CLINICAL CONCEPTS AND COMMENTARY

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Approaches to the Prevention of Perioperative Myocardial Ischemia

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PREVENTION of perioperative myocardial ischemia is essential to avoid the mechanical, metabolic, and electrophysiologic changes associated with acute imbalances in the relationship between myocardial oxygen supply and demand. Myocardial ischemia of sufficient severity or prolonged duration may result in reversible (*e.g.*, myocardial stunning) or irreversible (*e.g.*, infarction) damage, malignant ventricular arrhythmias, or cardiogenic shock. These potentially disastrous consequences are associated with high morbidity and mortality in patients with coronary artery disease. Elective surgical procedures may be delayed until unstable coronary artery disease is treated by angioplasty or surgical revascularization.

Despite the prevalence of coronary artery disease and the frequent occurrence of myocardial ischemia, the anesthesiologist may implement important pharmacologic and anesthetic interventions that improve perioperative outcome. In addition, several exciting new drugs on the horizon promise to reduce the risk of myocardial ischemia or infarction. Although some of these new drugs act by altering the myocardial oxygen supply/demand relationship, others directly protect myocardium from ischemic injury. This brief review outlines established methods used for the prevention of myocardial ischemia and also discusses potential future therapeutic strategies that may attenuate the reversible and irreversible sequelae of ischemia. At present, the majority of data has been obtained in patients with severe coronary artery disease undergoing coronary artery bypass graft surgery. The applicability of results obtained in this patient population must be extrapolated with care to patients with less severe coronary disease or those undergoing noncardiac surgery.

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Myocardial Oxygen Supply and Demand

The classical relationship between myocardial oxygen supply and demand indicates that when oxygen demand exceeds supply, the imbalance results in myocardial ischemia (fig. 1). Fortunately, this supply/demand relationship may be favorably altered by a variety of pharmacologic agents in the perioperative period to prevent the onset of myocardial ischemia. Such interventions should be aggressively undertaken in a manner equal to the vigilance required for the detection of acute ischemic events. Objectives of treatment include reducing demand for oxygen by myocardium at risk for development of ischemia while simultaneously increasing oxygen supply to this tissue. Myocardial oxygen demand in the left ventricle is dependent on heart rate, myocardial contractility, and ventricular loading conditions. Heart rate is the most important of all physiologic factors that can be altered to reduce demand. Increases in heart rate not only lead to profound increases in oxygen consumption but also jeopardize perfusion in regions distal to

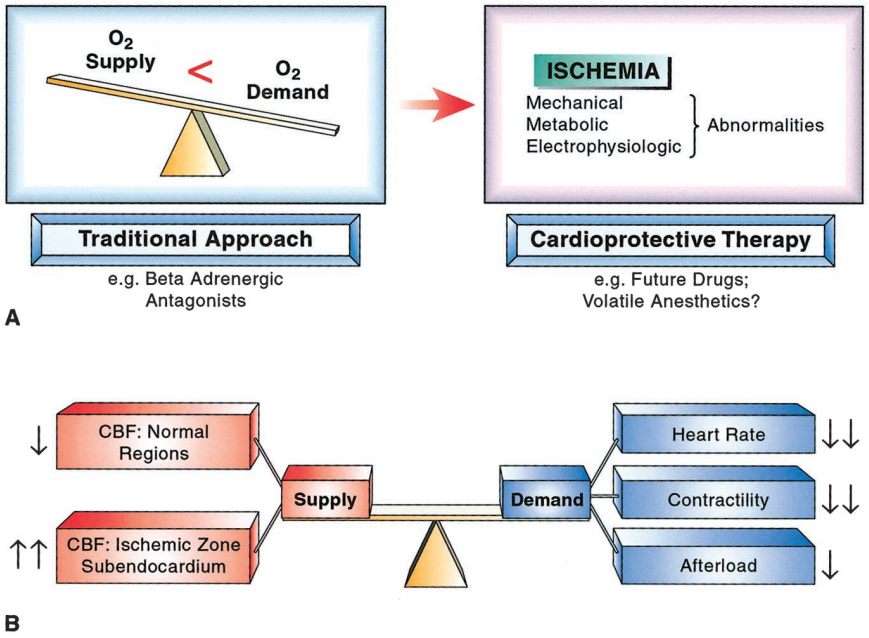

Fig. 1. (*A*) Representation of oxygen demand exceeding supply, resulting in ischemic sequelae. Note that traditional approaches to this problem address myocardial oxygen balance. In contrast, new cardioprotective therapies may not prevent an ischemic episode, but instead reduce the metabolic, mechanical, and electrophysiologic consequences of ischemia. (*B*) Mechanisms by which β-adrenoreceptor antagonists improve balance of myocardial oxygen supply and demand. Arrows indicate directional changes produced by β-blockers. CBF = coronary blood flow.

coronary artery stenoses by reducing the duration of diastole. These actions are most pronounced in the left ventricular subendocardium. As stenosis severity increases, and with it the risk of ischemia and infarction, the role of coronary perfusion pressure (the difference between aortic diastolic and left ventricular end-diastolic pressures) gains greater significance. Myocardial blood flow is autoregulated to a relatively constant level under normal conditions, but the ability of the distal coronary vascular bed to dilate in response to increasing stenosis

Table 1. Present and Potential Examples of Antiischemic/Cardioprotective Therapy*

Beta adrenoceptor antagonists	**Of Known Clinical Benefit**
Nitrates	**Depending on the Etiology**
Ca++ channel antagonists	**of Ischemia**
Drugs that shift the oxyhemoglobin dissociation curve	
Synthetic O_2 carriers	
Optimized blood rheology and hemoglobin concentration	
Antiplatelet drugs	
Specific bradycardic agents	
K_{ATP} channel agonists	
Acadesine and adenosine enhancing drugs	Potentially Useful Agents
Growth factors	
Na^+/H^+ exchange inhibitors	
Opioid $delta_1$ receptor agonists including morphine	
Interference with adhesion molecules	
Inhibitors of the glycoprotein IIb-IIIa receptor	

*This table includes agents with known clinical benefit and others that have questionable utility and/or require further investigation.

severity will eventually become exhausted. Finally, in the presence of severe stenosis, autoregulation fails to maintain coronary blood flow, and perfusion to the affected territory becomes directly dependent on coronary perfusion pressure. Deleterious increases in myocardial contractility and oxygen use may occur during the perioperative period because of β_1-adrenoceptor stimulation by endogenous catecholamines. Left ventricular preload and afterload also affect myocardial oxygen demand by altering end-diastolic and end-systolic wall tension, respectively. Many other factors, such as blood rheology, hematocrit, and coronary collateral blood flow, influence the myocardial oxygen supply/demand relationship as well. The degree to which any of these factors may result in myocardial ischemia is specific for each patient. Small decreases in coronary perfusion pressure or increases in heart rate may produce detrimental effects depending on the specific degree of coronary artery disease. Thus, clinical investigations of frequency of and morbidity associated with ischemia during anesthesia are difficult to conduct. The severity of coronary artery disease represents a major confounding variable that is difficult to control during clinical investigations. For example, a large increase in heart rate may be well tolerated in a patient with mild coronary artery disease. In contrast, a small increase in heart rate may be accompanied by global deterioration of left ventricular function secondary to profound ischemia in a patient with severe multivessel disease.

Traditional pharmacologic approaches to the prevention and treatment of ischemia focus on the oxygen supply/demand relationship; however, novel therapeutic strategies are being studied intensively. Newer modalities may alter myocardial oxygen demand at the cellular or mitochondrial level independent of systemic and coronary hemodynamics. A list of potentially useful drugs and techniques (some of which are as yet only experimental) is shown in table 1. It is important to recognize that no single method of treatment is ideal for all patients because of the multifactorial basis of myocardial ischemia. Furthermore, all therapeutic approaches have limitations, and the cost and benefit of each requires careful evaluation. However, for the vast majority of patients with coronary artery disease undergoing anesthesia, prevention of myocardial ischemia affords a benefit that greatly outweighs the potential cost of an ischemic episode. Thus, the rationale for a "wait and see" strategy that uses intensive monitoring techniques to identify the onset of ischemia followed by initiation of treatment is not well founded. Such an approach may ultimately place the patient at far greater risk for development of complications because treatment of protracted myocardial ischemia and its consequences is inherently more difficult than primary prevention of ischemia. Prophylaxis against myocardial ischemia is of the utmost importance for the patient with coronary artery disease, and the use of β-adrenoceptor antagonists to achieve this goal has a firm scientific basis that may well exceed the relative importance of the type of anesthetic chosen for the patient at risk.

Pharmacologic Prophylaxis

Administration of β-adrenoceptor antagonists (using the protocol of Mangano *et al.*[1]) to patients with coronary artery disease undergoing surgery has been recommended by the American College of Physicians. To date, β-adrenoceptor antagonists are the only well-established means of prophylaxis against myocardial ischemia that demonstrate a reduction of morbidity and mortality in this patient population. Atenolol has been shown to be antiischemic, protect against myocardial reinfarction, and reduce overall mortality caused by cardiac death and congestive heart failure in both the immediate and remote perioperative periods.[1,2] The investigation by Mangano *et al.*[1] has been criticized because of differences in the preoperative and postoperative medical management of study groups, *i.e.*, the group treated with β-adrenergic antagonists had more aggressive medical management before surgery and possibly afterward as well. Nevertheless, this study demonstrates the efficacy of β-blockers in patients undergoing noncardiac surgery. Selective dosing of β-adrenoceptor antagonists may exert greater benefits than arbitrary, predefined doses of these drugs. Raby *et al.*[3] demonstrated that esmolol administered to maintain a heart rate lower than a previously established ischemic threshold significantly reduced the incidence of postoperative ischemic events. Although individualized treatment with a dose regimen targeted to achieve a specific heart rate in each patient may be more labor intensive, this technique is more rational than a "single unit dose" strategy.

The antiischemic mechanism of β-blockers is related to reductions in heart rate and myocardial contractility. The decrease in heart rate increases the duration of diastole, enhances coronary perfusion time, increases subendocardial blood flow, and reduces myocardial oxygen consumption. β-adrenoceptor antagonists are also capable of causing "reverse" coronary steal by increasing coro-

nary vascular tone in normal regions by reducing oxygen demand. These drugs attenuate the adverse effects of sympathetic nervous system activation, including increases in heart rate and myocardial contractility, decreases in coronary blood flow secondary to constriction of large epicardial coronary vessels, coronary cyclical flow phenomena at the stenosis site generated by platelet aggregation and dispersion, and overall plaque instability. In addition, β-blockers have important antiarrhythmic properties. In the vast majority of patients, the reduction in heart rate produced by β-adrenoceptor antagonists is compensated by an increase in stroke volume *via* the Frank-Starling mechanism, and cardiac output remains unchanged. If administration of a longer-acting oral β-adrenoceptor antagonist is a concern because of potential side effects (*e.g.*, history of bronchospastic lung disease), an antagonist with a short half-life, *e.g.*, esmolol, can be used to assess the individual tolerance for this class of drugs.

α_2-Adrenoceptor agonists, including clonidine, dexmedetomidine, and mivazerol, have been studied by multiple investigators and deserve special comment. These drugs exert beneficial cardiovascular effects by reducing central sympathetic nervous system activity. α_2-Agonists prevent tachycardia, hypertension, and increased sympathetic tone during and after surgery. However, the degree of reduction in heart rate produced by these drugs is difficult to predict, and the concomitant reduction in efferent sympathetic nervous system activity to the arterial vasculature may cause simultaneous reductions in coronary perfusion pressure. The α_2-agonists may have a potential advantage over β-blockers because of their ability to attenuate the adverse effects of sympathetic nervous stimulation mediated by peripheral α- as well as β-adrenoceptors. Mivazerol has been shown to reduce the incidence of perioperative tachycardia and myocardial ischemia.[4] This study was completed in a relatively small group of patients and was not powered to detect differences in cardiac outcome. Thus, large-scale clinical trials have yet to demonstrate convincingly the efficacy of α_2-agonists in the reduction of morbidity and mortality in patients with coronary artery disease.

Nitrates are a mainstay in the medical management of myocardial ischemia. Nitroglycerin reduces myocardial oxygen demand by decreasing left ventricular preload and end-diastolic wall tension. Nitroglycerin also increases coronary collateral perfusion by dilating large epicardial coronary arteries and collateral conduit vessels. This drug is also a donor of nitric oxide, which may have direct cardioprotective properties. Despite well-established beneficial effects, intraoperative prophylaxis with nitroglycerin has yielded equivocal results in patients with coronary artery disease. For example, Coriat *et al.*[5] demonstrated that nitroglycerin reduced the incidence of intraoperative ischemia, whereas Thomson *et al.*[6] showed no such benefit at an identical dose (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Differences in results may be related to the patient populations studied (noncardiac *vs.* cardiac surgery). Nitrates may actually be deleterious if a decrease in coronary perfusion pressure occurs, especially in patients with relative hypovolemia. Increasing intravascular volume and temporary use of phenylephrine may be useful.[7] Thus, treatment with these drugs should probably be limited to ongoing ischemia. In a similar fashion, calcium channel antagonists do not seem to be useful for prophylaxis of intraoperative myocardial ischemia,[8] although these drugs are capable of reversing ischemia caused by coronary artery vasospasm. The calcium channel antagonists have a variety of cardiovascular effects. Nifedipine and nicardipine have a predominant action on peripheral arterial tone and may produce baroreflex-mediated increases in heart rate that can result in an increase in myocardial oxygen consumption. In contrast, diltiazem reduces heart rate and may offer some benefit in the treatment of intraoperative ischemia,[9] but this has yet to be established firmly by large clinical trials.

Recent experimental and clinical investigations have demonstrated that brief periods of ischemia before a prolonged insult are capable of markedly reducing the extent of tissue injury, a process known as ischemic preconditioning. The brief period of ischemia renders the myocardium resistant to a subsequent ischemic insult, reducing myocardial stunning and infarction. The question that arises is: Are perioperative periods of transient stress beneficial by eliciting ischemic preconditioning? This is possible, but the lack of control over the degree of severity and duration of such episodes represents an important danger that in and of itself may result in tissue injury. On the other hand, it would be ideal if ischemic preconditioning could be mimicked by a drug that does not cause ischemia.

Selection of Anesthetic Technique

Considerable debate still remains over the advantages and disadvantages of regional compared with general anesthesia for the patient with coronary artery disease.

Advocates of regional anesthesia contend that this technique causes a greater reduction of intraoperative stress responses. Thoracic epidural anesthesia may even be used as an alternative approach in the management of unstable angina. Volatile anesthetics alone antagonize adrenergic responses to stress, and these agents are even more effective in the presence of small doses of opioids. Unfortunately, no definitive study has proven that one approach (regional *vs.* general anesthesia) is superior to the other. It seems highly unlikely that this controversy will be easily answered because implementing clinical trials that control for the type of surgery, concomitant drug therapy, and severity of coronary artery disease is an extraordinarily difficult task. Epidural or intrathecal local anesthetics or opioids may be beneficial for some patients with coronary artery disease, principally through limiting autonomic responses to stress. Similarly, aggressive control of intraoperative hemodynamics and use of adjuvant drugs, including opioids, during and after volatile anesthesia may be equally efficacious and present equivalent relative risk. In addition, volatile anesthetics have recently been shown to have important cardioprotective effects in experimental animals, enhancing the functional recovery of stunned myocardium and reducing the extent of myocardial infarction after brief and prolonged coronary artery occlusion and reperfusion, respectively.[10] These data should not be simply viewed as beneficial side effects of volatile anesthetics, but instead may eventually represent a therapeutic approach to intraoperative patient care. Morphine and other δ opioid receptor agonists also exert cardioprotective effects *in vivo*. However, whether these exciting experimental results with volatile anesthetics and opioids will translate into reductions in morbidity and mortality in patients with coronary artery disease has yet to be established by clinical trials.

Large-scale investigations have also not definitively shown that combined regional and general anesthesia offers any significant benefits. In fact, the likelihood of significant hypotension is probably increased with a combined technique. Particularly lacking are comparisons of neural blockade to other therapeutic alternatives, *e.g.*, β-adrenoceptor blockade. However, a reduction in hypercoagulability and thrombotic events has been described using a combined technique in a small study of patients undergoing peripheral vascular surgery.[11] Conversely, the combination of regional and general anesthesia may limit the ability of the anesthesiologist to deliver cardioprotective volatile anesthetics because arterial pressure and autonomic reflex activity may be substantially reduced during regional anesthesia.

A major potential problem of regional anesthesia in patients with coronary artery disease is a decrease in coronary perfusion pressure resulting from a reduction in sympathetic nervous system tone to the venous and arterial vasculature. In the presence of a critical coronary artery stenosis (in which autoregulation of coronary blood flow is absent), a reduction in arterial pressure will be accompanied by a proportionate decrease in coronary blood flow distal to the stenosis. Likewise, general anesthesia has its potential shortcomings. The stress of tracheal intubation and emergence from anesthesia can result in large increases in sympathetic nervous system stimulation that may produce unacceptable increases in heart rate, myocardial contractility, and left ventricular afterload. Administration of high inspired concentrations of volatile anesthetics may also lead to increases in sympathetic activity. However, no specific volatile or opioid-based anesthetic technique has been shown to be superior to another in preventing ischemic events.[12,13]

Experimental evidence indicates that volatile anesthetics may have direct cardioprotective effects that decrease the extent of myocardial ischemic injury, including stunning or infarction. This effect has been termed "anesthetic-induced preconditioning" and is mediated by adenosine triphosphate–dependent potassium channel activation in cardiac myocytes *via* a mechanism similar to that observed during ischemic preconditioning.[10] Preliminary clinical evidence for anesthetic-induced preconditioning does not yet exist. Only preliminary results of one study have recently been reported.[14] Volatile anesthetics may prove to be useful in patients with coronary artery disease provided that the relationship between myocardial oxygen supply and demand is not adversely affected.

Myocardial Ischemia in the Postoperative Period

The potential for the patient with coronary artery disease to develop intraoperative myocardial ischemia is dependent on the specific surgical procedure performed. For example, patients have a greater incidence of ischemic episodes during major vascular surgery compared with cataract surgery. Unfortunately, the occurrence of ischemic events does not end with the conclusion of surgery and anesthesia, but persists with even greater frequency in the postoperative period and, if left

untreated, can result in myocardial infarction. Proinflammatory responses initiated during the surgical procedure continue into the postoperative period and contribute to an increased risk of myocardial ischemia. Release of cytokines, the occurrence of hypercoagulability and diminished fibrinolytic activity, endothelial dysfunction and atherosclerotic plaque instability, hemodynamic changes, and increases in sympathetic nervous system activity associated with anesthetic emergence and suboptimal pain management have been identified as important factors mediating the increased incidence of ischemia postoperatively. Regional anesthesia and postoperative pain control may produce antiischemic actions *via* effects on cytokine or neurohumoral-mediated pathways. A better understanding of how perioperative pathophysiologic processes can be modulated for the benefit of the patient is required. Sympathetic activation caused by postoperative pain is highly deleterious for the patient with coronary artery disease, and treatment of pain with intrathecal or epidural opioids with or without local anesthetics (ideally administered at the onset of the surgical procedure) or patient-controlled analgesia is as essential to postoperative management as is continued administration of β-adrenoceptor antagonists. Patients who require prolonged mechanical ventilation represent a special problem because typical sedatives/hypnotics such as benzodiazepines may not eliminate sympathetic nervous system activation resulting from tracheal stimulation. Liberal use of systemic opioids (preferably morphine for additional cardioprotective benefits from δ_1-receptor stimulation) may be required to attenuate this adverse effect. Importantly, the severity of ischemic events can be profoundly diminished by adequate analgesia.[15] α_2-agonists may also find a role in the immediate postoperative period. The treatment of myocardial ischemia in the postoperative period may ultimately be more challenging than the intraoperative management.

Summary

Goals for the perioperative management of patients with coronary artery disease include:

- Prevent increases in sympathetic nervous system activity: reduce anxiety preoperatively; prevent stress response and release of catecholamines by appropriate use of opioids or volatile anesthetics and β-adrenoceptor antagonists; β-blocker therapy should be initiated before and continued during and after the surgical procedure.
- Decrease heart rate: reduction in heart rate increases oxygen supply to ischemic myocardium and reduces oxygen demand; the use of β-blockers is the most effective means to reduce or attenuate deleterious increases in heart rate.
- Preserve coronary perfusion pressure: decreases in diastolic arterial pressure in the presence of severe coronary artery stenoses will lead to decreases in blood flow; preservation of perfusion pressure by administration of fluid or phenylephrine or a reduction in anesthetic concentration may be critical.
- Decrease myocardial contractility: reduces myocardial oxygen demand and can be accomplished with β-adrenoceptor antagonists or volatile anesthetics.
- Precondition myocardium against stunning and infarction: in the future, this may accomplished by stimulating the adenosine triphosphate–dependent potassium channel with agents such as volatile anesthetics and opioid δ_1-receptor agonists.

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