Perioperative Cardiac Morbidity

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The Problem

CARDIOVASCULAR DISEASE IN THE UNITED STATES
CARDIOVASCULAR DISEASE is a major health-care problem in the United States, affecting one in four Americans.

(65/239 million).1,2,† The annual mortality rate for cardiovascular disease is 1 million, which exceeds that of all other diseases combined and accounts for one of every two deaths in the United States (fig. 1). Annual morbidity exceeds 2.5 million: 1.5 million myocardial infarctions (MI), 0.6 million strokes, and 0.4 million cases of congestive heart failure (CHF). Total morbidity and mortality costs per year surpass $83 billion.3

Although hypertension is the most prevalent form of cardiovascular disease (59.1 million), coronary artery disease (6.7 million) causes the highest morbidity (MI, CHF) and mortality (541,000 deaths annually) (figs. 2 A–C).† Consequently, the diagnostic testing of patients with coronary artery disease (CAD) has increased substantially.

ANNUAL CARDIOVASCULAR DISEASE STATISTICS

Fig. 1. U. S. annual mortality statistics. (Source: National Center for Health Statistics, U. S. Public Health Service, Department of Health and Human Services, [1988].)

Fig. 2. U. S. annual cardiovascular disease (CVD) statistics. (Sources: National Center for Health Statistics, U. S. Public Health Service, Department of Health and Human Services [1988], and estimates by the American Heart Association [1988] and National Heart, Lung, and Blood Institute [1988].) A (top left) Prevalence of CVDs in the U. S. HTN = hypertension; CAD = coronary artery disease; Rhythm = heart rhythm disorder; PVD = peripheral vascular disease; CeVD = cerebrovascular disease; CHF = congestive heart failure; RHD = rheumatic heart disease. The total of the individual estimates exceeds 64,890,000, since many people have more than one cardiovascular disorder. B (bottom left) Annual number of first and recurrent morbid cardiovascular events in the U. S. (1988). MI = myocardial infarction. C (top right) The annual U. S. mortality associated with individual CVDs (1988). D (bottom right) Estimated costs associated with the three most costly CVDs in the U. S. (1988).
PERIOPERATIVE CARDIAC MORBIDITY

Table 1. Coronary Artery Disease: Incidence, Prevalence, Mortality, and Cost Projections

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
<th>Prevalence</th>
<th>Mortality</th>
<th>Cost*</th>
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<tr>
<td>1980</td>
<td>692,117</td>
<td>5,977,405</td>
<td>432,613</td>
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<td>1985</td>
<td>729,235</td>
<td>6,700,639</td>
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<td>1990</td>
<td>759,583</td>
<td>7,230,904</td>
<td>540,557</td>
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<td>1995</td>
<td>792,006</td>
<td>7,625,001</td>
<td>567,798</td>
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<td>834,522</td>
<td>7,973,869</td>
<td>596,777</td>
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<td>888,438</td>
<td>8,385,046</td>
<td>608,434</td>
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<tr>
<td>2010</td>
<td>933,750</td>
<td>8,939,816</td>
<td>632,504</td>
<td>47.4</td>
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</table>


(>850,000 cardiac catheterizations annually), as has the use of pharmacologic therapies (nitrates, β-blockers, calcium-channel blockers) and antithrombotic therapies (streptokinase, tissue plasminogen activator). The number of angioplasties has increased dramatically to 300,000 per yr, surpassing the number of coronary artery bypass graft (CABG) surgeries (285,000 per yr). The annual cost of CAD-related care exceeds $35 billion (fig. 2 D).

Cardiovascular disease will continue to be a major health-care problem. The prevalence of cardiovascular disease increases with age, and the population of the United States is aging rapidly. Twenty-five million people (10%) are now over the age of 65, including 2.7 million older than 85. By the middle of the next century, the population over 65 is expected to increase to 66 million, many of whom are likely to have cardiovascular disease (fig. 3). Although we have reduced cardiovascular disease death rates by 20–30%, the predominant influence of aging will offset this decreased mortality by increasing the incidence of cardiovascular disease. An example of such projections for CAD is given in table 1. Additionally, we have recently discovered a population of 2–5 million with a subclinical form of CAD known as silent myocardial ischemia, indicating that our current statistics for CAD (6.7 million) may underestimate its prevalence in the general population. The prognosis for silent ischemia appears to be similar to that for clinically manifest CAD, suggesting that it too will contribute to cardiovascular disease morbidity and mortality.

THE IMPACT OF CARDIOVASCULAR DISEASE ON ANESTHESIA AND SURGERY

The prevalence of cardiovascular disease substantially affects both cardiac and noncardiac surgery. It has doubled the annual number of cardiac surgeries to 400,000 (including 285,000 CABG surgeries and 48,000 valve re-
placements), and increased the annual cost of cardiac surgical care to more than $5 billion. Despite the introduction of angiotensin and laser surgery, the number of cardiac surgeries will increase as prevalence increase.

The impact of cardiovascular disease on noncardiac surgical patients is even greater, and will be the focus of this review. In 1988, more than 25 million patients required noncardiac surgery versus 400,000 cardiac surgeries. The noncardiac surgical patients at risk for cardiac morbidity or mortality number close to 7–8 million annually (fig. 4); approximately 1 million people have diagnosed CAD (classical angina, Q-waves on preoperative electrocardiogram [ECG]), 2–3 million two or more major risk factors for CAD, and 4 million are over the age of 65.‡ Moreover, 25% of the noncardiac surgical population require major intra-abdominal, thoracic, vascular, neurologic, or orthopedic procedures that further stress existing cardiac risk factors. For example, 40–70% of patients undergoing major vascular surgery without clinically evident CAD have angiographically demonstrable coronary stenoses.

The future impact of cardiovascular disease on anesthesia and surgery is likely to be substantial given that the largest number of operations and the greatest length of stay now occur in the over-65 age group (figs. 5 A, B). Over the next 30 yr the number of noncardiac surgical procedures will increase by 50% (to 38 million), as the percentage of surgical patients over 65 increases from 25 to 35%. The total number of older noncardiac surgical patients in whom cardiovascular disease is prevalent will thus double from 6 million to 12 million, thereby increasing the number of noncardiac surgical patients at risk for adverse cardiac outcome.

THE PROBLEM OF PERIOPERATIVE CARDIAC MORBIDITY

Does the prevalence of cardiovascular disease in noncardiac surgical patients increase perioperative compli-

![PREVALENCE OF CAD PER 1000 POPULATION](Fig. 3. Prevalence of CAD in four age groups in the U.S. (Sources: National Center for Health Statistics, U.S. Public Health Service, Department of Health and Human Services [1988]; and estimates by the American Heart Association [1988] and National Heart, Lung, and Blood Institute [1988]).)
cations? Is perioperative cardiac morbidity (PCM) a problem in patients undergoing noncardiac surgery?

PCM is the leading cause of death following anesthesia and surgery. It is generally defined as the occurrence of MI, unstable angina, CHF, serious dysrhythmia, or cardiac death during the intraoperative or in-hospital postoperative periods.

However, assessment of PCM is difficult. For example, asymptomatic transmural MIs can be detected by daily histories, ECGs, and cardiac enzyme levels, but most postoperative MIs are silent and many are subendocardial, requiring the use of more sensitive detection techniques, such as radionuclear imaging. Even then, smaller subendocardial infaracts (≤5 g) may not be perceived. Similarly, the detection of serious dysrhythmias requires the use of continuous postoperative ECG (Holter or real-time) monitoring, as well as continuous preoperative monitoring, to distinguish new from chronic dysrhythmias. Diagnosis of postoperative CHF is complicated because postoperative pulmonary congestion may be precipitated not only by heart failure, but also by decreased osmotic pressure or pulmonary capillary leak due to pre-existing pulmonary disease, sepsis, or over-transfusion. The presence of such conditions would necessitate the use of sensitive techniques for assessing ventricular function (radionuclear, echocardiographic). Thus, accurate detection of adverse cardiac outcomes following noncardiac surgery is difficult, and it is not surprising that reported outcome rates vary markedly.

What outcome data exist for PCM? The outcome data available are accumulated from approximately 100 studies spanning 35 yr. Most of the early studies were retrospective, whereas recent studies are prospective, focusing primarily on the outcomes of MI or cardiac death. Outcome data for unstable angina, CHF, or serious dysrhythmias are few. The available information is summarized in the following section (and table 2); myocardial ischemia, though not an outcome per se, is included for completeness.

Myocardial Ischemia. Intraoperative myocardial ischemia, diagnosed by ECG, transthoracic echocardiography (TEE), or lactate changes, occurs in 18 to 74% of patients with CAD undergoing noncardiac surgery. ECG studies suggest that ST changes most commonly occur in the lateral leads (V4, V5), and have a variable duration (1–258 min). The segmental wall-motion and thickening changes detected by TEE or cardiac catheterization are more sensitive indicators of ischemia than ECG ST-segment changes, but other characteristics of wall-motion changes, such as their location and duration, are unknown.

Intraoperative ischemia can be precipitated by increases in myocardial oxygen demand caused by tachycardia, hypertension, anemia, stress, sympathomimetic drugs, or

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§ The term "ischemia" is used throughout this text. However, both nonischemic and ischemic etiologies can exist for the ECG, TEE, and pulmonary capillary wedge pressure changes. It is difficult to distinguish among these etiologies since no absolute reference standard for ischemia exists and, even if available, would be difficult to apply perioperatively. Thus, "ECG ischemia" in this review should be interpreted as "ECG changes that may be consistent with ischemia," and similarly for the other techniques.
discontinuation of β blockers. However, as many as 50% or more of the ischemic episodes may be unrelated to the indices of oxygen demand, suggesting decreased oxygen supply as the primary cause. 27-38,42 Potential etiologies for decreased supply include external factors, such as hypotension, tachycardia, increased filling pressures, anemia, or hypoxemia. In addition, internal factors like acute coronary artery thrombosis and spasm also may play a role, 43-46 although no data are available for determining their importance in the perioperative setting. Finally, the relationship of intraoperative ECG, TEE, or cardiokymographic changes to outcome has not been investigated in patients undergoing noncardiac surgery.

Little is known about the postoperative period. However, recent preliminary studies suggest that the incidence of postoperative myocardial ischemia may be much higher than that of intraoperative or preoperative baseline ischemia. 33,47 These studies also suggest that postoperative episodes are generally silent, can occur as late as 7 days (or more) after surgery, and may be associated with a chronically elevated heart rate. Other potential causes of postoperative ischemia include alterations in oxygen supply due to external factors, or acute thrombosis and/or spasm. However, the role and relative importance of such factors remain unknown, as does the relationship of postoperative myocardial ischemia to outcome.

Myocardial Infarction. The incidence of MI after noncardiac surgery in the general population is 0.0-0.7%. 17,48,49 A perioperative infarction rate of 1.1% has been reported in patients with CAD, 50 and a (nonfatal) infarction rate of 1.8% in patients over 40 yr with or without CAD. 16 Reinfarction rates ranging from 5 to 8% 17,51-53 have been reported for patients with prior infarction, rates of 1-15% 11,16,19,54-56 for those who have had vascular surgery, and rates of up to 37% 17,22,51-53 for those with recent MI (table 2). However, the rates attained in patients with prior infarction have been challenged by Rao et al., 15 who found an overall reinfarction rate of only 1.9%, increasing to only 5.7% when the previous infarction was recent (<3 months). Aggressive intraoperative monitoring and extended stay in an intensive care unit (ICU) were used in Rao’s study group; however, the beneficial effect of such monitoring and treatment modalities has not been confirmed.

Few characteristics of perioperative MIs are known. Most perioperative MI seems to occur postoperatively and silently, 14-25 making them difficult to detect and precise onset difficult to determine. A number of factors may be responsible for the silent nature of perioperative MI, including altered pain perception due to residual anesthetic effects, administration of analgesics, or competing somatic stimuli (such as incisional pain). As with silent ischemia, the mechanism is still uncertain. The etiology of perioperative MI is also uncertain, and little information is available. There are, however, a number of proposed hypotheses for the etiology of MI and the other acute ischemic syndromes—unstable angina and sudden ischemic death. 44-46,66,67 It appears that these syndromes may share the same pathophysiology and represent a continuum of change involving atherosclerotic plaque rupture, intraluminal thrombosis, and coronary arterial wall spasm. With progressive atherosclerosis, the raised coronary artery lesion causes local blood flow disturbances, producing

| TABLE 2. Estimated Incidence of Perioperative Cardiac Morbidity (Noncardiac Surgery) |
|---------------------------------|-----------------|------------------|
| | Outcome | Incidence | References |
| Myocardial ischemia | | |
| Preoperative | 94% | 33 |
| Intraoperative | 18-74% | 27-38, 42 |
| Postoperative | 27-38% | 33, 47 |
| Myocardial infarction | | |
| General population | 0.1-0.7% | 17, 48, 49 |
| Prior MI | 1.9-7.7% | 15, 17, 22, 51, 52, 53 |
| Vascular surgery | 1-15% | 11, 16, 19, 54-65 |
| Recent MI | 0-37% | 15, 17, 22, 51-53, 127 |
| Unstable angina | unknown | |
| Congestive heart failure | | |
| Intraoperative | 4.8% | 15 |
| Postoperative | 3.6% | 16 |
| Serious dysrhythmias | | |
| Intraoperative | 0.9-36% | 92-94 |
| Postoperative | 14-40.5% | 94 |
| Cardiac death with PMI | 36-70% | 14, 48 |
shear stresses on the delicate fibrous cap of the lesion. Plaque rupture ensues and precipitates intimal hemorrhage into the plaque and, more importantly, luminal thrombosis with platelet aggregation and adhesion. Powerful biochemical mediators are released from: 1) the aggregating platelets, including vasoactive thromboxane and serotonin;\textsuperscript{45,68–71} 2) infiltrating leukocytes, including free radicals and chemo-attractant and coronary constrictor leukotrienes;\textsuperscript{72–74} and 3) abnormal arachidonic acid metabolism, including prostacyclins, prostaglandins, and other platelet proaggregants.\textsuperscript{73,75} As a result, thrombosis rapidly progresses and vasospasm is exacerbated. The thrombosis assumes a dynamic and unstable nature. Fibrolysis, recanalization, and peripheral embolization precipitate cyclic reduction in coronary flow and distal perfusion pressure, manifested by unstable symptoms. Eventually, complete occlusion occurs, resulting in transmural MI and, when extensive or associated with dysrhythmia, sudden ischemic death. In the perioperative period, a number of factors may exacerbate this process and precipitate acute MI, including: 1) increased coronary artery shear stresses due to alterations in contractility, blood pressure, coronary flow, and coronary tone;\textsuperscript{43,44,46,76} 2) enhanced platelet aggregation due to increased catecholamines, changes in blood viscosity and coronary flow, and abnormal hemostasis;\textsuperscript{68–70,76–83} and 3) precipitation of vasospasm by release of humoral mediators during stress.\textsuperscript{43,46,66,67,84} However, few data are available, and the role of these factors in the perioperative period is undetermined.

Unstable Angina. Although the incidence of unstable angina following noncardiac surgery is unknown, data are available on the incidence of stable angina. In 1,600 Coronary Artery Surgery Study registry patients, Foster et al.\textsuperscript{50} reported an 8.7% incidence of postoperative chest pain in patients with CAD undergoing noncardiac surgery versus 4.5% in patients without CAD, and 5.1% in those with previous CABG (P = 0.004). However, the incidence of ischemia may be substantially higher because of its silent nature. Recent studies suggest that in patients with or at risk for CAD, the incidence of postoperative ECG ST changes may be as high as 38%, with more than 85% of the episodes being silent.\textsuperscript{35,47}

As discussed earlier, unstable angina (or ischemia) may reflect cyclic coronary obstruction produced by an unstable thrombus associated with varying degrees of vasospasm. A number of perioperative factors can exacerbate this cyclic obstruction, including the catecholamine, hemodynamic, and rheologic stresses already cited. Unfortunately, little information is available.

Congestive Heart Failure. Two large-scale studies have investigated CHF in noncardiac surgical patients\textsuperscript{5,16} and suggest that the incidence of perioperative CHF is not insignificant in at-risk patients. Rao et al.\textsuperscript{15} found a 4.8% (29/609) incidence of intraoperative CHF (pulmonary capillary wedge pressure [PCWP] > 25 mmHg) in patients with previous MI, and Goldman et al.\textsuperscript{16} found a 3.6% incidence of postoperative CHF in patients older than 40 with or without CAD. Several etiologic factors may play a role. In patients with CAD, isolated regional ischemia (producing papillary muscle dysfunction), global ischemia, or infarction may impair diastolic relaxation and systolic contraction, and precipitate CHF. The underlying pathophysiologic mechanisms include: 1) decreased actinomy- cin-ATPase activity and reduction of high-energy phosphates; 2) decreased synthesis of and intramyocardial depletion of norepinephrine; and 3) decreased function of the sarcoplasmic reticulum, with accumulation of intracellular calcium.\textsuperscript{85–89} In addition, perioperative increases in afterload or preload (secondary to catecholamine, temperature, fluid shift, or respiratory changes) will mechanically affect both diastolic and systolic function, and exacerbate CHF.\textsuperscript{90,91} The presence of cardiomyopathy (dilated or obstructive) or valvular heart disease may also contribute. The relative contribution of these ischemic and mechanical effects remains uncertain, since few perioperative studies have used sufficiently sensitive detection techniques allowing discrimination.

Serious Dysrhythmias. Although a number of studies have addressed the incidence and characteristics of intraoperative dysrhythmias,\textsuperscript{92} only a few have used continuous recording techniques\textsuperscript{93,94} and none have studied postoperative dysrhythmias in conjunction with the preoperative baseline pattern. The reported incidence of intraoperative dysrhythmias ranges from 13 to 84%, with ventricular dysrhythmias ranging from 3 to 60%.\textsuperscript{93–95} The incidence of serious dysrhythmias (e.g., persistent multifocal premature ventricular contractions, ventricular tachycardia, ventricular fibrillation) has been reported to range between 0.9% and 6.0%.\textsuperscript{93} During recovery from anesthesia, Bertrand et al.\textsuperscript{94} reported a 48% incidence of dysrhythmias, with 28% ventricular. However, it is unclear whether these were new dysrhythmias or a recapitulation of the preoperative pattern. Furthermore, the relationship of perioperative serious dysrhythmias to ischemia or to other in-hospital or long-term adverse cardiac outcomes is unknown.

Cardiac Death. In patients without CAD, Foster et al.\textsuperscript{50} reported a 0.5% cardiac mortality rate versus 2.4% in patients with CAD. In patients over 40 yr of age, with or without CAD, Goldman et al.\textsuperscript{16} reported a rate of 1.9%. The mortality rate associated with perioperative MI ranges from 36 to 70%.\textsuperscript{4,48} Mortality rates associated with other cardiac outcomes are unknown.

In summary, PCM is the primary cause of death following anesthesia and surgery, but many of its characteristics are unknown. Approximately 50,000 patients per yr sustain a perioperative MI and 20,000 of these die.
The cost of an in-hospital MI is approximately $12,000,\textsuperscript{96} resulting in health-care costs of hundreds of millions of dollars for perioperative MI alone.

**ATTEMPTED SOLUTIONS TO THE PROBLEM**

The problem of PCM is analogous to that faced by CAD investigators in the 1950s: only when predictors of CAD were identified (in studies such as that in Framingham) could rational approaches to prevention and treatment be developed to reduce morbidity.\textsuperscript{97} Similarly, although perioperative MI was first identified as a problem in 1952,\textsuperscript{98} but a decade passed before investigators attempted to determine the predictors of infarction (fig. 6). As a result, between 1961 and 1976, investigators, including those from the Mayo Clinic, identified historical preoperative predictors of PCM, readily obtainable from the routine history and physical examination.\textsuperscript{17–20,51,99,100} However, multiple study designs (retrospective vs. prospective) and analyses (univariate vs. multivariate) were used, leading to controversial results. Most predictors had as many studies supporting as refuting their prognostic value. Only one predictor, recent MI, was consistently identified, resulting in the commonly accepted practice of delaying surgery 6 months after an MI. In 1977, the first multifactorial approach was designed by Goldman et al.\textsuperscript{10} who assigned a relative value to a series of preoperative predictors and developed a cardiac risk index. Although several studies have challenged the usefulness of this index,\textsuperscript{54,101,102} the importance of this study remains unquestioned. In 1983, using an assertive approach to perioperative monitoring and therapy, Rao et al.\textsuperscript{15} demonstrated substantially improved reinfarction statistics; however, independent studies confirming their findings have not been performed.

In 1984, the first of a series of studies addressed the prognostic value of specialized preoperative cardiac testing. Exercise stress testing\textsuperscript{21,103–105} and radionuclide\textsuperscript{106,107} and dipyridamole thallium imaging\textsuperscript{108–111} were evaluated over the next 5 yr, and advocated for use in patients undergoing noncardiac surgery. The results, however, are preliminary.

### PCM OUTCOME STUDIES

<table>
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<tr>
<th>YEAR</th>
<th>FINDING</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952</td>
<td>PERIOPERATIVE MI IDENTIFIED AS A PROBLEM</td>
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<tr>
<td>1977</td>
<td>MULTIFACTORIAL APPROACH TO IDENTIFY PREOPERATIVE RISK FACTORS</td>
<td>16</td>
</tr>
<tr>
<td>1983</td>
<td>RECENT MI DATA CHALLENGED</td>
<td>15</td>
</tr>
<tr>
<td>1984</td>
<td>SPECIALIZED PREOPERATIVE TESTS (EST, RN, DT) RECOMMENDED FOR DETERMINING RISK</td>
<td>21, 55, 102–111</td>
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<tr>
<td>1985</td>
<td>INTRAOPERATIVE (DYNAMIC) RISK FACTORS IDENTIFIED: ECG, TEE ISCHEMIA</td>
<td>26, 27, 32, 33, 41, 42, 112</td>
</tr>
<tr>
<td>1987</td>
<td>POSTOPERATIVE (DYNAMIC) RISK FACTORS STUDIED</td>
<td>26, 33, 41, 47</td>
</tr>
</tbody>
</table>

**Fig. 6.** Chronology of the most important findings of outcome studies assessing perioperative cardiac morbidity.
In 1985, an important series of studies emerged. Until that time, outcome studies were attempting to solve the problem of PCM by identifying the preoperative predictors. Implicit in this approach was that the preoperative chronic disease state of the patient was primarily responsible for PCM. However, the entire perioperative period is dynamic. Intraoperative and postoperative alterations in hemodynamics, catecholamines, and the ischemic state may be equally important determinants of PCM. Outcome studies since then have emphasized this by focusing on the intraoperative “dynamic” predictors of PCM, particularly myocardial ischemia. The results of Slogoff and Keats and Smith et al. demonstrate the importance of intraoperative ischemia, at least in patients undergoing CABG surgery. Furthermore, recent studies in these patients suggest that the postbypass and postoperative periods may be equally or more important. However, only preliminary evidence now documents the importance of perioperative myocardial ischemia in patients undergoing noncardiac surgery.

The controversies surrounding the predictors of PCM in noncardiac surgical patients have resulted in a number of diagnostic and therapeutic dilemmas (fig. 7). Each of the three perioperative periods is associated with challenging and important questions. Preoperatively, should we delay surgery 6 months after recent MI, or can we infer from Rao et al.’s study that delay may no longer be necessary? Should the cardiac risk index suggested by Goldman et al. be used routinely to identify high-risk patients? Or, should nonroutine specialized tests, such as dipyridamole thallium imaging, be used in patients undergoing major vascular procedures or in high-risk subsets of these patients? Intraoperatively, in which patients should we use multiple-lead ECG, pulmonary artery monitoring, or TEE? Is choice of anesthetic agent or technique crucial? Should isoflurane be avoided in patients with CAD? Postoperatively, does prolonged ICU monitoring result in lower cardiac morbidity? If so, which patients should be monitored and for how long? Finally, what are the cost implications of such perioperative monitoring and therapeutic decisions in our present environment of health-care cost containment? We will address these challenging questions by reviewing the results of the perioperative outcome studies, and identifying the preoperative, intraoperative, and postoperative predictors of PCM.

The Preoperative Predictors

The preoperative period has been the most extensively studied for potential historical and diagnostic test predictors of outcome in patients undergoing noncardiac surgery (table 3). Several of these, such as recent MI and current CHF, are established predictors that identify the highest-risk patients. Most, however, remain controversial. Each will be discussed, beginning with historical predictors, followed by those derived from diagnostic (routine and nonroutine) testing.

Before proceeding, it should be noted that the studies cited and compared in this review have been performed

CURRENT DIAGNOSTIC AND THERAPEUTIC DILEMMAS

**ANESTHETIC CHOICE ISSUES:**
1. REGIONAL VS. GENERAL
2. INHALATIONAL VS. NARCOTIC
3. CORONARY STEAL

**THERAPEUTIC ISSUES:**
1. RANGES FOR HEMODYNAMIC CONTROL
2. INDICES: HRXBP, BP/HR
3. SPECIFIC CV THERAPES

**DISPOSITION ISSUES:**
1. EXTENDED ISCHEMIA MONITORING
2. PROLONGED ICU CARE

**USE OF COSTLY SPECIALIZED TESTS:**
1. EST, ECHO, RN, DT

**USE OF SPECIALIZED MONITORS FOR DIAGNOSIS OF ISCHEMIA:**
1. COMPUTERIZED ST TEE
2. PA CATHETERS

**PRE-OP**

**INTRA-OP**

**POST-OP**

Fig. 7. Cardiovascular tests, procedures, and care regimen dilemmas and controversies for the three perioperative periods.
over a period spanning 35 yr. Thus, they differ in a number of ways, including study design, methodology, and analysis. Study design differences include: 1) observational \(^{15-20,51,52,99,100}\) versus interventional; \(^{120-125}\) 2) cross-sectional \(^{11,124,125}\) versus longitudinal; \(^{15,16,50,62,63}\) and 3) retrospective \(^{17,18,22,51,126}\) versus prospective. \(^{15,16,19,20,52,55}\) Methodologic differences include: 1) study population size—large-scale \(^{15,17,22,50}\) versus small-scale; \(^{23,54,55,60,108-110,127}\) 2) selection criteria—age greater than 40 yr. \(^{16,101}\) history of CAD \(^{18}\) or MI, \(^{15,17,20,51,52,99,100}\) or required vascular surgery; \(^{21,54,55,102-111,129}\) 3) predictor variable type—routine historical/clinical; \(^{15-20,51,52,99,100}\) specialized test-derived; \(^{21,55,102-111}\) or physiologic; \(^{26,27,32,41,112}\) 4) predictor variable period of measurement—preoperative; \(^{15-22,51,52,55,100,102-111,130}\) intraoperative; \(^{26,27,32,41,112}\) or postoperative; \(^{83,47}\) 5) outcome variable type, measurement period, and criteria; and 6) data analysis differences, such as use of univariate \(^{17,20,51,52,99,100}\) versus multivariate analysis. \(^{16,50,131}\) The differences among these studies are critical to their interpretation, \(^{192,132}\) and have been previously reviewed in editorials that have accompanied most of them. The purpose of the present review is to summarize only their results. A detailed review of their design and methodology limitations is beyond the current scope, and the reader is referred to the accompanying editorials.

**HISTORICAL PREDICTORS**

**Age.** By the year 2055, the population of the United States will grow by an estimated 49% (to 331 million), with the elderly population (>65 yr) increasing approximately three times as fast (162%) to constitute 20% of the total population (66 million). Forty percent of all surgical procedures will be performed in patients over age 65, potentially compromised by MI, because the incidence of CAD increases with age. Although age does not appear to affect resting ejection fraction, left ventricular volume, and regional wall motion, \(^{134,135}\) it does depress cardiac response to different forms of stress, such as exercise or exogenous catecholamines. \(^{134,166,177}\) Consequently, aged patients incur greater surgical complications requiring more intensive and costly hospital care. \(^{138-141}\) For example, perioperative MI is now the leading cause of postoperative death in the elderly undergoing noncardiac surgery. \(^{126}\)

Data supporting the predictive value of age \(^{16,18,19,50,100,101}\) are equal to those refuting it \(^{17,20,22,55,126}\) (table 3). Results from a study by Carliner et al. \(^{101}\) indicate a 38% incidence of ischemia, MI, or cardiac death in patients older than 70 versus 7% in those aged 40–49, whereas Driscoll et al. \(^{19}\) report that age is a significant predictor only when other factors are present. Age may not be as important as the patient’s overall physiologic status. \(^{142,143}\)

**Previous Myocardial Infarction.** Patients with prior MI are at greater risk for perioperative reinfarction (5–8%) \(^{17,22,51,52,64}\) than those without prior MI (0.1–0.7%), \(^{17,48,49}\) and have a reinfarction mortality rate of 36–70%. The more recent the previous MI, the more likely is reinfarction. Within 3 months, the reinfarction rate exceeds 30%; at 3–6 months, it is 15%; and after 6 months, approximately 6%. \(^{17,22,51,52,144}\)

Several studies have challenged these data (table 3). Foster et al. \(^{50}\) studied 1,600 patients (Coronary Artery Surgery Study registry) undergoing noncardiac surgery with CAD (458 patients), without CAD (399), or after a previous CABG (743). Multivariate analysis did not demonstrate that a history of MI, including one within 6 months of noncardiac surgery, had a statistically significant independent association with operative mortality or cardiac morbidity. Wells and Kaplan \(^{127}\) detected no myocardial reinfarction in 48 patients undergoing surgery within 3 months of an infarction. Rao et al. \(^{15}\) found that reinfarction occurred in only 1.9% of 733 patients who had a previous MI. Perioperative reinfarction occurred in only 5.7% of patients whose MI was less than 3 months old, and in 2.3% with an MI 4–6 months’ old. Eighty-nine percent (651/733) of their patients undergoing elective noncardiac surgery had arterial catheters, 83% (607/733) had pulmonary artery catheters, and 60% (439/733) had extended ICU care (3–4 days postoperatively). From Rao’s findings, some have inferred that preoperative optimization of the patient’s status, aggressive invasive monitoring and therapy, and prolonged ICU stay may significantly reduce reinfarction rates and decrease PCI. However, whether use of these modalities helped to lower reinfarction rates cannot be determined from their study. \(^{145}\) Moreover, the cost of implementing such care for surgical patients with or at risk for CAD is considerable. Thus, the clinical and financial implications of Rao’s findings are substantial, and require independent confirmation before being applied.

**Angina.** Angina usually is associated with angiographically significant (>70% stenosis) CAD. That is, 90% of males older than 40 and females older than 60 who have angina have significant coronary stenosis. \(^{146}\) Atypical angina is less often (30–65%) associated with angiographic CAD. \(^{146}\)

A history of stable angina significantly increases the risk of MI and sudden death in ambulatory patients with CAD, but is a controversial predictor in noncardiac surgical patients (table 3). A number of studies support angina

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### TABLE 3. Preoperative Risk Factors: Historical

<table>
<thead>
<tr>
<th>Factor</th>
<th>Supported</th>
<th>Refuted</th>
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<tbody>
<tr>
<td>Valvular heart disease</td>
<td>Skinner10 1964, Goldman14 1977</td>
<td>---</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Cigarette smoking</td>
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<tr>
<td>Previous CABG surgery</td>
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<td>Previous PTCA</td>
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<td>Cardiovascular therapy</td>
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<tr>
<td>Risk indices</td>
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</tbody>
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ASA = American Society of Anesthesiologists classification.  
CCS = Canadian Cardiovascular Society.

as a predictor.17,19,55,64,89,147 However, Goldman et al.16 found that stable angina was a "conspicuously insignificant" predictor using either univariate or multivariate analysis, and Foster et al.50 found that only the use of preoperative nitrates was predictive and angina per se was not, using multivariate analysis. One explanation for the low perioperative risk associated with stable angina (in a number of studies15,16,22,50,101,127,155) may be that 75% or more of ischemic episodes in patients with CAD, are painless or silent,7,8 placing these patients at risk because of ischemia per se, the presence of symptoms of angina conferring no additional risk.9,10 The importance of other angina-related factors, such as severity, character (e.g., Prinzmetal's) and instability, have not been studied.

**Congestive Heart Failure.** Approximately 2.3 million people in the United States have CHF,1 and in hospitalized patients aged 65 or older, CHF is the leading diagnosis-related group.** Clinical or radiologic evidence of left ventricular failure is associated with a poor prognosis in patients with CAD, and is one of the most important predictors of short- and long-term cardiac mortality in the patient with acute MI. The 5-yr survival rate of patients with heart failure is less than 50%.** In patients with an ejection fraction less than 0.30 (determined by radionuclear imaging), 1-yr cumulative mortality is as high as 30%.148-151 Two-year mortality is approximately 78% in those who have an elevated filling pressure (>15 mmHg) and a depressed stroke work index (<20 g-m/m²), compared with 10% in patients with compensated left ven-
tricular function (PCWP <15 mmHg and normal stroke work index). 152

Preoperative CHF is a predictor of PCM, 15,16,50,147,153 but the predictive value of specific signs is controversial. Goldman et al. 16 suggested that two signs of heart failure have predictive value, a third heart sound and jugular venous distention, but that others, like cardiomegaly, do not. Foster et al. 50 found that a number of signs and symptoms, such as a third heart sound or orthopnea, were univariate predictors of outcome, but that only the left ventricular wall-motion score was predictive using multivariate analysis. The usefulness of other more quantified measures, such as ejection fraction (one of the best measures of global ventricular function), 152 has been studied, 90,106,107,147 and findings suggest that a depressed preoperative ejection fraction (<0.40, as determined by radionuclear imaging or ventriculography) is predictive of perioperative MI, reinfarction, and perioperative ventricular dysfunction.

Hypertension. The most common cardiovascular disease in the United States is hypertension, affecting more than 59 million people. 1 Hypertension is a risk factor for ischemic heart disease, CHF, and stroke. 154,155 Both the severity of systolic and diastolic hypertension, and the co-presence of other major predictors are important. The risk of fatal and nonfatal MI in patients with diastolic hypertension (>90 mmHg) is increased markedly in the presence of hypercholesterolemia, cigarette smoking, and ECG abnormalities. 156 Treatment of hypertension reduces mortality associated with stroke and heart failure, but apparently not MI. 155,157–161

Whether preoperative hypertension is predictive of PCM remains controversial (table 3). Some investigators have shown that patients with untreated, poorly treated, or labile preoperative hypertension are at greater risk for perioperative blood pressure lability, dysrhythmias, myocardial ischemia, and transient neurologic complications. 17,19,20,22,53,162–167 Withdrawal of preoperative hypertensive medications, such as β blockers, calcium-channel blockers, or clonidine, is associated with greater perioperative blood pressure lability. 158–172 Prys-Roberts et al. 162 suggested that preoperative hypertension predicted perioperative MI, and others supported hypertension as a predictor of PCM. 17,19,20,22,53,163 However, Foster et al. 50 found it to be only a univariate predictor, and Goldman et al. 173 Rao et al., 15 and others 129,158 demonstrated that mild-to-moderate preoperative hypertension did not predict irreversible cardiovascular outcomes. Rather, preoperative hypertension may predict several probable “intermediates” of outcome, such as intraoperative blood pressure lability and myocardial ischemia. The issue remains unresolved.

Diabetes Mellitus. Diabetes mellitus is a risk factor for CAD, imposing as much as a two- to threefold increase in the risk for atherosclerotic disease. 174 In diabetics, MI is the leading cause of death 124 and appears to be associated with more complications and a lower overall survival rate than in nondiabetics. 125,175 MI and myocardial ischemia in diabetics tend to be silent, more so than in other subgroups of patients. Asymptomatic diabetics with CAD commonly display transient ST depression on ambulatory monitoring, and perfusion defects during thallium stress testing. 176,177 The etiology of the silent ischemic pattern may be related to altered sensory afferents. 178 Diabetics with abnormal autonomic tone (20–40% of diabetics) appear to be at particular risk of myocardial ischemia, infarction, and cardiomyopathy. 176,178–180 Even in the absence of myocardial ischemia, cardiovascular morbidity is increased due to diabetic cardiomyopathy. 179

Initial studies reported a strong association between diabetes and PCM, then others found that diabetes was significantly predictive only when other factors, such as CHF, were present. 16,20,22,53 Recent studies using more sensitive techniques have reaffirmed diabetes as a potential predictor. 17,19,50,56,147 Altered autonomic versus normal tone in diabetics may indicate greater intraoperative risk for blood pressure lability. 181 The presence of diabetes in vascular surgery patients may identify a population in whom dipyridamole thallium imaging may be useful. 110 The relative risks of type I (insulin-dependent) versus type II diabetes and treated versus untreated diabetes, and the benefits of therapy and of controlling perioperative glucose levels need to be analyzed.

Dysrhythmias. Dysrhythmias are not uncommon and are usually benign in healthy patients without known heart disease. In the presence of CAD or left ventricular dysfunction, they become ominous. 182 Frequent premature ventricular contractions with evidence of ventricular dysfunction increase risk in patients with chronic ischemic heart disease. 183,184 In patients with acute MI, ventricular dysrhythmias or conduction disturbances detected in the late-hospital period indicate a poor outcome. 185,186 The association of ventricular dysrhythmias and hypokalemia in patients with acute ischemia increases their risk of developing ventricular fibrillation. 187

Few studies have adequately assessed the importance of preoperative dysrhythmias. The available data suggest that frequent premature ventricular contractions or rhythms other than normal-sinus on the preoperative ECG are independent predictors in patients undergoing noncardiac surgery. 16,50,95,153,229 On the other hand, the presence of bifascicular or trifascicular (complete or incomplete) block, right bundle-branch block, or left anterior hemiblock does not appear to increase perioperative risk, unless these conditions are associated with a more serious condition, such as MI. 188,189

Peripheral Vascular Disease. Ischemic heart disease is common in patients with disease of the carotid artery, the
aorta, or the peripheral circulation. For example, significant coronary artery stenosis (>70%) is present in 14–78% of these patients, regardless of their CAD symptoms. Long-term prognosis in patients with peripheral vascular disease is related to the stability of the ischemic heart disease and the degree of ventricular dysfunction.

Patients with peripheral vascular disease undergoing vascular surgery have a high risk of PCM. MI occurs in as many as 15% of these patients and accounts for more than 50% of their perioperative mortality. CAD also is prevalent: Hertz et al. found that only 8% of these patients have normal preoperative angiograms. Thus, their high perioperative and long-term morbidity and mortality may be related to the presence of CAD or the stresses of peripheral vascular surgery. In contrast, Goldman et al. report no increased risk of perioperative MI or cardiac death due to peripheral vascular procedures, but a high risk of postoperative pulmonary edema with aortic surgery. For nonvascular surgery, the perioperative risk associated with the presence of peripheral vascular disease is unknown.

Valvular Heart Disease. The prognosis for patients with valvular heart disease depends on disease type and severity, and the timeliness of surgical repair. The perioperative risk associated with preoperative valvular heart disease in noncardiac surgical patients is difficult to assess because of other confounding factors commonly associated with valvular disease, including ventricular dysfunction, dysrhythmias, pulmonary hypertension, and CAD. Limited data indicate that aortic stenosis is associated with increased perioperative mortality, but other abnormalities may not be. For example, Goldman et al. found that aortic stenosis was a significant predictor associated with a fourteen-fold increase in mortality. Although they also found an increased risk of postoperative CHF with mitral stenosis and insufficiency, only aortic stenosis was associated with increased mortality in the absence of other predictors (e.g., an S3 gallop or jugular venous distention). Because so few studies have been performed, the predictive value of either aortic or mitral valvular disease is uncertain.

Cholesterol. The anatomic configuration and physiologic changes associated with atherosclerotic plaque are remarkably similar in patients who have the familial or nonfamilial form of hypercholesterolemia. Both forms are predictive of cardiovascular mortality: the Framingham Study and the Multiple Risk Factor Intervention Trial demonstrated a direct relationship between serum cholesterol and cardiovascular mortality. Therapeutic trials conducted by the Helsinki Heart Study and the Lipid Research Center have shown that treating elevated serum cholesterol may reduce this mortality. The perioperative risk associated with hypercholesterolemia is unknown.

Cigarette Smoking. The Framingham Study demonstrated an increased risk of MI in smokers, with a disproportionate number of patients suffering both infarction and death from CAD. Smoking has acute and chronic effects on myocardial oxygen supply and demand. The acute effects on oxygen supply include increased coronary vascular resistance (especially in the presence of stenosis) and increased carboxyhemoglobin levels. The increase in rate pressure product results in increased oxygen demand. The chronic effects of smoking include vasocostriction, enhanced platelet aggregation, and loss of endothelial integrity, leading to accelerated atherosclerosis. However, Foster et al. found that cigarette smoking was neither a univariate nor multivariate predictor of adverse cardiac outcome following noncardiac surgery. Other data are not available.

Previous Coronary Artery Bypass Graft (CABG) Surgery. Previous CABG surgery appears to confer protection against the development of PCM. At least 12 studies involving more than 2,000 patients report a significantly lower postoperative infarction rate and cardiac mortality in prior CABG patients undergoing noncardiac surgery. Data pooled from these studies show the postoperative incidence of MI in these patients to be 0–1.2% versus 1.1–6% in patients without prior CABG surgery, and mortality to be 0.5–0.9% versus 1–2.4%. For example, Foster et al. studied 1,600 registry patients (Coronary Artery Surgery Study) and found a 0.9% (7/743) mortality in those with previous CABG undergoing noncardiac surgery, and 2.4% (11/458) in patients without prior CABG (P = 0.009). Mortality in patients with previous CABG was not statistically different from that in patients without CAD undergoing noncardiac surgery: 0.5% (2/399). In contrast, studies of simultaneous CABG and noncardiac surgery report higher mortalities (4–13%), attributed to the unstable nature of either the coronary or vascular disease.

Previous Percutaneous Transluminal Coronary Angioplasty. Introduced approximately 8 yr ago, coronary angioplasty is now performed in more than 300,000 patients annually in the United States, and now exceeds the number of CABG surgeries performed annually. In addition, newer adaptations of this technique, such as coronary atherectomy using mechanical and laser technologies, are being introduced. The complication rates associated with angioplasty have decreased and the short- and long-term outcomes have improved. There are no data on the effects of angioplasty in patients undergoing subsequent noncardiac surgical procedures.

Cardiovascular Therapy. The beneficial effects of nitrates, β blockers, and calcium-channel blockers in patients
with CAD are well known. Preoperative withdrawal of these therapies is associated with a higher incidence of perioperative ischemia, dysrhythmias, MI, and cardiac death.\textsuperscript{168–172} The possible prophylactic benefit of these pharmacologic therapies is being investigated. Several studies suggest that preoperative oral \textbeta-wave blocker therapy or preinduction iv \textbeta-blocker administration decreases the incidence of intraoperative ischemia in both cardiac and noncardiac surgical patients.\textsuperscript{34,120–122} Additionally, \textbeta-blocker therapy may be more effective prophylactically than preoperative calcium-channel blocker therapy.\textsuperscript{123,211} Preoperative administration of clonidine has been shown to decrease anesthetic requirement,\textsuperscript{212,218} catecholamines,\textsuperscript{212} and intra- and postoperative blood pressure lability in CABG patients\textsuperscript{212} and in hypertensive patients undergoing noncardiac surgery.\textsuperscript{213} However, neither of these recent studies was blinded, and both involved only a limited number of patients (20 and 30, respectively).\textsuperscript{214} Thus, although a number of cardiovascular medications may be potentially useful, larger-scale outcome studies, particularly in patients undergoing noncardiac surgery, are necessary to identify the subgroups of patients who will benefit from prophylactic therapy.

\textit{Risk Indices.} Several multivariate risk indices have been proposed for quantifying preoperative predictors. These include the American Society of Anesthesiologists\textsuperscript{'} (ASA) classification,\textsuperscript{215} the cardiac risk index,\textsuperscript{16} the New York Heart Association (NYHA) classification,\textsuperscript{216} and the Canadian Cardiovascular Society (CCS) classification.\textsuperscript{216} The most widely used are the ASA and cardiac risk index classifications. By multivariate analysis of 1,001 patients undergoing noncardiac surgery, Goldman et al.\textsuperscript{16} identified, weighed, and summed nine significant predictors to form the cardiac risk index. Based on this index, four patient cohorts were classified according to progressively increased risk of morbid outcome. Goldman et al.\textsuperscript{'}s study was the first to attempt to develop a multivariate risk index using prospective analysis of a large group of patients. The general applicability of the cardiac risk index and other indices has been challenged,\textsuperscript{50,54,101,109,217} with each supported or refuted by an equal number of studies (table 3). No consistently accurate and generally applicable risk index has been developed.

\section*{Diagnostic Testing Predictors}

The controversial status of most historical predictors presents a preoperative assessment dilemma. How can we evaluate perioperative risk in the patient who is older, has previous MI, stable angina, and hypertension? In the 1980s, several investigators concluded that the historical predictors were relatively insensitive, and that only nonroutine preoperative cardiac testing could evaluate risk accurately. The diagnostic tests suggested for preoperative assessment of noncardiac surgical patients include exercise stress testing, echocardiography, radionuclear imaging, and, most recently, dipyridamole thallium imaging. Studies exploring their effectiveness as predictors are still few, and the results, at times, controversial (table 4). Cost potentially limits their use. Individual tests range from $250–$1,500; if applied routinely, even in a subgroup of the noncardiac surgical population at risk, the annual increase in national health-care costs would be in the tens-to-hundreds of millions of dollars. For example, preoperative use of dipyridamole thallium imaging in one-half of the population requiring vascular procedures would increase the annual costs in excess of $100 million. The following sections review the routine and nonroutine testing modalities.

\textit{Twelve-Lead Electrocardiography (ECG).} Preoperative ECG abnormalities appear to be common, occurring in

\begin{table}
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\begin{tabular}{|l|l|l|}
\hline
\textbf{Factor} & \textbf{Author, Reference, Year} & \textbf{Refuted} \\
\hline
12-lead ECG & Driscoll\textsuperscript{19} 1961, Baers\textsuperscript{219} 1965, Hunter\textsuperscript{220} 1968, Cooperman\textsuperscript{195} 1978, Mauney\textsuperscript{20} 1970, von Knorring\textsuperscript{28} 1981, Carliner\textsuperscript{101,102} 1985, 1986 & Goldman\textsuperscript{225} 1978 \\
& Goldman\textsuperscript{16} 1977, Foster\textsuperscript{20} 1986 & —
\hline
Chest x-ray abnormalities & Gage\textsuperscript{197} 1977, Cutler\textsuperscript{194,195} 1979, 1981, Gerson\textsuperscript{192} 1985, von Knorring\textsuperscript{28} 1986 & —
\hline
Exercise-stress testing & — & —
\hline
Ambulatory monitoring & Raby\textsuperscript{246} 1989 & —
\hline
Precordial echocardiography & — & —
\hline
Transesophageal echo & — & —
\hline
Radionuclear imaging & Pasterнак\textsuperscript{106,107} 1984, 1985, Gerson\textsuperscript{192} 1985 & —
\hline
Dipyridamole-thallium imaging & Boucher\textsuperscript{35} 1985, Brewster\textsuperscript{111} 1985, Cutler\textsuperscript{193} 1987, Leppo\textsuperscript{109} 1987, Eagle\textsuperscript{116} 1987, Eagle\textsuperscript{151} 1989 & —
\hline
Magnetic resonance imaging/spectroscopy & — & —
\hline
Cardiac catheterization & Hertz\textsuperscript{11,12} 1984, 1985 & —
\hline
\end{tabular}
\caption{Preoperative Risk Factors: Diagnostic Tests}
\end{table}
40–70% of CAD patients undergoing noncardiac surgery. The most frequent abnormality is ST-T wave changes (65–90%), followed by signs of left ventricular hypertrophy (10–20%), and Q-waves (0.5–8%). In Rabin and Horne's study of 812 patients, 40% of preoperative ECG abnormalities were new, occurring within 24 months before surgery, and were related to age and the presence of known cardiac disease. Despite the widespread use of preoperative ECG to obtain a baseline profile of patients with suspected or known heart disease, only a few prospective studies have explored its predictive value. Carliner et al. studied 200 patients older than 40 undergoing elective noncardiac surgery and found that an abnormal preoperative ECG was the only statistically significant independent predictor of adverse cardiac outcome, even more predictive than preoperative exercise stress test changes. Specifically, ST-T wave ischemic or nonspecific changes and intraventricular conduction delays were the abnormalities which occurred most frequently in the patients with outcomes. In contrast, Goldman et al. found that ECG abnormalities, including old Q-waves, ST-T wave changes, or bundle branch blocks, had no significant predictive value. Further study is therefore necessary.

Chest Radiography (x-ray). In patients with CAD, chest x-ray abnormalities are predictive of ventricular function abnormalities detectable by ventriculography. For example, the presence of cardiomegaly indicates a low ejection fraction (<0.40) in over 70% of patients with CAD. Since a low preoperative ejection fraction predicts PCM, preoperative radiographic cardiomegaly also might predict PCM. Foster et al. have reported cardiomegaly to be a univariate predictor. However, Goldman et al. dispute this finding, but support the presence of a tortuous or calcified aorta on the preoperative chest x-ray as a predictor.

Exercise Stress Testing. Exercise stress testing is a relatively inexpensive, noninvasive test commonly used to diagnose chest pain of unknown origin and to determine prognosis for patients with known CAD. It is highly predictive of subsequent cardiac events when ST changes are: 1) characteristic; 2) large (>2.5 mm); 3) immediate (first 1–3 min); 4) sustained into the recovery period; or 5) associated with subnormal increases in blood pressure. Exercise stress testing has limited value for generalized screening in healthy asymptomatic patients.

Controversy surrounds the preoperative use of exercise stress testing to predict patients most likely to develop adverse cardiac outcome. Several studies have demonstrated that a positive ischemic response and a low exercise capacity predict outcome following noncardiac surgery. Cutler et al. found that perioperative MI occurred in 37% of vascular surgery patients with a positive ischemic response versus 1.5% without. Preoperative exercise stress testing also proved a more sensitive indicator than the clinical history or preoperative ECG results. Twenty-seven percent of patients with a negative history and normal preoperative ECG had a positive exercise stress test: 26% of these developed perioperative MI. Cutler et al. argued that such asymptomatic patients would escape identification by risk-factor analysis and recommended routine use of preoperative exercise stress testing. In contrast, Carliner et al. found that preoperative exercise stress testing did not independently predict cardiac risk in noncardiac surgical patients over age 40: the routine preoperative ECG was the only statistically significant independent predictor in their population. Thus, the effectiveness of preoperative exercise stress testing in identifying at-risk patients remains controversial.

Ambulatory ECG Monitoring. Ambulatory ECG monitoring has proven successful in detecting ST-segment changes in patients with CAD. Frequent episodes of ST depression, indicative of subendocardial ischemia, occur during normal daily activities. Typically, these episodes are asymptomatic (silent) and probably unrelated to heart rate. That they represent myocardial ischemia remains to be determined, but preliminary results suggest that they are associated with myocardial perfusion abnormalities.

Preoperative Holter monitoring has been evaluated for preoperative screening of noncardiac surgical patients. Preliminary results indicate that 18–40% of surgical patients with or at risk for CAD have frequent ischemic episodes during the 48 h preceding surgery, that most (>75%) of these episodes appear to be clinically silent, and that preoperative ischemia may predict outcome.

Precordial Echocardiography. Precordial echocardiography is a noninvasive, relatively inexpensive imaging technique that is used to assess ventricular and valvar function, regional wall motion and thickening and pericardial tamponade, and to diagnose MI, left ventricular aneurysms, septal rupture, papillary muscle abnormalities and thrombus formation. This technique is prognostic of both short- and long-term outcomes in patients with acute MI, but its preoperative prognostic value is unknown. However, radionuclear and angiographic studies have shown that preoperative ventricular dysfunction or segmental wall-motion abnormalities detected using either technique predict perioperative ventricular dysfunction. Since echocardiography provides similar information less invasively and expensively, it is potentially more useful.

Transesophageal Echocardiography (TEE). Awake TEE is now used for characterizing left atrial thrombi, valvular vegetations and prosthetic valvular function, and for as-
scessing dissecting aortic aneurysm. Its predictive value in noncardiac surgical patients has not been studied.

Radionuclide Imaging. Radionuclide imaging is used to detect MI, quantify myocardial perfusion abnormalities, and calculate ventricular performance and wall-motion indices. Technetium pyrophosphate (hot-spot imaging) and thallium 201 (cold-spot imaging) are used for MI imaging. Technetium pyrophosphate imaging is sensitive (≥90%) and moderately specific (≥50%) for detection of acute MI, and most useful 2–3 days after a suspected MI. Thallium imaging also is highly sensitive (≥90%) (particularly during the first 24 h after a suspected MI), but not as specific as pyrophosphate imaging. The perfusion defect imaged may be infarction (fixed defect) or ischemia (transient defect). Stress thallium imaging, performed under conditions of near-maximal coronary blood flow (exercise, dipyridamole), is more sensitive than rest imaging and capable of detecting perfusion heterogeneities with stenoses as low as 50%. Both MI (fixed defect) and myocardial ischemia (redistribution abnormality) are detectable using any of these stress imaging techniques. Exercise thallium scintigraphy reportedly has 90% sensitivity in patients with multiple-vessel disease and 60% in those with single-vessel disease. Specificities are generally greater than 90%, with few false positives. Dipyridamole thallium imaging is both sensitive (93%) and specific (80%) for detection of coronary stenoses in patients selected for coronary angiography. It is also sensitive (92%), but not specific (44%), for detection of long-term (1–2 yr) outcome following acute MI. Positron-emission tomography and single-photon emission computed tomography are other imaging techniques being explored.

The predictive value of preoperative radionuclide imaging has been studied primarily in vascular surgery patients. During lower extremity revascularization or abdominal aortic aneurysm resection, the gated-pool-determined ejection fraction has been shown to be an independent predictor of PCM. Pasternack et al. found that an ejection fraction of less than 0.35 was associated with a 75–85% incidence of perioperative MI and an ejection fraction greater than 0.35, with a 19–20% incidence. Exercise radionuclide ventriculography has been studied in older patients scheduled for elective abdominal or thoracic surgery. The inability to exercise for 2 min (with heart rate > 99 beats/min) was found to be the best predictor of PCM. Neither resting ejection fraction nor historical predictors were as significant.

Preoperative dipyridamole thallium imaging recently has been studied in patients undergoing vascular surgery. Though unblinded and uncontrolled, these studies demonstrated that preoperative dipyridamole thallium imaging is highly sensitive (89–100%), reasonably specific (53–80%), and superior to historical predictors or exercise stress testing. The negative predictive value (identifying the absence of abnormality) is nearly 100%. The positive predictive value (identifying the presence of abnormality) is low (17–50%), because of the large number of false positives, but increases when reperfusion criteria include two or more dysfunctional segments, or when high-risk subsets of patients are chosen for preoperative imaging. For example, Eagle et al. found that patients with a history of angina, prior MI, CHF, or diabetes mellitus had an outcome event rate of 37% versus 0% in patients without these predictors. Thus, dipyridamole thallium imaging may permit additional risk stratification in selected subgroups of patients. Additionally, thallium redistribution abnormalities may predict patients most likely to develop TEE-detectable regional wall-motion abnormalities during major noncardiac surgery, although not adverse outcome.

Magnetic Resonance Imaging/Spectroscopy. Magnetic resonance imaging of the heart is a relatively noninvasive technique that provides high resolution tomographic and three-dimensional images. Recent studies in animals and humans indicate that magnetic resonance imaging can reliably detect acute MI, wall thinning and aneurysm formation, and subtle atrial and ventricular defects. Magnetic resonance spectroscopy can now quantify intracellular pH and the levels of high-energy compounds within living cells. Recent spectroscopy studies focus on the pathophysiologic mechanisms associated with myocardial ischemia. Because magnetic resonance imaging and spectroscopy have not been studied in patients undergoing surgery, their perioperative value in surgical patients with CAD is unknown.

Cardiac Catheterization. Cardiac catheterization has been the "gold standard" for quantifying ventricular function and assessing coronary circulation. Studies in patients undergoing CABC surgery have shown that ventricular function indices, such as ejection fraction, wall-motion abnormalities, end-diastolic volume and change in end-diastolic pressure, are predictive of perioperative ventricular dysfunction and short- and long-term outcome. Angiographic findings demonstrate significant left-main or multivessel disease also are predictive of short- and long-term outcome.

Preoperative coronary angiography in patients undergoing vascular and general surgery has been studied, particularly by Cleveland Clinic investigators. These studies indicate that a relatively high incidence of coronary stenosis exists in these patients, regardless of symptoms or other predictors. They also demonstrate that patients...
who had CABG surgery before vascular surgery had lower rates for early (1.5% vs. 12%) and late mortality (12% vs. 26%), and a higher cumulative 5-yr survival rate (72% vs. 43%) than patients without prior CABG. Thus, the information obtained from angiography and ventriculography is useful for diagnosing patients who require CABG surgery before noncardiac surgery. It also may be useful for predicting PCF. For example, a low ejection fraction (<0.40) determined by radionuclear imaging predicts PCF in patients undergoing vascular surgery, suggesting that the ejection fraction derived from preoperative ventriculography may be similarly predictive. However, the expense and morbidity associated with cardiac catheterization, and the existence of alternative less costly and less risky techniques limit its application, even in high-risk patients.

**Preoperative Predictors—Conclusions**

Recent (<6 months) MI and current CHF are the only two consistently proven preoperative predictors of PCF. The value of other historical predictors, such as previous (old) MI, angina, previous CHF, hypertension, diabetes, and age, is still unresolved. Although selected populations may benefit from the use of specialized nonroutine testing, the efficacy and cost effectiveness of these tests remain controversial.

**The Intraoperative Predictors**

That the preoperative disease state affects outcome is clear. However, intraoperative factors also appear to affect outcome substantially, independent of the disease state. Over the past two decades, researchers have studied the "classical" intraoperative predictors, such as choice of anesthetic, immediacy of surgery, site of surgery, and duration of anesthesia and surgery. Recently recognized is that dynamic events occurring intraoperatively may cause PCF, including hypertension, hypotension, tachycardia, myocardial ischemia (ECG, TEE), ventricular dysfunction and dysrythmias. The importance of these dynamic predictors is unknown: What are the acceptable ranges of blood pressure in the patient with CAD? Should CAD patients undergoing major surgery be monitored using TEE because it is more sensitive than ECG? Is there a "best anesthetic" for the patient with CAD? Current data on the classical and dynamic intraoperative predictors are summarized in the following sections (and table 5).

**Classical Predictors**

*Choice of Anesthetic.* Does the choice of anesthetic affect surgical outcome? This question has been studied for the last 35 yr and every known anesthetic and technique investigated. Three controversies persist for patients with cardiac disease: 1) use of regional versus general anesthesia; 2) use of inhalational versus narcotic anesthesia; and 3) use of isoflurane in patients with CAD (potential coronary artery steal).

A number of studies in patients with cardiac disease have compared the effects of regional versus general anesthesia on the incidence of perioperative infarction, dysrhythmias, and CHF. Studies by Rao et al., Steen et al., Backer et al., and Prough et al. have suggested no difference in infarction rate during general and regional (spinal, epidural, upper extremity, local) anesthesia. For example, Rao et al. reported a 1.8% (12/659) reinfarction rate in patients undergoing general anesthesia versus 2.7% (2/74) for regional anesthesia. Backer et al. documented the safety of local anesthesia and/or retrobulbar block in 195 patients with prior infarction undergoing 288 ophthalmic procedures. No reinfarctions occurred in this group; however, no reinfarctions occurred in the group undergoing general anesthesia (21 patients, 26 procedures) either. Regional anesthesia may, however, benefit patients with prior MI undergoing transurethral prostatectomy: the reinfarction rate for spinal anesthesia has been reported to be less than 1%, versus 2–8% for general anesthesia. (Other studies have suggested that regional is superior to general anesthesia, but study limitations restrict their applicability.) Studies of the incidence of dysrhythmias using continuous ECG and intermittent techniques suggest no significant difference between regional and general anesthesia. Kuner et al. found no difference between anesthetic techniques (dysrhythmia incidence with general anesthesia = 66% vs. 52% with regional); but that surgical site was predictive, with the incidence of dysrhythmias ranging from 53–100%, depending on the site. Although only limited data are available for CHF, they suggest that such patients benefit from the use of regional anesthesia. Goldman et al. found that spinal anesthesia was not associated with new or worsening heart failure, compared with 4% of patients in new failure and 22% with worsening of preexisting failure during general anesthesia. In addition, Yeager et al. recently reported that only 1/28 (3.6%) patients receiving epidural anesthesia (and "light levels of general anesthesia") and postoperative epidural analgesia developed CHF versus 10/25 (40%) patients given general anesthesia and postoperative parenteral narcotic analgesia. Thus, regional anesthesia may offer an advantage over general anesthesia for certain types of surgery (prostate resection) or for specific patients (history of CHF). Otherwise, no one technique demonstrates a consistent advantage.

The use of inhalational versus narcotic anesthesia in patients with cardiac disease is still debated, although the cardiovascular effects of both techniques and the physiologic differences between them are well docu-
Table 5. Intraoperative Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Supported</th>
<th>Author, Reference, Year</th>
<th>Refuted</th>
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<tbody>
<tr>
<td>Classical risk factors</td>
<td></td>
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<tr>
<td>Anesthetic</td>
<td>Rao^{16} 1983</td>
<td></td>
<td></td>
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<tr>
<td>Site of surgery</td>
<td>Tarhan^{17} 1972,</td>
<td>Goldman^{16} 1977,</td>
<td>Driscoll^{19} 1961, Knapp^{21}</td>
</tr>
<tr>
<td></td>
<td>Steen^{22} 1978,</td>
<td>Steen^{22} 1978,</td>
<td>1962, Topkinc^{22} 1964,</td>
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<tr>
<td></td>
<td>Rao^{16} 1983,</td>
<td>Larsen^{17} 1987</td>
<td>Arkinc^{16} 1964, Mauney^{20}</td>
</tr>
<tr>
<td>Duration of anesthesia/surgery</td>
<td>Arkin^{16} 1964,</td>
<td>Coghill^{27} 1967,</td>
<td>1970, Goldman^{16} 1977, Steen^{22}</td>
</tr>
<tr>
<td></td>
<td>Coghill^{27} 1967,</td>
<td>Mauney^{20} 1970,</td>
<td>1978, von Knorrinc^{23} 1979,</td>
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<td>Steen^{22} 1978</td>
<td>von Knorrinc^{23} 1981, Foster^{28}</td>
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<td></td>
<td>Larsen^{17} 1987</td>
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<td>1986, Driscoll^{19} 1961, Topkin^{22}</td>
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<td></td>
<td>Vacanti^{88} 1970,</td>
<td>Goldman^{16} 1977,</td>
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<td>Djokovic^{16} 1979,</td>
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<td>Larsen^{17} 1987</td>
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<td>Dynamic risk factors</td>
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<td>Steen^{22} 1978</td>
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<td>1978, Mahar^{100} 1978, Riles^{100}</td>
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<td>Chamberlain^{23} 1964,</td>
<td>1979, Erokl{128} 1980, von</td>
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<td>Tachycardia</td>
<td>Rao^{16} 1983</td>
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<td>Myocardial ischemia</td>
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<tr>
<td>Ventricular dysfunction</td>
<td>Smith^{21} 1985</td>
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<tr>
<td>Dysrhythmias</td>
<td>Rao^{16} 1983</td>
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<td></td>
<td>Saphin^{10} 1975,</td>
<td>Steen^{22} 1978</td>
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mented. Their differences imply that one anesthetic may perform better than another in selected risk groups. However, most outcome studies have not demonstrated a difference between anesthetics in the patient with cardiac disease (table 5). Ten of 11 outcome studies of more than 3000 noncardiac surgical patients with CAD have concluded that anesthetic type does not affect outcome.^{16-20,22,51-55,126} Only one study, (Rao et al.)^{15} has suggested a difference: narcotic-nitrous oxide-relaxant anesthesia was found to be associated with a significantly (P < 0.005) higher incidence of myocardial reinfarction—7.0% versus 0.5-1.5% for other general anesthetics, and 2.7% for regional anesthesia. However, five of these 11 studies were retrospective,^{17,18,22,51,126} resulting in incomplete and nonstandardized data collection. Of the six prospective studies,^{15,16,19,20,52,53} only two thoroughly measured cardiac outcomes^{15,53} and none used a random anesthetic assignment.^{145} More rigorous methods may (or may not) demonstrate differences between the inhalational and iv narcotic techniques. Rao et al.'s unique findings have been challenged by two large-scale outcome studies of patients undergoing CABG surgery,^{273,274} which report that anesthetic choice does not affect outcome. However, these studies also have limitations, precluding absolute resolution of the issue.^{114}

The potential for inducing coronary artery steal in cardiac patients has provoked arguments for restricting the use of isoflurane. A moderate coronary vasodilator, isoflurane may cause coronary steal in patients with coronary artery stenosis and a "steal-prone" anatomy.^{29,119,275} Since it is the most commonly used anesthetic and CAD is the most commonly encountered disease, their potential relationship is important to define. Studies in animals and humans spanning the last 5 yr have demonstrated that isoflurane produces moderate coronary vasodilation of the epicardial resistance vessels, less vasodilation than adenosine, but more than halothane or enflurane.^{29,115-119,275-279} In a canine model of chronic coronary occlusion, Buffington et al.^{118} found that isoflurane, as the primary anesthetic, can cause coronary steal. However, Cason et al.^{278} found that isoflurane as an adjuvant (even at 1.5 MAC) to high-dose narcotic anesthesia in dogs produced neither significant vasodilation nor coronary steal. In vascular surgery and CABG patients, Reiz et al.^{29} and Moffitt et al.^{276} found that isoflurane reduced coronary perfusion pressure without reducing coronary blood flow, and was associated with ischemia in 48% (10/21) and 27% (3/11) of patients, respectively. Although the mechanism for ischemia in these patients could have been coronary artery steal, definitive data are lacking. In contrast, several studies in patients undergoing cardiac and noncardiac surgery suggest that isoflurane produces no more intraoperative ischemia than other anesthetics.^{273,280-283} In humans, therefore, the issues of isoflurane-induced ischemia and isoflurane-induced coronary steal remain unresolved.

Site of Surgery. Patients undergoing thoracic or upper abdominal surgery have a two- to threefold higher risk
of perioperative cardiac complications\textsuperscript{15-17,29,147} (table 5). However, von Knorring et al.\textsuperscript{59} found that the site, as well as the duration, of surgery did not affect outcome in 214 patients with CAD undergoing general orthopedic or trauma surgery. Factors such as intraoperative hypotension were more important. Thus, the presence of confounding variables complicates analysis.\textsuperscript{10,50,52,53,153}

Patients with CAD undergoing major vascular surgery are unquestionably at increased risk for perioperative MI, CHF, and cardiac death. Infarction rates as high as 15–40\% have been reported during aorto-iliofemoral aneurysm repair and aorto-femoral bypass grafting.\textsuperscript{11,56,57-61,64,284-286} The intraoperative stresses associated with vascular surgery, combined with underlying CAD, appear to be responsible for the high complication rate.\textsuperscript{11,57-60}

\textbf{Duration of Anesthesia and Surgery.} Procedures lasting more than 3 h are associated with greater PCM\textsuperscript{16,18,30,22,287} (table 5). Usually, they are also major surgical procedures associated with greater hemodynamic changes and other stresses. Whether the duration of anesthesia and surgery \textit{per se} has an independent effect on outcome is, therefore, unclear.\textsuperscript{15,17,19,25,53,126}

\textbf{Emergency Surgery.} Most studies support that emergency surgery increases the risk of PCM by two- to fivefold\textsuperscript{16,18,126,147,288} (table 5). Only one study,\textsuperscript{15} suggests no increased risk associated with emergency procedures.

\textbf{CLASSICAL PREDICTORS—CONCLUSIONS}

Among the classic intraoperative predictors, emergency surgery, vascular surgery, and prolonged (>3 h) thoracic or upper abdominal surgery appear to be independent predictors of perioperative morbidity, while choice of anesthetic does not.

\textbf{DYNAMIC PREDICTORS}

Acute imbalances in myocardial oxygen supply and demand may produce ischemia that may, in turn, result in irreversible cardiac morbidity. Dynamic intraoperative changes may, therefore, predict PCM. The following are the preliminary findings (table 5).

\textbf{Hypertension.} Acute hypertension affects both myocardial oxygen demand and supply. During systemic hypertension, peak systolic ventricular pressure increases and produces commensurate increases in wall tension, which increases myocardial oxygen consumption. Effects on myocardial oxygen supply depend on the status of ventricular function. In the nonfailing ventricle, hypertension may elevate diastolic pressure above increases in left ventricular end-diastolic pressure, thereby raising coronary-perfusion pressure.\textsuperscript{289-292} Buffington et al.\textsuperscript{293} demonstrated in dogs that elevation of mean blood pressure to 120 mmHg in the presence of severe stenosis was well tolerated in the nonfailing heart. At any given heart rate, regional ventricular function was better when blood pressure was elevated. However, in the failing ventricle, the increases in the end-diastolic pressure may exceed the increases in the arterial diastolic pressure and decrease coronary perfusion pressure.\textsuperscript{294,295} Intramyocardial wall tension also may increase precipitously and elevate coronary vascular resistance.\textsuperscript{296} In addition, sympathetic coronary constriction during the hypertensive episode may decrease coronary flow.\textsuperscript{297-299} Studies in humans undergoing cardiac and noncardiac surgery have failed to demonstrate a conclusive causal relationship between acute intraoperative hypertension and myocardial ischemia.\textsuperscript{15,26,28,30,35-35,112,300-303}

Most studies suggest that fewer than 15\% of ischemic episodes are associated with hypertension.\textsuperscript{15,26,33-35,112,301-303} but some have shown that acute hypertensive episodes precede as many as 50\% of intraoperative ischemic episodes.\textsuperscript{28,30,300} Thus, the effects of hypertension on the ischemic state of the ventricle depend on several factors for which physiologic studies in animals and humans have yet to establish causal relationships.

The predictive importance of intraoperative hypertension for PCM is unresolved (table 5). The studies of Plumlee et al.\textsuperscript{49} and Steen et al.\textsuperscript{52} suggest a relationship between hypertension and outcome, while others do not.\textsuperscript{15,16,65,129} Steen et al. found that the perioperative reinfarction rate was significantly higher in hypertensive patients (9.2\% vs. 4.4\% nonhypertensive patients), while Rao et al.\textsuperscript{15} reported that reinfarction occurred in three of eight patients who developed hypertension with tachycardia, but in none of those who developed only hypertension.

\textbf{Hypotension.} Although hypotension reduces myocardial wall tension, decreasing oxygen demand, its effects on coronary blood flow appear to predominate. As diastolic blood pressure falls below the autoregulatory limit, coronary blood flow decreases. In animal models with coronary stenosis, this decrease in oxygen supply is associated with new or worsened ischemic dysfunction.\textsuperscript{304-306}

At least 13 studies have investigated the relationship between intraoperative hypotension and myocardial ischemia in cardiac and noncardiac patients.\textsuperscript{26-28,30,35-35,112,162,301-303,307} Five of these have found a causal relationship.\textsuperscript{26,35,162,302,307} For example, Lieberman et al.\textsuperscript{35} showed that ischemia could occur with as little as 6\% decrease in mean arterial pressure. Kotter et al.\textsuperscript{303} found that 25\% of ischemic events (6/24) were associated with a 20\% or greater decrease in systolic blood pressure. The animal studies of Buffington et al.\textsuperscript{296} and Hickey et al.\textsuperscript{304} support these findings, suggesting that in the presence of severe stenosis, decreases in arterial pressure cause or worsen ischemic dysfunction evaluated by lactate determinations, systolic thickening changes, or ECG changes. Thus, a causal relationship between hypotension and
ischemia may exist; however, neither the degree nor the duration of hypotension necessary to precipitate ischemia has been determined.

Intraoperative hypotension does, however, appear to be an important predictor of PCM. The results of outcome studies conducted over the last 35 yr (table 5) are consistent with the physiologic findings.15,16,19,20,22–24,49,55,65,98,128,129,173,203,204 Steen et al.22 reported a significantly higher reinfarction rate (15.2% vs. 3.2%, \( P < 0.001 \)) among patients who developed intraoperative systolic hypotension (≥30%, ≥10 min). Rao et al.15 found that intraoperative hypotension was the strongest dynamic predictor of perioperative MI: nine of 12 patients who developed intraoperative hypotension reinfarcted perioperatively. Among the studies cited (table 5), only the retrospective study of Nachlas et al.308 refuted hypotension as a predictor, finding no significant difference in mortality between patients who had intraoperative hypotension (systolic blood pressure decrease > 40 mmHg) and those who did not (11.5% vs. 8.1%, respectively, \( P = \) not significant).

Tachycardia. Increases in heart rate deleteriously affect myocardial oxygen supply (decreased diastolic filling time) and oxygen demand (increased minute work). In animals with coronary stenosis, increasing heart rate precipitates or worsens ischemia,609,910 while decreasing heart rate improves it.311 Studies in anesthetized patients undergoing cardiac and noncardiac surgery have demonstrated a causal relationship between intraoperative tachycardia and intraoperative ischemia.36–28,30,33–35,112,501–503,307 Some suggest that the combination of tachycardia and hypotension is particularly ominous.55,293

Intraoperative tachycardia as a predictor of PCM has not been thoroughly investigated. Although Slogoff and Keats112 have suggested a causal relationship between tachycardia and outcome in patients undergoing CABG surgery, only one study in noncardiac surgical patients (Rao et al.15) suggests such a relationship. Perioperative MI occurred in two of 16 patients with tachycardia and in three of eight hypertensive patients with tachycardia. Although not statistically significant, these data suggest a relationship between tachycardia and PCM.

Myocardial ischemia. A number of technologies have been used to identify and characterize intraoperative ischemia, including: ECG, TEE, pulmonary artery monitoring, radionuclear imaging, cardiokymography, and biochemical assays. We will focus on those studies addressing these technologies in patients undergoing noncardiac surgery.

ECG ST abnormalities: Sensitive techniques for the measurement of intraoperative myocardial ischemia have been recently introduced, including multiple-lead ECG and TEE, which permit identification of characteristics of intraoperative ischemia in noncardiac surgical patients. Intraoperative ECG changes consistent with myocardial ischemia are present in 18–74% of noncardiac surgical patients with CAD.27–51,33–35,38 Most changes are ST depression; ST elevation appears to be uncommon.27,58 London et al.27 have demonstrated that most ST changes occur laterally, with 90% in leads V4 and V5, and vary in duration (1–258 min). Although there are several nonspecific etiologies for ST changes, such as ventricular hypertrophy or altered electrical activity, these are usually chronic conditions and not reversible. Consequently, reversible ST changes are likely to be ischemic. T-wave changes also occur,47,512 but these are more nonspecific than ST changes. The data describing the relationship of ECG changes to indices of supply and demand are not consistent. However, "nondemand" ischemia may constitute up to 50% or more of the intraoperative episodes.27,30,35 Although such ischemia may be due to atherosclerotic plaque rupture with accelerated thrombosis and vessel spasm,45–46 the etiology remains unknown.

Do intraoperative ECG ST abnormalities predict PCM? It is unclear whether patients who develop ECG ST changes indicative of myocardial ischemia during noncardiac surgery are at greater risk for intra- and postoperative MI. Studies by Slogoff and Keats112,515 in patients undergoing CABG support this hypothesis: prebypass ischemia increased the risk of MI by two- to threefold. In their first study, 37% (377/1023) of their patients developed ST changes prior to bypass and had an infarction rate of 6.9%, in contrast to the 2.5% rate in the 63% (646/1023) who did not develop prebypass ischemia. (Ischemia time and surgical rating of the anastomoses were also predictors using multivariate analysis.) Pursuing this question further, Knight et al.26,136 demonstrated that a chronic, often "silent" pattern of ischemia existed preoperatively in CABG patients. Such a pattern may exist in noncardiac surgery patients.53 Furthermore, the intraoperative pattern of ischemia was no worse than the preoperative pattern, implying that anesthesia and surgery may not be as stressful as previously assumed, and that the intraoperative pattern may simply recapitulate the chronic preoperative pattern. However, definitive outcome studies, contrasting the relative predictive value of preoperative, intraoperative, and even postoperative ischemia are unavailable, especially in noncardiac surgery patients.

TEE wall-motion/thickening abnormalities: Segmental wall-motion and wall-thickening abnormalities are more sensitive and earlier indicators of myocardial ischemia than ECG changes in both animals and humans.314–316 In 1935, Tennant and Wiggers314 demonstrated that with coronary artery ligation, regional contractile failure occurred almost immediately. The earliest changes appear to be bio-
chemical: oxygen deprivation causing insufficient ATP production (anaerobic glycolysis), a decrease in ATP turnover, cellular acidosis, and entrapment of calcium. Mechanical dysfunction results, manifested by the inability of the myocardial wall to thicken, followed by wall-motion abnormalities, progressing from hypokinesis to akinesis to dyskinesia.\textsuperscript{315,316} Endocardial ECG ST changes occur, and are followed by surface ECG changes. In previously compromised hearts, or in those that develop global ischemia, diastolic compliance then decreases, filling pressure increases, and systolic dysfunction occurs. Although a number of sensitive techniques are available for detection of ischemia, such as magnetic resonance spectroscopy, radio-labeled lactate determinations, or direct measurement of end-diastolic pressure, they are impractical. The most sensitive, practical detector of intraoperative ischemia appears to be TEE. In patients undergoing coronary angioplasty, wall-motion abnormalities are more sensitive and earlier indices of myocardial ischemia than surface ECG changes.\textsuperscript{316} In humans undergoing either cardiac or non-cardiac surgery, TEE wall-motion and thickening abnormalities, consistent with ischemia, are more common than ECG changes,\textsuperscript{32,41,42} even when continuous 12-lead ECG is used.\textsuperscript{42} Most ECG changes are accompanied by TEE changes, but the converse has not been reported. Other characteristics of TEE ischemia, such as the frequency, duration, magnitude, and relationship to supply and demand, have not been studied.

Do intraoperative TEE abnormalities predict PCWP? Preliminary data indicate that TEE wall-motion and wall-thickening changes indicative of myocardial ischemia, even when unaccompanied by ECG changes, are predictive of PCWP.\textsuperscript{35,41,517} Smith \textit{et al.}\textsuperscript{32} found that four of 50 major vascular or CABG patients who developed a perioperative MI had intraoperative wall-motion abnormalities, and only one of four had ECG abnormalities. Three of four had persistent intraoperative wall-motion abnormalities occurring in the same area as the infarct, and the fourth had a transient wall-motion abnormality. Leung \textit{et al.}\textsuperscript{41} found that the presence of immediate postbypass wall-motion abnormalities was the best predictor of PCWP in patients undergoing CABG surgery. Fifty patients undergoing elective CABG surgery were studied using continuous TEE and ECG intraoperatively and intermittently in the ICU. The incidence of wall-motion abnormalities exceeded the incidence of ST changes throughout all periods. Neither prebypass TEE abnormalities nor ECG abnormalities occurring at any time predicted adverse outcome. Only postbypass TEE abnormalities predicted outcome: 6/18 patients with postbypass wall-motion abnormalities had adverse outcome \textit{versus} 0/32 without abnormalities. In noncardiac surgical patients, London \textit{et al.}\textsuperscript{42} reported a 33% incidence of intraoperative TEE wall-motion abnormalities in 95 patients with or at risk for CAD. Eight of the nine patients who developed adverse cardiac outcomes had preceding intraoperative wall-motion abnormalities. Though suggestive, these data are only preliminary; the predictive value of TEE in noncardiac surgery patients remains unknown.

Pulmonary artery monitoring of ischemia: Pulmonary artery monitoring provides information useful in assessing ventricular systolic and diastolic function and pulmonary transudation of fluids. Measurement of PCWP has been suggested as an early and sensitive indicator of myocardial ischemia, to be used when the ECG is nondiagnostic.\textsuperscript{113} Data from animal and human studies demonstrate that during acute coronary occlusion, exercise precipitates ECG ST changes, and early and marked increases in left ventricular end-diastolic pressure.\textsuperscript{518-523} Thus, end-diastolic pressure appears to be an early and sensitive marker of ischemia. Whether PCWP is as sensitive a measure as end-diastolic pressure in either animals or humans is unknown. Studies in patients with acute MI challenge the possibility. Rahimtoola \textit{et al.}\textsuperscript{304} have shown that left ventricular end-diastolic pressure increases during ischemia, due to the effects of end-atrial systolic emptying on the stiffened and ischemic left ventricle, but that these increases are not reflected in the mean left ventricular diastolic pressure, the left-atrial pressure, or the PCWP. The PCWP was up to 15 mmHg lower than the left ventricular end-diastolic pressure and did not increase significantly during ischemia. Although acute increases in PCWP (or development of V-waves) may reflect ischemia,\textsuperscript{115,581} the absence of a change in PCWP does not ensure the absence of ischemia. Häggmark \textit{et al.}\textsuperscript{38} reported that in vascular surgery patients the sensitivity, specificity, and predictive value (positive and negative) of PCWP abnormalities (≥5 mmHg change from baseline, or the development of an abnormal waveform) for ischemia (ECG or cardiokymography abnormalities, or lactate production) ranged between 40 and 60%. In CABG patients, Lieberman \textit{et al.}\textsuperscript{55} also found a low positive predictive value (24%), but a higher negative predictive value (85%); however, the PCWP was no better than central venous pressure measurement, except in patients with moderate to severe preoperative ventricular dysfunction. Leung \textit{et al.}\textsuperscript{502} found that 61% of TEE wall-motion abnormalities in CABG patients occurred without significant changes (>20% of control) in heart rate, systolic arterial pressure, or pulmonary artery pressure. Only 10% of episodes were accompanied by 5 mmHg or greater changes in pulmonary artery pressure. Roizen \textit{et al.}\textsuperscript{56} found that 11/12 patients developed TEE wall-motion abnormalities when the aorta was cross-clamped above the suprasceliac artery, but that PCWP remained normal (≤12 mmHg) in 10/12 with only 2/12 having transient increases. Therefore, these studies question the value of pulmonary artery catheterization and monitoring for detection of intra-
operative ischemia, except perhaps in patients with preoperative ventricular dysfunction. Further study is warranted.

Radionuclide imaging of ischemia: Radionuclide imaging techniques allow assessment of ischemia as well as ventricular function, and have been used in several intraoperative studies of patients with CAD. However, when used intraoperatively, they are primarily research tools, without widespread clinical application.

Cardiokymographic detection of ischemia: Cardiokymography is a noninvasive technique that allows analog representation of anterior wall motion. The probe is a capacitive plate placed over the chest wall emitting a low-energy, high-frequency (10 MHz) electromagnetic field. Motion within the field produces a change in capacitance, and therefore frequency of the oscillation, which is converted to the output voltage signal. Its limitations include the inability to detect wall motion that is not anterior, the presence of interfering noise produced by other artificial motion, and the inability to maintain probe position during prolonged surgery or thoracic surgery. Previous studies have demonstrated that cardiokymography is more sensitive and specific an indicator of CAD than the ECG. Exercise cardiokymography has been shown to have similar sensitivity and specificity as exercise thallium scintigraphy, and significantly better than exercise electrocardiography. In surgical patients, Bellows et al. demonstrated a 33% (8/24) incidence of cardiokymographic changes indicative of ischemia in patients with CAD (vs. 4% [1/25] in patients without CAD), with 1/8 having ECG ST abnormalities, and 3/8 increased PCWP (≥4 mmHg). Hägemark et al. compared cardiokymography, single-lead (V5) ECG, PCWP, and lactate extraction (left anterior descending artery) in 53 vascular patients with CAD. Seventy-four percent of the patients developed one or more forms of ischemia, with 83% of the episodes detected by cardiokymography, 44% by ECG, 39% by PCWP, and 13% by lactate production. The relationship of cardiokymographic changes to TEE wall-motion abnormalities, or to adverse cardiac outcome, is unknown.

Biochemical markers of myocardial ischemia (lactate and radiolabeled lactate markers): Lactate production is one of the most accurate measures of myocardial ischemia. Because of the regional nature of myocardial ischemia and the complex relationship between lactate uptake and production, serum lactate measurement is an insensitive marker of ischemia. Radiolabeled lactate determinations permit differentiation between uptake and production and are sensitive markers. However, techniques for sampling lactate and radiolabeling lactate are research tools having limited clinical use.

Ventricular Dysfunction. Increased ventricular filling pressure, associated with ventricular dysfunction, deleteriously affects both myocardial oxygen supply (coronary artery back-pressure, coronary vascular resistance) and demand (wall tension). In animals, the failing ventricle may not only precipitate ischemia, but also exacerbate the effects of hypotension, hypertension, and tachycardia on the ischemic state of the ventricle. Conversely, ischemia can precipitate ventricular dysfunction and increase end-diastolic pressure, particularly with severe coronary artery stenosis when myocardial oxygen demand is increased (e.g., exercise). Data from one large-scale study suggest a relationship between intraoperative dysfunction and outcome. Rao et al. found that PCWP exceeded 25 mmHg in 29/607 patients monitored using pulmonary artery catheters. Twenty-eight percent (8/29) of these patients with elevated PCWP developed perioperative MI versus less than 1% of those with no increase in PCWP. Several other studies have suggested that operative mortality was decreased in patients undergoing aortic aneurysm repair monitored with pulmonary artery catheters. However, these studies have a number of limitations and further investigation is necessary.

Dysrhythmias. Studies using noncontinuous ECG recording techniques report that the incidence of dysrhythmias during noncardiac surgery varies from 0.9–70%. The range of these incidences likely is due to highly variable monitoring regimens, as well as differences in the inclusion criteria. Continuous ECG recording was used in two studies of dysrhythmias in a total of 254 noncardiac surgical patients. The incidence of dysrhythmias was 70%; 28% were ventricular. The first study, (Kuner et al., 1967) in 154 noncardiac surgical patients who revealed an overall incidence of dysrhythmias of 62%. This incidence was higher during general versus regional anesthesia (66% vs. 52%), neurologic and thoracic surgery versus peripheral surgery (100%, 90% vs. 56%), and in intubated versus nonintubated patients (72% vs. 44%). Twenty-one percent of the dysrhythmias were ventricular (premature ventricular contractions: 18%; ventricular tachycardia: 3%). Surprisingly, pre-existing heart disease did not influence the incidence of dysrhythmias (62% vs. 59%). The second study, by Bertrand et al. in 1971, found an 84% incidence of dysrhythmias in 100 noncardiac surgical patients. The intraoperative incidence was significantly higher than that during the preinduction phase (84% vs. 28%), particularly during intubation and extubation, when 72% of dysrhythmias occurred. Bertrand et al. reported a 43% incidence of ventricular dysrhythmias, with the incidence of ventricular dysrhythmias being greater in patients with than without heart disease (60% vs. 37%).

Of the four studies attempting to define the predictive value of intraoperative dysrhythmias, two report that they are predictors of PCOM and two that they are not.
or type of dysrhythmias (other than tachycardia) and perioperative reinfarction. Goldman et al. found a 4% incidence of new supraventricular tachyarrhythmias and a 7% incidence of intraoperative bradycardia, but both types of dysrhythmia were unrelated to PCM. Steen et al.'s results generally support dysrhythmia's predictive value, but only indirectly: all eight of their patients who reinfarcted intraoperatively had clinical signs of either hypotension or dysrhythmia. None of these studies has rigorously measured intraoperative dysrhythmias using continuously recorded ECG techniques.

**Dynamic Intraoperative Predictors—Conclusions**

Both intraoperative hypotension and tachycardia predict PCM. Hypertension remains a controversial predictor, and ventricular dysfunction and dysrhythmias have not been adequately studied. Myocardial ischemia, as indicated by ECG, TEE, or cardiokymography, is a suggested predictor, but the data apply principally to patients undergoing CABG surgery. Left ventricular end-diastolic pressure is a sensitive measure of ischemia, but preliminary studies suggest that PCWP may be too insensitive. Finally, other measures, such as radionuclear imaging or lactate determination, used primarily in research studies, are impractical for routine clinical use.

**Postoperative Predictors**

The postoperative period can be stressful, due to the onset of pain during emergence from anesthesia, fluid shifts, temperature changes, and alteration of respiratory function. Marked changes occur in plasma catecholamine concentrations, hemodynamics, ventricular function, and coagulation following noncardiac surgery, particularly in patients with pre-existing cardiac disease. These stresses place the patient at increased risk for development of adverse cardiac outcome. Because most outcome studies have focused on the pre- and intraoperative periods, there are, as yet, no identified postoperative predictors of adverse outcome.

What is known about postoperative hemodynamic and ischemic changes? Recent studies in both cardiac and noncardiac surgery have shown that heart rate commonly increases postoperatively by 25–50% over intraoperative values, and that tachycardia (heart rate > 100 beats/min) occurs in 10–25% of patients. Whether postoperative tachycardia is related to ischemia remains unknown. However, these preliminary studies suggest that ischemia does occur most commonly during the postoperative period and persists for 48 h or longer following noncardiac surgery. Also, these postoperative ischemic episodes usually are not manifest by symptoms of typical or atypical chest pain, symptoms of hypoperfusion, or ventricular failure. Postoperative ischemia thus appears to be silent, and therefore difficult to detect.

A number of factors could account for the silent nature of postoperative ischemia. Patients with ambulatory ischemia have a similar incidence of silent ischemia (>70% of episodes are silent), possibly due to defects in pain threshold and perception. Moreover, postoperative residual anesthetic or analgesic effects and competing somatic sensory innervation (e.g., incisional pain) may further blunt the perception of, reaction to, or communication of painful ischemic symptoms. Supporting this hypothesis is the finding that most postoperative infarcts are silent (>60%) compared with relatively few nonsurgical infarctions (10–15%).

Is postoperative myocardial ischemia a predictor of PCM? The answer is unknown. However, if postoperative ischemia is proven to be an important predictor of morbidity, extended postoperative monitoring and aggressive treatment of ischemia would be indicated, appreciably altering postoperative practice. The cost of such care could be substantial.

**Conclusions**

Perioperative cardiac morbidity is and will continue to be an important health-care problem. Of the 25 million patients who undergo anesthesia and surgery in the United States annually, approximately 2–3 million have, or are at risk for, CAD; an additional 4 million are over the age of 65, and 5 million undergo major surgery. As the elderly population grows at three times the rate of other groups, the prevalence of cardiac disease will increase in our surgical population. The current incidence of PCM in this at-risk population remains unacceptably high, ranging from 2 to 15%.

Over the past 35 yr, approximately 100 outcome studies have examined the problem of PCM in patients undergoing noncardiac surgery. Most have focused on preoperative historical predictors, of which only a recent MI or present CHF are proven predictors of PCM. The efficacy and cost-effectiveness of specialized preoperative cardiac testing, such as exercise stress testing or dipyridamole thallium imaging, remain controversial. Outcome studies of intraoperative predictors have shown that anesthetic choice does not affect outcome, but that emergency surgery, major vascular surgery, and prolonged thoracic or upper abdominal surgery are associated with increased risk. Among the dynamic intraoperative predictors, hypotension and tachycardia appear to predict outcome. Myocardial ischemia, although potentially important, has not been studied rigorously in patients undergoing noncardiac surgery. Studies of the postoperative period are few. Preliminary data suggest that the post-
operative predictors for perioperative cardiac morbidity may be at least as critical as intraoperative factors.

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