Trends in Cardiovascular Medicine 26 (2016) 515–523

Available online at www.sciencedirect.com

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Cardiovascular toxicity of nicotine: Implications for electronic cigarette use

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ABSTRACT

The cardiovascular safety of nicotine is an important question in the current debate on the benefits vs. risks of electronic cigarettes and related public health policy. Nicotine exerts pharmacologic effects that could contribute to acute cardiovascular events and accelerated atherogenesis experienced by cigarette smokers. Studies of nicotine medications and smokeless tobacco indicate that the risks of nicotine without tobacco combustion products (cigarette smoke) are low compared to cigarette smoking, but are still of concern in people with cardiovascular disease. Electronic cigarettes deliver nicotine without combustion of tobacco and appear to pose low-cardiovascular risk, at least with short-term use, in healthy users.

Key words: Cigarette smoking, Electronic cigarettes, Nicotine, Cardiovascular disease.

Introduction

Worldwide in the 21st century, tobacco smoke from cigarettes remains the single largest preventable cause of morbidity and premature death, including cardiovascular disease (CVD), and is an urgent public health target [1,2]. As medical advances have shifted the global burden of disease from etiologies like infection and trauma to chronic disease, decreasing use of manufactured products that cause or exacerbate chronic disease is the most logical population intervention. Promoting the use of products that deliver nicotine, but not combustion products has been advocated as one approach to promoting smoking cessation and reducing the harm from smoking. The objectives of this article are to review data on the cardiovascular pharmacology and toxicology of nicotine and to assess the likelihood that products that deliver nicotine without combustion of organic materials, such as nicotine medications or electronic cigarettes, are likely to cause or aggravate cardiovascular disease.

Cigarette smoking and cardiovascular disease

To understand the potential adverse cardiovascular effects of nicotine, it is necessary to consider what we know about cigarette smoking and CVD. Cigarette smoking is one of the

The preparation of this article was supported by US Public Health Service grants P50 CA180890 (NLB) from the National Cancer Institute, and Food and Drug Administration Center for Tobacco Products and the training grant R25 CA113710 (ADB). The authors thank Tyson Douglass for editorial assistance.

Dr. Benowitz is a consultant to several pharmaceutical companies that market medications to aid smoking cessation and has served as a paid expert witness in litigation against tobacco companies. The other authors have no conflicts to disclose.

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http://dx.doi.org/10.1016/j.tcm.2016.03.001
1050-1738/

major causes of premature CVD around the world [1–3]. Smoking markedly increases the risk of acute coronary and cerebrovascular events, including myocardial infarction, stroke, and sudden death. Smoking accelerates atherogenesis producing premature atherosclerosis in epicardial coronary arteries, the aorta, carotid, and cerebral arteries, as well as peripheral circulation. Other cardiovascular effects of smoking include aggravation of stable angina pectoris, intermittent claudication, vasospastic angina, and restenosis after thrombolysis or angioplasty of coronary or peripheral arteries. Cigarette smoking also promotes progression/aggravation of heart failure, chronic kidney disease, and cardiovascular morbidity and mortality in people with chronic kidney disease, and increases the risk of developing atrial fibrillation.

The Table summarizes various adverse effects of cigarette smoking on cardiovascular health. Smokers experience acute myocardial infarction on average at a younger age than non-smokers, and myocardial infarction is associated with more thrombus and less severe underlying atherosclerosis. Paradoxically, smokers who quit smoking after myocardial infarction have a much better prognosis than non-smokers because they have less severe underlying atherosclerosis and multiple reversible pathophysiological adverse effects caused by smoking.

Mechanisms by which smoking causes cardiovascular disease

Several excellent recent reviews have examined the mechanisms by which smoking causes cardiovascular disease [3–8]. In brief, the major mechanisms of smoking-induced CV disease (many of which are overlapping) are (1) oxidative injury, (2) endothelial damage and dysfunction, (3) enhanced thrombosis, (4) chronic inflammation, (5) hemodynamic stress, (6) adverse effects on blood lipids, (7) insulin resistance and diabetes, (8) reduced oxygen delivery by red blood cells, and (9) arrhythmogenesis. Enhanced angiogenesis has also been of concern, although its relevance to human cardiovascular disease has not yet been established.

The Fig. illustrates some of the mechanisms contributing to acute cardiovascular events. Each mechanism will be discussed in more detail in relation to the effects of nicotine later in this review.

Constituents of tobacco smoke that contribute to CVD

Cigarette smoke contains more than 9000 chemicals, and greater than 69 known carcinogens, the vast majority of which are the products of tobacco combustion [3,6]. Constituents of most concern with respect to cardiovascular disease are (1) oxidizing chemicals, (2) carbon monoxide, (3) volatile organic compounds, (4) particulates, (5) heavy metals, and (6) nicotine.

Oxidizing chemicals such as free radicals (a puff of cigarette contains 10^{17}), reactive oxygen species, and reactive nitrogen species are thought to be the main contributors to atherogenesis and thrombogenesis from cigarette smoke. Oxidative damage occurs by endothelial cell activation, dysfunction, and damage [both reducing bioavailability of nitric oxide (NO) and depleting endogenous antioxidants], inflammation, platelet activation, and lipid abnormalities [3,7].

Chronic exposure to carbon monoxide that can produce a carboxyhemoglobin concentration as high as 10% in heavy smokers, produces a functional anemia as it binds more readily to hemoglobin than oxygen, outcompeting for and blocking oxygen-binding sites, and impairing release of the oxygen that does bind. Carbon monoxide–related hypoxemia not only worsens pre-existing conditions (angina pectoris, CHF, intermittent claudication, or COPD), it contributes to smoking-related thrombogenesis via increased blood viscosity as the body compensates by increasing red blood cell mass.

Toxic organic chemicals in cigarette smoke include polycyclic hydrocarbons (PAHs) and reactive aldehydes such as acrolein, formaldehyde, and acetaldehyde. PAHs accelerate atherosclerosis in some animal models. Aldehydes form reactive oxygen species with downstream effects described above [3,6,7]. Additionally, acrolein co-localizes with intimal atherosclerotic macrophages, modifies apolipoprotien A-1, the major protein in

Table – Cardiovascular disorders causing by cigarette smoking.

Vascular disease	*Myocardial disease*
Accelerated atherosclerosis	Increases risk and aggravation of heart failure
Acute myocardial infarction	Hypertensive heart disease
Shorter exercise time to angina	
Coronary spasm	*Inducing cardiac risk factors*
Stroke	Diabetes, type 2
Aortic aneurysm	Dyslipidemia
Peripheral obstructive arterial disease	Hypertension, including malignant hypertension
Stent thrombosis after PCI	Hypertensive renal disease
Graft occlusion after coronary bypass surgery	
	Others
Arrhythmias	Impaired wound healing
Sudden cardiac death	Erectile dysfunction
Atrial fibrillation	Reproductive disorders
Implantable debrillator shocks	Macular degeneration