特 集 (special edition)

Perioperative Cardiac Morbidity: New Developments & Controversies

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Introduction

Approximately one in four Americans (65/239 million) has cardiovascular disease and, of these, nearly 7 million have symptomatic coronary artery disease (CAD). As many as 5 million other patients have asymptomatic or, silent myocardial ischemia. These figures will continue to be high due to the growth of our aging population.

The effect on patients undergoing anesthesia and surgery is substantial. Three million of the 20 million (15%) patients undergoing surgery yearly in the United States, have, or are at risk for, CAD. Four million of additional patients are over the age of 65.[1] Despite advances in perioperative care, cardiac morbidity and mortality in patients undergoing noncardiac surgery remain unacceptably high, ranging from 2 to 20 %.[1-13]

Previous solutions of this problem of perioperative cardiac morbidity focused on preoperative identification. These studies, conducted between 1961 and 1976, found that patients with recent myocardial infarction (<6 months) were at particularly high risk of reinfarction (as much as 37%). The recommendation of delaying surgery six months in these patients evolved. The important study by Goldman and colleagues in 1977 demonstrated that a multiplicity of predictors was significant, and the cardiac risk index was formulated.[6] Subsequently (1983), Rao *et al.*[14] questioned the high reinfarction rate and implied that lower rates could be achieved by more intensive perioperative monitoring. Following this, in 1985, a number of investigators advocated more sophisticated preoperative testing to identify the at-risk patient, such as exercise stress testing, radionuclide ventriculography, and dipyridamole thallium imaging.[8-12]

Most studies prior to 1985 focused on the preoperative identification of at-risk patients. But the entire perioperative period is stressful, and dynamic physiologic changes may be equally important predictors of outcome. It was found that intraoperative ischemia occurred in 20-78% of patients with CAD, as detected by multiple-lead electrocardiography (ECG) or transesophageal echocardiography (TEE).[2] The two important studies by Smith *et al.*[15] and Slogoff and Keats[16] examined the relationship between intraoperative ischemic episodes and outcome and suggested a strong association. As a result, there is increased emphasis on the detection of intraoperative ischemia as a result of these studies, and more sophisticated monitoring has been introduced into the operating room. We will review several of these modalities.

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The Evolution of Intraoperative Monitoring

Intraoperative cardiovascular monitoring has advanced rapidly over the past four decades—progressing from the finger-on-the-pulse technique (1930s, '40s) to invasive blood pressure monitoring (1970s). Although it was introduced in the late 1950s, intraoperative ECG was not in general use until the late 1960s. Measurement of cardiac filling pressures using pulmonary artery (PA) catheterization was not in general intraoperative use until the late 1970s. In the 1980s, two significant advances occurred: continuous oxygen saturation measurement using pulse oximetry, and intraoperative TEE. Presently, pulse oximetry is in widespread use throughout the United States, and TEE is rapidly gaining acceptance. Each of these has undergone significant change and will, undoubtedly, undergo further change over the next decade. There is clearly a trend towards noninvasive techniques; however, invasive techniques, such as PA catheterization and monitoring, will continue to play an important role in anesthetic practice.

Electrocardiographic Detection of Perioperative Myocardial Ischemia

A number of clinical studies have found a high incidence of ECG evidence of ischemia (20-78% of patients) in patients with CAD undergoing both cardiac and noncardiac surgery (summarized in Table 1), and these studies suggest the importance of detecting ischemia perioperatively. Until only recently, however, the optimal lead number and location were controversial. Work by Blackburn, Taylor and Okamata in the late 1960s demonstrated that 85% of ST-depression episodes during exercise treadmill testing occur in leads II or V_5.[17] Following that, Chaitman *et al.* demonstrated that a 14-lead ECG system improved the predictive value of the treadmill test, especially in patients with multi-vessel disease,[18] and Fuchs *et al.* demonstrated that leads V_5 and V_6 have the highest prevalence of positivity, but also showed that 12% of all positive stress tests were negative in these leads.[19]

However, the lead-localization data provided by exercise stress testing in ambulatory patients may not be applicable to the intraoperative setting. For example, during exercise stress testing, myocardial oxygen consumption is increased multiple-fold primarily due to an increase in heart rate, and therefore cardiac output. Systemic vascular resistance generally decreases. During anesthesia and surgery, however, the major hemodynamic changes are usually related to vascular resistance, with only moderate (<30%) increases in heart rate and decreases in cardiac output. Also, patients are supine or prone *vs*, standing. Despite several case reports suggested intraoperative use of the modified V_5 lead in the mid-1970s, the question of lead-localization was not rigorously examined until 1988 when London *et al.* studied 105 patients with known or suspected CAD undergoing noncardiac surgery with general anesthesia using continuous intraoperative recording of the 12-lead ECG.[20] They found that sensitivity was greatest in V_5 (75%) and V_4 (61%), and intermediate in V_6 (37%), V_3 (33%), and II (24%). Other leads had low sensitivity (<14%). The combination of leads V_4 and V_5 increased sensitivity to 90%, increasing to 96% by combining II, V_4, and V_5, and to 100% when V_2 and V_3 (five leads), were used. A relatively high incidence of lateral (V_4, V_5) ischemia therefore occurs in patients with CAD undergoing both cardiac and noncardiac surgery. The time course and duration of ischemia remains unknown, as does its relationship to indices of myocardial supply and demand.

A number of advances have been made recently in intraoperative ECG monitoring, including the use of multiple-lead systems, adaptation of

Table 1 Major clinical studies of perioperative ischemia

Author Year	Patients Studied	Type of Surgery	Definition of Ischemia	Monitor used for Ischemia Detection	Leads	Patients Ischemic (%)	Duration Ischemia	Outcome
Roy (1979)	CAD 29	Noncardiac	>1 mm 3 beats	Exercise ECG system	V_5	38	—	27% postop ischemia, 9% infarction
Wilkinson (1981)	CAD 26	CABG	>1 mm	Routine ECG, CS catheter	V_6	69	—	Unable to correlate
Reiz (1981)	Acute MI 6	Major abdominal	>1 mm	Routine ECG, CS catheter	V_5	66	—	No apparent complications
Coriat (1982)	CAD 51	Vascular	>1 mm 3 beats	Holter monitor (unspecified)	CM5	39	>5 mm	No apparent complications
Sonntag (1982)	CAD 9	CABG	—	Routine ECG, CS catheter	—	78	—	—
Reiz (1983)	CAD 21	Vascular	—	Routine ECG, CS catheter	V_5	47	—	No apparent complications
Backofen (1984)	s/p CABG 37	Noncardiac	Definite >2 mm	Routine ECG	2 V_5	Definite 20	—	7.5% postop infarction
Coriat (1984)	CAD 45	Vascular	>1 mm 10 beats	Holter monitor (unspecified)	D2 CM5	64	>5 mm	No apparent complications
Thomson (1984)	CAD 20	CABG	>1 mm	Holter monitor (unspecified)	2 CS5	50	—	—
Slogoff (1985)	CAD 1023	CABG	>1 mm	Routine ECG	2 V_5	37	—	Infarction in 7% of patients with ischemia
London (1988)	CAD 105	Noncardiac	>1 mm	12-lead (continuous)	All	24	med=10 min	3% postop infarction
Knight (1988)	CAD 50	CABG	>1 mm	Holter monitor	2	60	16-41 min	14% had major outcomes. Unable to find significant relationship with ischemia.
Häggmark 1989	CAD 53	Major abdominal	—	Routine ECG, cardiokymography	V_5	74	—	5.7% postop infarction
Mangano (1990)	CAD 474	Major Noncardiac	>1 mm	Holter monitor	CC5 CM5	41	med.=20 min	Postoperative ischemia most important predictor

CAD (coronary artery disease), CABG (coronary artery bypass grafting), CS (coronary sinus catheter), MI (myocardial infarction), and—(not specified)

ambulatory monitoring to the intraoperative setting, and more invasive ECG montioring including esophageal, cardiac, and tracheal placement of electrodes. Future developments include multiple-lead, microcomputer-assisted dysrhythmia and ST-segment detection will be introduced. Prototype microcomputer-augmented cardiograph (MAC, Marquette Electronics, Milwaukee, WI) which continuously displays an ST-trend plot in an orthogonal lead set (V_5, aVF, and V_1) have been developed. In addition, Hollenberg *et al.*[21-23] have used a computer-assisted 12-lead ECG system (Marquette Electronics CASE 2) and derived a treadmill exercise score which improved the ability to quantify the extent of coronary disease. Similar significant advances are expected for algorithm development for detection of dysrhythmias, ST segments, and R-wave and T-wave changes.

Recently, postoperative myocardial ischemia has been identified as the most important predictor of adverse outcome and it confers a 9.2-fold increase in the odds of such outcomes.[40] These results emphasize the postoperative period and detection and treatment of ischemia, and may be the key to reducing perioperative cardiac morbidity.

Pulmonary Vascular Pressure Monitoring

The usefulness of PA monitoring during anesthesia and surgery has been addressed in several studies.[24-26] During coronary artery bypass graft surgery, the advantages of PA monitoring over central venous pressure monitoring were demonstrated in patients with ejection fractions <0.4 or significant wall-motion abnormalities.[23] However, in patients with good myocardial function (ejection fraction >0.50 and no dyssynergy), the central venous pressure was an accurate correlate of the pulmonary capillary wedge pressurs (PCWP), and demonstrated that PA monitoring may be unnecessary in this large group of patients with good cardiac function.

Relationship to Outcome

Only a few studies have assessed the effects of PA catheterization and monitoring on cardiac outcome. Indirect data are provided in several studies. In 1977, Goldman *et al.* demonstrated that patients presenting for noncardiac surgery with signs or symptoms of congestive heart failure had increased risk for developing perioperative cardiac failure.[5] From this study, it can be inferred that monitoring and early treatment of cardiac failure may reduce perioperative morbidity. Rao *et al.* studied 733 patients with previous myocardial infarction undergoing noncardiac surgery, and had a reinfarction rate of 1.9%.[12] The reinfarction rate was significantly lower than those previously reported (6-7%). Eighty-three percent (609) of these 733 patients were monitored with PA catheters. Twenty-nine of these 609 patients had a PCWP>25 mmHg intraoperatively, and had a 28% incidence of myocardial reinfarction. The reinfarction rate was only 1% (6/580), however, in patients with PCWP<25 mmHg. Thus, elevation of PCWP may be a predictor of infarction and, therefore, that PA monitoring for detection of ischemia may be useful in patients with ischemic heart disease undergoing noncardiac surgery.

Animal studies provide evidence supporting this hypothesis. Following acute myocardial ischemia, left ventricular end-diastolic pressure rises early and usually precedes ECG changes in the ST segment. The PCWP may be insensitive, however. The mean left ventricular diastolic pressure, and therefore PCWP, may not reflect the changes in left ventricular end-diastolic pressure. For example, in patients with acute myocardial infarction, it has been shown that left ventricular end-diastolic pressure can exceed PCWP by 10 to 15 mmHg during ischemia.[27] However, conclusive statements can be made only with further study regarding the sensitivity of PCWP during left ventricular ischemia. One study demonstrated that abnormalities of PA wedge pressure tracing occurred in 55% of the patients thought to develop ischemia, whereas ST-segment changes were present in only 44%.[28] A second study found that 89% of patients who developed signs of ECG ischemia under isoflurane anesthesia and temporary pacing developed V-waves.[29] More recently Häggmark *et al.*[30] found that the specificity and sensitivity of PCWP for detection of ischemia (ECG, cardiokymography, lactate production) ranged between 40 and 60 percent. Lieberman *et al.*[31] also found only a 24% positive predictive value, although the negative predictive value was high. Most recently, Leung *et al.*[32] demonstrated that only 7% of ischemia events were preceded by increases in pulmonary artery pressure. Thus, the PA catheter is an excellent monitor for assessment of ventricular function; however, its low sensitivity for detection of myocardial ischemia limits that application. Further study is warranted, however.

Transesophageal Echocardiography

Two-dimensional TEE is currently gaining widespread use since its introduction in the United States in 1983.[33-36] TEE allows: (1) assessment of the ischemic state *via* measurement of regional wall-motion and wall-thickening changes; (2) assessment of ventricular function *via* measurement of estimated ejection fraction, ventricular volumes and wall-shortening; and (3) measurement of other related phenomena, such as valvular function and intracardiac air and masses. Recent advances include the addition of Doppler,[37] color flow,[38] and contrast echocardiography.[39] TEE's limitations include: (1) cost—ranging from $75,000 to $235,000; (2) size—approximately the size of a portable chest radiography system; and (3) information access—such as lack of on-line quantification of images (volume, ejection fraction, wall motion). It is expected that TEE will gain even more widespread acceptance as an intraoperative monitor, despite the disadvantages, because of its ease of use, safety and sensititvity.

Equipment and Technique

The transducer frequencies range between 1 and 7 MHz ("ultrasound" frequencies). One mm resolutions are possible at the high end of the range (5-7 MHz), but penetration is decreased. Penetration is improved at the lower frequencies (1-3 MHz), but resolution is less (2-3 mm). Precordial echocardiography uses frequencies of 2-3 MHz allowing penetration of the chest wall, but with a resolution of 2 mm, at best. TEE uses frequencies of 3.5 to 7 MHz, since penetration is not a problem, thereby affording excellent resolution. The TEE echoprobe is a modified 9 mm (diameter) gastroscope with a 110 cm flexible shaft which permits 120 degree angulation of the transducer in two planes. The most common view used for detection of wall-motion and wall-thickening abnormalities is the short-axis view, and segmental wall-motion abnormalities can be readily detected in the anterior, septal, posterior, and lateral walls. Wall-thickening abnormalities are not as easily detected because of the difficulty in delineating the epicardium. End-systolic, end-diastolic and stroke "areas", as well as ejection fraction area can be estimated on-line or quantified off-line. TEE thus allows intraoperative assessment of ventricular function as well as ischemia.

Complications

With over 5000 uses in surgical patients in the United States, the technique has been shown to be safe, and complications are rare and minor. During sitting craniotomy with the head flexed, transient vocal cord edema has been reported. Another possible complication, esophageal burn, has been minimized by using temperature sensors attached to the distal end of the echoprobe. Other complications can be minimized by avoiding its use in patients with esophageal disease, external constriction of the esophagus (left atrial myoma or thoracic aneurysm) or coagulopathies.

Clinical Findings

Animals studies have demonstrated that following coronary occlusion, the ischemic myocardium develops wall-thickening and wall-motion abnormalities, which often precede ECG changes and may offer a more sensitive means of detecting myocardial ischemia. A study by Smith *et al.* demonstrates such sensitivity.[15] Of 50 patients undergoing coronary artery bypass graft or major vascular surgery, new segmental wall-motion abnormalities were detected in 24 (48%). New ECG ST changes occurred in only six patients (12%). All patients with ST changes had TEE changes. In contrast, 18 of the 24 patients had TEE changes without ECG changes. Of the four patients with a perioperative myocardial infarction, all had TEE changes, but only one had intraoperative ECG changes.

The prognostic value of TEE in patients undergoing coronary artery bypass graft surgery has been investigated recently by Leung *et al.*[32] Using continuous TEE, ECG

(Holter), 50 patients undergoing elective coronary artery bypass graft surgery were prospectively studied. Hemodynamic measurements were made during the prebypass, post-bypass, and early postoperative intensive care unit (ICU) periods (first 4 h). The distribution of myocardial ischemia during the perioperative periods was prebypass: TEE 20%, ECG 7%; postbypass: TEE 36%, ECG 25%; ICU: TEE 25%, ECG 16%. Only postbypass TEE ischemia was predictive of outcome (myocardial infarction, ventricular failure, and cardiac death). None of the 32 patients without TEE ischemia had adverse outcome; whereas, 6/18 patients with postbypass TEE ischemia had adverse outcomes. Most (73%) of the echocardiographic ischemic episodes occurred without acute change (±20% of control) in heart rate, blood pressure, or PA pressure. TEE appears to be a more sensitive clinical monitor than ECG, and may be a better predictor of cardiac morbidity. Its widespread perioperative use is not warranted presently, until the value of TEE, relative to other monitoring modalities, such as ECG and PA monitoring, is determined.

Conclusion

The detection of intraoperative myocardial

Table 2 Variables Associated with 83 Cardiac Outcomes Among 474 Patients Undergoing Noncardiac Surgery

	Odds Ratio	95% Confidence Interval	P Value	No. With Outcome and Variable/No. With Variable
Univariable models*				
Previous myocardial infarction	1.7	1.1−2.8	0.03	38/167
Definite coronary artery disease	1.9	1.2−3.1	0.01	54/248
History of dysrhythmia	2.8	1.7−4.7	0.0001	37/123
History of congestive heart failure	2.9	1.6−5.0	0.0002	25/77
History of claudication	2.7	1.7−4.4	0.0001	42/150
Diabetes mellitus (treated with medication)	1.6	0.94−2.8	0.08	22/93
Preoperative use of nitrates	1.6	0.97−2.6	0.06	30/132
Preoperative use of digoxin for congestive heart failure	5.8	2.3−15	0.0001	10/19
Serum creatinine > 0.023 μmol/L†	2.3	1.1−5.0	0.03	11/35
ASA score ≥ 3	2.5	1.3−5.0	0.007	72/354
Cardiac risk index (per 10 units)	1.8	1.2−2.7	0.002	
Vascular surgery	2.4	1.5−3.9	0.0003	44/168
Narcotic anesthesia	2.2	1.2−4.2	0.01	16/54
Preoperative Holter ischemia‡	3.1	1.8−5.3	0.0001	28/84
Intraoperative Holter ischemia §	2.1	1.2−3.7	0.005	27/104
Postoperative Holter ischemia¶	3.3	1.9−5.6	0.0001	46/167
Multivariate model				
History of dysrhythmia	2.2	1.3−3.9	0.006	
Preoperative use of digoxin for congestive heart failure	3.32	1.1−11	0.04	
Vascular surgery	1.8	1.1−3.2	0.03	
Postoperative Holter ischemia	2.8	1.6−4.9	0.0002	

* All variables are binary (yes or no) unless otherwise indicated. ASA denotes American Society of Anesthesiologists.

† Values in parentheses are 95 percent confidence intervals.

‡ Based on a denominator of 429 patients.

§ Based on a denominator of 423 patients.

¶ Based on a denominator of 407 patients.

Table 3 Variables Associated with 15 CAD Outcomes among 474 Patients Undergoing Noncardiac Surgery.

	Odds ratio	95% confidence interval	P value	No. with outcome and variable/No. with variable
Univariable models*				
History of claudication	3.4	1.2−9.7	0.02	9/150
Activity level ≥ 5†	4.3	1.2−16	0.02	3/28
Preoperative use of nitrates	2.3	.83−6.6	0.1	7/132
Serum creatinine ≥ .023 μmol/L‡	5.0	1.5−17	0.004	4/35
Postoperative Holter ischemia §	9.2	2.0−42	0.004	12/167
Multivariable model				
Postoperative Holter ischemia	9.2	2.0−42	0.004	

* All variables are binary (yes/no) unless otherwise indicated.

† Severely limited (bed to chair) or medically restricted.

‡ Equivalent to 2 mg/d*l*.

§ Based on denominator of N=407 patients.

Table 4 Results of Multivariable Analysis of Variables Associated with 30 Congestive Heart Failure Outcomes among 459 Patients without CAD Outcomes, and 38 Ventricular Tachycardia Outcomes among 430 Patients without CAD or Congestive Heart Failure Outcomes.

	Odds ratio	95% confidence interval	P value
Variables associated with congestive heart failure*			
History of dysrhythmia†	3.0	1.4−6.7	0.006
Diabetes mellitus (treated with medication)†	2.4	1.0−5.7	0.04
Duration of anesthesia and surgery (per hour)‡	1.2	1.1−1.4	0.002
or			
Vascular surgery†	3.5	1.6−7.9	0.002
Narcotic anesthesia‡	2.5	1.0−6.5	0.05
or			
Isoflurane/narcotic anesthesia†	.35	.16−.76	0.008
Variables associated with ventricular tachycardia*			
Preoperative Holter ischemia	7.8	2.9−21	0.0001
Preoperative use of digoxin for congestive heart failure	12	2.8−50	0.0009

* All variables are binary (yes/no).

† Statistics for model containing history of dysrhythmias, diabetes, vascular surgery, and isoflurane/narcotic anesthesia.

‡ Statistics for model containing history of dysrhythmias, diabetes, duration of anesthesia and surgery, narcotic anesthesia.

ischemia is a relatively new area of study but is rapidly evolving. Clearly, we will be besieged by a number of invasive and noninvasive monitors which will allow more sensitive and specific detection. Prior to acceptance of these technologies, however, their effect on outcome must be determined.

Most Recent Results

My colleagues and I have recently published an article investigating the predictors of perioperative cardiac morbidity in at-risk patients undergoing elective noncardiac surgery. We studied 474 men with (243) or at high risk of (231) CAD, collecting historical, clinical, laboratory, and physiologic data during hospitalization and for 6 to 24 months after operation. We assessed myocardial ischemia by continuous electrocardiographic monitoring beginning 2 days before operation and continuing for 2 days after.

Postoperative cardiac events occurred in--hospital for 83 patients (18%) and were classified as ischemic events (cardiac death, MI, or unstable angina), detected in 15 patients; CHF, detected in 30 patients; and ventricular tachycardia, detected in 38 patients (Tables 2-4). Postoperative myocardial ischemia occurred in 41% of the patients monitored and was associated with a 2.8-fold increase in the odds of all adverse cardiac outcomes (95% confidence interval, 1.6-4.9; $p<0.004$). Multivariate analysis disclosed no other clinical, historical, or perioperative variable as independently associated with ischemic events, including cardiac risk index, history of previous MI or CHF, or the occurrence of preoperative or intraperative ischemia.

Our results demonstrate that postoperative myocardial ischemia during the first 48 hours after operation confers a nearly three-fold increase in the odds of having an adverse cardiac outcome and, more importantly, a nine-fold increase in the odds of having an ischemic event. Thus, these results highlight the importance of the postoperative period, extending the work of previous investigators who have demonstrated the importance of the patient's preoperative chronic disease state and of physiologic changes during operation. They also suggest greater emphasis on the postoperative period, during which early postoperative ischemia is an important correlate of adverse cardiac outcome. Patients may warrant more intensive monitoring and intervention during this period than previously assumed. Most significantly, these results suggest that increased attention and resources focusing on the prevention of (and possibly therapy for) postoperative ischemia may well be the key to reducing perioperative cardiac morbidity.

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(Circ Cont 13(3): 347～356, 1992)