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REVIEW | *Integrative Cardiovascular Physiology and Pathophysiology*

Cardiovascular injury induced by tobacco products: assessment of risk factors and biomarkers of harm. A Tobacco Centers of Regulatory Science compilation

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Conklin DJ, Schick S, Blaha MJ, Carll A, DeFilippis A, Ganz P, Hall ME, Hamburg N, O'Toole T, Reynolds L, Srivastava S, Bhatnagar A. Cardiovascular injury induced by tobacco products: assessment of risk factors and biomarkers of harm. A Tobacco Centers of Regulatory Science compilation. *Am J Physiol Heart Circ Physiol* 316: H801–H827, 2019. First published February 1, 2019; doi:10.1152/ajpheart.00591.2018.—Although substantial evidence shows that smoking is positively and robustly associated with cardiovascular disease (CVD), the CVD risk associated with the use of new and emerging tobacco products, such as electronic cigarettes, hookah, and heat-not-burn products, remains unclear. This uncertainty stems from lack of knowledge on how the use of these products affects cardiovascular health. Cardiovascular injury associated with the use of new tobacco products could be evaluated by measuring changes in biomarkers of cardiovascular harm that are sensitive to the use of combustible cigarettes. Such cardiovascular injury could be indexed at several levels. Preclinical changes contributing to the pathogenesis of disease could be monitored by measuring changes in systemic inflammation and oxidative stress, organ-specific dysfunctions could be gauged by measuring endothelial function (flow-mediated dilation), platelet aggregation, and arterial stiffness, and organ-specific injury could be evaluated by measuring endothelial microparticles and platelet-leukocyte aggregates. Classical risk factors, such as blood pressure, circulating lipoproteins, and insulin resistance, provide robust estimates of risk, and subclinical disease progression could be followed by measuring coronary artery Ca^{2+} and carotid intima-media thickness. Given that several of these biomarkers are well-established predictors of major cardiovascular events, the association of these biomarkers with the use of new and emerging tobacco products could be indicative of both individual and population-level CVD risk associated with the use of these products. Differential effects of tobacco products (conventional vs. new and emerging products) on different indexes of cardiovascular injury could also provide insights into mechanisms by which they induce cardiovascular harm.

biomarkers; cardiovascular; nicotine; risk factors; tobacco

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in smokers. Worldwide, more smokers die from heart disease than from respiratory disease or all forms of cancer combined (104). In the United States, 30% of coronary deaths per year can attributed to smoking (370), and in both developed and developing countries, the use of tobacco products remains the leading cause of preventable death and disease (221). However, the relationship between tobacco use and CVD is complex. The use of tobacco products affects multiple forms of CVD as well its major risk factors. However, smoking is a

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CVD risk factor, independent of traditional risk factors such as hypertension, dyslipidemia, or diabetes. Hence, tobacco products also impart cardiovascular injury through mechanisms distinct from traditional CVD risk factors. Therefore, for the evaluation and assessment of the cardiovascular effects of tobacco products, it is important to consider not only traditional CVD risk factors but also changes in other mechanisms known to impact cardiovascular health, such as inflammation, coagulation, and oxidative stress.

The relationship between tobacco use and CVD is further complicated by the multiplicity of cardiovascular effects that result from smoking and potentially the use of other tobacco products as well (Fig. 1). Overall, smoking, even on an occasional basis, significantly increases the risk of CVD [relative risk (RR): 1.5, 95% confidence interval (CI): 1.0 to 2.3] (232). And yet, the actual susceptibility varies with different manifestations of CVD. It is known, for example, that smokers are two to four times more likely to develop coronary heart disease (CHD) and two times more likely to suffer a stroke (35). In women aged 35–39 yr old, the risk for ischemic heart disease nearly triples in those who smoke 1−4 cigarettes/day (48, 232). Similarly, smoking is a robust risk factor for atrial fibrillation (309), and smokers are almost 4 times more likely to die from aortic aneurysm than nonsmoking men and women (370) and 10 times more likely to develop peripheral vascular disease (35). Given such distinct manifestations of smoking-induced cardiovascular injury, it is important to estimate as well as to understand the effects of different tobacco products on different manifestations of CVD, which may differ not only with the type of CVD evaluated but also with the type of tobacco product used.

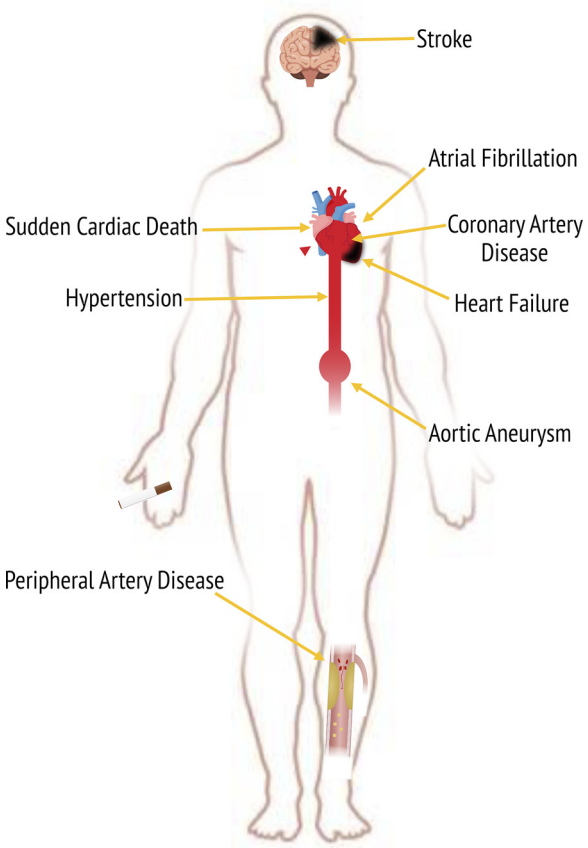

Fig. 1. Cardiovascular outcomes associated with chronic smoking.

An understanding of the cardiovascular effects of tobacco products cannot be gleaned from the effects of tobacco products on respiratory disease risk or the risk of cancer. The cardiovascular effects of tobacco product use seem to be unique, as they display distinct characteristics. For instance, because of their lower capacity to detoxify xenobiotics (44), cardiovascular tissues are more sensitive to tobacco smoke and other inhaled pollutants than others, and cardiovascular effects appear at levels of exposure lower than those required to cause other diseases, such as cancer (46, 331). CVD risk is elevated at very low levels of exposure to tobacco smoke. For example, the effects of secondhand exposure are nearly as large as active smoking (23), and, like smoking, it increases the progression of subclinical CVD (190). Moreover, even though the dose-response relationship between lung cancer and smoking shows no threshold and the risk is monotonically distributed, the relationship between CVD risk and smoking is markedly nonlinear, where 80% of the risk of smoking >20 cigarettes/day is associated with <3 cigarettes/day (301). Even 1 cigarette/day is associated with 30–50% of the risk of CHD and 34–65% of the risk of stroke seen with 20 cigarettes/day (141). When the effects of cigarettes per day and pack-years on CVD risk are compared, cigarettes per day modifies the linear RR association with pack-years. Smoking fewer cigarettes per day for a longer time conveyed more risk of CHD and stroke than smoking more per day for a shorter time (229). This may be due to either the higher sensitivity of cardiovascular tissue to tobacco products or because the constituents or chemicals in tobacco products that elevate CVD risk are not the same as those that cause cancer or respiratory disease. However, unlike the effects on cancer, cardiovascular effects are readily reversible on cessation (3). As with accrual of disease risk, the decrease in RR of CVD after cessation appears to also be modified by smoking intensity, with risk declining slowest among those who smoked fewer cigarettes per day for a longer time. Clearly, the cardiovascular effects of tobacco product use cannot be assessed or predicted by knowing the chemicals, constituents, or doses of tobacco products that cause cancer or respiratory disease.

Reliable and robust assessments of the cardiovascular effects of tobacco product use, independent of its effects on other tissues, has become increasingly urgent with the advent of a plethora of new tobacco products on the market. Products such as e-cigarettes, little cigars, cigarillos, and water pipes or hookah, introduced or popularized during the last 15 yr, represent a major public health concern, particularly in relation to CVD. Here, we review recent evidence linking the use of tobacco products with CVD risk, with specific attention to new and emerging tobacco products. We discuss the effects of tobacco products on traditional CVD risk factors as well as their effects on mechanisms and process that contribute to CVD development, such as inflammation and thrombosis. We review recent evidence on the effects of tobacco products on autonomic regulation of cardiovascular function and subclinical progression of CVD. Given the long latency period between tobacco exposure and the development of major clinical adverse health effects, validated biomarkers of tobacco-related disease outcomes are needed to evaluate new and emerging tobacco products over a shorter timeframe. Based on this

review of extant literature, we provide specific recommendations for evaluating the cardiovascular effects of new and emerging tobacco products and for assessing their cardiovascular risk by using appropriate biomarkers of cardiovascular injury and dysfunction (Fig. 2).

EFFECTS OF TOBACCO PRODUCTS ON TRADITIONAL CVD RISK FACTORS

Blood Pressure

Based on recent estimates, 46% of the United States population of ≥20 yr of age has hypertension, defined as a systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 80 mmHg. Elevated BP is a major risk factor for CHD, myocardial infarction (MI), peripheral arterial disease (PAD), stroke, kidney failure, and heart failure (387). In addition to being an independent risk factor for many of these same diseases, cigarette smoking has direct cardiovascular effects that affect BP (395, 400). Even brief (<15 min) durations of cigarette smoking (84) result in an increase in heart rate (HR), BP, and aortic stiffness (313). Some of these effects may be attributable to nicotine, as nicotine exposure, either through smoking or intravenous administration, leads to acute (within 5–10 min) increases in both BP and HR (38). In studies on acute cigarette smoking, increases in BP and HR were accompanied by increases in plasma norepinephrine and epinephrine levels. Nevertheless, these changes were prevented by adrenergic blockade, suggesting a role of the sympathetic nervous system (82). Baroreflex activation may also play a role (295).

Epidemiological studies, including the Physicians' Health Study, have shown an increase in the risk of incident hypertension (RR: 1.15) for current smokers compared with never smokers (145). Nevertheless, some studies have observed minimal effects on BP (305) or even reductions in BP caused by smoking (133). The chronic effects of smoking on BP are difficult to determine due to confounding associated with smoking-induced weight loss, which may lead to reductions in BP (70). Some of the hemodynamic effects of cigarette smoking may be more transient and, therefore, missed during routine BP checks. Nevertheless, ambulatory BP monitoring in both normotensive smokers and smokeless tobacco users showed 5 mmHg higher mean daytime BP compared with nonusers (53).

Elevated BP also is a major risk factor for renal failure. Cigarette smoking has a dose-dependent association with impaired renal function, as measured by reduced albuminuria in epidemiological studies (296). Studies of acute exposure have shown that smoking and nicotine cause glomerular hyperfiltration, which makes interpretation of a single estimated glomerular filtration rate measure difficult (238). Changes in renal function, including a rapid renal function decline (a ≥30% reduction in estimated glomerular filtration rate over several years of followup) (144), have a dose-dependent association with smoking. Ultimately, smoking-induced renal injury leads to a vicious cycle whereby worsening renal function results in hypertension and further renal injury. In summary, current evidence shows that both nicotine and smoking are associated with increases in BP, sympathetic nervous system activation, and renal dysfunction. Well-controlled studies examining the effects of other tobacco delivery devices, such as e-cigarettes, on BP are limited. Studies of e-cigarette use have shown increases in HR and BP to the same extent as observed with conventional cigarettes (45). In contrast, other studies have reported minimal effects of BP and, unlike combustible cigarettes, no reduction in coronary flow reserve (37). Among patients with arterial hypertension, switching from cigarettes to e-cigarettes was associated with a reduction in BP (299).

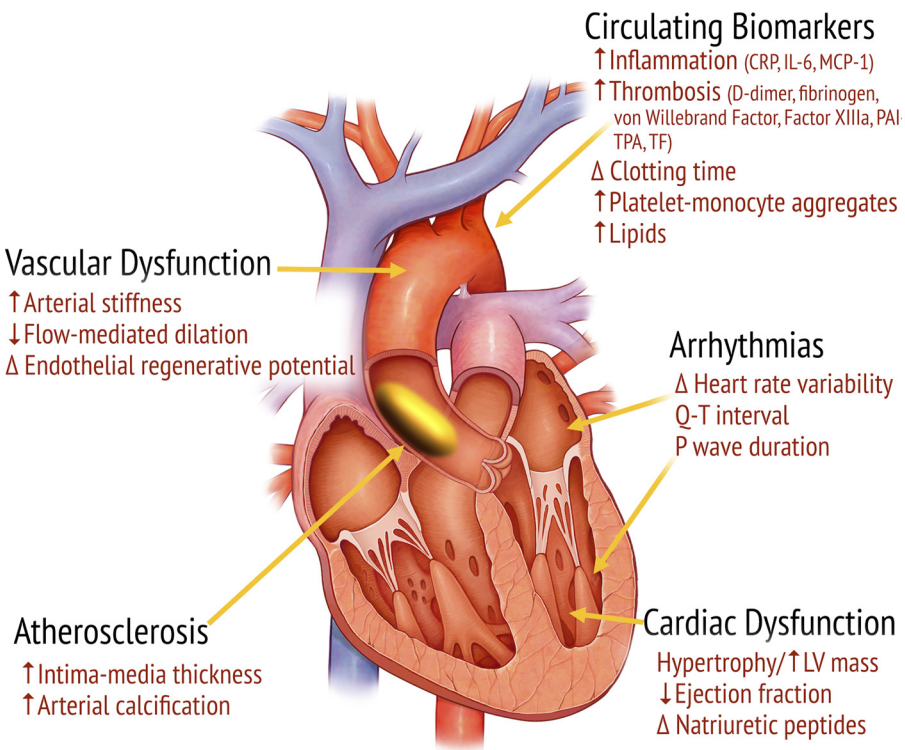

Fig. 2. Cardiovascular effects of smoking. CRP, C-reactive protein; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; PAI, plasminogen activator inhibitor; TPA, tissue plasminogen activator; TF, tissue factor.

Differences in the nicotine content of e-cigarettes used in different studies may explain the disparate results of these studies. Additional indepth investigations into the effects of novel tobacco products on acute and chronic changes in BP are warranted.

Blood Lipids

Lipids are important sources of energy and serve as precursors for hormone production and components of cell membranes. Transport of lipids through plasma is mediated by lipoprotein particles (315), which are classified according to size and density, including low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Lipoprotein levels in blood are thought to be causally related to CVD and are biomarkers of CVD risk (281, 308, 315), including higher total cholesterol (TC), triglycerides, and LDL levels as well as lower HDL levels. Tobacco smoking disrupts lipid and lipoprotein metabolism and is associated with an increase in TC, triglycerides, and LDL levels and a decrease in HDL levels (68, 79). In addition to cigarette smoking, water pipe smoking has also been found to be significantly associated with dyslipidemia and higher triglyceride levels (106, 334). Contradictory evidence exists regarding the relationships between smokeless tobacco use and lipid and lipoprotein levels (286, 311). Effects of other new and emerging tobacco products on blood lipid and lipoprotein levels remain unclear.

Total cholesterol. TC levels refer to the sum of cholesterol in LDL, HDL, and very-low-density lipoprotein (VLDL) particles. Abnormal TC is often defined as >200 mg/dl (273a). Prospective studies have consistently found an increased risk for incident CVD associated with higher TC levels (215). Serum levels of TC have been reported to be 3% (95% CI: 2.7–3.3) higher in current tobacco smokers than in nonsmokers (79). A positive linear correlation ($P < 0.001$) has been observed between smoking dose and TC levels (79). A study of 47 smokeless tobacco users and 44 nonusers found significantly ($P = 0.008$) higher TC in smokeless tobacco users (204.23 ± 23 mg/dl) compared with nonusers (185.48 ± 38.03 mg/dl) (47). Another study also reported higher TC levels in 25 participants who chewed tobacco compared with 25 nonusers (190.50 vs. 163.80 mg/dl, $P < 0.001$) (311). The effects of other tobacco products on TC levels are not well characterized and merit further investigation.

HDL-cholesterol. HDL-cholesterol levels are inversely associated with incident CVD (133a, 308). HDL-cholesterol levels of <40 mg/dl are considered abnormal (273a). A meta-analysis of 302,430 people without initial vascular disease, from 68 long-term prospective studies, found that 15 mg/dl (1 SD) higher HDL levels at baseline were associated with a significant reduction in risk of incident CVD [hazard ratio: 0.78, 95% CI: 0.74–0.82] (133a). In addition, the ratio of TC to HDL-cholesterol has been reported as a strong lipid predictor of incident CVD (267) and ischemic heart disease mortality (215). Tobacco smoking is associated with lower HDL levels. Current smokers were found to have 5.7% lower HDL levels than nonsmokers (79). A recent analysis of 17,293 National Health and Nutrition Examination Survey (NHANES) participants demonstrated that circulating HDL correlated inversely with serum cotinine and that former smokers had no difference in HDL relative to nonsmokers (330). Smoking cessation is associated with significant increases in HDL-cholesterol levels (68, 123). Significant increases in HDL-cholesterol are typically observed within 3 wk after smoking cessation (115). After a 1-yr prospective, controlled clinical trial including 923 adult smokers, smoking cessation was associated with an increase in HDL-cholesterol levels by 2.4 ± 8.3 mg/dl compared with 0.1 ± 8.8 mg/dl observed among persistent smokers (123).

The effects of other tobacco products on HDL-cholesterol are less well studied. A cross-sectional study including 325 water pipe users and 1,707 nonsmokers did not find significant differences in HDL-cholesterol levels associated with water pipe use. However, in sex-stratified analyses, water pipe use among male subjects is associated with an increased odds ratio (OR: 1.75, 95% CI: 1.11–2.78) for low HDL-cholesterol compared with nonsmokers (334). Contradictory evidence exists characterizing the associations between smokeless tobacco use and HDL-cholesterol levels. A study of 47 smokeless tobacco users and 44 nonusers found significantly ($P = 0.02$) lower HDL-cholesterol in smokeless tobacco users compared with nonusers (47). Another study reported that HDL-cholesterol levels were 22% lower in a group of 25 people who used chewing tobacco than levels in 25 nontobacco chewers or smokers ($P < 0.01$) (311). However, a large cross-sectional study found that snus users had higher levels of HDL-cholesterol compared with never-snus users after adjusting for age, sex, smoking, and education (286).

LDL-cholesterol. LDL-cholesterol levels are an important risk factor for CVD (315). LDL particles are the primary carriers of cholesterol to peripheral tissues and may be a causal agent for the initiation and progression of atherosclerotic plaque (110, 273a). High LDL levels (>160 mg/dl) are associated with an increased risk of mortality (hazard ratio: 2.28, 95% CI: 1.80–2.88) and CVD mortality (hazard ratio: 3.60, 95% CI: 2.33–5.57) compared with LDL< 100 mg/dl (151). LDL levels are consistently higher in smokers compared with nonsmokers. One study reported 1.7% higher LDL levels in smokers compared with nonsmokers, with a positive linear trend between LDL levels and smoking dose (79). Smoking cessation was not significantly associated with lower LDL-cholesterol levels compared with persistent smokers in a 1-yr prospective controlled clinical trial of 923 adult smokers (123). Other tobacco products, such as smokeless tobacco, may also associate with higher LDL-cholesterol levels. Higher LDL-cholesterol levels were reported in a group of 47 smokeless tobacco users compared with 44 nonusers (47). Another study reported LDL-cholesterol levels to be 16.27% higher in a group of 25 people who used chewing tobacco compared with levels in 25 nontobacco chewers (311).

Triglycerides. Triglycerides serve as important sources of energy, which can vary in saturation and length. Triglycerides transported by chylomicrons deliver dietary lipids into the cells of the small intestinal villi after meals, whereas triglycerides transported by VLDL particles deliver fatty acids produced in the liver or from stored adipose tissue triglyceride to cells (127). Prospective studies have found that elevated fasting and nonfasting triglycerides are associated with increased CVD risk, independent of HDL-cholesterol (171). High triglycerides are significantly associated with incident MI, CHD, and death (267, 273a, 280, 281, 329).

Tobacco smoking is consistently associated with higher triglyceride levels (68, 79). A meta-analysis of 13 studies

found tobacco smokers had, on average, a 9.1% higher level of triglycerides compared with nonsmokers (79). A positive linear trend was reported between smoking dose and triglyceride levels (79). No consistent changes in triglyceride levels have been reported after smoking cessation (68, 123). Use of other tobacco products, such as water pipe and smokeless tobacco, has been associated with alterations in triglyceride levels. A cross-sectional study including 325 water pipe users and 1,707 nonsmokers reported that water pipe smokers were significantly more likely to have hypertriglyceridemia (OR: 1.63, 95% CI: 1.25–2.10) compared with nonsmokers (334). Smokeless tobacco use was also associated with higher triglycerides in some cross-sectional studies (47, 311). For instance, significantly higher triglycerides were found among 47 smokeless tobacco users compared with 44 nonusers (158.83 ± 57.73 vs. 130.80 ± 63.45) (47). However, a large cross-sectional study, including >2,000 snus users and >20,000 nonusers, did not identify significant associations between daily or extensive snus use and triglyceride levels compared with nonusers after adjusting for age, sex, smoking, and education (286). To date, significant effects of the use of e-cigarettes or other new and emerging products on triglyceride levels have not been reported.

Insulin Resistance

Insulin resistance is a strong CVD risk factor. Individuals with diabetes have been found to have the same risk of an acute cardiovascular event as an individual who has already had a MI (142, 241). Insulin resistance resulting in diabetes is associated with a prothrombotic inflammatory state and induces atherogenic changes in blood lipids. These changes increase the risk of CHD, peripheral artery disease, and stroke. Both type 1 and type 2 diabetes (T2D) are associated with a two- to fivefold increase in CVD risk (178). Heart disease is the leading cause of death in diabetics, accounting for >70% of death in people with diabetes (33).

Smoking combustible cigarettes has been reported to be a risk factor for T2D, and the estimated risk of diabetes in smokers is ~50% (102). Less is known about the effects of other tobacco products, although consumption of smokeless tobacco has been associated with T2D risk and insulin resistance (283, 293). The recent Surgeon General's report concluded that smoking is causative of T2D (370). This link between smoking and T2D is supported by several meta-analyses (288, 389). Nevertheless, there is contrary evidence showing no relationship between tobacco use and insulin resistance or incident diabetes (196) or between nicotine and insulin resistance (20). Current research demonstrates heterogeneity in the association between smoking and glycated hemoglobin (HbA1c) levels, fasting blood glucose levels, and 2-h postchallenge glycemia (43, 237, 251). Furthermore, it has been reported that heavy smoking moderately increases the T2D risk in obese men, but light smoking reduces the risk in lean men (271). Two meta-analyses used to support the causal relationship between tobacco use and diabetes show considerable heterogeneity in the evidence used to complete the study (288, 389). Indeed, extant meta-analyses used prior studies that often examined the association of smoking and T2D in participants of similar race and sex, typically Caucasian men, despite racial and sex differences in the metabolism of nicotine. Recently, it has been reported that African-American individuals who smoke >20 cigarettes/day evince a small increase in incident diabetes (388).

Several mechanisms have been proposed by which exposure to tobacco products could cause diabetes, including the development of insulin resistance (105). However, the relationship between tobacco use and insulin resistance or diabetes may be confounded by a variety of factors. For example, insulin resistance is often associated with a higher body mass index, a well-known risk factor for diabetes. However, smokers have a lower body mass index than nonsmokers. Further confounding the relationship between smoking and diabetes in the finding that smokers have increased central adiposity compared with nonsmokers of similar body mass index (60), which could contribute to both insulin resistance and diabetes. Moreover, smoking trends differ with race, ethnicity, and sex, which may create different exposure patterns based on race, ethnicity, and sex. The association between the use of tobacco products, insulin resistance, and incident diabetes also could be affected by temporal trends in tobacco use. Over the past decades, cigarettes and smoking patterns have changed drastically. Among smokers, there has been an overall reduction in the average number of cigarettes smoked per day, filtered cigarettes introduced in the late 1950s gained the majority of market share in the 1980s (369), and low-tar cigarettes were introduced in the 1980s. In addition, procedures for processing tobacco have changed, and a variety of flavors and chemicals that change the bioavailablity of nicotine have been added. All of these changes affect the amount and type of harmful and potentially harmful constituents in the product, which could account for the variability between different studies looking at smoking and diabetes.

SMOKING AND SUBCLINICAL CVD

Carotid Intima-Media Thickness

Carotid intima-media thickness (cIMT), a measure of thickening of the inner two layers of the carotid artery, reflects atherosclerosis and the systemic process of arteriosclerosis (337). cIMT is a useful tool for measuring progression of subclinical disease (337), and, even though it has fallen out of favor in clinical practice [receiving a class III recommendation in the latest risk prediction guidelines (128)], it remains a useful test in the research setting. Coronary artery calcification (CAC) is a superior risk predictor of cardiac risk (124), but cIMT may perform as well as CAC for prediction of stroke (113). cIMT testing is particularly valuable among younger individuals (318), especially women, where there is concern for exposure to ionizing radiation (CAC involves low doses of radiation) and in whom atherosclerotic plaque may not yet have calcified. Tobacco smoking has been strongly associated with greater cIMT. In the Multi-Ethnic Study of Atherosclerosis (MESA) (254), current smokers were found to have an adjusted 0.09 mm greater cIMT compared with never smokers, whereas former smokers had an adjusted 0.05 mm greater cIMT than never smokers. Smoking burden (measured in pack-years) was positively associated with cIMT among former smokers in MESA, and times since quitting in former smokers is associated with significantly less cIMT.

Coronary Artery Calcification

CAC is a marker of subclinical coronary atherosclerosis. It is measured using routine cardiac-gated noncontrast computed tomography (CT) of the heart (273), typically using the Agatston score, which uses both the area of calcium and its peak CT attenuation (calcium density) to produce a score for each calcified lesion in the coronary arteries (8). An Agatston score of zero (CAC = 0) is associated with very low risk of future cardiac events, with increasing scores associated with increasing risk of adverse cardiovascular outcomes (92). CAC is best thought of as an "integrator" of all prior accumulated risk exposures (51), and it is used to improve risk prediction and guide preventive approaches (128, 160). CAC can be present in up to 20% of individuals in their 30s and up to 80% by 80 yr. In general, CAC is present in ~50% of patients at the age of ~55 yr, although this varies by sex and race/ethnicity. MESA has published reference values (247, 248), which can be used to calculate the 10-yr risk of a cardiac event (249, 250).

Tobacco smoking is closely associated with the presence and burden of CAC. In the MESA cohort, current smoking was associated with a 1.79-fold adjusted increased risk of having CAC, whereas former smoking was associated with a 1.38-fold adjusted risk of CAC, compared with never smokers (254). Among ever smokers, smoking burden in pack-years was strongly predictive of CAC, and among former smokers, time since quitting has been associated with significantly lower odds of having advanced CAC above the 75th percentile for age/sex/race. CAC also may help to stratify risk in smokers (253). For example, current smokers with CAC > 100 have a 3.75-fold adjusted risk of cardiac events compared with current smokers with CAC = 0. Similarly, former smokers with CAC > 100 have a 2.35-fold risk of cardiac events compared with former smokers with CAC = 0. However, because smoking is also associated with acute thrombotic events independent of coronary atherosclerosis burden, it remains perhaps the most potent risk factor even when CAC = 0. No data are currently available on the association between the use of novel tobacco products and CAC; however, ongoing studies such as the Miami Heart (MiHEART) Study and the existing National Institutes of Health/National Heart, Lung, and Blood Institute cohort studies [i.e., the Coronary Artery Risk Development in Young Adults (CARDIA) study] are actively exploring this issue.

THROMBOSIS

Plasmatic Coagulation Factors

Platelets are versatile blood cells that regulate hemostasis and control blood loss after vascular injury (154, 155, 324). On activation, platelets release several constituents stored in their dense and alpha granules, such as platelet factor 4 (PF4), D-dimer, fibrinogen, selectins, and homocysteine (203). Exposure of selectins on platelets results in interaction of platelets with immune cells (339). Activated platelets bind to plasma fibrinogen via cell surface receptors, primarily the integrin GPIIb/IIIa (298). This interaction mediates platelet aggregation and thrombus formation. Excessive and persistent platelet activation contributes to inflammation and the development of atherothrombosis (176, 321, 360). Smoking and smoking intensity are strongly associated with increased circulating markers of thrombogenesis, including D-dimer, fibrinogen, and homocysteine (Table 1) (6). Moreover, chronic smoking increases circulating levels of thrombopoietin, which mediates platelet activation and platelet-monocyte adhesion to promote thrombosis (234). Given the critical role of thrombosis in MI as well as stroke, smoking-induced elevations in these markers denote increased risk of cardiovascular events.

Platelet-Leukocyte Aggregates

Platelet activation could be measured by agonist-induced platelet aggregation in vitro (343, 346), ex vivo platelet-leukocyte adducts (152, 209, 242, 343), and release of platelet granular contents and fibrinogen binding (343, 347). In animal models, overall platelet function is best assessed in vivo in blood vessel injury models, such as ferric chloride-induced carotid artery injury (52, 236). A majority of studies on tobacco exposure and platelets have used tobacco smoke from cigarettes to establish a role for platelet activation and susceptibility toward a prothrombotic state in humans (26, 111, 170, 174). However, water pipe smoking has also been reported to enhance platelet activation, as evident by the increased formation of thromboxane B_2 (393). Moreover, in vitro studies have suggested that e-cigarette aerosol extracts augment human platelet aggregation and adhesion to fibrinogen and von Willebrand factor (172). Studies in animal models have shown that cigarette smoke activates platelets, which can then bind to either leukocytes or the endothelium (114, 209, 343). Further support for a prothrombotic effects of tobacco products comes from studies showing that nose-only exposure to water pipe smoke in mice shortens the thrombotic occlusion time in pial arterioles and venules (275). Taken together, both animal studies and human data suggest that most tobacco products, including cigarette smoke as well as new and emerging tobacco products such e-cigarettes and hookah, could induce platelet activation.

An increase in platelet activity by tobacco products is unlikely to be mediated by nicotine, because in vitro, nicotine inhibits human platelet activation (323), and 12 wk of exposure to nicotine in mice does not affect platelet activation (242). However, acrolein, which is abundant in cigarette smoke, induces murine platelet aggregation in vitro and increases platelet-leukocyte aggregate formation in mice (343). In apolipoprotein E-null mice, exposure to acrolein increases the formation of PF4, which augments endothelial activation and exacerbates atherosclerosis (347). In humans, the urinary metabolite of acrolein, 3-hydroxypropylmercapturic acid, is significantly higher in smokers than in nonsmokers and is positively associated with increased circulating levels of platelet-leukocyte aggregates (88), suggesting that acrolein, at least in part, contributes to smoking-induced platelet activation. Further studies are required to examine the effect of other constituents of tobacco products, cigarette smoke, and electronic nicotine delivery system-derived aerosols on platelet function.

Blood Clotting Time and Thrombus Formation

Tobacco smoking could be linked to more than two-thirds of sudden cardiac deaths, secondary to acute atherothrombosis. Smoking cessation results in an immediate reduction in atherothrombotic events, even before a change in atherosclerotic burden is detectable (81). Banning smoking in public spaces has been found to reduce the incidence of acute atherothrom-

Table 1. *Human pathophysiological biomarkers*

Outcome	Cigarettes (Acute)		Cigarettes (Chronic)		E-Cigarette (Acute or Chronic)		Smokeless/Nicotine		Hookah		Secondhand Smoke	
	Change	Reference(s)	Change	Reference(s)	Change	Reference(s)	Change	Reference(s)	Change	Reference(s)	Change	Reference(s)
Endothelial dysfunction (flow-mediated dilation)	↑	64, 211, 307, 355	↑	28, 34, 66, 146, 332, 378, 402	↑	64	↑	276, 319, 325, 345	?		↑	23, 66
Arterial stiffness	↑	313, 379, 382	↑	55, 185, 212, 240, 326	↑	381	↑	1	?		?	
Coronary artery calcification	? unlikely to change acutely		↑	253	?		?		?		?	
Carotid intima-media thickness	? unlikely to change acutely		↑	254	?		?		?		?	
Pressor or hypertension	↑	39, 84, 130, 313, 351	↑	145	↑	396	↑	39, 53, 325, 394	↑	71	↔	153
			↔	305	↑ ↓	77						
			↓	133								
Thrombosis	↑	50, 403	↑	152	?		?		?		↑	312
Heart rate variability (SDNN, RMSSD, and high frequency)	↓	30, 95, 156, 199, 231, 261, 297, 391	↓	149, 221	↓	264, 265	↓	183, 344	↓	71	↓	302, 378
	↑	130										
QT	↑	216, 329	↑	94, 108, 180, 181, 342, 358	?		↔	216	?			
			↓	194								
			↔	320, 404								
Left ventricular hypertrophy	? unlikely to change acutely		↑	191, 269, 376	?		?		?		?	
			↔	147, 210								
			↓	290								
Systolic function	↔	107	↑	258	↔	107	↔	353	?		?	
			↔/↓	210								
Diastolic function	↓	107	↓	210, 258	↔	107	↓	126, 352, 353	?		?	

↑, Increases outcome; ↓, decreases outcome; ↔, has equivocal or no effect on outcome; ?, unknown; RMSSD, root means squared of successive differences; SDNN, standard deviation of normal RR intervals.

botic events within months of implementation (24, 65, 291, 328). Tobacco smoke is an important prothrombotic factor, specifically associated with sudden cardiac death secondary to plaque erosion (thrombus overlying an intact plaque with no necrotic core) (57, 58, 335, 377).

Atherothrombosis arises from interplay between platelet activation (resulting in platelet aggregation) and a cascade of circulating proteolytic reactions, resulting in fibrin production. Platelets and fibrin together make up the arterial thrombus. Inflammation promotes atherothrombosis, and tobacco smoking is associated with higher levels of a multitude of circulating inflammatory markers in humans [i.e., leukocytes, C-reactive peptide (CRP), homocysteine, IL-6, and TNF] (41, 42, 304, 356, 363). These elevations are dose dependent and return to levels indistinguishable from nonsmokers within 5 yr of smoking cessation (22, 96, 256). Nitric oxide (NO) and PGI_2 are produced by endothelial cells and are pivotal in maintaining coronary blood flow by inhibiting platelet activation and aggregation. Smoking inhibits the rate-limiting enzyme of NO production, NO synthase. This results in lower circulating levels of NO (27, 284). In addition, platelets from smokers also make less NO and are less responsive to NO-mediated antiactivation/antiaggregation actions (150, 179). Moreover, PGI_2 is lower in the umbilical blood of babies born from mothers who smoke during pregnancy compared with babies of nonsmoking mothers (2). Tissue factor, an abundant glycoprotein that is normally restricted to cells that do not come into direct contact with blood, is exposed to blood when tissue is damaged and is a primary stimulant to thrombosis. Smoking is associated with an increase in circulating tissue factor, increased endothelial expression of tissue factor, and greater tissue factor levels in human atherosclerotic plaques (56, 245, 327).

Tobacco smoking is also associated with prothrombotic changes in the concentration and activation state of multiple coagulation factors in humans, including von Willebrand factor, tissue factor, fibrinogen, factor XIIIa, plasmin activator inhibitor 1, and tissue plasminogen activator (15, 29, 99, 304, 327, 341). Circulating fibrinogen is an independent risk factor for acute cardiovascular events, and tobacco smoking is a potent and dose-dependent determinant of fibrinogen levels (163, 175, 349, 366). In smokers, fibrinolysis is impeded (7) and endothelial production of tissue plasminogen activator is reduced (277, 278). Fibrinolysis is further inhibited secondary to a dose-dependent increase in the quantity and activity of plasminogen activator inhibitor 1 (143, 244, 341). Products of platelet activation that cause platelet activation (PF4, β-thromboglobulin, platelet-activating factor, and thrombin) are higher in smokers than nonsmokers (36, 49, 170, 174, 182) and are thought to be responsible for the observed activation of platelets from nonsmokers when exposed to serum from smokers (49, 233). Platelets from smokers have higher P2Y12 expression, a key receptor for platelet activation (368). Finally, blood viscosity is positively associated with atherothrombotic events and increases with smoking in a dose-dependent manner, independent of other traditional CVD risk factors (228, 367). Mediators of the relationship between smoking and blood viscosity include higher hematocrit, fibrinogen, leucocytes, and blood cell aggregation among tobacco smokers (103, 304). Nevertheless, there is a gap in knowledge regarding new and emerging tobacco products on thrombogenicity of blood and blood viscosity. For example, recently published research has shown that either use of e-cigarettes in young healthy humans or exposure of mice to e-cigarette aerosol increases several prothrombotic markers (279, 306), which further emphasizes the growing urgency to study the effects of emerging tobacco products on thrombogenicity.

AUTONOMIC NERVOUS SYSTEM BALANCE

Role of the Autonomic Nervous System

The sympathetic and parasympathetic arms of the autonomic nervous system (ANS) generally have opposing influences on cardiovascular homeostasis. Long-term sympathetic activation promotes cardiac hypertrophy and negative remodeling by stimulating adrenergic receptor-mediated signal transduction and increasing cardiac workload. Sympathetic activation also promotes a host of pathogenic processes, including arrhythmia, myocardial ischemia, oxidative stress, inflammation, thrombosis, atherosclerosis, diminished cardiac regenerative capacity, and decreased cardiac mechanical performance, all of which may cause or exacerbate heart disease (62, 359). Conversely, β-blockers reduce heart failure mortality (16), corroborating the integral role of adrenergic activation in heart disease progression. In contrast to sympathetic activation, parasympathetic dominance is generally considered salutary, although abrupt increases in vagal tone may promote atrial or ventricular fibrillation and cardiac arrest. ANS modulation of the heart is readily measured by HR and HR variability (HRV) from an ECG, and HRV parameters inversely predict cardiovascular mortality and morbidity, including heart failure, CAD, and metabolic syndrome (90, 201, 206, 207, 273, 357a, 365). Catecholamines (in blood, urine, or saliva) and sympathetic nerve activity (SNA) may also be measured; however, SNA is nonspecific to cardiac modulation as it involves measures of neurons peripheral to the heart (e.g., skin, muscle, renal), and compensatory parasympathetic activation may counter increases in circulating catecholamines by direct inhibition of cardiac sympathetic nerve terminals (374).

Tobacco products can trigger sympathetic dominance through many pathways, including stimulation of autonomic neurons by nicotine, irritant receptor activation, obstructive sleep apnea, nicotine withdrawal, central oxidative stress, and compensatory reflexes to vascular dysfunction—and many of these simultaneously. Nicotine induces sympathetic excitation by stimulating catecholamine release via activation of nicotinic acetylcholine receptors on postganglionic sympathetic nerve terminals and adrenal medullae (139). Cigarette smoke exposure also causes oxidative stress within the central nervous system (101), which may mediate its hypertensive and sympathetic effects (371), as increased superoxide in the brain directly triggers sympathetic dominance and hypertension (54, 59, 120, 121, 148, 149, 222, 401, 405). Tobacco smoke, nicotine, acrolein, and reactive oxygen species (ROS) also activate vagal afferent fibers populated with capsaicin-sensitive receptors that are linked to autonomic responses (205, 322, 354) and potentially the transient receptor potential ankyin 1 channel (73, 74).

Although it is difficult to delineate the role of individual constituents of tobacco smoke, nicotine has clear autonomic effects. In young, nicotine-naive adults, oral nicotine (4 mg) lozenges caused sympathetic activation 15–30 min after administration, as indicated by increased HR (+3.9%), decreased high frequency (HF) (−17%), and decreased root mean square

of successive differences (RMSSD; −6.1%) (344). Similarly, snuff has been found to acutely increase HR, mean BP, and circulating epinephrine in habitual users (394). A side-by-side comparison of acute cardiac effects of cigarettes, oral snuff, chewing tobacco, and nicotine gum (2 mg) in smokers demonstrated comparable increases in HR and BP, although smokeless tobacco induced more prolonged responses than cigarettes and nicotine gum and more pronounced initial increases than nicotine gum (39). Use of second-generation e-cigarettes acutely increases HR and BP comparable with conventional cigarette smoking (396). In healthy, nonsmoking young adults, a 10-min e-cigarette use significantly increased arterial pressure and HR with a nicotine (18 mg) solution but had the inverse effect with a nicotine-free solution (77). Incidentally, measures of muscle SNA tended to increase but failed to attain statistical significance. In a more recent case-controlled study, 23 e-cigarette users were compared with 19 non-e-cigarette users by HRV measured after ≥12 h of nicotine fasting (265). Nicotine-fasted e-cigarette users had a 20% lower HF HRV, whereas low-frequency (LF) HRV and LF/HF were both increased. Although the study lacked time-domain HRV parameters, the authors did show that controlled breathing induced equivalent increases in HF among chronic e-cigarette users as it did in the naive group; thus, e-cigarette use likely decreased HF independent of any alterations in respiratory patterns. In a subsequent study involving nonsmokers who were also not current e-cigarette users, 33 volunteers used e-cigarettes either with or without nicotine or puffed on an empty e-cigarette (264). During use of e-cigarette with nicotine, HF significantly decreased and LF and LF/HF increased. Notably, the authors found that the effects on HRV were more pronounced when HRV data from e-cigarette use with nicotine were subdivided according to measurable increases in nicotine/cotinine in plasma. Use of e-cigarettes without nicotine, or even use of e-cigarettes with nicotine but no measurable increase in plasma nicotine/cotinine, resulted in no significant effects on HRV. The decreases in HF with both acute and chronic e-cigarette use, and independent of respiratory alterations, lend plausibility that e-cigarette use increases sympathetic regulation, which is at least partly dependent on nicotine.

Among smokers, acute nicotine withdrawal is associated with a decrease in HR and systolic BP, but exposure to smoking cues during withdrawal increases HR. Notably, these effects of nicotine withdrawal are ablated by the smoking cessation drug varenicline (138). Other tobacco smoke constituents may independently alter autonomic balance, including metals (63, 225, 294), polyaromatic hydrocarbons (87), volatile organic compounds (VOCs) [e.g., acrolein (205, 292)], gases [e.g., carbon monoxide (CO) (357)], and particulate matter (PM) (61, 63, 85, 225, 361). Multiple studies have demonstrated that active and passive cigarette smoke exposures similarly alter HRV, indicative of sympathetic dominance both immediately and after abstaining overnight (30, 95, 156, 199, 231, 261, 391). Even acute 2-h exposures to modest levels of secondhand cigarette smoke (mean respirable particulate concentration: 78 $\mu g/m^3$, nicotine concentration: 34 $\mu g/m^3$) in an airport smoking area decreased HRV during exposure in nonsmokers (302). Long-term exposure to secondhand cigarette smoke also has been associated with increased 24-h HR and diastolic BP as well as trends of decreased HF HRV (109). Notably, in such cross-sectional studies, effects may fail to reach statistical significance because of high variability in HRV between subjects; in such cases, using each subject as his/her own control during a preexposure period may markedly enhance sensitivity. Rodent studies have provided somewhat similar evidence of tobacco smoke-induced autonomic imbalance, suggesting that higher-level exposures to secondhand smoke may cause sympathetic dominance. Exposure of mice for 6 h/day to secondhand smoke at a total suspended particulate concentration of 30 mg/m^3 cumulatively decreased HRV during the entire 12-h night after each of three exposures, whereas exposures at 2.4 mg/m^3 did not (69).

Measures of SNA at noncardiac sites have provided mixed results owing partly to tissue-specific autonomic regulation. Narkiewicz et al. (272) found that cigarette smoke in healthy young habitual smokers (92% men/8% women) acutely decreases muscle SNA (measured with microelectrodes inserted into the peroneal nerve) while increasing skin SNA, plasma norepinephrine, and systolic BP. Although the authors attributed this counterintuitive depression in muscle SNA to baroreflexes to smoking-induced hypertension, another study in healthy young male habitual snuff users saw no similar effects on peroneal SNA during snuff use, despite equivalent acute increases in mean BP (394). More nuanced findings have emerged in female cigarette smokers, who had diminished fluctuations in muscle SNA with baroreflexes or progression through the menstrual cycle but had accentuated muscle SNA with the cold pressor reflex test (260). Moreover, among hypertensive individuals (73% men/27% women), smokers have increased resting SNA relative to nonsmokers (167). Collectively, these discrepancies suggest that cigarette smoke may acutely depress muscle SNA through a mechanism independent of nicotine, baroreflexes, and cardiac sympathetic modulation, whereas the long-term effects of smoking include increased muscle SNA.

Tobacco smoke may cause cardiovascular injury through its sympathetic effects. Subchronic exposures to high levels of cigarette smoke in hypertensive rats caused left ventricular (LV) hypertrophy and increased expression of hypertrophy-associated genes (258), and similar exposures in normotensive rats increased urinary norepinephrine, remodeling-associated MAPK activation, and LV end-diastolic and end-systolic diameters, while decreasing fractional shortening, indicating LV dilatation and impaired contractility (136). Administration of a dual β-adrenergic receptor antagonist, propranolol, over a comparable exposure prevented these latter effects (100). Nevertheless, dual β-adrenoceptor inhibition may exacerbate some smoke-induced cardiovascular effects relative to selective β_1-adrenoceptor inhibition. To this effect, acute delivery of propranolol can prevent smoking from causing β_2-adrenoceptor-mediated vasodilation in habitual smokers, ultimately resulting in a marked increase in diastolic and mean arterial pressure. Conversely, β_1-adrenoceptor blockade can prevent tachycardia and increases in systolic BP with tobacco smoke (364). A separate study in normotensive heavy smokers (>20 cigarettes/day) showed that repeated smoking caused progressive systolic and diastolic hypertensive responses and increases in HR but also increased HRV (135); notably, β_1-adrenergic blockade prevented smoking from increasing HR yet failed to prevent increases in BP.

Electrophysiology

Smoking has been linked with arrhythmia and ECG changes consistent with acute myocardial ischemia. In men with atypical chest pain and no or minimal indication for CAD, ectopic beats increased during smoking and in the first hour thereafter, with supraventricular arrhythmias significantly increasing and ventricular premature beats tending to increase (310). Smoking significantly decreased HRV in these individuals and also corresponded with ischemic ST-T changes in 10% of participants. Similarly, mice exposed to high levels of secondhand smoke (for 3 days, 30 mg/m^3, 6 h/day) evince decreased HRV and increased sensitivity to electrically induced atrioventricular block as well as ventricular tachycardia (69). In human nonsmokers, chewing nicotine gum acutely increases HR and P-wave duration, which is predictive of atrial fibrillation (189, 239). Nicotine replacement therapy (NRT) in smokers can unmask the short-term effects of tobacco products; 29-day NRT improved ventricular repolarization, decreased corrected QT interval (QT_c), and decreased sympathetic influence (increased RMSSD and decreased HR) (216). Irrespective of autonomic assessments, many studies have demonstrated associations between smoking and prolongation of QT_c or T peak-to-end interval (94, 108, 180, 181, 342, 358), although some studies have either found no relationship (320, 404) or shortening of nomogram-QT_c associated with smoking (194).

It remains unclear whether e-cigarette exposure alters the ECG similar to conventional cigarettes. In one study, switching from conventional cigarettes to e-cigarettes (2.0% nicotine) for 12 wk induced up to a 34% reduction in urine nicotine equivalents but increased QT_c >30 ms relative to baseline in ~14% of subjects, whereas 10% of those who continued conventional cigarette smoking were similarly affected (80). Although this study lacked an NRT group, clearly the benefits of NRT to repolarization observed previously (216) were not recapitulated here by switching to e-cigarettes. Also of note, exposure to CO (119, 287, 338), benzene (202), and PM (25, 97, 98, 116, 130, 220, 224, 314) have all been associated with adverse ECG changes, whereas prolonged acrolein exposure (6 h) at levels comparable to cigarette smoke also can increase arrhythmia susceptibility in rodents (157, 158, 205).

CARDIAC PERFORMANCE AND MASS

In recent epidemiological studies, long-term exposure to cigarette smoke has been linked to echocardiographic indications of structural and functional alterations in both the LV and right ventricle (RV), consistent with hypertrophic cardiomyopathy (Table 1). Among 4,580 elderly participants in the Atherosclerosis Risk in Communities Study (ARIC) study who were free of CAD and heart failure, current smokers had increased LV mass and mass-to-volume ratio and decreases in LV end-diastolic volume, RV end-diastolic area, and RV end-systolic area relative to nonsmokers when adjusting for age, sex, and race. Both the LV *E*/*E′* ratio [an inverse correlate of LV diastolic function (17, 18, 289, 336)] and ejection fraction (EF), an index of systolic performance, were increased significantly in current smokers relative to never smokers (269). Thus, smoking may induce a hypertrophic phenotype concomitant with diastolic dysfunction and enhanced EF, a phenotype resembling heart failure with preserved EF, in which slight enhancements in EF are not uncommon relative to control populations (198). In a cohort of 4,129 black participants of the Jackson Heart Study, cigarette smoking was found to be an important risk factor for LV hypertrophy and incident heart failure admission, even after adjusting for effects on CHD (191).

In contrast to current smokers, among the 23 morphological and functional measures in the ARIC study, former smokers only had increased global longitudinal strain (269). On adjusting for several additional covariates, former smokers had increased LV concentric remodeling compared with never smokers, although all other morphological and functional measures were unaffected. In the Echocardiographic Study of Hispanics/Latinos (ECHO-SOL) panel study, participants were ~20 yr younger on average (and smoked 16 pack-yr less) than ARIC participants, yet smoking duration and intensity both correlated with a multitude of LV and RV structural and functional alterations (210). Similar to the ARIC study, LV mass in the ECHO-SOL study increased with increasing smoking frequency, duration, and lifetime pack-years. LV *E*/*e′* positively correlated with smoking frequency. LV EF and diastolic and systolic volumes were unaffected by smoking frequency, duration, or lifetime pack-years, but current and former smokers each had slightly but significantly lower EF than never smokers. These findings suggest that smoking may less overtly alter systolic function while instead promoting progression toward heart failure with preserved EF.

When examining hypertensive smokers alone and controlling for age, an earlier age of smoking initiation corresponded with a relatively lower LV EF, whereas smoking more cigarettes per day had no apparent effect on EF but corresponded with significantly decreased LV mass (210). Similarly, both current and former smoking was associated with decreased LV mass in healthy young male smokers, even after adjusting for body weight, physical activity, and systolic BP (290). Although these findings oppose observations in older hypertensive individuals (376) as well as hypertensive animal models subjected to subchronic cigarette smoke exposure at high PM levels (258), others have found no associations between smoking and LV hypertrophy in patients with borderline or sustained hypertension (147). Thus, substantial uncertainty remains about the relationship between smoking and LV mass when considering dose as well as covariates such as hypertension, age, ethnicity, and sex. However, in the ECHO-SOL study, there was a dose-dependent relationship between intensity and duration of cigarette smoking and increased LV mass and lower RV function (210).

In the ECHO-SOL study, impaired RV stroke volume and RV outflow track velocity time interval were associated with age at smoking initiation, daily cigarette consumption, and lifetime pack-years (210). Associations between smoking and impaired RV function and structure were most pronounced in those with measurable airway obstruction, which is not surprising, given that chronic obstructive pulmonary disease is common with smoking and corresponds with RV dysfunction and remodeling, even in the absence of pulmonary hypertension (168). Less is known about the long-term effects of smokeless tobacco or nicotine on cardiac structure and function. Neither regular snus users nor cigarette smokers had any measurable impairment in LV systolic function after a 5-h

period of nicotine abstinence but had slowed deceleration times relative to nonnicotine users (353). Additionally, snuff use, and thus nicotine exposure, acutely impaired diastolic function in both ventricles of healthy volunteers (352). Similarly, Giacomin et al. (126) observed that even smoking a single cigarette can acutely impair both LV and RV diastolic function. Of these effects, LV diastolic dysfunction may be particularly significant, as it has been associated with higher risk of CVD or death (274). Others recently found that smoking a single cigarette impaired diastolic function, but inhaling an e-cigarette for 7 min did not (107).

BIOCHEMICAL MARKERS OF CARDIAC DYSFUNCTION AND INJURY

Biochemical markers of tobacco product-associated cardiac dysfunction and risk have been identified. For example, the levels of natriuretic peptides and their more stable NH_2-terminal propeptides (NT-pro), which are common markers of cardiac disease, have been found to be positively associated with ventricular dysfunction, including isolated diastolic dysfunction, and heart failure progression. In a comparison of 75 healthy habitual smokers and 73 nonsmokers, NT-pro-B-type natriuretic peptide (NT-proBNP) levels increased with the number of cigarettes smoked. This was inversely correlated with SD of normal RR intervals (SDNN) HRV (9), suggesting a potential autonomic link between cigarette smoke and ventricular dysfunction. In another study of 969 men, current, but not former, smokers had elevated NT-proBNP levels, whereas duration of cessation in former smokers had a weak yet significant inverse association with NT-proBNP levels (285). Interestingly, even secondhand smoke exposure has been associated with increased NT-proBNP (197). In 9,649 participants of the ARIC study free from overt CAD or heart failure, total pack-years was positively associated with NT-proBNP and high-sensitivity troponin T (TnT) among ever smokers, and current smokers had a higher incidence of elevated NT-proBNP and high-sensitivity TnT relative to never smokers (270). Despite the obvious potential for smoking to confound the predictive validity of NT-proBNP for cardiac mortality, in 796 smokers free of CVD and followed prospectively for 1.5 yr, elevated NT-proBNP level continued to significantly predict mortality (348).

Although less is known about emerging and alternative tobacco products in their effects on natriuretic peptides, chronic exposure to hookah smoke can increase levels of natriuretic peptides and cardiac troponin I (cTnI) in mice (275). Surprisingly, cTnI, a marker commonly used to indicate acute MI, has recently been found to be depressed in current smokers (n = 2,550) and to be more weakly associated with cardiovascular death and hospital admission for acute MI or heart failure than in never smokers (n = 3,824) and former smokers (n = 2,341) (235). Although the etiology of this relationship remains puzzling, these findings suggest that smoking may diminish the prognostic accuracy of cTnI, perhaps by affecting cardiomyocyte injury. Perhaps the relationship between smoking and troponin may be specific to the I isoform. For example, Al Rifai et al. (6) recently found no significant correlation between cardiac TnT and cotinine levels in 843 smokers; however, this study did not involve a control population of nonsmokers.

VASCULAR INJURY

Endothelial Dysfunction, Damage, and Repair

A healthy endothelium promotes vascular health by mediating vasodilation, limiting inflammation, and regulating thrombosis (112). In humans, endothelial function can be assessed by measuring flow-mediated dilation (FMD), the vasodilation produced by increased shear stress, a stimulus for endothelial NO release (112, 255). Impaired FMD predicts CVD risk (78, 129), and FMD declines with age. Cigarette smoking acutely lowers FMD (64, 211, 355), and endothelial function is impaired by nicotine exposure as well (Table 1). However, the impairment induced by nicotine in isolation is less than that of smoking a cigarette of matched nicotine content, suggesting that additional smoke components contribute to adverse endothelial effects (276). In studies of acute cigarette smoking, decreases in FMD were accompanied by increases in ROS and inflammatory markers (11, 64). Multiple studies have demonstrated lower FMD in chronic smokers compared with nonsmokers (34, 67, 146, 332, 378, 402). When baseline FMD is too low (<4% for occlusion below the elbow), acute stimuli may not yield further decrements in FMD. For this reason, FMD may not be a useful biomarker in acute, interventional studies in older study participants or in very heavy smokers. Antioxidant treatments improve FMD in smokers, suggesting a contribution of oxidative stress (165, 166). Smoking cessation improves FMD (188), indicating that it could be a sensitive indicator of improvements in vascular function after smoking cessation. Limited evidence is available to evaluate the effects of other tobacco delivery devices on FMD. Acute e-cigarette use induced a decrease in FMD, although the absolute magnitude of the decrease was less (but not statistically different) than that caused by traditional cigarette smoking (64). Acute and chronic oral tobacco use has also been associated with lower FMD (319, 345). However, further studies are needed to evaluate the acute and chronic effects of e-cigarettes and other novel tobacco delivery devices on endothelial function.

Arterial Stiffness

Arterial stiffening due to changes in both structural and functional arterial properties has emerged as a novel cardiovascular risk factor (78, 262). The standard noninvasive approach to measuring aortic stiffness involves tonometric assessment of carotid-femoral pulse-wave velocity (362). Higher carotid-femoral pulse-wave velocity represents faster pulse-wave transit time in the aorta and is a valid measure of central aortic stiffening. Higher aortic stiffness has been associated with higher cardiovascular events in multiple longitudinal studies (380). Augmentation is a measure of relative wave reflection that reflects the proportion of central arterial pressure that is determined by secondary reflected waves superimposed on the forward pressure wave. Several factors influence augmentation index (AI), including aortic stiffness, peripheral arterial tone, and systolic ejection period; thus, it is not a precise measurement of aortic stiffness (362).

Multiple studies have indicated that traditional cigarette smoking acutely increases carotid-femoral pulse-wave velocity that may reflect an acute reduction in endothelial function (Table 1) (379, 382). Acute exposure to nicotine also increases AI and carotid-femoral pulse-wave velocity (1). Several studies have shown that AI is greater in chronic smokers than in

nonsmokers (55, 185, 212, 240, 326). Smoking cessation is associated with lower pulse-wave velocity and AI (185, 398). There is limited evidence indicating that e-cigarettes alter arterial stiffness. In a mouse model, 8 mo of e-cigarette exposure also increased pulse-wave velocity comparable to traditional cigarette smoke exposure (282). In young, otherwise healthy smokers, using an e-cigarette for 30 min increased carotid-femoral pulse-wave velocity just as much as traditional cigarette smoking did, but use of an e-cigarette for 5 min had a more modest effect on carotid-femoral pulse-wave velocity (381). More information is needed to determine the chronic effects of e-cigarette and other tobacco products on arterial stiffness and to assess whether switching (or dual use) tobacco products (e.g., from combustible cigarettes to e-cigarettes) affects arterial stiffness.

Endothelial Progenitor Cells (or Circulating Angiogenic Cells)

In addition to measuring endothelial function, endothelial health could also be evaluated by measuring circulating levels of endothelial progenitor cells (EPCs). These cells represent a rare population of circulating blood cells (<0.1–1% of leukocytes) of sublymphocytic size (3–5 μm) that possesses cell surface antigens, identifying these cells as having both stem (e.g., c-kit$^+$, Sca-1$^+$, CD34$^+$, and CD133$^+$) and endothelial cell (e.g., VEGF receptor2$^+$/KDR$^+$/Flk-1$^+$ and CD309$^+$) character. EPCs share markers for stemness (e.g., CD34, c-kit, or Sca-1) and endothelial markers (Flk-1, CD31, CD144, CD62, and CD105). EPCs likely derive from bone marrow, are recruited to the blood on injury, and have been found to promote the growth of blood vessels in vivo and to form capillary tubes in two-dimensional cultures (19). Several groups have reported that the levels of EPC in peripheral blood and their phenotypic properties in culture are associated with cardiovascular health (89, 169). In a study by Hill et al. (169), the number of colonies in culture that grew from blood-derived EPCs (identified as CD34$^+$/CD133$^+$/KDR$^+$ cells) were positively associated with FMD but inversely related to CVD risk. The number of EPCs thus serves as a surrogate of endothelial health, endothelium repair potential, and revascularization potential (169, 200, 375), and may be useful for assessing endothelial injury induced by tobacco products.

Multiple studies have shown that cigarette smoking reduces circulating levels of EPC and affects their angiogenic properties. Smokers with preexisting CAD have lower levels of EPCs (399). The numbers of EPCs in light (<20 cigarettes/day) and heavy (≥20 cigarettes/day) smokers is lower than in nonsmokers (200). Light smoking also reduces the number of EPCs counted as acetylated LDL$^+$/*Ulex europaeus* (UE-)lectin$^+$ outgrowth cells, and no acetylated LDL$^+$/UE-lectin$^+$ EPCs could be cultured from heavy smokers (200). Smoking cessation (4 wk) improves EPC levels, an effect that was greater in light smokers than in heavy smokers (200). Interestingly, smoking just one cigarette increases EPCs within 4 h in light (<10 cigarettes/mo) smokers, suggesting stimulation of a signal for EPC mobilization/recruitment (e.g., endothelium injury). Smoking also can impair EPC functions, including proliferation, migration, differentiation, adhesion, and tube-forming capacity (259). These effects are accompanied by enhanced oxidative stress (259). EPC number and function are positively correlated with the levels of plasma antioxidants and NO_x levels, both of these are reduced in smokers (259). Notably, these effects are similar to those of aging (159) and are well associated with endothelium dysfunction. The effects of using e-cigarettes on EPCs are not known, but a brief session of vaping or smoking in smokers and nonsmokers led to significant endothelium dysfunction (64).

Nicotine increases EPC migration, adhesion, and tube-forming capacity of EPCs in vitro (351, 384). Moreover, nicotine treatment in vivo improved EPC mobilization and angiogenesis in a murine model of revascularization, i.e., hindlimb ischemia (161, 162). Because nicotine induces effects opposite to those of cigarette smoke, it seems likely that other constituents of tobacco smoke, such as VOCs, including acrolein, benzo[*a*]pyrene, and PM may impair EPC number and function in smokers. Support for this idea comes from studies performed in other exposure settings. For example, secondhand smoke, a mixture of PM, airborne nicotine, and VOCs (125), impacts EPCs. A brief (30 min) secondhand smoke exposure increased EPC levels in healthy, young, nonsmoking volunteers (164). These effects are complicated. Secondhand smoke exposure increases EPC chemokinesis, but it decreases EPC chemotaxis (164). Nonetheless, secondhand smoke exposure is accompanied by increases in vascular injury markers, reflecting that secondhand smoke induces acute vascular injury and perhaps EPC recruitment for repair (164). In contrast, long-term exposure to secondhand smoke is associated with suppressed EPC levels in both children and adolescents (134). A recent study of the acute effects of e-cigarette showed decreases in circulating EPCs after a single use in healthy smokers (13).

Other constituents of tobacco products also affect EPCs. For example, benzo[*a*]pyrene induces EPC dysfunction in vitro (186, 373). Exposure to acrolein, as inferred from the level of major urinary metabolite 3-hydroxypropylmercapturic acid, is inversely associated with EPC levels in both smokers and nonsmokers (88). Low-level acrolein (0.5–1 ppm) inhalation exposure in mice decreases EPC (Flk-1$^+$/Sca-1$^+$) levels (75, 386). Suppression of EPC level was accompanied by an increase in the number of bone marrow-derived Flk-1$^+$/Sca-1$^+$ cells, a decrease in active bone marrow matrix metalloproteinase-9, suppressed VEGF signaling in the aorta, and overall lower plasma nitrite/nitrate, indicating an impaired EPC mobilization. These effects were fully reversed within 7 days after cessation of exposure (386). Parallel effects on EPCs and aortic VEGF signaling are manifest in mice after a 9-day exposure to concentrated ambient PM ($PM_{2.5}$) (140). However, additional work is required to determine how different constituents of tobacco smoke affect EPC levels, and whether, in addition to cigarette smoking, the use of other tobacco products is also associated with change in the levels and the function of circulating EPCs that contribute to overall endothelium repair and health.

Endothelial Microparticles

Although EPC levels and function are reflective of endothelial health, endothelial injury could be more directly indexed by measuring endothelial cell-derived microparticles. Multiple cell types produce membranous, nuclear vesicles upon their activation or during apoptosis (14, 72, 372). Microparticles and exosomes are the two most commonly studied vesicles. Al-

though they share many properties, they differ in their size, mode of generation, and identifying, characteristic proteins (246). Microparticles range from 100 to 1,000 nm in diameter and are shed from plasma membranes. As a result, they contain phosphatidyl serine and thus are capable of binding fluorescent annexin V. As plasma membrane fragments, microparticles also contain transmembrane molecules (e.g., integrins) and other membrane proteins, which are indicative of their site of origin. Endothelium-derived microparticles are $CD31^+$, whereas those from platelets are $CD41^+$, and those from lymphocytes are $CD14^+$. In contrast, exosomes are somewhat smaller in size (50–100 nm). They are generated through intracellular vesicle-forming processes and are secreted through active, exocytotic mechanisms (14, 72, 372). Exosomes too have a characteristic set of protein markers, such as flotillin, CD63, and TSG101. Measurements of microparticles and exosomes have found utility as indictors of disease severity and progression (10, 40, 132, 187, 297). For example, elevated levels of endothelial cell-derived microparticles are characteristic of several cardiovascular disorders, including CAD, hypertension, atherosclerosis, heart failure, and arrhythmia (40), and are generally indicative of CVD risk (83). Similarly, high levels of endothelial microparticles are associated with vascular dysfunction in end-stage renal failure (10), and the phenotypic signature of these microparticles (expressing markers of apoptosis or activation) can be used to assess the functional status of the endothelium (187). Similarly, leukocyte-derived microparticles are associated with venous thrombogenesis (268). This utility as a diagnostic and prognostic indicator has proven particularly useful in patients with cancer (131).

Recent work suggests that the level of circulating microparticles reflects cigarette smoke exposure. For example, smoking one cigarette promotes an increase in circulating microparticles from many sources, including platelets (263), leukocytes (21, 263), and the endothelium (263). In many cases, increases in circulating microparticles are indicative of smoking-induced pathology. For instance, smokers who present with evidence of emphysema have higher plasma levels of endothelial microparticles, consistent with the idea that emphysema is associated with capillary apoptosis (132). In a rat model, cigarette exposure was associated with an increase in endothelial microparticles and impaired pulmonary function that likewise could result from the apoptosis of lung endothelial cells (226). Microparticles may also be an agent of smoking-induced pathologies. In vitro treatment of mononuclear cells with cigarette smoke extract produced microparticles with enhanced procoagulant (219) and proteolytic (217) activities or microparticles that were enriched with specific microRNAs (21, 333). Consistent with this idea that pollutant and toxin inhalation induces endothelial damage, it has been found that young, healthy humans exposed to acute increase in $PM_{2.5}$ evince elevated levels of microparticles derived from the apoptotic ($CD31^+/CD41^-$) but not activated ($CD62E^+$) endothelium (300). A recent study of the acute effects of single e-cigarette use showed decreases in E-selectin-positive microparticles in healthy smokers (13). Thus, identification and quantification of microparticle populations can be an effective index of exposure to tobacco products and other inhaled pollutants generated by conventional and novel tobacco products.

INFLAMMATION

The role of inflammation in the development of atherosclerosis is well established (12). Alterations in vascular inflammatory profiles and cell adhesion molecules are consistently observed in tobacco smokers compared with never-smokers and may contribute to the development of CVD (12). Inflammatory profiles previously demonstrated to be biomarkers of CVD and consistently found to be higher in current smokers compared with nonsmokers include CRP (32, 42, 117, 214, 254, 385) and IL-6 (42, 214, 254). Cell adhesion molecules and chemokines play an important role in the recruitment of leukocytes to sites of infection and injury. The cell adhesion molecule ICAM-1 (42, 195, 214) and chemokine monocyte chemoattractant protein-1 [MCP-1, aka chemokine (C-C motif) ligand 2 (CCL2)] (214, 252) have been shown to be useful as biomarkers of cardiovascular injury. Recent analysis of the microRNA signature of cigarette smoking was found to be associated with systemic inflammatory markers and correlated with expression of genes involved in immune function (390), providing further support to the notion that smoking induces a state of chronic low-grade inflammation.

C-Reactive Peptide

Serum CRP is an acute phase reactant primarily produced by the liver in response to cytokines, such as IL-1 and IL-6 (31). CRP levels have been used to predict CVD risk (31, 193, 266, 397), and elevated CRP correlates with many traditional CVD risk factors, including smoking (32, 42, 117, 214, 254, 385), diabetes, and obesity (397). CRP can modestly improve CVD prediction models beyond the use of traditional risk factors (266). In a meta-analysis of 160,309 people, CRP levels were found to be directly associated with increased risk of CAD (RR: 1.37, 95% CI: 1.27–1.48), ischemic stroke (RR: 1.27, 95% CI: 1.15–1.40), and vascular mortality (RR: 1.55, 95% CI: 1.37–1.76) after adjustment for traditional CVD risk factors (192). Significantly higher CRP levels have been consistently observed in current smokers compared with never smokers (32, 42, 117, 214, 254, 385). For instance, one study of men aged 60–79 yr old reported an average CRP level of 2.53 mg/l in cigarette smokers compared with 1.35 mg/l in never smokers (385). Studies have associated higher levels of CRP with smoking intensity, including cigarettes per day and pack-years smoked (6, 254). Higher CRP levels have also been observed in former smokers compared with never smokers yet trended to decrease with increased time since quitting in former smokers (254). A recent analysis of 17,293 participants in NHANES demonstrated that both high-sensitivity CRP and white blood cell counts were positively correlated with smoking status and serum cotinine levels (330). Similarly, elevations in circulating CRP have been found in smokers ($n = 414$) relative to never smokers ($n = 548$), along with increases in chemokine markers of T cell chemotaxis and eosinophil recruitment (340).

The effects of tobacco products other than combustible cigarettes on CRP levels have not been well studied. A study that examined primary pipe/cigar smokers and CRP found similar CRP levels in pipe/cigar users and never smokers (385). A cross-sectional study using NHANES data from 1999 to 2008 did not detect differences in CRP levels between smokeless tobacco consumers and nonconsumers of tobacco (243). Also, a cross-sectional study of oral moist snuff users did

not find an association between snuff use and CRP levels compared with never users (383). However, a study of 47 smokeless tobacco users compared with 44 nonusers found twice the levels of CRP in smokeless tobacco users (0.66 ± 0.46 vs. 0.32 ± 0.30 mg/l, $P = 0.001$) (47).

Interleukin-6

IL-6 is a circulating cytokine secreted by activated leukocytes and adipocytes (218). IL-6 promotes CRP production and is associated with CVD risk factors, including obesity and tobacco smoking (42, 214, 254). Many studies have demonstrated that an elevated IL-6 level is a biomarker of CVD risk (31, 350). For instance, a study of apparently healthy men found higher median plasma IL-6 concentrations at baseline among men who subsequently had an MI during a 6-yr followup than those who did not (1.81 vs. 1.46 pg/ml) (317). In this study, men in the highest quartile of IL-6 had a 2.3 times higher risk of MI (RR: 2.3, 95% CI: 1.3–4.3) than men in the lowest quartile. Although IL-6 was moderately correlated with CRP ($r = 0.43$, $P < 0.001$), the relationship of IL-6 with MI remained significant ($P < 0.001$) after controlling for CRP levels (317). Circulating IL-6 levels ≥5 ng/l have been associated with a higher risk (RR: 3.19, 95% CI: 1.94–6.21) of mortality in patients with unstable CAD compared with IL-6 levels of <5 ng/l (223). Circulating IL-6 is also predictive of long-term survival after MI (184) and for the presence of obstructive CAD (OR: 1.213, 95% CI: 1.059–1.389) (137).

Tobacco smoking is associated consistently with higher levels of IL-6 (6, 42, 117, 254). Al Rifai et al. (6) recently reported that smoking frequency and, separately, ln-transformed cotinine levels, are positively correlated with IL-6 as well as high-sensitivity CRP and fibrinogen levels in 843 smokers. Higher levels of IL-6 have also been measured in former smokers than in never smokers, which significantly declined with time since quitting (254). The role of IL-6 in smoking-induced changes has been further implicated via decreases in circulating soluble IL-6 receptor among smokers ($n = 414$) relative to never smokers ($n = 548$), accompanied by decreased IL-15, IL-1 receptor antagonist, IL-1β, IL-16, stem cell factor, and VEGF receptor 3, increases in ratios of inflammatory CCLs, and increased CRP levels (340). However, the effects of other tobacco products on IL-6 are not well studied. A study of 13 smokeless tobacco users compared with 12 nonusers did not find a significant ($P > 0.05$) difference in IL-6 levels (47). A preliminary study in C57BL/6J mice reported increased IL-6 after cigarette smoke exposure but did not find significant increases in IL-6 after exposure to e-cigarettes (177). However, another in vivo study using A/J mice showed increases in IL-6 gene expression after 4-mo inhalational exposure to nicotine-containing e-cigarette aerosol (122), and, similarly, an in vitro study of human airway epithelial cells as well as experiments in mice found increases in IL-6 levels after exposure to e-cigarette aerosols (213).

Intercellular Adhesion Molecule-1

Leukocyte adhesion to the vascular endothelium is an important early event observed in atherosclerosis (303). Leukocyte migration to sites of injury or infection depend on interactions with cell surface adhesion molecules (257). Alterations in some adhesion molecule levels have been used to predict CVD risk, and ICAM-1 has been found to associate with CVD risk factors, including tobacco smoking (42, 195, 214). ICAM-1 is a glycoprotein that is expressed in response to injury, infection, or inflammation on the surface of endothelial cells, leukocytes, and smooth muscle cells (350). ICAM-1 mediates leukocyte recruitment and adhesion to the endothelium (204). Soluble ICAM-1 is a cleavage product of ICAM-1. Elevated levels of endothelial cell surface-bound ICAM-1 will lead to elevated levels of soluble ICAM-1 (208). This is an important concept but is not necessarily true in all cases (392). Because expression of ICAM-1 (and/or VCAM-1) and its cleavage from the membrane surface are two completely different processes, one process can be affected differentially from the other.

Higher soluble ICAM-1 levels have been shown to be biomarkers of CVD risk (230, 316, 350) and associated with CVD risk factors, including older age, cholesterol, BP, body mass index, diabetes, and smoking (42, 195, 214). In healthy men enrolled in the Physicians' Health Study, the highest quartile of soluble ICAM-1 levels (>260 ng/ml) was associated with a higher risk of MI (adjusted RR: 1.8, 95% CI: 1.1–2.8) compared with the lowest quartile (<193 ng/ml) after a 9-yr followup period. This association remained significant after adjustment for traditional CVD risk factors and CRP levels (316). Elevated soluble ICAM-1 levels were also associated with the development of symptomatic PAD during a 9-yr followup period in middle-age men, with median soluble ICAM-1 levels of 285.2 ng/ml at baseline in men that subsequently developed PAD compared with 267.8 ng/ml among the referent group (303). Higher soluble ICAM-1 levels are also consistently associated with tobacco smoking (42, 195, 214, 316). Smokers in the Framingham Heart Study had soluble ICAM-1 levels 25% higher than nonsmokers (309 ± 100 vs. 251 ± 78 ng/ml) (195), whereas smokers in the Physicians Health Study had soluble ICAM-1 levels of 283.9 ng/ml compared with 229.0 ng/ml in nonsmokers (316). The effects of other tobacco products on ICAM-1 and soluble ICAM-1 have not been reported.

Monocyte Chemoattractant Protein-1

MCP-1 (also known as CCL2) is a chemokine ligand that can be induced by oxidative stress, cytokines, or growth factors (350). MCP-1 is a key chemokine influencing monocyte and macrophage migration and infiltration, a critical step in atherogenesis. Higher levels of MCP-1 are associated with traditional CVD risk factors, including older age, hypertension, diabetes, hypercholesterolemia, and with tobacco smoking (91, 214, 252). MCP-1 levels have also been used to predict an increased risk of MI or death (86) and are associated with PAD and incident CHD risk, independent of other CVD risk factors (173). The effects of other tobacco products on MCP-1 levels are unclear. Human vascular endothelial cells exposed to extracts of smokeless tobacco in vitro increased production of MCP-1 and increased neutrophil migration (118). In an in vivo study, A/J mice showed increases in MCP-1 gene expression after 4 mo inhalational exposure to nicotine-containing e-cigarette aerosol (122).

EVALUATION OF CVD RISK IMPOSED BY THE USE OF TOBACCO PRODUCTS: CURRENT CHALLENGES AND FUTURE DIRECTIONS

Decades of research has led to the identification of a wide range of CVD risk factors and biomarkers that are affected by the use of tobacco products, which affect almost all major CVD manifestations. Collectively, these data provide overwhelming and convincing evidence that the use of tobacco products has adverse cardiovascular effects. This conclusion builds a compelling case for tobacco use cessation and abstinence, as a critical strategy for maintaining cardiovascular health and preventing CVD. Nevertheless, it remains unclear to what extent changes in different CVD risk factors (e.g., hypertension, dyslipidemia, and insulin resistance) contribute to the overall cardiovascular morbidity and mortality associated with smoking; to what extent changes in biomarkers of thrombosis, inflammation, ANS, and vascular dysfunction reflect the CVD risk of smoking; and which component of tobacco products inflicts which type of injury, e.g., nicotine, VOCs, PM, etc. Such evaluations have been increasingly important and urgent with the advent of novel tobacco products, such as e-cigarettes, and the increasing popularity of tobacco conventional products such as smokeless tobacco products, cigarillos, and hookahs and their variants, e.g., e-hookah. The extensive literature on the cardiovascular effects of smoking suggests that it may be important to evaluate the effects of tobacco products on all major CVD manifestations (events and outcomes), including ischemic heart disease, MI, heart failure, aortic aneurysms, peripheral artery disease, stroke, and sudden cardiac death. Because no specific dose-response relationships between smoking and each of these conditions are available, it is difficult to presuppose that one specific CVD manifestation may be more sensitive to tobacco product exposure than another condition. This leaves a lot of uncertainty regarding CVD risk of using emerging tobacco delivery platforms.

Even though the evaluation of the cardiovascular effects of tobacco products must ultimately rely on "hard" end points, such as cardiovascular events, such events take many years of continued use to occur. However, the risk of such events could be estimated "early" by evaluating changes in cardiovascular processes and biomarkers associated with smoking that are predictive of cardiovascular events and mortality. As discussed above, several such processes and biomarkers have been identified. Hence, for assessing CVD risk associated with the use of new and emerging tobacco products, it may be important to consider not only classical CVD risk factors (e.g., BP) but also cardiac and vascular dysfunction and their associated biomarkers. In this regard, measurements of cardiovascular function, particularly FMD and ECG changes, and in biomarkers of endothelial injury, such as EPCs and endothelial microparticles, may be more informative in evaluating early and acute changes. In comparison, changes in arterial stiffness, CAC, and cardiac contractile function could be assessed for studying long-term, chronic effects on CVD progression and risk. Measurements of biomarkers of inflammation, thrombosis, and oxidative stress may be particularly useful in delineating early and continued risk, as well as the progression and severity of cardiovascular injury and dysfunction. Although changes in some of these CVD processes and biomarkers have been evaluated in users of new and emerging tobacco products, additional studies are required for a more comprehensive evaluation of their CVD risk profile. This is particularly important for assessing the relative CVD risk of different tobacco products and for their appropriate placement in the continuum of risk. Such assessments are also important for evaluating the "reduced harm" claims for new and emerging tobacco products. This is more challenging, given that tobacco product use, especially among young adults, is better described by dual- and poly-use patterns of behavior (i.e., use of two or more tobacco products), daunting for assessment of both individual tobacco product exposure and of tobacco product-specific harm. Thus, biomarkers of cardiovascular harm will be aided by the development of newer biomarkers of exposure that are specific to new and emerging tobacco products, another challenge for the field (76, 227).

A key challenge in the use of biomarkers and indexes of CVD risk is their lack of specificity for tobacco products. In addition to the use of tobacco products, indexes of cardiovascular function are affected by a variety of different exposures and conditions. For instance, there are significant effects of body mass index, age, sex, and race on CRP (117) as well as several other biomarkers of inflammation, thrombosis, and endothelial injury. As such, no CVD biomarker specific to tobacco products has been identified to date. This may be in part because cardiovascular injury and dysfunction is an outcome of a range of stressors and exposures not unique to tobacco products, and biomarkers reflect cardiovascular injury, regardless of its cause. Nevertheless, careful consideration of covariates, such as infection, comorbidities, and other CVD risk factors, such as age, sex, race, and body mass index, or carefully designed exposure experiments could minimize confounding and provide reliable attribution of injury/events to tobacco product exposure. Longitudinal within-person changes may be helpful in further providing reliable estimates.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.J.C., S.F.S., M.J.B., A.P.C., A.D., P.G., M.E.H., N.M.H., T.E.O., L.M.R., S.S., and A.B. drafted manuscript; D.J.C., S.F.S., M.J.B., A.P.C., A.D., P.G., M.E.H., N.M.H., T.E.O., L.M.R., S.S., and A.B. edited and revised manuscript; D.J.C., S.F.S., M.J.B., A.P.C., A.D., P.G., M.E.H., N.M.H., T.E.O., L.M.R., S.S., and A.B. approved final version of manuscript; N.M.H. and A.B. prepared figures.

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