REVIEW ARTICLE

Martin J. London, MD
Section Editor

The Pathophysiology of Perioperative Myocardial Infarction: Facts and Perspectives

Giora Landesberg, MD, DSc, MBA

MYOCARDIAL ISCHEMIA and infarction continue to be major causes of perioperative morbidity and mortality in adult patients undergoing noncardiac surgery. However, despite numerous studies that investigated almost every predictor of postoperative myocardial infarction (PMI), its mechanism is still the subject of debate.[1,2] The last decade has seen intense clinical research interest in perioperative myocardial ischemia and infarction. This effort has shed new light on the field and resolved some of the controversy surrounding the entity of PMI. Based on several new studies, the following are now generally accepted.

1. Perioperative myocardial ischemia peaks during the early postoperative period and is significantly associated with myocardial infarction and cardiac complications.[3-5] Intraoperative ischemia is less common and is infrequently associated with PMI. Thus, in contrast to earlier concerns, anesthesia per se, either general or regional, if administered without complications, is not a risk factor for the high-risk cardiac patient undergoing noncardiac surgery. Rather, it is postoperative stress (including emergence from anesthesia), which precipitates ischemia, infarction, and cardiac mortality.
2. PMI is preceded almost exclusively by ST depression-type ischemia. ST elevation-type ischemia leading to the majority of infarctions in nonsurgical patients is relatively uncommon after noncardiac surgery.[5]
3. PMI is mostly silent (>50%) and most often is a non-Q wave rather than Q-wave infarction.[5-7]
4. The majority of PMIs occur within the first 24 to 48 hours after surgery,[3-6] not on the third to fifth postoperative days as reported in the older literature.[8,9]
5. Mortality after PMI is <10% to 15%, similar to the in-hospital mortality after nonsurgical non-Q infarction. This is in contrast to older data showing a higher (>50%) mortality after PMI.[10,11]

In light of these data, it is justified to re-examine the following questions concerning the pathophysiology of PMI. Is the pathophysiology of PMI different from the typical nonsurgical myocardial infarction (MI)? Does the understanding of the pathophysiology affect the ability to effectively prevent, diagnose, or treat PMI? And does the pathophysiology of PMI teach anything about MI in general?

THE PATHOGENESIS OF MI IN NONSURGICAL PATIENTS

The Vulnerable Plaque

A central concept in the current understanding of the pathogenesis of MI is the distinction between stable and unstable or "vulnerable" coronary plaque.[12,13] Histopathological studies have shown that rapidly growing atheromatous plaques are composed of a substantial inner lipid core containing a large mass of thrombogenic lipids and macrophages bearing tissue factors. The lipid core in these plaques is surrounded by a relatively thin fibrous cap, which often exhibits local inflammation, degradation, and repair of its matrix. In these young and rapidly growing plaques, if the matrix removal from the fibrous cap by inflammation exceeds the deposition of the fibrous cap matrix overlying the lipid-rich, necrotic core of the plaque, it becomes unstable and vulnerable to fissuring and rupture. In contrast, the mature or stable atheromatous plaque is characterized by a small inner lipid core covered by a relatively thick and stable fibrous cap.

Cycles of small fissuring and disruptions of the fibrous cap, leading to local platelet aggregation, mild degrees of thrombosis, myocyte migration, and healing of the fibrous matrix, are believed to be part of the natural evolution of the growing atheromatous plaque. By this mechanism, relatively slowly accruing epicardial coronary plaques may progress to high-grade stenosis or even to complete occlusion without precipitating acute MI because this slow process is usually accompanied by the concomitant growth of collateral coronary circulation. However, during the same process of atherosclerosis, in those plaques that are lipid laden and with thin and unstable fibrous cap, abrupt rupture of the plaque may occur. Plaque disruption is thought to occur as a result of the physical shear forces acting on it from inside the lumen or secondary to inflammatory and degradation processes within the plaque it-

From the Department of Anesthesiology and C.C.M. Hadassah University Hospital, Jerusalem, Israel.

Address reprint requests to Giora Landesberg, MD, DSc, MBA, Stanford Medical Informatics, Stanford University, 251 Campus Drive at Welch Road, MSOB x215, Stanford, CA 94305-5479. E-mail: gxl@SMI.Stanford.EDU

1053-0770/03/1701-0019$30.00/0

doi:10.1053/jcan.2003.18

Key words: Myocardial infarction, myocardial ischemia, postoperative, noncardiac surgery, pathophysiology

self. In either case, the acute plaque disruption leads to a complex interaction among the lipids, smooth-muscle cells, macrophages, and collages exposed from the lipid core to the circulation, which promote an excessive local platelet activation and thrombin generation. The resultant thrombus may occlude the coronary blood vessel and interrupt coronary blood flow, leading to myocardial ischemia. If ischemia is severe and prolonged, myocardial necrosis may occur. Thus, rupture of an unstable or vulnerable coronary plaque is considered to be the common pathophysiologic mechanism of the vast majority of acute coronary syndromes ranging from unstable angina through non-Q-wave acute MI (AMI) and Q-wave AMI.

Acute Coronary Syndromes

Because the entire spectrum of acute coronary syndromes, unstable ischemia, Q-wave, and non-Q MI, is believed to arise from the same pathophysiologic pathway (ie, rupture of a vulnerable plaque and subsequent coronary thrombosis), they are also perceived as a continuum of clinical-pathological phenomena. The differences in the clinical manifestations of the various acute coronary syndromes, according to this model, are determined by the degree and duration of plaque rupture, thrombus deposition, and coronary occlusion. Minor, repeated plaque rupture accompanied by relatively short-term or partial coronary occlusion by thrombosis or vasoconstriction causes unstable angina pectoris.[13] More severe plaque rupture with prolonged, yet reversible coronary occlusion in the presence of adequate collateral circulation leads to non-Q MI (NQMI). Severe and prolonged coronary occlusion, especially if the affected myocardial territory is fed by poor collateral circulation, may result in Q-wave infarction.

The onset of an acute coronary syndrome is often triggered by external factors or conditions.[14] Myocardial infarction occurs at increased frequency in the morning,[15,16] particularly within the first hour after awakening[17]; on Mondays, during winter months and on colder days the year around; and during emotional stress[18] and vigorous exercise.[19] The pathophysiologic mechanisms responsible for the nonrandom and apparently triggered onset of infarction are unknown but are thought to be related to (1) plaque disruption triggered by surges in sympathetic activity with sudden increases in blood pressure, pulse rate, heart contraction, and coronary blood flow[20]; (2) coronary thrombosis on previously disrupted or complicated plaques, caused by fluctuations in the systemic thrombotic tendency because of platelet hyperaggregability, hypercoagulability, and/or impaired fibrinolysis; and (3) vasoconstriction, occurring either locally, around an unstable coronary plaque, or generalized secondary to sympathetic stimulation.

Acute coronary thrombosis is thought to occur secondary to an abrupt plaque rupture or change in the morphology of the coronary plaque. Yet, primary hypercoagulable or thromogenic state of the circulation can favor focal thrombosis: Platelet aggregation and the generation of thrombin may be activated by circulating catecholamines.[21] Hypercoagulability and enhanced platelet reactivity at the site of vascular damage occur in hypercholesterolemia,[22] in cigarette smokers,[23] and in metabolic abnormalities such as high plasma levels of homocysteine and lipoprotein. Hypercholesterolemia and cigarette smoking are also associated with abnormal endothelial function, thus favoring thrombosis, vasoconstriction, and local inflammation in the vascular wall.[24] Although some studies suggested that defective fibrinolysis, more specifically high levels of plasminogen-activator inhibitor, is a risk factor for ischemic heart disease and MI,[25] the results of other studies were less convincing.[26]

The Degree of Coronary Stenosis

It was long assumed that the risk of myocardial infarction posed to the patient with a given coronary artery stenosis is related to the severity of coronary obstruction: The greater the degree of narrowing, the greater is the risk of myocardial infarction and death. Conversely, mild or moderate stenoses (less than 50%) were assumed to pose less risk.[27-29] Among medically treated patients in the Coronary Artery Surgery Study, 12-year survival was 91% in patients with chronic angina and angiographically normal vessels, 86% in single-vessel disease with 30% to 50% obstruction, 79% in patients with 50% to 70% stenosis, and 74% in patients with 70% stenosis or more.[30] However, this concept has been challenged lately. Studies using repeated angiograms to investigate the effects of lipid-lowering drugs have shown that although active lipid-lowering treatment decreased the severity of coronary stenosis by only 0.3% to 1.1%, there was a striking reduction from 19% to 6% in clinical events (fatal or nonfatal myocardial infarction).[31] A plausible explanation for this apparent discrepancy was that endothelial function and the propensity for plaque rupture were significantly reduced by the lipid-lowering drugs.

Additional studies have shown that sudden total or near-total arterial occlusion frequently develops in arteries that previously appeared to have minimal stenosis.[32-34] Ambrose and colleagues[31] compared the degree of baseline coronary stenosis in patients who underwent 2 separate coronary arteriograms and had experienced either MI or new total occlusion without infarction during that interval. In the infarct group, 78% of the culprit lesions were initially of less than 70% stenosis; whereas in the noninfarct group, 61% of the lesions that subsequently progressed to total occlusion were initially greater than 70%. The lesions responsible for Q-wave MI (QMI) were characterized by a mean coronary stenosis of only 34%. Little and colleagues[32] reviewed the coronary arteriograms of patients from both before and shortly after AMI. They found that 66% of the culprit arteries had less than 50% stenosis on the initial arteriogram, and almost all of them had less than 70% stenosis. This discrepancy between the angiographic severity of coronary stenosis and the likelihood of MI is explained by the inability of the angiogram to identify unstable plaques that are at high risk of rupture and distinguish them from critical yet stable coronary stenosis. Moreover, these data corroborate the concept that the younger and less mature coronary plaques are the ones most likely to rupture and cause acute infarction.

However, these data contradict earlier evidence that both the number of coronary vessels involved in the disease and the severity of stenosis are important predictors of survival. Hence, there is an unresolved contradiction between 2 sets of data: one showing that MI occurs mainly in patients with low-grade coronary stenosis and the other showing that high-grade coronary stenosis is associated with worse long-term survival. If MI

occurs more often in patients with low-grade stenosis, why would patients with high-grade coronary stenosis have poorer long-term survival? The most common, yet unproven, explanation for this apparent paradox is that patients with high-grade coronary artery disease have a higher incidence of sudden death, presumably secondary to fatal arrhythmia or congestive heart failure. It is also hypothesized that patients with high-grade stenoses may concurrently have low-grade coronary lesions, which may disrupt and cause myocardial infarction. The possible role of prolonged, stress-induced ischemia in the myocardial deterioration of patients with high-grade stenoses and low threshold for ischemia is rarely discussed in this context.

QMI Versus NQMI

Delineation of the differences between QMI and NQMI is essential to understanding the pathophysiology of PMI. The distinction between QMI and NQMI was proposed in the early 1980s based on evidence that the terms transmural and nontransmural infarction did not correlate with anatomic findings. The differentiation between QMI and NQMI became a standard clinical practice with the demonstration that the evolution of Q waves bears important prognostic implications. More than a decade ago, it already became apparent that (1) NQMI involves a smaller volume of myocardial necrosis than QMI; (2) short-term (in-hospital) mortality of NQMI is lower than that of QMI; (3) NQMI has a higher incidence of recurrent angina and reinfarction, reflecting a greater residual jeopardized myocardium than QMI; and (4) the long-term morbidity and mortality after NQMI are at least equal, and in most studies higher than after QMI.[35]

Because the development of Q waves cannot be predicted on the patient's arrival to the emergency room and may not occur for many hours after the onset of acute MI, the differentiation between ST-segment elevation versus non-ST elevation MI is more important at the time of initial presentation of MI. In current cardiology practice, whether or not a Q wave develops is less important than the establishment of ST elevation because of its implication for therapeutic thrombolysis. This even led some cardiologists to advocate that the distinction between QMI and NQMI is meaningless and should be abandoned.[36] Nevertheless, in clinical practice, as well as in clinical investigations, NQMI maintains its firm position as a separate clinical entity.

Angiographic Findings in QMI Versus NQMI

Numerous angiographic as well as autopsy studies have shown that the prevalence of total coronary occlusion in the infarct-related artery (IRA) in QMI is very high (>90%) in the first 6 hours after the initiation of infarction but tends to decline to 45% to 53% within days or weeks because of spontaneous thrombolysis and recanalization.[37,38] In marked contrast, studies using repeated angiography found that total coronary occlusion of the IRA occurs in only 26% to 39% of the patients in the first hours after NQMI[39] and that this proportion increases moderately over the next hours and days after the infarction, in contrast to the spontaneous recanalization in Q-wave infarction.[40] Moreover, Dewood et al[40] found a stenosis of 70% or more of the IRA in almost all patients (97%) who had angiography within the first 24 hours after NQMI and in all patients who had angiography 72 hours to a week after the onset of infarction (Fig 1).[40] In addition, collateral vessels beyond the occluded artery were seen in more than 85% of the patients with total coronary occlusion early after the NQMI,[2] implying that the IRA was either occluded or had a high-grade stenosis long before the NQMI because it usually takes days or weeks for collateral circulation to develop. These findings are therefore in marked contrast to the other studies showing that the majority of myocardial infarctions occur in coronary arteries with less than 70% stenosis.

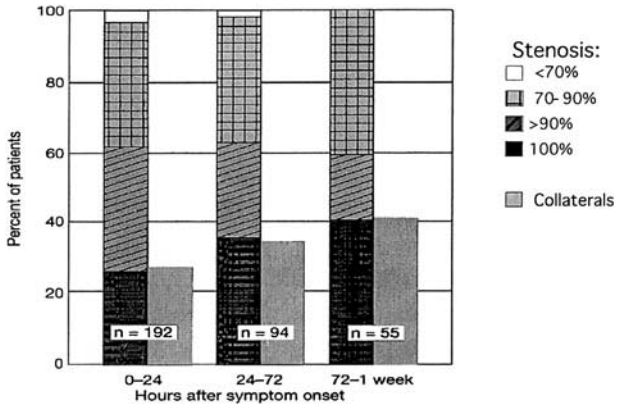

Fig 1. Prevalence of total coronary artery occlusion during the early hours of transmural myocardial infarction. (Reprinted with permission.[37]) 1980;303:897.

It is almost impossible to resolve these conflicting data unless clinicians accept that there are 2 types of MI. One starts with an abrupt occlusion of a relatively insignificant (<70%) coronary stenosis. This type of infarction is more likely to present with ST elevation-type ischemia and result in QMI. The other type begins with a relatively high-grade stenosis (>70%) and is probably more likely to present with ST depression-type ischemia and culminate in NQMI. Obviously, there may be a significant overlap between those 2 types of infarctions.[41] Between one third to half of the patients with NQMI present with ST-segment elevation[42] and approximately 25% of patients admitted with ST elevation do not develop Q waves. The primary coronary interventions currently performed by either thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), or coronary stenting early after the onset of ST elevation-type infarction also prevent many infarctions from evolving into Q-wave MIs.

Clinical Characteristics of Patients With NQMI

Many studies compared the pre-admission clinical characteristics of patients with NQMI and QMI. In 1 study of 3,700 patients aged 65 to 79 years admitted to 2 different hospitals, patients with NQMI had a higher prevalence of diabetes mellitus, previous congestive heart failure, and angina pectoris than those who developed QMI.[43] Up to 70% of patients with NQMI have had a prior MI[44] and have a higher prevalence of baseline ECG abnormalities such as ST depression, T-wave inversion, left ventricular hypertrophy, and left bundle-branch block.

Table 1. In-hospital and Long-Term Mortality After Q Wave Versus non–Q Wave MI

	In-hospital Mortality				Long-Term Mortality			
	QMI		NQMI		QMI		NQMI	
	Total No. of Patients	% Deaths	Total No. of Patients	% Deaths	Total No. of Patients	% Deaths	Total No. of Patients	% Deaths
Early series (1973-1981)	3,436	25% (11%-28%)	1,072	15% (3%-23%)	1,835	25.4% (18%-30%)	624	35% (17%-49%)
Late series (1985-1995)	5,369	16% (5%-29%)	2,360	9% (0%-17%)	5,516	12.1% (<1%-64%)	2,280	16.4% (2%-59%)

NOTE. Patients with NQMI have lower in-hospital mortality but higher long-term mortality than patients with QMI. QMI versus NQMI, p value = 0.001. QMI versus NQMI, p value = 0.001.

Abbreviations: QMI, Q wave myocardial infarction; NQMI, non–Q wave myocardial infarction.

Prognosis After NQMI

Although NQMI is considered a smaller infarction than QMI,[35] its prognostic implications are not at all negligible. Leibson and Klein[45] summarized the data of all the investigations comparing short-term and long-term survival in patients with QMI versus NQMI (Table 1). The overall data consistently show that although the early, in-hospital morbidity and mortality after NQMI are lower than after QMI, long-term survival is worse after NQMI. It is conceivable, therefore, that the prognosis after NQMI are determined not only by the acute infarction itself, which is considered smaller in NQMI versus QMI. Rather, long-term prognosis after NQMI is poorer compared with QMI because these patients are generally sicker, have more advanced coronary artery disease, have poorer left ventricular function, and have a larger volume of myocardium at risk.[44]

ST Depression Versus ST Elevation-Type NQMI

Numerous studies suggest that ST depression appears to indicate a more unfavorable outcome than ST elevation. A meta-analysis of 15 studies compared the outcome of the patients with NQMI on the basis of ST elevation, ST depression, and T-wave inversion.[44] Death and reinfarction during hospitalization developed in 18% of those with ST depression, 8% with ST elevation, and 6% with isolated T-wave changes. Postdischarge events were also higher in the ST depression group, with 22% mortality or reinfarction in patients with ST depression, compared with 9% in the ST elevation group and 16.5% in the isolated T wave abnormality group. Another study that evaluated NQMI subgroups showed that patients with ST depression had a lower left ventricular ejection fraction on admission compared with patients who had ST elevation on admission (44% *v* 51%); they had more in-hospital complications and a higher 1-year mortality (29% *v* 11%).[46] Thus, NQMI patients presenting with ST depression are sicker and have poorer prognosis than those admitted with ST-segment elevation.

Pathophysiology of NQMI

Reconciling the evidence of coronary thrombosis as the proximate cause of infarction with angiographic studies showing open infarct-related artery after NQMI has led to the following hypothesis on the mechanism of NQMI: angioscopic visualization of dynamic, forming, and dissolving thrombus in the coronary arteries of patients with unstable coronary syndromes suggests that not all intracoronary thrombi are permanent and that NQMI may result from transient or incomplete coronary occlusion by thrombus. This theory is partially supported by studies[47] showing that patients dying of NQMI more often have patent infarct vessels and are twice as likely to manifest contraction band necrosis, a histologic feature of reperfusion, when compared with patients dying of similar size QMI. This hypothesis is also supported by the findings that NQMIs tend to be smaller, with earlier peak of serum creatine kinase-MB isoenzyme (CK-MB) suggesting washout phenomenon.[48] Coronary thrombus was reported in 47% of patients with NQMI catheterized within 24 hours of chest pain,[49] and both aspirin and heparin have been shown to be clinically effective in patients with NQMI.[50] This theory, however, does not provide a good explanation why thrombolysis has been disappointing and may be harmful in the treatment of unstable angina and NQMI.[51] In current practice, only ST elevation-type ischemia is an indication for thrombolytic therapy, and ST depression is an absolute contraindication for such treatment.[52] Similarly, the fact that antiplatelet and antithrombotic therapy improve outcome does not necessarily prove that coronary thrombosis is the initial event in the evolution of NQMI, rather that the prevention of subsequent thrombosis by these medications after the onset of ischemia improves outcome in unstable angina pectoris (AP) and NQMI.[53] The pathophysiology of NQMI is therefore much more complex and the increase in myocardial oxygen consumption per unit time in the setting of fixed coronary stenosis may also have a role in the genesis of at least some portion of NQMIs.

IS PMI DIFFERENT?

One major difference between PMI and nonsurgical MI is that nonsurgical MI occurs mostly outside the hospital and when the patients arrive at the emergency room they already have signs and symptoms of acute infarction. Therefore, the causes and circumstances leading to onset of nonsurgical MI can only be retroactively speculated. In contrast, PMI occurs inside the hospital mainly within the first few days after surgery while these patients can still be intensely monitored and observed. In particular, studies using continuous ECG monitoring starting before surgery and continuing for hours or days after the end of surgery allow for a unique insight into the whole process of MI from before, during, and after the evolution of PMI, a process that is rarely attainable in nonsurgical MI.

Table 2. Studies Using Perioperative Holter Monitoring in Which Postoperative Ischemia Duration Has Been Reported

Reference	No. of Patients	Postoperative Ischemia Duration: Mean ± SD (median)	Association Between Ischemia Duration and Outcome
Frank et al[61]	1	9 h	Patient died
Mangano et al[62]	100	207 ± 350 [51] min	Not reported
Pasternack et al[63]	385	7.0 ± 12.1 h	Cardiac complications if ischemia longer than 1% of monitoring time
Raby et al[64]	115	85 ± ?	More cumulative ischemia in patients with cardiac events (mean: 136 *v* 53 min p = not significant)
Landesberg et al[4]	151	171 ± 264 [65] min	Cumulative ischemia >120 min predicted cardiac complications
Ganz et al[65]	1	12 h	Patient died
Andrews et al[66]	145	125 ± 143	Cumulative ischemia >120 min predicted cardiac complications
Fleisher et al[67]	145	Not reported	Ischemia >30 min most significantly associated with cardiac complications

The Role of Prolonged, Stress-Induced, ST Depression-Type Ischemia

Numerous studies have shown that Holter-detected silent ischemia is associated with cardiac morbidity and mortality in ambulatory patients with CAD,[54,55] as well as in high-risk cardiac patients undergoing noncardiac surgery.[3,4] A number of investigations have also attempted to show improved cardiac outcome by prophylactic therapy to prevent silent ambulatory or postoperative ischemia.[56-58] Nevertheless, whether silent ischemia is just a marker for more extensive CAD or may also play a mechanistic role in the evolution of myocardial infarction and cardiac death has always been debated.[59,60]

Several studies using perioperative ECG monitoring have shown that postoperative ischemia duration, and not only ischemia per se, is associated with cardiac complications after major noncardiac surgery (Table 2). However, these studies using Holter monitoring and CK-MB to detect perioperative ischemia and infarction may not have been accurate enough to determine the true association between the electrocardiographic signs of ischemia and the biochemical evidence of PMI. Holter monitoring as used in these studies, especially those using only 2 ECG leads, is of relatively limited sensitivity (37%-50%) and specificity (88%-92%) for detecting myocardial ischemia.[61,62] Similarly, the most common biochemical marker for infarction, CK-MB isoenzyme, is of inadequate specificity for identifying PMI.[63]

By using continuous 12-lead ECG with ST trend monitoring and troponin-I (cTn-I) measurements in the first 3 postoperative days in 185 patients undergoing major vascular surgery, it has recently been shown[5] that the rise in cTn-I (peak levels: 21.1±26.5 ng/mL; range, 3.3-100.2) occurred during or shortly after prolonged (>100 minutes), silent, postoperative ischemia and that the duration of ischemia was strongly associated with the peak cTn-I level. Moreover, ischemia was preceded in all cases by an increase in heart rate (heart rate at the onset of ischemia was 104 ± 19 and at peak ischemia 115 ± 19, compared with 86 ± 14 in the 30 minutes before the onset of ischemia) and the majority (67%) of ischemic events, including those culminating in PMI, started within 2 hours from the end of surgery and emergence from anesthesia (Fig 2). In addition, ischemic ECG changes were transient and reverted completely to baseline in all patients including those with PMI, except for 1 patient with new, persistent T-wave inversion. Rapp et al[64] who correlated postoperative Holter monitoring results with cardiac troponin-T measurements in 20 patients undergoing major vascular surgery have obtained similar results.

Postoperative ischemia and infarction most often start at or shortly after the end of surgery, a time characterized by increases in heart rate, blood pressure, sympathetic discharge, and procoagulant activity.[65] Two studies[6,66] showed that the increase in troponin-I or T signifying PMI occurred in most patients already within 12 to 24 hours after surgery. In 1 of these studies,[66] the increase in cTn-I, measured every 6 hours postoperatively, occurred already within 6 to 12 hours after surgery in 75% of the patients with PMI. By extrapolation, it can be concluded that the ischemia leading to the PMI started 6 to 8 hours before the rise in troponin-I, which is approximately the time of the end of surgery. These findings are in line with the recent data using continuous, on-line 12-lead ECG monitoring in which the majority of prolonged ischemic events begin around the end of surgery.[5]

The Role of Prolonged Tachycardia

The acute effects of tachycardia have been studied extensively. Heart rate is a well-known determinant of myocardial energy demand as well as supply.[67] It is well recognized that an increase in heart rate in the presence of stable coronary artery

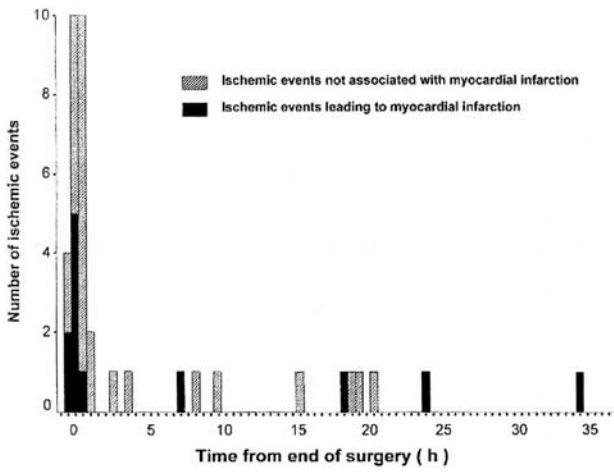

Fig 2. Time of onset of longest ischemia relative to surgery in vascular surgery patients monitored with continuous 12-lead ECG. (Reprinted with permission.[5])

stenosis causes impairment of subendocardial/epicardial blood flow distribution because of the shortening of the diastolic time interval, and thus may cause subendocardial ischemia and myocardial dysfunction. The short-term effects of tachycardia-induced ischemia on myocardial perfusion-contraction matching in patients as well as in animals with limited coronary blood flow have been well shown.[68,69] Tachycardia has also been shown to increase infarct size after acute coronary occlusion in dogs[70] but not in pigs (presumably because of the poor coronary collateral circulation in pigs and consequently the creation of maximal ischemia in the territory of the occluded coronary artery, regardless of changes in heart rate).[66] In contrast, other studies reported normal recovery of regional systolic myocardial function in dogs with severe coronary stenosis after 30 minutes of rapid atrial pacing[71] or gradual recovery to near normal myocardial function during reperfusion after sustained (9 hours) regional dysfunction produced by prolonged coronary stenosis.[72]

Numerous clinical trials have indicated that elevated heart rate is a significant independent predictor of reinfarction and mortality after acute MI.[73,74] Heart rate correlates with the circadian variation in the occurrence of acute MI,[75] and β-blockade significantly reduces mortality after acute MI in proportion to the decrease in heart rate. Nevertheless, the potential role of heart rate in the pathogenesis of MI has received relatively minor attention.[73] One experimental study has shown that prolonged tachycardia-induced ischemia, lasting 1 to 4 hours, in the presence of fixed coronary stenosis that causes no ischemia at resting heart rate, leads to patchy subendocardial necrosis in the open-chest anticoagulated dog model.[76]

The Beneficial Effect of β-Blockers

β-Blocking agents improve long-term survival in patients with known coronary artery disease. A meta-analysis of trials from the prethrombolytic era involving >27,000 patients showed that β-blocker therapy started in the convalescence period of acute MI reduces long-term mortality by 23%.[77] There is no difference between cardioselective and noncardioselective β-blockers in their beneficial effect, yet β-blockers with intrinsic agonist activity do not have the same beneficial effect on long-term survival as pure β-blocking agents do. β-Blockers are especially helpful for reducing mortality in patients with pump failure, silent myocardial ischemia, and in those who do not undergo coronary revascularization.[78,79] Mortality is reduced even in patients who receive less than 50% of the dosage found to be effective in preventing cardiac death in large randomized trials.[80]

There is also a growing bulk of evidence showing that β-blockade reduces perioperative myocardial ischemia[81] and cardiac complications in patients undergoing noncardiac surgery.[82,83] A randomized controlled trial of prophylactic atenolol therapy, administered just during the perioperative period in patients at risk for cardiac complications, showed a reduction in long-term (6 months up to 2 years) mortality, although not associated with a significant reduction in perioperative cardiac morbidity or mortality.[84] In a more recent randomized placebo-controlled trial in high-risk patients undergoing major vascular surgery, oral bisoprolol at a dose of 5 or 10 mg daily, begun at least 7 days before and continued until the 30th day after surgery, reduced 30-day cardiac death, and nonfatal PMI from 34% in the control group to 3.4% in the bisoprolol group.[2] This latter study is especially unique because it is the first study showing that β-blockade prevents MI and cardiac death in the short term, not only in long-term survival. Despite the indisputable importance of this study, it presented no clue for the possible mechanism by which β-blockade had such an outstanding effect on perioperative cardiac outcome.

The mechanism by which β-blockers prevent myocardial infarction is apparently unclear. β-Blockers have no proven antiatherogenic, antithrombotic, fibrinolytic, or antispasmodic effects in humans. On the contrary, β-blockers may induce or potentiate atherogenic dyslipoproteinemia,[85] platelet aggregation,[86] and vasoconstriction.[87] It is generally accepted that an important mechanism by which β-blockers prevent myocardial infarction is by blunting cardiovascular sympathetic surges. More specifically, it is quite convincing that the protective effect of β-blockers is related to their heart rate–lowering efficacy: the lower the heart rate, the better the protection against reinfarction and sudden death[73] as well as fewer perioperative cardiac events. Only β-blockers without intrinsic sympathomimetic activity reduce mortality in patients after myocardial infarction.[88] A similar effect on reinfarction has been obtained by the heart rate–reducing calcium antagonists, such as verapamil[89] and diltiazem,[90] in sharp contrast to the results obtained with the heart rate–increasing calcium antagonist nifedipine.[91] Although heart rate data in those trials showing the beneficial effect of β-blockers on mortality after myocardial infarction were usually presented for descriptive purposes only, the trends generally showed increased mortality with higher heart rates.[73] A retrospective analysis of the data from the Timolol Multicenter Study[92] showed the prognostic importance of resting heart rate on mortality and that the beneficial effect of timolol on mortality was primarily related to heart rate reduction. A significant relation between heart rate reduction and the percent reduction in mortality was also obtained with meta-analysis of several other trials.[93]

One mechanism by which β-blockers and possibly heart rate–reducing calcium antagonists prevent infarction is by delaying or preventing plaque disruption by reducing the mechanical and hemodynamic stress on vulnerable plaques. Another mechanism often suggested is the ability of β-blockers to prevent catecholamine-induced fatal arrhythmia. An alternative mechanism, however, which is more in line with the findings on prolonged, perioperative ischemia, is that β-blockers prevent myocardial infarction by preventing prolonged, stress-induced (or tachycardia-induced) ST depression-type ischemia even in the presence of stable, yet severe nonvulnerable coronary plaques.

Plaque Rupture and Coronary Thrombosis in Pathologic Studies

Autopsy studies have shown that acute coronary occlusion often cannot be found in patients who die following postoperative myocardial infarction.[94] Recently, two retrospective studies specifically investigated the coronary pathology of fatal PMI. Dawood et al[95] performed histopathological analyses of

the coronary arteries of 42 patients who died from PMI within 30 days after surgery, comparing them to 25 randomly selected non-postoperative fatal infarctions. In only 7% of the patients with PMI was plaque rupture identified. Intra-plaque hemorrhage, with or without plaque fissuring, was found in 45%, and intra-coronary thrombosis in 28%. All together 55% of the patients had at least one of these intra-coronary pathologies. In 45% of the patients none of the above pathologies has been found. Although intra-plaque hemorrhage is frequently found in patients who die secondary to unstable coronary syndromes, intra-plaque hemorrhage if not associated with fissuring or damage to the fibrous cap may also be an incidental finding in patients with atherosclerosis.[96] Moreover, intraluminal coronary thrombosis found in postmortem studies does not necessarily imply that thrombosis was the initial cause of infarction. Rather, coronary thrombosis may also occur as a result of the low coronary blood flow and stasis during prolonged ischemia, in coronary arteries with severe but stable stenosis.[12]

Cohen and Aretz[97] analyzed the coronary pathology of 26 patients who died within 76 hours from a PMI. Sixteen patients (61.5%) had pathologically confirmed transmural MI, and 10 (38.4%) had subendocardial MI. Plaque rupture was found in 12 (46%) of the patients, 7 (64%) of whom also had coronary thrombosis. Two other patients had coronary thrombosis but no plaque rupture. An interesting finding in their study was the difference in the time from surgery to death between the 2 groups of patients with and without plaque rupture. Although the time to death in the patients with plaque rupture was more or less evenly distributed along the 17 postoperative days, most (71%) of the patients without plaque rupture died within the first 3 postoperative days with a peak incidence at the second postoperative day (Fig 3). Hence, there are 2 types of fatal PMI: one that occurs randomly during the whole postoperative period and is associated with plaque rupture and one that is not associated with plaque rupture and occurs mostly in the immediate (2-3 days) postoperative period. The fact that the patients without evidence of plaque rupture died early postoperatively is compatible with the data from the other studies showing that the majority of PMIs occur early postoperatively after prolonged stress-induced ischemia triggered by the surge in sympathetic output in the immediate postoperative period. Because death after PMI is relatively uncommon and because mortality after acute coronary plaque rupture is expected to be higher than after stress-induced ischemia, the fact that only roughly 50% of the patients who died from PMI had plaque rupture or coronary thrombosis implies that the incidence of plaque rupture and coronary thrombosis in nonfatal PMI is probably significantly lower than 50%. Again, this is in marked contrast to the much higher incidence of plaque rupture and coronary thrombosis in nonsurgical MI.[98]

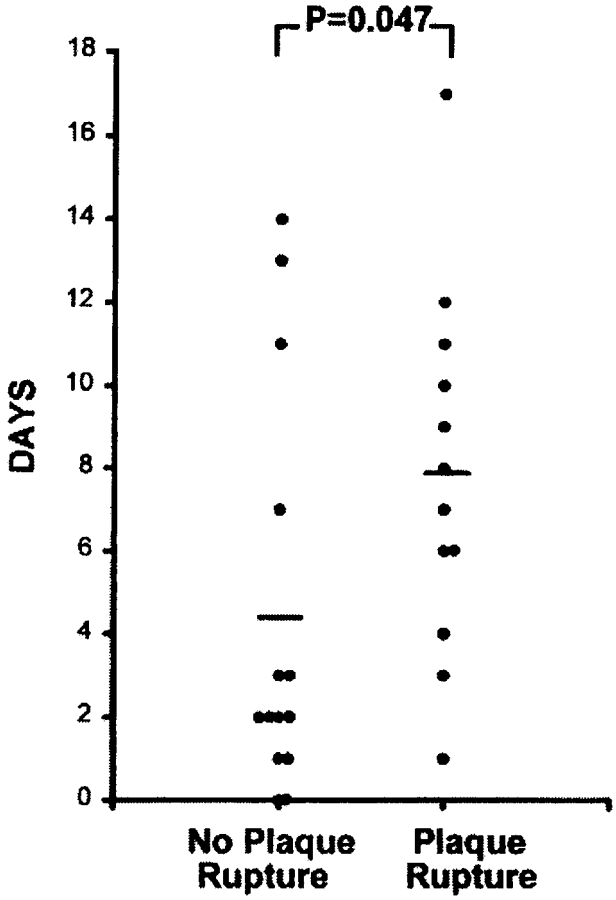

Fig 3. Time from the end of surgery to death in the 2 groups of patients, with and without plaque rupture on pathological examination of the coronary arteries.

SUMMARY: THE PATHOPHYSIOLOGY OF PMI

As mentioned earlier, the exact mechanism underlying PMI is not known and is most commonly believed to resemble that of nonsurgical MI (ie, acute plaque rupture and coronary thrombosis caused by the abrupt increases in blood pressure, heart rate, coronary tone, and platelet aggregability[99] and the decrease in fibrinolytic activity[100] occurring postoperatively). However, when combining all the data on perioperative ischemia and infarction in high-risk patients undergoing noncardiac surgery, it is also possible to propose the following scenario (schematic representation in Fig 4).

1. Ischemia starts in most patients (67%) immediately after the end of surgery and during emergence from anesthesia,[4] a time period characterized by increased heart rate, blood pressure, sympathetic discharge,[101] and procoagulant activity.[53] Such ischemia is most often silent and is almost exclusively denoted by ST depression on continuous ECG monitoring. Postoperative ischemia is preceded by an increase in heart rate, although heart rate at peak ischemia may not exceed 90 to 100 beats/min. If not monitored continuously by ST trend analysis, the silent, postoperative ischemia may easily be overlooked because the ischemic ST changes revert completely to baseline in almost all cases, even in patients who exhibit prolonged ischemia and MI as indicated by an increase in cardiac troponin levels.[5] In approximately one-third of the patients with unnoticed or untreated ischemia, postoperative ischemia lasts more than 100 minutes.
2. Patients with prolonged ST depression-type ischemia may subsequently have an increase in troponin signi-

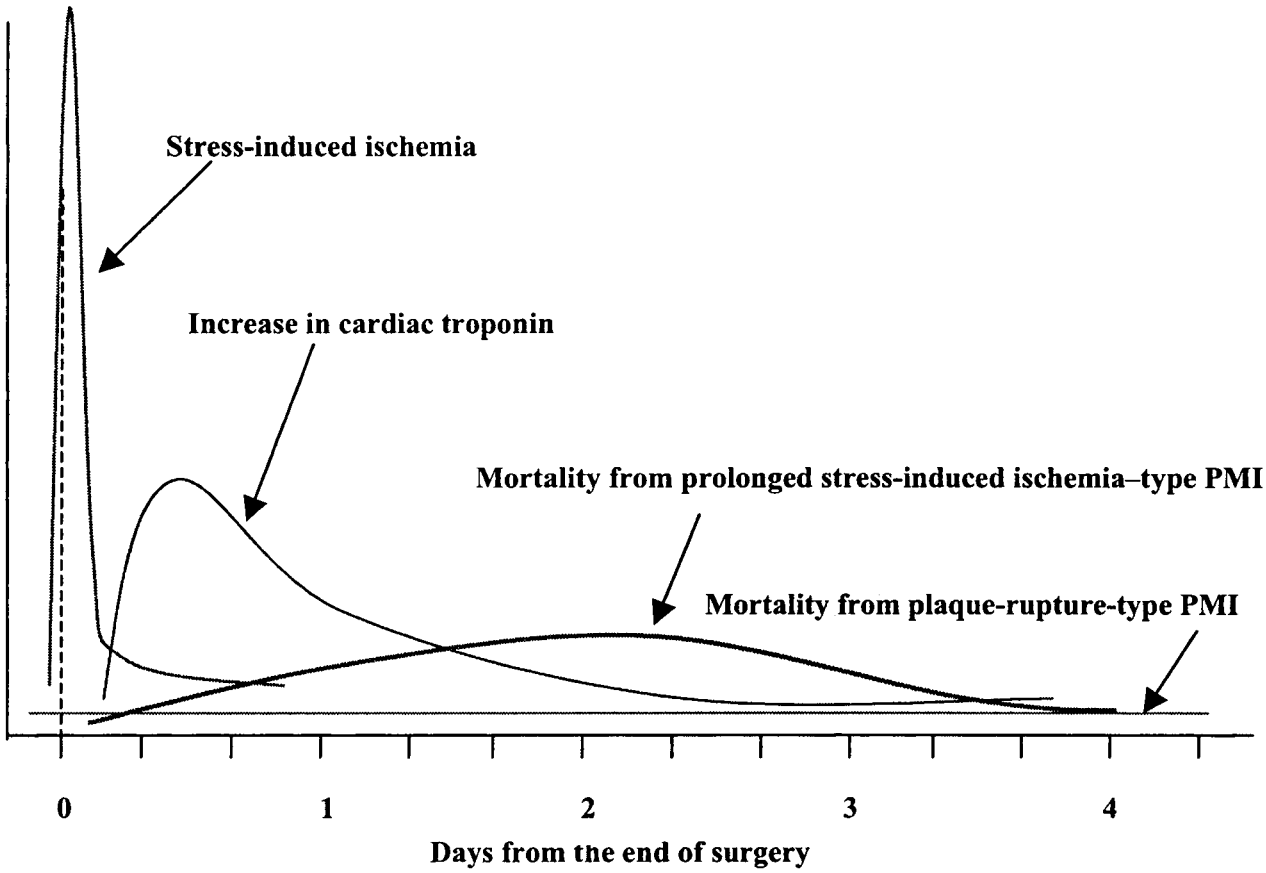

Fig 4. The time sequence of perioperative ischemia, infarction, and cardiac death after noncardiac surgery.

fying PMI. Only approximately 50% of PMI patients will show signs or symptoms of MI.[4] The other 50% of PMIs are silent and will be completely unnoticed unless serum troponin levels are routinely taken and if the ECG with ST trend analysis is not continuously monitored in the postoperative period. The increase in troponin starts in most patients within 8 to 24 hours from the end of surgery, which corresponds to the time of onset of prolonged ischemia shortly after the end of surgery.

3. Because the increase in troponin occurs during or shortly after prolonged ST depression-type ischemia, without sudden conversion to ST elevation, it is assumed that PMI is most likely the consequence of the prolongation of stress-induced ischemia and not because of plaque rupture. Whether stress-induced ischemia, per se, in the presence of severe, yet fixed coronary stenosis is sufficient to cause PMI or PMI occurs secondary to coronary thrombosis caused by low coronary flow and stasis or with the addition of coronary vasoconstriction associated with prolonged ischemia[102,103] is unknown. Nevertheless, postoperative ischemia can quite easily be prevented or treated by β-blockers, hence preventing subsequent PMI and cardiac complications.
4. In approximately 50% of the patients who die secondary to PMI, no plaque rupture or thrombosis is found in their coronary arteries at autopsy, despite their extensive coronary artery disease. The peak incidence of cardiac death in these patients is in the first 1 to 3 postoperative days,[76] which corresponds to the peak incidence of prolonged, stress-induced, ST depression-type PMI. In the other 50% of patients with fatal PMI, in whom plaque rupture or coronary thrombosis is detected, the timing of death is evenly distributed in the postoperative period, with no special correlation to the end of surgery.[76]

A Generalized Model of MI

An important lesson from the studies on PMI for medicine in general, not only for perioperative physicians, is that prolonged, stress-induced, ST depression-type ischemia may lead to myocardial infarction. There is not enough evidence to argue conclusively against plaque rupture as the final pathway, though, and it is doubtful if such evidence will ever be available. Based on the abundance of data gathered on PMI in the last decade, it is highly likely that NQMI may occur not only as a result of sudden rupture of an unstable coronary plaque but also because of the prolonged stress-induced, ST depression-type ischemia in

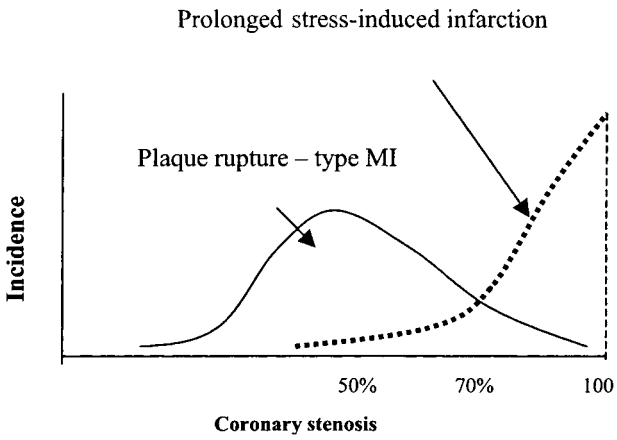

Fig 5. A schematic demonstration of the 2 types of MI.

the presence of severe yet stable coronary artery disease. This concept may help explain the benefits of β-blockers in preventing MI and cardiac death in the general cardiac population as well as in postoperative patients. This mechanism may also explain the marked differences in the angiographic findings between QMI and NQMI and possibly the nonresponsiveness of ST depression-type infarction to thrombolytic therapy.

In summary, in addition to the well-known mechanism of plaque rupture and coronary thrombosis as the primary cause of MI, there is an additional mechanism of prolonged, stress-induced infarction. Although plaque rupture and coronary thrombosis-type infarction occurs mainly with relatively nonoccluding coronary plaques (<70% stenosis), stress-induced infarction occurs in patients with more severe, probably critical, yet stable coronary artery disease (Fig 5).

REFERENCES

1. Mangano DT: Adverse outcomes after surgery in the year 2001—A continuing odyssey. Anesthesiology 88:561-564, 1998

2. Poldermans D, Boersma E, Bax JJ, et al: The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. N Engl J Med 341:1789-1794, 1999

3. Mangano DT, Browner WS, Hollenberg M, et al: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 323:1781-1788, 1990

4. Landesberg G, Luria MH, Cotev S, et al: Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. Lancet 341:715-719, 1993

5. Landesberg G, Mosseri M, Zahger D, et al: Myocardial infarction following vascular surgery: The role of prolonged, stress-induced, ST-depression-type ischemia. J Am Coll Cardiol 37:1839-1845, 2001

6. Badner NH, Knill RL, Brown JE, et al: Myocardial infarction after noncardiac surgery. Anesthesiology 88:572-578, 1998

7. Goldman L, Adler J: General anesthesia and noncardiac surgery in patients with heart disease, in Braunwald E, Zipes DP, Libby P (eds): Heart Disease: A Textbook of Cardiovascular Medicine (ed 6). Philadelphia, PA, Saunders, 2001, pp 2084-2095

8. Tarhan S, Moffitt EA, Taylor WF, Guiliani ER: Myocardial infarction after general anesthesia. JAMA 220:1451-1454, 1972

9. Rao TL, Jacobs KH, El-Etr AA: Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 59:499-505, 1983

10. Saphir O, Priest WS, Hamburger WW, et al: Coronary arteriosclerosis, coronary thrombosis and the resulting myocardial changes. Am Heart J 10:567, 1935

11. Mauney FM, Ebert PA, Sabiston DC: Postoperative myocardial infarction: a study of predisposing factors, diagnosis and mortality in a high-risk group of surgical patients. Ann Surg 172:497-503, 1970

12. Fuster V, Badimon L, Badimon J, Chesebro JH: The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 326:242-250, 310-318, 1992

13. Yeghiazarians Y, Braunstein JB, Askari A, Stone PH: Unstable angina pectoris. N Engl J Med 342:101-114, 2000

14. Muller JE, Abela GS, Nesto RW, Tofler GH: Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. J Am Coll Cardiol 23:809-813, 1994

15. Quyyumi AA, Panza JA, Diodati JG, et al: Circadian variation in ischemic threshold: A mechanism underlying the circadian variation in ischemic events. Circulation 86:22-28, 1992

16. Bridges AB, McLaren M, Scott NA, et al: Circadian variation of tissue plasminogen activator and its inhibitor, von Willebrand factor antigen, and prostacyclin stimulating factor in men with ischaemic heart disease. Br Heart J 69:121-124, 1993

17. Gnecchi-Ruscone T, Piccaluga E, Guzzetti S, et al. Morning and Monday: critical periods for the onset of acute myocardial infarction: The GISSI 2 Study Experience. Eur Heart J 15:882-887, 1994

18. Trichopoulos D, Katsouyanni K, Zavitsanos X, et al: Psychological stress and fatal heart attack: the Athens (1981) earthquake natural experiment. Lancet 1:441-444, 1983

19. Mittleman MA, Maclure M, Tofler GH, et al: Triggering of acute myocardial infarction by heavy physical exertion: protection against triggering by regular exertion. N Engl J Med 329:1677-1683, 1993

20. Curfman GD: Is exercise beneficial—Or hazardous—To your heart? N Engl J Med 329:1730-1731, 1993

21. Braunwald E. Zipes DP, Libby P: Heart Disease: A Textbook of Cardiovascular Medicine (ed 6). Saunders, PA, 2001, p 2105

22. Badimon JJ, Badimon L, Turitto VT, Fuster V: Platelet deposition at high shear rates is enhanced by high plasma cholesterol levels. Atheroscleros Thromb 11:395-402, 1991

23. Fuster V, Chesebro JH, Frye RL, Elveback LR: Platelet survival and the development of coronary artery disease in the young adult: effect of cigarette smoking, strong family history and medical therapy. Circulation 63:546-551, 1981

24. Drexler H, Hornig B: Endothelial dysfunction in human disease. J Mol Cell Cardiol 31:51-60, 1999

25. Epstein FH. Plasminogen-activator inhibuitor type-1 and coronary artery disease. N Engl J Med 342:1792-1801, 2000

26. Oseroff A, Krishnamurti C, Hassett A, et al: Plasminogen-activator and plasminogen-activator inhibitor activities in men with coronary artery disease. J Lab Clin Med 113:88-93, 1990

27. Humphries JO, Kuller L, Ross RS, et al: Natural history of ischemic heart disease in relation to angiographic findings. Circulation 49:489, 1974

28. Proudfit WJ, Bruschke AVG, MacMillan JP, et al: Fifteen-year survival study of patients with obstructive coronary artery disease. Circulation 68:986, 1983

29. Harris PJ, Behar VS, Conley JJ, et al: The prognostic significance of 50 percent coronary stenosis in medically treated patients with coronary artery disease. Circulation 62:240, 1980

30. Emond M, Mark MB, Davis KB, et al: Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. Circulation 90:2645, 1994

31. Brown G, Albers JJ, Fisher LD, et al: Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 323:1289, 1990

32. Ambrose JA, Tannenbaum MA, Alexopoulos D: Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 12:56, 1988

33. Little WC, Constantinescu M, Applegate RJ, et al: Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 78:1157, 1988

34. Fishbein MC, Siegel RJ: How big are coronary arteries that rupture? Circulation 94:2662-2666, 1996

35. Klein LW, Helfant RH: The Q-wave and non-Q wave myocardial infarction: Differences and similarities. Prog Cardiovasc Dis 29: 205-220, 1986

36. Phibbs B, Marcus F, Marriott HJC, et al: Q-Wave versus non-Q wave myocardial infarction: A meaningless distinction. J Am Coll Cardiol 33:576-582, 1999

37. DeWood MA, Spores J, Notske RN, et al: Prevalence of total coronary artery occlusion during the early hours of transmural myocardial infarction. N Engl J Med 303:897, 1980

38. Betriu A, Castaner A, Sanz GA, et al: Angiographic finding 1 month after myocardial infarction: A prospective study of 259 survivors. Circulation 65:1099, 1982

39. Keen WD, Savage MP, Fischman DL, et al: Comparison of coronary angiographic findings during the first six hours of non-Q-wave and Q-wave myocardial infarction. Am J Cardiol 74:324, 1994

40. DeWood MA, Stifter WF, Simpson CS, et al: Coronary arteriographic findings soon after non-Q wave myocardial infarction. N Engl J Med 315:417, 1986

41. Boden WE, Gibson RS, Schechtman KB, et al: ST segment shifts are poor predictors of subsequent Q wave evolution in acute myocardial infarction. A natural history study of early non-Q wave infarction. Circulation 79:537-548, 1989

42. Willich SN, Stone PH, Muller JE, et al: High-risk subgroups of patients with non-Q wave infarction based on direction and severity of ST segment deviation. Am Heart J 114:1110-1119, 1987

43. Guadangnoli E, Hauptman PJ, Ayanian JK, et al: Variation in the use of cardiac procedures after acute myocardial infarction. N Engl J Med 333:573-578, 1995

44. Gibson RS: Non-Q-wave myocardial infarction, in Fuster V, Ross R, Topol EJ (eds): Atherosclerosis and Coronary Artery Disease. Philadelphia, PA, Lippincott Raven, 1996, pp 1097-1123

45. Leibson PR, Klein L: The non-Q wave myocardial infarction revisited: 10 years later. Prog in Cardiovasc Dis 39:399-444, 1997

46. Willich SN, Stone PH, Muller JE, et al: High-risk subgroups of patients with non-Q myocardial infarction based on direction and severity of ST segment deviation. Am Heart J 114:1110-1119, 1987

47. Friefeld AG, Schuster EH, Bulkley BH, et al: Nontransmural versus transmural myocardial infarction: A morphologic study. Am J Med 75:423-432, 1983

48. Gibson RS: Non-Q wave myocardial infarction: Diagnosis, prognosis and management. Curr Probl Cardiol 13:9-72, 1988

49. The TIMI 3A Investigators: Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest. Results of the Thrombolysis in Myocardial Ischemia (TIMI IIIA) Trial. Circulation 87:38-52, 1993

50. Violaris AG, Campbell S: Low-dose aspirin and heparin in unstable coronary artery disease. Lancet 337:489-490, 1991

51. Anderson HV, Cannon CP, Stone PH, et al: One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave MI. J Am Coll Cardiol 26:1643-1650, 1995

52. Braunwald E, Antman E, Beasley JW, et al: ACC/AHA Guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction: Executive summary and recommendations. Circulation 102:1193-1209, 2000

53. Theroux P, Waters D, Qiu S, et al: Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. Circulation 88:2045-2048, 1993

54. Deedwania PC, Carbajal EV: Silent ischemia during daily life is an independent predictor of mortality in stable angina. Circulation 81:748-756, 1990

55. Pepine CJ, Sharaf B, Andrews TC, et al: Relation between clinical, angiographic and ischemic findings at baseline and ischemia-related adverse outcomes at 1 year in the Asymptomatic Cardiac Ischemia Pilot study. J Am Coll Cardiol 29:1483-1489, 1997

56. Davies RF, Goldberg AD, Forman S, et al, for the ACIP Investigators: Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: Outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 95:2037-2043, 1997

57. Pepine CJ, Cohn PF, Deedwania PC, et al: Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). Circulation 90:762-768, 1994

58. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 335:1713-1720, 1996

59. Pepine CJ: Prognostic implications of silent myocardial ischemia. N Engl J Med 334:113-114, 1996

60. Fox KM, Mulcahy DA: Therapeutic rationale for the management of silent ischemia. Circulation 82:II155-160, 1990

61. Sharp SD, Mason JW, Bray B: Comparison of ST depression recorded by Holter monitors and 12-lead ECGs during coronary angiography and exercise testing. J Electrocardiol 25:323-331, 1992

62. Raby KE, Barry J, Treasure CB, et al: Usefulness of Holter monitoring for detecting myocardial ischemia in patients with nondiagnostic exercise treadmill test. Am J Cardiol 72:889-893, 1993

63. Adams JE 3rd, Sicard GA, Allen BT, et al: Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. N Engl J Med 330:670-674, 1994

64. Rapp HJ, Rabethge S, Luiz T, et al: Perioperative ST-segment depression and troponin T release. Identification of patients with highest risk for myocardial damage. Acta Anaesthesiol Scand 43:124-129, 1999

65. Breslow MJ, Parker SD, Frank SM, et al: Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. Anesthesiology 79:1202-1209, 1993

66. Garcia-Dorado D, Theroux P, Elizaga J, et al: Influence of tachycardia and arterial hypertension on infarct size in the pig. Cardiovasc Res 22:620-626, 1988

67. Indolfi C, Ross J Jr: The role of heart rate in myocardial ischemia and infarction: Implications of myocardial perfusion-contraction matching. Prog Cardiovasc Dis 36:61-74, 1993

68. Canty JM, Giglia J, Kandath D: Effect of tachycardia on regional function and transmural myocardial perfusion during graded coronary pressure reduction in conscious dogs. Circulation 82:1815-1825, 1990

69. Ross J Jr: Myocardial perfusion contraction matching: implications for coronary heart disease and hibernation. Circulation 83:1076-1083, 1991

70. Shell WE, Sobel BE: Deleterious effects of increased heart rate on infarct size in the conscious dog. Am J Cardiol 31:474-479, 1973

71. Gewirtz H, Williams DO, Most AS: Recovery of myocardial function following brief versus prolonged atrial pacing stress in the presence of coronary stenosis. Cardiovasc Res 18:702-710, 1984

72. Matsuzaki M, Gallagher KP, Kemper WS, et al: Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion. Circulation 68:170-182, 1989

73. Hening R, Gilpin E, Cowell JW, et al: Prognosis after acute myocardial infarction: A multivariate analysis on mortality and survival. Circulation 59:1124-1136, 1979

74. ISIS-1 (First International Study of Infarct Survival) Collaborative Group: Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction. Lancet 2:57-65, 1986

75. Cohen MC, Muller JE: Onset of acute myocardial infarction: Circadian variation and triggers. Cardiovasc Res 26:831, 1992

76. Landesberg G, Zhou W, Aversano T: Tachycardia-induced subendocardial necrosis: A noncoronary-thrombosis cause of postoperative myocardial infarction. Anesth Analg 88:973-979, 1999

77. Held PH, Yusuf S: Effects of beta-blockers and calcium channel blockers in acute myocardial infarction. Eur. Heart J 14:18, 1993

78. Pepine CJ, Cohn PF, Deedwania PC, et al: Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life: The Atenolol Silent Ischemia Study. Circulation 90:762-768, 1994

79. CIBIS-II Investigators and Committees: The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. Lancet 353:9-13, 1999

80. Barron HV, Viskin S, Lundstrom RJ, et al: Beta-blocker dosage and mortality after myocardial infarction: Data from a large health maintenance organization. Arch Intern Med 158:449-453, 1998

81. Wallace A, Layug B, Tateo I, et al: Prophylactic atenolol reduces postoperative myocardial ischemia. Anesthesiology 88:7-17, 1998

82. Pasternack PF, Imparato AM, Baumann FG, et al: The hemodynamics of beta-blockade in patients undergoing abdominal aortic aneurysm repair. Circulation 76:III1-7, 1987

83. Stone JG, Foex P, Sear JW, et al: Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients. Br J Anaesth 61:675-679, 1988

84. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 335:1713-1720, 1996

85. Rabkin SW, Huff MW, Newman C, et al: Lipids and lipoproteins during antihypertensive drug therapy. Comparison of doxazosin and atenolol in a randomized, double-blind trial: The Alpha Beta Canada study. Hypertension 24:241, 1994

86. Knight CJ, Panesar M, Wilson DJ, et al: Different effects of calcium antagonists, nitrates, and beta-blockers on platelet function. Possible importance for the treatment of unstable angina. Circulation 95:125-132, 1997

87. Feldman RD, Christy JP, Paul ST, Harrison DG: Beta-adrenergic receptors on canine coronary collateral vessels: Characterization and function. Am J Physiol 257:H1634, 1989

88. Kendall MJ, Lynch KP, Hjalmarson A: β-Blockers and sudden cardiac death. Ann Intern Med 123:358, 1995

89. The Danish Study Group on Verapamil in Myocardial Infarction: Effect of verapamil on mortality and major events after acute infarction Am J Cardiol. 66:779, 1990

90. Gibson RS, Boden WE, Theroux P, et al: Diltiazem and reinfarction in patients with non-Q wave myocardial infarction: Results of a double-blind randomized multicenter trial. N Engl J Med 315:423-429, 1986

91. Wilcox RG, Hampton JR, Banks DC, et al: Trial of early nifedipine in acute myocardial infarction: The TRENT stud. BMJ 293:1204-1208, 1986

92. Gunderson T, Grottum P, Pedersen T, et al, for the Norwegian Multicenter Study Group: Effect of timolol on mortality and reinfarction after acute myocardial infarction: Prognostic importance of heart rate at rest. Am J Cardiol 58:20-25, 1986

93. Kjekshus JK: Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trals. Am J Cardiol 57:43F-49F, 1986

94. Calvin JE, Kieser TM, Walley VM, et al: Cardiac mortality and morbidity after vascular surgery. Can J Surg. 1986 29:93-7

95. Dawood MM, Kutpa DK, Southern J, et al: Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 57:37-44, 1996

96. Park AE, McCarthy WJ, Pearce WH, et al: Carotid plaque morphology correlates with presenting symptomatology. J Vasc Surg 27:872-878, 1998

97. Cohen MC, Aretz TH: Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 8:1333-1390, 1990

98. Davies MJ, Thomas AC: Plaque fissuring: The cause of acute myocardial infarction, sudden ischemic death and crescendo angina. Br Heart J 53:363, 1985

99. Green LH, Seroppian E, Handin RI: Platelet activation during exercise-induced myocardial ischemia. N Engl J Med 302:193-197, 1980

100. Rosing DR, Brakman P, Redwood DR: Blood fibrinolytic activity in man: diurnal variation and the response to varying intensities of exercise. Circ Res 27:171-184, 1970

101. Sametz W, Metzler H, Gries M, et al: Perioperative catecholamine changes in cardiac risk patients. Eur J Clin Invest 29:582-587, 1999

102. Nabel GE, Selwyn AP, Ganz P: Paradoxical narrowing of atherosclerotic coronary arteries induced by increases in heart rate. Circulation 81:850-859, 1990

103. Sambuceti G, Marzilli M, Marraccini P, et al: Coronary vasoconstriction during myocardial ischemia induced by rises in metabolic demand in patients with coronary artery disease. Circulation 95:2652-2659, 1997