Myocardial Ischemia - Association with Perioperative Cardiac Morbidity

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The development of ambulatory electrocardiographic recorders and analyzers and the application of transesophageal echocardiography in the mid-1980's enabled investigators to quantify and describe the occurrence of silent as well as symptomatic ischemia in the perioperative period. Several technical advances which have recently occurred in ECG monitoring include the use of miniaturized digital computing equipment to store and analyze data. In addition, real time ST-segment analysis has become widely available on multicomponent monitors in both the operating room and intensive care units.

The incidence of perioperative myocardial ischemia depends on the patient population, the surgical procedure, and the monitoring technique used. Several studies in the early 1990's have shown that cardiac morbidity in patients undergoing major, noncardiac surgery is best predicted by postoperative myocardial ischemia, rather than tradition preoperative clinical predictors. Long duration postoperative ischemia may be the factor most significantly associated with adverse cardiac outcome. Postoperative pain, physiological and emotional stress may all combine to cause tachycardia, hypertension, increase in cardiac output, and fluid shifts which, in high risk patients, might result in subendocardial ischemia and eventual myocardial infarction. If postoperative myocardial ischemia is the cause of late postoperative myocardial infarction in patients undergoing non-cardiac surgery, then treatment of postoperative myocardial ischemia should reduce morbidity. In addition, reducing pain and stress and avoiding postoperative hypoxemia might prevent postoperative myocardial ischemia and minimize the need for extensive preoperative cardiac evaluation.

HISTORICAL PERSPECTIVES

The ever expanding interest in perioperative myocardial morbidity and mortality is due, at least, to an increased prevalence of major non-cardiac procedures in patients with known or suspected CAD[b]. Cardiovascular disease, especially coronary artery disease, continues to be a significant cause of morbidity and mortality in the perioperative period [1].

Chronology and historical milestones in the understanding of perioperative myocardial morbidity are outlined in Table 1. Perioperative myocardial infarction was first identified as a clinical problem by a pathologist, Louis B. Wilson, on review of the 57,000 operative procedures performed at the Mayo Clinic 1899–1911 [2]. Amongst 47 deaths attributed to postoperative pulmonary embolism, there was one patient who died of coronary occlusion on the first postoperative day following gastroenterostomy for duodenal ulceration. More than two decades were to pass before investigators sought to determine predictors of, and factors associated with, perioperative myocardial infarction. Masters et al. [3] reviewed 625 patients with acute myocardial infarction at the Mount Sinai

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[b]*Abbreviations used:* PCM, perioperative cardiac morbidity; AECG, ambulatory electrocardiography; CAD, coronary artery disease; CABG, coronary artery bypass grafting; RWMA, regional wall motion abnormalities; EAA, epidural anesthesia and analgesia.

Table 1. Perioperative Cardiac Morbidity - Historical Perspectives.

Years	Authors	Findings	Reference(s)
1912	Wilson, L. B.	Myocardial Infarct Post Gastroenterostomy	2
1938	Master, A. M., Dack, S., and Jaffe, H. L.	Series of 35 MI's - Clinical Features/ Etiology	3
1950	Kannel, W. B.	Framingham Epidemiology Studies	4
1952	Wroblewski, F. and LaDue, J. S.	Perioperative MI Reevaluated	5
1964	Toplins, M. J., Artrusio, J. F., Arkins R. et al.	MI Risk Quantified	6, 7
1972/1978	Tarhan S., Steen, P. A. et al.	Perioperative Risk Factors Identified	8, 9
1977	Goldman et al.	Multifactorial Approach - Cardiac Risk Index	11
1983	Rao et al.	Recent MI Data- Reassessment	12
1984	Pasternack, P. F. Cutler, B. S. et al.	Laboratory Preoperative Cardiac Testing	13, 14, 15
1985	Slogoff, S. and Keats, A. S.	Intraoperative Ischemia	41, 42
1988–1990	Knight, A. A. Mangano, D. T. et al.	Systematic evaluation of pre, intra, and postoperative myocardial ishemia	26, 27, 28, 39, 43

Hospital, New York, from 1931 to 1937. Thirty-five of these myocardial infarctions followed a surgical procedure. The authors suggested acute thrombosis, with platelet deposition and aggregation superimposed on an atherosclerotic plaque, as the likely etiologic mechanisms of perioperative myocardial infarction. Intraoperative contributing factors were thought to include hypotension, shock, blood loss, tachycardia, arrhythmias and hypoxia.

The Framingham coronary artery disease investigators began their landmark long-term, observational and prospective studies in 1950 to determine the host and environmental factors predisposing to cardiovascular disease [4]. The increased awareness of cardiovascular risk factors provided by the Framingham Study research reports encouraged public health campaigns against smoking in the 1960's, hypertension in the 1970's, and against cholesterol in the 1980's. These efforts may have contributed to the remarkable decline in deaths in the United States attributable to cardiovascular disease in the past two decades.

Although the clinical features associated with perioperative myocardial infarctions were superficially reported again in 1952 [5], a decade passed before investigators attempted to determine the predictors of infarction. In 1964, two separate groups of investigators, Topkins and Artusio [6] and Arkins et al. [7], simultaneously reported a 10-fold increased incidence of postoperative myocardial infarction, with significantly increased mortality, in patients with prior preoperative infarction. The rate of reinfarction was related to the interval between infarction and surgery.

During the late 1960's and the 1970's, investigators from the Mayo Clinic identified preoperative predictors of PCM[b], readily obtainable from the routine history and physical examination [8–9]. Patients operated on within three months of a previous infarction had a 37% reinfarction rate. This perioperative infarction rate decreased to 11% if the infarct had occurred three to six months previously and stabilized at 4% to 5%, if the interval was more than six months. Risk factors associated with significantly increased reinfarction rates included preoperative hypertension, intraoperative hypotension, and thoracic or upper abdominal operations of more than 3 hrs duration. The conclusions from these studies were questioned because multiple study designs (retrospective vs. prospective) and analyses (univariate vs. multivariate) were used [10]. Many of these predictors subsequently had as many studies supporting as refuting their prognostic value. Only one predictor, recent myocardial infarction, was consistently identified, resulting in the commonly accepted practice of delaying elective surgery for 6 months after a myocardial infarction.

The first multifactorial approach to the study of factors involved in perioperative cardiac morbidity was reported in 1977 by Goldman et al. [11]. These investigators assigned a relative value to a series of preoperative predictors and developed a cardiac risk index for patients undergoing noncardiac surgery. Rao et al. [12], using an aggressive approach to perioperative monitoring and therapy, demonstrated a substantial reduction in reinfarction rates compared with historical controls. However, independent studies from other institutions confirming these findings have not yet been reported.

MYOCARDIAL ISCHEMIA - ASSOCIATION WITH PERIOPERATIVE CARDIAC MORBIDITY

Until the early 1980's, investigators attempted to identify perioperative clinical factors for cardiac complications, such as recent myocardial infarction and congestive cardiac failure. From the mid 1980's, laboratory based investigations became available to assess ventricular function and identify potentially ischemic myocardium. In 1984, the first of a series of studies addressed the prognostic value of specialized preoperative cardiac testing, including exercise stress testing [13], radionuclide angiography [14], and dipyridamole-thallium scanning [14]. These techniques, evaluated over the next five years, were advocated for use in high cardiac risk patients undergoing noncardiac surgery. Subsequent negative results, however, tempered initial enthusiasm [16–17].

In the 1980s silent myocardial ischemia emerged as a topic of significant clinical interest. This was largely because of a great number of publications demonstrating that approximately 70% of the ischemic episodes in patients with symptomatic coronary artery disease are not associated with angina [18], that approximately 10–15% of acute myocardial infarctions are silent [19], and that some asymptomatic patients successfully resuscitated after cardiac arrest subsequently have exercise-induced silent ischemia as the only manifestation of underlying coronary artery disease [20]. Given these observations, and assuming that asymptomatic ST-segment abnormalities in patients with coronary artery disease reflects myocardial ischemia, the question arose as to whether it was clinically imperative to document the existence, duration and magnitude of silent ischemic episodes in order to evaluate and optimally treat the patient with coronary artery disease [21].

Several AECG studies have now demonstrated a circadian pattern of myocardial ischemia, as detected by ischemic ST-segment changes [22–23]. The frequency of ischemic episodes, whether silent or painful, increases in the early morning and wanes in the early afternoon and evening. The onset of acute myocardial infarction and sudden death also exhibit circadian rhythms, with patterns that are remarkably similar to those

observed for myocardial ischemia [24–25]. One implication of these findings is that when ischemia is most common in the early morning, severe and prolonged episodes may progress and lead to acute myocardial infarction and sudden death.

Several studies in the early 1990's have shown that cardiac morbidity in patients undergoing major, noncardiac surgery is best predicted by postoperative myocardial ischemia, rather than tradition preoperative clinical predictors [26–27]. Long duration postoperative ischemia, rather than the mere presence of postoperative ischaemia, may be the factor most significantly associated with cardiac outcome [28].

DETECTION OF MYOCARDIAL ISCHEMIA - CONTINUOUS AECG MONITORING

The development of ambulatory electrocardiographic recorders and analyzers and the application of transesophageal echocardiography (TEE) in the mid-1980's enabled investigators to quantify and describe the occurrence of silent as well as symptomatic ischemia in the perioperative period. Several technical advances which have recently occurred in ECG monitoring include the use of miniaturized digital computing equipment to store and analyze data. In addition, real time ST-segment analysis has become widely available on multicomponent monitors in both the operating room and intensive care units.

Deanfield et al. [29] have validated the technology of AECG recording as a reasonably accurate marker for myocardial hypoperfusion in patients with known coronary artery disease. Criteria for ischemia detection included horizontal or downstroking ST-segment depression of at least 1 mm from baseline, 60–80 msec (depending on heart rate) after a J point, at least 1 min duration and separated by at least 1 min or normal baseline from other discrete episodes.

AECG technical issues include the frequency of response characteristics of the recording device, the basic format for recording ST-segment data (digital/analogue), choice of leads and duration of monitoring [30]. To accurately measure ST-segment shift intraoperatively, the monitor must be in the diagnostic mode. In the monitor mode, the lower frequencies are filtered to reduce noise, and some of the ST-segment data are lost. It should be noted that this use of a diagnostic mode may overestimate the ST-segment displacement by some monitors [31].

The format of data recording and storage with AECG recorders can be either analog or digital. The analog tape system offers the advantages of full-disclosure recording but requires postrecording analysis with the assistance of a trained technician. The digital system offers on-line recording and analysis of data. Appropriate validation must be performed comparing the digital recordings and analysis to reference ECG data. In addition to analysis capability, the digital systems are equipped with alarms, which my be activated by preset criteria, to indicate onset of ST-segment depression, heart rate changes, and arrhythmias.

The optimal number and location of leads for AECG monitoring is controversial. Consensus opinion would indicate that bipolar V5 lead is the best single lead, and a bipolar "inferior" limb lead II is the best choice for a second lead. London et al. [32], in an intraoperative study of 105 non-cardiac surgical patients, concluded that, although lead V5 was the most sensitive, only 80% of ischemic episodes detected by a 12-lead system were detectable using a combination of Lead II and V5. Sensitivity increased to 96% by combining leads II, V4, and V5. The use of all three leads would appear to be the optimal arrangement for most clinical needs and is recommended if the clinician has this capability.

The optimal duration of AECG recording may be up to seven days in the postoperative period. This approach may be impractical because of patient factors such as dis-

charge from hospital, patient compliance, and technical factors, such as tape and battery changes. In practice, 48 hrs of postoperative recording may suffice. This duration significantly reduced the variability associated with shorter periods of monitoring [33].

PREOPERATIVE MYOCARDIAL ISCHEMIA

Current consensus does not support the use of AECG monitoring as a screening tool for detecting coronary artery disease (CAD) [30]. Little information is available regarding the diagnostic accuracy of AECG monitoring in patients with no known history of CAD, particularly in those patients with a relatively low pre-test probability of CAD. The use of preoperative ST-segment monitoring should be restricted to patients with a known history of CAD or who are at risk for disease, based on cardiac risk factors or conditions such as aortic/peripheral vessel occlusive or aneurysmal disease, in whom the pretest probability of disease is high. Several caveats deserve mention. AECG recordings were unreliable in up to 15% of patients in one recent study [34]. AECG recordings may not be diagnostic of ischemia in the presence of conduction defects or abnormal baseline ST-segments. Patients with left ventricular hypertrophy, left or right bundle branch block, and resting baseline ST-segment depression greater than 1 mm associated with hypokalemia or digoxin therapy may not be suitable candidates for AECG recording.

The incidence of preoperative myocardial ischemia in noncardiac patients varies depending on the population studied and the time of evaluation prior to surgery [35]. Several authors have evaluated patients undergoing aortic and peripheral vascular surgery. Raby et al. [34], in a study of 176 patients with peripheral vascular disease undergoing elective vascular surgery, reported an 18% incidence of preoperative myocardial ischemia during the 24–48 hrs of monitoring from 2 to 9 days prior to surgery. Ninety-seven percent (73/75) of ischemic episodes were silent. Thirty-eight percent of patients with preoperative ischemic ST-segment changes suffered a subsequent major cardiac ischemic event, while only 1% of patients without preoperative ischemia had such postoperative complications. Pasternack et al. [36] studied patients during the 24 to 48 hrs prior to vascular surgery and reported a 24% (48/200) incidence of preoperative ischemia. However, Ouyang et al. [37] and McCann and Clements [38] reported preoperative ischemia in only 12% (3/24) and 14% (7/50), respectively, in their patient population. The percentage of patients who were ambulatory as opposed to bedridden varied among the studies, and the increased stress of ambulation may account for some of the discrepancies [35].

Knight et al. [39] used AECG recording to study 50 men with severe coronary artery disease undergoing elective coronary artery bypass grafting. They reported that 21 (42%) of the 50 patients demonstrated preoperative ischemia during the 2 days prior to surgery; 87% of the episodes were silent. The symptomatic episodes were associated with greater ST-segment changes compared with the painless episode. More than 75% of all episodes occurred without an initial increase in heart rate. In this study, the presence of preoperative myocardial ischemia was not predictive of postoperative cardiac morbidity.

INTRAOPERATIVE MYOCARDIAL ISCHEMIA

Despite the absence of convincing data, anesthesiologists have for many decades suspected an association between perioperative ischemic episodes and postoperative myocardial infarction [40]. The landmark study by Slogoff and Keats [41] in 1985 clearly established the association. Until that time, outcome studies attempted to solve the problem of PCM by identifying the preoperative predictors [10]. Implicit in this approach was that the preoperative chronic disease state of the patient was primarily responsible for PCM. Intraoperative and postoperative alterations in hemodynamics, catecholamines, and

myocardial ischemia may be equally important determinants of PCM.

The incidence of intraoperative myocardial ischemia depends on the patient population, the surgical procedure, and the monitoring technique used. Studies by Slogoff and Keats [41–42] confirmed that patients undergoing coronary artery bypass grafting (CABG) who develop ECG ST-segment changes indicative of ischemia during the pre-bypass period had a 2- to 3-fold increased risk of MI. In their first study [41], 37% (377/1023) of their patients who developed ST changes prior to bypass had an infarction rate of 6.9%, in contrast to the 2.5% (646/1023) who did not develop pre-bypass ischemia. However, Knight et al. [43] demonstrated that a chronic and often silent pattern of ischemia existed preoperatively in CABG patients. These investigators have demonstrated that the intraoperative incidence of myocardial ischemia was no worse than the preoperative pattern [39], implying that modern anesthesia and surgery may not be as stressful as previously assumed, and that the intraoperative pattern may simply reflect the chronic preoperative pattern.

The surgical procedure may influence the incidence of ischemia. Of note, high incidence of myocardial ischemia have been reported following surgery which involves cross clamping of the abdominal or thoracic aorta [44]. A more proximal placement of the aortic clamp may be associated with a greater incidence of myocardial ischemia. Using two-dimensional TEE, Roizen et al. [45] observed significant increases in left ventricular end-systolic and end-diastolic volumes, decreases in left ventricular ejection fraction and frequent regional wall motion abnormalities (RWMA) with supraceliac aortic cross clamp. However, in virtually all studies of non-cardiac surgery patients, intraoperative myocardial ischemia was not an independent predictor of perioperative cardiac morbidity. Only in a sub-group of patients undergoing carotid endarterectomy did Pasternack et al. [36] report a significant higher incidence and duration of intraoperative myocardial ischemia in patients who subsequently sustained a myocardial infarction.

The incidence of myocardial ischemia is very much dependent on the monitoring technique employed. Intraoperative myocardial ischemia may be detected by ECG ST-segment changes (V5 most consistently), pulmonary artery occlusion pressure, and V-wave development, or segmental wall thickening changes detected by transesophageal echocardiography or cardiokymography [46]. The earliest physiologic changes following experimental coronary ligation are changes in myocardial wall thickening, followed by changes in the endocardial and surface ECG [47].

Using TEE and AECG recorders, Leung et al. [48] reported different results in 50 patients undergoing elective coronary artery bypass grafting. A 20% incidence of regional wall motion wall abnormality and a 7% (3 out of 44) incidence of ischemic ECG changes were noted during the pre-bypass period. During the post-bypass period, they reported 30% incidence of RWMA and 25% incidence of post-bypass ECG changes. Discrepancy between the two monitoring modalities reflect the fact that 82% of the echocardiographic episodes of ischemia were not associated with changes on the ECG. Although the differences may reflect differences in the sensitivity of the two monitoring modalities, it may also reflect differences in the pathophysiological effects of myocardial ischemia.

POSTOPERATIVE MYOCARDIAL ISCHEMIA

Several studies in the early 1990's have shown that cardiac morbidity in patients undergoing major vascular surgery is best predicted by postoperative myocardial ischemia, rather than tradition perioperative clinical predictors [26–27]. The study of perioperative myocardial ischemia (SPI) Research Group, in a study of 474 men with known or suspected coronary artery disease undergoing non-cardiac surgery, reported

ischemic ST-segment changes during the preoperative period in 20% of patients, intraoperative period in 25%, and postoperative period in 41%. Postoperative myocardial ischemia was associated with a 2.8-fold increase in the odds of all adverse cardiac outcomes. In contrast, preoperative ischemic ST-segment changes were not found to be significantly correlated with cardiac outcome. Long duration postoperative ischemia, rather than the mere presence of postoperative ischemia, may be the factor most significantly associated with cardiac outcome [28].

The intense procoagulant activity and sympathetic stimulation in the postoperative period has been implicated in the development of coronary vasospasm, thrombosis, and rupture of atheromatous plaque, thus leading to myocardial ischemia and infarction [10]. However, this mechanism may not be a very plausible because ST-depression is the most common ECG change and the classic ST-elevation marker for acute coronary occlusion is rare in the postoperative period [28].

The neurohumoral stress response to major surgery is the subject of clinical interest and investigation [49]. Measurement of coagulation activity in the postoperative period consistently demonstrates elevations of platelet reactivity, factor VIII, and von Willebrand factor (vWf). Antithrombin III, the principal inhibitor of thrombin activity, progressively decreases during the early postoperative period. Patients undergoing peripheral vascular surgery have postoperative increases in platelet reactivity and in factor VIII related antigen and have decreases in antithrombin III levels, indicative of a hypercoagulable state, that may be associated with early arterial graph failure. Tuman et al. [50] reported that patients about to undergo peripheral vascular surgical procedures were hypercoagulable before operation compared with control patients without atherosclerotic heart disease. The use of EAA attenuated this hypercoagulability postoperatively. The authors suggested that decreases in cortisol, renin, aldosterone, and catecholamine levels associated with EAA might translate to higher antithrombin III and lower fibrinogen levels with attenuated platelet activity postoperatively, consistent with the thromboelastographic findings in their study.

As most cardiovascular mortality occurs in the hours and days after completion of vascular surgery, postoperative stress-induced hypercoagulability could play a causal role. Epidural anesthesia and analgesia continuing into the postoperative period may attenuate the postoperative stress response in specific patient populations. Mechanisms may include epidurally-mediated alterations in lower limb blood flow, as well as stress hormone and vWf concentrations. Epidural anesthesia increases blood flow to both calf and femoral veins [51]. Blood flow in the legs of patients with occlusive atherosclerotic disease is increased after epidural anesthesia [52]. This effect may be enhanced when postoperative epidural analgesia includes a dilute solution of local anesthetic to maintain some degree of sympathetic block after arterial reconstruction. The stress-mediated release of cortisol, catecholamines, corticotropin, antidiuretic hormone and other metabolic precursors are blunted by high levels of epidural anesthesia [53].

Alternatively, postoperative pain, physiological and emotional stress may all combine to cause tachycardia, hypertension, increase in cardiac output, and fluid shifts which, in high risk patients, might result in subendocardial ischemia and eventual myocardial infarction [28]. Intermittent brief periods of myocardial ischemia have been reported to have a cumulative effect and may cause myocardial necrosis. The clinical features of postoperative myocardial ischemia are of interest. Mean heart rates are generally higher in the postoperative period than before or during surgery. Thus, it seems that the cascade of events leading to postoperative cardiac complications begins with long duration subendocardial ischemia rather than acute coronary occlusion.

Hypoventilation secondary to pain, central respiratory depression, and upper airway

obstruction have all been proposed as mechanisms for hypoxemia commonly observed in the postoperative period [54]. Gill et al. [55] used continuous and concurrent oximetry and AECG to study the relationship between hypoxemia and silent myocardial ischemia in the perioperative period in 11 patients with cardiovascular disease. Episodes of postoperative hypoxemia during which ischemia occurred were significantly longer in duration (5 min or more) and more severe (SpO_2 <85%) than those episodes during which ischemia did not occur. Similarly, the duration of episodes of ischemia associated with hypoxemia were significantly longer than those events during which hypoxemia did not occur. The close correlation between the overall hourly ischemic and hypoxemic times emphasizes the relationship between hypoxemia and ischemia.

SUMMARY

Several recent studies have shown that cardiac morbidity in patients undergoing major, noncardiac surgery is best predicted by postoperative myocardial ischemia, rather than tradition preoperative clinical predictors. Postoperative myocardial ischemia is virtually always silent and has been documented up to 7 days postoperatively.

The postoperative period is associated with significantly higher heart rates than either the pre- or intra-operative period. The generalized tachycardia may be the result of surgical pain and stress. In addition, weaning from mechanical ventilation in the intensive care unit has been associated with both myocardial ischemia and infarction. Circadian variation in postoperative myocardial ischemia has been reported, with the majority of ischemic episodes occurring during the morning hours.

If postoperative myocardial ischemia is the cause of late postoperative myocardial infarction in patients undergoing non-cardiac surgery, then treatment of postoperative myocardial ischemia should reduce morbidity. In addition, reducing pain and stress and avoiding postoperative hypoxemia might prevent postoperative myocardial ischemia and minimize the need for more extensive cardiac evaluation.

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