Nicotine and Impact on Health: Implications for Cardiorespiratory Safety of E-cigarettes

Neal L Benowitz MD
University of California San Francisco

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Disclosures

• Consultant to pharmaceutical companies that market smoking cessation products

• Paid expert in litigation against tobacco companies.
The population risk vs benefit of use of electronic cigarettes is strongly influenced by the relative safety of e-cigarettes compared with conventional cigarettes.
Nicotine Mimics the Neurotransmitter Acetylcholine: Both Bind to “Nicotinic Cholinergic Receptors”
Major Safety Concerns for Nicotine

- Addiction
- Cardiovascular Disease
- Reproductive Toxicity
- Infectious Disease Risk
- Respiratory Disease
- Cancer

- Definite
- Probable
- Probable
- Possible
- Unlikely
Constituents of Cigarette Smoke and E-cigarette Emissions
Tobacco Smoke Chemicals That May Contribute To Cardiopulmonary Disease

• Oxidizing chemicals*
• Carbon monoxide*
• Volatile organic compounds (like acrolein)*
• Particulates*
• Cadmium & other heavy metals
• Nicotine

* combustion products
Constituents of E-liquid and emissions

**E-liquids**
- Nicotine
- Propylene glycol
- Vegetable glycerin
- Flavorants (including potential toxins: diacetyl, cinnamaldehyde, benzaldehyde)
- Tobacco specific nitrosamines
- Metals (including chromium, nickel, silver, tin, lead)

**Emissions (thermal products)**
- Oxidizing chemicals
- Particles (including nanoparticles)
- Aldehydes (including formaldehyde, acetaldehyde, acrolein)
Nicotine and Cardiovascular Disease
Nicotine and cardiovascular disease: possible mechanisms

• Sympathetic neural stimulation ("fight or flight")
• Hemodynamic stress
• Endothelial dysfunction
• Adverse effects on blood lipids
• Insulin resistance/diabetes
• Arrhythmogenesis
• Angiogenesis
• Myocardial fibrosis
Hemodynamic Effects of Nicotine

- Increased heart rate and BP
- Increased myocardial contractility and myocardial work
- Coronary vasoconstriction / Reduced coronary flow reserve
- Cutaneous vasoconstriction
Epinephrine Excretion: Cigarette Smoking, E-Cigarettes, Abstinence

Study Arm

- Tobacco
- E-Cigarettes
- Abstinence

n=14

Epinephrine (µg/g creatinine)

*p < 0.05
Mechanisms by which E-cigarettes could cause Acute CV Events

E-cigarette Aerosol

Oxidizing Chemicals
Particulates
Acrolein

Inflammation

Platelet Activation
Thrombosis

Endothelial Dysfunction

Coronary Vasconstriction

Myocardial Ischemia
Myocardial Infarction

Myocardial Blood Flow
Coronary Occlusion

Nicotine

Sympathetic Nervous System Activation
Catecholamine Release

Ventricular Arrhythmogenesis

Heart Rate
Blood Pressure
Myocardial Contractility

Myocardial Demand for oxygen and nutrients

Sudden Death
Health Effects of Smokeless Tobacco:
Natural Experiment on Effects of Nicotine without Combustion Toxicants
Snus Products

Swedish snus

American snus
Smokeless tobacco and CVD: Swedish snus

• Similar daily nicotine exposure, but slower absorption
• No effect on platelet activation or carotid intimal thickness
• Case control studies – no increase in risk of MI or stroke; small but significant increase in case fatality
• Increased mortality with continued snus after MI
• Increased risk of heart failure, but not atrial fibrillation
Continued Snus Use After Myocardial Infarction Increases Mortality

SWEDEHEART MI register
2474 snus users - 27% Quit
6934 smokers – 61 % Quit
2 year follow up

Mortality (per 1000 pyr)

- Snus: 9.7% (Q), 18.7% (U)
- Cigarettes: 13.7% (Q), 28.4% (U)

(Arefalk, 2014)
Conclusions: Nicotine and Cardiovascular Disease

• Biological plausibility and epidemiological evidence that nicotine may contribute to acute CV events
• Short term nicotine use poses little CV risk
• Long term nicotine use may be harmful in the presence of CVD
• Nicotine is much less hazardous than smoking and replacing cigarettes with clean nicotine would be a substantial benefit for CV health
Empirical Evidence on CV Effects of E-cigarettes in People

- Increased heart rate and blood pressure (nicotine effects)
- Increased arterial stiffness (conflicting reports)
- Endothelial dysfunction (reduced FMD; increased circulating EPCs)
- Reduced heart rate variability
- Oxidative stress (incr LDL oxidizability)
- Case report of atrial fibrillation
Nicotine and Respiratory Disease
Nicotine and respiratory disease: possible mechanisms

- Promotion of airway and smooth muscle proliferation
- Emphysema type changes in rodents
- Impaired apoptosis (programmed cell death) in lung tumor cells
- Reduced cough reflex
- Immune suppression
- Impaired in utero lung development
Empirical evidence of pulmonary toxicity of E-cigarettes

- Cell culture: cytotoxicity, oxidant stress
- Animals models: inflammation, impaired host defenses (bacterial and viral infections), impaired in utero lung development
- Human: increased respiratory symptoms, increased airway reactivity, oxidant stress (reduced expired NO), reduced cough reflex, suppression of inflammatory gene expression (nasal epithelium)
Caveats in interpreting studies of EC toxicity

• ECs are highly variable in emissions, including nicotine and thermal degradation products
• Preclinical EC studies do not accurately replicate human dosing or duration
• Acute effects of EC on biomarkers of cardiopulmonary risk might not be useful predictors of future event
• Epidemiologic studies of CV and respiratory illness difficult to interpret because most EC users current or former smokers, and most are young.
Conclusions Regarding Cardiopulmonary Safety of E-cigarettes

• Although ECs might pose some CP risk, particularly for people with existing CP disease, based on quantitative and qualitative comparisons, the risk of ECs is most likely considerably less than that of conventional cigarette smoking.

• The adoption of ECs rather than cigarette smoking is likely to result in an overall benefit for CP health.

• Caveat: ECs differ markedly in emissions and likely CP risk.
References
