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Strategies to Reduce Cardiac Risk in Noncardiac Surgery

Where Are We in 2005?

CARDIOVASCULAR morbidity and mortality after noncardiac surgery continues to be an area of active investigative interest because of its clinical and economic impact.[1] With the aging of the population, increasing numbers of patients present to surgery with complex comorbidities. Preoperative cardiovascular evaluation has been an area of intense interest and has led to the development of several sets of guidelines.[2,3] These guidelines initially focused on the extensive identification of the presence and extent of coronary artery disease in patients with known or major risk factors. More recently, the focus has shifted to randomized trials that have addressed the issue of interventions to reduce this risk.[1] Yet inherent in any approach to reduction in cardiovascular complications after noncardiac surgery is the need to understand the pathophysiology of perioperative cardiovascular morbidity.[4] In this issue of ANESTHESIOLOGY, Le Manach *et al.*[5] add to the available knowledge on the subject and propose an additional approach to reduction of perioperative cardiac morbidity through the use of monitoring.

Le Manach *et al.* studied 1,152 consecutive patients who underwent abdominal infrarenal aortic surgery and identified four patterns of cardiac troponin I (cTnI) release after surgery. One group did not have any abnormal concentrations, whereas a second group had only mild increases of cTnI. It is interesting to note that two groups demonstrated increases of cTnI consistent with a perioperative myocardial infarction (PMI). One demonstrated acute (< 24 h) and early increases of cTnI above threshold, and the other demonstrated prolonged low levels of cTnI release, followed by a delayed (> 24 h) increase of cTnI. The authors suggest that these two different patterns represent two distinct pathophysiologies: acute coronary occlusion for early morbidity and prolonged myocardial ischemia for late events. Although the separation of these two patterns is clearly arbitrary, as highlighted in the limitations section of the article, there is some basis for these processes in the literature.

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Given the available evidence, it is plausible that the authors have identified two distinct types of PMI. However, an early pattern of cTnI increase was seen in 38% of the study cohort (21 of 55 patients). Previous studies have demonstrated that virtually all events are preceded by prolonged ischemia (with either a cumulative duration of > 2 h or a single episode of > 30 min), suggesting that the incidence of PMI secondary to coronary occlusion may be lower than 38%.[6,7] Similarly, most PMIs are not associated with Q waves, and the fatality rate has decreased in recent years, further supporting the idea that many of these early PMIs may not be due to acute coronary occlusion.[6,7]

One of the first publications describing the pathogenesis of cardiovascular risk in noncardiac surgery was published in the 1940s, in which coronary artery thrombosis was shown in an autopsy series.[8] The presence of acute coronary thrombosis in the intraoperative and postoperative period in patients who sustain major or fatal cardiac events has been confirmed in a subsequent autopsy series by Dawood *et al.*[9] Cohen and Aretz[10] identified 26 cases of fatal postoperative myocardial infarction with coronary arteries available from autopsy. Coronary plaque rupture was associated with almost half of the fatal postoperative myocardial infarction cases. Ellis *et al.*[11] performed a case–control study of 63 patients who had sustained a nonfatal myocardial infarction after undergoing major vascular surgery and who had undergone previous cardiac catheterization. They found that acute complete coronary thrombosis, which preoperatively served viable myocardium and nonobstructive lesions, was the most common cause of perioperative myocardial infarction or death.

An alternative mechanism for the genesis of acute myocardial infarction is secondary to supply:demand mismatches superimposed on a high-grade or critical coronary stenosis. Multiple investigators have demonstrated the association between perioperative tachycardia and myocardial infarction, as well as the benefits of perioperative β-blocker therapy titrated to control heart rate.[12–15] The importance of hemodynamics has been further supported by several clinical investigations, which demonstrated a relation between prolonged ST-segment changes, particularly ST-segment depression, and subsequent cardiovascular morbidity.[6,7] Additional etiologies have included cold-induced stress and anemia.[16,17]

How then do we use this information? Clearly, any

approach to the reduction of perioperative cardiac morbidity must incorporate the multifactorial pathogenesis of PMI into a multimodal approach to reduction of morbidity. Therefore, no single approach may be successful. Several medical therapies have demonstrated promise in reducing but not eliminating PMI.[1] Despite several randomized trials suggesting that perioperative β-blockade significantly reduces PMI, two recent investigations suggest that β-blocker therapy is not as effective as originally suggested.[13,14,18,19] Those studies in which β blockade is titrated to control heart rate demonstrated the best efficacy, supporting the importance of controlling tachycardia and minimizing the probability of prolonged ischemia. Perioperative statin therapy has been shown to reduce PMI in a case–control trial and a randomized trial.[20,21] The benefits of this agent most likely reflect the stabilization of coronary plaques, consistent with the proposed pathogenesis of early PMI. A recent large-scale randomized trial of preoperative coronary revascularization compared to medical therapy in major vascular surgery patients was unable to demonstrate different survival rates at an average of 2.7 yr postoperatively, which further supports the lack of a simple approach to this problem.[22]

As old and new agents continue to be evaluated as means of reducing PMI, Le Manach *et al.* propose a different approach: monitoring perioperative cTnI concentrations and early institution of treatment for those patients with increased cTnI before it leads to irreversible necrosis. Further research is required to determine whether early and aggressive antiischemic therapy in patients who have cTnI concentrations above threshold ($>$ 1.5 ng/ml) will lead to reduced morbidity and whether the increased cost of monitoring is worth any potential reduction in morbidity. A great deal of research has been targeted to develop strategies to reduce PMI in noncardiac surgery. Although we are beginning to develop some answers, we still have much to learn.

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Preoperative Smoking Cessation

How Long Is Long Enough?

ANESTHESIOLOGISTS do not need to be reminded of the devastating consequences of cigarette smoking. Our practices are affected on a near-daily basis—we often care for patients who require surgery for diseases caused by smoking, and we manage smoking-related perioperative morbidity such as respiratory complications. Usually, we successfully deal with these challenges and deliver these patients safely back to their families. However, the consequences of smoking do not end at the recovery room door. Surgeons have long maintained that the healing of surgical wounds is impaired in smokers, and most clinical and experimental studies confirm that smoking status is a risk factor for wound dehiscence and infections.[1–6] Two important recent prospective studies show that preoperative abstinence from smoking can reduce the risk of wound-related complications. These studies, one in orthopedic surgery patients[7] and one in volunteers,[8] found dramatic reductions in the frequency of wound-related complications when smokers quit from 4 to 8 weeks before surgery. These studies did not address whether more brief periods of abstinence also reduce risk. In this issue of ANESTHESIOLOGY, Kuri *et al.*[9] attempt to answer this question.

Why is wound healing impaired in smokers? Clinical studies suggest that wounds requiring wide surgical undermining, such as facelifts, are particularly vulnerable.[4,10,11] This implies that decreased tissue oxygenation, an important determinant of wound healing,[12] may be a key factor. Smoking a cigarette decreases subcutaneous oxygen tension in humans,[13] consistent with the ability of smoke constituents, such as nicotine and carbon monoxide, to produce peripheral vasoconstriction and to impair the capacity of hemoglobin to carry oxygen, respectively. However, many other factors could also contribute. Nicotine or other components of cigarette smoke could directly affect the function of cells such as fibroblasts and immune cells important to healing,[14,15] although recent evidence suggests that the topical application of nicotine to wounds may in fact stimulate angiogenesis and accelerate wound healing.[16] Microvascular disease caused by smoking may also interfere with angiogenesis *via* impaired release of mediators such as nitric oxide that are important for wound repair.[17,18]

To the extent that impaired wound healing is caused by the acute pharmacologic effects of smoke constituents, even relatively brief periods of abstinence should be beneficial. For example, concentrations of nicotine and carboxyhemoglobin decrease dramatically within 12 h after the last cigarette.[19] If changes in immune function or endothelial function are involved, a longer period may be required for full benefit. Studies attempting to determine how the duration of abstinence affects perioperative risk are inherently difficult, given that it is almost impossible to implement the optimal study design of randomly assigning patients to different durations of abstinence from cigarettes. Rather, studies depend on spontaneous changes in smoking behavior to obtain varying abstinence durations. This raises the possibility of selection bias. Smokers with more severe disease or those undergoing more extensive medical procedures are more likely to quit smoking.[20,21] Therefore, characteristics of patients who are able to quit within a few weeks of surgery may differ in important ways from those who continue to smoke.

Accepting this limitation, Kuri *et al.* examined a patient population with both a high prevalence of smoking and a high rate of wound-related complications—patients requiring resection of head and neck cancers, followed by free flap reconstruction. Although a retrospective study, with the problems inherent in such a design, determination of smoking history and ascertainment of wound-related complications were appropriately conservative, and other patient characteristics were nicely matched. "Smokers" were defined as those patients who had smoked within a week. Because no information is given regarding how many of these patients had quit before hospital admission, the effects of brief periods of abstinence ($<$ 1 week) could not be evaluated. In multivariate analysis, odds ratios for patients reporting at least 1 week of preoperative abstinence indicated at least a threefold decrease in risk for wound-related complications (defined as an event requiring surgical intervention postoperatively) for all groupings of durations, although this was not statistically significant for those reporting 1–3 weeks of abstinence. This lack of significance is the basis of the authors' conclusion that 3 weeks of abstinence is required for benefit, but is more likely a function of relatively small numbers of patients studied. Presentation of the frequency of impaired wound healing as a function of a 3-week moving time average suggested that risk declined

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steadily over approximately the first 6 weeks of abstinence, although this analysis permits no statistical conclusions and itself demonstrates considerable variability (*e.g.*, the sudden appearance of a high frequency of complications at 7–10 weeks of abstinence). What seems clear is that the longer the duration of abstinence the better, as supported by a separate analysis showing a significant correlation between the duration of abstinence and wound-related complications. The inability to define a clear threshold for the duration of abstinence that confers benefit mirrors studies that examine the influence of preoperative abstinence duration on pulmonary risk. These studies also could only conclude that "longer is better,"[22–25] suggesting that several months of abstinence is necessary for full benefit.

Although the data of Kuri *et al.* do not provide definitive answers to the question of how long is long enough to significantly reduce the risk of wound-related complications, their study is a valuable addition to the body of evidence suggesting that preoperative smoking cessation can improve perioperative outcomes. However, the most important question may not be the optimal duration of preoperative abstinence but whether smokers can maintain long-term abstinence after surgery, because even if preoperative abstinence had no effect on perioperative outcomes, we should still help our surgical patients quit smoking. Increasing evidence suggests that surgery represents a golden opportunity for smokers to quit, with great benefit to their health.[26–28] For example, even in the absence of any interventions by medical personnel, the rate of spontaneous quitting is increased in surgical patients compared with the general population of smokers, especially in those undergoing more extensive procedures.[28] Effective tobacco interventions, modeled on those currently available in ambulatory settings, could take advantage of this natural tendency and further increase quit rates. Surgery could thus serve as a "teachable moment" to promote prolonged abstinence, if only we will take the time to teach.[29] A recent survey suggests that surgeons and anesthesiologists are not consistently doing so.[26] This is not surprising, because few surgical specialists are familiar with the dramatic advances that have occurred during the past 20 yr in the treatment of tobacco dependence.[30] There are now methods of proven efficacy that can at least double the chances that smokers will quit.[30] Optimal application of these techniques to the surgical setting will require answers to several questions. How can surgeons and anesthesiologists best incorporate tobacco interventions into their busy practices? How can surgical patients effectively access other resources such as "quitlines" and nicotine treatment specialists? Is it safe to use nicotine replacement therapy in surgical patients? In the meantime, simply asking about tobacco use and providing strong, personalized, and consistent advice that patients abstain for as long as possible before and after surgery are steps that anesthesiologists can take now to help their patients deal with tobacco dependence—if we accept that it is our responsibility to do so.

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