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Perioperative Abstinence from Cigarettes

Physiologic and Clinical Consequences

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Chronic exposure to cigarette smoke produces profound changes in physiology that may alter responses to perioperative interventions and contribute to perioperative morbidity. Because of smoke-free policies in healthcare facilities, all smokers undergoing surgery are abstinent from cigarettes for at least some period of time so that all are in various stages of recovery from the effects of smoke. Understanding this recovery process will help perioperative physicians better treat these patients. This review examines current knowledge regarding how both short-term (duration ranging from hours to weeks) and long-term smoking cessation affects selected physiology and pathophysiology of particular relevance to perioperative outcomes and how these changes affect perioperative risk. It will also consider current evidence regarding how nicotine replacement therapy, a valuable adjunct to help patients maintain abstinence, may affect perioperative physiology.

APPROXIMATELY 23% of adults in the United States smoke cigarettes,[1] and millions of these patients undergo surgery annually. Their smoking status can affect many perioperative outcomes. This is not surprising, because smoking can profoundly alter physiology, both by contributing to the pathophysiology of diseases such as chronic obstructive pulmonary disease and atherosclerosis and *via* the acute pharmacologic actions of smoke constituents such as carbon monoxide and nicotine (fig. 1). Chronic exposure to nicotine also dramatically changes the function of nicotinic acetylcholine receptors, which are ubiquitous in the nervous system (and many other tissues). Because of smoke-free policies in healthcare facilities, all smokers requiring surgery are abstinent from tobacco for at least some period of time. Although the long-term physiologic consequences of abstinence from smoking are in many instances well characterized, much less is known about the initial responses to smoking cessation. This information is of practical importance to anesthesiologists, who daily encounter patients who are in various stages of recovery from the effects of cigarette smoke. Changes in physiology produced by abstinence from cigarettes may have clinically relevant effects on anesthetic management and perioperative outcome. Important clinical questions such as the optimal timing of preoperative smoking cessation and whether anesthesiologists should recommend brief preoperative abstinence at all depend on such knowledge.

This review will survey current knowledge regarding how both short-term (duration ranging from hours to weeks) and long-term smoking cessation affects selected physiology of particular relevance to perioperative outcomes and how these changes affect perioperative risk. It will also examine the effects of nicotine replacement therapy (NRT), a valuable adjunct to help patients maintain abstinence.

Cardiovascular Function

Mechanisms of Injury and Recovery

Smoking is clearly a major risk factor for cardiovascular diseases such as coronary artery and peripheral vascular disease.[2] Smoking increases myocardial work by increasing heart rate, blood pressure, and myocardial contractility,[3,4] at least in part by increasing sympathetic tone and circulating catecholamines.[5] Although smoking a cigarette actually increases coronary artery blood flow in people with normal coronary arteries, in those with coronary artery disease, smoking may cause coronary vasoconstriction.[6] These hemodynamic effects are primarily caused by nicotine, both *via* direct peripheral effects and by increasing sympathetic outflow.[4,7] Oxygen delivery is impaired by carboxyhemoglobin, levels of which may exceed 10% in smokers. Exhaled carbon monoxide, easily measured using a relatively inexpensive handheld device, is a useful tool to quantify smoking behavior.[8] Carbon monoxide not only binds to hemoglobin, reducing the amount available to carry oxygen, but also shifts the oxyhemoglobin dissociation curve to the left, impeding release of oxygen from hemoglobin.[9] These effects contribute to exercise-induced angina in smokers with coronary artery disease[10–12] and increase the frequency of ventricular arrhythmias.[13] Carbon monoxide may also inhibit other proteins that contain heme, such as cytochrome C oxidase, an effect that could

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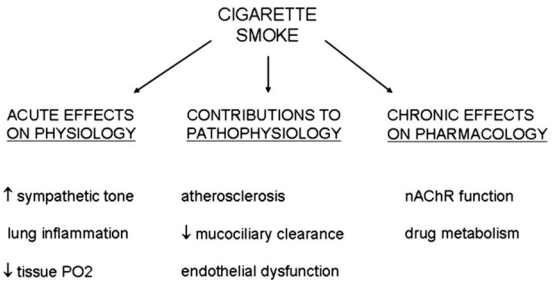

Fig. 1. Categories of mechanisms by which exposure to cigarette smoke may affect responses of patients undergoing anesthesia. The specific examples listed under each category are representative, not exhaustive. nAChR = nicotinic acetylcholine receptor; Po_2 = partial pressure of oxygen.

impair mitochondrial respiration.[14,15] Other substances in cigarette smoke, such as cyanide, may also affect respiration.[16] In addition to affecting these factors regulating myocardial oxygen supply and demand, smoking promotes atherosclerosis. Salient mechanisms may include endothelial injury,[17–21] oxidant injury,[22] enhanced thrombosis,[23] and adverse effects on blood lipids.[24,25] The contribution of nicotine to accelerated atherosclerosis is unclear[4] because there are many other constituents of cigarette smoke that could also play a role. For example, compounds such as tobacco glycoproteins have proinflammatory effects that could contribute to atherosclerosis.[26]

Abstinence from cigarettes decreases cardiovascular risk. Quitting decreases the risk for all-cause mortality in smokers with coronary artery disease by approximately one third.[27] The time needed to fully realize this benefit is unknown, given that some time must elapse before risk can be assessed, but is estimated to be at least several months.[28] How risk decreases over the first days and weeks of quitting is unclear. To the extent that the acute effects of smoke constituents such as nicotine and carbon monoxide increase the risk of ischemia, cessation should have rapid benefit, because the half-lives of nicotine and carboxyhemoglobin are relatively brief (approximately 1 and 4 h, respectively, although there is wide variability among individuals).[29,30] Given that smoking acutely decreases measures of integrated cardiovascular function such as maximal exercise capacity[31–33] and endothelium-mediated vasodilation,[19,34] it is plausible that even brief cessation (*i.e.*, over a few hours) may be beneficial.[35] However, improvement in smoking-related disease such as atherosclerosis may occur more slowly, if at all.

Perioperative Risk

The presence of cardiac disease increases the risk for major perioperative cardiac morbidity and mortality.[36] Because smoking contributes to cardiac disease, smoking in this way contributes to perioperative cardiac risk. However, it is not clear whether status as an active smoker itself (apart from the presence of smoking-related cardiac disease) increases the perioperative risk of cardiac events.[37] To the extent that the acute pharmacologic effect of smoke constituents such as nicotine and carbon monoxide contribute to ischemia, even relatively brief abstinence should be beneficial. The concept is supported by a study finding that electrocardiographic signs of ischemia in anesthetized patients were correlated with carbon monoxide levels, an index of recent cigarette use.[38] However, with some exceptions, most studies have been unable to identify preoperative smoking status as an independent risk factor for major cardiac events (*e.g.*, myocardial infarction) during and after either cardiac or noncardiac surgery, although few studies have carefully assessed smoking behavior.[36,39–42] Major indices of cardiac risk do not include preoperative current smoking status as a predictor of cardiac outcomes.[36,43] Postoperative smoking behavior can affect cardiac outcomes after surgery. For example, sustained postoperative abstinence from cigarettes reduces long-term mortality after cardiac revascularization.[44,45]

Cardiovascular Risk of NRT. Nicotine replacement therapy, *via* delivery systems such as patches or gum, is a valuable therapy for tobacco dependence. Because nicotine may contribute to the deleterious effects of smoking on the cardiovascular system, the safety of therapeutic nicotine in patients with cardiovascular disease was initially questioned. However, overwhelming evidence now supports the safety of NRT in patients with cardiac disease.[4] Available experimental trials suggest that NRT does not adversely affect, or may in fact improve, many of the factors leading to cardiovascular risk. NRT does not affect the patency of experimental coronary artery bypass grafts.[46] Smokers improve their coagulation profiles when quitting using NRT,[47,48] and nicotine itself has little effect on human platelet function *in vivo*.[49] NRT does not produce significant adverse cardiac effects in healthy volunteers[50] or in smokers, even if they continue smoking.[51,52] Multiple clinical trials show that NRT is safe in patients with cardiovascular disease.[53–55] Transdermal NRT does not increase the frequency of cardiac events in cigarette smokers with coronary artery disease, even if they continue smoking.[55,56] NRT may even reduce cardiovascular risk if smoking rate is reduced. For example, NRT significantly decreases the extent of exercise-induced myocardial ischemia assessed by exercise thallium perfusion imaging in smokers with coronary artery disease, even if they continue smoking.[57]

These results suggest that the benefits of NRT to aid patients with coronary heart disease stop smoking far outweigh the risk of continued smoking or NRT itself.[4] This is likely due to the facts that (1) other components of cigarette smoke besides nicotine contribute to adverse effects and (2) the serum concentrations of nicotine produced by NRT are less than the peak concentrations produced by cigarettes.[30,58] Even if patients

continue to smoke during NRT, their total nicotine intake is approximately the same as during their usual smoking, because they reduce their cigarette consumption.[59] These considerations should also apply in the perioperative period, suggesting that NRT could be a valuable tool to manage tobacco dependence in the perioperative period. NRT does have hemodynamic effects that may need to be addressed in patients at risk. For example, increases in heart rate after tracheal intubation are exaggerated in smokers receiving nicotine patches preoperatively.[60]

Respiratory Function

Mechanisms of Injury and Recovery

Smoking is a major cause of pulmonary disease. Symptomatic chronic obstructive pulmonary disease develops in approximately 15% of smokers,[61] and up to an additional 50% have development of chronic bronchitis without airway obstruction.[62] Even smokers without overt symptoms demonstrate changes in lung morphometry and immune function.[63,64] The mechanisms of injury are complex and multifactorial.[65] Smoking induces an inflammatory state in the lung; the number of inflammatory cells such as macrophages and neutrophils is increased, and their function is altered.[66–68] Compared with nonsmokers, alveolar macrophage function is impaired in smokers. These cells are less metabolically active and less able to release inflammatory mediators, impairing their ability to mount an effective response to infection.[69–73] Airway epithelial structure and function are altered, although it may be difficult to separate the effects of smoking *per se* from the consequences of smoking-related pathology such as chronic bronchitis. The net effects on mucus production and transport are complex, in part because of difficulties inherent in measuring these parameters. In general, smoking produces goblet cell hyperplasia and other structural epithelial abnormalities, affects the volume and composition of mucus, and decreases mucociliary clearance.[74–81] Eventually, other structural changes in the airway wall develop, including increased smooth muscle and fibrosis,[82] and as a result, smokers exhibit an accelerated age-related decline in forced expiratory volume in 1 s compared with nonsmokers.[83] In smokers without overt chronic obstructive pulmonary disease, airway reactivity in response to inhaled bronchoconstrictors is increased compared with nonsmokers for inhaled muscarinic agonists such as methacholine but not histamine.[84] However, the ability of inhaled irritants such as aerosols of capsaicin and citric acid to produce cough is diminished in healthy smokers without overt lung disease.[85–88] These findings may reflect a depletion of neuropeptides from sensory nerves responsible for cough or other means by which smokers become more tolerant to inhaled irritants (including cigarette smoke). These results in humans are in marked distinction to those in animal models, which consistently demonstrate increases in cough and airway reactivity after smoke exposure.[89]

The process of how the lung recovers from chronic smoke exposure is complex. Recovery depends on the severity of smoking-related pathology (*e.g.*, whether the smoker has developed overt obstructive lung disease), but several general principles are apparent.[84] With abstinence, symptoms of cough and wheezing decrease within weeks.[90,91] Abstinence slows the accelerated decline in forced expiratory volume in 1 s observed in smokers.[92] In asymptomatic smokers, goblet cell hyperplasia and mucus production decreases with cessation, and mucociliary clearance improves.[75,93,94] These improvements probably also occur in smokers with chronic bronchitis and chronic obstructive pulmonary disease, at least in the central airways. Inflammatory markers such as the number of alveolar macrophages decrease with abstinence, but other inflammatory consequences, such as fibrosis, alveolar destruction, and smooth muscle hyperplasia, may be permanent.[95] Airway hyperreactivity to muscarinic agonists generally decreases.[84] Many of these changes are inferred from cross-sectional studies comparing smokers and long-term former smokers and thus represent the effects of at least several months of abstinence. Few longitudinal studies of quitters are available, especially those providing information over the first few days and weeks of abstinence. Mucus production over the initial weeks of recovery has not been quantified, although anecdote suggests that it is increased. Cold symptoms and cough may be increased during this time period before subsiding after several months of abstinence.[96] Mucociliary clearance seems to at least partially improve in smokers, requiring at least 1 week to show improvement.[97] Measures of lung inflammation such as altered alveolar macrophage number and function change only over a period of months, if at all.[98–101]

Perioperative Risk

Smoking status is a consistent univariate risk factor for several perioperative pulmonary complications (PPCs); *i.e.*, when other factors are not accounted for, smokers are more likely to have development of PPCs.[102–105] These complications include respiratory failure,[106] unanticipated intensive care unit admission,[107] pneumonia,[108] airway events during induction (cough, laryngospasm),[109] increased need for postoperative respiratory therapy or aerosol therapy,[110,111] and various combinations of these individual events with others, such as bronchospasm and increased airway secretions. A lack of standardized definitions of adverse perioperative outcomes among studies often poses difficulties in study interpretation, especially because some outcomes are quite subjective. For example, because clinicians may expect smokers to be at risk for PPCs, they may be more

prone to order respiratory or aerosol therapy, which in some studies itself counts as a PPC.

When multivariate analysis is performed, accounting for other factors such as lung disease and pulmonary function, most observational studies find that current smoking status is an independent risk factor for PPCs,[106,108,112–116] although there are exceptions.[114,117,118] Because smoking status may affect the severity of pulmonary disease, it still may be difficult to separate the risk posed by smoking itself from the risks caused by smoking-related pulmonary disease. However, exposure of children to environmental tobacco smoke increases their risk of PPCs, suggesting that even relatively low level exposure to smoke has clinical consequences.[119]

Several mechanisms may contribute to perioperative risk. Excessive production of mucus itself seems to be a risk factor for pulmonary complications, independent of smoking status, such that smoking-induced bronchitis could be contributory.[120,121] The clinical impression of more "irritable" airways in smokers is supported by some but not all studies. The sensitivity of upper airway reflexes to chemical stimulants is increased in smokers.[122,123] Irritation of the airway by desflurane, manifested by increases in pulmonary resistance and coughing, is enhanced in smokers,[124,125] again suggesting sensitization of reflex responses to chemical irritants. However, pulmonary resistance measured after tracheal intubation is not different between smokers and nonsmokers, although smokers have impaired responses to bronchodilators.[126] Also, the frequency and amplitude of coughing in intubated patients during emergence from isoflurane anesthesia is not affected by smoking status.[127] Important elements of lung defenses against infection are impaired during anesthesia to a greater degree in smokers compared with nonsmokers. Bronchial mucus transport during general anesthesia is slowed in smokers compared with nonsmokers.[128] Prolonged anesthesia increases lung macrophage aggregation and decreases microbicidal activity in all patients, but these changes are markedly greater in smokers compared with nonsmokers.[129,130]

Effects of Abstinence on Risk

Observational studies suggest that prolonged abstinence from smoking decreases the risk of many PPCs.[105,110,111,116] Only a few studies have attempted to define the duration of abstinence necessary for benefit. Two observational studies examined the frequency of PPCs (defined as the need for respiratory therapy that exceeded standard of care) in patients undergoing coronary artery bypass grafting. In a retrospective analysis,[110] the frequency of PPCs was not different between those who continued to smoke until surgery (48%) and those who quit within 8 weeks before surgery (56%). In contrast, the rate of PPCs was significantly less in smokers who quit more than 8 weeks before surgery (17%), a rate similar to that of nonsmokers (11%). A subsequent prospective study[111] of 192 patients confirmed these results, although the number of patients who were current smokers[18] and who had stopped within 8 weeks[21] was not sufficient to make statistical comparisons between these groups. In multivariate analysis, fewer smoke-free days was an independent predictor of PPCs. A logistic model based on this analysis suggested that at least 12 weeks of abstinence was needed for full benefit. It also suggested a small increase in the predicted rate of PPCs over the first month of abstinence, but again, this finding was based on a relatively small number of patients and could not be statistically evaluated. A recent study of PPCs in thoracic surgery patients attempted to correlate duration of abstinence with PPC frequency but was not sufficiently powered to perform meaningful univariate analysis comparing different durations of abstinence.[114] Another study of mostly males undergoing noncardiothoracic surgery[116] found that current smoking was a significant independent risk factor for PPCs (odds ratio, 4.2; 95% confidence interval, 1.2–14.8) but not past smoking (defined as $>$ 2 weeks of abstinence; odds ratio, 1.9; 95% confidence interval, 0.5–6.5). However, in univariate analysis, reducing cigarette consumption (by an average of 34%) within the month before surgery in fact increased the risk of PPCs.

All of these studies were observational, and the possibility for selection bias is high.[113] In a general population of smokers, those with more severe disease, or those undergoing more extensive medical procedures, are more likely to quit smoking or reduce cigarette consumption.[131,132] Therefore, because the interval from scheduling to surgery is usually within weeks to months, 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. Nonetheless, given that recovery of the lung from cigarette smoke apparently requires several weeks to months, it is plausible that a similar duration of time might be required before full benefit in reducing PPCs is observed. Consistent with this concept, Kotani *et al.*[133] found that 6 months of abstinence was required before the response of selected pulmonary cytokines and alveolar macrophages to anesthesia and surgery was similar to that of nonsmokers. The risk profile over time may differ among individual PPCs. For example, increased sensitivity to upper airway stimulation by chemical irritants during anesthesia diminishes within only a few days of smoking abstinence.[122]

Although further study is needed, current evidence suggests that in terms of reducing PPCs, the longer the duration of abstinence is, the better, at least within the first few months of cessation. The evidence suggesting an increase in risk during the first weeks of quitting is insufficient to support any recommendation that smok-

ers not strive for preoperative abstinence, even if only for a brief period before surgery.[105,116]

Wound and Bone Healing

Perioperative Risk and Mechanism of Injury

Most (but not all) evidence supports the clinical impression that smokers are more likely to have development of postoperative wound-related complications, such as dehiscence and infection.[113,134–143] The risk seems to be greatest in wounds requiring wide surgical undermining, such as face-lifts.[135] Animal models also indicate that exposure to smoke increases wound-related complications,[144–146] although, of interest, not the viability of free flaps requiring vascular anastomoses.[147–149]

Of the multiple mechanisms that could be responsible for impaired wound healing, factors decreasing tissue oxygenation, which is an important determinant of wound healing,[150] have attracted the most attention. Smoke constituents such as nicotine and carbon monoxide can decrease tissue oxygenation *via* peripheral vasoconstriction and impaired carrying capacity of hemoglobin, respectively.[151–154] Survival of experimental skin flaps in animal models is impaired in animals receiving chronic nicotine,[155–157] albeit in doses that achieve plasma nicotine levels above those maintained in active smokers—and far above those in patients receiving NRT. At least 2 weeks of nicotine administration is required to observe deleterious effects,[157] suggesting that these effects are not caused by acute vasoconstriction. Several other factors could contribute to smoking-related wound complications. Smoke constituents could directly affect the function of cells such as fibroblasts and immune cells important to healing.[158,159] Most of these cells express nicotinic acetylcholine receptors,[160] making it possible that nicotine could directly inhibit cellular responses to injury,[161–164] although most studies use concentrations of nicotine that are far above those achieved *in vivo*. Recent studies suggest that the topical application of nicotine to wounds may in fact stimulate angiogenesis and accelerate wound healing.[165–167] Microvascular disease caused by smoking may also interfere with angiogenesis *via* impaired release of substances such as nitric oxide that are important for wound repair.[168–171] Nicotine may modulate the neurogenic component of inflammatory response to tissue injury,[172,173] *via* direct effect on both peripheral and central neural mechanisms and indirect effects on sympathetic tone.[174–178] The clinical effects of these actions are uncertain because depending on the mode of administration (*e.g.*, location, acute *vs.* chronic) and dose of nicotine used, nicotine can either increase or decrease indices of neurogenic inflammation.

The healing of bone may also be impaired in smokers. Smoking status is a risk factor for nonunion of spinal fusions,[179–185] especially when smoking is continued postoperatively, and the healing of fractures may be delayed.[186–192] Smoking has significant effects on bone metabolism and is a major risk factor for osteoporosis, which may itself contribute to impaired bone healing.[193] As is the case with wound healing, the components of smoke responsible for these effects are not known, but nicotine at relatively high concentrations significantly affects several measures of bone metabolism.[194–200] However, other studies have found little effect of nicotine alone on bone properties in experimental animals,[201] and studies of the effect of relatively high-dose nicotine on spinal fusions in animals have found effects on subjective but not objective measures of fusion.[202–204]

Effects of Abstinence on Risk

Recent evidence suggests that preoperative smoking cessation can reduce wound-related complications. Møller *et al.*[137] randomized smokers scheduled to undergo hip or knee replacement to a control or smoking intervention group. The latter received counseling and NRT, beginning 6–8 weeks preoperatively. Sixty-four percent of these patients were able to quit smoking (compared with only 8% in the control group), and a further 23% reduced their consumption. The relative risk for wound-related complications was dramatically reduced in the intervention group (by 83%). Sorensen *et al.*[205] performed a series of punch biopsies in healthy volunteers and observed the rate of subsequent wound infection during a 2-week period. Three groups were examined: subjects who had never smoked, smokers who continued to smoke, and smokers who abstained. In smokers, the wound infection rate was 12%, compared with 2% in nonsmokers. Within 4 weeks of abstinence (the minimum period of abstinence studied), wound infection rates were similar in the abstinent smokers and the subjects who had never smoked. In another study, Sorensen *et al.*[206] randomized patients scheduled to undergo colorectal surgery to receive a stop-smoking intervention approximately 2 weeks before surgery or no intervention. They found no difference in the frequency of postoperative wound-related complications. Interpretation of this finding is complicated by (1) the low numbers of subjects studied (approximately 30 in each group), (2) a relatively small difference between groups in the proportion of patients who self-reported preoperative abstinence, and (3) the fact that many patients in the control group also reduced their cigarette consumption postoperatively. In an observational study, Kuri *et al.*[207] reported that prolonged abstinence reduced the rate of wound-related complications in patients undergoing head and neck surgery, but there were insufficient numbers of patients studied to determine whether shorter periods of abstinence were also beneficial. Therefore, the duration of preoperative abstinence needed for benefit remains undefined. To the extent that risk is mediated by the acute pharmacologic

effects of smoke constituents such as nicotine and carbon monoxide, benefit should accrue relatively quickly after cessation. If changes in immune function or endothelial function are significant factors increasing risk, a longer period may be required for full benefit. Obviously, postoperative smoking behavior may also affect the risk of complications.

There is little information regarding how smoking cessation affects bone healing. The adverse effects of nicotine on spinal fusion rates in animal models are reversible when nicotine administration is discontinued 1 week before surgery.[204] In a retrospective observational study of patients undergoing spinal fusion, Glassman *et al.*[179] found that the rate of nonunion was approximately twice as high in patients who continued smoking after surgery compared with never-smokers. For smokers who quit postoperatively, their nonunion rate approached that of the never-smokers. The ability to quit smoking preoperatively did not affect nonunion rates when considered as a univariate factor (*i.e.*, without considering postoperative smoking behavior), although those patients who were able to quit preoperatively were more likely to also maintain postoperative abstinence. Considering that many weeks are required for healing of spinal fusions,[208] it is not surprising that postoperative smoking behavior may be more important than preoperative behavior in determining outcome.

Risk of NRT to Wound Healing. Clinical concerns have been raised regarding whether perioperative nicotine administration will itself contribute to the risks of wound-related complications. As reviewed in the earlier section, "Perioperative Risk and Mechanism of Injury," the contribution of nicotine to the pathogenesis of wound-related complications is not clear. The doses of nicotine used in animal studies reviewed above produce plasma nicotine levels considerably in excess of those achieved by NRT, such that these studies do not provide useful information regarding the effects of NRT as clinically applied. Two experimental human studies are of relevance. Fulcher *et al.*[209] examined microvascular responses to standardized cold challenge in chronic smokers before smoking cessation, and at 2 and 7 days after quitting and the institution of NRT with patches. During NRT and smoking cessation, microvascular responses were significantly improved compared with before cessation and in fact were similar to that of a control group of nonsmokers. This suggests either that other components of cigarette smoke were responsible for changes in microvascular function observed before quitting or that the dose of nicotine provided by NRT was not sufficient to affect these responses. The study of Sorensen *et al.*[205] (reviewed above) showing that abstinence from smoking reduced the rate of wound infections in volunteers also included an experimental group of smokers that received NRT *via* patches to help them maintain abstinence. The infection rate was not different between abstinent smokers who did or did not receive NRT. Therefore, the limited information currently suggests that NRT would not contribute to wound-related complications, although more evidence is needed. Certainly, NRT can decrease exposure to higher nicotine doses and other smoke constituents to the extent that it promotes abstinence, which is otherwise very difficult for smokers to achieve in the postoperative period.[132]

Nervous System Function

Mechanisms of Action and Recovery

Cigarettes function as a means to rapidly deliver nicotine to the central nervous system (CNS). Nicotine activates several subtypes of nicotinic acetylcholine receptors (nAChRs), pentameric complexes of subunits that function as ligand-gated ion channels.[210] The actions of these receptors, which are ubiquitous in both central and peripheral nervous systems, on integrated neural function are incompletely understood.[211] Their predominant role in the CNS seems to be the modulation of neurotransmitter release.[210] Because nAChRs affect multiple neurotransmitter systems, the net effects of nicotine on CNS function are very complex. The psychoactive effects of nicotine (and several other addictive drugs) seem to be mediated in part *via* activation of dopaminergic neurons with the ventral tegmental area, which project to the nucleus accumbens,[212] although other systems are certainly also involved.

Exposure to nicotine can induce feelings of reward and pleasure but also can produce unpleasant effects, especially in subjects naive to the drug. The development of tolerance to nicotine is a prominent characteristic of its actions.[211] Tolerance may arise from the rapid desensitization during continued nicotine exposure that is characteristic of several nicotinic receptor subtypes. Prolonged exposure to nicotine can also induce long-lasting plastic changes in CNS function. As a result of these changes, both humans and animal models have development of aversive withdrawal symptoms when nicotine intake is reduced or eliminated. Symptoms include both somatic complaints (*e.g.*, gastrointestinal symptoms, increased appetite) and affective symptoms (*e.g.*, craving for cigarettes, depressed mood, anxiety, dysphoria, irritability).[213,214] Prevention of these symptoms may be an important motivational factor in the maintenance of smoking behavior. They may be manifest within hours of abstinence from nicotine and may last for several weeks. The neurobiology of nicotine dependence and withdrawal is complex but probably involves multiple neurotransmitters, including dopamine, opioid peptides, glutamate, and serotonin, that mediate different aspects of withdrawal.[211]

Of possible relevance to the perioperative period, neuronal nAChRs modulate pain. In animals, systemic nicotine produces a modest antinociceptive effect.[215,216]

Other nicotinic agonists can have potent analgesic properties, albeit accompanied in many cases by unacceptable systemic toxicity.[217] Although activation of nAChRs on peripheral nerves produces pain,[218,219] application of nicotinic agonists to different sites in the central nervous system can have either pronociceptive or antinociceptive effects, depending on location and dose.[220–222]

Perioperative Consequences

Several factors might affect the responses of smokers' nervous systems to anesthesia and surgery, including (1) chronic CNS changes produced by prolonged exposure to smoke, (2) acute effects of nicotine or other smoke constituents still present from recent preoperative smoking, and (3) effects of nicotine withdrawal during abstinence from smoking. The importance of these factors in the perioperative period is only beginning to be explored. Clinically, two issues may be of importance: how smoking status affects requirements for anesthesia and analgesia and how nicotine withdrawal might affect recovery from surgery in abstinent smokers.

Neuronal nAChRs are inhibited by isoflurane and propofol at clinically relevant concentrations, raising the possibility that nicotine could affect anesthetic requirements.[223] The acute administration of nicotine (but not other nicotinic agonists) produces a small decrease in minimum alveolar concentration in mice.[224] It is not known whether smoking status affects minimum alveolar concentration in humans.

The effects of smoking on pain perception in humans are complex, and some of the findings of experimental studies are inconsistent.[225–230] In general, most studies find that smoking a cigarette increases both tolerance and threshold to painful stimulation. In one of the best controlled studies, Pauli *et al.*[231] found that 12 h of smoking abstinence did not affect pain thresholds (to thermal stimulation) in males but that smoking a cigarette itself decreased pain thresholds in these abstinent smokers. Jamner *et al.*[232] found that nicotine administered *via* patch increased pain thresholds (to electrical stimulation) in male but not female subjects, both in smokers and in nonsmokers. Compared with nonsmokers, pain thresholds were increased in male smokers abstinent for 6 h but not in females.

Clinically, smoking is a risk factor for a number of painful conditions, including low back and musculoskeletal pain.[233–235] Increased requirements for postoperative opioids have been reported in smokers after coronary artery bypass grafting,[236] oral surgery,[237] and pelvic surgery.[238] In a general surgical population, smokers reported higher pain scores both before and after surgery but did not experience greater increases in pain postoperatively compared with nonsmokers,[132] although pain was only a secondary endpoint in this study. Intranasal nicotine administered at the end of surgery significantly reduces pain scores and analgesic requirements in nonsmokers.[239] Therefore, smoking status and nicotine could clearly affect perioperative pain, but more data are needed to establish the clinical relevance of these effects.

Many smokers view cigarettes as a stress management tool. Most studies suggest that smoking a cigarette reduces measures of stress, but this may simply represent self-medication for incipient nicotine withdrawal symptoms.[240] Nonetheless, abstinence from cigarettes could exacerbate stress engendered by the surgical experience itself. In a prospective observational study of a general surgical population, Warner *et al.*[132] found that although smokers did report higher baseline levels of stress preoperatively, changes in stress over the perioperative period did not differ between smokers and a control group of nonsmokers. Nicotine withdrawal scores suggested that smokers did not consistently experience withdrawal symptoms in the immediate postoperative period, including patients highly dependent on nicotine preoperatively. Consistent with these results, a subsequent randomized clinical trial in smokers undergoing elective surgery could find no effect of active nicotine patches on stress or nicotine withdrawal compared with placebo patches, although nicotine did affect some aspects of postoperative smoking behavior.[241] These results may be consistent with previous studies showing that withdrawal symptoms may be lessened under stressful situations that demand forced abstinence, such as military training or prisons.[242,243] The finding that nicotine withdrawal symptoms may be minimal in the postoperative period suggests that this may be an excellent opportunity for smokers to attempt sustained abstinence.

Implications for Perioperative Smoking Interventions

Chronic exposure to cigarette smoke produces profound changes in the physiology of many organ systems, changes that may alter responses to perioperative interventions and contribute to perioperative morbidity. All smokers undergoing surgery are in various states of recovery from these effects, a process whose initial stages are incompletely understood. Better knowledge of this process would help perioperative physicians better define and manage this process. This is important in part because the perioperative period may present unique opportunities for smokers to attempt prolonged postoperative abstinence.[113,132,244–252] The potential of the surgical experience to serve as a "teachable moment" for smoking abstinence is only beginning to be explored.[252,253] A large body of evidence (mostly obtained in ambulatory settings) supports the efficacy of interventions to help smokers quit.[254] Although more work is necessary to adapt, validate, and disseminate these meth-

ods in the perioperative setting (as reviewed elsewhere[251,252]), the evidence presented in this article suggests at least two general principles that can inform approaches to perioperative smoking interventions.

First, although smokers have development of surprisingly few symptoms of nicotine withdrawal during the first few days after surgery in this setting of forced abstinence, most quickly relapse to smoking in the absence of treatment.[132,241] NRT has proven to be both safe and effective in treating tobacco dependence, even in patients with smoking-related diseases.[254] Although more study is needed, available evidence suggests that it may also be safe and effective in the perioperative period[241,248,255] and should be considered a useful tool in surgical patients. There is little doubt that the use of NRT in this setting is far preferable to continued smoking.

Second, regarding the timing of preoperative smoking cessation, it is likely that the longer the duration of preoperative abstinence is, the better, especially with regard to pulmonary complications. However, there is no evidence that brief preoperative abstinence is harmful; rather, it may be beneficial for some outcomes. Postoperative abstinence may also have benefit for some outcomes, even if preoperative abstinence is not achieved. Therefore, although interventions should target smokers at the earliest opportunity (*e.g.*, the time of surgical scheduling), those not able to maintain preoperative abstinence should not be ignored as opportune subjects for interventions at any time in the perioperative period. Sustained abstinence produces tremendous benefits to the long-term health of the surgical patient (or anyone) who smokes; this consideration alone provides sufficient justification for concerted efforts to help these patients quit.[132,241]

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