Cigarette Smoking and Cardiovascular Disease: Pathophysiology and Implications for Treatment

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This 3-issue series of articles in *Progress in Cardiovascular Diseases* provides a comprehensive review of how cigarette smoking causes cardiovascular disease, the treatment of cardiovascular disease in smokers, and treatment of tobacco addiction in people with cardiovascular disease. The topic is complex, and there is, appropriately, some overlap in the material covered by various authors. In this article, I will attempt to integrate the information on the pathophysiology of smoking and cardiovascular disease and to discuss the implications of pathophysiologic mechanisms for the treatment of smokers with cardiovascular disease.

Epidemiology of Tobacco Use and Cardiovascular Disease

Cigarette Smoking and Cardiovascular Diseases

As reviewed in detail by Burns,[1] smoking causes 140,000 premature deaths from cardiovascular disease annually in the United States, representing about 30% of all smoking-related deaths. Cigarette smoking acts synergistically with other cardiovascular risk factors to increase cardiovascular morbidity and mortality. Thus, in some countries of the world where poorly controlled hypertension, diabetes, and hyperlipidemia may have a higher prevalence than in the United States, cardiovascular disease is likely to account for an even greater proportion of total smoking-related mortality. Smoking increases the risk of cardiovascular events during surgery in general, and the risk of recurrent ischemic disease after coronary artery bypass graft surgery.[2,3] Smoking increases the risk of re-occlusion after myocardial infarction.[4]

As noted by Burns,[1] cigarette smoking has been shown both to accelerate atherogenesis and to precipitate acute cardiovascular events. However, cigarette smoking produces a different magnitude of increased risk for different cardiovascular diseases. For example, the risk is highest for peripheral vascular disease and aortic aneurysm, and is lowest for cerebrovascular disease. For coronary heart disease, smoking increases the risk of sudden death more than the risk of acute myocardial infarction. Among people with acute myocardial infarction, smokers have less severe underlying coronary atherosclerosis than do nonsmokers. The risks of sudden death or myocardial infarction fall rapidly, within days to months, after smoking cessation.

These observations suggest that smoking has a greater impact on acute coronary events than on coronary atherogenesis. Mechanisms by which smoking causes acute cardiovascular events include thrombosis, endothelial dysfunction, and inflammation, as will be discussed later. These effects are predicted to reverse quickly after smoking cessation, based on the epidemiologic observations. The observation that sudden death is increased out of proportion to acute myocardial

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infarction suggests that arrhythmogenesis is another important mechanism in smoking-related cardiovascular disease.

Epidemiologic research provides potential insights related to treatment. The idea that thrombosis is a key element of smoking-related myocardial infarction in cigarette smokers has implications for the type of revascularization selected for treatment of acute coronary syndromes, as reviewed by Metz and Waters,[5] In relation to smoking cessation, the data on relative risk and excess deaths in smokers of different ages are informative. The relative risk of cardiovascular events is much greater in younger versus older smokers, primarily because cardiovascular events are rare in young nonsmokers.[1] Although the relative risks decline considerably with age, the absolute excess mortality caused by smoking rises progressively with age. This means that smoking cessation remains a key aspect of cardiovascular preventive medicine even in the elderly.

The dose-response observations in epidemiologic studies may be relevant to therapeutics as well. An analysis of the dose-response curve for cigarettes per day versus ischemic heart disease shows that the risk increases sharply with only a few cigarettes per day, then tends to plateau at higher levels of consumption.[1,6] It is unclear whether this plateau reflects a threshold effect of various tobacco smoke toxins at lower levels of exposure, or whether this observation reflects that fact that smokers tend to titrate their intake of nicotine by how intensively they smoke each cigarette (as opposed to smoking different numbers of cigarettes), so that their actual exposure to nicotine and other tobacco smoke toxins is much less than the difference in cigarette consumption. In any case, the dose-response observations suggest that harm reduction strategies involving smoking fewer cigarettes (as opposed to quitting entirely) may not be an effective way to reduce smoking-induced cardiovascular disease.

Environmental Tobacco Smoke and Cardiovascular Disease

Nonsmokers who are exposed to secondhand smoke from spouses who smoke experience on average a 30% excess risk of ischemic heart disease death and nonfatal myocardial infarction, as reviewed by Law and Wald.[6] The excess risk is about one-third of that experienced by a person who smokes 20 cigarettes per day, despite an exposure to tobacco smoke that is less than 1% of the exposure from smoking 20 cigarettes per day. This raises some interesting questions about the pathogenesis of smoking-related ischemic heart disease.

The chemical causes and mechanisms of ischemic heart disease with low levels of tobacco smoke exposure are poorly understood. Secondhand smoke exposure has been shown to activate platelets and to produce endothelial dysfunction, both in experimental animals and in people exposed to secondhand smoke.[6] Blood levels of nicotine and carbon monoxide are quite low in such individuals, making it unlikely that these are playing an etiologic role. The most likely chemical cause appears to be oxidant gas exposure, which can be significant, even with secondhand smoke exposure.[7,8] Exposure to oxidizing gases could explain both the hypercoagulable state and endothelial dysfunction, as will be reviewed later. If oxidizing gases are shown to be causative of ischemic heart disease in passive smokers, the potency of this effect may have implications for understanding and preventing environmental exposures other than cigarette smoking that cause cardiovascular disease.

The implications of an excessive risk of ischemic heart disease in people exposed to secondhand smoke are clear and important. Secondhand smoke has been estimated to cause 35,000 excess cardiovascular events per year.[9] Prevention of such events requires elimination of secondhand smoke exposure in public places and in the workplace, and education about not smoking within the home. Individuals who already have cardiovascular disease may be more susceptible, and such individuals should take special care to avoid exposure to secondhand smoke.

Smokeless Tobacco and Cardiovascular Disease

As reviewed by Asplund,[10] smokeless tobacco, primarily oral snuff, is widely used in Sweden, the United States, and in some Asian and African countries. In the United States, 8% of adult men use smokeless tobacco, and use is particularly common among athletes (such as baseball players). In Sweden, 27% of men use smokeless tobacco (called snus in Sweden).

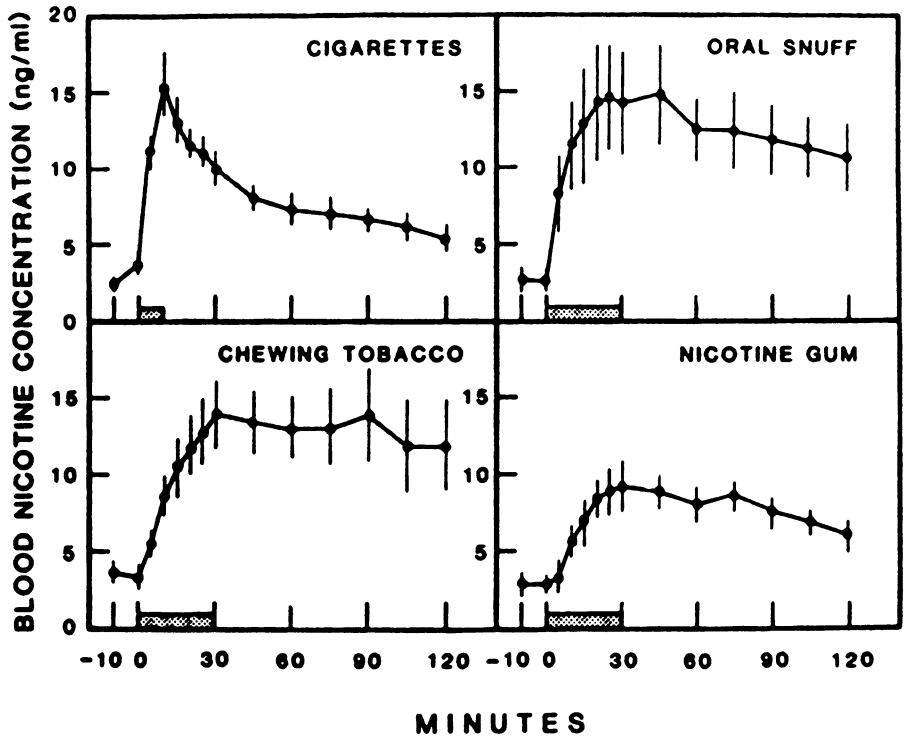

Fig 1. Mean (± SEM) blood concentrations of nicotine in 10 subjects who smoked cigarettes for 9 minutes ($1_{1/3}$ cigarettes), used oral snuff (2.5 g), used chewing tobacco (mean, 7.9 g), and chewed nicotine gum (two 2-mg pieces). Shaded bars above the time axis indicate the period of exposure to tobacco or nicotine gum. (From Benowitz, NL, Porchet H, Sheiner L, et al: Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. Clin Pharmacol Ther 44:23, 1988; with permission.)

Studies of the cardiovascular effects of smokeless tobacco are informative in understanding the pathophysiology of smoking-induced cardiovascular disease. Smokeless tobacco users take in as much nicotine as do cigarette smokers, but smokeless tobacco users are not exposed to oxidant gases, carbon monoxide, and other combustion products.[11] Therefore, an analysis of the effects of snuff use compared to smoking will provide insight into the role of nicotine versus the effects of other tobacco smoke toxins. One caveat is that nicotine from cigarette smoke is inhaled rapidly and delivered in high concentrations in the arterial blood to the heart and other body organs.[12] In contrast, nicotine from smokeless tobacco is absorbed slowly and peak arterial levels are much lower than those seen in cigarette smokers (Fig 1). The rapidity of absorption and the peak arterial blood concentrations are determinants of the magnitude of at least some of the cardiovascular effects of nicotine.[13] Therefore, it is possible that nicotine absorbed from cigarette smoke would be more harmful than nicotine absorbed slowly from smokeless tobacco, even if the daily exposure is the same.

Reflecting the actions of nicotine, smokeless tobacco produces sympathomimetic effects similar to those produced by cigarette smoking.[10,12] Both smoking and smokeless tobacco acutely increase blood pressure and heart rate. These effects are most prominent shortly after use, but with regular use of either product there is a persistent increase in heart rate throughout the day.[14] Of note, however, neither cigarette smoking nor smokeless tobacco use is associated with an increased risk of hypertension, as measured when a person has not used tobacco just prior to blood pressure measurement.[15] Studies of various cardiovascular biomarkers indicate that smokeless tobacco does not produce the inflammatory reaction seen in smokers, nor does it produce endothelial dysfunction, platelet activation, or evidence of oxidant

stress, as reviewed by Asplund. Specifically, white blood cell count, levels of C-reactive protein and fibrinogen, antioxidant vitamin levels, and thromboxane A_z metabolite excretion (the latter reflecting the platelet activation) are similar in smokeless tobacco users and in people who do not use tobacco.[10] Likewise, lipid profiles are similar in smokeless tobacco users and in nontobacco users. Of some concern with respect to cardiovascular disease, however, is the report of an increased risk of noninsulin–dependent diabetes mellitus in snuff users.[16] Although there is only 1 study reporting this association to date, this observation suggests that nicotine contributes to insulin resistance. If smokeless tobacco use were indeed a cause of diabetes, this would contribute to overall cardiovascular risks.

Studies of clinical cardiovascular disease indicate that smokeless tobacco use is much less hazardous than cigarette smoking.[10] In contrast to smokers, snuff users do not have increased carotid artery atherosclerosis as determined by ultrasound. Two case control studies find no evidence that smokeless tobacco use is associated with an increased risk of myocardial infarction, whereas cigarette smoking increases the risk as expected. One cohort study in Sweden did report an increased risk for death of cardiovascular disease in snuff users, although this risk was considerably lower than was the risk for cigarette smokers. The reason for the discrepancies between the 2 control case studies and the cohort study is unclear. It is clear, however, that the use of smokeless tobacco is much less hazardous than cigarette smoking.

We can conclude from the studies on smokeless tobacco that nicotine, at least in a slow release form (such as is the case from smokeless tobacco and from most nicotine replacement medications), is much less hazardous than cigarette smoking. This supports the idea that nicotine can be safely used to aid smokers in quitting and would probably be reasonably safe for long-term maintenance of nicotine addiction instead of cigarette smoking for those who cannot break their addiction.

Pathophysiology of Cigarette Smoking and Cardiovascular Disease

A number of articles from this symposium address mechanisms by which cigarette smoking may increase the risk of cardiovascular disease. In this section, I will try to synthesize and integrate data on various mechanisms.

Constituents of Cigarette Smoke That Contribute to Cardiovascular Disease

Three constituents of cigarette smoke have received the greatest attention as potential contributors to cardiovascular disease. These are nicotine, carbon monoxide, and oxidant gases. There has also been some research on polycyclic aromatic hydrocarbons and other constituents of tobacco smoke that may contribute to atherogenesis.

Nicotine is absorbed rapidly from cigarette smoke, producing arterial blood levels of 40 to 100 ng/mL after each cigarette.[17] The dose of nicotine absorbed from each cigarette is typically 1 to 2 mg. Although there are sharp peaks in plasma nicotine levels after each cigarette, trough levels tend to rise over the first 6 to 8 hours of the day with regular smoking.[18] This accumulation pattern is consistent with an elimination half-life of nicotine of 2 hours.[19] Plasma nicotine levels plateau in the early afternoon and remain at plateau until bedtime in regular smokers (Fig 2). Significant levels of nicotine are found in the blood even upon waking in the morning. Thus, the regular smoker is exposed to significant levels of nicotine 24 hours per day.

As is discussed in more detail later, nicotine is a sympathomimetic drug that releases catecholamines both locally from neurons and systemically from the adrenal. Studies of the pharmacodynamics of nicotine have shown that the intensity of maximal effect of nicotine is greater with more rapid delivery.[13] Pharmacodynamic studies also indicate that tolerance rapidly develops to effects of nicotine, but that this tolerance is incomplete.[20] Tolerance is evidenced by the observation that, with constant intravenous infusion of nicotine, heart rate increases when nicotine levels in the blood are relatively low. As the infusion continues, heart rate plateaus despite a progessive rise in blood levels of nicotine.[21] The same phenomenon is seen comparing heart rate acceleration and blood nicotine levels during regular cigarette smoking throughout the day.[22]

Heart rate measured by ambulatory monitoring is higher throughout the day when smokers are

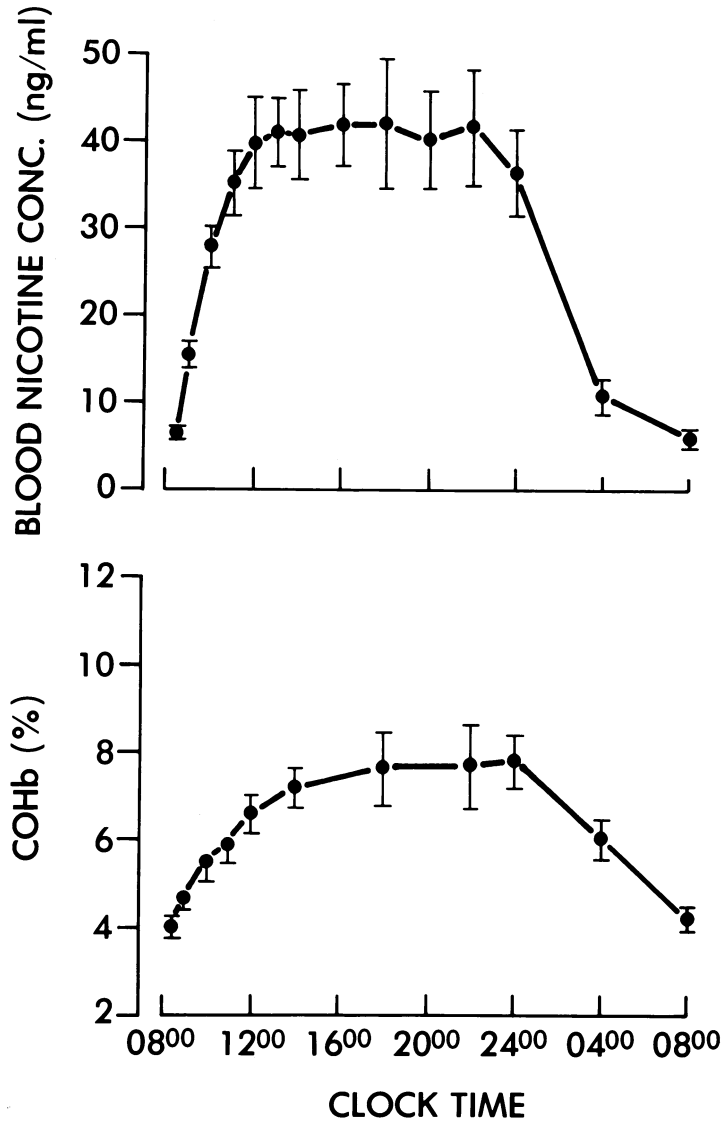

Fig 2. Mean (± SEM) blood nicotine and carboxyhemoglobin concentrations (conc) in cigarette smokers. Subjects smoked cigarettes every half hour from 8:30 AM to 11:00 PM, for a total of 30 cigarettes as day. COHb = carboxyhemoglobin. (Adapted from Benowitz NL, Kuyt F, Jacob P III: Circadian blood nicotine concentrations during cigarette smoking. Clin Pharmacol Ther 32:758, 1982; with permission.)

smoking compared with when not smoking.[22] The extent of elevation of heart rate is independent of the blood level of nicotine absorbed from the cigarettes. The elevated heart rate is presumed to reflect persistent sympathic nervous stimulation, which may be an important mechanism by which nicotine can contribute to cardiovascular disease. As discussed later, nicotine may also play a role in producing endothelial dysfunction, lipid abnormalities, and insulin resistance in smokers.

Carbon monoxide is a major constituent of cigarette smoke. In regular smokers, carboxyhemoglobin levels average about 5%, but may be 10% or higher in heavy smokers. This compares with levels of 0.5% to 2% in nonsmokers, depending on their exposure to automobile exhaust. As for nicotine, elevated carboxyhemoglobin concentrations persist for 24 hours a day in smokers (Fig 2).

Carbon monoxide binds avidly to hemoglobin, reducing the amount of hemoglobin available to carry oxygen and impeding oxygen release by hemoglobin. Inhaling carbon monoxide at levels comparable with those found in cigarette smokers has been shown to reduce exercise tolerance in patients with angina pectoris, intermittent claudi-

cation, and chronic obstructive lung disease.[23,24] Carbon monoxide exposure in people with obstructive coronary disease also results in a greater degree of exercise-induced ventricular dysfunction, as well as increased number and complexity of ventricular arrhythmias during exercise.[25] Carbon monoxide inhalation reduces the ventricular fibrillation threshold in animals.[26]

Long-term carbon monoxide exposure also results in an elevated red cell mass in smokers. Carbon monoxide reduces oxygen carrying capacity, resulting in a state of relative hypoxemia. In response to hypoxemia, red blood cell mass increases, allowing more oxygen to be carried to body organs. Increased red blood cell mass contributes to increased blood viscosity, which is believed to contribute to the hypercoagulable state in smokers.

Cigarette smoke delivers a high concentration of oxidizing chemicals to the smoker.[27] These chemicals include oxides of nitrogen and a number of different free-radicals, found both in the gas and tar phases of cigarette smoke. Exposure to oxidant chemicals in smoke is associated with depletion of endogenous levels of antioxidants, manifested as lower blood levels of vitamin C in smokers compared with nonsmokers.[28] Cigarette smoking also increases levels of lipid peroxidation products in the plasma and the urine.[29] Oxidant stress is believed to contribute to a number of the potential mechanisms of cardiovascular disease, including inflammation, endothelial dysfunction, lipid abnormalities (oxidation of LDL) and platelet activation.[30]

Polycyclic aromatic hydrocarbons (PAHs), found in the tar fraction in cigarette smoke, are reported to accelerate atherosclerosis in experimental animals. Weekly injections of benzo-(a)pyrene and 7,12 demethyl benz(a)anthracene, at doses below those that produce tumors, increase atherosclerotic plaque development in the aortas in cockerels.[31] Likewise, inhaled butadiene, a vapor phase component of cigarette smoke, increases atherosclerotic plaque size in the same animal model.[32] A mechanism of atherogenesis is speculated to be a mutation of smooth muscle or other cells that become the source of an atherosclerotic plaque.

Hemodynamic Effects of Cigarette Smoking

Cigarette smoking produces coronary ischemia by adversely affecting the balance between myocardial oxygen and nutrient demand and myocardial blood supply (Fig 3). The increased myocardial oxygen demand is a consequence of the effects of nicotine stimulating the sympathetic nervous system and the heart.

Cigarette smoking acutely increases plasma levels of norepinephrine and epinephrine and enhances 24-hour urinary excretion of these catecholamines.[33] Cigarette smoking increases heart rate both acutely (up to 20 beats per minute) as well as throughout the day with regular dosing (average increase 7 beats per minute as measured during ambulatory monitoring).

The hemodynamic effects of cigarette smoking are mediated primarily by nicotine. Intravenous nicotine, nicotine nasal spray, and nicotine chewing gum all increase heart rate up to 10 to 15 beats per minute and increase systolic blood pressure up to 5 to 10 mmHg, responses similar to the effects of cigarette smoking. Nicotine increases cardiac output by increasing both heart rate and myocardial contractility. Nicotine constricts some vascular beds such as the skin. Cutaneous vasoconstriction explains the reduction in fingertip skin temperature that is seen with the administration of nicotine. Nicotine appears to dilate other vascular beds, such as skeletal muscle. Skeletal muscle vasodilation may in part be a result of the increase in cardiac output, although release of epinephrine from nerve terminals may also contribute. The increases in heart rate and myocardial contractility are mediated by the beta adrenergic effects of nicotine. The net result of increased heart rate, blood pressure, and myocardial contractility is an increase in myocardial work, which then requires an increase in myocardial blood flow.

An important hemodynamic effect of cigarette smoking is on coronary arterial blood flow. As reviewed by Czernin and Waldherr,[34] cigarette smoking acutely increases coronary blood flow in healthy individuals by up to 40%. This increase appears to be a response to the increase in myocardial work. In anesthetized dogs, coronary blood flow exhibits a biphasic response to nicotine.[35] Initially, coronary blood flood increases—in the large coronary vessels as well as in the

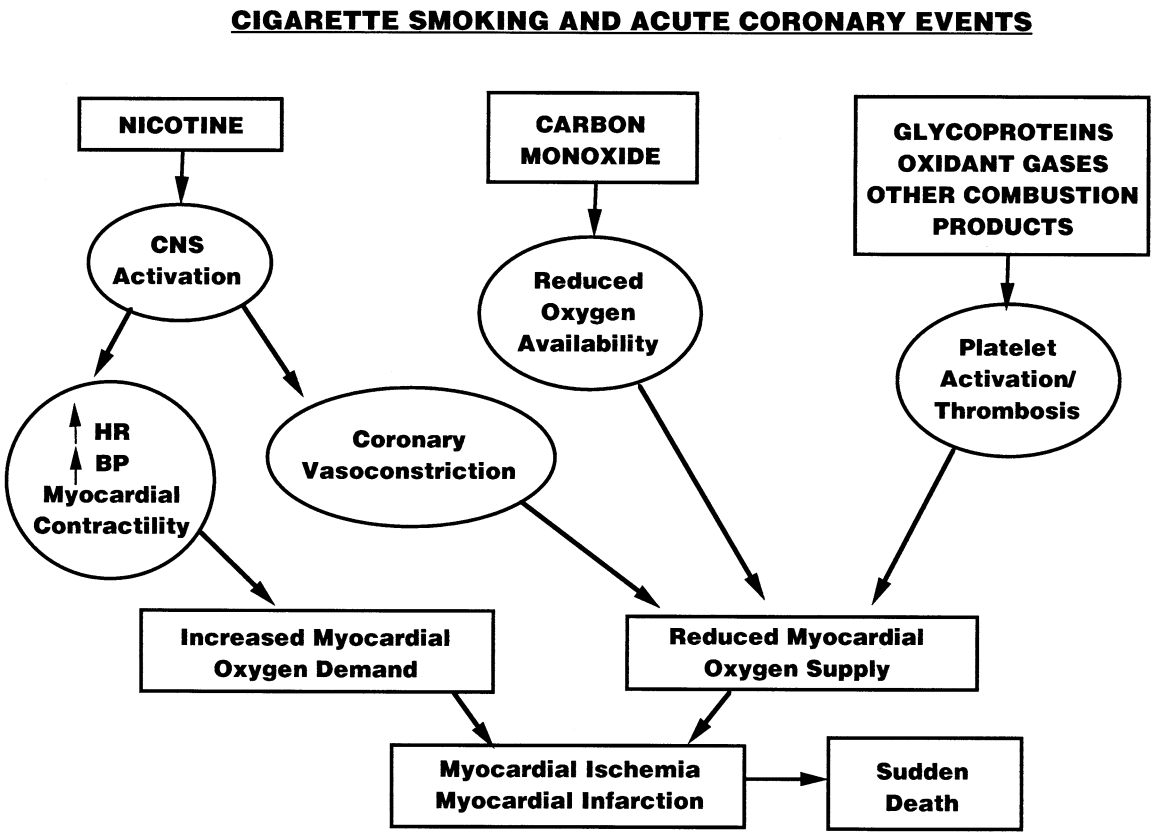

Fig 3. Overview of mechanisms by which cigarette smoking causes acute cardiovascular event.

smaller resistance vessels—believed to result from increased myocardial metabolic demand. Subsequently, coronary blood flow decreases.

Cigarette smoking impairs the response of coronary blood flow to an increase in myocardial oxygen demand (that is, reduces coronary vasodilatory flow reserve). Thus, the increase in coronary blood flow is less than expected based on the level of myocardial work in the absence of nicotine. There is considerable evidence, as reviewed by Czernin and Waldherr,[34] as well as Puranik and Celemajer,[36] that cigarette smoking causes coronary arterial endothelial dysfunction. The consequence of endothelial dysfunction includes reduced nitric oxide (NO) release. Exhaled nitric oxide has been used as an indicator of pulmonary nitric oxide synthesis and release. Cigarette smoking is associated with reduced levels of exhaled nitric oxide, and smoking cessation results in normalization of nitric oxide release.[37,38]

Cigarette smoking may also be associated with coronary vasoconstriction. Although in an individual without coronary artery disease, cigarette smoking increases coronary blood flow, in the presence of coronary disease, cigarette smoking decreases coronary blood flow.[39] In smokers with coronary artery disease, cigarette smoking increases coronary vascular resistance, an effect that can be blocked by alpha adrenergic blockers.[40] The latter observation indicates that the mechanism is, at least in part, the sympathetic neural stimulating effect of nicotine.

Intracoronary doppler ultrasound measurements demonstrate that cigarette smoking constricts epicardial arteries as well as increases total coronary vascular resistance.[41] Thus, the impairment of coronary blood flow by cigarette smoking results from the constriction of both epicardial and resistance blood vessels. After pretreatment with calcium channel blocking agents or nitroglycerin, cigarette smoking increases coronary blood flow in patients with coronary artery disease

who had no increase after cigarette smoking alone, supporting the idea that cigarette smoking is directly producing coronary vasoconstriction.[42] The chewing of 4 mg nicotine gum by healthy nonsmokers blunts the increase in coronary blood flow that occurs with increased heart rate, produced either by nicotine or cardiac pacing.[43] This confirms that nicotine is capable of constricting coronary arteries, even at low doses in human beings.

Nicotine has been shown to worsen myocardial dysfunction in "regionally stunned" ischemic myocardium of anesthetized dogs. In a placebo-controlled experiment, transient ischemia was induced in dogs by 15 minutes of left anterior descending coronary artery clamping.[44] Segmental shortening recovered to only 29% of pre-ischemic baseline in nicotine pretreated animals compared with 54% in saline-treated control dogs. The doses of nicotine administered to the animals did not alter heart rate, blood pressure, or blood flow or cause myocyte necrosis.

Cigarette smoking is associated with an increased risk of vasospastic angina, and a poorer response to medication in patients who have vasospastic angina.[45] Cigarette smoking during angiography has been observed to acutely produce coronary vasospasm.[46]

As mentioned previously, carbon monoxide may also contribute to the adverse hemodynamic effects of cigarette smoking. By producing a functional anemia, carbon monoxide increases the need for coronary blood flow, especially during physical exertion. An inadequate coronary blood flow vasodilatory reserve produced by cigarette smoking, in face of the carbon monoxide-mediated need for increased coronary blood flow, could contribute to myocardial ischemia with exercise in smokers.

Smoking and the Endothelium

Endothelial injury and/or dysfunction is believed to be an initiating event in atherogenesis as well as a major factor in causing acute cardiovascular events. Cigarette smoking produces endothelial injury and dysfunction, seen both in peripheral and coronary arteries. Other cardiovascular risk factors, hypercholesterolemia, diabetes, and hypertension, also produce endothelial dysfunction.

As reviewed by Puranik and Celermajer,[36] the endothelium is important in regulating vascular tone as well as influencing coagulation, leukocyte adhesion, and immune function. Endothelial dysfunction results in impaired vasodilatory reserve, a prothrombotic state, increased neutrophil and monocyte adhesion to blood vessels, and promotion of inflammation. These actions serve to accelerate atherogenesis and aggravate or potentiate acute cardiac ischemia, resulting in acute ischemic events.

There is considerable evidence that cigarette smoking produces endothelial damage. Anatomical changes in the endothelium have been described in the umbilical arteries of babies of smoking mothers.[47] Cigarette smoking impairs flow-mediated endothelium-dependent peripheral arterial vasodilation, an effect that is at least partly reversible after smoking cessation.[48] Smokers without atherosclerosis have coronary vasoconstrictor effects to acetylcholine that, in the presence of normal endothelial cell function, produce vasodilation.[49] Vasodilation in response to infusion of acetylcholine into the brachial artery is reduced by cigarette smoking, and the impairment is greater in the presence of hypercholesterolemia.[50]

The endothelium produces its vascular effects via the release of a number of small molecules including nitric oxide, prostacyclin, tissue plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1). Nitric oxide and prostacyclin are vasodilators and have anti-platelet aggregation effects. tPA promotes and PAI-1 inhibits fibrinolysis. Smoking-associated changes in secretion of these chemicals may result in vasoconstriction and enhanced coagulation.

The mechanism by which smoking causes endothelial dysfunction is thought to be primarily the effects of oxidant chemicals. Oxidant chemicals degrade nitric oxide and reduce nitric oxide release, therefore antagonizing the actions of nitric oxide to dilate blood vessels and inhibiting platelet aggregation. Smokers have lower than normal levels of antioxidant vitamins, reflecting consumption of these vitamins in response to ongoing oxidant stress. Administration of vitamin C reverses the impairment in endothelium-mediated vasodilation in smokers, consistent with an oxidant mechanism of endothelial dysfunction.[51]

Nicotine itself may have injurious effects on endothelial cells. Nicotine in concentrations sim-

ilar to those found in the blood of cigarette smokers alters the structural and functional characteristics of cultured vascular smooth muscle and endothelial cells.[52,53] Oral nicotine administered to rats to achieve blood levels comparable with those in human smokers produces myointimal thickening of the aorta after experimental injury (denudation of the endothelium with a balloon catheter).[54] The excessive myointimal thickening in nicotine-treated animals is consistent with persistent injury to endothelial cells. Increased numbers of circulating endothelial cells in the venous blood (reflecting endothelial injury), and a decrease in platelet aggregate ratios (reflecting platelet aggregation) have been found in regular nonsmokers who for experimental purposes smoke tobacco but not when they smoke nontobacco cigarettes, further suggesting a role of nicotine.[55] Nicotine has been shown to induce endothelial dysfunction in animals as well as people.[56-59]

Nicotine may also influence endothelial function in other ways. In studies of cultured endothelial cells, nicotine enhances the release of basic fibroblast growth factor and inhibits the production of transforming growth factor β1, increases DNA synthesis, mitogenic activity, and endothelial proliferation.[60,61] In apolipoprotein E-deficient mice, nicotine has been shown to stimulate angiogenesis and accelerate atherosclerotic plaque development.[62] The effect of nicotine to stimulate angiogenesis was mediated by increased endothelial production of nitric oxide, prostacyclin, and vascular endothelial growth factor (VEGF). The relevance of this research to the situation of human smokers is unclear, because whereas the effects of nicotine on angiogenesis in mice were dependent on nitric oxide release, the net effect of smoking in people seems to be impairment of nitric oxide release.

Of note with respect to endothelial function and therapeutics is that angiotensin-converting enzyme (ACE) inhibition normalizes impaired bradykinin-mediated, endothelium-dependent venodilation in smokers.[63] Furthermore, coronary vasomotor responses to acetylcholine in patients with coronary artery disease improved in response to the ACE inhibitor quinapril to a much greater extent in smokers compared with nonsmokers.[64] Angiotensin converting enzyme inhibitors have been shown to have antioxidant activity, which could be the mechanism of benefit in smokers.

Hypercoagulable State

Smoking-mediated thrombosis appears to be a major factor in the pathogenesis of acute cardiovascular events. Epidemiologic evidence indicates that cigarette smoking increases the risk of acute myocardial infarction and sudden death more than it increases the risk of angina pectoris. The former are believed to be mediated by thrombosis, the latter primarily by hemodynamic factors. As reviewed by Metz and Waters,[5] the extent of revascularization in patients with myocardial infarction after treatment with thrombolysis is greater in smokers than in nonsmokers. Smokers, at the time of myocardial infarction, are younger, have fewer cardiac risk factors, and have less severe underlying coronary disease than do nonsmokers. Enhanced thrombosis superimposed on less severely stenotic arteries best explains these observations. In men with sudden death, cigarette smoking is much more likely to be present when there are pathological findings of acute thrombosis (75% of cases) compared with where the findings are plaque without thrombosis (41%).[65] Conversely, in nonsmokers, stable plaque without thrombosis was the more common finding.

Cigarette smoking can enhance thrombosis by several mechanisms. Smoking produces platelet activation, which may be related to endothelial dysfunction and/or direct effects of oxidant chemicals, as discussed previously. Smoking-related endothelial dysfunction results in reduced release of nitric oxide, which normally inhibits platelet activation, and reduced secretion of tPA and increased secretion of PAI-1, which result in impaired fibrinolysis.

Platelet-derived nitric oxide release has been shown to be impaired in smokers.[66] Cigarette smokers demonstrate reduced release of tPA from coronary arteries in response to Substance P (endothelium-dependent vasodilator).[67] Cigarette smokers have higher levels of PAI-1 compared to nonsmokers.[68] Nicotine has been shown to increase PAI-1 mRNA expression and protein production in cultured brain endothelial cells.[69]

Cigarette smoking may also affect the thrombogenicity of atherosclerotic plaques. Tissue factor is a thrombogenic factor that contributes to thrombosis after plaque disruption. In apolipoprotein E-deficient mice fed high cholesterol diets, exposure to cigarette smoke results in higher levels of

tissue factor, as well as higher levels of vascular cell adhesion molecule 1 (VCAM-1) and greater numbers of macrophages in atherosclerotic plaques compared with mice without smoke exposure.[70] Similar differences were found in tissue factor levels and activity in carotid artery plaques in smokers compared with nonsmokers. Aspirin treatment of the smoke-exposed mice or aspirin use in the smokers was associated with lower levels of tissue factor in the plaque, suggesting a possible protective role of aspirin in smokers.

The role of oxidant chemicals in producing the hypercoagulable state is suggested by platelet aggregation studies, in which incubation of platelets from nonsmokers with plasma from smokers results in hyperaggregability.[71] This effect is seen using plasma of smokers taken immediately after smoking a cigarette, but not prior to smoking. The effect on the smokers' plasma was blocked by treatment of the plasma with antioxidants. Peroxidation of free fatty acids appears to mediate the enhancement of thrombin-induced platelet aggregation in these studies.

The chronic inflammatory response to smoking is associated with increases in fibrinogen levels. Carbon monoxide, by reducing oxygen-carrying capacity, results in a state of relative hypoxemia. In response to hypoxemia, red blood cell mass increases. Both increased fibrinogen levels and increased red cell mass increase blood viscosity, which contributes to enhanced thrombosis. Activation of platelet aggregation is evidenced by increased urinary excretion of metabolites of platelet-derived thromboxane A_2.[72]

The implications of the hypercoagulable state are seen both in the epidemiology of smoking-related cardiovascular events, as discussed above, as well as in the rapid rate of decline in the risk of such events after smoking cessation. A hypercoagulable state can result in acute myocardial infarction in individuals who have less severe underlying coronary disease. Therefore, smokers who quit smoking have a better prognosis than do nonsmokers after myocardial infarction. The hypercoagulable state produced by smoking may also be important in understanding the toxicity of therapeutic interventions. For example, cigarette smoking protects from tPA-induced cerebral hemorrhage in patients being treated for ischemic stroke.[73]

Inflammation

Cigarette smoking results in a chronic inflammatory state, as evidenced by increased levels of circulating leukocytes, increased C-reactive protein, and increased levels of acute phase reactants such as fibrinogen.[74-76] Cigarette smoking enhances the recruitment and adhesion of leukoyctes to blood vessel walls, an integral step in vascular inflammation.[77] Cigarette smoke also activates monocytes.

Inflammation is believed to contribute to atherogenesis; and white blood cell counts, C-reactive protein, and fibrinogen are all powerful predictors of future cardiovascular events.[78]

The mechanisms by which cigarette smoking promotes inflammation are unclear. Oxidant stress appears to play a major role. Oxidized LDL is a pro-inflammatory stimulus. Lipid peroxidation products have also been shown to be pro-inflammatory, acting in part on the PAF receptor. The antioxidant vitamin C was shown to prevent leukocyte adhesion to the endothelium and leukocyte-platelet aggregation in hamsters.[77] In the same animal model, it was shown that leukocyte adhesion and the formation of leukocyte-platelet aggregates was mediated by platelet activating factor (PAF)-like agonists.[79] This PAF-like factor was derived from oxidative modification of phospholipids, and was distinct from biosynthetic PAF. Generation of the PAF-like lipids was inhibited by vitamin C treatment. In contrast to these findings, the effect of sera from smokers to promote monocyte-endothelial cell adhesion (associated with increased levels of intercellular adhesion molecule, ICAM), was found to be reversed by oral L-arginine, but not by vitamin C.[80] This latter study suggests that smoking-related impairment of nitric oxide release is an important determinant of increased adhesion.

Nicotine may contribute to inflammation by acting as a chemotactic agent for neutrophil migration.[81] Nicotine has been shown to enhance leukocyte-endothelial interactions, resulting in greater leukocyte rolling and adhesion in the cerebral microcirculation in mice.[82] Nicotine has been reported to act on human monocyte-derived dendritic cells to stimulate an inflammatory response.[83] Dendritic cells are antigen-presenting cells that are required for initiation of adaptive immunity. These cells have been detected in the

walls of arteries and in atherosclerotic lesions. Nicotine was shown to be a potent inducer of the expression of a variety of co-stimulatory molecules and to increase secretion of the pro-inflammatory cytokine IL-12 in cultured dendritic cells. Nicotine augmented the capacity of dendritic cells to stimulate T-cell proliferation and cytokine secretion. Finally, intravenous injection of nicotine increased the movement of dendritic cells into atherosclerotic lesions in vivo in apolipoprotein E-deficient mice. This line of research suggests that nicotine could contribute to adaptive immunity, which may play a role in atherogenesis. On the other hand, switching from smoking to transdermal nicotine results in a significant decline in leukocyte count, suggesting that nicotine is not the main determinant of the inflammatory response.[84]

Cigarette Smoking and Insulin Resistance

Diabetes is a major risk factor for accelerated cardiovascular disease. As reviewed by Eliasson,[85] cigarette smoking is a risk factor for the development of Type 2 diabetes. This increased risk declines after smoking cessation. Furthermore, smokers with insulin-dependent diabetes require higher doses of insulin and have higher hemoglobin A1c levels than do nonsmokers. Among nondiabetics, cigarette smoking is associated with insulin resistance, as evidenced both by euglycemic insulin clamp studies and by studies of glucose/insulin responses to glucose loading. Cigarette smoking increases the risk of microvascular complications of diabetes, including faster progression of renal disease and an increased risk of diabetic neuropathy. Cigarette smoking also increases the risk of macrovascular disease, including coronary artery disease, peripheral vascular disease and strokes among diabetics.

The mechanisms by which cigarette smoking causes insulin resistance are not fully elucidated, but there is evidence for a role of nicotine. Intravenous infusion of nicotine reduces insulin secretion in Type 2 diabetics.[86] The use of tobacco snuff was reported in one study to be a risk factor for Type 2 diabetes,[16] but this study had a small number of cases. Another study of insulin levels in snuff users found no evidence that snuff altered insulin sensitivity.[10] The long-term use of nicotine gum or transdermal nicotine after smoking cessation has also been reported to be associated with insulin resistance.[87,88]

Of interest is that hyperinsulinemia itself can cause endothelial dysfunction, as measured by flow-mediated vasodilation in human beings.[89] Impaired endothelial function was reversed by vitamin C treatment, suggesting an oxidative stress mechanism. Furthermore, in smokers insulin sensitivity as measured by steady state plasma glucose levels is improved by vitamin C treatment, further suggesting a role of oxidant stress.[90]

Another likely mechanism by which nicotine produces insulin resistance is activation of the sympathetic nervous system. Nicotine also increases release of corticosteroids and growth hormone, which may contribute to insulin resistance. Smokers have higher levels of free fatty acids and triglycerides after meals, which has been associated with insulin resistance. Cigarette smoking does not appear to affect insulin secretion, consistent with a primary effect on insulin resistance.

The implications of smoking-induced insulin resistance are quite evident. Smoking not only acts as a major risk factor for cardiovascular disease itself, but also serves to induce and/or aggravate diabetes, therefore enhancing another risk factor. Smoking and diabetes affect cardiovascular risk synergistically. Both act to increase oxidant stress, produce endothelial dysfunction, and enhance coagulation. Thus, the rate of progression of vascular disease in diabetics is much greater in smokers compared with nonsmokers. The above research raises the possibility of a role for antioxidant therapy to moderate the development of insulin resistance in smokers. Finally, these studies indicate that nicotine may contribute to insulin resistance that has implications for the safety of long-term administration of nicotine medications.

Smoking and Lipid Abnormalities

Cigarette smoking is associated with a more atherogenic lipid profile, including lower high-density lipoprotein (HDL) and higher low-density lipoprotein (LDL) cholesterol levels compared to nonsmokers.[91] Nicotine could contribute to lipid abnormalities by accelerating lipolysis and/or by inducing insulin resistance.[92] The time course of lipid changes after smoking cessation indicates that HDL levels begin to rise within 2 weeks of cessation.[93] Levels of very low density lipoprotein

(VLDL) are higher; HDL cholesterol levels (primarily HDL-2) are lower; triglycerides are higher; and apoprotein A1 levels are higher in smokers compared with nonsmokers.[94] Smokers have higher levels of oxidized LDL, which is believed to promote atherogenesis.[95] Oxidized LDL is taken up preferentially by macrophages, which become the foam cells that are an integral part of the atherosclerotic plaque.

Nicotine, by release of catecholamines, induces lipolysis and releases plasma-free fatty acids.[92] These free fatty acids are primarily taken up by the liver, which might be expected to increase the synthesis of VLDL, consistent with the changes described in cigarette smokers.

Studies of the effects of nicotine on lipids in animals are conflicting. Injection of nicotine or feeding of nicotine has been reported to increase total cholesterol in rabbits and monkeys receiving a high cholesterol diet.[96,97] Nicotine feeding in squirrel monkeys for 2 years has been shown to increase plasma levels of LDL. The mechanism in monkeys includes both accelerated synthesis of LDL through lipolysis of HDL and VLDL and impaired clearance of LDL.

However, most studies in human beings given nicotine find that nicotine delivered in pharmaceutical forms does not have an adverse effect on lipid profiles. In one study, nicotine chewing gum (2 mg 8 times a day) was given to healthy nonsmokers for 2 weeks. No changes in plasma concentrations of triglycerides; total HDL or LDL cholesterol; or apolipoprotein A1 or B were noted.[98] In another study, 20 nonsmokers with ulcerative colitis received transdermal nicotine (15 mg/day for 12 week period), and no changes in plasma lipid were found.[99] Data from smokers who stopped smoking and used transdermal nicotine indicate that lipids change toward normal while nicotine is administered.[100]

Genetic Determinants of Smoking-Induced Cardiovascular Disease

Although cigarette smoking is extraordinarily hazardous, many smokers do not appear to suffer injury from their addiction. Fifty percent of lifelong smokers die prematurely from smoking-related disease, but 50% do not. Among smokers, some develop severe cardiovascular disease, which may result in death at a very early age, whereas some appear to be resistant to cardiovascular disease despite heavy life-long smoking. The sources of variability include the presence of other risk factors to be sure, but also include genetics.

In addition to furthering our understanding of who is at risk for smoking-induced disease, genetic studies are also useful in furthering our understanding of pathogenesis. Wang et al[101] have reviewed the genetic influences of cigarette smoking-induced cardiovascular diseases from both of these perspectives.

Most of the published research on genetic influences on smoking-induced disease in human beings has been candidate gene studies. That is, the presence of particular genes that are suspected to play a role in cardiovascular disease are studied. The risks of individuals with gene alleles are examined for interactions with cigarette smoking status. Conclusions from this type of research are often problematic due to the small numbers of subjects studied, inhomogeneity of subjects related to racial differences, and/or frequent nonreplication of study results. However, such research does yield provocative findings related to the mechanisms of smoking and cardiovascular disease.

The types of genes that have been studied are those that activate or detoxify cigarette smoke toxins, or those that play a role in cardiovascular physiology. For example, CYP1A1 is an enzyme present in the lungs that activates smoke carcinogens. CYP1A1 gene-smoking interactions have been reported for smoking and lung cancer. Wang et al[102] describe an interaction involving the rare C allele of CYP1A1, which is thought to be associated with high inducibility or enhanced catalytic activity of the enzyme. They found that the presence of the C allele was associated with an increased risk of 3-vessel coronary artery disease in light smokers, but not in heavy smokers. A lack of effect in heavy smokers may relate to the large toxin load, emphasizing the importance of looking at dose-response relationships. The mechanism of this interaction is unclear. Possibly it is related to greater activation of some cardiovascular toxin (such as polyaromatic hydrocarbons), or perhaps it is related to the role of CYP1A1 in intracellular oxidative processes.

Genes involved in nitric oxide synthesis have been studied because of the central role of nitric oxide in endothelial function and atherogenesis.

Cigarette smoke is a source of nitric oxide, but cigarette smoking also reduces endothelial cell release of nitric oxide, as discussed previously. Cigarette smoke both degrades nitric oxide by generation of oxidants such as peroxynitrite and reduces the activity of the endothelial enzyme eNOS, which is involved in the synthesis of nitric oxide. A considerable proportion of the variability in eNOS activity is genetically determined. Wang et al[103]has shown in in-vitro studies that genetic differences in the eNOS promoter fragment influence the transcription response to cigarette smoke extract. Interactive effects between eNOS DNA variants with cigarette smoking and cardiovascular risk have been reported in people as well. For example, in current smokers and ex-smokers the uncommon $eNOS_{4a}$ gene polymorphism was found in excess in individuals with severe coronary stenosis compared with those with mild or no stenosis. However, no such effect was seen in nonsmokers.[104] This genotype was also associated with an increased risk of myocardial infarction. It was concluded that the $eNOS_{4a}$ allele poses a particular risk for coronary heart disease in smokers, although the mechanism of this interaction has not yet been elucidated.

The p53 gene has been of interest as a risk factor for cancer and possibly atherosclerosis. The p53 protein is a transcription factor that suppresses growth and triggers apoptosis. The action of p53 on the proliferation of cells and/or apoptosis could contribute to the risk of atherogenesis. Cigarette smoking can mutate the p53 gene, resulting in uncontrolled cell growth and an increased risk of cancer. Wang describes an interaction between the p53 HaeIII variant in intron 1 and the MspI variant in intron 6, and cigarette smoking in association with the risk of coronary artery disease.[105] Other studies, however, have been inconclusive with respect to a role of p53 gene mutations in coronary artery disease. Thus, the importance of the smoking p53 gene interaction for heart disease remains speculative.

Because oxidative stress plays an important role in smoking-induced coronary artery disease, the role of antioxidant systems in determining cardiovascular risk is important. Some key elements of the antioxidant system as described by Wang are the enzyme superoxide demutase (SOD), which scavenges oxygen free radicals; glutathione, which inhibits intracellular oxidation; and paraoxonase, an antioxidant associated with high-density lipoprotein particles.[101] Smoking has been associated with lower levels of antioxidants, including SOD, in blood. Individuals with myocardial infarction have lower levels of SOD. A large proportion of the individual variation in SOD is genetically determined. It would seem logical that genetic differences in SOD might interact with cigarette smoking in determining cardiovascular risks. Studies to investigate this possibility are ongoing.

A number of other gene-environment interactions involving cigarette smoking have been described. An interaction between the G-455A β-fibrinogen gene promoter and cigarette smoking influencing plasma fibrinogen levels has been reported.[106] The A-raising effect on fibrinogen levels was greater in smokers compared to nonsmokers. The presence of the glycoprotein III_a P1(A2) polymorphism is associated with increased risk of ST elevation, acute myocardial infarction in smokers, but not in nonsmokers.[107] Conversely, the gene mutation is less common in smokers compared to nonsmokers and those who present with non-ST elevation acute coronary syndromes. This study suggests that smoking plus a genetic predisposition to coagulation increases the risk of acute coronary thrombosis.

The factor V Arg_{506} Gln mutation is associated with reduction in the anticoagulation effect of activated protein C, and is associated with an increased risk of venous thrombosis. The presence of the FV:Q^{506} allele interacts with cigarette smoking in predicting the risk of myocardial infarction or death in patients presenting with acute coronary syndrome.[108] The combination of this allele plus smoking was associated with a much greater risk.

An interaction between the presence of a null polymorphism for the glutathione S-transferases M1 and T1 with smoking has been reported. This enzyme detoxifies chemicals in tobacco smoke. The presence of a null allele has been associated with an increased risk of coronary heart disease, with a multiplicative increase in risk when combined with cigarette smoking.[109] This finding suggests that some chemical in cigarette smoke that is normally detoxified by GST contributes to coronary heart disease.

Paraoxonase is an enzyme associated with high density lipoproteins that protects against lipid

peroxidation. A polymorphism in the paraoxonase gene, $PON1_{192Arg}$ was found to be more common in Costa Rican patients with myocardial infarction, but this association was seen only in nonsmokers.[110] Cigarette smoke extract was shown to decrease paraoxonase activity, and it is speculated that the detrimental effect of smoking on the enzyme outweighs any genetic influence.

Finally, serotonin is a vasoconstrictor in the presence of atherosclerosis. Serotonin levels are modulated by the serotonin transporter. The L-gene promoter polymorphism of the serotonin transporter gene has been associated with an increased risk of early onset coronary heart disease in Japanese men.[111] An interaction was observed between cigarette smoking and this polymorphism, suggesting that the polymorphism poses a particular risk for smokers.

In summary, Wang et al[101] have provided several examples, and I have described several more examples of gene-smoking interactions that appear to influence the risk of cardiovascular disease in smokers. This type of research helps us to identify which smokers are at risk of cardiovascular disease and to identify mechanisms by which smoking produces cardiovascular injury.

Cigarette Smoking and Cardiovascular Disease: Implications for Treatment

In this section I will discuss the implications of research on the pathophysiology of cigarette smoking-induced cardiovascular disease on the treatment of smokers with cardiovascular disease. First, I will summarize the implications of cigarette smoking for the treatment of cardiovascular disease, then I will discuss the implications of cardiovascular disease for the treatment of nicotine addiction. Finally, I will comment on the economic aspects of smoking cessation therapy in relation to other preventive cardiology interventions.

Implications of Cigarette Smoking for Treatment of Patients with Cardiovascular Disease

As discussed above, cigarette smoking produces cardiovascular disease by a variety of mechanisms. Most prominent with respect to acute cardiovascular events are promotion of thrombosis, endothelial dysfunction, inflammation, and coronary vasoconstriction.

Smokers with acute myocardial infarction are more likely to have underlying thrombosis and probably more thrombus compared with nonsmokers. Consistent with this idea, smokers with acute myocardial infarction do better after thrombolysis compared with nonsmokers. Although coronary angioplasty works well with smokers and may be preferred for all patients with acute myocardial infarction, thrombolysis seems to be a reasonable alternative for smokers with myocardial infarction. This observation may be particularly relevant where angioplasty is not immediately available and requires that the patient be transferred to another facility for the procedure. In this case, immediate thrombolysis may be preferrable to more delayed angioplasty in a smoker, whereas delayed angioplasty may provide a better outcome in a nonsmoker.

In smokers with myocardial infarction who cannot quit, there is a high recurrence rate for myocardial infarction. Although there are no empirical data yet, it would seem that if a smoker does not quit smoking, more intensive anticoagulant therapy may be beneficial. For example, long-term warfarin therapy, in addition to the usual aspirin treatment, might be considered.

Smokers who have undergone percutaneous coronary revascularization or coronary artery bypass graft surgery have a higher likelihood of recurrent obstruction of their coronary vessels if they continue to smoke. Thus, interventions including prolonged anticoagulation and vigorous lipid lowering may be even more important in smokers than in nonsmokers after coronary revascularization.

Smokers are more likely to experience coronary vasospasm, and those with vasospasm respond less well to treatment with calcium channel blockers. Smokers with vasospastic angina may require multiple coronary vasodilators—that is, nitrates plus calcium channel blockers—for adequate control of vasospastic complications. Since smoking is a major cause of endothelial dysfunction, other therapies that improve endothelial function, such as lipid-lowering drugs, angiotensin converting enzyme inhibitors, and vigorous control of diabetes may be particularly beneficial in smokers.

Cigarette smoking may alter the response to

some cardiac medications. Cigarette smoking accelerates the metabolism of some cardiac drugs such as flecanide and perhaps propranolol.[112,113] Cigarette smoking induces resistance to insulin, potentially requiring greater doses of insulin or hypoglycemic medications to obtain adequate glycemic control. Cigarette smoking, because of its combined alpha and beta adrenergic agonist effects, may result in a poorer blood pressure response to nonselective beta blockers (epinephrine reversal-like phenomenon). On the other hand, the administration of propranolol in the Beta Blocker Heart Attack Trial (BHAT) resulted in the survival and reinfarction benefit after myocardial infarction in the entire population, but subgroup analysis revealed that the benefit was primarily in smokers.[114] The greater benefit in smokers may be due to antagonism of the sympathomimetic effects of nicotine.

Oxidant stress underlies many of the pathophysiologic manifestations of cigarette smoking. Antioxidant vitamins have been shown in various studies to reverse endothelial dysfunction, to antagonize procoagulant effects, to reduce some inflammatory effects, and to reduce insulin resistance associated with cigarette smoking. Although antioxidant therapy has not been proven to be of benefit in preventing or treating cardiovascular disease in the general population, specific studies in smokers, a population that is most likely to benefit, are suggested.

Smoking Cessation Therapy in Patients with Cardiovascular Disease

This topic has been reviewed by Thompson and Rigotti,[115] and by Joseph and Fu.[116] The reasons why smokers with cardiovascular disease need to quit smoking are obvious. Not only does smoking directly accelerate atherogenesis and cause acute cardiovascular events, but it contributes to or acts synergistically with other risk factors such as hyperlipidemia and diabetes. Although cigarette smoking does not cause hypertension per se, cigarette smoking does enhance the likelihood of complications in patients with hypertension, including the development of renal disease and the development of malignant hypertension.[117] Cigarette smoking is a substantial contributor to morbidity and mortality in patients with left ventricular dysfunction.[118] The mortality benefit in stopping smoking in such patients is equal to or greater than the benefit of therapy with angiotensin converting enzyme inhibitors, beta blockers, or spironolactone. Smoking cessation is particularly important in individuals with diabetes. Smoking increases cardiovascular risks markedly in diabetics, including the risk of progression of diabetic nephropathy. Smoking also increases insulin resistance and makes diabetes more difficult to control. For these and other reasons, smoking cessation in patients with cardiovascular disease should be of utmost priority.

Smoking cessation therapy in patients with cardiovascular disease is not easy. Most patients who continue to smoke in face of known cardiovascular disease are highly addicted. Acute events, such as myocardial infarction, provide powerful motivation for cessation, and 50% of smokers do quit after acute myocardial infarction. Other hospital admissions for cardiovascular disease should also be viewed as an opportunity to motivate cessation as well.

Studies of smoking cessation in patients with cardiovascular disease in clinics in general have shown low quit rates. Research to develop methods to enhance smoking cessation in such individuals is clearly needed.

Medications that are currently approved for smoking cessation are nicotine, available in a variety of delivery systems, and bupropion. As reviewed by Joseph and Fu,[116] there has been and still is considerable concern among health care professionals and patients that nicotine is harmful and should be avoided in the presence of cardiovascular disease. Nicotine may, as discussed previously, contribute to cardiovascular disease. Its hemodynamic effects increase myocardial energy consumption and increase the demand for blood flow. Nicotine has direct effects on blood vessels and may produce endothelial dysfunction, both of which could contribute to vasoconstriction. Nicotine may contribute to insulin resistance and to the development of a more atherogenic lipid profile in smokers.

Although these pose valid safety concerns for nicotine, cigarette smoking is clearly much more hazardous. A major action of smoking, the induction of a hypercoagulable state with development of thrombosis, appears not to be a consequence of nicotine, but rather of the combustion products of smoking. The delivery of carbon monoxide,

which both reduces oxygen delivery to the heart and via its effects on red blood cell mass, contributes to hypercoagulability, is a combustion product. And, of course, cigarette smoke delivers nicotine as well. The dose of nicotine from cigarettes in most smokers is similar to or greater than that derived from used doses of nicotine medication.[33] Furthermore, nicotine from cigarette smoke is delivered into the arterial circulation rapidly, maximizing the pharmacologic and potentially pathologic effects, whereas nicotine from pharmaceutical preparations is absorbed much more slowly, resulting in much lower peak arterial concentrations.

There has been concern about the risk of taking nicotine medications and smoking at the same time. When the nicotine patch was first introduced, newspaper articles reported on smokers who smoked while using the patch and developed heart attacks.[119] However, subsequent research indicated that the risk of smoking while using nicotine replacement therapy is no greater than the risk of smoking alone. The explanation is in part a flat dose-response to nicotine, and in part due to the fact that when people do smoke while they are using nicotine replacement therapy in an attempt to quit, their intake of nicotine is often no more than modestly increased compared to that during usual smoking. The flat dose-response curve for nicotine is evidenced in studies in which, after a threshold effect of nicotine is seen, little additional effect is seen in spite of increasing nicotine blood levels.[21] Furthermore, in experimental studies of smoking cigarettes along with nicotine patches (up to 63 mg per day, 3 nicotine patches), the cardiovascular effects of cigarette smoking plus nicotine patches were observed to be similar to those of cigarette smoking alone.[120]

In support of these theoretical considerations are clinical trial data showing that nicotine patch therapy in patients with cardiovascular disease or nicotine gum therapy in people with chronic obstructive lung disease (a population in whom the prevalence of cardiovascular disease is high) find no evidence that nicotine medication increases cardiovascular risk.[116,121] A study by Mahmarian and colleagues[122] is particularly informative in respect to the safety of combining smoking with nicotine replacement therapy. These investigators found that the administration of nicotine patches to smokers with known coronary artery disease reduced the size of the myocardial perfusion defect during exercise, despite higher nicotine levels while on the patch compared to when smoking alone. Improved perfusion is most likely a consequence of lesser smoking and less intake of combustion gases, as evidenced by lower carbon monoxide levels. This study supports the idea that the combustion products are much more important as determinants of ischemia than is nicotine.

Bupropion has been less well studied in smokers with cardiovascular disease than has nicotine, but the available studies suggest that the drug is safe in such patients. The pharmacologic concern with bupropion is its sympathomimetic effect, which is especially evident at higher doses. Some individuals experience an increased heart rate or blood pressure with bupropion, raising concern about precipitating myocardial ischemia in patients with severe coronary obstruction. As has been observed for nicotine, clinical trials of bupropion in patients with cardiovascular disease suggest that the drug is safe.[116]

In summary, the risks of nicotine or bupropion in patients with cardiovascular disease have not been fully elucidated, but the available data—both in patients with cardiovascular disease as well as in experimental studies of the clinical pharmacology of these medications—suggest that the risks are not great. In contrast, cigarette smoking remains the greatest preventable cause of morbidity and mortality from cardiovascular disease in young and middle-aged people. Nicotine and bupropion have been shown to substantially increase the likelihood of smoking cessation. The benefit of such pharmacotherapy to aid smoking cessation in patients with cardiovascular disease who cannot stop smoking without such therapy far outweighs the risk of continued smoking or of the medications themselves.

Cost-Benefit of Smoking Cessation Therapy

Lightwood[123] in this volume presents a detailed discussion of the economic impact of smoking as a cause of cardiovascular disease. In direct medical cost alone, cigarette smoking cost the U.S. health care system $75 billion in 1998. Analysis of the dollars spent on cardiovascular disease may underestimate the true social impact. This is because many nonsmokers will eventually develop cardiovascular disease anyway, but at a later age than

smokers. The greatest economic impact of cardiovascular disease is seen when it affects middle-aged people, where smoking is associated with a much greater relative risk for disease as compared to the elderly. When younger smokers develop cardiovascular disease, not only do they lose more years of life, but they also lose substantial potential wages and are not available to make other contributions to family or society.

Physicians and health care planners need to consider the cost versus benefits of smoking cessation compared with other preventive strategies. For example, there is consensus that hypertension and hyperlipidemia should be vigorously treated to prevent cardiovascular disease. Smoking cessation is often relegated to a lower level of priority. Smoking is considered to be more of a lifestyle issue than a medical issue, and smoking cessation is perceived by many physicians as one for which they have not been trained to and/or do not have time to treat. Furthermore, there is less compensation from insurance companies for smoking cessation compared with other medical treatments. However, the cost versus benefit equation is much more favorable for smoking cessation than in other forms of preventive treatments. The cost per life year saved depends on age and gender of the smoker and the type of therapy provided. For the typical treatment regiment of nicotine replacement therapy, providing gum or patch, and brief physician counseling, the cost ranges from about $2,000 to $6,000 per life year saved compared to no treatment.[123] This is in contrast to the estimated $9,000 to $26,000 cost per life year saved for the treatment of moderate to severe hypertension or $50,000 to $196,000 for the treatment of hyperlipidemia in primary prevention.[124]

Conclusions

These 3 issues of *Progress in Cardiovascular Diseases* provide a comprehensive review of cigarette smoking and cardiovascular disease. The pathophysiology of smoking as a cause of cardiovascular disease is complex and is not fully understood. However, the available information provides important insight not only into smoking but also into general mechanisms of atherogenesis and acute cardiovascular events, and how chemical factors may contribute. Even if smoking disappears, the research described in these issues will help elucidate workplace and other environmental factors that might be contributing to cardiovascular disease.

Acute myocardial infarction and sudden death in smokers have a somewhat different pathophysiology from that seen in nonsmokers. The role of thrombosis is greater, and the presence of thrombosis may provide guidance in selecting the optimal approaches to revascularization and to preventive pharmacotherapy.

Smoking cessation has been recognized for many years as perhaps the most important intervention in preventive cardiology. Disappointingly, smoking cessation is not part of the routine practice for many physicians, including cardiologists—who see the direct consequences of this behavioral disorder.

Smoking cessation therapy is more cost-effective than any other preventive cardiology measure, and should be a component of every health plan and every cardiology practice. Elimination of smoking offers the single best opportunity for improving cardiovascular health in the United States and around the world.

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