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Introduction

This chapter reviews the epidemiology of smoking-induced cardiovascular disease (CVD) and the mechanisms by which tobacco smoke is thought to cause CVD. The discussion includes use of biomarkers to diagnose smoking-induced CVD and treatment implications of the pathophysiology of the disease. The link between

secondhand smoke and CVD has been reviewed in the 2006 report of the Surgeon General, *The Health Consequences of Involuntary Exposure to Tobacco Smoke* (U.S. Department of Health and Human Services [USDHHS] 2006), so discussion of secondhand smoke in this report is limited.

Tobacco Use and Cardiovascular Disease

Cigarette smoking is a major cause of CVD, and past reports of the Surgeon General extensively reviewed the relevant evidence (U.S. Department of Health, Education, and Welfare [USDHEW] 1971, 1979; USDHHS 1983, 2001, 2004). Cigarette smoking has been responsible for approximately 140,000 premature deaths annually from CVD (USDHHS 2004). More than 1 in 10 deaths worldwide from CVD in 2000 were attributed to smoking (Ezzati et al. 2005). In the United States, smoking accounted for 33 percent of all deaths from CVD and 20 percent of deaths from ischemic heart disease in persons older than 35 years of age (Centers for Disease Control and Prevention 2008). Cigarette smoking also influences other cardiovascular risk factors, such as glucose intolerance and low serum levels of high-density lipoprotein cholesterol (HDLc). However, studies have reported that smoking increases the risk of CVD beyond the effects of smoking on other risk factors. In other words, the risk attributable to smoking persisted even when adjustments were made for differences between persons who smoke and nonsmokers in levels of these other risk factors (Friedman et al. 1979; USDHHS 1983, 2001, 2004; Shaper et al. 1985; Criqui et al. 1987; Ragland and Brand 1988; Shaten et al. 1991; Neaton and Wentworth 1992; Freund et al. 1993; Cremer et al. 1997; Gartside et al. 1998; Wannamethee et al. 1998; Jacobs et al. 1999a). For example, in one study, the effect of cigarette smoking on the risk of coronary heart disease (CHD) was evident even among persons with low serum levels of cholesterol (Blanco-Cedres et al. 2002).

Beyond its status as an independent risk factor, smoking appears to have a multiplicative interaction with the other major risk factors for CHD—high serum levels of lipids, untreated hypertension, and diabetes mellitus (USDHHS 1983). For instance, if the presence of smoking alone doubles the level of risk, the simultaneous presence of another major risk factor is estimated to quadruple the risk (2×2). The presence of two other risk factors with

smoking results in approximately eight times the risk ($2 \times 2 \times 2$) of persons with no risk factors. Cigarette smoking also is a cause of peripheral arterial disease (PAD), aortic aneurysm, CHD, and cerebrovascular disease, but the relative risk (RR) of disease varies with the vascular bed (USDHEW 1971, 1979; USDHHS 1983, 2001, 2004). The highest RRs are observed for diseases of peripheral arteries in the lower extremities, and the lowest are for stroke; RRs are intermediate for CHD and aortic aneurysm.

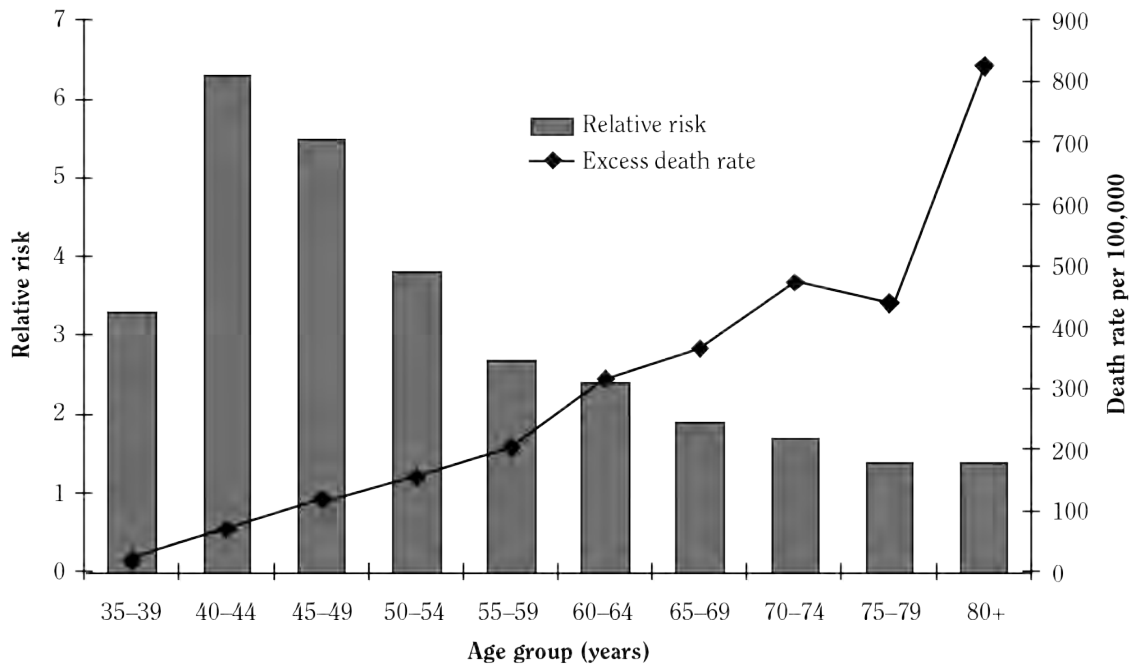
The general mechanisms by which smoking results in cardiovascular events include development of atherosclerotic changes with narrowing of the vascular lumen and induction of a hypercoagulable state, which create risk of acute thrombosis (USDHHS 1983, 2004). The rapid decline in risk of a recurrent myocardial infarction (MI) after smoking cessation (USDHHS 1990) supports the role of smoking in thrombosis. In addition, abundant evidence demonstrates that smoking contributes to development of atherosclerotic plaque (Strong and Richards 1976; Auerbach and Garfinkel 1980; Solberg and Strong 1983; USDHHS 1983, 2004).

Estimation of Risk

The risk of CHD from cigarette smoking can be described in terms of RR and excess risk (Thun et al. 1997). The RR is the ratio of CHD rates for populations of smokers to rates for lifetime nonsmokers. Excess risk is the difference between the rates of disease for smokers and nonsmokers.

These two estimates of risk can lead to conflicting impressions of the changes in smoking-related CHD risks with advancing age. The RRs and excess death rates for CHD are shown by age group in data from Cancer Prevention Study II (CPS-II) (Thun et al. 1997), sponsored by the American Cancer Society (see Figure 6.1 for data on men).

Figure 6.1 Relative risk and excess death rate for coronary heart disease among men, by age group



Source: Burns 2003. Adapted from Thun et al. 1997 with permission from Elsevier, © 2003.

Note: Data are from the American Cancer Society's Cancer Prevention Study II; data table for above data found at end of chapter.

The RRs were highest at younger ages (35 to 54 years) and declined steeply with advancing age. This finding leaves the false impression that the disease burden of CHD from smoking declined with age or was low among older smokers. However, excess CHD death rates for smokers by age group presented different evidence. The high RR for CHD at younger ages can be explained in part because mortality rates are low for death from CHD at those ages and because coronary events in young people occur primarily among smokers. Even though RR declined with increasing age, because the absolute rate of deaths from CHD increased markedly, the magnitude of the CHD burden produced by smoking increased with advancing age.

The age at onset of substantial excess risk differs by disease. For smokers, age-specific excess death rates attributable to CHD, lung cancer, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) are illustrated by data from CPS-II (Figure 6.2 shows data for men) (Thun et al. 1997). For persons younger than age 45 years, CHD was the dominant cause of increased mortality attributable to cigarette smoking. Excess rates for death from lung cancer increased steeply after age 50 years, and excess death rates from COPD were largely confined to the seventh and eighth decades of life. Late in life, excess

deaths from COPD matched and those from lung cancer exceeded the excess death rates attributable to CHD. The RR for death from a cerebrovascular disease among smokers was substantially elevated among younger smokers (RR = 4 to 5; data not shown). However, the absolute rate of stroke at these younger ages was low, and this finding resulted in a low excess mortality rate. At older ages, the death rate from stroke in the general population increased and the RR among smokers declined, thus moderating the excess death rate attributable to smoking.

Coronary Heart Disease

Cigarettes Smoked per Day

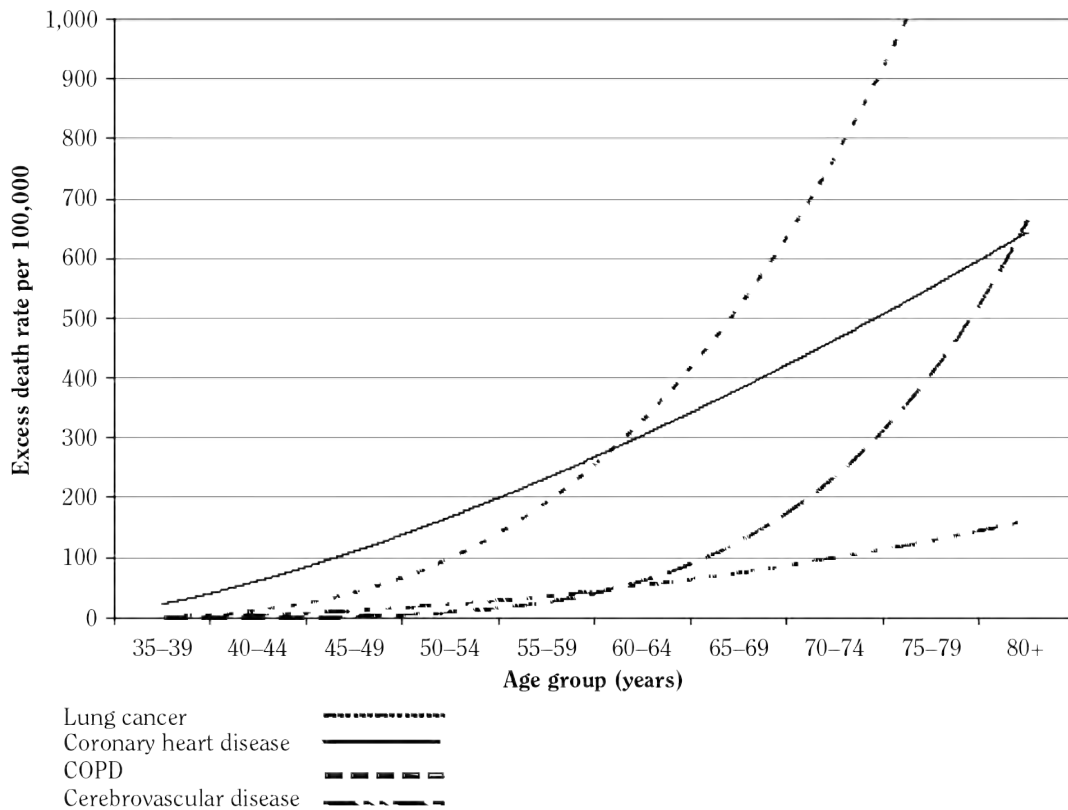
Studies showed increased risk of having CHD at all levels of cigarette smoking, and increased risks were evident even for persons who smoked fewer than five cigarettes per day (Rosengren et al. 1992; Prescott et al. 2002; Bjartveit and Tverdal 2005). Prospective mortality studies conducted in the 1960s and 1970s showed a clear increase in CHD mortality with an increase in the number of cigarettes smoked per day, regardless of the actual number

(Doll and Peto 1976; USDHHS 1983). Other studies suggested that risk increased up to at least 40 cigarettes per day (Miettinen et al. 1976; Willett et al. 1987). However, more recent data appeared to show an increase in CHD risk with more cigarettes smoked per day only up to about 25 cigarettes; the risk increased relatively little even with further increases in cigarette consumption (Neaton and Wentworth 1992; Rosengren et al. 1992; Thun et al. 1997).

Law and Wald (2003), who conducted a meta-analysis of five large studies of smoking and CHD, demonstrated a nonlinear dose-response relationship between the number of cigarettes smoked per day and the RR of disease (Figure 6.3). The researchers suggested that the effect of cigarette smoking on risk of CHD may have a low threshold and that the dose-response characteristics of the risk relationship are less steep at higher doses. This hypothesis was used to explain the seeming anomaly of a high RR of CHD associated with relatively low exposure to

secondhand smoke. By using serum levels of cotinine (a metabolite of nicotine) as biomarkers of exposure, Whincup and colleagues (2004) explored the dose response relationship between exposure to cigarette smoke and CHD in persons involuntarily exposed to cigarette smoke. More than 2,000 men who said they did not smoke had blood levels of cotinine measured in 1978–1980 and then had follow-up for 20 years. Nicotine exposure was examined by quartiles of blood cotinine as follows: less than or equal to 0.7 nanograms per milliliter (ng/mL), 0 to 1.4, 1.5 to 2.7, and 2.8 to 14.0. Hazard ratios for CHD, which included deaths and non-fatal MIs, were significantly increased at all upper quartiles (hazard ratios, 1.43 to 1.57) compared with the lowest exposure quartile, after adjustment for established CHD risk factors. Hazard ratios were also higher at the first and second five-year follow-ups (3.73 to 10.58 and 1.95 to 2.48, respectively) than those at later follow-ups. The

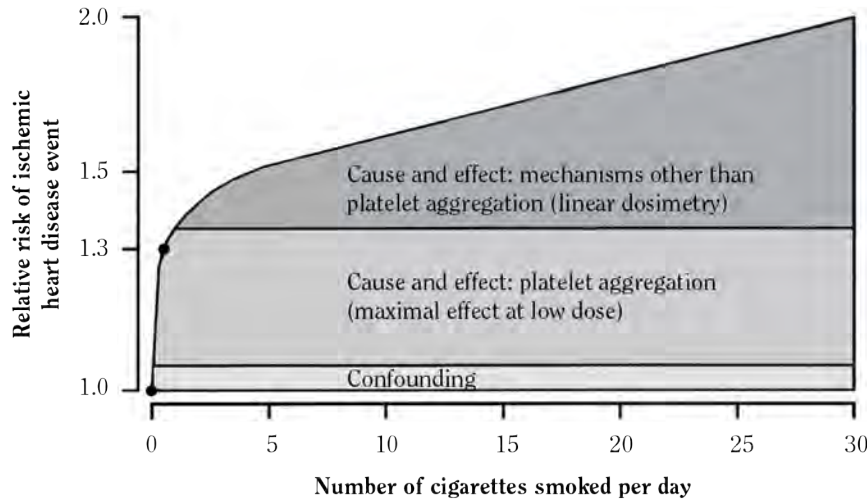
Figure 6.2 Age-specific excess death rates among male smokers for coronary heart disease, lung cancer, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease



Source: Burns 2003. Adapted from Thun et al. 1997 with permission from Elsevier, © 2003.

Note: Data are from the American Cancer Society's Cancer Prevention Study II; data table for above data found at end of chapter.

Figure 6.3 Dose-response relationship between number of cigarettes smoked per day and relative risk of ischemic heart disease



Source: Law and Wald 2003. Reprinted with permission from Elsevier, © 2003.

Note: The dose-response relationship between exposure to tobacco smoke and ischemic heart disease events is compartmentalized into separate associations attributable to confounding (difference between smokers and nonsmokers in blood pressure, body weight, blood lipids, and diet), cause and effect maximal at low dose, and cause and effect with linear dosimetry.

substantial cardiovascular risk attributable to involuntary exposure to cigarette smoke (USDHHS 2006) and the practice in most CVD studies of not excluding from the control group persons who had secondhand smoke exposure have resulted in underestimation, in many research reports, of the effects of active smoking compared with no exposure to cigarette smoke.

The data on secondhand smoke and CHD risk indicate that the dose-response relationship between exposure to smoke and cardiovascular effects is nonlinear. Another consideration is that the number of cigarettes smoked per day may not provide a linear measure of exposure to tobacco smoke. When carboxyhemoglobin or serum cotinine levels were used as measures of the smoke taken in, persons who smoked more cigarettes per day had higher levels of these biologic substances (Benowitz 1996). Even so, the carboxyhemoglobin and cotinine levels were substantially lower than those predicted by linear extrapolation from data on persons who reported smoking 1 to 20 cigarettes per day (Law et al. 1997). Among smokers of 40 or more cigarettes per day, the levels of these biomarkers were 35 percent lower than those predicted by linear extrapolation from data on persons who reported smoking fewer than 20 cigarettes per day.

At the same reported number of cigarettes per day, cotinine levels varied substantially (Benowitz 1996).

Smokers titrate cigarette smoke to achieve a consistent intake of nicotine by altering the number of cigarettes smoked per day or by changing the puffing pattern—that is, by taking deeper, faster, more, or longer puffs (National Cancer Institute [NCI] 2001). When these smoking behaviors fail to restore the level of nicotine intake, as they may with cigarettes that have very low machine-measured yields, smokers may increase the number of cigarettes per day to maintain the same level of nicotine intake.

These observations suggest that the number of cigarettes smoked per day may have become a less precise measure of exposure to tobacco smoke with the introduction of cigarettes with low machine-measured yields of tar and nicotine. This diminished precision of cigarettes smoked per day as a measure of exposure may account for some of the discordance between studies that define increased risk by an increase of more than one pack per day in the number of cigarettes smoked. By using serum cotinine as an indicator of nicotine intake and exposure to tobacco smoke in the population demonstrates a linear increase for 10 to 15 cigarettes per day. However, as use exceeds 10 to 15 cigarettes per day, a progressively smaller increment in serum cotinine for each increment in the number of cigarettes smoked per day is observed (Caraballo et al. 1998; O'Connor et al. 2006). This flattening of the relationship between exposure and cigarettes smoked per

day was similar to flattening of the relationship between the RR of CHD and the number of cigarettes smoked per day. Thus, researchers should be cautious about defining the absence of a continuing increase in risk among smokers of more than 20 cigarettes per day as evidence that increases in actual exposure are not accompanied by increases in risk.

Duration of Smoking

Researchers have not always demonstrated a significant relationship between duration of cigarette smoking and CHD risk when adjustment was made for other risk factors and the number of cigarettes smoked per day (Kuller et al. 1991; Tverdal 1999). Variation in the number of cigarettes smoked per day and in the products smoked during the lifetime of a smoker is often substantial, but this variable is not well captured in epidemiologic studies.

Age is colinear with duration of smoking, because the two variables grow in tandem after a person starts to smoke and the RRs for smoking and CHD decline with advancing age. Furthermore, most smokers begin to smoke during adolescence, which promotes the colinearity. These realities make it difficult to estimate the independent contributions of age and duration of smoking to risk of CHD in multivariate models. However, the two studies of the American Cancer Society are a good source of data, because each study consists of more than 1 million men and women (Burns et al. 1997; Thun et al. 1997). Analyses of these data stratified by age and the number of cigarettes smoked per day showed steady increases in CHD mortality rates with increasing duration of smoking for persons younger than age 70 years. Using data from

CPS-I, investigators calculated the risk of developing CHD by age and duration of smoking (see Table 6.1 for data on White men) (Burns et al. 1997). For almost all age groups younger than age 70 years, RRs increased with increasing duration of smoking. Data from CPS-II on men (Thun et al. 1997) also demonstrated a pattern of increasing RR with age-specific mortality due to CHD and increasing duration of smoking for each level of cigarettes smoked per day (Table 6.2). Even though data in these analyses were not adjusted for potential differences in other cardiovascular risk factors, the findings presented a convincing picture of increasing risk of CHD with longer duration of smoking.

Smoking Cessation

The risks of MI and death from CHD are lower among former smokers than among continuing smokers in many studies, including those with data adjusted for levels of other risk factors (Gordon et al. 1974; Åberg et al. 1983; USDHHS 1990; Kuller et al. 1991; Frost et al. 1996). The risk fell rapidly, decreasing about one-half in one year (Lightwood and Glantz 1997). Risks appear to remain slightly elevated for more than a decade after persons stopped smoking, but in some studies this increased risk was not statistically significant (Dagenais et al. 1990; Omenn et al. 1990; Kawachi et al. 1993a, 1994; Jacobs et al. 1999a; Qiao et al. 2000). Among smokers who had MI or angiographically documented CHD, persons who stopped smoking had a substantially lower rate of reinfarction than did those who continued to smoke. Reduction in risk was evident within the first year after MI. Risk continued to be lower among former smokers than among continuing

Table 6.1 Rate ratios for coronary heart disease among White men, by age and duration of cigarette smoking^a

Age (years)	Duration of smoking (years)							
	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59
40–44	1.95	2.47	4.23	NR	NR	NR	NR	NR
45–49	1.79	2.5	2.66	2.64	4.39	NR	NR	NR
50–54	2.06	2.25	2.22	2.74	2.82	3.4	NR	NR
55–59	1.71	1.66	2.13	2.03	2.43	2.99	2.17	NR
60–64	1.83	1.44	1.86	1.75	1.92	2.12	2.45	4.06
65–69	1.34	1.56	1.52	1.61	1.49	1.6	2.09	2.25
70–74	1.17	1.14	1.23	1.08	1.55	1.26	1.53	1.78
75–79	1.09	1.2	1.31	1.12	1.55	1.46	0.94	1.36

Source: Adapted from Burns et al. 1997.

Note: **NR** = data not reported; data table for above data found at end of chapter.

^aFrom Cancer Prevention Study I, American Cancer Society.

Table 6.2 Death rates and rate ratios for death from coronary heart disease among men, by age and duration of smoking by number of cigarettes smoked per day^a

Number of cigarettes/day	Age (years)	Death rates (per 100,000) ^b				Rate ratios ^c			
		20–29 yrs smoking	30–39 yrs smoking	40–49 yrs smoking	≥50 yrs smoking	20–29 yrs smoking	30–39 yrs smoking	40–49 yrs smoking	≥50 yrs smoking
1–19	50–59	241.1	276	277.9	NR	2.7	3.1	3.2	NR
1–19	60–69	340.6	560.3	643.5	866.5	1.1	1.8	2.1	2.8
20	50–59	213.9	272.6	493.4	956.4	2.4	3.1	5.6	NR
20	60–69	299.9	509	729.5	1,088.9	1	1.6	2.4	3.5
21–39	50–59	195.8	237.4	367.2	NR	2.2	2.7	4.2	NR
21–39	60–69	232.2	350.8	607.2	1,113.4	NR	1.1	2	3.6
40	50–59	144.9	281.6	321.4	664.5	1.6	3.2	3.7	NR
40	60–69	470.8	458.3	607.6	988.3	1.5	1.5	2	3.2

Source: Adapted from Thun et al. 1997.

Note: NR = data not reported; data table for above data found at end of chapter.

^aFrom Cancer Prevention Study II, American Cancer Society (CPS-II).

^bCPS-II data, Appendix Table 10, Thun et al. 1997.

^cCPS-II data, Appendix Table 12, Thun et al. 1997.

smokers for prolonged periods after the first MI (Daly et al. 1983; Omenn et al. 1990). Studies also demonstrated rapid reduction in risk after persons stopped smoking among populations at high risk for CHD (Ockene et al. 1990) and among women (Kawachi et al. 1993a, 1994).

Patients with angiographically documented CHD who stopped smoking at the diagnosis of CHD (Vlietstra et al. 1986) or before diagnosis (Hermanson et al. 1988) had lower death rates from MI or CHD than did continuing smokers. In addition, the benefit of stopping smoking did not decline with advancing age.

In the 16-year follow-up of the Multiple Risk Factor Intervention Trial Research Group (1990, 1996), mortality from CHD was 11.4 percent lower in the “special intervention” group than in the “usual care” group. This result may illustrate the benefit of stopping smoking, because one of the interventions targeted smoking cessation. A trial of advice to civil servants in London, England, to stop smoking demonstrated an 18-percent reduction in mortality from CHD in the intervention group versus the control group after 10 years of follow-up (Rose et al. 1982). Suskin and colleagues (2001) reported that in addition to benefits for CHD, stopping smoking also reduces morbidity and mortality in patients with left ventricular dysfunction. In this study, the benefits of stopping smoking on mortality and recurrent congestive heart failure requiring hospitalization were similar to the benefits from treatments with

angiotensin-converting-enzyme (ACE) inhibiting drugs, β -blockers, or spironolactone, which are mainstays for the treatment of heart failure.

Women

Women have lower absolute rates of CHD than do men. However, cigarette smoking has been associated with higher RR of MI (Njølstad et al. 1996) and higher CHD mortality (Kawachi et al. 1994; Thun et al. 1997) among women than among men. The absolute increase in risk of CHD from smoking is similar for men and women (USDHHS 1983, 2001).

A prospective evaluation of fatal and nonfatal CVD events among women in the Nurses' Health Study (Willett et al. 1987) found that smoking was an independent cause of CVD. Age-adjusted risks of disease increased progressively with more cigarettes smoked per day up to 45 or more per day. Even when the combined risks of fatal CHD and nonfatal MI were adjusted for levels of other risk factors, risks increased with increasing numbers of cigarettes per day.

Researchers have demonstrated a rapid decline in excess risk of CHD in women after they stopped smoking cigarettes. Even so, 10 to 14 years of nonsmoking are required before risks approach those of lifetime nonsmokers (Kawachi et al. 1993a, 1994).

Race and Ethnicity

In 2004, heart disease mortality was higher among African Americans than among Whites (National Heart, Lung, and Blood Institute [NHLBI] 2007). From 1999 through 2004, the prevalence of acute MI was higher for African Americans than for Whites aged 35 through 54 years; however, for ages 55 years and older, the prevalence of acute MI was higher among Whites (NHLBI 2007).

The INTERHEART study is a case-control investigation of acute MI in 52 countries in Africa, Asia, Australia, the Middle East Crescent, and North and South America (Teo et al. 2006). The odds ratio (OR) for acute MI in smokers was 2.95 for this large multiethnic population compared with lifetime nonsmokers. In addition, the risk of MI was higher among persons who smoked bidis than among nonsmokers in countries where use of this form of tobacco is common.

Researchers also identified cigarette smoking as a significant risk factor for CHD among Hispanic populations (Mendelson et al. 1998) and Asian populations (Kiyohara et al. 1990; Miyake et al. 2000; Lam et al. 2002).

Sudden Death

Most sudden death is due to CVD. In many epidemiologic studies, RRs for sudden cardiac death were higher than RRs for CHD or MI among persons who smoked. The RRs for sudden death among current smokers, compared with lifetime nonsmokers, often exceeded 3.0 (USDHEW 1971, 1979; Dawber 1980; Kannel and Thomas 1982; USDHHS 1983; Wannamethee et al. 1995; Sexton et al. 1997). In multivariate analyses of the combined data from the Framingham Heart Study and the Albany Study, which examined sudden cardiac death in men aged 45 through 64 years, cigarette smoking was the risk factor with the highest statistical significance (Kannel et al. 1975). In a study of data from the 1986 National Mortality Followback Survey among persons with no history of CHD, cigarette smoking was the only modifiable risk factor associated with sudden coronary death and it was one factor associated with increased risk of sudden coronary death among persons with known CHD (Escobedo and Zack 1996; Escobedo and Caspersen 1997). Cigarette smoking was also associated with risk of sudden cardiac death in the 18-year follow-up of the Honolulu Heart Program (Kagan et al. 1989) and the 28-year follow-up of the Framingham Heart Study (Cupples et al. 1992).

Peters and colleagues (1995) found an association between smoking cessation and reduction in death from cardiac arrhythmia for patients with left ventricular

dysfunction after MI. Finally, the risk of recurrent cardiac arrest among smokers surviving out-of-hospital cardiac arrest was lower among persons who then stopped smoking than among those who continued to smoke (Hallstrom et al. 1986).

Stroke

After adjustment of data for other risk factors, cigarette smokers have higher risk of stroke and higher mortality from cerebrovascular disease than do lifetime nonsmokers, and a dose-response relationship is evident (USDHHS 1983, 2001, 2004; Neaton et al. 1984; Colditz et al. 1988; Wolf et al. 1988; Kannel and Higgins 1990; Kuller et al. 1991; Freund et al. 1993; Hames et al. 1993; Håheim et al. 1996; Tanne et al. 1998; Jacobs et al. 1999a; Sharrett et al. 1999; Djoussé et al. 2002). In addition, in the 20-year follow-up of a prospective study of mortality that controlled for other cardiovascular risk factors, cigarette smoking increased the risk of death from stroke and mortality rates grew the number of cigarettes smoked increased (Hart et al. 1999).

In a meta-analysis of data from 32 studies, the overall RR for stroke associated with cigarette smoking was 1.5 (95 percent confidence interval [CI], 1.4–1.6) (Shinton and Beevers 1989). The RRs varied with the stroke subtypes: 1.9 for cerebral infarction, 0.7 for cerebral hemorrhage, and 2.9 for subarachnoid hemorrhage. The researchers reported a dose-response relationship between the number of cigarettes smoked per day and the RR. The data suggested a sustained higher risk of stroke among former smokers younger than age 75 years than the risk for nonsmokers in the same age group. For all ages combined, RR for former smokers was 1.2.

During the 26-year follow-up of the cohort in the Framingham Heart Study, cigarette smoking was a significant risk factor for stroke (Wolf et al. 1988). The risk declined, however, among smokers who had stopped smoking for two years and was similar to that of lifetime nonsmokers after five years of abstinence from smoking. In the 12-year follow-up of the Nurses' Health Study (Kawachi et al. 1993b), RR for stroke among current smokers was 2.58 compared with nonsmokers, but it was 1.34 among former smokers compared with nonsmokers. Once those who stopped smoking had abstained for two to four years, their risk for stroke could not be distinguished from that of lifetime nonsmokers. In addition, the pattern of decline in total risk for stroke after stopping smoking remained the same after adjustments for other risk factors.

Aortic Aneurysm

Mortality studies consistently demonstrated higher risk of death from abdominal aortic aneurysm among cigarette smokers than among nonsmokers (Hammond and Horn 1958; Weir and Dunn 1970; USDHHS 1983, 2004; Strachan 1991; Nilsson et al. 2001). In addition, the risk rose with an increasing number of cigarettes smoked per day (Kahn 1966; Hammond and Garfinkel 1969; Burns et al. 1997; Blanchard et al. 2000; Vardulaki et al. 2000).

Studies have demonstrated an association of cigarette smoking with prevalence of aortic aneurysm or aortic dilation, as determined by ultrasonography in cohorts of men and women, even after adjustment for a large number of known risk factors (Alcorn et al. 1996; Lee et al. 1997; Wilmink et al. 1999; Jamrozik et al. 2000; Lederle et al. 2001). The U.S. Preventive Services Task Force (2005) recommended a one-time screening by ultrasonography for abdominal aortic aneurysm among men aged 65 to 75 years who had ever smoked. Cigarette smoking has been associated with increased growth of abdominal aortic aneurysms (Brady et al. 2004). This finding suggests that more frequent monitoring of smokers for this condition is necessary. With increasing duration of abstinence from smoking, the risk of developing an abdominal aneurysm appears to slowly decline (Wilmink et al. 1999).

Peripheral Arterial Disease

Cigarette smoking and diabetes are well established as the major risk factors for PAD, and a strong dose-response relationship for smoking was observed even after adjustment for other CVD risk factors (Weiss 1972; Kannel and Shurtleff 1973; USDHHS 1983; Wilt et al. 1996; Price et al. 1999; Meijer et al. 2000; Ness et al. 2000). Data from the Framingham Heart Study demonstrated increased risk of PAD among both young and older male and female cigarette smokers after adjustment for other cardiovascular risk factors. In addition, this risk increased with the increase in the number of cigarettes smoked per day, and this result was statistically significant (Freund et al. 1993). The Framingham Offspring Study reported a similar finding (Murabito et al. 2002). Finally, researchers have observed a significantly higher rate of late arterial occlusion in patients who continued to smoke after peripheral vascular surgery than in those who stopped smoking (Wray et al. 1971; Ameli et al. 1989; Wiseman et al. 1989). Among smokers with claudication, progression to critical limb ischemia is reduced in those who stopped smoking (Jonason and Bergström 1987).

Pipes, Cigars, and Low-Tar Cigarettes

“Low-tar” or “light” cigarettes were designed to produce low machine-measured yields of tar and nicotine (NCI 2001). Design characteristics of low-tar cigarettes include increased ventilation and more rapid cigarette burn rate. By changing the way they smoke or the number of cigarettes smoked, persons who smoke these products can obtain as much nicotine as from “regular” or “full-flavored” cigarettes, thereby satisfying their addiction (USDHEW 1979; NCI 2001). Comprehensive reviews of this issue concluded that use of low-tar cigarettes has not resulted in meaningful reduction in the risk of CVD (NCI 2001; Stratton et al. 2001; Scientific Advisory Committee on Tobacco Product Regulation 2002; USDHHS 2004).

Compared with persons who smoke cigarettes, smokers who exclusively smoke pipes or cigars have lower risk for many smoking-related diseases (NCI 1998). Smoke from pipes and cigars contains the same toxic substances as cigarette smoke, but those who use a pipe or cigar usually smoke at lower intensity; observation indicates that they tend not to inhale the smoke, thus reducing their exposure to its toxic substances (USDHEW 1979; NCI 1998; Shanks et al. 1998). Most current cigar users are young males who often smoke less than one cigar daily (NCI 1998); no data on risk for this population are available. For older adults who regularly use cigars, particularly those who smoke more than one cigar per day or inhale the smoke, risk of CHD is modestly higher than that for nonsmokers (NCI 1998; Iribarren et al. 1999; Jacobs et al. 1999b; Baker et al. 2000). Studies have reported similar increases in risks for CHD and cerebrovascular disease for persons who smoke a pipe exclusively (Henley et al. 2004).

Summary

Cigarette smoking and involuntary exposure to cigarette smoke are major causes of CHD, stroke, aortic aneurysm, and PAD. The risk is seen both as an increased risk of acute thrombosis of narrowed vessels and as an increased degree of atherosclerosis in the blood vessels involved. The cardiovascular risks attributable to cigarette smoking increase with the number of cigarettes smoked and with the duration of smoking. However, risk is substantially increased even by exposure to low levels of cigarette smoke as with exposure to secondhand smoke or smoking a few cigarettes per day. Risks are not reduced by smoking cigarettes with lower machine-measured

yields of tar and nicotine. Smokers of only pipes or cigars seem to have lower risks of CVD than do cigarette smokers. However, cigarette smokers who switch to pipes or cigars often inhale the tobacco smoke and may not

experience the lower CVD risk of persons who primarily smoke a pipe or cigar. Stopping cigarette smoking and eliminating exposure to secondhand smoke rapidly and substantially reduce risks of various CVDs.

Secondhand Tobacco Smoke and Cardiovascular Disease

The 2006 Surgeon General's report on involuntary exposure to tobacco smoke (USDHHS 2006) and Barnoya and Glantz (2005) extensively reviewed risks of CVD among nonsmokers exposed to secondhand tobacco smoke. They found a causal relationship among both men and women between exposure to secondhand smoke and increased risks of CHD morbidity and mortality. Pooled RRs from meta-analyses indicated a 25- to 30-percent increase in risk of CHD from exposure to secondhand smoke. The study by Whincup and associates (2004), which was based on blood levels of cotinine in men, suggested a 50- to 60-percent increase in risk of CHD from exposure to secondhand smoke. The risk of acute MI appeared to decline rapidly after cessation of exposure to secondhand smoke, as evidenced by a decline in hospital admissions

for MI after smoke-free laws were put in place (Dinno and Glantz 2007; Lightwood and Glantz 2009; Meyers et al. 2009). As for stroke, the evidence was insufficient to infer a causal relationship between increased risk of CHD morbidity and mortality and exposure to secondhand smoke. Studies of the effects of secondhand smoke on subclinical vascular disease, particularly thickening of the walls of the carotid arteries, also suggest a causal relationship between exposure to secondhand smoke and atherosclerosis. As mentioned previously, the substantial CVD risk associated with involuntary exposure to cigarette smoke indicates that the risks estimated in most studies of active smoking are biased downward because the control groups generally included large numbers of persons with exposure to secondhand smoke.

Pathophysiology

This section on pathophysiology focuses primarily on mechanisms by which cigarette smoking may increase risk of CVD.

Cigarette Smoke Constituents and Cardiovascular Disease

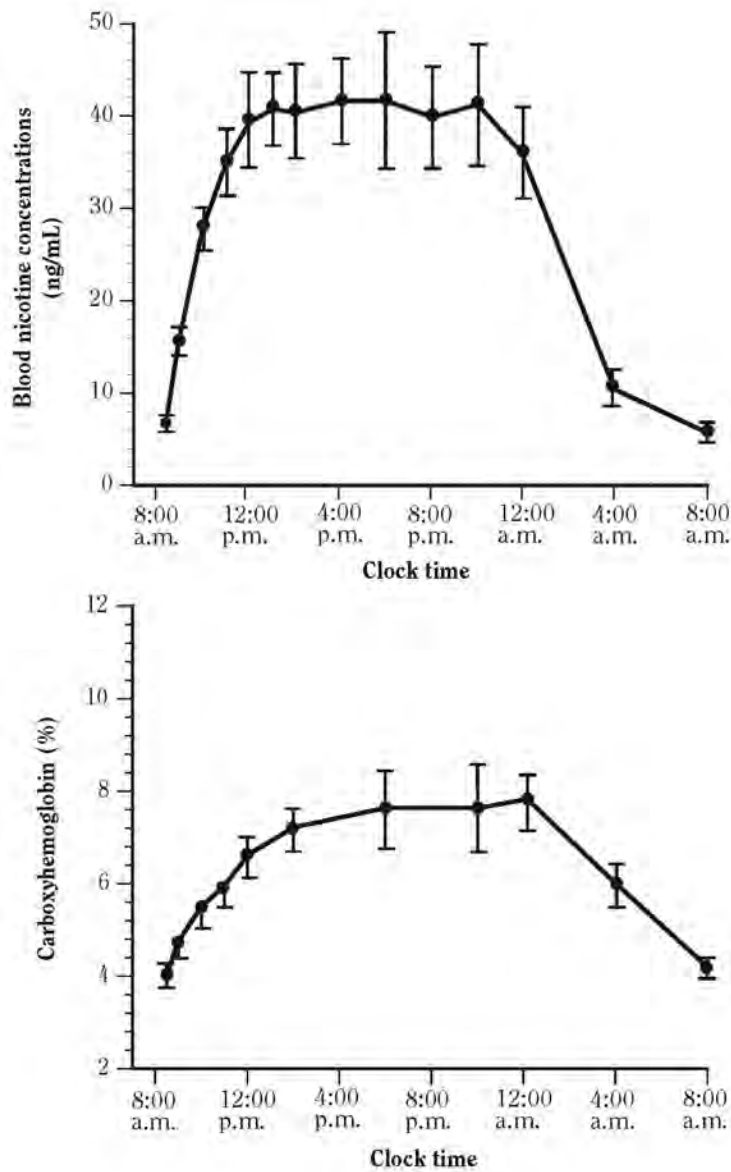
Three constituents of cigarette smoke have received the greatest attention as potential contributors to CVD: nicotine, carbon monoxide (CO), and oxidant gases. Some research also investigated the contributions of polycyclic aromatic hydrocarbons (PAHs), particulate matter, and other constituents of tobacco smoke to the pathophysiology of CVD including atherogenesis (Brook et al. 2004; Vermeylen et al. 2005; Bhatnagar 2006).

Nicotine, which is absorbed rapidly from cigarette smoke, was found in arterial blood levels of 40 to 100 ng/mL after each cigarette was smoked (Henningfield et al. 1993). The typical dose of nicotine systematically absorbed from each cigarette is 1 to 2 milligrams (mg). Although

plasma nicotine levels peaked sharply after each cigarette, trough values also rose during the first six to eight hours of regular smoking during the day (Benowitz et al. 1982a). This accumulation pattern was consistent with an elimination half-life for nicotine of two hours (Benowitz et al. 1982a). In persons who smoke regularly, venous plasma levels of nicotine reached a plateau in early afternoon and remained at that level until bedtime (Figure 6.4). Significant levels of nicotine were in the smoker's venous blood even on waking in the morning. Thus, these findings indicate that the regular smoker is exposed to significant levels of nicotine 24 hours per day.

Nicotine is a sympathomimetic drug that releases catecholamines both locally from neurons and systemically from the adrenal gland. In studies of the pharmacodynamics of nicotine, the intensity of its maximal effect was greater with more rapid delivery (Porchet et al. 1987). Pharmacodynamic studies also indicated that although tolerance to the effects of nicotine developed rapidly, tolerance was incomplete (Porchet et al. 1987). In one study, a constant intravenous infusion of nicotine increased the

Figure 6.4 Plasma nicotine and carboxyhemoglobin concentrations throughout a day of cigarette smoking



Source: Benowitz 2003. Adapted from Benowitz et al. 1982b with permission from Elsevier, © 2003.

Note: Mean (\pm standard error of measurement) blood nicotine and carboxyhemoglobin concentrations in cigarette smokers. Participants smoked cigarettes every half-hour from 8:30 a.m. to 11:00 p.m., for a total of 30 cigarettes per day. **ng/mL** = nanograms per milliliter.

heart rate even though nicotine levels in the blood were relatively low. As the infusion continued, the heart rate reached a plateau despite a progressive rise in blood levels of nicotine (Benowitz et al. 1982a). The same phenomenon was observed in comparisons of acceleration of heart rate with level of blood nicotine during regular cigarette smoking throughout the day (Benowitz et al. 1984).

In another study, heart rate measured by ambulatory monitoring was higher throughout the day when persons were smoking than when they were not smoking (Benowitz et al. 1984). The extent of elevation was independent of the blood level of nicotine absorbed from the cigarettes. The researchers concluded that the elevated heart rate reflected persistent stimulation of the sympathetic

nervous system, a possible contributing factor to CVD. Nicotine may also contribute to endothelial dysfunction, lipid abnormalities, and insulin resistance (Benowitz 2003).

CO is a major constituent of cigarette smoke. In regular smokers, carboxyhemoglobin levels average about 5 percent, compared with 10 percent or higher in heavy smokers (Benowitz et al. 1982b). These values compare with levels of 0.5 to 2 percent in nonsmokers, depending on exposure to automobile exhaust. Like nicotine levels, elevated carboxyhemoglobin levels persist for 24 hours a day in smokers (Figure 6.4).

CO exposure can aggravate ischemia and worsen symptoms in persons with vascular disease, although it is not clear that CO contributes directly to atherosclerosis (Benowitz 2003). CO binds avidly to hemoglobin, reducing the amount of hemoglobin available to carry oxygen and impeding release of oxygen by hemoglobin. In some studies, inhalation of CO at levels comparable to those in cigarette smokers reduced exercise tolerance in patients with angina pectoris, intermittent claudication, or COPD (Calverley et al. 1981; Allred et al. 1989). Another study reported that CO exposure in persons with obstructive coronary disease resulted in a greater degree of exercise-induced ventricular dysfunction and an increase in the number and complexity of ventricular arrhythmias during exercise (Sheps et al. 1990). Inhaling CO reduced the threshold for ventricular fibrillation in animals (DeBias et al. 1976).

Long-term CO exposure in smokers resulted in greater red blood cell mass and reduced the oxygen-carrying capacity of red blood cells, resulting in relative hypoxemia (Benowitz 2003). In response to hypoxemia, red blood cell masses increased to maintain the amount of oxygen needed by organs in the body. The increase in red blood cell mass increased blood viscosity and may contribute to hypercoagulation in smokers.

Cigarette smoke delivers a high level of oxidizing chemicals to smokers, including oxides of nitrogen and many free radicals from both the gas and tar phases of cigarette smoke (Church and Pryor 1985). Exposure to oxidant chemicals in smoke was associated with depletion of endogenous levels of antioxidants, manifested as lower blood levels of vitamin C in smokers than in nonsmokers (Lykkesfeldt et al. 2000). Cigarette smoking also was reported to increase levels of lipid peroxidation products in the plasma and urine of smokers (Morrow et al. 1995). Study results also indicated that oxidant stress contributes to several potential mechanisms of CVD, including inflammation, endothelial dysfunction, lipid abnormalities such as oxidation of low-density lipoprotein (LDL), and platelet activation (Burke and FitzGerald 2003).

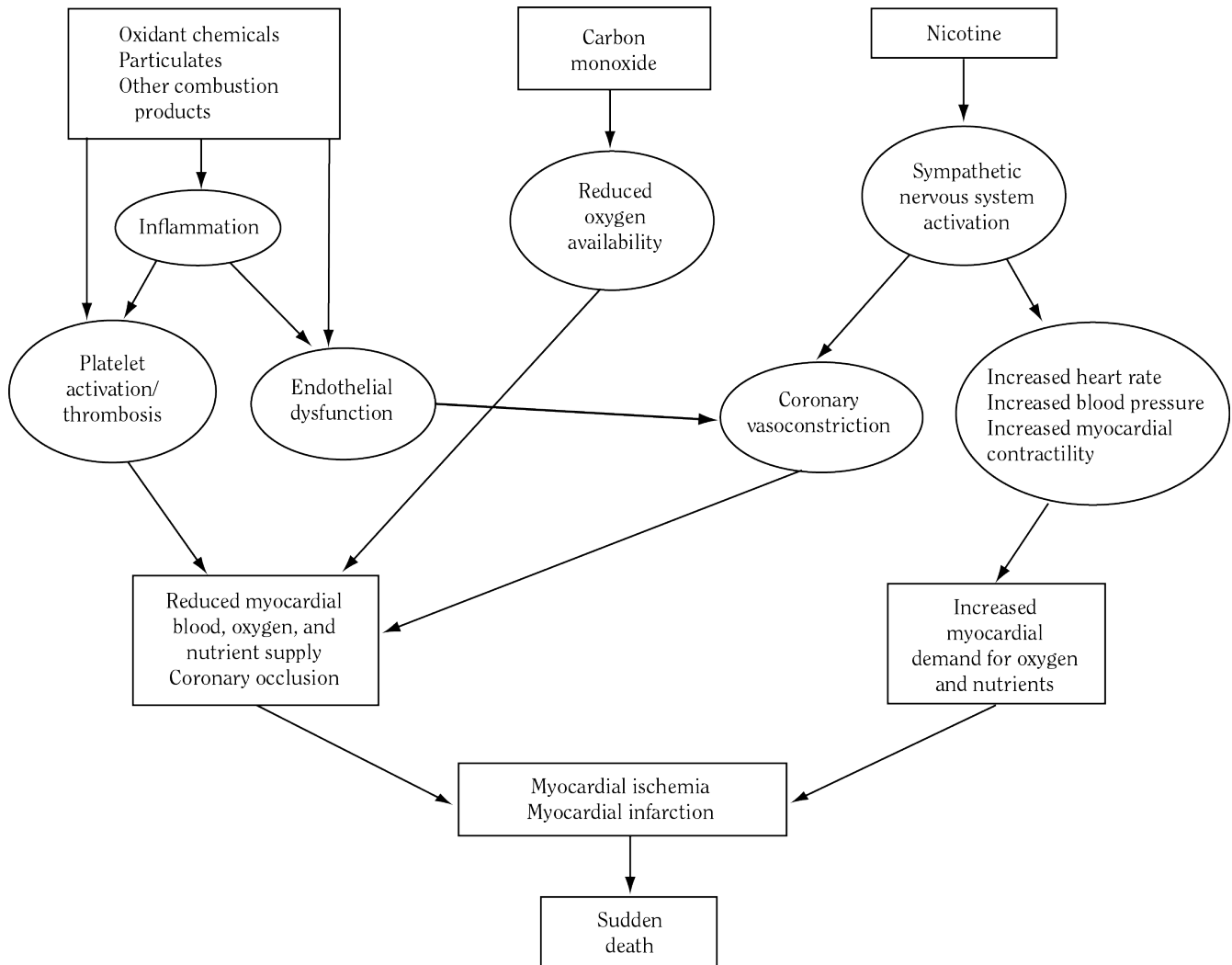
Acrolein, a reactive aldehyde produced by endogenous lipid peroxidation, is present at high levels in cigarette smoke. Acrolein binds covalently to form protein adducts, and acrolein-induced modification of proteins has been implicated in atherogenesis. Acrolein modifies apolipoprotein A-I (APO A-I), the major protein in HDL (Shao et al. 2005). HDL protects against atherosclerosis. Acrolein-protein adducts co-localize with APO A-I in macrophages in the intima of human atheromatous blood vessels (Szadkowski and Myers 2008).

Acrolein also oxidized thioredoxins 1 and 2 in endothelial cells. Thioredoxins are prominent antioxidant proteins that regulate the oxidation-reduction balance critical for normal cell function. These results suggest that oxidation of thioredoxins can result in dysfunction and death of endothelial cells, contributing to atherosclerosis. In addition, acrolein induces production of the enzyme cyclooxygenase-2 (COX-2) in human endothelial cells *in vitro* (Park et al. 2007). This finding is relevant because COX-2 is expressed in atherosclerotic lesions and may participate in atherogenesis. Acrolein may contribute to thrombogenicity in smokers by inhibiting antithrombin activity (Gugliucci 2007). Finally, acrolein induces hypercontraction in isolated human arteries and could contribute to smoking-induced coronary vasospasm (Conklin et al. 2006).

Cigarette smoke contains a number of metals, including aluminum, cadmium, copper, lead, mercury, nickel, and zinc. Metals in cigarette smoke catalyze the oxidation of cellular proteins (Bernhard et al. 2005). This reaction may lead to structural damage, endothelial dysfunction, and detachment of endothelial cells from the walls of blood vessels. Mixtures of metals and oxidants may be particularly damaging to endothelial cells. Cadmium levels are higher in serum of smokers, and cadmium accumulates in the aortic walls of smokers (Abu-Hayyeh et al. 2001). Epidemiologic evidence indicates an association between serum levels of cadmium and lead and CVD, including hypertension and MI (Abu-Hayyeh et al. 2001).

PAHs found in the tar fraction of cigarette smoke reportedly accelerated atherosclerosis in experimental animals. Weekly injections of benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene, at doses below those that produce tumors, increased development of atherosclerotic plaque in the aortas of cockerels (Penn and Snyder 1988). Similarly, inhaled butadiene, a component of the vapor phase of cigarette smoke, increased the amount of atherosclerotic plaque in the same animal model (Penn and Snyder 1996). The researchers speculated that one mechanism of atherogenesis is a mutation, followed by hyperproliferation of smooth muscle or other cells that may contribute to growth of atherosclerotic plaque.

Figure 6.5 Overview of mechanisms by which cigarette smoking causes an acute cardiovascular event



Source: Benowitz 2003. Reprinted with permission from Elsevier, © 2003.

Studies of the cardiovascular effects of smokeless tobacco may be informative for understanding the pathophysiology of smoking-induced CVD. Oral and nasal smokeless tobacco products have been used for centuries around the world (International Agency for Research on Cancer [IARC] 2007). Traditional smokeless tobacco products vary widely among countries; however, similar to Sweden, forms of oral snuff are the most common types of products used in the United States (Substance Abuse and Mental Health Services Administration 2009). These

products contain a large array of chemicals, including nicotine, nitrosamines, nitrosamine acids, PAHs, aldehydes, and metals (IARC 2007). A recent systematic review reported that studies from both the United States and Sweden showed an increased risk of death from MI and stroke related to the frequency and duration of use of smokeless tobacco products (Boffetta and Straif 2009). This review relied heavily (85–89 percent of the weight) on results of a large U.S. cohort study conducted in two waves between 1959–1971 and 1982–1988 and may

not represent risk associated with products currently marketed in the United States and Europe. As in cigarettes, nicotine is the principal alkaloid in smokeless tobacco products, and the concentrations of nicotine (mg/gram [g] tobacco) are similar between cigarettes and the types of oral snuff sold in the United States (Djordjevic and Doran 2009). An analysis comparing the effects of using oral snuff with those of smoking cigarettes provided insights into the role of nicotine versus the effects of other toxins from tobacco smoke on CVD and cardiovascular risk factors (Benowitz et al. 1988, 1989). In addition clinical trials of nicotine patches in patients with known CVD have not shown that transdermal nicotine increased cardiovascular risk (Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease 1994; Joseph et al. 1996). In the study of 3,094 middle-aged smokers with chronic obstructive lung disease, the U.S. Lung Health Study found no evidence of increased cardiovascular risk in subjects who quit smoking by using nicotine gum versus those who quit without use of nicotine gum (Murray et al. 1996). These studies and related evidence suggest that chemicals other than nicotine may contribute to the elevated risk of death from MI and stroke. In the INTERHEART study, the OR of acute MI was 2.23 among those who used only smokeless tobacco compared with those who used no tobacco. The OR was comparable to that of current cigarette smokers (OR = 2.95) compared with those who used no tobacco (Teo et al. 2006). In addition, the risk of acute MI among smokers who also used smokeless tobacco was the highest risk related to tobacco use (OR = 4.09), suggesting that some of the toxicants involved in the elevated cardiovascular risk could be contained in both tobacco smoke and smokeless products. Smokeless tobacco products have been found to have significant amounts of numerous other toxicants and carcinogens, particularly tobacco-specific nitrosamines as well as volatile aldehydes and PAHs (Stepanov et al. 2008). Additional research on these and other toxicants in smokeless tobacco, such as heavy metals like cadmium, is needed to understand the observed cardiovascular risks among users of smokeless tobacco products.

Mechanisms

Cigarette smoking produces acute myocardial ischemia by adversely affecting the balance of demand for myocardial oxygen and nutrients with myocardial blood supply (Figure 6.5). The increase in demand for oxygen in the myocardium is a consequence of nicotine stimulation of the sympathetic nervous system and the heart. Cigarette smoking acutely increases levels of plasma norepinephrine and epinephrine and enhanced 24-hour urinary excretion of these catecholamines (review by Benowitz and Gourlay 1997). Regular smoking increases the heart rate both in the short term (up to 20 beats per minute) and throughout the day (average increase, 7 beats per minute), as measured during ambulatory monitoring. Nicotine also increases heart rate, blood pressure, and myocardial contractility. These hemodynamic changes result in increases in myocardial work that in turn require increased myocardial blood flow.

In healthy persons, cigarette smoking increases coronary blood flow in response to increases in myocardial work. In smokers, the response in coronary blood flow to increased myocardial demand was impaired (i.e., reduced coronary vasodilatory reserve) (Czernin and Waldherr 2003). Cigarette smoking played a direct role by constricting coronary arteries through nicotine-mediated action on α -adrenergic receptors and by induction of endothelial dysfunction by nicotine and oxidizing chemicals (Nicod et al. 1984; Puranik and Celermajer 2003). In addition, oxidant chemicals contribute to platelet activation and thrombogenesis (Burke and FitzGerald 2003).

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

In addition to the mechanisms described in Figure 6.5, cigarette smoking has effects on inflammation, insulin sensitivity, and lipid abnormalities that most likely contribute to smoking-induced CVD.

Hemodynamic Effects

Blood Pressure and Heart Rate

In 1907, Erich Hesse published “The Influence of Smoking on the Circulation,” which documents his observations on the effects of smoking on heart rate and blood pressure (Hesse 1907). In most study participants, both heart rate and blood pressure increased immediately after smoking. Hesse observed a greater response in blood pressure after smoking in persons who smoked than in non-smokers. Speculating that the increases in blood pressure and heart rate reflected stimulation of the heart or nervous system, he instituted a rule prohibiting patients with a “heart weakness” from smoking, to avoid unnecessary strain and stress for the heart muscle. Many investigators confirmed Hesse’s observations on the hemodynamic effects of cigarette smoking (Deanfield et al. 1986; Czernin et al. 1995; Barutcu et al. 2004).

The positive chronotropic, inotropic, and blood pressure effects of smoking are explained by nicotine-induced activation of the sympathetic nervous system (review by Benowitz 2003). Nicotine promotes the release of epinephrine and norepinephrine from the adrenal medulla and terminal nerve endings, resulting in increased heart rate and greater contractility through stimulation of myocardial β_1 receptors. Peripheral vascular resistance increases through α -receptor mediated vasoconstriction that in turn increases blood pressure. Coronary β_2 and α_2 receptors are also stimulated: stimulation of β_2 receptors promoted vasodilation, and stimulation of α_2 receptors promoted vasoconstriction (Cryer et al. 1976; Benowitz 2003).

Cryer and colleagues (1976) elucidated the mechanisms behind observed hemodynamic changes during smoking. They observed more than a 150-percent increase in plasma epinephrine levels (from 44 to 113 picograms [pg]/mL) at 10 minutes after participants started to smoke a cigarette. Norepinephrine values increased to a smaller degree (from 227 to 315 pg/mL) at 12.5 minutes after the start of smoking. These increases were associated with significant increases in heart rate and blood pressure. Pretreatment with α -receptor blockers and β -receptor blockers had little effect on the increase in plasma levels of catecholamines, but increases in blood pressure and heart rate were eliminated. This study confirmed that smoking-induced increases in blood pressure and heart rate are attributable to adrenergic mechanisms.

The hemodynamic effects of cigarette smoking are mediated primarily by nicotine, although oxidizing chemicals in tobacco smoke also affect vascular function.

Intravenous nicotine, nicotine nasal spray, and nicotine chewing gum all increased the heart rate up to 10 to 15 beats per minute and raised systolic blood pressure by up to 5 to 10 millimeters of mercury (mm Hg), responses similar to the effects of cigarette smoking (Gourlay and Benowitz 1997). Nicotine increased cardiac output by increasing both heart rate and myocardial contractility. Different vascular beds express different types and ratios of adrenergic receptors. Therefore, not all vascular responses to nicotine or tobacco smoke are the same. For example, nicotine constricts some vascular beds, such as the skin, and cutaneous vasoconstriction explains the reduced temperature of the fingertip observed with administration of nicotine (Benowitz et al. 1982a). Conversely, nicotine appears to dilate other vascular beds, such as skeletal muscle (Diana et al. 1990). Vasodilation of skeletal muscle may partly result from the increase in cardiac output, although the release of epinephrine from nerve terminals may also contribute. The net result of increases in heart rate, blood pressure, and myocardial contractility is an increase in myocardial work, followed by increased myocardial blood flow.

Coronary Blood Flow

An important hemodynamic consequence of cigarette smoking is its effect on blood flow in the coronary arteries. Cigarette smoking acutely increased coronary blood flow by up to 40 percent, apparently a response to the increase in myocardial work (review by Czernin and Waldherr 2003).

In anesthetized dogs, coronary blood flow showed a biphasic response to nicotine. Initially, researchers hypothesized that increases in coronary blood flow—in the large coronary vessels as well as the smaller vessels—resulted from an increase in myocardial metabolic demand.

Cigarette smoking impairs the response of coronary blood flow to an increase in myocardial demand for oxygen; that is, it reduces the coronary vasodilatory flow reserve. Thus, the increase in coronary blood flow based on the level of myocardial work is less than would be expected in the absence of exposure to tobacco smoke. Considerable evidence indicates that cigarette smoking causes dysfunction of the coronary arterial endothelium (see “Endothelial Injury or Dysfunction” later in this chapter).

Cigarette smoking may also be associated with coronary vasoconstriction. Although cigarette smoking increases coronary blood flow in a person who does not have CHD, it may decrease coronary blood flow in the presence of coronary disease. Regan and colleagues (1960) measured coronary sinus blood flow in seven male volunteers with documented CHD before and after they smoked two cigarettes during a period of about 25 minutes; cardiac work increased by about 30 percent during smoking. Even so, in response to smoking, coronary blood flow fell in three patients, did not change in three patients, and increased in one patient. Similar paradoxical responses were observed after long-term smokers were exposed to cold by testing with cold pressors (Campisi et al. 1998). In the testing, the hand is immersed in ice water for one to two minutes. This painful procedure evokes a mixed adrenergic response involving coronary receptors α_1 and α_2 (vasoconstriction), β_2 (vasodilation), and myocardial β_1 (indirect coronary vasodilation). Endothelial α_2 receptors that promote indirect coronary vasodilation may also be involved. In healthy volunteers, cold-induced increases of about 30 percent in the product of heart rate and blood pressure were associated with appropriate and similar increases in blood flow. In contrast, smokers showed no measurable increases in blood flow in response to the cold. Campisi and colleagues (1998) ascribed this observation to coronary endothelial dysfunction.

Kaufmann and colleagues (2000) provided additional evidence for the association between smoking and endothelial dysfunction. Using quantitative positron emission tomography, they found that coronary microvascular function was abnormal in smokers but could be restored by infusion of vitamin C. Earlier, Zeiher and colleagues (1995) used quantitative coronary angiography to measure the effects of long-term smoking on the diameter of the coronary artery at study entry, during flow-mediated coronary vasodilation, and after intracoronary administration of nitroglycerin. The study population consisted of patients with or without mild disease of the left anterior descending coronary artery and no other cardiac problems. Flow-mediated vasodilation was markedly blunted in long-term smokers. In a study of smokers with CHD, cigarette smoking increased coronary vascular resistance, an effect that can be blocked by α -adrenergic blockers. This finding indicates that the mechanism of increased coronary artery resistance is at least partly due to stimulation of the sympathetic nervous system by nicotine.

Intracoronary measurements by Doppler ultrasonography demonstrated that cigarette smoking constricts epicardial arteries and increases total coronary vascular resistance. This result indicates that impairment of coronary blood flow by cigarette smoking results from constriction of both epicardial and resistance blood vessels.

In one study, after pretreatment with calcium-channel-blocking agents or nitroglycerin, cigarette smoking increased coronary blood flow in patients with CHD who had manifested no increase after cigarette smoking alone (Winniford et al. 1987). This finding that coronary vasodilator drugs, which block chemically mediated vasoconstriction, permit the usual increase in coronary blood flow in response to increased myocardial work supports the hypothesis that cigarette smoking directly produces coronary vasoconstriction. In another study, chewing 4 mg of nicotine gum by healthy nonsmokers blunted the increase in coronary blood flow that occurs with increased heart rate produced by cardiac pacing (Kajiser and Berglund 1985). This result confirmed that even low doses of nicotine can directly constrict coronary arteries in humans.

Another study found that nicotine worsened myocardial dysfunction in "regionally stunned" ischemic myocardium of anesthetized dogs (Przyklenk 1994). In a placebo-controlled experiment, transient ischemia was induced in dogs by clamping the left anterior descending coronary artery for 15 minutes. Segmental shortening of the myocardium recovered to only 29 percent of the preischemic baseline values in dogs pretreated with nicotine, compared with 54 percent 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.

In patients with vasospastic angina, cigarette smoking is associated with increased occurrence of the condition and a poorer response to medication compared with the response in nonsmokers (Caralis et al. 1992). The researchers observed that cigarette smoking during coronary angiography (cardiac catheterization) produced an acute coronary vasospasm.

Schelbert and colleagues (1979) extensively studied the relationship of coronary vasomotion, endothelial function, and myocardial blood flow to potential reversibility of coronary vasomotor abnormalities. They adopted a noninvasive approach by measuring blood flow with positron emission tomography using ^{13}N ammonia: (1) at rest during testing with cold pressors to probe endothelium-dependent coronary vasomotion and (2) during dipyridamole-induced hyperemia to assess endothelium-independent coronary vasomotion. Using this protocol, Czernin and associates (1995) investigated the effects of short- and long-term smoking on myocardial blood flow and flow reserve in smokers. The investigators sought to determine whether abnormalities in coronary vasomotion in response to cold could be reversed in response to L-arginine infusion (Campisi et al. 1998, 1999). The findings indicated that short-term and long-term smokers had normal coronary vasodilatory capacity. Short-term smoking, however, reduced flow reserve in both short- and

long-term smokers. Also, exposure of long-term smokers to cold resulted in abnormal blood flow. The smoking-associated abnormalities in vasomotion were restored by intravenous L-arginine, and this result further implicates the endothelium as the target of toxic substances contained in cigarette smoke. Campisi and colleagues (1999) quantified myocardial blood flow during exposure to cold while L-arginine, the substrate of ENOS, was infused intravenously for 45 minutes at a dose of 30 g as 10 percent arginine hydrochloride. This infusion produced significant improvement in responses of myocardial blood flow to cold. In addition to active smoking, exposure to secondhand smoke for 30 minutes abruptly reduces coronary blood flow velocity in nonsmokers, as assessed by echocardiography (Otsuka et al. 2001).

Smoking and the Endothelium

Endothelial Injury or Dysfunction

Endothelial injury and dysfunction are thought to contribute to the initiation of atherogenesis and to have a major role in acute cardiovascular events. Cigarette smoking produces endothelial injury and dysfunction in both peripheral and coronary arteries. Other cardiovascular risk factors such as hypercholesterolemia, diabetes, and hypertension also produce endothelial dysfunction.

The healthy endothelium is a diaphanous film of tissue that invests the luminal surface of all blood and lymphatic vessels. In larger-conduit vessels, the endothelium forms a monolayer between the circulating blood and the vessel wall. The tissue capillaries, which are the smallest conduits for blood and lymphatic flow, are composed exclusively of endothelial cells. Because of the ubiquity of endothelial cells, the surface area of the endothelium in a human weighing 70 kilograms (kg) is 1,000 to 4,000 square meters—equivalent to two to four tennis courts—with a weight of approximately 1 kg (Wolinsky 1980). The endothelium produces a variety of paracrine factors that regulate vascular homeostasis, including proteins, lipids, and small molecules that (1) can relax or activate the underlying vascular smooth muscle, (2) regulate the interaction of the vessel wall with circulating blood elements, and (3) modulate vessel structure (Aird 2005). In healthy persons, the endothelium primarily exerts a vasodilator influence that reduces vascular resistance and maintains blood flow. The endothelium maintains the blood's fluidity by elaborating anticoagulant substances and

Summary

Cigarette smoking impairs the vascular endothelial function and activates the sympathetic nervous system. These effects can result in inappropriate reduction in or failure to increase coronary blood flow in response to increases in myocardial demand. Together with long-term atherosclerotic damage from smoking, these effects contribute to ischemic cardiac events. Coronary endothelial dysfunction clearly increases the risk for cardiovascular events. The smoking-induced alterations in vasomotor function appear to be substantially reversible, which underscores the importance of smoking cessation programs and policies to promote a smoke-free environment.

generally resists adherence of platelets and infiltration of immune cells.

Regeneration of Endothelium

With aging, the normal functioning of the endothelium requires replacement of apoptotic or injured cells. Normally, the turnover of endothelial cells is low, on the order of 0.1 percent of the cells undergoing mitosis at any time (Wright 1972). The rate of endothelial turnover increases, however, in areas of disturbed flow (bends, branches, or bifurcations of blood vessels). The length of chromosome telomeres documents that endothelial aging occurs more rapidly in these areas (Chang and Harley 1995). Furthermore, the accelerated aging in these areas may lead to focal senescence, which is demonstrated by impaired endothelium-dependent vasodilation (McLenachan et al. 1990).

Persons who smoke may have impaired ability to regenerate the endothelium. The endothelial monolayer is regenerated in part from circulating endothelial progenitor cells derived from bone marrow, and the supply of these cells may be a key determinant of endothelial health. The number of circulating endothelial progenitor cells, which is estimated by ex vivo colony counts or by analysis using fluorescence-activated cell sorting, is directly associated with the ability of the endothelium to induce vasodilation (Hibbert et al. 2003; Hill et al. 2003). Smokers have reduced numbers of circulating endothelial progenitor

cells and impaired endothelium-dependent vasodilation (Vasa et al. 2001, Hill et al. 2003). In addition, smoking cessation was associated with a rebound in the number of circulating endothelial progenitor cells and improvement in endothelium-dependent vasodilation (Moreno et al. 1998; Kondo et al. 2004).

Endothelial Dysfunctions

A variety of endothelial dysfunctions may contribute to disorders of vessel tone and structure that precede clinical vascular disease. Cardiovascular risk factors such as hypercholesterolemia, hypertension, diabetes, and use of tobacco cause endothelial aberrations long before clinical vascular disease becomes evident. Endothelial dysfunction is the first step in vascular disease, because it leads to vascular inflammation, cell proliferation, and thrombosis, which contribute to progression of vascular disease.

Endothelial generation of adhesion molecules increases in smokers, as evidenced by higher plasma levels of soluble adhesion molecules (Blann et al. 1997, 1998). These molecules include soluble forms of the vascular cell adhesion molecule (sVCAM) and the intercellular adhesion molecule (sICAM). The soluble adhesion molecules, which are shed from the endothelium, reflect the increased endothelial production of these adhesion molecules in the context of vascular inflammation. Endothelial adhesion molecules are required for adherence to blood leukocytes and their infiltration into the vessel wall (Gimbrone 1995). The increased elaboration of adhesion molecules is an endothelial dysfunction that promotes leukocyte infiltration, vascular inflammation, and progression of atherosclerosis. Studies have associated elevated levels of either sVCAM or sICAM with increased risk of cardiovascular events (Blankenberg et al. 2001).

Smoking also impairs the ability of the endothelium to resist thrombosis. Compared with nonsmokers, smokers have higher levels of von Willebrand factor protein (MacCallum 2005) and tissue factor (Matetzky et al. 2000; Sambola et al. 2003), which may be generated by the endothelium. Tissue factor activates the coagulation cascade, and von Willebrand factor protein mediates adherence of platelets to the vessel wall (MacCallum 2005). Furthermore, study findings indicate that smoking impairs capacity to lyse the thrombus that is formed. Plasma levels of tissue plasminogen activator (tPA), a thrombolytic protein produced by the endothelium, are reduced in smokers (Newby et al. 2001). In contrast, smoking increases levels of plasminogen activator inhibitor-1

(PAI-1) (Simpson et al. 1997). By interfering with the function of tPA, PAI-1 reduces thrombolytic capacity (MacCallum 2005). Imbalance in thrombolytic capacity attributable to higher PAI-1 values or reduction in tPA levels is associated with occurrence of adverse cardiovascular events.

The healthy endothelium elaborates vasodilator substances such as nitric oxide (NO), prostacyclin, atrial natriuretic peptide, endothelium-derived hyperpolarizing factor, and adrenomedullin (Chen and Burnett 1998; Busse and Fleming 2003; Brain and Grant 2004). In doing so, the healthy endothelium increases the diameter of the blood vessels and reduces resistance to blood flow. When the endothelium becomes diseased, synthesis and bioactivity of the vasodilators are reduced, and the balance tips in favor of endothelium-derived vasoconstrictors such as endothelin and thromboxane (Vanhoutte et al. 2005). This derangement in endothelial function has clinical consequences. Because vasodilator function is impaired, coronary vascular resistance increases, and ischemia can result. Furthermore, endothelial vasodilator dysfunction in the coronary arteries of humans is associated with reversible myocardial perfusion defects, which are associated with other vascular abnormalities (Hasdai et al. 1997b). These abnormalities include expression of adhesion molecules, adherence and infiltration of leukocytes, and proliferation of smooth muscle cells.

Most of the endothelium-derived vasodilators also oppose key processes involved in atherogenesis (cell adhesion, proliferation, and inflammation) (Cooke and Dzau 1997a,b). Thus, by reducing the generation or bioactivity of endothelial vasodilators, exposure to tobacco can accelerate atherosclerosis. This mechanistic explanation for tobacco-related CVD is supported by the finding that dysfunction of endothelial vasodilators is an independent predictor of vascular events (Schächinger et al. 2000; Suwaidi et al. 2000; Gokce et al. 2003). The role of these mechanisms involving NO is vascular protection, which is impaired by exposure to tobacco.

Nitric Oxide and Vascular Homeostasis

NO induces vasodilation by stimulating soluble guanylate cyclase to produce cyclic guanosine monophosphate (Ignarro et al. 1984). NO, which has a short half-life, avidly interacts with sulfhydryl-containing proteins, heme proteins, and oxygen-derived free radicals. By virtue of its

ability to nitrosylate proteins, NO may change their activity or behavior (Hess et al. 2005). The significant increase in vascular resistance induced in animals and humans exposed to pharmacologic antagonists of ENOS reflects the physiological importance of this endothelium-derived vasodilator (Rees et al. 1989; Vallance et al. 1989).

Endothelium-derived NO also inhibits adherence of platelets and leukocytes to the vessel wall (Kubes et al. 1991; Tsao et al. 1994). This effect is mediated partly by activation of cyclic guanosine monophosphate and phosphorylation of intracellular signaling proteins such as vasodilator-stimulated phosphoprotein (Smolenski et al. 1998). In addition, NO suppresses expression of adhesion molecules and chemokines that regulate endothelial interactions with circulating blood elements (Tsao et al. 1996, 1997). These observations suggest that NO is an endogenous antiatherogenic molecule. Impairment of *ENOS* contributes to the pathologic alterations in vascular reactivity and structure observed in atherosclerosis (Cooke and Dzau 1997a,b). The pharmacologic inhibition or genetic deficiency of *ENOS* inhibits endothelium-dependent vasodilation, impairs blood flow in tissues, and raises blood pressure (Huang et al. 1995; Kielstein et al. 2004). Furthermore, NO deficiency promotes adherence to and intimal accumulation of mononuclear cells and accelerates formation of lesions in animal models of atherosclerosis (Kuhlencordt et al. 2001). In contrast, enhancing production of NO in the vessel wall slows or even reverses atherogenesis and restenosis (Cooke et al. 1992; von der Leyen et al. 1995; Candipan et al. 1996). NO is a survival factor for endothelial cells, and it induces apoptosis of macrophages and proliferation of vascular smooth muscle cells (Wang et al. 1999).

Certain polymorphisms of the *ENOS* gene predict development of CHD (Ichihara et al. 1998; Tsukada et al. 1998; Yoshimura et al. 1998). The *ENOS* gene *GLU298ASP* polymorphism is more prevalent in patients with variant angina, essential hypertension, and acute MI (Hibi et al. 1998; Miyamoto et al. 1998; Shimasaki et al. 1998; Yoshimura et al. 1998). Intriguingly, this polymorphism is associated with greater sensitivity to the effects of smoking on endothelial vasodilator function. Young men who are carriers of the *ENOS* **ASP298* allele have increased susceptibility to smoking-associated reduction in endothelial function (Leeson et al. 2002). Similarly, a quadruple repeat of a sequence of 27 base pairs in *intron 4 of the *ENOS* gene (allele **a*) is associated with increased risk of CHD and acute MI (Ichihara et al. 1998). Smokers who are homozygous for the *ENOS* allele **a* are at risk for more severe CHD than are those who are not homozygous (Wang et al. 1996).

Endothelium-Dependent Vasodilation

The effect of exposure to tobacco on endothelium-dependent vasodilation in humans was assessed by observing its effect on flow-mediated vasodilation. As blood flow through a vessel is increased, the vessel relaxes. In animal models, this flow-mediated vasodilation was abolished by removing the endothelium (Pohl et al. 1986). When a pharmacologic antagonist of ENOS was used, flow-mediated vasodilation in the rabbit iliac artery depended on the endothelial release of NO (Cooke et al. 1991). Celermajer and colleagues (1992) used duplex ultrasonography to record flow-mediated vasodilation of the brachial artery in response to hyperemic vasodilation of the forearm. The investigators induced vasodilation by using a blood pressure cuff inflated to suprasystolic pressures to transiently occlude blood flow in the forearm. Joanides and colleagues (1995) extended this finding by showing that flow-mediated vasodilation of the brachial artery could be abolished by pharmacologic antagonism of ENOS. Subsequently, numerous studies used this approach to document impairment of flow-mediated, endothelium-dependent vasodilation in smokers and in persons exposed to secondhand smoke (Celermajer et al. 1993, 1996; Barua et al. 2001). Researchers also observed that tobacco use impaired endothelium-dependent vasodilation in the coronary microcirculation. Intracoronary infusion of acetylcholine induced vasodilation that was partly attributable to release of NO, and this response was blunted in persons who smoked (Kugiyama et al. 1996).

Impairment of Endothelium-Dependent Vasodilation

Many factors contribute to the ability of tobacco to impair endothelial function. Tobacco use adversely affects the ENOS pathway. Exposure of cultured endothelial cells derived from human coronary arteries or umbilical veins to sera from smokers reduced expression and activity of ENOS (Barua et al. 2001, 2003). The researchers attributed this effect partly to the oxygen-derived free radicals in tobacco smoke. In addition, the half-life of NO was markedly shortened by oxidative stress (Rubanyi and Vanhoutte 1986).

Superoxide anion reacts avidly with NO to form a peroxynitrite (ONOO⁻) anion, which itself is a highly reactive free radical (Beckman and Koppenol 1996). Other sources of free radicals that may inactivate NO and

impair endothelial vasodilator function include activated leukocytes, xanthine oxidase, the mitochondrial electron-transport chain, and uncoupling of ENOS itself (Heitzer et al. 2000; Barua et al. 2003; Kayyali et al. 2003; Sydow and Münzel 2003; Guthikonda et al. 2003). Investigators postulated that this uncoupling occurs when amounts of the NOS cofactor tetrahydrobiopterin or the NO precursor L-arginine are insufficient. These conditions involve transfer of electrons from ENOS to oxygen and thus formation of a superoxide anion.

Oxidative stress also impairs the NOS pathway by increasing accumulation of asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of ENOS produced by all cells during degradation of methylated nuclear proteins (Vallance et al. 1992; Tran et al. 2003). Most of the ADMA produced is degraded by the enzyme dimethylarginine dimethylaminohydrolase. Oxidative stress impairs the activity of this enzyme and leads to accumulation of ADMA and suppression of ENOS (Cooke 2004).

Blood levels of antioxidant vitamins are lower than normal in smokers, reflecting endogenous consumption of these vitamins in response to ongoing oxidant stress (Lykkesfeldt et al. 2000). Administration of vitamin C reverses the impairment of endothelium-mediated vasodilation in smokers, a finding consistent with an oxidant mechanism of endothelial dysfunction (Heitzer et al. 1996).

Nicotine itself may injure endothelial cells. Studies showed that in levels similar to those found in the blood of cigarette smokers, nicotine altered structural and functional characteristics of cultured vascular smooth muscle and endothelial cells (Csonka et al. 1985; Thyberg 1986). In one study, oral nicotine administered to rats to achieve blood levels comparable to those in human smokers produced myointimal thickening of the aorta after an experimental injury (denudation of the endothelium with a balloon catheter) (Krupski et al. 1987). The excessive myointimal thickening in nicotine-treated animals is consistent with persistent injury to endothelial cells. Studies reported increased numbers of circulating endothelial cells in the venous blood, reflecting endothelial injury, and decreased platelet aggregate ratios, reflecting platelet aggregation in persons who had never smoked but who, for experimental purposes, smoked cigarettes containing tobacco (Davis et al. 1985). These results were not observed in nonsmokers who smoked cigarettes that did not contain tobacco. These findings further support a role for nicotine in injury to endothelial cells.

Nicotine may influence endothelial function in other ways. In studies of cultured endothelial cells, nicotine enhanced release of the basic fibroblast growth factor

and inhibited production of transforming growth factor β_1 (Villablanca 1998; Cucina et al. 1999). Nicotine also increased DNA synthesis, mitogenic activity, and endothelial proliferation. Nicotine has been shown to induce endothelial dysfunction (Chalon et al. 2000; Sarabi and Lind 2000; Neunteufl et al. 2002).

Pathologic Angiogenesis

Another endothelial function influenced by exposure to tobacco is development of new blood vessels (angiogenesis). Angiogenesis requires activation of endothelial cells by an angiogenic cytokine, followed by endothelial cell proliferation and migration and the formation of tubes. Exposure to secondhand smoke promotes tumor angiogenesis and growth (Zhu et al. 2003). Human lung cancer cells implanted in a subcutaneous or orthotopic location grew more rapidly in mice when they were exposed to secondhand tobacco smoke. Furthermore, these mice had higher plasma levels of vascular endothelial growth factor, and capillary density in their tumor nodules was greater than that in control mice. Mecamylamine, an antagonist of the nicotinic acetylcholine receptor (nAChR), abolished the effects of exposure to secondhand smoke. These observations indicate that secondhand smoke increases tumor angiogenesis and growth, at least partly through a nicotine-mediated mechanism.

Researchers observed the effect of nicotine in promoting pathologic angiogenesis in numerous murine models of tobacco-related diseases, including lung cancer, atherosclerosis, and retinopathy (Heeschen et al. 2001, 2002; Natori et al. 2003; Shin et al. 2004; Suñer et al. 2004). Tumor angiogenesis was required for tumor growth, and correspondingly, promotion of tumor angiogenesis accelerated tumor growth (Folkman 2003). Conversely, antiangiogenic agents inhibit progression of cancer and are now approved as treatment for some advanced human malignant diseases (Jain 2005). The effect of nicotine on promotion of tumor angiogenesis may be attributable to a direct effect on endothelial cells. In clinically relevant levels, nicotine promoted endothelial processes that may be involved in tumor angiogenesis. At these doses, nicotine promoted survival, proliferation, and migration of endothelial cells (Heeschen et al. 2001, 2002). Nicotine also induced elaboration and release of angiogenic factors, including NO, prostacyclin, vascular endothelial growth factor, and fibroblast growth factor (Carty et al. 1996; Heeschen et al. 2001a; Lane et al. 2005). These effects of nicotine were mediated by nAChRs on the endothelium (Heeschen et al. 2002). Conversely, pharmacologic inhibition or genetic deficiency of endothelial

nAChRs reduced angiogenic response to nicotine. A variety of human lung cancer cells synthesized acetylcholine or expressed nAChRs. Nicotine increased growth of these cells *in vitro*, but this effect was inhibited by antagonists of the nAChRs (Schuller 2002).

The importance of pathologic angiogenesis in growth of tumors is well known. Less widely recognized, however, is the role of neovascularization in progression of atherosclerotic plaque. Large atherosclerotic plaques in human coronary arteries are well vascularized by microvessels originating from the vasa vasorum (Barger et al. 1984). In mice with hypercholesterolemia, growth of atheroma can be inhibited by antiangiogenic agents, and in the same murine models, nicotine promoted neovascularization of plaque and its progression in the aorta (Heeschen et al. 2001; Moulton et al. 2003). The effect of nicotine in increasing neovascularization and progression of plaque may partially explain increased risk of atherosclerotic disease in persons who smoke.

Similarly, in a model of age-related macular degeneration in mice, nicotine stimulated retinal neovascularization (Suñer et al. 2004). This effect was antagonized by hexamethonium, another antagonist of nAChRs. In a clinical study, the most virulent form of age-related maculopathy is associated with retinal neovascularization that contributes to visual deterioration, and tobacco smokers are at greater risk of age-related macular degeneration than are nonsmokers (Christen et al. 1996; Seddon et al. 1996). Thus, a variety of tobacco-related diseases are characterized by pathologic neovascularization, an effect that may be promoted by nicotine.

Notwithstanding nicotine's effect as a promoter of neovascularization, long-term exposure to tobacco may impair therapeutic angiogenesis. In a murine model of hindlimb ischemia, short-term exposure to nicotine paradoxically increased capillary density and improved regional blood flow in the ischemic hindlimb (Heeschen et al. 2001, 2003). However, long-term exposure to nicotine for 16 weeks (about one-third of the life span of a mouse)

before induction of ischemia obliterated angiogenic response to nicotine (Konishi et al. 2010).

The relevance of animal models for research on nicotine and angiogenesis to human smokers is not clear. It is important to differentiate studies that show effects of pure nicotine from those in which the exposure is to tobacco smoke. In mice, effects of nicotine on angiogenesis depended on release of NO, but the net effect of smoking in humans seems to be impaired release of NO. Also, most studies on angiogenesis involve short-term administration of nicotine, although tolerance to the effects of nicotine may develop with long-term use.

Inhibition of ACE normalized impaired bradykinin-mediated, endothelium-dependent venodilation in smokers (Chalon et al. 1999). Furthermore, coronary vasomotor responses to acetylcholine in patients with CHD improved in response to the ACE inhibitor quinapril to a much greater extent in smokers than in nonsmokers (Schlaifer et al. 1999). ACE inhibitors have an antioxidant activity, which could contribute to the clinical benefit in smokers.

Summary

The endothelium, a delicate monolayer of cells that invests all blood vessels, is a major regulator of vascular reactivity and structure. Healthy endothelium maintains vascular homeostasis by promoting fluidity of the blood, vasodilation, and relaxation of the underlying vascular smooth muscle. Endothelial dysfunction regularly accompanies and promotes vascular disease. Endothelial vasodilator dysfunction is an independent risk factor for major adverse cardiovascular events and mortality. Active smoking and involuntary exposure to cigarette smoke injure endothelial cells and impair endothelial vasodilation. Thus, each type of exposure to tobacco or tobacco smoke contributes to the development of CVD.

Thrombogenic Effects

This section on thrombogenic effects reviews the state of knowledge of mechanisms by which smoking or secondhand smoke exposure may predispose a person to thrombosis, a pathologic reaction that commonly results in smoking-related MI or stroke. Smoking-mediated thrombosis appears to be a major factor in the pathogenesis of acute cardiovascular events.

Epidemiologic evidence indicates that cigarette smoking increases risk of acute MI and sudden death more than it increases risk of angina pectoris. Researchers hypothesize that risk of acute MI and sudden death is mediated by thrombosis, whereas angina is mediated primarily by hemodynamic factors. Successful revascularization in patients with MI after treatment with

thrombolysis is more likely in smokers than in nonsmokers (Bowers et al. 1996). At the time of MI, smokers are younger and have fewer cardiac risk factors and less severe underlying coronary disease than do nonsmokers (Metz and Waters 2003). Enhanced thrombosis superimposed on less severely stenotic arteries best explains these observations. In men who died suddenly, a history of cigarette smoking was significantly more likely when pathologic examination showed acute thrombosis (75 percent of cases) than when the finding was plaque with no thrombosis (41 percent) (Burke et al. 1997). Conversely, stable plaque with no thrombosis was the more common finding in nonsmokers.

Thrombosis occurs when fibrinogen is converted to fibrin, a process involving interaction of platelets, blood-borne proteins, endothelial cells, and subendothelial vascular tissue. An endogenous antithrombotic mechanism involves these same components. Imbalance in these pathways results in predisposition to thrombosis. Virchow's triad, first described in 1856 and modified by Aschoff in 1924, provides a framework for risk factors for thrombosis that is still valid. These authorities described the cardinal risk factors as "alterations in blood coagulation," "alterations in blood flow," and "alterations in the blood vessel wall."

Alterations in Blood

Blood contains platelets, red blood cells, and leukocytes suspended in plasma. Plasma in turn contains a variety of coagulation proteins and lipids that also contribute to the clotting process. Smokers tend to develop MI at a lower burden of atheroma than do nonsmokers. This finding suggests a greater role for formed elements of blood or for cardiac electrical instability in cardiovascular events in smokers.

Platelets

Platelets, although only a minor component of the solid phase of blood, are critical to the coagulation process and are important mediators of the impact of smoking on cardiovascular outcomes (Figure 6.6).

Turnover and Activation

Studies have reported that sudden cardiac death is 2.5 times higher in smokers than in nonsmokers (Kannel et al. 1984; Goldenberg et al. 2003). Research findings broadly implicated activation of platelets and subsequent focal ischemia in sudden cardiac death among smokers. The turnover of platelets is accelerated in cigarette smokers (Fuster et al. 1981). Researchers related the

number of newly formed reticulated platelets, rather than absolute platelet count, to incidence of thrombotic events (Rinder et al. 1998).

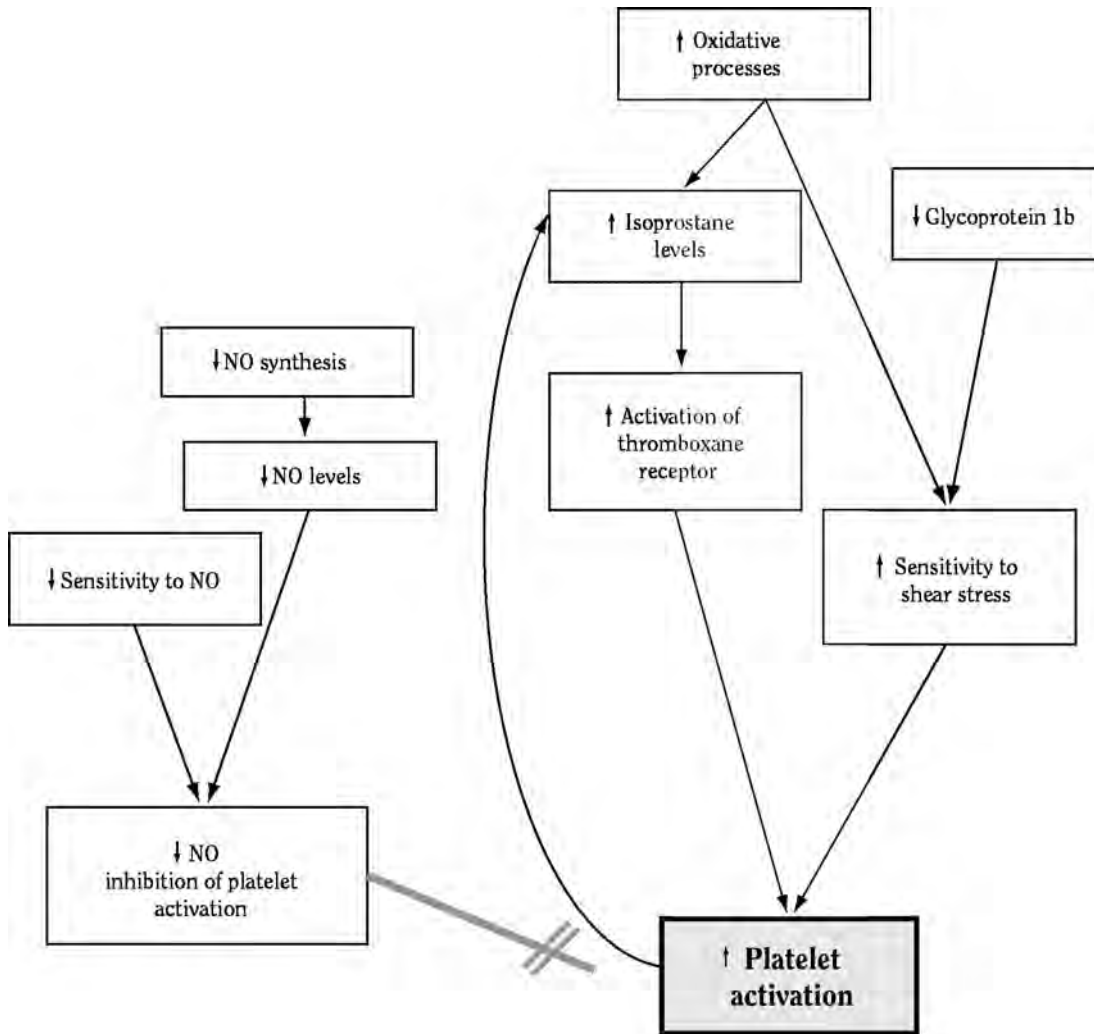
Urinary excretion of thromboxane metabolites (TxMs), such as 2,3-dinor thromboxane B₂ (TxB₂) and 11-dehydro TxB₂, which are markers of platelet activation *in vivo*, increases in smokers in a dose-dependent manner (Murray et al. 1985). Studies demonstrated increases in levels of urinary TxM among smokers who were monozygotic twins but divergent for smoking behaviors (Lassila et al. 1988). These increases were also observed in young Swedish army recruits who smoked but had no apparent vascular disease (Wennmalm et al. 1991). Studies also showed that mainstream and sidestream smoke directly promoted platelet activation and enhanced activation induced by shear stress (Rubenstein et al. 2004).

Elevated levels of TxM observed in persons who smoke decreased substantially within days of smoking cessation, although they did not reach the levels found in nonsmokers (Rangemark et al. 1993; Saareks et al. 2001). In an *ex vivo* study, platelets from smokers showed greater aggregation than those from nonsmokers (Takajo et al. 2001). A decline in platelet aggregation during 14 days of abstinence from smoking was reversed rapidly after smoking was resumed (Morita et al. 2005). *Ex vivo* aggregability, however, is a crude index of *in vivo* platelet activation and aggregation. Some studies reported diminished *ex vivo* aggregability in smokers. This finding suggests that partial activation *in vivo* resulted in the harvest of a less responsive subset of platelets for study *ex vivo*. Increased levels of urinary TxMs in smokers may be attributable to activation of both platelets and macrophages. Low-dose aspirin, which inhibits COX activity in platelets, substantially depressed the increment of TxM in smokers, leading investigators to hypothesize that TxM was principally derived from the activity of platelet COX-1 rather than macrophage COX-2 (Nowak et al. 1987; McAdam et al. 2005).

Generation of Nitric Oxide

Platelets constitutively express ENOS. Although platelet-derived NO is a modest inhibitor of platelet activation *in vitro*, it may be critical to inhibit recruitment of platelets to a growing thrombus (Freedman et al. 1997). Aggregating platelets obtained from patients with acute coronary syndromes produced less NO than did those from patients with stable angina (Freedman et al. 1998). Such findings must be interpreted with caution, however, because results reflect *in vivo* platelet activity (see "Turnover and Activation" earlier in this chapter). In one study, levels of platelet-derived NO were lower in smokers than in nonsmokers (Takajo et al. 2001). This

Figure 6.6 Potential sites of actions and mechanisms of effects of smoking on platelets



Note: Smoking decreases NO-mediated inhibition of platelet activation and increases platelet activation through oxidative stress and other mechanisms. **NO** = nitric oxide.

finding was associated with lower levels of intraplatelet-reduced glutathione—a marker of oxidative stress and increased platelet aggregation. In another study, both the platelet-derived release of NO and the glutathione levels recovered in a time-dependent manner after smoking cessation, but they rapidly decreased again when smoking was resumed (Morita et al. 2005). Abstinence from smoking was also associated with decreased agonist-induced platelet aggregation ex vivo. Furthermore, levels of intraplatelet nitrotyrosine and urinary 8-hydroxy-2'-deoxyguanosine,

which are markers of oxidative stress, were also depressed after smoking cessation. One study showed that supplementation with vitamin C restored NO levels and platelet aggregation in current smokers to levels observed in non-smokers (Takajo et al. 2001). Another study demonstrated that the normal morning increase in platelet sensitivity to NO ex vivo was lost in smokers, leaving platelets potentially more susceptible to activation during early morning hours, when MIs are most common (Sawada et al. 2002). In yet another study, platelets from smokers were less

sensitive to administration of nitroglycerin, a documented NO donor (Haramaki et al. 2001).

Oxidative Stress and Platelet Function

Cigarette smoke has been shown to be an abundant source of free radicals (Church and Pryor 1985). Levels of isoprostanes—quantitative indices of in vivo oxidative stress—are higher in smokers than in nonsmokers (Reilly et al. 1996; Chehne et al. 2001; Dietrich et al. 2002), and they decrease with smoking cessation (Reilly et al. 1996; Praticò et al. 1997). In addition to serving as biomarkers of oxidative stress, isoprostanes may serve as secondary messengers that exert biologic effects, at least in vitro.

Studies demonstrated elevated production of isoprostanes and decreased levels of reduced glutathione in the platelets of smokers (Takajo et al. 2001). Intraplatelet levels of nitrotyrosine, which is a marker of modification of proteins induced by oxidative stress, decreased with smoking abstinence but increased rapidly when smoking was resumed, together with return of increased sensitivity to agonist-induced platelet aggregation ex vivo (Morita et al. 2005). In another study, products from activated platelets induced oxidative stress in vascular smooth muscle cells, which is associated with increased expression of tissue factor, a highly thrombogenic protein (Görlach et al. 2000). Other investigators showed that administration of antioxidants to persons with diabetes, just as to smokers, decreased production of isoprostane and urinary TxM (Davì et al. 1999) and decreased platelet aggregation ex vivo (Salonen et al. 1991).

Isoprostanes and Platelet Function

In one study, platelets oxidized ex vivo demonstrated increased aggregation induced by shear stress, an effect that is only partly inhibited by administration of aspirin (Chung et al. 2002). In another study, oxidation of platelet membranes was associated with reduced expression of glycoprotein Ib, a receptor for the von Willebrand factor that is critical to platelet activation and aggregation under conditions of shear stress (Escobar and White 2000). The researchers postulated that decreased expression of glycoprotein Ib indicates a highly reactive status of platelets.

Some evidence indicates that isoprostanes may act as platelet and vascular agonists through ligation of the thromboxane A₂ receptor (TP) (Audoly et al. 2000). To date, no molecular evidence exists for a distinct isoprostane receptor (Praticò et al. 1996). One study reported that infusion of isoprostanes elevated blood pressure and activated platelets—effects that are lost in mice lacking TP. Binding of isoprostane iPF_{2α}-III to TP promoted change in platelet shape and facilitated response to other proaggregatory stimuli (Praticò et al. 1996). In another study,

however, isoprostane alone did not induce platelet activation and partially blocked the proaggregatory effects of TP agonists and high-dose collagen (Cranshaw et al. 2001). Also, isoprostane iPF_{2α}-III was reported to decrease the antiplatelet activity of NO (Minuz et al. 1998). Some researchers speculated that this isoprostane has a role in the resistance to low-dose aspirin observed in patients with CVD (Csiszar et al. 2002). It is not known, however, how these effects, which are demonstrable in vitro, relate to endogenous levels of isoprostanes attained locally in vivo under conditions of oxidative stress.

Summary

Thus, platelets from smokers demonstrate a dose-dependent increase in activity and adhesiveness that rapidly decreases with smoking abstinence. Findings suggest that the inhibitory NO pathway is impaired and responsiveness to other agonists is increased at least partially through the mediation of TP.

Red Blood Cells

Hematocrit in Adults

Smoking is associated with an increase in hematocrit or red blood cell mass attributable to increased levels of CO and carboxyhemoglobin. Hematocrit decreases with smoking cessation, but increased blood viscosity and deformability of red blood cells may persist (Haustein et al. 2004). Increases in hematocrit and blood viscosity are associated with increasing risk of CVD. It is unclear, however, whether these risk factors are independent of smoking and other conventional risk factors, particularly in women (Lowe et al. 1997; Irace et al. 2003; Woodward et al. 2003). When data are adjusted for smoking, hypertension, and high cholesterol, viscosity remains a significant risk factor for stroke and for PAD but not for ischemic heart disease. This finding suggests that the effect of high viscosity may be an independent risk factor for stroke or PAD (Lee et al. 1996; Lowe et al. 1997).

Hematocrit in Neonates

Researchers showed that the effects of smoking on hematocrit were transmitted to the fetus during pregnancy. Some studies reported a dose-dependent increase in hemoglobin levels in infants of mothers who smoked (al-Alawi and Jenkins 2000; Habek et al. 2002). Furthermore, infants born to mothers who smoked more than 20 cigarettes per day had higher rates of fetal hypoxia, polycythemia, and neurological complications than did infants of nonsmoking mothers.

Leukocytes

Polymorphonuclear Leukocytes

In one study, persons who smoked had higher numbers of circulating polymorphonuclear leukocytes than did nonsmokers (Sela et al. 2002). In other research, neutrophils from smokers had higher levels of myeloperoxidase (Bridges et al. 1985) and increased expression of integrins CD11b, CD15, and CD63, which are markers of leukocyte activation (Gustafsson et al. 2000). Furthermore, when stimulated, these leukocytes released superoxide at a faster rate than did leukocytes from nonsmokers (Sela et al. 2002), which further increased local oxidative stress. Studies documented a greater variety of circulating cellular adhesion molecules, including ICAM-1, VCAM, P-selectin, and E-selectin, in smokers than in nonsmokers (Mazzone et al. 2001; Bermudez et al. 2002). An increase in these cellular adhesion molecules (monocytes) may facilitate recruitment of inflammatory cells to sites of vascular injury (Figure 6.7).

Monocytes

Monocytes from smokers demonstrated increased expression of the integrins CD11b and CD18, which augment adhesiveness of monocytes to endothelial cells, at least in vitro (Weber et al. 1996). This process is thought to be mediated by activation of protein kinase C (Kalra et al. 1994) and is attenuated by supplementation with

vitamin C (Weber et al. 1996). In one study, isoprostane $ipF_{2\alpha}$ -III inhibited adhesion of monocytes to cultured dermal cells or renal endothelial cells in rats but paradoxically increased adhesion of monocytes to human endothelial cells in the umbilical vein (Leitinger et al. 2001; Kumar et al. 2005). Adhesion of monocytes to endothelial cells may increase their access into the subendothelium, where they differentiate into macrophages and promote atherogenesis (Ross 1999). Differentiation of monocytes into macrophages depends on production of intracellular reactive oxygen species induced by nicotinamide adenine dinucleotide phosphate, but no evidence exists for a role of cigarette smoking in this differentiation (Barbieri et al. 2003).

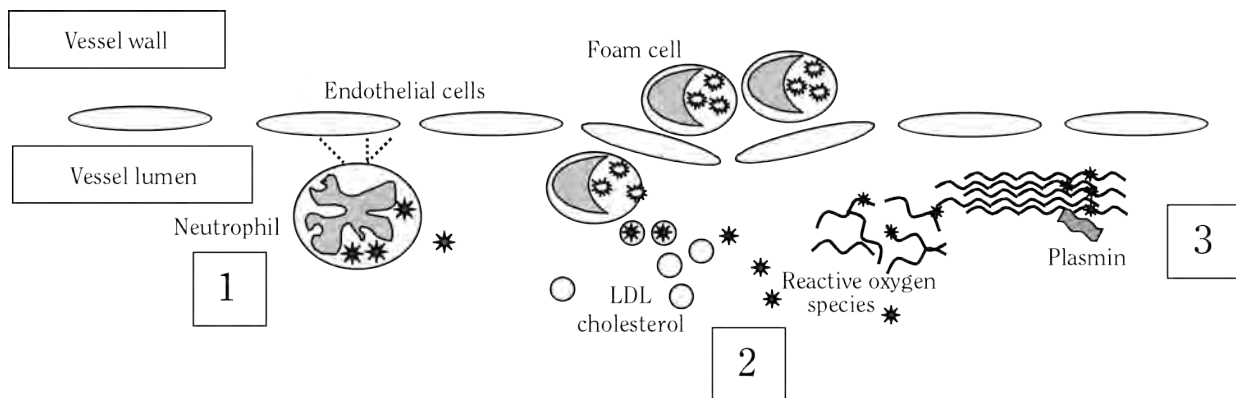
Summary

In summary, smoking induced changes in the numbers and activity of polymorphonuclear leukocytes and monocytes. In addition, it promoted expression of chemoattractant and adhesion molecules and integrins, which would be expected to increase recruitment of activated leukocytes to areas of oxidative stress, including sites of platelet deposition after vascular injury.

Circulating Proteins

In addition to its effects on the cellular elements of blood, smoking alters the proteins involved in the coagulation pathway by changing procoagulant factors in

Figure 6.7 Potential sites of effects of smoking on thrombosis through oxidative stress and other mechanisms



Note: 1. Increased numbers and activation of polymorphonuclear leukocytes; increased production of superoxide radicals; and increased expression of integrins and adhesion molecules on leukocytes and endothelial cells. 2. Increased oxidation of LDL cholesterol; oxidized LDL cholesterol taken up more easily into macrophages to produce foam cells; and increased adhesiveness of monocytes to endothelial cells. 3. Increased levels of fibrinogen; increased nitration of tyrosine residues on fibrinogen, rendering it more thrombogenic; impaired activity of plasmin; and decreased thrombolysis. **LDL** = low-density lipoprotein.

the circulation and anticoagulation factors derived from the endothelium.

Fibrinogen

Study findings indicate that circulating levels of fibrinogen increase in smokers and decrease with smoking cessation (Thomas et al. 1995; Hunter et al. 2001; Tuut and Hense 2001). Also, research suggests that elevated fibrinogen values are an independent risk factor for CHD (Paramo et al. 2004) and deep-vein thrombosis (Vayá et al. 2002). For CVD, the predictive effect was reportedly similar and additive to traditional cardiovascular risk factors (Woodward et al. 1998). The effect of fibrinogen on CVD is partly attributable to smoking and seems to be mediated through alterations in rates of synthesis by the liver. Use of snuff is not associated with increased fibrinogen levels (Eliasson et al. 1995).

Nitration of tyrosine residues, a marker of NO-dependent damage, is increased in smokers (Petruzzelli et al. 1997). Presence of these residues depends strictly on availability of nitrogen dioxide radicals that are in turn derived from ONOO⁻ (Kirsch et al. 2002). Tyrosine nitration modifies a variety of proteins, including fibrinogen (Petruzzelli et al. 1997; Pignatelli et al. 2001). Nitrogenated fibrinogen is more reactive and thrombogenic than is native fibrinogen (Gole et al. 2000), a fact that seems attributable to accelerated formation of clots without modification in plasmin-induced thrombolysis (Vadseth et al. 2004). The antioxidants glutathione and vitamin C protect against formation of nitrogenated fibrinogen by interfering with interaction of nitrate radicals with tyrosine (Kirsch and de Groot 2000; Kirsch et al. 2001). ONOO⁻ is likely to derive from interaction of NO from cigarette smoke with superoxide radicals from pulmonary macrophages (Deliconstantinos et al. 1994). In studies of both animal models and human volunteers, even brief exposure to tobacco smoke induced prolonged production (>30 minutes) of ONOO⁻, apparently from pulmonary macrophages (Deliconstantinos et al. 1994).

Plasmin

Circulating plasminogen is activated to plasmin by fibrin, thrombin, and tPA. Plasminogen has fibrinolytic and collagenase activities. In vitro studies showed that levels of ONOO⁻ increased in smokers and that ONOO⁻ induced nitration of plasminogen in a concentration-dependent manner and reduced proteolytic activity of plasmin (Nowak et al. 2004). This effect is partially reduced by glutathione.

C-Reactive Protein

Chronic, low-level inflammation—reflected by elevated levels of C-reactive protein (CRP) and other biomarkers—is an important risk factor for atherosclerosis (Koenig et al. 1999). Investigators reported that levels of CRP, which likely contributes to both oxidative stress and mitogenic and fibrogenic characteristics of atherosclerotic plaque, are higher in smokers than in nonsmokers in a dose-dependent manner (Bakhrú and Erlinger 2005). This increase persisted even after adjustment for diabetes, lipid profile, and CVD, as well as age, gender, and race. More important, five years after smoking cessation, CRP levels were decreased to levels similar to those in lifetime nonsmokers. This finding suggests vascular healing. The timeframe is consistent with that observed in the multinational monitoring of trends and determinants of CVD (MONICA) (Dobson et al. 1991) and in the Northwick Park Heart studies (Meade et al. 1987). In those studies, cardiovascular risk was reduced at two to five years after a person stopped smoking.

Oxidized Low-Density Lipoprotein Cholesterol

In vitro research on oxidative modification of LDL cholesterol (LDLc) by extracts from cigarette smoke showed a significant increase in atherogenicity (Chisolm and Steinberg 2000). In one study, LDL isolated after participants smoked six or seven cigarettes was more susceptible to ex vivo oxidation than was LDL isolated after 24 hours of abstinence from smoking (Harats et al. 1989). In another study, oxidizability of LDL ex vivo decreased with smoking cessation (Sasaki et al. 1997). Oxidized LDL, but not native LDL, interacted with scavenger receptors on lipid-laden lung cells (foam cells) and was readily incorporated into atherosclerotic plaque. Findings in other studies suggest that oxidized LDL prompts migration and degranulation of neutrophils (Sedgwick et al. 2003) and increases expression of the Toll-like receptor, a transmembrane protein in macrophages, thus promoting their activation (Xu et al. 2001).

Clinical studies produced conflicting data on the ability of cigarette smoke to oxidize LDLc and on the role of cigarette smoke in the process in vivo. Findings in several studies (Scheffler et al. 1992; Mahfouz et al. 1995; Kagota et al. 1996; Gouaze et al. 1998; Yamaguchi et al. 2005), but not all studies (Princen et al. 1992; Siekmeier et al. 1996; Marangon et al. 1997; van den Berkmortel et al. 2000), suggest that smoking increases oxidation of LDLc. Studies of an animal model suggest a similar oxidative

effect (Yamaguchi et al. 2002, 2004). In one study, modification of LDLc by cigarette smoke was diminished in a dose-dependent manner by administration of fluvastatin (Yamaguchi et al. 2002; Franzoni et al. 2003). Fluvastatin is a potent scavenger of the peroxy radical. A similar clinical study showed no decrease in oxidized LDL with administration of atorvastatin, despite improvement in endothelial function (Beckman et al. 2004). It is unclear whether failure to demonstrate an association between improved endothelial function and oxidative stress in the study of atorvastatin reflects a true independence of these effects, a distinction from fluvastatin, or limitations attributable to the small sample size.

Thus, cigarette smoking may induce changes in both coagulation and fibrinolytic pathways to promote a prothrombotic state. In addition to its effects on inflammatory cells, smoking promotes production of inflammatory markers and acute-phase reactants.

Alterations in Blood Vessels

Nitric Oxide

Cigarette smoking has injurious effects on the vascular endothelium (see "Smoking and the Endothelium" earlier in this chapter). Abnormalities in the release of chemical mediators occur as a consequence of endothelial dysfunction and are likely to contribute to the prothrombotic condition of smokers. Examples include decreases in NO-mediated inhibition of interactions between platelets and the blood vessel wall, in platelet-induced NO, and in inhibition of platelet activation (see "Platelets" earlier in this chapter). Blood vessel tone is more sensitive to low NO levels than is platelet function (Loscalzo 2001). The importance of NO deficiency mediated by oxidative stress in thrombosis is suggested by familial childhood stroke resulting from deficiency in glutathione peroxidase. This condition decreases NO levels in association with both increased expression of P-selectin in platelets and platelet aggregation and activation (Kenet et al. 1999).

Prostacyclin Production

In vitro studies showed impaired production of prostacyclin by vascular cells exposed to cigarette smoke extracts. In vivo studies, however, showed increased biosynthesis of prostacyclin that is presumed to be reactive to accelerated interactions of platelets and neutrophils with vessel walls in smokers (Murray et al. 1990; Lassila and Laustiola 1992). Consistent with this concept, levels of markers of platelet and leukocyte activation were greater in smokers than in nonsmokers. Thus, the augmented

biosynthesis of prostacyclin is likely to reflect a compensatory reaction by the vascular endothelium.

von Willebrand Factor

Studies reported higher circulating levels of von Willebrand factor in smokers than in nonsmokers (Blann and McCollum 1993; Smith et al. 1993), and findings indicated that these levels may precede clinically overt atherosclerosis (Prisco et al. 1999). The von Willebrand factor is essential for initial adhesion of activated platelets to the vessel wall and for expansion of thrombi. It is unclear to what degree high levels of von Willebrand factor might contribute to the increased thrombosis and atherogenesis observed in smokers.

Tissue Factor

Tissue factor is a prothrombotic protein made by numerous cells in the blood vessel wall, predominantly macrophages but also vascular smooth muscle and endothelial cells. Tissue factor is released when the endothelium is injured and can start the clotting cascade. Studies assessing the effects of smoking on tissue factor yielded mixed results (Barua et al. 2002; Sambola et al. 2003). The immunoreactivity of tissue factor was higher in specimens of plaque obtained during endarterectomy from smokers than in those from nonsmokers (Matetzky et al. 2000). In mice with APO E deficiency that were fed high-cholesterol diets, exposure to cigarette smoke resulted in higher levels of tissue factor and VCAM-1 and higher macrophage counts in atherosclerotic plaques than in those of unexposed mice (Lykkesfeldt et al. 2000). Aspirin treatment of cigarette smokers and of mice exposed to smoke was associated with lower levels of tissue factor in plaque. This finding indicates that aspirin may have a protective role for smokers.

Tissue Plasminogen Activator

Vascular endothelial cells and other tissues secrete tPA. This protein has a central role in fibrinolysis, which limits expansion of clots during thrombosis and eventually dissolves the clot during thrombolysis. Evidence from the Physicians' Health Study indicates that high levels of tPA are an independent risk factor for stroke and suggests that activation of the endogenous fibrinolytic system occurs years before arterial vessels become occluded (Ridker et al. 1994). PAI-1, which is also secreted by vascular endothelial cells, opposes the actions of tPA.

Data on the effects of smoking on tPA and PAI-1 are conflicting (Blann et al. 2000; Enderle et al. 2000; Matetzky et al. 2000; Newby et al. 2001). Using an in vitro model, researchers showed that serum from smokers

impaired tPA production by human umbilical vein endothelial cells but that PAI-1 production was unchanged (Barua et al. 2002). In an *in vivo* model, bradykinin (Newby et al. 1999; Pretorius et al. 2002) and substance P (Newby et al. 1999; Pretorius et al. 2002) stimulated the production of tPA, which had decreased in smokers, but there was no effect on the release of methacholine-induced tPA. Vitamin C failed to ameliorate this decrease (Pellegrini et al. 2004). Studies showed that levels of PAI-1 may decrease after smoking cessation (Simpson et al. 1997).

Thus, the evidence suggests that smoking decreases the production of tPA and perhaps also increases the amount of PAI-1 produced. These changes would be expected to impair fibrinolytic activity. Alternatively, a population-based study demonstrated increased levels of fibrinogen, but fibrinolytic activity in smokers did not differ from that in nonsmokers (Eliasson et al. 1995). Another study suggested that differences between smokers and nonsmokers in thrombolysis may be evident only in older adults (Ikarugi et al. 2003).

Summary

A variety of abnormalities can be observed in endothelial cell function among smokers compared with nonsmokers. These abnormalities affect the ability of the endothelium to modulate vascular tone, platelet function, thrombogenesis, and thrombolysis. Administration of antioxidants mitigates some but not all of these abnormalities. The relative importance of these abnormalities and their interactions in clinical settings remains to be elucidated.

Exposure to Secondhand Tobacco Smoke

In one study, levels of fibrinogen and coagulation factor VII were higher in nonsmoking adolescent offspring of smokers than in nonsmoking adolescent offspring of nonsmokers (Stavroulakis et al. 2000). This finding is in keeping with a prothrombotic state in smokers. In addition, levels of PAI-1 were lower in nonsmoking offspring of smokers. This result suggests decreased fibrinolysis, but there was no difference in tPA levels. Levels of thrombomodulin, which is produced by the vascular endothelium and has anticoagulant effects, were higher in nonsmoking offspring of smokers, but levels of von Willebrand factor were unchanged. Another study demonstrated that TxM levels increased in one exposure to secondhand smoke; after six hours of exposure, levels approached those observed in smokers (Schmid et al. 1996). In other

research, exposure to secondhand smoke decreased sensitivity of platelets to the inhibitory effects of prostacyclin *in vitro* (Burghuber et al. 1986).

Thus, many of the effects from active smoking can be observed in persons involuntarily exposed to cigarette smoke. The magnitude of the effect of secondhand smoke is relatively large considering the low systemic exposure to tobacco smoke for nonsmokers compared with that for active smokers and supports the finding of high cardiovascular risk at low levels of exposure to smoke.

Nicotine and Thrombosis

Nicotine replacement therapy (NRT) does not seem to increase the acute risk of thrombosis, even in patients with established cardiac disease (Joseph et al. 1996). However, investigators have not fully studied cardiovascular effects of extended administration of nicotine, which might be used as an adjunct for persons trying to stop smoking (Stratton et al. 2001). The high urinary excretion of TxM in smokers declines rapidly after smoking cessation. In one study, this decline did not occur in smokers who were using NRT, suggesting that nicotine may be contributing to platelet activation (Saareks et al. 2001). However, other studies in which smokers switched to nicotine patches found a decline in eicosanoid excretion and that long-term use of smokeless tobacco, which results in nicotine exposure similar to that of cigarette smokers, does not increase urinary excretion of TxM (Wennmalm et al. 1991; Benowitz et al. 1993). These findings suggest that nicotine *per se* does not activate platelets. When nicotine or cotinine was added to the platelet-rich plasma of nonsmokers, platelet-dependent formation of thrombin increased (Hioki et al. 2001). The magnitude of the effect was similar to that observed in smokers, even though the basal nicotine levels in smokers were higher than those in nonsmokers. When cultured endothelial cells from the human brain were exposed to nicotine, tPA levels were unchanged (Zidovetzki et al. 1999). Rather, PAI-1 messenger RNA and protein expression increased, favoring a prothrombotic state. Alternatively, when transdermal nicotine was administered to nonsmokers, the release of tPA induced by substance P was greater than that in nonsmokers who had received placebo patches (Pellegrini et al. 2001). This finding suggests a more favorable effect *in vivo*.

A study of cardiovascular biomarkers indicates that smokeless tobacco produced neither the inflammatory reaction found in smokers nor endothelial dysfunction, activation of platelets, or evidence of oxidant stress (Axelsson et al. 2001). Leukocyte counts; levels of CRP,

fibrinogen, and antioxidant vitamins; and lipid profiles were similar in users of smokeless tobacco and in persons who did not use tobacco.

Summary

Multiple factors produced in the blood and released from the vasculature determine the likelihood of a clinically significant thrombosis. Cigarette smoke and components of the smoke stimulate formation or activity of factors that favor the development of thrombosis. It remains to be seen whether biomarkers of individual

cardiovascular risk among smokers will emerge and which genetic variants might particularly influence these risks in smokers. The implications of the hypercoagulable state are observed both in the epidemiology of active and involuntary smoking-related cardiovascular events and in the rapid rate of decline in the major component of excess risk for those events after smoking cessation. A hypercoagulable state can result in acute MI in persons who have less severe underlying coronary disease, so smokers who stop smoking have a better prognosis than do nonsmokers after MI. A more gradual decline of residual risk may reflect resolution of smoking-induced vascular injury, which in turn stimulates platelet activation.

Inflammation

Studies demonstrate that cigarette smoking results in a chronic inflammatory state, evidenced by increased counts of circulating leukocytes, CRP, and acute-phase reactants such as fibrinogen (Tracy et al. 1997; Jensen et al. 1998; Tuut and Hense 2001). Cigarette smoking also activates monocytes and enhances recruitment and adhesion of leukocytes to blood vessel walls, an integral step in vascular inflammation (Lehr et al. 1994). Research indicates that inflammation contributes to atherogenesis, because high leukocyte counts and high levels of CRP and fibrinogen are all powerful predictors of future cardiovascular events (Libby et al. 2002).

However, the mechanisms by which cigarette smoking promotes inflammation are not completely elucidated. As discussed previously, oxidant stress appears to be a critical factor; oxidized LDL is a proinflammatory stimulus (see "Cigarette Smoke Constituents and Cardiovascular Disease" earlier in this chapter). Studies also show that the products of lipid peroxidation are proinflammatory, acting in part on the receptor for platelet-activating factor (PAF). In hamsters, the antioxidant vitamin C prevented adhesion of leukocytes to the endothelium and leukocyte-platelet aggregation (Lehr et al. 1994). In the same animal model, adhesion of leukocytes and formation of leukocyte-platelet aggregates were mediated by PAF-like agonists (Lehr et al. 1997). This PAF-like factor was derived from oxidative modification of phospholipids and was distinct from biosynthetic PAF. Treatment with vitamin C inhibited generation of PAF-like lipids. In contrast, oral L-arginine but not vitamin C reversed the effect of sera from smokers by promoting monocyte-endothelial cell adhesion, which is associated with higher levels of ICAM (Newby et

al. 2001). The study findings suggest that smoking-related impairment of NO release is an important determinant of increased adhesion of monocytes to endothelial cells.

Nicotine may contribute to inflammation by acting as a chemotactic agent for migration of neutrophils (Nicod et al. 1984). One study indicates that nicotine enhanced leukocyte-endothelium interactions, resulting in greater leukocyte rolling and adhesion in the cerebral microcirculation of mice (Nitenberg et al. 1993). Nicotine reportedly acts on human monocyte-derived dendritic cells to stimulate an inflammatory response (Nowak et al. 1987). Dendritic cells, which were detected in the walls of arteries and in atherosclerotic lesions, present antigens and are thus required for the start of adaptive immunity. Studies showed that nicotine is a potent inducer of expression of a variety of co-stimulatory molecules and that it increases secretion of the proinflammatory cytokine interleukin-12 in cultured dendritic cells (Aicher et al. 2003). Nicotine augmented the capacity of dendritic cells to stimulate proliferation of T cells and cytokines. Finally, intravenous injection of nicotine increased the movement of dendritic cells into atherosclerotic lesions in vivo in mice deficient in APO E. This line of research suggests that nicotine could contribute to adaptive immunity, which may have a role in atherogenesis. However, switching from smoking to transdermal nicotine resulted in a significant decline in the leukocyte count (Benowitz et al. 1993). In addition, use of smokeless tobacco did not produce higher leukocyte counts or higher CRP levels than are seen in persons who do not use tobacco. These observations suggest that nicotine is not the main determinant of the inflammatory response in smokers.

Smoking and Diabetes

Cigarette smoking is widely known to increase the risks of CVD. Even so, this knowledge does not appear to influence smoking behaviors among patients with diabetes, who bear a higher risk of cardiovascular morbidity and mortality than those who do not have diabetes (Haffner et al. 1998). Surveys found that smoking patterns were similar in patients with diabetes and comparable populations without that disorder (Ford et al. 1994; Gill et al. 1996).

Numerous experimental studies demonstrated that smoking had negative effects on the metabolism of glucose and lipids in persons with or without diabetes. Investigators reported that cigarette smoking in patients with diabetes was associated with deterioration of metabolic control (Madsbad et al. 1980; Bott et al. 1994) and increased risk of microvascular and macrovascular complications and death (Chase et al. 1991; Morrish et al. 1991). Furthermore, cigarette smoking increases risk of type 2 diabetes in the general population (Will et al. 2001). This risk may be mediated through direct metabolic effects alone or in combination with a metabolically unfavorable lifestyle.

Risk

In several prospective studies, cigarette smoking was associated with increased risk of type 2 diabetes in both men and women (Willi et al. 2007). Generally, these prospective studies were large and population based. Most of the information was collected by mailing participants a questionnaire, which in some cases, was supplemented with information from medical records. Most of these studies included follow-up of more than 10 years. Results were generally presented after adjustments for possible covariates.

In the Health Professionals Follow-Up Study, the RR of developing diabetes among men who smoked 25 or more cigarettes per day was 1.94 (95 percent CI, 1.25–3.03) when nonsmokers were the reference group (Rimm et al. 1995). In a smaller British study, the risk of diabetes was 50 percent higher among smokers, but this finding was not independent of other risk factors, such as obesity and low levels of physical activity (Perry et al. 1995). Another British study demonstrated that RR for diabetes in men who smoked was approximately 1.7, after adjustments for the effects of age, body mass index, physical

activity, alcohol intake, social class, undiagnosed CHD, and treatment for hypertension (Wannamethee et al. 2001). Mean follow-up was almost 17 years. The increased risk of diabetes was lower 5 years after smoking cessation, and the risk normalized 20 years later. A Japanese study found similar results and also reported a positive correlation between use of tobacco products and risk of diabetes (Uchimoto et al. 1999).

Almost identical results were presented in the Physicians' Health Study (Manson et al. 2000). During 12 years (255,830 person-years¹) of follow-up, the risk of diabetes in men who smoked more than 20 cigarettes per day was 70 percent higher than that in nonsmokers, after adjustment for multiple variables. The results also showed a significant positive association between the risk of developing diabetes and higher consumption of cigarettes (Manson et al. 2000). In addition, the Insulin Resistance Atherosclerosis Study monitored a cohort of 906 study participants for five years with equal representation of African Americans, Hispanics, and Whites (Foy et al. 2005). For all persons studied, current smoking was associated with development of diabetes: the adjusted OR was 2.66 (95 percent CI, 1.49–4.77). Among participants who had normal glucose tolerance at baseline, the OR was 5.27 (95 percent CI, 2.11–13.16).

At least three other studies of men confirmed the main results of these prospective studies (Feskens and Kromhout 1989; Kawakami et al. 1997; Ko et al. 2001). There have been fewer studies with women, but two major prospective surveys yielded similar results. In the Nurses' Health Study (114,247 women; 1,277,589 person-years of follow-up), RR for diabetes in heavy smokers was 1.42, after adjustments for other risk factors (Rimm et al. 1993).

In an analysis of data from the Nurses' Health Study after 16 years of follow-up, Hu and colleagues (2001) showed that the strongest predictors of diabetes were being overweight or obese. In addition, poor diet, smoking, abstinence from alcohol, and low levels of physical activity were all independently associated with the risk of developing diabetes. Adjusted RR for developing diabetes was approximately 1.4 for smokers compared with nonsmokers.

Data from CPS-I, a prospective cohort study conducted between 1959 and 1972, were used to analyze the correlation between tobacco use and risk of diabetes in both men and women (Will et al. 2001). In comparison

¹Person-year = the sum of the number of years that each member of a population has been smoking.

with the risk of developing diabetes for nonsmokers, the risks were higher for men who smoked more than one pack of cigarettes per day (RR = 1.19) or two packs per day (RR = 1.45). Risks were also higher for women who smoked more than one pack per day (RR = 1.21) or two packs per day (RR = 1.74). After smoking cessation, the risk returned to normal after 5 years for women and after 10 years for men (Will et al. 2001).

Only a few studies, all from the 1970s or 1980s, failed to demonstrate a positive association between smoking and diabetes, likely due to inadequate study design or lack of power in the study to test this hypothesis (Medalie et al. 1975; Keen et al. 1982; Wilson et al. 1986).

It is generally accepted that risk increases more for type 2 diabetes than for type 1, because type 1 diabetes is relatively rare among the age groups in the studies. Risk for type 2 diabetes is also consistent with the adverse metabolic effects of smoking (see "Insulin Resistance" later in this chapter). Type 1 diabetes is insulin deficiency caused by autoimmune destruction of pancreatic beta cells; in type 2 diabetes, insulin resistance is combined with impaired secretion of insulin (Reaven 1988; Kahn 2001).

Metabolic Control

Some studies examined the effects of cigarette smoking on the body's requirement for insulin and metabolic control in patients with diabetes. In a cross-sectional study, Madsbad and colleagues (1980) investigated the relationship between insulin doses and related variables in patients treated with injections of insulin. Insulin doses and serum levels of triglycerides were significantly higher in the 114 persons who smoked than in the 163 who did not smoke, and these values increased in a dose-dependent manner in relation to the number of cigarettes smoked. Hemoglobin A_{1c} (HbA_{1c})—a marker of long-term glucose elevation—was not measured in this study, but blood and urine levels of glucose did not differ between the two groups. This finding suggests that in patients who smoke, a larger insulin dose is needed to achieve metabolic control similar to that in patients who do not smoke.

In a cross-sectional study of 192 patients with type 1 diabetes, smoking was more common in those with higher HbA_{1c} values (Lundman et al. 1990). Other differences between the smokers and nonsmokers were in attitudes toward diabetes, psychological well-being, and similar factors.

In a relatively large prospective study that examined the effects of intensified insulin treatment and of an educational program, smoking was the most

consistent determinant of HbA_{1c} levels in relatively young participants treated with insulin (Bott et al. 1994). The investigators performed a three-year follow-up on 697 patients with diabetes who had no debilitating late complications. HbA_{1c} levels were higher throughout the study in smokers but eventually improved to levels similar to those in nonsmokers, presumably because of the educational program.

Insulin Resistance

The metabolic effects of smoking have been generally studied in persons who did not have diabetes. Insulin sensitivity was usually determined by using the euglycemic hyperinsulinemic clamp technique (DeFronzo et al. 1979). This technique or a slightly modified version of it is considered to be the gold standard in metabolic studies.

In 1993, Attvall and colleagues showed that short-term smoking caused impaired insulin sensitivity in healthy young men. Separately, two cross-sectional studies of men compared uptake of insulin-mediated glucose (insulin sensitivity) in smokers and nonsmokers (Facchini et al. 1992; Eliasson et al. 1997a). Insulin sensitivity was significantly lower (by 10 to 40 percent) in smokers. The degree of insulin resistance was positively correlated with tobacco use, and in long-term users of nicotine gum, with serum cotinine values (Eliasson et al. 1994, 1996). Because cotinine is a metabolite of nicotine, serum and urine levels of cotinine reflect the amount of nicotine use. Insulin resistance in smokers normalized eight weeks after smoking cessation, despite a weight gain of 2.7 kg (Eliasson et al. 1997a).

Smokers in these two cross-sectional studies had signs of insulin-resistance syndrome, such as significantly high serum levels of free fatty acids (FFAs) and triglycerides and low levels of HDLc (Facchini et al. 1992; Eliasson et al. 1997b). In the study by Eliasson and colleagues (1997b), smokers had a high proportion of atherogenic small and dense LDL particles, high fibrinogen levels, and high PAI-1 activity compared with those of nonsmokers. PAI-1 activity among long-term users of nicotine gum was similar, but effects on lipids were not as pronounced as those in smokers (Eliasson et al. 1996).

One aspect of insulin-resistance syndrome that attracted attention was postprandial hypertriglyceridemia, a phenomenon associated with CVD and insulin resistance (Patsch et al. 1992; Jeppesen et al. 1995). This phenomenon is also observed in smokers (Axelsen et al. 1995; Eliasson et al. 1997b), but its cause is unknown. One possible

explanation is the inability of smokers to adequately clear triglyceride-rich chylomicrons and their remnants from the body (Mero et al. 1997).

Other studies that did not use exact measurements of insulin sensitivity reported changes in glucose metabolism in smokers compared with nonsmokers. Compared with nonsmokers, smokers were hyperinsulinemic and relatively glucose intolerant (Eliasson et al. 1991; Zavaroni et al. 1994; Frati et al. 1996; Ronnema et al. 1996). A large cross-sectional study showed that after adjustments for confounding factors, smoking behaviors were clearly correlated with HbA_{1c} values in persons who did not have diabetes (Sargeant et al. 2001), but researchers have debated the importance of HbA_{1c} in persons who do not have diabetes. Even so, these findings add support to the hypothesis that use of tobacco exerts adverse effects on glucose homeostasis.

Results in a few studies did not support these findings. Godsland and Walton (1992) found no differences in insulin sensitivity between women smokers and nonsmokers, but this result may be attributable to lower levels of tobacco use. In addition, the results were from analysis of data obtained to test a different hypothesis. In a study of metabolic changes in patients with or without hypertension, no differences in insulin sensitivity between smokers and nonsmokers were detected (Nilsson et al. 1995). However, the study design likely did not enable discrimination between metabolic changes caused by hypertension and those caused by smoking.

In patients with type 1 diabetes, Helve and colleagues (1986) examined cross-sectional and short-term effects of smoking on insulin sensitivity. Despite elevated levels of circulating epinephrine, cortisol, growth hormone, and glucagon after smoking, no effect of smoking on insulin sensitivity was observed. The investigators concluded that fluctuations in blood glucose and metabolic control disguised the influence of smoking in these patients with diabetes. In a study of 28 smokers and 12 nonsmokers with type 2 diabetes, the researchers measured insulin sensitivity by using euglycemic clamps (Targher et al. 1997). Smokers had higher insulin resistance and glucose intolerance than did nonsmokers. The researchers concluded that smoking markedly and in a dose-dependent manner aggravated insulin resistance observed in patients with type 2 diabetes (Targher et al. 1997).

Axelsson and colleagues (2001) reported that nicotine administered intravenously to nonsmokers caused a marked reduction (about 30 percent) in insulin sensitivity in those with type 2 diabetes but not in healthy control participants. These results suggest that nicotine and possibly tobacco use or other environmental factors may have

particularly adverse effects in persons susceptible to diabetes but not in those who are healthy (insulin sensitive).

Microvascular Complications

Microvascular complications in diabetes (retinopathy, nephropathy, and neuropathy) are linked to metabolic control in both type 1 and type 2 disease (*New England Journal of Medicine* 1993; *Lancet* 1998). The mechanisms for development of microvascular complications are not fully understood, although several pathogenetic pathways have been suggested (Brownlee et al. 1984; Tomlinson 1999; Cai and Boulton 2002). Hyperglycemia has a central role as a trigger for subsequent events, such as conversion of glucose to sorbitol by aldose reductase; nonenzymatic glycosylation of proteins and receptors in susceptible tissues; increased exposure to oxidative stress; and activation of protein kinase C and mitogen-activated protein kinases. Researchers have suggested that these pathogenetic pathways lead to the disturbances in morphology and function found in diabetic nephropathy, retinopathy, and neuropathy (Brownlee et al. 1984; Tomlinson 1999; Cai and Boulton 2002).

Nephropathy

Some studies showed that smoking increased risk of microvascular complications in diabetes. Several studies of patients with type 1 diabetes reported negative effects of tobacco use on albuminuria and renal function. Chase and colleagues (1991), for example, showed that the albumin excretion rate was 2.8 times higher in smokers than in nonsmokers, after statistical corrections for glycemic control, duration of diabetes, age, gender, and blood pressure. In addition, albuminuria progressed at a more rapid rate in smokers than in nonsmokers.

Smoking promoted progression of renal disease in persons with type 2 diabetes (Biesenbach et al. 1997; Chuahirun and Wesson 2002; Chuahirun et al. 2003). Biesenbach and colleagues (1997) studied only 36 patients, but follow-up lasted 13 years. At study entry, smokers and nonsmokers had similar clinical and laboratory characteristics, but progression of nephropathy and development of atherosclerotic disease progressed more rapidly in the smokers than in the nonsmokers. Multiple regression analysis showed that only tobacco use and blood pressure levels were independently associated with impairment in renal function. This finding underscored the roles of smoking and vascular disease in susceptibility to renal disease (Biesenbach et al. 1997). In two prospective

studies by Chuahirun and colleagues (2002, 2003), the effects of cigarette smoking on acceleration of nephropathy in patients with type 2 diabetes were confirmed even in those who had optimal therapy for hypertension. Research presented further evidence of functional and structural changes in the glomeruli of patients with type 2 diabetes who smoke (Baggio et al. 2002). In a study of 96 patients who had biopsy of the kidney, electron and light microscopy demonstrated significant changes in glomeruli and basal membranes that corresponded to impaired glomerular filtration rates in the smokers.

Retinopathy

Generally, investigators have not considered smoking to be a substantial risk factor for diabetic retinopathy (Porta and Bandello 2002). Findings in fairly large studies with mixed populations showed no strong support for such an association, except in older adults with certain conditions (Walker et al. 1985; Moss et al. 1991). At least two studies of patients with type 1 diabetes, however, suggest that smoking does predispose these patients to retinopathy (Mulhauser et al. 1986, 1996). In addition, Chase and colleagues (1991) showed that retinopathy was more common in patients with type 1 diabetes who smoked than in those who did not smoke, but after adjustments for covariates, differences were not statistically significant. The study also reported accelerated progression of retinopathy in patients who smoked. Thus, smoking may be a risk factor for diabetic retinopathy, but only in certain subgroups.

Neuropathy

The role of tobacco in the development of diabetic neuropathy is relatively difficult to examine because of methodologic problems and the frequent prevalence of confounding factors (Westerman et al. 1992). Diabetic neuropathy usually develops during a long period, and it may affect different sensory, motor, and autonomic nerve fibers in varying degrees in individuals. This variation makes it difficult to standardize study methods. One case-control study reported that risk of neuropathy was three times higher in patients with type 1 diabetes who smoked than in those who did not smoke (Mitchell et al. 1990). Smoking was not related to neuropathy in patients with type 2 diabetes. In a study of young patients treated with insulin, independent risk factors for progression of distal sensory neuropathy, apart from poor glycemic control, were cigarette smoking, greater height, and female gender (Christen et al. 1999). Other studies in patients with type 1 diabetes confirmed the roles of glycemic control and smoking behaviors in development of clinical neuropathy (Maser et al. 1989; Reichard 1992).

Macrovascular Complications

The multiple effects of smoking on the vascular and hemostatic systems and on inflammation are reviewed elsewhere in this chapter (see "Hemodynamic Effects," "Smoking and the Endothelium," "Nicotine and Thrombosis," and "Inflammation" earlier in this chapter). Diabetes patients are particularly susceptible to some effects of smoking, because their risk of cardiovascular morbidity and mortality is elevated (Jarrett et al. 1982; Manson et al. 1991; Morrish et al. 1991).

In a study cohort in London, England, in the prospective Multinational Study of Vascular Disease in Diabetes, sponsored by the World Health Organization, smokers with type 1 or type 2 diabetes had significantly increased risk of CHD, but not stroke, during the eight-year follow-up (Morrish et al. 1991). In the Diabetes Control and Complications Trial (*New England Journal of Medicine* 1993), designed to study the role of intensive insulin treatment and optimized glycemic control in type 1 diabetes, smoking was not a significant risk factor for macrovascular complications. Because the participants were relatively young, this trial was not optimally designed to study the role of tobacco use. Other studies with slightly older participants who had type 1 diabetes reported that smoking increased risk of CHD (Moy et al. 1990; Sinha et al. 1997).

Among patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study, cigarette smoking was a significant and independent risk factor for CHD (Turner et al. 1998), stroke (Kothari et al. 2002), and PAD (Adler et al. 2002). Also, an analysis of data from the Nurses' Health Study demonstrated that for women with type 2 diabetes, a dose-effect relationship existed between smoking behaviors and mortality (Al-Delaimy et al. 2001). Compared with nonsmokers, risk of mortality from all causes was 1.64 for women who smoked 15 to 34 cigarettes per day and 2.19 for women who smoked more than 34 cigarettes per day. Ten years after smoking cessation, risk of mortality had normalized. Researchers published similar data on smoking and CHD risk in the same cohort (Al-Delaimy et al. 2002).

A relatively large prospective study that analyzed the effects of smoking cessation on cardiovascular risk in persons with diabetes compared mortality risk for former smokers with that for lifetime nonsmokers (Chaturvedi et al. 1997). Compared with mortality risk for lifetime nonsmokers, risk of death from all causes was approximately 50 percent higher for patients who had stopped smoking during the past one to nine years and 25 percent higher for those who had not smoked for more than nine years. Smoking cessation reduced mortality risk among persons with diabetes, but risks remained high several years

after smoking cessation and were highly dependent on the duration of smoking.

Pathophysiological Mechanisms

Having diabetes, even for nonsmokers, is associated with long-term exposure to oxidative stress, impaired endothelial function, and dyslipidemia (Brownlee et al. 1984; Turner et al. 1998; Dogra et al. 2001; Cai and Boulton 2002; Komatsu et al. 2002). The causes of type 2 diabetes are still not fully understood, although the main metabolic aberrations are well characterized. Research showed that type 2 diabetes is caused by insulin resistance in combination with relative impairment of insulin secretion (Reaven 1988; Kahn 2001). Published studies have not demonstrated a significant impairment in insulin secretion among cigarette smokers (Epifano et al. 1992; Facchini et al. 1992; Persson et al. 2000), but several studies documented a negative effect of smoking on insulin sensitivity (Facchini et al. 1992; Eliasson et al. 1997a,b).

Cigarette smoking and intake of nicotine increase the circulating levels of insulin-antagonistic hormones (i.e., catecholamines, cortisol, and growth hormone) (Kershbaum and Bellet 1966; Cryer et al. 1976; Wilkins et al. 1982; Kirschbaum et al. 1992). Smoking also activates the sympathetic nervous system (Niedermaier et al. 1993; Lucini et al. 1996). Nicotine likely impairs insulin

sensitivity directly or indirectly through these and possibly other mechanisms. An additional negative factor for insulin-mediated glucose uptake is high circulating levels of FFAs, secondary to increased lipolysis (Bergman and Ader 2000). Research has shown that smoking acutely elevates circulating FFA levels (Kershbaum and Bellet 1966).

Researchers have proposed, but not fully elucidated, the potential role of endothelial dysfunction or inflammation in development of insulin resistance and type 2 diabetes.

Summary

Many clinical and experimental studies have found significant associations between cigarette smoking and development of diabetes, impaired glycemic control, and diabetic complications (microvascular and macrovascular). A different lifestyle of smokers, in contrast to that maintained by nonsmokers, may also contribute to these effects. Most of the reviewed studies, however, either attempted to statistically adjust for confounding factors or were designed to examine short-term effects of tobacco and nicotine.

The development of type 2 diabetes is another harmful consequence of cigarette smoking, one that adds to the heightened risks of CVD. In diabetes care, smoking cessation is crucial to facilitating glycemic control and limiting development of complications.

Lipid Abnormalities

Cigarette smoking is associated with an atherogenic lipid profile likely to contribute to risk of CVD.

Epidemiologic Observations

Several observations are central to the relationship between cigarette smoking and lipids. Compared with nonsmokers, smokers have higher levels of triglycerides associated with very-low-density lipoprotein (VLDL), total triglycerides, and APO B, in addition to modest increases in LDLc and lower levels of plasma HDLc and APO A-I (Billimoria et al. 1975; Criqui et al. 1980; Wilson et al. 1983; Craig et al. 1989; Muscat et al. 1991; Freeman and Packard 1995; Villablanca et al. 2000). These findings are robust and are reported in numerous survey studies. Researchers observed a dose-response relationship

between the number of cigarettes smoked per day and plasma lipid levels (Muscat et al. 1991). In contrast, plasma lipid and lipoprotein levels in former smokers typically are similar to those in nonsmokers.

The ratio of LDLc to HDLc, which is used as a measure of atherogenic risk, is higher in smokers than in nonsmokers. Cigarette smoking is thought to raise the LDLc to HDLc ratio by 15 to 20 percent. Increased levels of plasma triglycerides are associated with lower HDLc levels, but reduction in HDLc from cigarette smoking persists even after corrections for levels of total triglycerides. Early epidemiologic studies, such as the Lipid Research Clinics Program Prevalence Study and the Framingham Heart Study (Criqui et al. 1980; Muscat et al. 1991; Freeman and Packard 1995), emphasized lower HDLc values as the primary effect of cigarette smoking.

Researchers have estimated, however, that these effects of cigarette smoking on plasma lipids and lipoproteins account for only 10 percent of the observed 70 percent increase in risk of vascular disease associated with cigarette smoking (Craig et al. 1989). In the Edinburgh Artery Study, for example, adjusting for known CHD risk factors reduced the RR of CHD in heavy smokers from 3.94 to 2.72 and the RR in moderate smokers from 2.72 to 1.70 (Price et al. 1999). However, cigarette smoking still accounted for 75 percent of the risk of developing PAD, after adjustment for other known risk factors, such as hyperlipidemia and type 2 diabetes (Lu and Creager 2004). Other researchers reported similar findings (Cullen et al. 1998). Cigarette smoking thus appears to have atherogenic effects that are not explained by traditional CHD risk factors, including abnormal levels of blood lipids.

Analyses of mechanisms related to lipid and lipoprotein metabolism may be required for understanding the atherogenicity of cigarette smoking. Such mechanisms include lipid oxidation; changes in composition of lipoproteins; alterations in plasma- and lipoprotein-associated lipid transfer enzymes; changes in metabolism of fatty acids; effects on levels of postprandial lipids; and changes in cholesterol fluxes, particularly reverse cholesterol transport (RCT). The following discussion reviews the effects of cigarette smoking on these potential underlying mechanisms.

Lipoprotein Composition and Apolipoprotein Levels

Cigarette smoking clearly reduces APO A-I and the ratio of A-I to A-II (Mero et al. 1998). APO A-I is a major component of HDL particles. The reduction in A-I levels observed in smokers is similar to, although perhaps somewhat lower than, the reduction in HDLc levels seen in this population. For example, Mero and colleagues (1998) documented that levels of plasma APO A-I were 4 to 6 percent lower and HDLc values were 6 to 9 percent lower in moderate-to-heavy smokers. The effects of cigarette smoking on APO B and other APOs are also well documented (Billimoria et al. 1975; Craig et al. 1989; Muscat et al. 1991; Villablanca et al. 2000).

Researchers have associated abnormalities in different subfractions of HDL with different risks of CHD. Cigarette smoking reduced different HDL subfractions in different studies (Billimoria et al. 1975; Craig et al. 1989; Muscat et al. 1991). Even so, the true atherogenicity of different HDL subfractions remains controversial. The role of altered HDL subfractions in arterial disease associated with cigarette smoking requires further study.

Plasma- and Lipoprotein-Associated Lipid Transfer Enzymes

Several enzymes in plasma—either free or associated with lipoproteins—are involved in transport and use of lipids. Lipoprotein lipase (LPL) activity is involved in clearance of total triglycerides from triglyceride-rich lipoproteins (TGRLs), particularly the chylomicra formed in persons after a meal containing fat. Cigarette smoking reportedly reduced plasma LPL activity after a mixed meal (Freeman et al. 1998). Reduced LPL activity may contribute to the reduced clearance of TGRLs reported for total triglycerides, APO B, and retinyl-ester components of TGRLs (Mero et al. 1998). In another study, the cholesterol ester transfer protein (CETP) received considerable attention as a therapeutic target for raising HDLc levels (Brousseau et al. 2004; Ruggeri 2005). CETP mediates transfer of cholesterol esters between HDL and other lipoproteins (VLDL and LDL). However, controversy exists as to whether CETP activity is beneficial or deleterious to the process of RCT. Moreover, the proatherogenic or antiatherogenic consequences of changing HDLc by the CETP mechanism remain uncertain (Ruggeri 2005). Studies have reported both increases and decreases in plasma CETP activity in smokers (Dullaart et al. 1994; Zarinin et al. 2004).

Some studies measured other enzymes in smokers. For example, cigarette smoking did not appear to markedly alter lecithin cholesterol acyltransferase activity (McCall et al. 1994).

Oxidized Lipoproteins

Many investigators hypothesized that oxidized LDL is highly atherogenic (Dullaart et al. 1994; Zarinin et al. 2004), and studies reported increased oxidative damage to LDL in smokers (Ambrose and Barua 2004). However, attribution of a precise atherogenic contribution from oxidative damage to LDL remains speculative. The inadequacy of the metrics of pro-oxidative and antioxidative status in vivo needs to be resolved before the role of oxidative damage to LDL can be adequately evaluated.

Postprandial Lipid Changes

Traditionally, plasma lipid and lipoprotein measurements used to evaluate CHD risks have, for largely technical reasons, been performed in the fasting (postabsorptive) state. Plasma levels of metabolites are more easily characterized in steady-state conditions than in a nonsteady state. From a pathophysiological perspective,

however, events in the postprandial state may be critical in atherogenesis (Zilversmit 1979). Some studies explored effects of cigarette smoking on postprandial lipid metabolism (Mero et al. 1998). For example, total triglycerides increased to higher levels after a mixed meal in smokers than in nonsmokers. These researchers observed increases in plasma APO B level and reductions in levels of APO A-I, lipoprotein A-I, HDLc, and LDL-APO B after a meal. Other investigators postulated that the mechanisms underlying altered postprandial lipid changes in smokers include lower LPL activity (Freeman et al. 1998), but higher endogenous production of VLDL-total triglycerides by the liver has not been excluded. The postprandial effects of cigarette smoking in particular and their role in atherogenesis in general are not completely understood.

Metabolism of Free Fatty Acids

Changes in FFAs (nonesterified fatty acids) are attributed to an increase in adipocyte lipolysis, and they represent the most well-characterized mechanistic action of cigarette smoking in the context of alterations in lipids and lipoproteins. Many studies reported higher plasma levels of FFAs in smokers than in nonsmokers (Kershbaum et al. 1963; Bizzi et al. 1972; Walsh et al. 1977; Hellerstein et al. 1994; Neese et al. 1994).

Using stable (nonradioactive) isotopes to measure FFA kinetics, researchers demonstrated that cigarette smoking immediately and markedly increased influx of FFAs into the bloodstream and thereby raised plasma levels of FFA (Hellerstein et al. 1994; Neese et al. 1994). Plasma FFAs are primarily derived from adipose tissue by lipolytic breakdown of stored triglycerides. Catecholamines stimulate hormone-sensitive lipase activity in adipose tissue and oppose various antilipolytic actions of insulin. Increases in FFA levels and flux induced by smoking were temporally correlated with increases in plasma epinephrine levels (Watts 1960; Bizzi et al. 1972; Arcavi et al. 1994; Hellerstein et al. 1994; Neese et al. 1994). These increases are prevented by β -adrenergic blockers. Nicotine increases the adrenal medullary release of epinephrine in persons with nontolerance of nicotine (Arcavi et al. 1994). Therefore, the model implicated as the cause of increases in plasma FFA levels induced by cigarette smoking seems clear: cigarette smoking \rightarrow nicotine \rightarrow increased plasma epinephrine \rightarrow increased lipolysis in adipose tissue \rightarrow increased release of FFAs into plasma \rightarrow increased plasma levels of FFA.

The fate of FFAs released into the bloodstream in response to cigarette smoking is also relevant. Cigarette smoking increases expenditure of energy through the activity of nicotine and catecholamines (Ilebekk et al.

1975; Perkins et al. 1989; Hellerstein et al. 1994; Neese et al. 1994). However, most of the FFAs released in response to cigarette smoking are not oxidized but taken up and reesterified to triglycerides in tissues, particularly the liver. This conclusion was partly based on kinetic studies that compared the rates at which plasma FFA appeared with whole-body rates of fat oxidation (Hellerstein et al. 1994; Neese et al. 1994). These studies demonstrated that the rate of FFA influx into plasma in response to cigarette smoking greatly exceeded changes in whole-body fat oxidation.

Accordingly, the catabolic effects of cigarette smoking on total adipose triglycerides do not directly promote oxidation of body fat (weight loss); instead, the primary result is overproduction of VLDL-total triglycerides (Hellerstein et al. 1994; Neese et al. 1994). This “futile cycle,” a substrate cycle in which adipose triglycerides are converted to hepatic VLDL triglycerides, is modestly wasteful of energy. It accounts for about 5 percent of the thermogenic effects of long-term cigarette smoking—for example, fewer than 10 kilocalories (kcal)/day if cigarette smoking increases total energy expenditure by 200 kcal/day. This cycle, however, may be the central driving force behind the atherogenic dyslipidemia associated with cigarette smoking. Overproduction of VLDL-total triglycerides typically results in elevated plasma levels of VLDL-total triglycerides and APO B, as well as increased numbers of LDL particles (Sniderman et al. 2001). Furthermore, high VLDL-total triglycerides contribute to lowering of HDLc through CETP-mediated transfer of cholesterol-ester from HDL to VLDL particles (Brousseau et al. 2004; Ruggeri et al. 2005). Influx of FFAs into the liver for reesterification and secretion of total triglycerides is most likely a major reason for the low HDLc levels observed in smokers, but perhaps it does not represent the entire effect of smoking on HDLc (Criqui et al. 1980; Muscat et al. 1991; Freeman and Packard 1995).

If nicotine-stimulated release of catecholamine is responsible for the hypertriglyceridemia and low HDLc levels observed in smokers, NRT as an adjunct to smoking cessation should logically prevent improvements in plasma lipids and lipoproteins after smoking cessation. Moffatt and colleagues (2000) reported that nicotine-patch therapy prevented the normalization of HDLc levels observed with smoking cessation in the absence of the nicotine patch. The patch also prevented weight gain after smoking cessation (Allen et al. 2005), a finding consistent with the hypothesis that shared catecholamines are the basis for two important effects of cigarette smoking: weight reduction and dyslipidemia. Other studies, however, did not confirm that use of the nicotine patch as an agent for smoking cessation prevents improvements in HDL levels (Allen et al. 1994). In addition, lipid profiles

are similar in persons who use smokeless tobacco and in those who do not use any form of tobacco. To the extent that dyslipidemia contributes to vascular disease associated with cigarette smoking, it is important to determine the full range of effects of NRT on lipid and lipoprotein metabolism.

Reverse Cholesterol Transport

RCT refers to the pathway by which cholesterol is mobilized from tissues, carried through the blood, and excreted from the body. HDL and its associated membrane receptors (e.g., SR-B₁, ABC-A₁, and ABC-G₁), plasma enzymes (e.g., CETP and phospholipid transfer protein), APOs (e.g., APO A-I), and hepatobiliary enzymes (e.g., cholesterol 7 α -hydroxylase) constitute a system that mediates the complex process of RCT through pathways that are increasingly well characterized in molecular terms (Neese et al. 1994; Tall 1998). RCT is generally accepted as the leading explanation for the cardioprotective activity of HDL, although other actions of HDL (e.g., antioxidative and anti-inflammatory) may also be involved.

Flux through the RCT pathway and, thus, antiatherogenic activity cannot be predicted simply from plasma levels of HDL or APO A-I (Tall 1998). Thus, changes in levels of HDLc, VLDL-total triglycerides, and other lipoproteins may not fully capture the effects of cigarette smoking on pro-atherogenic or antiatherogenic fluxes such as RCT. Until more recently, however, there were no viable techniques for measuring RCT fluxes. Therefore, this question could be addressed only indirectly—for example, through changes in lipid transfer proteins in plasma that may influence the efficiency of RCT. Studies reported decreases in activity of CETP and phospholipid transfer protein in smokers after they had smoked a cigarette (Zaratin et al. 2004).

Reduced capacity for remodeling HDL particles in the vascular compartment could alter these fluxes in a manner not reflected by HDLc levels. This possibility will remain speculative, however, until RCT fluxes are measured in humans. The ability to directly measure effects of cigarette smoking on the cardioprotective process of RCT could provide a major tool for advancing understanding of the role of lipids in causing vascular disease associated with cigarette smoking.

Effects of Smoking Cessation

Research on smoking cessation largely confirmed the associations observed in smokers (Gordon et al. 1975;

Rabkin 1984; Stamford et al. 1986; Critchley and Capewell 2004). Many studies documented the return of normal levels of plasma lipids and lipoproteins after cessation of cigarette smoking.

Therapeutic Implications of Pathogenic Mechanisms

If stimulation of lipolysis underlies the atherogenic dyslipidemia associated with cigarette smoking, inhibition of lipolysis might be an effective therapeutic strategy to improve blood lipid profiles in smokers or persons receiving NRT. This strategy is an attractive approach in one sense because inhibition of lipolysis does not block the thermogenic actions of nicotine. The cycle of lipolysis and reesterification accounts for less than 5 percent of the increase in energy expenditure observed in cigarette smokers (Hellerstein et al. 1994; Neese et al. 1994). Another consideration is that if FFAs released by lipolysis are involved in the insulin resistance reportedly associated with cigarette smoking (Facchini et al. 1992), lipolysis inhibitors may have an additional therapeutic use.

Niacin, a hypolipidemic agent, is thought to act at least partly by inhibiting total triglyceride lipolysis in adipose tissue (Meyers et al. 2004). The use of niacin in smokers who are at high risk for CHD has not been fully investigated. The side effects of niacin, including cutaneous flushing and worsening of insulin resistance in some persons, perhaps from effects on pancreatic islet function, may discourage its clinical use. The impact of niacin and its analogs on lipolysis is complex. They induce a rebound overshoot of lipolysis after initial inhibition, but niacin does reduce production of VLDL-total triglycerides (Wang et al. 2001).

Other strategies for use of lipolysis inhibitors to prevent CHD related to cigarette smoking may require development of specific antilipolytic agents that are well tolerated. One possibility is the thiazolidinedione class of insulin-sensitizing drugs. In one study, such drugs reduced lipolysis in adipose tissue, perhaps by activating glyceroneogenesis and thereby promoting intra-adipocytic reesterification of FFAs (Chen et al. 2005). No studies are known to have tested the efficacy of thiazolidinediones in smokers to determine effects on lipid abnormalities or sensitivity to insulin. However, recent research indicates that rosiglitazone (a thiazolidinedione) increases CHD risk, although pioglitazone, another drug in the same class, does not increase this risk (Lincoff et al. 2007; Nissen and Wolski 2007). Thus, it is unclear whether the possible benefits of this class of drugs in smokers will be pursued.

Summary

Effects of cigarette smoking on standard measures of blood lipids and lipoproteins are well characterized. The most important effects are to lower levels of HDLc and increase levels of total triglycerides. The metabolic mechanisms underlying these changes are known to some extent, particularly the catecholamine-mediated increase in adipocyte lipolysis, changes in plasma levels

of FFAs, and reesterification of FFAs by the liver. However, the predicted effect from changes in standard lipid risk factors for vascular disease associated with cigarette smoking appears to be modest. Future research will reveal whether this estimation of a modest effect is a true estimate of the pathogenic importance of smoking-induced changes in blood lipid levels or an inability to measure the full effects of cigarette smoking on atherogenesis.

Cardiovascular Biomarkers

Biomarkers of smoking-related CVD risk are useful for stratifying individual risk and, perhaps, for assessing product risk. Biomarkers for CVD risk can be divided into three categories: (1) constituents of cigarette smoke that contribute to CVD, (2) physiological changes involving potential mechanisms of CVD, and (3) chemical biomarkers of cardiovascular dysfunction and disease (Table 6.3). Studies showed that cigarette smoking altered many of the CVD biomarkers, as evidenced by comparisons of smokers with nonsmokers and former smokers. However, fewer studies prospectively examined reversal of such changes after smoking cessation. More important, to date, there are no data on how changes in smoking-related biomarkers predict risk of disease.

Three constituents of cigarette smoke received the greatest attention as potential contributors to CVD: CO measured as exhaled CO or as blood carboxyhemoglobin, nicotine, and oxidant chemicals (Benowitz 2003). These constituents are used as general biomarkers of exposure to tobacco or tobacco smoke. Apparently, no direct measures of levels of oxidizing chemicals in the body have been developed, but numerous measures of the biologic consequences of exposure to oxidizing chemicals exist. Exposure to particulate matter in cigarette smoke is likely to contribute to CVD in smokers (Brook et al. 2004; Vermeylen et al. 2005; Bhatnagar 2006), but no direct biomarkers of particulate exposure are available. Particulate matter appears to affect oxidative stress, coagulability, and inflammation, for which biomarkers are available. A lesser body of research suggests that PAHs and other constituents of tobacco smoke may also contribute to atherogenesis (Penn and Snyder 1988, 1996). Urine levels of PAH metabolites can also be measured in smokers; 1-hydroxypyrene is most widely used for this purpose.

Cigarette smoke exposes the smoker to high levels of potentially oxidizing chemicals (Burke and FitzGerald 2003). In one study, cigarette smoking increased levels of lipid peroxidation products, such as F₂-isoprostanes, in

the plasma and urine (Nowak et al. 1987). Other markers of oxidative stress in smokers included higher plasma levels of oxidized LDL and oxidized fibrinogen, higher urine levels of substances reactive with thiobarbituric acid, and reduced plasma levels of antioxidant vitamins such as E, C, and beta-carotene.

The hemodynamic effects of cigarette smoking can be observed while a person smokes a cigarette. These effects include elevation in heart rate, blood pressure, and cardiac output. Coronary blood flow, as assessed by coronary perfusion studies, may increase or decrease with smoking, depending on underlying atherosclerosis and endothelial function (Czernin and Waldherr 2003).

Researchers have proposed numerous biomarkers for measuring endothelial dysfunction, and many of these biomarkers are affected by cigarette smoking. The functional assessment most widely used is flow-mediated arterial vasodilation (Puranik and Celermajer 2003), a test that measures the diameter of the brachial artery in response to changes in forearm blood flow. The brachial artery is imaged by using Doppler ultrasonography before and after release of a blood pressure cuff that is inflated over the forearm to occlude arterial blood flow. With release of the cuff, the increase in blood flow triggers an increase in the diameter of the brachial artery that is mediated by release of NO and prostacyclin by endothelial cells. Many researchers demonstrated impairment of flow-mediated dilation in populations of active smokers and persons exposed involuntarily to cigarette smoke, but estimates of impairment in persons with no exposure to smoke overlapped considerably with those for the other two groups. Other potential markers of endothelial dysfunction that can be measured in the blood include ADMA, von Willebrand factor, tPA, E-selectin, and P-selectin. Prostacyclin metabolites can be measured in the urine (Cooke 2000). Selectins are adhesion molecules released by both endothelial cells and platelets (Ley 2003).

Table 6.3 Biomarkers of risk for cardiovascular disease from exposure to cigarette smoke

Biomarker	Measurement of:	Study			
		Smokers vs. nonsmokers	Change with smoking cessation	Dose-response relationship	Change with reduced smoking
Chemical biomarkers					
Carbon monoxide	Delivery of potential chemical toxins	SRNT Subcommittee on Biochemical Verification 2002	SRNT Subcommittee on Biochemical Verification 2002	Benowitz and Jacob 1984	Hecht et al. 2004
Nicotine and cotinine	Delivery of potential chemical toxins	SRNT Subcommittee on Biochemical Verification 2002	SRNT Subcommittee on Biochemical Verification 2002	Benowitz and Jacob 1984	Benowitz et al. 1983
Physiological and biochemical markers					
Blood pressure	Hemodynamic effects	Benowitz et al. 2002	Benowitz et al. 2002		
C-reactive protein	Inflammation	Bazzano et al. 2003	Bazzano et al. 2003	Bazzano et al. 2003	
Carotid and femoral artery intima-media thickness	Atherosclerosis	Wallenfeldt et al. 2001			
Circulating endothelial precursor cells	Endothelial function	Kondo et al. 2004	Kondo et al. 2004	Kondo et al. 2004	
E-selectin	Endothelial function	Bazzano et al. 2003	Bazzano et al. 2003		
Fibrinogen	Hypercoagulable state	Bazzano et al. 2003	Bazzano et al. 2003	Bazzano et al. 2003	
Flow-mediated dilation	Endothelial function	Czernin and Waldherr 2003	Czernin and Waldherr 2003	Czernin and Waldherr 2003	
Glucose-clamping studies	Insulin resistance	Eliasson et al. 1997a	Eliasson et al. 1997a	Eliasson et al. 1997a	
HDL cholesterol	Lipid marker	Stubbe et al. 1982	Stubbe et al. 1982		
Heart rate	Hemodynamic effects	Benowitz et al. 1984	Benowitz et al. 1984		
Hemoglobin A _{1c}	Insulin resistance	Sargeant et al. 2001			
Homocysteine	Hypercoagulable state	Bazzano et al. 2003	Bazzano et al. 2003	Bazzano et al. 2003	

Table 6.3 Continued

Biomarker	Measurement of:	Study			
		Smokers vs. nonsmokers	Change with smoking cessation	Dose-response relationship	Change with reduced smoking
Insulin/glucose ratio	Insulin resistance	Zavaroni et al. 1994			
Interleukin-6	Inflammation	Bermudez et al. 2002	Bermudez et al. 2002		
Nuclear coronary perfusion studies	Hemodynamic effects	Czernin and Waldherr 2003			Mahmariyan et al. 1997
Oxidized LDL cholesterol	Oxidative stress/lipid marker	Panagiotakos et al. 2004	Panagiotakos et al. 2004		
P-selectin	Endothelial function	Bazzano et al. 2003	Bazzano et al. 2003		
Red blood cell mass	Hypercoagulable state	Blann et al. 1997	Blann et al. 1997		
Serum concentrations of vitamin C	Oxidative stress	Lykkesfeldt et al. 2000			
Serum triglycerides	Lipid marker	Axelsen et al. 1995			
Soluble intercellular adhesion molecule-1	Inflammation	Scott et al. 2000	Scott et al. 2000	Scott et al. 2000	
Thiobarbituric acid reactive substances	Oxidative stress				
Tissue plasminogen activator	Hypercoagulable state	Simpson et al. 1997			
Urine F ₂ -isoprostanes	Oxidative stress	Morrow et al. 1995	Pilz et al. 2000		
Urine thromboxane A ₂ metabolite	Hypercoagulable state	Nowak et al. 1987	Saareks et al. 2001		
von Willebrand factor	Endothelial function	Blann et al. 1997	Blann et al. 1997		
White blood cell count	Inflammation	Jensen et al. 1998	Jensen et al. 1998	Jensen et al. 1998	

Note: **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **SRNT** = Society for Research on Nicotine and Tobacco.

Markers of the hypercoagulable state include increased urine levels of thromboxane A_2 metabolites. Thromboxane A_2 is released when platelets aggregate *in vivo*, and its metabolites in urine are a useful noninvasive measure of the point of activation (Nowak et al. 1987). Other relevant biomarkers of a hypercoagulable state include fibrinogen, red blood cell mass, blood viscosity, tPA, PAI-1, homocysteine, and P-selectin (Benowitz 2003).

Biomarkers used to assess an inflammatory state include total leukocyte and neutrophil counts and levels of CRP, fibrinogen, and interleukin-6 (Pearson et al. 2003). In addition, the counts of several cell-surface adhesion molecules increased in inflammatory states. These molecules included ICAM, sVCAM-1, and monocyte chemoattractant protein-1.

Another study found several markers to be useful for assessing insulin resistance (Eliasson 2003). For example, in persons with insulin resistance, levels of plasma glucose were likely to be elevated in fasting status and two hours after eating. HbA_{1c} levels, which reflect plasma glucose levels throughout the day, were elevated in persons in a hyperglycemic state. The ratio of insulin to glucose after glucose loading was useful as an index of insulin sensitivity. The most definitive investigations were glucose-clamping studies, in which insulin levels were measured when the glucose level was constant or vice versa.

Numerous standard markers of lipids may be altered in cigarette smokers. These markers include HDLc, LDLc, the ratio of total cholesterol to HDL, and serum triglyceride levels.

Nuclear coronary perfusion studies with or without physical exercise are among several functional studies for diagnosing cardiovascular dysfunction or disease. They indicate that cigarette smoking reduces cardiac perfusion in patients with coronary disease (Czernin and Waldherr 2003). Reserve in endothelial function can be assessed by studying flow-mediated dilation (see "Endothelium-Dependent Vasodilation" earlier in this chapter). Findings in another study indicate that vascular disease can be assessed by measuring intima-media thickness of the

carotid and femoral arteries by ultrasonography, which provides a direct measure of early atherosclerotic changes in blood vessels (de Groot et al. 2004).

Numerous cardiovascular biomarkers that might be used to assess the effects of cigarette smoking and involuntary smoking and that are expected to increase the risk of CVD are discussed here. Many biomarkers, however, do not reflect causal pathways related to development of CVD. Instead, they reflect the pathophysiological effects of the constituents of cigarette smoke. In addition, many biomarkers are influenced by processes and risk factors that are independent of cigarette smoking. Many of the same abnormalities produced by smoking are also produced by diabetes, hypercholesterolemia, and hypertension. Thus, it is unclear which biomarkers are most specific to cigarette smoking. It is also unclear which biomarkers best predict the risk of CVD attributable to cigarette smoke. Also, a given biomarker profile can indicate any of several marked differences in a person's susceptibility to CVD.

The potential exists to develop improved biomarkers for CVD by using advances in high-throughput genomics and by examining the relationships of gene polymorphisms or alterations in protein expression or activity to smoking-induced disease (Zhang et al. 2001). Emerging genomic and proteomic technologies may cast light on the signaling pathways activated by smoking and the constituents of tobacco smoke that culminate in cardiovascular dysfunction. Such approaches may also contribute to an understanding of individual differences in susceptibility to the cardiovascular complications of smoking.

Numerous studies of clinical genetics examined differences in susceptibility to smoking-induced CVD as a function of different genetic variants (Wang et al. 2003). Such studies, combined with genomic and proteomic approaches, may provide mechanistic information on pathogenesis and, in combination with other biomarkers, may result in better predictions of cardiovascular risk in smokers.

Smoking Cessation and Cardiovascular Disease

Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with or without CVD (USDHHS 1990). Smoking directly accelerates atherogenesis, causes acute cardiovascular events, and contributes to and acts synergistically with other risk factors, such as hyperlipidemia and diabetes (see "Smoking and Diabetes" earlier in this chapter). Although cigarette smoking

does not cause hypertension, smoking is associated with higher blood pressure in persons with hypertension and enhances the likelihood of complications, including progression of renal disease in patients with hypertension (Green et al. 1986; Mann et al. 1991; McNagny et al. 1997; Regalado et al. 2000). One study demonstrated that cigarette smoking was a substantial contributor to morbidity

and mortality in patients with left ventricular dysfunction (Suskin et al. 2001). In such patients, the benefit of reducing the likelihood of death by smoking cessation is equal to or greater than the benefit of therapy with inhibitors of ACE, β -blockers, or spironolactone. Smoking cessation is particularly important in patients with diabetes. For these patients, smoking markedly increases cardiovascular risks, including the risk that diabetic nephropathy will progress. Smoking also increases insulin resistance and increases the difficulty of controlling diabetes. For these and other reasons, smoking cessation in patients with CVD is an essential therapeutic intervention.

The 1990 Surgeon General's report on smoking cessation (USDHHS 1990) outlines the evidence that stopping smoking helps to prevent CVD, and subsequent research has reinforced this concept (Hasdai et al. 1997a; van Domburg et al. 2000; Wilson et al. 2000). Estimates in case-control and cohort studies indicate that most risk reduction for mortality occurred in the first one to three years after smoking cessation, and approximately one-half of the risk of smokers for a nonfatal MI was eliminated in the first year after cessation. It takes about three to five years of abstinence from smoking for most of the excess CVD risk to be gone (USDHHS 1990; Lightwood and Glantz 1997).

Smoking cessation after MI reduces the risk of cardiovascular morbidity and mortality by 36 to 50 percent (USDHHS 1990; Kumanan et al. 2000; Wilson et al. 2000; Rea et al. 2002; Critchley and Capewell 2003). Smoking cessation is highly cost-effective (Krumholz et al. 1993; Lightwood 2003) and is recommended in professional guidelines for prevention of recurrent cardiovascular events in persons with known CVD (Smith et al. 2001). Evidence supports the central roles of smoking cessation and eliminating exposure to secondhand smoke in preventing development and progression of CVD (USDHHS 1990, 2006; Benowitz and Gourlay 1997; Hasdai et al. 1997a; van Domburg et al. 2000; Wilson et al. 2000; Goldenberg et al. 2003).

Methods

Tobacco use and dependence are determined by complex physiological and psychological factors. Use of nicotine causes tolerance, physical dependence, and a withdrawal syndrome when smoking is stopped (USDHHS 1988). Use of tobacco is a learned behavior that becomes part of the daily routine of a smoker and is often used to cope with stress, anxiety, anger, and depression (USDHHS 1988; Rigotti 2002).

Interventions to achieve smoking cessation target both the physiological and psychological factors that

contribute to tobacco use. Evidence from randomized controlled clinical trials of cessation methods has been summarized in meta-analyses conducted independently by two groups—the U.S. Public Health Service (PHS) and the Cochrane Database of Systematic Reviews (the Cochrane Library). These reviews document the efficacy of both psychosocial counseling and pharmacologic agents for cessation (Fiore et al. 2000, 2008). Combination of the two methods is the most effective strategy. Interventions in psychosocial counseling range from brief counseling by the physician to intensive, cognitive-behavioral counseling interventions during several weeks. There is a dose-response relationship between behavioral treatment and smoking cessation; that is, the efficacy of counseling interventions increases with increased intensity and duration of the program (Fiore et al. 2000, 2008; USDHHS 2000). The U.S. Food and Drug Administration (FDA) has approved pharmacotherapy for tobacco dependence. The pharmacotherapy includes five types of NRT (gum, transdermal patch, nasal spray, vapor inhaler, and lozenge), sustained-release bupropion, and varenicline. PHS designated these medications as first-line therapies for smoking cessation in *Treating Tobacco Use and Dependence: Clinical Practice Guidelines* (Fiore et al. 2000). Two other drugs—nortriptyline and clonidine—were efficacious in randomized controlled trials and were shown to be effective in the Cochrane review and in meta-analyses conducted for development of the PHS guidelines (Fiore et al. 2000, 2008; Gourlay et al. 2004; Hughes et al. 2004b). These drugs have not been approved by FDA for use in smoking cessation, and in the PHS report, they are designated as second-line interventions. There is no evidence to support use of alternative therapies such as acupuncture and hypnosis for smoking cessation (Abbot et al. 1998; Fiore et al. 2000, 2008; White et al. 2002).

Interventions

Multiple randomized controlled clinical trials demonstrated the benefits of counseling patients with CVD on smoking cessation (Table 6.4) (Thomson and Rigotti 2003). In contrast, relatively few clinical trials tested the safety or efficacy of pharmacotherapy for treating smokers with CVD (Table 6.5). Researchers raised concerns about the safety of NRT and sustained-release bupropion in patients with CVD, because both agents can have sympathomimetic activity and can theoretically increase myocardial work, and NRT might also reduce the myocardial oxygen supply through coronary vasoconstriction by aggravating endothelial dysfunction (Benowitz and Gourlay 1997).

Table 6.4 Randomized controlled trials of counseling for smokers hospitalized with cardiovascular disease

Study	Population	In-hospital counselor, duration of counseling	Postdischarge counseling	Smoking cessation rates (%)	RR or OR (95% CI) p value
Taylor et al. 1990	Acute MI I vs. C: 86 vs. 87 5 hospitals San Francisco Bay, California	Nurse Average duration 3.5 hours for baseline and postdischarge counseling	TC: 1, 2, 3 weeks, then every month x 4 CV for relapse after smoking cessation	12 months I vs. C: 61 vs. 32	1.9 (1.3, 2.8) p <0.001
Ockene et al. 1992	Coronary angiogram I vs. C: 135 vs. 132 3 hospitals Massachusetts	Health educator 30 minutes	TC: 1, 3 weeks; 3 months for relapse after smoking cessation; 2 and 4 months for relapse after smoking cessation	12 months SR: 57 vs. 48 I vs. C: 35 vs. 28 3-vessel CAD I vs. C: 65 vs. 41	1.5 (0.9, 2.4) p = 0.06 1.4 (0.8, 2.4) p = 0.19 13.4 (3.1, 58.0)
DeBusk et al. 1994	Acute MI I vs. C: 131 vs. 121 5 hospitals San Francisco Bay, California	Nurse Duration not stated	TC: 2 days, 1 week, monthly x 6	12 months I vs. C: 70 vs. 53	p = 0.03
Rigotti et al. 1994	Coronary artery bypass graft I vs. C: 44 vs. 43 Massachusetts General Hospital, Boston	Nurse 60 minutes	TC: once per week x 3	12 months I vs. C: 61 vs. 54	p >0.52
Dornelas et al. 2000	Acute MI I vs. C: 54 vs. 46 Hartford Hospital Hartford, Connecticut	Psychologist Duration not stated	TC: <1, 4, 8, 12, 16, 20, and 26 weeks	6 months SR: 67 vs. 43 12 months SR: 55 vs. 34 FV: 66 vs. 37	p <0.05 p = 0.04 p <0.05
Hajek et al. 2002	Acute MI or cardiac bypass surgery I vs. C: 267 vs. 273 17 hospitals England	Nurse 20–30 minutes	None	12 months I vs. C: 37 vs. 41	p = 0.40
Quist-Paulsen and Gallefoss 2003	Acute MI, unstable angina, or cardiac bypass surgery I vs. C: 100 vs. 118 1 hospital Norway	Cardiac nurses (no training) Duration not stated	TC: 2 days, 1 week, 3 weeks, 3 months, 5 months CV: 6 weeks	12 months I vs. C: 50 vs. 37	Absolute risk reduction: 35% (0%, 26%)

Note: CAD = coronary artery disease; CI = confidence interval; CV = clinic visit; FV = validated by family; I vs. C = intervention versus control; MI = myocardial infarction; OR = odds ratio; RR = relative risk; SR = self-reported; TC = telephone call.

Table 6.5 Randomized controlled trials of pharmacologic interventions for smoking cessation in patients with cardiovascular disease

Study	Population	Treatment	Counseling (I & C)	Smoking cessation rates ^a (%)	RR or OR (95% CI), p value	Adverse events (I vs. C)
Transdermal nicotine						
Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease 1994	Stable outpatients with CVD I vs. C: 77 vs. 79 General medical and cardiology clinics Media advertising 4 centers United States	14 mg could be increased to 21 mg after 1 week 5 weeks	Group counseling weekly x 5	5 weeks I vs. C: 36 vs. 22	p <0.05	No differences in episodes of angina or change in blood pressure, heart rate, or EKG readings
Joseph et al. 1996 Joseph and Antonnucio 1999	Stable outpatient veterans with CVD I vs. C: 288 vs. 287 10 Veterans Affairs medical centers United States	21 mg x 6 weeks 14 mg x 2 weeks 7 mg x 2 weeks	Behavioral counseling 15 minutes at study entry 10 minutes at 1 and 6 weeks	14 weeks I vs. C: 21 vs. 9 6 months I vs. C: 14 vs. 11 12 months I vs. C: 10 vs. 12	p = 0.001 p = 0.67 p = 0.41	No difference in primary endpoints (death, MI, cardiac arrest, or admission to hospital) or secondary endpoints (other CVD)
Tzivoni et al. 1998	Stable outpatients with CAD in smoking cessation program I vs. C: 52 vs. 54 2 centers Israel	21 mg (>20 cigarettes/day) or 14 mg (<20 cigarettes/day) 2 weeks	Smoking cessation program Group meetings weekly	2 weeks I vs. C: 73 vs. 52	p <0.05 ^b	No differences in EKG changes, exercise testing, or heart rate and blood pressure
Bupropion-sustained release						
Tonstad et al. 2003	Stable outpatients with CVD I vs. C: 313 vs. 313 28 centers in 10 European countries	150 mg BID 7 weeks Target date for smoking cessation 7–14 days after starting drug	TC: 1 day before smoking cessation 3 days afterward Monthly x 12 CV: brief counseling at 3, 6, and 12 months	12 months I vs. C: 27 vs. 12 Continuous abstinence weeks 4–52 I vs. C: 22 vs. 9	p <0.001 p <0.001	Cardiovascular events I vs. C: 24 vs. 14 (p = NS)

Table 6.5 Continued

Study	Population	Treatment	Counseling (I & C)	Smoking cessation rates ^a (%)	RR or OR (95% CI), p value	Adverse events (I vs. C)
Rigotti et al. 2006	Acute MI, unstable angina, or other CVD hospital admission I vs. C: 124 vs. 124 5 academic medical centers New England	150 mg BID 12 weeks Started during hospitalization	Nurse counseling for 40 minutes in hospital TC: 48 hours, 1, 3, 8, and 12 weeks after discharge	12 weeks I vs. C: 37 vs. 27 12 months I vs. C: 25 vs. 21	1.61 (0.74, 2.76) p = 0.08 1.23 (0.68, 2.23) p = 0.49	No difference in CVD mortality (0% vs. 2%) or in CVD events at 12 weeks (16% vs. 14%, IRR 1.22 [0.61–2.48]) or 1 year (26% vs. 18%, IRR 1.56 [0.88, 2.82])

Note: **BID** = twice a day; **CAD** = coronary artery disease; **CI** = confidence interval; **CV** = clinic visit; **CVD** = cardiovascular disease; **EKG** = electrocardiogram; **I vs. C** = intervention versus control; **IRR** = incidence rate ratio; **mg** = milligrams; **MI** = myocardial infarction; **NS** = not significant; **OR** = odds ratio; **RR** = relative risk; **TC** = telephone call.

^aAbstinence measured by point prevalence (no smoking in previous seven days) unless otherwise noted.

^bp value calculated with χ^2 test.

Counseling

Several randomized controlled clinical trials demonstrated the efficacy of counseling for patients hospitalized with CVD (Table 6.4). The evidence for efficacy is strongest for patients who had acute MI (Pozen et al. 1977; Taylor et al. 1990; Ockene et al. 1992; DeBusk et al. 1994; Dornelas et al. 2000). In one study, an intensive, nurse-managed intervention to achieve smoking cessation for 173 smokers hospitalized with an acute MI doubled the cessation rates at one year (61 versus 32 percent, $p < 0.001$) (Taylor et al. 1990). At the bedside, the nurse delivered a 30-minute cognitive-behavioral counseling session focused on self-efficacy and prevention of relapse. Additional counseling was delivered by telephone at one, two, and three weeks after discharge and then every month for four months. A second study of the same patients expanded the nurse-delivered counseling model to target multiple cardiac risk factors (DeBusk et al. 1994). This study also reported rates of smoking abstinence higher than those in the first study (Taylor et al. 1990). A third trial assigned 100 consecutive smokers admitted with MI to either minimal care or bedside counseling with seven follow-up telephone calls (Dornelas et al. 2000). Smoking cessation rates at one year were higher in the intervention group than in the minimal care group (55 versus 34 percent, $p < 0.05$). A more recent study of 240 smokers admitted to the hospital for MI, unstable angina, or cardiac bypass surgery demonstrated that counseling by cardiac nurses untrained in counseling and then follow-up counseling during the next five

months reduced smoking rates at one year (50 versus 37 percent, absolute risk reduction, 13 percentage points [95 percent CI, 0 to 26 percentage points]) (Quist-Paulsen and Gallefoss 2003).

Other studies that lacked the same intensity of follow-up after hospital discharge produced less impressive results. One study examined a multicomponent behavioral smoking intervention delivered to 267 patients having coronary angiography (Ockene et al. 1992). Compared with patients who did not receive the intervention, those with angiography had higher rates of validated smoking abstinence at 6 months (45 versus 34 percent) and 12 months (35 versus 28 percent), but these differences were not statistically significant. Two randomized trials (Rigotti et al. 1994; Hajek et al. 2002) and one partially randomized trial (Bolman et al. 2002) examined the effects of inpatient counseling with minimal follow-up in cardiac patients. These studies showed no improvement in abstinence rates with the counseling intervention versus usual care.

The most successful counseling interventions for cardiac inpatients include high-intensity baseline counseling with sustained contacts after discharge for prevention of relapse. However, even with the most successful counseling interventions, at least 40 percent of smokers who have cardiac disease resume smoking within one year. Guidelines for smoking cessation recommend addition of pharmacotherapy to counseling (Fiore et al. 2000, 2008). Pharmacotherapy has the potential to improve smoking cessation rates in smokers with CVD

(see “Nicotine Replacement Therapy” and “Bupropion” later in this chapter).

Nicotine Replacement Therapy

NRT helps smokers stop smoking and also reduces nicotine withdrawal symptoms, which begin a few hours after the last cigarette is smoked and can last up to four weeks (Hughes et al. 1992). The typical withdrawal syndrome is characterized by agitation, anxiety, depressed mood, difficulty concentrating, increased appetite, insomnia, irritability, restlessness, and an intense craving to smoke. Most smokers who stop smoking relapse to smoking within the first week, when withdrawal symptoms are strongest.

In multiple clinical trials, all the NRT products approximately doubled rates of smoking abstinence compared with rates for participants receiving a placebo (Fiore et al. 2000; Silagy et al. 2004). Meta-analyses conducted for PHS demonstrated ORs of 1.9 (95 percent CI, 1.7–2.2) for the nicotine patch and 1.5 (95 percent CI, 1.3–1.8) for nicotine gum. Meta-analyses from the Cochrane Library found similar results; ORs were 1.74 (95 percent CI, 1.57–1.93) for the patch and 1.66 (95 percent CI, 1.52–1.81) for the gum (Silagy et al. 2004). For smokers with greater dependence on nicotine, the 4-mg dose of nicotine gum was more effective than the 2-mg dose. Maximum effectiveness depended on correct chewing techniques. Similar ORs were reported after meta-analyses of data on the nicotine inhaler and nicotine nasal spray (Fiore et al. 2000). Only one study compared the efficacy of four forms of NRT (patch, gum, inhaler, and nasal spray); they demonstrated similar efficacy rates after 12 weeks of follow-up (Hajek et al. 1999).

Nicotine directly affects the cardiovascular system by multiple mechanisms (see “Cigarette Smoke Constituents and Cardiovascular Disease” earlier in this chapter). The various effects lead to increased heart rate, blood pressure, and myocardial contractility, and reduced coronary blood flow. Nicotine may also contribute to insulin resistance and development of a more atherogenic lipid profile. The nicotine dose in NRT products is usually lower than the dose from smoking, but there have been concerns about the safety of NRT in patients with CVD. Case reports in the medical literature described atrial fibrillation, MI, and stroke in patients receiving NRT (Joseph and Fu 2003). It is difficult to assess the cardiovascular risk from NRT on the basis of these reports, because of the inability to control for individual risk factors for these events, especially that these persons were smokers (Benowitz and Gourlay 1997; Joseph and Fu 2003).

To date, three randomized controlled trials of transdermal use of nicotine have been conducted in patients

with stable CVD. The first study enrolled 156 patients with CHD and randomly assigned them to receive either 14-mg nicotine patches or a placebo for five weeks (Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease 1994). The dose was increased to 21 mg if smoking persisted. Smoking abstinence was achieved at five weeks by 36 percent in the patch group and 22 percent in the placebo group ($p < 0.05$). Patients recorded all episodes of angina, palpitations, and other cardiac symptoms in daily diaries and had a 12-lead electrocardiogram at three time points. The nicotine patch did not affect the frequency of angina, arrhythmias, or depression of the ST segment (isoelectric period) on electrocardiograms during the five weeks of treatment, even in patients who smoked intermittently.

A second randomized trial of transdermal nicotine included 584 outpatients with CVD from 10 Veterans Affairs hospitals (Joseph et al. 1996). The participants were randomly assigned to receive 21-mg patches or a placebo for 10 weeks. Primary cardiovascular endpoints during 14 weeks of follow-up included MI, cardiac arrest, death, and hospital admission for angina, dysrhythmia, or congestive heart failure. The two groups did not differ in the proportion of patients who reached at least one cardiovascular endpoint (5.4 versus 7.9 percent, $p = 0.23$). Concomitant use of the nicotine patch and smoking was not associated with an increase in adverse events. Although use of the patch was safe in this population, no improvement was observed in rates of short-term or long-term smoking abstinence in comparisons with the placebo group (Joseph et al. 1996; Joseph and Antonuccio 1999).

A third trial tested use of the nicotine patch in 106 smokers with CHD (Tzivoni et al. 1998). Patients were randomly assigned to receive nicotine patches or placebo patches for two weeks. All patients had ambulatory electrocardiogram monitoring and exercise testing at study entry, after the first application of the patch, and at two weeks. No difference was observed at any of the three time points, between the patch and placebo groups, in resting heart rate, blood pressure, the number or duration of ischemic episodes, frequency of arrhythmias, exercise duration, or time to 1-mm depression of the ST segment on an electrocardiogram. In a randomized study of 234 patients with both cardiovascular and respiratory diseases, no increase in adverse events was observed in patients assigned to the nicotine patch or the placebo (Campbell et al. 1996).

In a case-control study, Kimmel and colleagues (2001) found no increased risk of a first MI with use of the nicotine patch in persons who stopped smoking or those who continued to smoke. Using a computerized database for general practice in the United Kingdom, Hubbard and

colleagues (2005) studied the relative incidence of MI and stroke in four two-week periods before and after the first prescription for NRT. They found a progressive increase in risk in the 56 days after the first NRT prescription but no evidence of increased cardiovascular events or mortality in the 56 days after the NRT prescription.

Meine and colleagues (2005) addressed the safety of transdermal nicotine in the setting of acute CHD. These investigators analyzed data in the Duke University Cardiovascular Databank for 9,991 smokers who had cardiac catheterization after hospital admission for unstable angina or non-ST-segment MI. This retrospective observational study compared outcomes of patients who did or did not receive transdermal nicotine during hospitalization. The study identified 194 patients who had been treated with transdermal nicotine during the hospital stay. The investigators used a "propensity score analysis" to compare patients receiving transdermal nicotine with matched patients from the database who did not receive the medication. Because patients were not randomly assigned to receive transdermal nicotine, selection bias could have confounded these results. In an attempt to reduce this bias, patients who did or did not receive transdermal nicotine were matched on demographic characteristics, diagnosis, cardiac risk factors, and mean cardiac ejection fraction. Rates of cardiac outcomes in the two groups were compared. No differences in 7-day, 30-day, or one-year mortality rates were observed. Patients receiving transdermal nicotine were not more likely to have coronary artery bypass grafting or percutaneous transluminal coronary angioplasty during hospitalization. It was not possible to control for the dose of medication received, the amount of smoking before hospital admission, or relapse to smoking after hospitalization. These results provide some evidence that NRT was safe in the setting of acute CVD, but randomized controlled trials are needed to establish the safety of NRT in patients who have unstable cardiac disease.

Other studies examined markers of exposure to tobacco smoke related to cardiovascular risk as surrogate endpoints for cardiovascular events in clinical trials. There was no evidence that NRT raised blood pressure in any of the efficacy trials, but these trials typically excluded patients with poor control of hypertension. In one small trial of 30 smokers with or without hypertension, NRT increased mean arterial pressure in smokers with normal blood pressure but not in smokers who had hypertension (Tanus-Santos et al. 2001).

To date, two studies have tested the effect of NRT on coronary circulation in smokers with CHD. One study examined the size of defects in myocardial perfusion in 36 patients with baseline CHD who were treated with nicotine patches (Mahmarian et al. 1997). Participants continued

to smoke but at reduced levels. The researchers concluded that use of the patch, even with concomitant smoking and higher plasma levels of nicotine, resulted in reduction of exercise-induced ischemia in a comparison with baseline values. This finding suggested that components of tobacco smoke other than nicotine are responsible for impaired coronary blood flow. The second study investigated the effect of nicotine gum on coronary perfusion in former cigarette smokers having angiography (Nitenberg and Antony 1999). The findings demonstrated that the gum did not reduce the surface area of normal or diseased segments of the coronary artery. Other studies of the effects of smoking cessation on lipids and thrombosis reported improvements in these markers, even among smokers using NRT (Allen et al. 1994; Lúdvíksdóttir et al. 1999; Eliasson et al. 2001; Haustein et al. 2002).

In summary, despite anecdotal reports of cardiovascular events attributable to use of NRT, data from multiple clinical trials of smokers with or without CVD show no evidence for increased cardiovascular risk when NRT is used to treat tobacco dependence. However, the safety of NRT has not been tested in a more acute setting, such as during hospitalization for a cardiovascular event. Observational data suggest that use of the nicotine patch in patients with unstable cardiac disease is probably safe (Meine et al. 2005), but randomized trials are needed to confirm these findings. Current PHS guidelines recommend that NRT be used with caution in smokers with unstable angina, MI in the past two weeks, or serious arrhythmia (Fiore et al. 2000).

Bupropion

Bupropion is an aminoketone approved by FDA in 1989 for treatment of depression and in 1997 for smoking cessation. The drug is included in national guidelines as first-line therapy for smoking cessation (Fiore et al. 2000, 2008). Its mechanism of action is not fully understood, but researchers think it acts by inhibiting neuronal uptake of norepinephrine and dopamine. Bupropion may also block activity of nAChRs. The mechanism of action for smoking cessation appears to be unrelated to the antidepressant effects of bupropion. A preparation of the drug for sustained release provides a better safety profile and more convenient dosing than does the immediate-release form.

Evidence from several randomized controlled trials shows that bupropion doubled the smoking cessation rates obtained with a placebo. Meta-analyses of data on bupropion for smoking cessation conducted by PHS and the Cochrane Library yielded ORs of 2.1 (95 percent CI, 1.5–3.0) and 2.06 (95 percent CI, 1.77–2.40), respectively (Fiore et al. 2000; Hughes et al. 2004b). One trial compared use of bupropion, a nicotine patch, bupropion plus

a patch, and a placebo among 893 participants (Jorenby et al. 1999). Smoking abstinence rates at one year were 15.6 percent in the placebo group, 16.4 percent in the nicotine-patch group, 30.3 percent in the bupropion group ($p < 0.0001$ versus the placebo group), and 35.5 percent in the bupropion-plus-patch group ($p < 0.0001$ versus the placebo group; $p = 0.06$ versus the bupropion-alone group).

The major risk of bupropion is that it lowers a person's seizure threshold. The risk of seizure from the sustained-release formulation is 0.1 percent, which is no different from that for other antidepressants (Hughes et al. 1999; Rigotti 2002). No seizures were reported in any of the clinical trials that tested sustained-release bupropion for smoking cessation.

As with NRT, early case reports of serious cardiovascular events with sustained-release bupropion raised questions about the safety of this agent in patients with CVD. These reports, which were mostly in Canada and England, included cardiac deaths, chest pain, MI, and myocarditis (Joseph and Fu 2003). Assessment of the contribution of bupropion to these events is difficult because evaluation of other cardiac risk factors in these patients was not possible.

To date, none of the efficacy trials of bupropion for smoking cessation has reported a significant increase in cardiovascular events. Two randomized controlled trials enrolled only smokers with CVD. The first trial enrolled 629 outpatients with stable CVD—that is, MI or an interventional cardiac procedure more than three months earlier and stable angina pectoris, PAD, or congestive heart failure (Tonstad et al. 2003). Patients were randomly assigned to receive bupropion or a placebo for seven weeks. This study found no differences in the number of deaths in the two groups—two in the bupropion group and two in the placebo group. Overall, 38 participants (6 percent) reported a single adverse cardiovascular event—24 in the bupropion group and 14 in the placebo group. The most common cardiovascular events were angina pectoris, hypertension, and palpitations; 13 events occurred in the bupropion group versus 8 events in the placebo group. No statistical tests were performed on the rates of adverse events. Patients who took bupropion were more likely to have stopped smoking at one year than were patients who took the placebo (27 versus 12 percent, $p < 0.001$).

A second trial enrolled 248 smokers hospitalized with acute CVD, including acute MI, unstable angina, or other cardiovascular conditions (Rigotti et al. 2006). Patients were randomly assigned to receive sustained-release bupropion or a placebo for 12 weeks, and all patients received intensive counseling during hospitalization and follow-up. At the one-year follow-up, the difference between death rates in the bupropion group (no

deaths) and in the placebo group (two deaths) was not statistically significant. During the 12 weeks of drug treatment, the difference between the number of cardiovascular events in the bupropion group (20 events) and the placebo group (17 events) was also not significant. Cardiovascular events included death, nonfatal MI, unstable angina, congestive heart failure, stroke, and coronary revascularization procedure. At the one-year follow-up, the number of cardiovascular events in the bupropion group (32 events, 26 percent) exceeded the number in the placebo group (22 events, 18 percent), but this difference was not significant. In addition, at one year, the difference between the smoking abstinence rates for the bupropion group (25 percent) versus the placebo group (21 percent) was not significant. However, the results after 12 weeks of drug treatment suggested that bupropion had short-term efficacy (37 versus 27 percent, $p = 0.08$).

In summary, sustained-release bupropion is effective and safe for treating smokers with stable CVD. The drug appears to be less efficacious in smokers hospitalized with acute CVD than in other groups of patients. Bupropion is the only medication for treating tobacco dependence that has been tested in patients with acute CVD, and it appears to be safe for those with either stable or acute disease.

Other Pharmacotherapy

Varenicline, a partial agonist of the $\alpha 4\beta 2$ nAChR, has been marketed for the treatment of tobacco dependence but its use in smokers with CVD has not yet been studied (Coe et al. 2005). The drug produces approximately 50 percent of the receptor stimulation provided by nicotine, but it blocks the effects of any nicotine taken in from cigarette smoking. Clinical trials have found it superior to bupropion in promoting smoking cessation, and prolonged administration has been shown to reduce relapse in smokers who had been abstinent 12 weeks after initial therapy (Gonzalez et al. 2006; Jorenby et al. 2006; Tonstad et al. 2006). Two other medications have been demonstrated to be effective for smoking cessation: nortriptyline, a tricyclic antidepressant, and clonidine, a central α -agonist antihypertension agent. However, neither drug has been approved by FDA for smoking cessation. Both agents have potential cardiovascular side effects, and the safety profile of these drugs should be considered carefully before use in smokers with CVD.

Meta-analyses of data on use of clonidine for treating smokers resulted in ORs for smoking abstinence of 2.1 (95 percent CI, 1.4–3.2) (Fiore et al. 2000) and 1.89 (95 percent CI, 1.30–2.74) (Gourlay et al. 2004). To date, no safety data for patients with CVD are available. However, clonidine is known to cause orthostatic hypotension, rebound hypertension from abrupt cessation of the drug,

and rarely, atrioventricular nodal blockade. Nortriptyline is also effective in promoting smoking cessation; meta-analyses yielded ORs of 3.2 (95 percent CI, 1.8–5.7) (Fiore et al. 2000) and 2.79 (95 percent CI, 1.70–4.59) (Hughes et al. 2004b). Nortriptyline was designated a second-line drug for smoking cessation in PHS clinical guidelines because of a smaller evidence base of support and greater side effects than those of other medications for smoking cessation. In general, tricyclic antidepressants are avoided in patients with CVD because of concerns about increased risks for arrhythmias and depression of myocardial contractility (Joseph and Fu 2003).

Although the focus of the preceding section (“Methods”) was on clinical interventions to reduce smoking, it is important to recognize that policy-based interventions, such as smoke-free environments and community and statewide tobacco control programs, are also important elements in a strategy to improve cardiovascular health. For example, smoke-free workplaces are a highly cost-effective approach to promoting smoking cessation with an impact on cardiovascular health (Ong and Glantz 2004). Decreases in admissions to hospitals have been observed after smoke-free laws have gone into effect (Dinno and Glantz 2007). The California Tobacco Control Program substantially accelerated the decline in the heart disease death rate in the state (Fichtenberg and Glantz 2000).

It should be noted that although long-term smoking quit rates after various interventions in cardiovascular patients may appear to be low (most less than 30 percent),

smoking cessation therapy has an important impact on CVD, and the cost per life saved is lower than that of many other therapeutic interventions for CHD that are considered to be the standard (such as treatment of hypertension and hyperlipidemia) (Lightwood 2003).

Summary

Smoking cessation is a key element in both primary and secondary prevention of CVD. Guidelines from PHS recommend counseling, NRT, sustained-release bupropion, and varenicline as first-line treatments to achieve smoking cessation. Studies show that NRT and bupropion are effective in patients with CVD, although not all trials demonstrated efficacy. Several studies have demonstrated the safety of NRT in patients with stable CVD, but randomized trials are needed to establish the safety of this treatment for patients hospitalized with acute disease. Bupropion appears to be safe in patients with stable or unstable CVD, but it is less effective in patients with acute disease. Varenicline is a partial agonist of the $\alpha 4\beta 2$ nAChR that is effective in treating tobacco dependence, but it has not yet been studied in smokers with CVD. The development of more effective pharmacotherapies to aid smoking cessation that are safe in persons with CVD is a high research priority.

Methods to Reduce Exposure

Evidence-based interventions for treating smokers include behavioral and pharmacological treatments, which significantly increase rates for long-term abstinence from smoking. Even so, absolute rates of abstinence are modest; they range from 8 to 25 percent, depending on the study population and the treatment. In addition, only a small proportion of smokers are interested in treatment at any given time. Interest in smoking cessation and success in achieving long-term abstinence are greater among patients with CVD than in the general population of smokers (Thomson and Rigotti 2003). Nevertheless, abstinence rates remain disappointingly low, particularly in light of the important health benefits for this population when they do stop smoking (USDHHS 1990; Burns 2003).

Suboptimal treatment outcomes prompted interest in testing interventions that might decrease the risk of smoking among those who continue to use tobacco.

These strategies are often termed “harm reduction” interventions, although data are limited as to whether harm is really lessened with reduced exposure to tobacco. To date, the effect of methods for reducing exposure on risk factors for CVD and on development of CVD has been evaluated in a limited number of clinical trials, prospective cohort studies, and epidemiologic studies.

Endpoints with respect to CVD that have been measured in studies of reduced exposure include measures of exposure to tobacco constituents (e.g., nicotine and CO); biomarkers of inflammation (e.g., CRP, leukocyte counts, and fibrinogen); thrombosis (e.g., fibrinogen and PAI-1); lipid abnormalities (e.g., levels of total cholesterol, HDLc, LDLc, triglycerides, APOs A-I and B, and HDLc to LDLc ratio); oxidative stress that reflects and may contribute to cardiovascular risk (e.g., F_2 -isoprostanes); and clinical outcomes (blood pressure, heart rate, angina, exercise tolerance, MI, other adverse events, and death) (Table 6.3).

Reduced Smoking

Important methodologic considerations in evaluating studies of reduced smoking include the extent and duration of smoking reduction, use of nicotine replacement products, doses, and timing of endpoint measurements (Table 6.6). In addition, some studies report outcome data on the basis of intention to treat all participants, regardless of whether treatment was successful. Others report only on subgroups who achieve specific goals for smoking reduction.

Eliasson and colleagues (2001) tested the effect of nicotine nasal spray on achieving smoking reduction and abstinence among 58 healthy adult smokers in an open-label cohort study. The primary goal for the first eight weeks of the study was to reduce daily smoking by 50 percent; participants were asked to stop smoking after eight weeks. Cardiovascular risk factors were evaluated at baseline, at eight weeks, and after eight weeks of abstinence. The 33 study participants provided data at all three time points. After participants completed eight weeks of smoking reduction, mean cigarette use decreased by 50.2 percent, expired CO dropped 17 percent, and plasma thiocyanate decreased by 20.1 percent. Significant improvements included fibrinogen levels (from 2.9 g/liter [L] to 2.65 g/L, $p = 0.011$); hemoglobin values (from 13.8 to 13.3 g/L, $p < 0.001$); leukocyte counts (from 7.0 to $6.2 \times 10^9/L$, $p = 0.005$); and HDLc to LDLc ratio (from 0.33 to 0.37, $p < 0.005$). Eight weeks of abstinence from smoking was associated with further improvements in hemoglobin levels, leukocyte counts, and HDL and LDL levels, and significant reduction in PAI-1 activity. These researchers did not observe improvements in HDLc and LDLc levels with reduction in smoking.

Hurt and colleagues (2000) conducted a small, open-label cohort study to test the effect of a nicotine inhaler on biomarkers of exposure to cigarette smoke among 23 heavy smokers. Levels of blood thiocyanate, several urine carcinogens, and expired CO were measured at study entry and at 4, 8, 12, and 24 weeks. Despite an average reduction among participants from 40 or more to 10 cigarettes per day, expired CO decreased only from 30.4 to 26.0 parts per million (ppm), reflecting compensatory smoking or misreporting of reduction in smoking. This change was not statistically significant.

In the U.S. Lung Health Study, 5,887 male and female smokers were randomly assigned to one of three groups: intervention for smoking cessation, including nicotine gum, plus bronchodilator therapy; intervention plus a placebo; or usual care (Hughes et al. 2004a). Among 3,923 participants in the intervention at the one-year follow-up, 1,722 continued to smoke daily. Reduction in the number of cigarettes smoked was not an objective of

the intervention, but 16 percent of those who continued to smoke daily smoked 1 to 24 percent fewer cigarettes than at baseline; another 27 percent reduced smoking by 25 to 49 percent; 19 percent, by 50 to 74 percent; and 11 percent, by 75 to 99 percent. The mean reduction in cigarettes smoked was 29 percent (from 32 to 22 cigarettes per day), and the mean reduction in CO levels was 24 percent (from 34 to 26 ppm). Thus, more than 80 percent of those who did not stop smoking achieved some level of reduction. However, the reduction in CO was not as large as the reduction in cigarettes per day. This finding again suggests compensatory smoking.

Hatsukami and colleagues (2005) examined the effect of smoking reduction on cardiovascular risk factors among 151 cigarette smokers interested in stopping smoking but not in reducing their smoking. Nicotine patches and gum were used to assist with reduction of smoking. The cardiovascular risk factors (CO and cholesterol levels, leukocyte counts, blood pressure, and heart rate) were measured for 12 weeks after study entry. Biomarkers did not change among persons who continued to smoke ad libitum, but the 61 persons who reduced smoking achieved significant improvements. Smokers who reduced the self-reported number of cigarettes smoked per day by 40 percent or more had significantly reduced leukocyte counts (from 7.39 to $6.98 \times 10^9/L$, $p < 0.001$); higher HDLc levels (from 50.3 to 52.8 mg per deciliter [dL], $p < 0.0167$); improved HDL to LDL ratios (from 0.47 to 0.49, $p < 0.0167$); lower APO B levels (from 103.7 to 103.0 mg/dL, $p < 0.0167$); lower systolic blood pressure (from 123.0 to 120.3 mm Hg, $p < 0.0167$); and lower heart rate (from 75.7 to 70.2 beats per minute, $p < 0.001$). Although some of these changes were statistically significant, they are modest, and the clinical importance is undetermined. Levels of triglycerides, total cholesterol, APO A-I, and diastolic blood pressure did not change, and LDLc levels increased from 122.1 to 124.4 mg/dL ($p < 0.0167$).

To date, only one randomized controlled trial of an intervention for smoking reduction among persons with known CVD has been conducted (Joseph et al. 2005). Treatment included behavioral counseling and NRT with patches and gum. The goal of this study of 152 participants was at least a 50-percent reduction in cigarettes smoked per day; usual care was the standard for comparison. At study entry, participants smoked an average of 27.4 cigarettes per day. At six months, the intervention group had reduced cigarette use by 39 percent, versus a decline of 25 percent in the usual care group, but this difference was not statistically significant. Biomarkers for carcinogenesis and CVD were measured, as were clinical outcomes. No significant differences between the treatment groups were observed for levels of CO, fibrinogen, F_2 -isoprostanes, or CRP, or for leukocyte counts. The groups did not differ in clinical

Table 6.6 Smoking reduction and cardiovascular disease endpoints: biomarkers and clinical outcomes

Study	Design	n	Follow-up	NRT	Reduction from baseline		
					CPD	Nicotine	CO (ppm)
Hurt et al. 2000	Open-label cohort	23	24 weeks	Inhaler	≥40 to 10**	- ^a	NS
Eliasson et al. 2001	Open-label cohort	33	9 weeks	Nasal spray	21.5 to 10.8**; 50.2%	-	-
Godtfredsen et al. 2003	Prospective cohort study	643 ^c	Mean 13.8 years	NA	≥50% ^d	Significant	13.2 vs. 8.7***
Hughes et al. 2004a	Reduction cohort in RCT	1,722	1 year	Gum	32 to 22; 29%	-	NS
Hatsukami et al. 2005	Reduction cohort in RCT	61	12 weeks	Patch and gum	24.16 to 6.93*; >40%	- ^f	19.9 to 6.77***
Joseph et al. ^h 2005	RCT	152	6 months	Patch and gum	27.7 to 16.8*	NS	NS

Note: **APO A-I** = apolipoprotein A-I; **APO B** = apolipoprotein B; **BP** = blood pressure; **CCSC** = Canadian Cardiovascular Society classification; **CO (ppm)** = carbon monoxide (parts per million); **CPD** = cigarettes/day; **Fibr** = fibrinogen concentrations; **g/L** = grams per liter; **Hb** = hemoglobin; **HDL** = high-density lipoprotein; **hs-CRP** = high-sensitivity C-reactive protein; **LDL** = low-density lipoprotein; **mg/dL** = milligrams per deciliter; **MI** = myocardial infarction; **n** = number in sample (or study) population; **NA** = not applicable; **NRT** = nicotine replacement therapy; **NS** = not significant; **PAI-1** = plasminogen activator inhibitor-1; **Plts** = platelets; **RCT** = reverse cholesterol transport; **SAEs** = serious adverse events; **Trigly** = triglycerides; **WBC** = white blood cells.

outcomes, including body weight, distance completed in a six-minute walking test, the proportion of participants completing that test, the prevalence and frequency of angina, the need for urgent cardiac care, and other serious adverse events. Because no significant differences between treatment groups were observed and because both groups achieved significant reductions in cigarette use from baseline, results for the entire cohort at six months were compared with the baseline data. There were no significant differences in biomarkers of cardiovascular risk, including leukocyte counts and levels of F₂-isoprostanes or CRP, but CO had decreased by 6.0 ppm (p = 0.007).

Godtfredsen and colleagues (2003) conducted a prospective cohort study in Denmark to examine changes in the incidence of MI after spontaneous reductions in cigarette use. This study included 10,956 men and 8,467 women who provided detailed information on smoking behavior during two examinations. Mortality registers and hospital registers were searched for an incident of hospital admission or a death attributable to MI. A sample consisting of pooled data from three population studies yielded 643 participants who were heavy smokers at study entry and were evaluated for the effects of reduced smoking.

These persons reported unassisted reductions in tobacco use by at least 50 percent and were compared

Study	Reduction from baseline						
	Hb (g/L)	WBC × 10 ⁹ /L	Fibr (g/L)	LDL (mg/dL)	HDL (mg/dL)	Other biomarkers	Clinical outcomes
Hurt et al. 2000	-	-	-	-	-	-	-
Eliasson et al. 2001	13.8 to 13.3**	7.0 to 6.2**	2.9 to 2.6*	NS ^b	NS	Plts NS PAI-1 NS	-
Godtfredsen et al. 2003	-	-	-	- ^e	NS	-	Systolic BP NS Diastolic BP 80.7 vs. 78.8*** Risk of MI NS
Hughes et al. 2004a	-	-	-	-	-	-	-
Hatsukami et al. 2005	14.49 to 14.40*	7.39 to 6.98***	-	122.14 to 124.36* ^g	50.27 to 52.82*	Trigly NS APO A-I NS APO B 103.74 to 103.0*	Systolic BP 122.97 to 122.29* Diastolic BP NS Heart rate 75.7 to 70.18***
Joseph et al. ^h 2005	NS	NS	NS	-	-	hs-CRP NS F ₂ -isoprostanes NS	6-minute walk, angina presences/frequency, CCSC classification, cardiac or other SAEs NS

^aThiocyanate concentrations increased from 189 to 198 micromoles/L (p <0.05).

^bHDL to LDL ratio increased from 0.33 to 0.37, p <0.005.

^cTotal cohort = 19,423.

^d22.2 grams tobacco per day in continued heavy smokers versus 10.5 grams per day in reducers (p <0.001).

^eTotal cholesterol NS.

^fAnatabine decreased from 4.69 to 3.02 nanograms per milligram of creatinine (statistically significant).

^gHDL to LDL ratio increased from 0.47 to 0.49, p <0.0167.

^hReduction in CPD reported for smoking reduction intervention group, significance tests reported for smoking reduction versus control group.

*p <0.05, **p <0.01, ***p <0.001.

with 1,379 persons who reported abstinence from smoking. Outcomes were adjusted for baseline cardiovascular risk factors. Smoking cessation was associated with a hazard ratio for MI of 0.71 (95 percent CI, 0.59–0.85), but smoking reduction was not associated with a statistically significant reduction in risk of MI (hazard ratio, 1.15 [95 percent CI, 0.94–1.40]). A subgroup analysis demonstrated significant reductions in levels of expired CO among persons who reduced cigarette smoking. The investigators concluded that the results were consistent with a short-term thrombogenic effect of tobacco exposure rather than with a cumulative effect of exposure.

They speculated that an approximate 50-percent reduction (from 20 g to 10 g of tobacco smoked per day) was not sufficient to improve cardiovascular risk. These epidemiologic data make an important contribution because they are population based and come from a large cohort of smokers who reduced their smoking during a period longer than the usual timeframe for clinical trials.

In summary, these studies show that a significant reduction in cigarette use, even to levels as low as 10 cigarettes per day, results in reduction of exposure to CO from tobacco smoke that is smaller than expected. This finding most likely reflects compensatory smoking. Some but

not all studies showed reduced exposure to nicotine, as well as improvements in values for hemoglobin, leukocyte counts, and fibrinogen and cholesterol levels. However, the improvements in values are relatively minor compared with those observed with abstinence from smoking. Many of these improvements occurred in study participants who were using NRT (see "Nicotine Replacement Therapy" below). None of the studies showed improvements in clinical outcomes of heart disease, consistent with evidence presented earlier that low levels of smoke exposure trigger many of the adverse cardiovascular effects of smoke (see "Exposure to Secondhand Tobacco Smoke" earlier in this chapter).

Nicotine Replacement Therapy

In addition to providing data on smoking reduction, the Lung Health Study of 3,094 persons offered a unique opportunity to examine the natural history and safety of prolonged use of nicotine gum among thousands of people during a five-year follow-up (Murray et al. 1996). Persistent smoking, but not use of nicotine gum, predicted fatal and nonfatal cardiovascular events and elevation of diastolic blood pressure.

In general, trials of smoking cessation and smoking reduction showed improvements in lipid profiles, even with NRT. Eliasson and colleagues (2001) observed that use of nicotine nasal spray for smoking reduction or cessation yielded significant improvements in HDLc to LDLc ratios at 9 weeks, with further improvements if smokers abstained from smoking for 17 weeks (see "Reduced Smoking" earlier in this chapter). In addition, significant improvements in fibrinogen levels and leukocyte counts were observed. A clinical trial of smoking cessation also reported significant decreases in hemoglobin values, leukocyte counts, and total and LDLc concentrations (Lúdvíksdóttir et al. 1999). In addition, HDLc to LDLc ratios improved among participants who abstained from smoking after three months of treatment with a nicotine nasal spray. Allen and colleagues (1994) also observed significantly increased HDLc levels in participants treated with the nicotine patch.

Investigators have noted improvements in markers of thrombogenesis among persons who abstained from smoking and were using medicinal nicotine. In one study, plasma fibrinogen levels were reduced among 164 men using a combination of a nicotine patch and gum for 12 weeks to stop smoking (Haustein et al. 2002). In another study, use of transdermal nicotine appeared to activate platelet aggregation less than smoking did (Benowitz et al. 1993).

Mahmarián and colleagues (1997) used single photon emission computed tomography to measure the combined effects of smoking and use of nicotine patches on myocardial perfusion. In 36 patients with known CHD who were treated with nicotine patches, the amount of heart muscle deprived of normal blood flow (size of perfusion defects) decreased despite increased serum nicotine levels. The baseline size of defects and changes in CO levels, but not in nicotine levels, predicted the size of perfusion defects. The researchers concluded that the reduction in the size of defects resulted from reduction in smoking that was facilitated by NRT and from decreased exposure to CO. They also concluded that nicotine patches were safe to use in smokers with heart disease.

Nitenberg and Antony (1999) used angiography to examine short-term effects of use of nicotine gum on perfusion of the coronary arteries in former cigarette smokers at study entry, after a test with immersion of the hand in cold water (cold pressor test) before and after administration of the gum. The gum did not augment the result of the cold pressor test, which constricted normal and diseased segments of the coronary artery, reducing their cross-sectional area, and it did not reduce the surface area of the arterial segments at rest or under conditions of sympathetic stimulation.

These results suggest that reduction of exposure to tobacco smoke through use of NRT or with abstinence from smoking is associated with improvements in biomarkers of cardiovascular risk.

Summary

Epidemiologic studies demonstrate a strong dose-response relationship between the number of cigarettes smoked per day and cardiovascular risk. The relationship is not linear, however, and even low levels of exposure to tobacco, such as a few cigarettes per day, occasional smoking, or exposure to secondhand tobacco smoke are sufficient to substantially increase risk of cardiac events. Some interventions have accomplished significant reductions in the number of cigarettes smoked per day, but the reductions in levels of biomarkers of exposure and biomarkers of cardiovascular risk factors are not proportional, probably because of compensatory smoking by study participants and the nonlinear dose-response relationship. The limited data on clinical outcome do not confirm reduction in cardiovascular events due to reduced smoking. Other methods for reducing exposure, including NRT with abstinence from smoking, are associated with more improvement in risk factors for CVD than is smoking reduction with or

without pharmacologic support. Accordingly, these methods hold more potential for reducing risk.

Implications

These findings suggest that to lower cardiac risk, interventions would have to reduce exposure to tobacco smoke to extremely low levels or eliminate the exposure. Studies of smoking reduction to date suggest that goals

would be difficult to accomplish. Reducing exposure by reducing smoking, therefore, appears to have limited promise for improving cardiac risk unless this method contributes to eventual smoking cessation (Hughes 2000). Because smoking cessation is associated with marked improvements in the risk of MI, sudden death, and stroke, it should be stressed as the goal for interventions dealing with dependence on tobacco. The safety and efficacy of long-term NRT use to reduce cardiovascular risk by maintaining smoking cessation have not been established.

Evidence Summary

Exposure to tobacco smoke is associated with accelerated atherosclerosis and an increased risk of acute MI, stroke, PAD, aortic aneurysm, and sudden death. Smoking appears to have both causal relationships and multiplicative interactions with other major risk factors for CHD, including hyperlipidemia, hypertension, and diabetes mellitus.

The cardiovascular risk attributable to cigarette smoking increases sharply at low levels of cigarette consumption and with exposure to secondhand smoke. The risk then tends to plateau at higher levels of smoking. This finding indicates a low threshold for effect and a nonlinear dose-response relationship. Some of the nonlinearity of the relationship between the number of cigarettes smoked per day and CVD risk may be due to impreciseness of this measure of actual exposure to smoke. However, the data on risk associated with exposure to secondhand smoke indicate a true nonlinear relationship between exposure and CVD risk. Cardiovascular risk is not reduced by smoking cigarettes of lower machine-delivered yields of nicotine or tar.

The constituents of tobacco smoke believed to be responsible for cardiovascular disease include oxidizing chemicals, nicotine, CO, and particulate matter. Oxidizing chemicals, including oxides of nitrogen and many free radicals, increase lipid peroxidation and contribute to several potential mechanisms of CVD, including inflammation, endothelial dysfunction, oxidation of LDL, and platelet activation.

Nicotine is a sympathomimetic drug that increases heart rate and cardiac contractility, transiently increasing

blood pressure and constricting coronary arteries. Nicotine may also contribute to endothelial dysfunction, insulin resistance, and lipid abnormalities. However, international epidemiologic evidence and data from clinical trials of nicotine patches suggest that chemicals other than nicotine contribute to an elevated risk of death from MI and stroke. CO reduces the delivery of oxygen to the heart and other tissues and can aggravate angina pectoris or PAD and can lower the threshold for arrhythmias in the presence of CHD. Exposure to particulates is associated with oxidant stress and cardiovascular autonomic disturbances that potentially contribute to acute cardiovascular events.

Cigarette smoking causes acute cardiovascular events such as MI and sudden death by adversely affecting the balance of myocardial demand for oxygen and nutrients and coronary blood flow. Smoking results in increased myocardial work, reduced coronary blood flow, and enhanced thrombogenesis. Enhancement of thrombogenesis appears to be particularly important in that smokers with acute MI have less severe underlying coronary artery disease than do nonsmokers with MI, but smokers have a greater burden of thrombus.

Several potential mechanisms appear to contribute to the effects of smoking in accelerating atherosclerosis. These mechanisms include inflammation, endothelial dysfunction, impaired insulin sensitivity, and lipid abnormalities. Cigarette smoking is a risk factor for diabetes and aggravates insulin resistance in persons with diabetes. The mechanism appears to involve both the effects of oxidizing chemicals in the smoke and the sympathomimetic effects of nicotine.

Conclusions

1. There is a nonlinear dose response between exposure to tobacco smoke and cardiovascular risk, with a sharp increase at low levels of exposure (including exposures from secondhand smoke or infrequent cigarette smoking) and a shallower dose-response relationship as the number of cigarettes smoked per day increases.
2. Cigarette smoking leads to endothelial injury and dysfunction in both coronary and peripheral arteries. There is consistent evidence that oxidizing chemicals and nicotine are responsible for endothelial dysfunction.
3. Tobacco smoke exposure leads to an increased risk of thrombosis, a major factor in the pathogenesis of smoking-induced cardiovascular events.
4. Cigarette smoking produces a chronic inflammatory state that contributes to the atherogenic disease processes and elevates levels of biomarkers of inflammation, known powerful predictors of cardiovascular events.
5. Cigarette smoking produces an atherogenic lipid profile, primarily due to an increase in triglycerides and a decrease in high-density lipoprotein cholesterol.
6. Smoking cessation reduces the risk of cardiovascular morbidity and mortality for smokers with or without coronary heart disease.
7. The use of nicotine or other medications to facilitate smoking cessation in people with known cardiovascular disease produces far less risk than the risk of continued smoking.
8. The evidence to date does not establish that a reduction of cigarette consumption (that is, smoking fewer cigarettes per day) reduces the risks of cardiovascular disease.
9. Cigarette smoking produces insulin resistance and chronic inflammation, which can accelerate macrovascular and microvascular complications, including nephropathy.

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Data table for Figure 6.1 Relative risk and excess death rate for coronary heart disease among men, by age group

Age group (years)	Relative Risk	Excess Death Rate
35-39	3.3	20.5
40-44	6.3	70.7
45-49	5.5	119.8
50-54	3.8	156.6
55-59	2.7	204.1
60-64	2.4	317.3
64-69	1.9	366.7
70-74	1.7	473.2
75-79	1.4	439.6
80+	1.4	825.7

Data table for Figure 6.2 age-specific excess death rates among male smokers for coronary heart disease, lung cancer, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease

Age group (years)	Lung Cancer	Coronary Heart Disease	Cerebro-Vascular Disease	COPD
35-39	1.4	20.5	11.9	
40-44	18.7	70.7	0.2	
45-49	35.5	119.8	16.3	3.2
50-54	109.9	156.6	19.0	11.1
55-59	200.8	204.1	29.0	19.9
60-64	349.5	317.3	49.8	40.3
64-69	560.1	366.7	81.4	140.5
70-74	874.1	473.2	108.2	234.5
75-79	1066.3	439.6	252.8	522.0
80+	1138.6	825.7	264.8	722.0

