST depression during exercise, and 20 of whom had no symptoms of ST changes. Electrical stimulation of the thigh and cold pressor testing showed that pain thresholds were higher in those with silent ischemia.

Further evidence that pain thresholds influence the occurrence of symptoms in patients with ischemia derives from a study in which electrical stimulation of dental pulp was performed. One hundred and eighty consecutive patients with CAD and exercise-induced myocardial ischemia were divided into 2 groups; those who experienced angina during exercise-induced ischemia (group 1, painful ischemia) and those who developed ischemia but without angina (group 2, silent ischemia). Demographics were similar between groups. All participants underwent electrical stimulation of their dental pulp at 3 graded intensities, with quantitative assessment of the resulting pain. Over 70% of group 1 participants experienced no pain even at maximal electrical currents, whereas only 20% of group 2 participants had the same lack of reaction to pulp stimulation. The authors concluded that in patients with silent myocardial ischemia general pain thresholds are lower compared to those with painful ischemia. In a follow-up study of patients undergoing percutaneous coronary intervention (PCI) who were similarly stratified, the same investigative team showed that compared to patients with pain during PCI, those who did not experience pain had higher thresholds for pain evoked by dental pulp stimulation, had lower mean threshold reaction to stimulation, and had lower mean maximal pain response to dental pulp stimulation (Figure 7). Thus, it appears that variable thresholds for myocardial ischemic pain can contribute to the presence of silent myocardial ischemia.

A contributing factor to the altered pain threshold in participants with silent ischemia might be endogenous endorphin production although this is controversial. Beta-endorphin concentrations were 50% higher at baseline and 2-fold higher during PCI in 33 patients who experienced no pain during the intervention compared to 20 participants who had angina with the procedure. These differences could not be explained by CAD severity, degree of ischemia during PCI, or demographic factors. A role for β-endorphins in silent ischemia was confirmed in another cohort of CAD participants by the same investigative team. However, not all studies show a similar difference in β-endorphins in patients with compared to those without exercise-induced angina.

In 3 special groups of patients silent myocardial ischemia appears to be related to permanent neural damage. Patients with heart transplantation have complete transection of ventricular nociceptive fibers and experience no angina early after the procedure. However, 1 year or more following...
orthotopic cardiac transplantation, reinnervation can occur leading to the resurrection of cardiac pain sensation during ischemia. Chronic disruption in cardiac innervation can also occur following myocardial infarction if the infarcted tissue includes sympathetic afferent fibers serving either the ischemic region or passing through to uninfarcted remote cardiac regions. A permanent loss of pain sensation occurs in patients with diabetes mellitus. Nesto et al showed that in a consecutive cohort of patients with and without diabetes who were otherwise similarly matched, 28% of diabetics compared to 68% of non-diabetics experienced angina during equivalent degrees of exercise testing. Others have made similar findings often in conjunction with evidence for diabetic autonomic neuropathy, which might also play a role in diabetic silent ischemia.

Gender differences in sympathetic innervations, especially after menopause might contribute to the differential prevalence of silent ischemia in men and women. However, not all studies have identified a higher percentage of silent ischemia in diabetic participants.

Direct evidence for sympathetic denervation in diabetes derives from in vivo and in vitro studies. Langer et al showed reduced MIBG uptake in hearts of diabetic patients with silent ischemia suggesting a link between silent ischemia in diabetes and autonomic denervation. Faerman et al studied autopsy specimens from 5 patients with diabetes and silent ischemia. In each case they observed fragmentation of afferent sympathetic fibers in the heart, a reduced number of fibers, and beaded thickening of the nerves, all consistent with an autonomic sensory neuropathy that might contribute to silent ischemia in diabetes. Thus, in specific circumstances the etiology of silent ischemia could involve anatomic disruption of cardiac sensory nerve fibers.

**Alternative Theory of Silent Myocardial Ischemia**

Although differences in ischemia intensity or duration, and pain threshold, might contribute to the incidence of silent ischemia, these theories fail to explain 2 key observations. First, whether spontaneous or induced silent ischemia occurs in the same patient during some but not all episodes of ischemia. Second, there is a trend toward a higher incidence of silent ischemia in patients with more severe or frequent ischemia. An alternate explanation of the mechanism of silent ischemia that is consistent with these observations involves the concept of ‘neural stunning’. This theory postulates that 1 brief episode of ischemia, which might be angina-provoking, induces a temporary inhibition in sympathetic neural conduction during which subsequent episodes of ischemia are rendered painless (Figure 8). This theory would explain how 1 episode of ischemia could be painful and the next painless in the same patient with the same ischemic stimulus. It would also predict a higher percentage of silent episodes of ischemia in patients with frequent ischemia.

Ischemic attenuation of sympathetic neural activity has been well-documented. Sympathetic efferent nerves to the heart are disrupted after permanent coronary occlusion. Brief periods of myocardial ischemia followed by reperfusion are associated with a temporary reduction in cardiac sympathetic nerve activity. The impairment appears to be related to altered sympathetic nerve conduction and not reduced neurotransmitter release because responses to bretylium and tyramine remain intact and because innervation to remote non-ischemic regions is also impaired. Increases in ischemic-zone potassium, adenosine, and hydrogen ion concentrations likely play a role in the reduced nerve conduction. These regional reductions in sympathetic innervation might increase susceptibility to malignant ventricular arrhythmias with worsening of prognosis.

The mechanism of neural stunning has been examined. Curiously adenosine plays an important causative role. As described above, bolus injections of adenosine can elicit cardiac pain sensation. However, more sustained cardiac ele-
vations in adenosine impair sympathetic neural conduction. After 15 min of intracoronary infusion of adenosine but not papaverine, cardiac sympathetic responses were impaired to that observed following a 15 min left ascending artery occlusion. The impaired sympathetic responsiveness following 15 min of ischemia could be prevented by intracoronary administration of adenosine deaminase (Figure 9) or by treating with the adenosine receptor blocker 8-sulfophenyltheophylline during the coronary occlusion, indicating that myocardial adenosine is capable of impairing cardiac sympathetic neurotransmission.

The concept of sympathetic neural stunning has been confirmed in cardiac sympathetic afferent fibers as well. Single unit activity of cardiac afferent A-delta and C fibers with receptive fields on the left ventricle, increased in response to bradykinin, mechanical probing and brief (1 min) myocardial ischemia. Afferent responses to repeat stimuli were reduced following 15 min of ischemia and 15 min of reperfusion produced by coronary occlusion and release. However, no reductions in stimulated afferent activity were observed in sham coronary occlusion studies. These findings indicate that brief periods of myocardial ischemia render sympathetic afferent nerves stunned, with the anticipated consequence of reducing cardiac sensation to repeated episodes of ischemia (Figure 8) and support the neural stunning hypothesis of silent myocardial ischemia. Clinical studies are needed to confirm this hypothesis by examining the temporal relationship and duration of painful and painless ischemic episodes in a large cohort of patients undergoing Holter monitoring.

**Prognostic Significance of Silent Myocardial Ischemia**

A number of studies have identified the prognostic importance of silent myocardial ischemia in various populations of patients with CAD. An analysis of participants undergoing exercise testing in the CASS trial revealed that the risk for sudden death and myocardial infarction at 7 years was directly related to presence of ischemia on testing, independent of symptoms. Subset analysis revealed that patients with 3-vessel CAD actually had worse prognosis with silent ischemia. Thus, silent ischemia portends at least as ominous a prognosis as angina pectoris in patients with CAD. The presence or absence of ischemia is most important. Absence of ischemia is associated with a good prognosis whereas presence of ischemia is associated with worse prognosis, both in men and women.

In patients following myocardial infarction, the prognostic value of ambulatory ST segment monitoring has been examined. Toyoda et al showed that silent ST segment depression on treadmill testing before discharge was more predictive at 36 months of major cardiac adverse events (MACE) than ST segment changes with pain. Gill et al showed that myocardial ischemia was detected in 23% of more than 400 patients before discharge following myocardial infarction. MACE at 1 year follow-up were almost 3-fold higher in patients with silent ischemia on Holter than in those without, however exercise testing performed before hospital discharge was not useful in predicting MACE in these same patients. With multiple logistic regression analysis only ambulatory monitoring added prognostically to standard clinical variables in predicting MACE at follow-up. A similar 1 year tripling in mortality rate was observed among post-infarction patients with vs without ischemia on ambulatory monitoring. The majority of ischemic episodes were silent in these patients. Tzivoni et al and Theroux et al have made similar observations, although early post-infarction angina also portends a prognosis.

A particularly compelling study was performed by Gottlieb et al who examined the 2 year MACE rate among 70 patients with unstable angina following discharge from the hospital. Thirty-seven patients had Holter ECG evidence of silent ischemia at bed rest during hospitalization (mostly asymptomatic), while 33 did not, despite similarly intensive antianginal treatment. After 2 years of follow-up the probability of not experiencing death or MI was significantly greater in the group without silent ischemia (Figure 10). Even after eliminating the 9 participants from the first group who had some symptomatic ischemia, results were unchanged. Thus, medical treatment to eliminate chest pain in patients with unstable angina does not improve prognosis if silent ischemic episodes persist. A similar conclusion
was reached by Matsumoto et al\textsuperscript{96} in a larger study of 1,895 patients when they were monitored an average of 27 months following acute coronary syndrome. Multivariate analysis showed that significant ischemia on stress perfusion imaging together with low ejection fraction yielding the highest predictive value for MACE.

A frequently considered question is whether silent ischemia has adverse prognosis when detected in the low-risk groups such as the general population. Although the incidence of silent ischemia in the general population does not warrant routine screening, even in other low risk groups the importance of silent ischemia is not clear. Gandhi et al found evidence for ambulatory silent ischemia in over half of 96 patients with typical angina but without CAD\textsuperscript{97} In these patients silent ischemia did not portend a worse prognosis when compared to a control population who had neither angina nor CAD. Interestingly the standard diurnal early morning increase in silent ischemia was not observed in this cohort.

Silent ischemia might be prognostically worse in populations with more intense ischemia. This is the conclusion reached by Klein et al in a study of patients with ischemic ST depressions on exercise testing\textsuperscript{98} Those with pain had more severe ischemia than those without. However in patients with most ischemia, the magnitude of ischemia no longer correlated with presence of symptoms. Narins et al also found that in patients with stable CAD, adverse outcomes were more prevalent in patients with painful vs silent ischemia\textsuperscript{99} In a separate low-risk group of 116 medically managed patients with CAD, 39% had ambulatory evidence of ischemic ST segment depression, with 82% being silent. However, the incidence of cardiac events was not increased in the group with silent ischemia\textsuperscript{100} The conclusion from these studies in low-risk patients is that ambulatory monitoring for ST segment changes is not of prognostic benefit. However, these studies are hampered by generally good prognosis with very low event rates.

Two general conclusions can be made. First, the prognostic value of silent ischemia is greater in high risk cohorts such as post-infarction patients or those with acute coronary syndromes. Second, it is the ischemia more than the symptoms that determine prognosis. Because silent ischemia is the more common manifestation of ischemia, its detection is an important adjunct to determining outcomes in higher risk patient populations\textsuperscript{101} In higher risk patients with chest pain, the traditional approach of eliminating angina might not be sufficient to improve prognosis.

![Figure 11](image)

**Figure 11.** Event-free 1 year survival in 283 patients in whom all ischemic episodes on 48-h Holter were suppressed by medical therapy (100% responders, n=97) vs those in whom treatment did not eliminate all ambulatory ischemic events (non-100% responders, n=187). Reproduced from Von Arnim et al\textsuperscript{102} with permission.

### Treatment Strategies for Silent Myocardial Ischemia

Treatment strategies for painful ischemia are also effective for silent ischemia. Beta-blockers, calcium channel blockers and nitrates in doses that reduce ischemic burden also reduce silent ischemia\textsuperscript{102–105} Beta-blockers tend to be more effective than calcium channel blockers in eliminating silent ischemic episodes\textsuperscript{106} As with painful ischemia, interventional options of PCI or coronary artery bypass grafting are generally more effective in reducing silent ischemic episodes\textsuperscript{107,108} The major question raised by the frequent occurrence of silent ischemia is whether it is important to treat silent as well as painful episodes of ischemia to achieve optimal outcomes. The implications are significant because it would require substantially more monitoring using frequent exercise or Holter testing in addition to a careful medical history. Several studies have attempted to answer this question which could have a profound impact on health care delivery in the evaluation and treatment of patients with CAD.

The Total Ischemic Burden European Trial (TIBET) enrolled 682 patients with chronic stable angina and ST segment depression on treadmill\textsuperscript{109} Half of the participants had evidence for silent ischemia on 24-h Holter monitoring. Patients were randomized to receive nifedipine, a \( \beta \)-blocker, or both, with follow-up for 2 years using MACE and treatment failure as endpoints. In this low-risk population, presence of silent ischemia did not affect cardiac prognosis. More aggressive medical therapy tended to reduce hard endpoints in groups with and without ischemia on Holter.

The Total Ischemic Burden Bisoprolol study (TIBBS) tested the effect on MACE of treating all ischemic events. A total of 520 patients with stable angina had 145 events over 1 year follow-up\textsuperscript{110} Those with more than 6 episodes of ischemia during the initial 8 week monitoring period had higher event rates (32.5%) than those with fewer than 2 episodes (13.2%). Patients in whom all ischemic events were prevented by treatment (100% responder) had a lower event rate (17.5%) than those in whom treatment was only partially effective (non-110% responder, 32%) (Figure 11). This study supports the concept that treating ischemia,
whether painful or asymptomatic is beneficial.

Finally, the Asymptomatic Cardiac Ischemia Pilot (ACIP) study examined 558 patients with CAD amenable for revascularization, silent ischemia on 48-h Holter monitoring, and ischemia on exercise testing.\footnote{111} Patients were randomized to medical treatment of angina, medical treatment of angina and ambulatory ischemic episodes, or revascularization. After 1 year, mortality was 4.4% in the angina-guided group, 1.6% in the ischemia-treated group, and significantly lower (0%) in those who were revascularized. At 2 years of follow-up similar trends persisted for endpoints of mortality and myocardial infarction (Figure 12).\footnote{112} Unfortunately this study was not powered to detect a difference in mortality between the medically treated groups; furthermore, medical therapy was only adjusted twice during the follow-up and maximal therapy was not achieved.\footnote{113} The authors concluded that revascularization yields superior outcomes compared to angina-guided or ischemia-guided medical therapy but that larger scale multicenter clinical trial is needed to assess the medical therapeutic approaches.

Future Directions

Substantial evidence indicates that silent ischemia portends a bad prognosis, particularly in higher risk patients. It is logical to conclude that monitoring for silent ischemia should help identify which of these patients requires more aggressive treatment. However, we will need to await the results of multi-centered clinical trials to define the optimal therapeutic approaches.

Perhaps a more important concern relates to the role of silent ischemia at the other end of the cardiovascular spectrum; namely, early disease recognition. Being able to identify the presence of ischemia earlier in the natural progression of coronary atherosclerosis might allow intervention before catastrophic symptoms such as myocardial infarction or sudden death which are currently 2 of the most common first symptoms of coronary disease. Ambulatory monitoring of completely asymptomatic patients will likely never be cost effective. However, targeting certain high-risk patients such as those with diabetes or multiple risk factors, might identify a group who would benefit from more aggressive medical or interventional therapy.

Another approach for earlier identification of patients with ischemia before catastrophic events is to tailor pharmacological approaches to enhance pain perception from the heart, ie, repair the defective sensory system that fails to warn patients about impending tissue damage. This might be accomplished by approaches that reduce neural stunning, reduce cardiac pain thresholds, or otherwise enhance cardiac pain perception. To this extent, nerve growth factor might be a therapeutic target because this endogenous compound is capable of preventing ischemic neural stunning.\footnote{114} The acid-sensing ion channel 3 is another target given its putative role in cardiac nociception.\footnote{47} This would allow patients to sense the presence of myocardial ischemia and seek attention and intervention earlier. Such strategies might have implications for reduced nociceptive signaling in other visceral pathological conditions such as gall bladder obstruction or esophageitis where chronic silent disease might lead to serious complications.

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