Title: Heat-Not-Burn Tobacco Products: an Emerging Threat to Cardiovascular Health

Mini-Review for AJP-Heart and Circulatory Physiology “Environmental Inhalants and Cardiovascular Disease" call for papers

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Running Head: Heat-Not-Burn Tobacco Products and CV Health

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Abstract (246 words):

Cigarette smoking is at all-time lows globally, but the use of electronic cigarettes has increased profoundly. Recent reports of electronic cigarette or vaping use-associated lung injury may lead individuals to explore novel methods of nicotine consumption, such as heat-not-burn devices. IQOS from Philip Morris, a heat-not-burn device, became available for purchase in the United States in October 2019. Philip Morris claims that 8.8 million people have abandoned traditional cigarettes in favor of IQOS; however, evidence suggests that it may act as a gateway or compliment to cigarette smoking, rather than a replacement. Surveys indicate that 96.3% of Korean IQOS users also smoke cigarettes and 45% of Italian users of IQOS had never smoked cigarettes. In the United States, Canada, and England, susceptibility of youth to trying IQOS was slightly lower than electronic cigarettes, but above cigarette smoking. Heat-not-burn products produce mainstream and second-hand emissions of harmful chemicals including nicotine, particulate matter, benzene, acrolein, and tobacco-specific nitrosamines. The levels of these emissions, despite being less than

35 those of traditional cigarettes, are potentially harmful to cardiovascular health. A study of current
36 smokers showed similar acute effects of heat-not-burn tobacco products and traditional cigarettes
37 on heart rate, blood pressure, and arterial stiffness. Rats exposed to IQOS had similar vascular
38 endothelial function impairment to those exposed to cigarettes. Heat-not-burn aerosol exposure of
39 cultured macrophages elicited increased oxidative stress, although less than that induced by
40 cigarette smoke. Further studies are needed to better understand the cardiovascular effects of heat-
41 not-burn tobacco products.

I. Heat-Not-Burn Tobacco Products in the Nicotine-Delivery Landscape

Cigarette smoking is at all-time lows globally, but use of electronic cigarettes has increased profoundly (21, 32). This trend is particularly pronounced in youth and young adults. Between 2017 and 2018, The National Youth Tobacco Survey showed a 78% increase in high school electronic cigarette use (to 20.8% of all high school students) (11). Similarly, the National Health Interview Surveys for those years report a 46.2% increase in young adult electronic cigarette use (to 7.6% of all young adults) (14). Despite these concerning trends, the recent appearance of "electronic cigarette or vaping use-associated lung injury" may lead individuals to explore novel methods of nicotine consumption (50). Heat-not-burn (HNB) tobacco products could fill this niche, with IQOS by Philip Morris available for purchase in the United States as of October 2019 (10).

HNB products release nicotine-containing, tobacco-flavored vapor without generating the hallmarks of combustion: fire, smoke, and ash. IQOS by Philip Morris achieves this by heating tobacco to a temperature of 350 degrees Celsius, compared to traditional cigarettes, which reach temperatures greater than 600 degrees Celsius. IQOS consists of a rechargeable holding device and a tobacco unit. The tobacco unit is made from tobacco leaves which have been ground, compressed into sheets, and compiled into a plug which resembles a short cigarette. This plug is inserted into the holder, which contains a heated blade and safety mechanisms to prevent burning (38).

While HNB products remain a small component of the nicotine consumption landscape, use and awareness are growing. Upon introduction in Japan (the first country to allow the sale of IQOS), cigarette sales were reduced (47). The response to HNB products in other countries is more concerning. In Italy, 45% of IQOS users have never smoked cigarettes (30). Current IQOS use in young Korean adults is 3.5% and 96.3% of Korean IQOS users report dual-use with combustible

cigarettes (22, 25). In surveys of youth in the United States, Canada, and England, there was an overall awareness of IQOS of 7.0% (highest in the United States, where awareness was reported at 9.1%) (12). In the same surveys, 38.6% of youth expressed interest in trying IQOS (highest in England, where 41.8% expressed interest) (12). In these three countries, susceptibility of youth to trying IQOS was 25.1%, placing it lower than electronic cigarettes (29.1%), but above cigarette smoking (19.3%) (12). According to the National Youth Tobacco Study, 1.6% of United States students are actively using HNB tobacco products (13). Philip Morris claims that 8.8 million people have abandoned combustible cigarettes in favor of IQOS (39); however, the aforementioned surveys of consumers in Italy, Korea, America, Canada, and England suggest that HNB tobacco products may be acting as a gateway or compliment to cigarette smoking, rather than a replacement (12, 22, 25, 30).

Moreover, the classification of these products, including IQOS, as "heat-not-burn" or "non-combustion" is dubious. Normal operation of IQOS causes charring of the tobacco unit and melting of the polymer filter; formaldehyde cyanohydrin (a toxic precursor of formaldehyde and cyanide) is released from the polymer filter at the lower temperatures achieved by the IQOS (16). Emission of this hazardous precursor indicates that HNB tobacco products are involved in generating environmental inhalants with potential adverse cardiovascular health effects (Fig. 1).

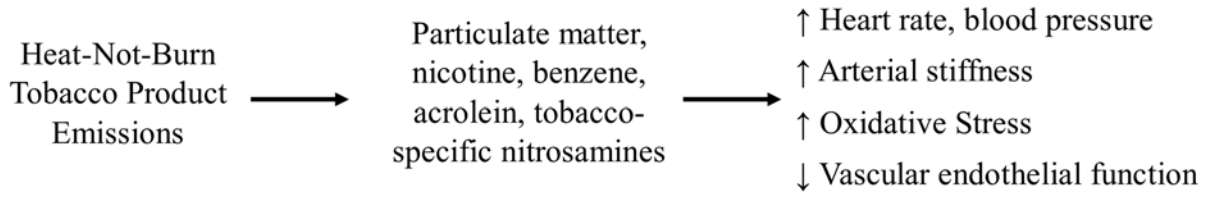

Fig. 1. Heat-not-burn tobacco products emit environmental inhalants and are associated with cardiovascular health effects. These effects include oxidative stress (5, 31), arterial stiffness (23), elevated heart rate and blood pressure (23), vascular endothelial dysfunction (5, 34).

II. Heat-Not-Burn Tobacco Products & Environmental Inhalants

Evidence indicates that HNB tobacco products contribute to pollution with environmental inhalants, particularly within indoor spaces. A survey of Japanese tobacco consumers suggests that indoor, public use of HNB tobacco products is common (80.1% of those surveyed), albeit significantly less common than indoor combustible cigarette smoking (96.7% of those surveyed) (49). Indoor use of HNB products may be bolstered by the regulatory environment of the United States. In April of 2019, only 13 states had instituted a ban on electronic cigarette use and vaping in public, smoke-free spaces (7). Abstracting the definition of smoke, coupled with ambiguously worded laws, further allows Philip Morris to circumvent the application of smoking bans to the IQOS HNB device (3).

A research group at Sapienza University of Rome has conducted multiple studies on HNB tobacco product-associated particulate matter. In one study, participants were placed in a small room, given a tobacco product (a combustible cigarette, an electronic cigarette, or one of two HNB products) and asked to puff once every 30 seconds (12 puffs per five-and-a-half minute session) (43). Particulate matter levels were assessed using a laser-based aerosol analyzer, placed to mimic the location of a second-hand smoke recipient. Particulate matter with diameters less than 1 μm, 2.5 μm, 4 μm, and 10 μm (PM_1, $PM_{2.5}$, PM_4, and PM_{10}) was elevated by all products, with most of the emissions falling into the PM_1 category. HNB tobacco products had significantly higher emissions of PM_1 when compared to electronic cigarettes, but significantly lower emissions compared to the combustible cigarette (43). Another study followed a similar protocol to compare the submicronic particles (SMPs, diameter less than 560 nm) generated in the second-hand smoke of cigarettes, electronic cigarettes, and IQOS in a small room (41). IQOS generated one-fourth of the SMPs of combustible cigarettes, and ambient SMPs from IQOS reduced more rapidly than those from cigarettes. The particles comprising IQOS second-hand smoke were sufficiently small

112 to result in significant alveolar deposition (41). These particulates have the capacity to enter into
113 systemic circulation where they alter hemostasis and cause direct damage to the heart and other
114 organs (48). The particulate emissions from IQOS systems may be particularly detrimental to at-
115 risk populations such as young children. Particle dosimetry modeling of the second-hand emissions
116 of multiple tobacco products showed an inverse relationship between age and dose received, with
117 3-month-old infants receiving the highest dose. Up to 80% of the particles received by infants were
118 small enough to enter the brain through the olfactory bulb. The estimated doses from IQOS were
119 less than those from traditional cigarettes, but up to 110% greater than those associated with
120 electronic cigarettes (42).

121 The findings by Protano et al. are reinforced by studies measuring the impact of cigarette
122 smoking, electronic cigarette use, and IQOS use on motor vehicle air quality. One study estimated
123 that 79.5% to 87.9% of particulate matter associated with IQOS use in vehicles is PM_1 (45). In
124 another study, IQOS significantly increased the air concentration of small SMPs (between 25 nm
125 and 300 nm), but had minor effects on $PM_{2.5}$ and larger SMPs (greater than 300 nm) (46). Nicotine
126 concentration in the air was also elevated by IQOS use in the vehicles. IQOS did not, however,
127 lead to elevations in air concentration of propylene glycol and formaldehyde as found with
128 electronic cigarettes and traditional cigarettes, respectively (46).

129 Operation of IQOS in an environmental chamber provides further evidence of HNB tobacco
130 product-associated environmental inhalants. Mainstream and second-hand emissions from IQOS
131 use generated high levels of nicotine, benzene, and acrolein. The levels of these substances were
132 significantly less than those generated by traditional cigarette smoking, but comparable to or
133 higher than electronic cigarettes (9). In an aerosol study using the Health Canada intense puffing
134 regime (two puffs per minute, each puff with a volume of 55 mL and a duration of two seconds),

IQOS delivered more nicotine (1.40 ± 0.16 mg) than three models of electronic cigarette (0.46 ± 0.06 mg; 0.51 ± 0.05 mg; and 0.82 ± 0.06 mg); both IQOS and the electronic cigarettes produced less nicotine than the combustible cigarette (1.99 ± 0.20 mg) (17). A second aerosol study found comparable nicotine (free-base and total) emission between IQOS and combustible cigarettes (44). Other characteristic IQOS emissions include reactive oxygen species, carbonyl compounds, and tobacco-specific nitrosamines (TSNAs), which are carcinogenic byproducts of tobacco curing (44). Levels of TSNAs in IQOS were significantly higher than electronic cigarettes, but lower than those found in conventional cigarettes (28). Ultimately, a comprehensive study performed by Philip Morris using two-dimensional gas chromatography with time-of flight mass spectrometry and liquid chromatography with high-resolution accurate mass spectrometry revealed 529 different compounds in the aerosol of HNB tobacco products. These 529 compounds are also found in the mainstream smoke of combustible cigarettes, hinting at a similar toxicological profile (4).

At present, the role of HNB tobacco products in the generation of environmental inhalants is not fully appreciated. Due to the novelty of the system and recent approval for sale in the United States, relatively few studies have been performed. Current results suggest that HNB products likely produce fewer inhalants than traditional cigarette smoke, but that the levels produced may still be significant and pose a risk to health. Additionally, multiple studies have demonstrated elevated emissions by HNB products when compared to electronic cigarettes (9, 17, 28, 41-43).

III. Cardiovascular Health Implications of Heat-Not-Burn Tobacco Products

While emission of pollutants from HNB tobacco products is likely reduced versus traditional cigarette smoking, these reductions may not be biologically significant. Philip Morris claims that IQOS is less harmful than traditional cigarettes, but this claim is not supported by their own clinical data. In a Japanese cohort (70 IQOS users, 41 conventional cigarette smokers, and 37 smoking

abstinent), just four of 13 biomarkers of harm were improved; in an American cohort (47 IQOS users, 32 conventional cigarette smokers, and 9 smoking abstinent), only one of 24 biomarkers of harm was improved. Biomarkers showing improvement by switching to IQOS from combustible cigarettes include high-density lipoprotein levels and inflammatory indicators (white blood cell count, soluble ICAM-1, and Prostaglandin F2 alpha) (19).

Both *in vivo* (human clinical and rat) and *in vitro* studies suggest negative cardiovascular health effects with HNB tobacco product use (Table 1). A study of 22 current smokers, with an average age of 33±5 and no comorbidities, showed similar acute effects of heat-not-burn tobacco products and traditional cigarettes on a panel of cardiovascular assessments: heart rate, blood pressure, carotid–femoral pulse wave velocity, and brachial–ankle pulse wave velocity. These findings were significantly elevated from baseline, suggesting that HNB tobacco products may induce arterial stiffness (23). A randomized trial of 20 cigarette smokers utilized a cross-over design to expose each participant to combustible cigarettes, electronic cigarettes, and HNB tobacco products. All three treatments resulted in significantly elevated Nox2-derived protein (an indicator of oxidative stress) in the blood and significantly reduced flow-mediated dilation (an indicator of vascular endothelial dysfunction) on ultrasound versus baseline; HNB products resulted in less oxidative stress than both electronic cigarettes and combustible cigarettes and less vascular endothelial dysfunction than traditional cigarettes (6). These clinical findings are supported by impairment of arterial flow-mediated dilation in Sprague-Dawley rats exposed to IQOS or cigarette smoke, even when exposures produced similar serum nicotine levels (34). Cultured mouse mononuclear macrophages exposed to HNB tobacco aerosols elicited increased oxidative stress (elevated reactive oxygen species and depleted intracellular glutathione) in both a time- and dose-related manner, although less than that induced by cigarette smoke (31).

The effects of HNB tobacco products on the respiratory system must also be considered in overall cardiovascular well-being. Datasets provided by Philip Morris show concerning pulmonary findings: IQOS-exposed rats experience pulmonary inflammation and humans that switch from combustible cigarettes to IQOS show no improvement in pulmonary function or inflammation (33). A clinical study of healthy smokers and non-smokers demonstrated significant, acute reductions in pulmonary function (measured by peak expiratory flow and forced expiratory flow at 25% and 50% of vital capacity) and increases in airway resistance following IQOS use (36). Furthermore, *in vitro* studies using IQOS aerosols shows cytotoxicity in human bronchial epithelial cells and other cells of the respiratory system (15, 29).

Additional detrimental health effects may be revealed upon further study of HNB tobacco products. The environmental inhalants discussed in previous sections have reported cardiovascular pathogenicity. The most well-established connection is the causal relationship between particulate matter and cardiovascular disease, with a plethora of known mechanisms and disease states (8). Exposure to $PM_{2.5}$ increased the odds of ventricular arrhythmia in patients with implanted cardioverter-defibrillators (37). $PM_{2.5}$ was temporally associated with elevated systolic blood pressure and increased risk of hypertension in a large cohort in Delhi, India. Increased waist-to-hip ratio (a marker of obesity) worsened the effects on PM2.5 on blood pressure (40). Similarly, nine months of $PM_{2.5}$ exposure in obese mice resulted in increased left ventricular end diastolic and systolic diameters, as well as cardiac inflammatory mRNA expression (20). Mice exposed to benzene vapor show elevated low-density lipoprotein levels and reduced circulation of angiogenic cells. Humans with elevated urinary levels of benzene metabolites have similarly reduced circulation of angiogenic cells, as well as increased cardiovascular risk scores (1). *In vitro* studies using acrolein are also able to replicate much of the NOX-2-associated vascular dysfunction

caused by electronic cigarettes (26). After eight weeks of inhaled nicotine exposure, our laboratory has shown elevated right ventricular systolic pressure and right ventricular hypertrophy in mice (35). Cardiac fibrosis, cardiomyocyte toxicity, and reduced cardiac function were found in young adult rats following six weeks of implantation with a subcutaneous nicotine pump (24). In a study of chronic electronic cigarette users, nicotine-containing electronic cigarettes induced acute elevations in heart rate, systolic blood pressure, diastolic blood pressure, and mean blood pressure; these effects were not replicated by a nicotine inhaler or a nicotine-free electronic cigarette, suggesting an interaction between nicotine and other tobacco product-associated environmental inhalants (2).

Table 1. Overall summary of heat-not-burn tobacco product emissions and their reported health consequences.

HNB-associated inhalants	Health Consequence
Particulate matter[41-43, 45-46]	↑ BP[40]; ventricular arrhythmias[37]; LV remodeling and cardiac inflammation[20]; heart failure, ischemic heart disease, stroke, and vascular endothelial dysfunction[8]
Nicotine[9, 17, 44, 46]	↑ BP, ↑ HR[2, 23]; RV remodeling and ↑ RVSP[35]; cardiomyocyte toxicity, cardiac fibrosis, and cardiac dysfunction[24]
Acrolein[9]	Vascular endothelial dysfunction and oxidative stress[5, 26, 31, 34]
Benzene[9]	↑ Low-density lipoprotein, ↓ circulating angiogenic cells, ↑ cardiovascular risk scores[1]
Tobacco-specific nitrosamines[28]	Various cancers
500+ additional compounds[4]	Arterial stiffness[23]; ↓ pulmonary function[36]; pulmonary inflammation[33]; bronchial epithelial cell toxicity[15, 29]

Blood pressure, BP; left ventricle, LV; heart rate, HR; right ventricle, RV; RV systolic pressure, RVSP

IV. Gaps in Knowledge

HNB tobacco products are an emerging source of environmental inhalants and a potential threat to human health. Recent regulations and fear surrounding the safety of electronic cigarettes may hasten the adoption of HNB tobacco products by United States consumers. This has been witnessed in Taiwan, where use of electronic cigarettes is illegal: the youth have adapted and now use IQOS at comparable rates to electronic cigarettes (2.33% vs 2.52%) (27).

The body of literature on HNB tobacco products is small, but expanding. Current evidence suggests that HNB tobacco products (and electronic cigarettes) are less dangerous than combustible cigarettes, but not without health risk. A promising clinical study has demonstrated that patients can be categorized into 5 distinct cohorts, each showing differential oxidative stress, platelet aggregation, and endothelial dysfunction in response to electronic cigarettes and HNB products (18). A greater understanding of the mechanisms underlying clustering of these cohorts could lead to safer recommendations for replacement of combustible cigarettes with electronic cigarettes or HNB tobacco products. The same research group has proposed an additional randomized trial to assess the effects of HNB tobacco products and electronic cigarettes on current cigarette smokers undergoing invasive coronary assessment of coronary artery disease (5). Further clinical, animal, and *in vitro* studies must be developed to explore the cardiovascular effects of HNB tobacco products. Presently, it is unclear how circulating levels of toxic byproducts from HNB use compare to those from electronic and combustible cigarette smoking. Early findings have highlighted dysfunction in the respiratory system and peripheral circulation, but how do HNB tobacco products affect the heart itself? What components of HNB tobacco product aerosols are leading to the observed health findings? What are the long-term consequences of HNB tobacco

product use? Answers to these questions and others will assist lawmakers and regulatory bodies around the globe in making informed decisions regarding this novel nicotine-delivery method.

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Disclosures

The authors declare no conflicts of interest, financial or otherwise.

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