The Role of Smoking Cessation in the Prevention of Coronary Artery Disease

Andrew L. Pipe · Sophia Papadakis · Robert D. Reid

Published online: 8 April 2010
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Abstract Smoking (tobacco addiction) is the most significant of the modifiable cardiovascular risk factors. Mistakenly described as a “habit” or “behavioral choice,” the onset of tobacco addiction quickly follows the acquisition of an ability to inhale cigarette smoke and is reflected in a transformation of neurophysiologic function and nicotine-receptor density. Thereafter, comfort and a degree of neurophysiologic “equanimity” require the regular administration of nicotine. Smokers inhale thousands of other chemicals, many of which play critical roles in the initiation and accentuation of atherosclerosis by influencing vasomotor activity, vascular dysfunction, oxidation of lipids, atheroma development, and thrombosis. Smoking cessation is a priority in the management of any patient with cardiovascular disease. The benefits of cessation accrue rapidly in such patients and have a pronounced effect on the likelihood of disease progression, hospital readmission, and mortality. All physicians must be familiar with the principles of cessation practice and be able to initiate smoking cessation attempts.

Keywords Nicotine · Tobacco addiction · Smoking · Atherosclerosis · Coronary artery disease · Myocardial infarction · Pharmacotherapy · Smoking cessation · Clinical practice

Introduction

Overwhelming evidence of the effectiveness of smoking cessation in the prevention and management of heart disease has been accumulating for years [1]. Unfortunately, outdated attitudes and misguided perspectives persist in the clinical community about the genesis and persistence of smoking behavior. To the uninformed, smoking still remains a “habit” or “lifestyle choice” that can be simply addressed with determination and the application of strong will. It remains the case that despite the availability of effective cessation interventions, smoking cessation has not figured prominently among the interventions provided by cardiologists [2]. In part, this may be because cardiologists view the responsibility for smoking cessation as resting with others, typically the primary care physician. More likely, the lack of an understanding of the neurophysiologic bases of nicotine addiction, unfamiliarity with the therapeutic principles of smoking cessation, and an unfortunate misperception of its efficacy and effectiveness, have contributed to an indifference to intervene in the cardiac setting. Smoking cessation should be seen as a fundamental responsibility of every cardiovascular specialist given the central role that smoking plays in inducing atherosclerosis and dramatically increasing the risk of myocardial infarction (MI), stroke, and peripheral vascular disease.

It has been noted that it is difficult to identify any condition that is as prevalent, lethal, and yet so prone to neglect as tobacco addiction [1]. One half of all smokers will die prematurely as a consequence of their tobacco use [3]. There can be no doubt of the causative role that tobacco addiction plays in the development and accentuation of cardiac disease; the evidence is overwhelming and has been accumulating for decades [4]. Tobacco use is a principal contributor to the development of coronary artery disease (CAD), sudden cardiac death, acute MI, heart failure, and the complications that inevitably follow. Deaths from CAD in smokers below the age of 45 years exceed the mortality produced by any other tobacco-related disease [5]. Smoking cessation may have a greater effect on reducing mortality among smoking patients with CAD than any other
intervention or treatment [6]. Sadly, tobacco use has been described as “reflecting a rare confluence of circumstances: a highly significant health threat; a disinclination among clinicians to intervene consistently; and the presence of effective interventions” [7].

Smoking and the Epidemiology of Cardiovascular Disease

The relationship between smoking and the development and evolution of atherosclerosis and the cardiovascular crises that typically follow is unquestioned. More than 140,000 smoking-caused premature deaths are calculated to occur annually in the United States [5], and it has been calculated that 52% of ischemic heart disease deaths in North America are attributable to smoking; the burden is similar elsewhere in the developed world [8]. The risk of MI is dramatically increased by cigarette smoking; the relationship is dose-related and linear. There is an eightfold elevation in the odds ratio for an MI in smokers consuming more than 40 cigarettes a day [9]. Regrettably, while the prevalence of smoking has been declining in many nations, rates of smoking in developing nations continue to rise and herald epidemics of tobacco-related disease for years to come. Approximately 100 million deaths resulted from tobacco use in the 20th century, and it has been estimated that 1 billion more will occur in the 21st century [10]. A significant proportion of these deaths will occur as a result of the development of heart disease.

Smoking and the Development of Atherosclerosis

There is overwhelming evidence of the impact of cigarette smoking on the development of CAD and MI as well as their underlying pathologic processes [4]. Even exposure to passive smoking is associated with a significant increase in risk: non-smokers exposed to the smoke of their smoking spouses experience a 30% excess risk of ischemic heart disease death [11]. There is evidence of the adverse impact of uterine exposure to maternal cigarette smoke in precipitating preatherosclerotic changes within the intima of fetal coronary arteries [12]. Autopsy studies demonstrate that smoking in young adults has been found to contribute to the development of advanced atherosclerotic lesions in the LAD vessels of those 15–34 years of age dying of external causes, even in the absence of other CVD risk factors [13].

Distortion of normal vasomotor function, the development of inflammation, the oxidation of lipids, and distorted coagulation mechanisms are central to the development and evolution of the atherosclerotic process [14]. Cigarette smoke contributes to each (Fig. 1).

Normal vasodilatation is compromised as a consequence of exposure to cigarette smoke and the resulting reduction of the endothelial-produced vasodilator, nitric oxide (NO) [15]. Smoking increases vascular resistance and contributes to coronary artery vasospasm, in part, by increasing the production of superoxide anions and other vasoconstricting agents [16]. Nicotine itself has been shown to alter the shape of endothelial cells, induce endothelial cell proliferation and intimal hyperplasia, and reduce prostacycline function [17, 18]. Nicotine’s effect is much less than that of cigarette smoke, arguing for the important role of many of the other toxic constituents of smoke.

Oxidant substances present in cigarette smoke irritate and damage endothelial surfaces. The resulting inflammation is a recognized promoter of endothelial damage, as cytokines, white blood cells, and other constituents of the atherosclerotic process are drawn to the site of injury. Monocyte adhesion and trans-endothelial migration increase as a consequence of exposure to cigarette smoke.

Smokers demonstrate increased levels of total cholesterol, triglyceride, and low-density lipoprotein (LDL), and their high-density lipoprotein levels are lower. Such a lipid profile predisposes to the development of atherosclerosis. Cigarette smoking also induces the oxidation of lipoproteins particularly LDL, accentuating the ability of these compounds to assault the arterial wall. There is evidence that in vivo oxidation injury associated with smoking quickly decreases with cessation but increases dramatically following the resumption of smoking [19]. In human males, cigarette smoking has been shown to increase the likelihood of plaque rupture and thrombosis, whereas in females, plaque erosion with superimposed thrombosis has been demonstrated to be more prevalent [20, 21].

Other constituents of tobacco smoke augment platelet aggregability and promote the adherence of platelet clusters to damaged endothelial surfaces [22]. Higher levels of fibrinogen, red blood cell counts, and blood viscosity all contribute to the prothrombotic environment noted in smokers [23]. Smoking markedly impairs the ability of the endothelium to release tissue plasminogen activator, adding to the likelihood of persistent arterial thrombosis [24].

Oxidative stress is said to be a common feature of the pathologic mechanisms unleashed by exposure to cigarette smoke; distorted endothelial and vasomotor function, proinflammatory changes at the vessel wall, increased platelet reactivity and decreased fibrinolysis, and lipid peroxidation can all be explained by this mechanism [14].

Nicotine Addiction: The Basis of Smoking

Smoking typically begins during adolescence in response to an array of pressures from peers or a desire to emulate adult
behavior. Once inhalation has been mastered, regular inhalations will rapidly entrain a number of neurophysiologic adaptations that result in addiction. Following inhalation, nicotine is rapidly delivered to the arterial circulation, quickly transported to the brainstem, and attaches to the $\alpha_4\beta_2$ nicotinic acetylcholine receptors. This receptor, a pentameric trans-membrane structure, opens in response to the conformational effects of the nicotine ligand and the result is a flow of ions into, and the resulting stimulation of, a neuron [25]. Neuronal stimulation in the brain stem initiates a cascade of neurologic stimulation culminating in the release of dopamine and other neuro-
transmitters (including serotonin, glutamate, and γ-aminobutyric acid) in the forebrain [26]. The brain very quickly becomes accustomed to regular stimulation of the nicotine receptors and elevated levels of dopamine and other factors; the discomfort of withdrawal symptoms and craving become apparent when dopamine levels and nicotine receptor stimulation decline. Simply put, the desire to smoke a cigarette occurs in the face of falling levels of nicotine stimulation and declining levels of dopamine and other neurotransmitters. The addictive nature of any drug is in part determined by the speed with which it can be ingested or consumed [26]. The inhalation of tobacco smoke delivers nicotine very rapidly to the arterial circulation, a delivery process facilitated by the drug delivery device, the cigarette, which is engineered to deliver a precise aliquot of nicotine as rapidly as possible. During smoking, arterial levels of nicotine are 10-fold those in the venous circulation [27]. No one should underestimate the addictive nature of nicotine. It is likely the most tenaciously addictive drug we confront. Smoking cessation may be far more difficult than those who have never smoked can imagine. There is a high degree of heritability in cigarette smoking and the ability to quit.

In many communities, the introduction of smoking bylaws, the elimination of tobacco advertising and sponsorship, and the creation of smoke-free environments have had a significant impact on reducing smoking rates. In Canada, only 17% of the population are now smokers [28]. Those for whom cessation was easier have largely quit; the remaining population of smokers reflects, arguably, those for whom cessation is more difficult. Many of today’s smokers admitted to hospitals will require more help with cessation than those who quit smoking in the past with minimal or no assistance. Most smokers know why they should not smoke, most smokers do not wish to smoke, and many smokers will make at least one or two quit attempts each year, but they are almost universally unsuccessful [26]. Nicotine addiction is anchored in the brain stem. The majority of smokers already understand that smoking is harmful, so smokers require help and not lectures.

The Cardiovascular Benefits of Smoking Cessation

There is no intervention in cardiovascular medicine in which significant patient benefits accrue so rapidly, or so profoundly, as with smoking cessation. The removal of tobacco smoke results in the elimination of the deleterious effects of the thousands of chemicals contained in cigarette smoke. Within weeks of cessation endothelial function, coagulation parameters, carboxyhemoglobin levels, lipoproteins, proinflammatory agents, and inflammatory biomarkers decline and circulatory function improves dramatically [29, 30]. For the patient with CAD, the result is a highly significant reduction in the likelihood of progression or complication of existing disease, and there is a significant reduction in the possibility of hospital re-admission, morbidity, and all-cause mortality [31]. The risk of MI decreases by 50% within 2 years of smoking cessation [32]. Successful smoking cessation in patients diagnosed with heart disease results in a 36% crude relative risk (RR) reduction of death (RR=0.64; 95% CI, 0.58–0.71), and a 32% relative risk reduction of the likelihood of re-infarction (crude RR=0.68; 95% CI, 0.57–0.82) [6]. The likelihood of death following MI is reduced more by smoking cessation than by any other secondary prevention strategies, exceeding that achieved by thrombolysis, acetyl salicylic acid, β-blockers, or statins [33]. The rates of restenosis following percutaneous coronary intervention, in bypass grafts, and death following bypass surgery are all decreased following cessation [34]. Consistent, international experience demonstrates that the incidence of acute MI in public places and workplaces has been significantly reduced following the introduction of smoking bans [35]. Smoking cessation is the only prevention strategy that is actually cost-saving over a 30-year period [36].

Smoking cessation should be the priority in the secondary prevention of cardiac disease [37]. Cardiologists do not typically effectively address this preventive priority [38]. It is important to ensure that a systematic approach is
adopted in every professional environment (office, clinic, and in-patient settings) that quickly permits the documentation of smoking status, stimulates the delivery of non-judgmental quitting advice, prompts an offer of assistance, ensures familiarity with the prescription of cessation pharmacotherapies, and facilitates appropriate referral to other physicians or programs for follow-up where appropriate [7, 39].

Consistency is the hallmark of a successful intervention system, so unless a systematic approach is adopted in every professional setting, the potential to dramatically enhance the cardiac health of patients will be diminished [1]. Contemporary recommendations clearly note that delivering minimal, “tactical” advice regarding cessation strategies is as effective as more highly structured behavioral treatments [7, 40]. Given that many cardiac patients are smokers, there is a unique opportunity in any hospital setting to provide specific, systematic assistance with cessation. Such programs can significantly enhance rates of cessation [41–43]. In our center, 20% of admitted cardiac patients are smokers [41]. The development and application of a systematic program (“The Ottawa Model”) involving identification, documentation, counseling, pharmacotherapy, and follow-up resulted in 44% of admitted smokers being smoke-free at 6-month follow-up (Fig. 2). In another setting, the delivery of an intensive smoking cessation intervention to patients admitted to a coronary care unit resulted in a dramatic reduction in readmission (RR reduction=44%) and all-cause mortality (RR reduction=77%) over a 24-month period and further demonstrates the potential of hospital-based interventions for cessation [31••].

The benefits of pharmacotherapy are distinct and well documented; it is the mainstay of successful cessation treatment. Physicians have access to three generations of first-line pharmacotherapies, each of which have significant, proven efficacy in enhancing the likelihood of successful cessation. These therapies are nicotine replacement therapy (NRT), bupropion, and varenicline.

The safety of NRT use in cardiac patients has been established in a variety of settings [44–47]. All cardiac professionals should be adept in its use. Bupropion effectively doubles the rate of smoking cessation when compared with placebo. Its safety and effectiveness have been specifically evaluated in the treatment of smokers with cardiovascular disease [48]. Varenicline, a partial α4β2 nicotinic acetylcholine receptor agonist, is effective in smokers with cardiovascular disease [49]. Clinical trials have consistently demonstrated the superiority of varenicline when compared with placebo (odds ratio=3.2) and bupropion (odds ratio=1.66) [50]. Evidence continues to emerge of the additional efficacy of modifying the dose of, prolonging the period of treatment with, and/or combining smoking cessation therapies.

Conclusions

The devastation wrought by tobacco and the important role it plays in the initiation and accentuation of heart disease is well understood. All cardiovascular physicians should become familiar with the initiation of smoking cessation treatments. Stopping smoking in those who have cardiac disease produces substantial clinical benefits that accrue more rapidly than those of any other preventive intervention. Cardiovascular specialists can dramatically reduce the predictable excess morbidity and mortality in their smoking patients by assisting with cessation. The development and implementation, in every professional setting, of a systematic approach to smoking cessation will significantly enhance the quality of care provided to all patients and optimize the likelihood of cessation. Smoking cessation is a fundamental clinical responsibility of all who treat smoking patients.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

• Of major importance


