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Heart rate and nicotine: a chronic problem

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Summary

Elevated resting heart rate is an independent risk factor for developing cardiovascular disease and increases the risk of adverse outcomes in patients with established cardiovascular disease. Heart rate elevated over time is particularly deleterious to health. Tobacco use has been widely reported to affect heart rate, due principally to the acute positive chronotropic effect of its key component, nicotine. This review explores the proposition that chronic nicotine consumption equates to chronic elevated heart rate.

Keywords

Heart rate, nicotine, tobacco, smoking, electronic cigarettes, smokeless cigarettes

Introduction

Heart rate is a fundamental measure of cardiac function, and is of prognostic and therapeutic significance for both cardiovascular and general health. Over the past 30 years, evidence has emerged to show elevated resting heart rate to be an independent risk factor for developing cardiovascular disease in the general population [1,2,3], which may be comparable in importance as a risk factor to smoking or hypertension [4].

Elevated resting heart rate is a prognostic indicator for several cardiac and non-cardiac disorders [5,6]. It is associated with an increased risk of further cardiac events and adverse outcomes in patients with established cardiovascular disease [7,8], and is an important risk marker for cardiovascular and all-cause mortality [9]. There is a strong independent association between elevated resting heart rate and Sudden Cardiac Death, including in studies of apparently healthy men and women [10].

Heart rate features in an ever-increasing number of national and international clinical guidelines, both within cardiology and beyond. Current cardiovascular disease prevention guidelines identify heart rate as an independent cardiovascular risk factor but refrain from identifying heart rate as an intervention target for primary prevention given the lack of outcomes data [11]. In preventive strategies, therefore, heart rate remains a marker of risk rather than a target for treatment. In secondary prevention and rehabilitation, elevated heart rate is a well established target for intervention, with management strategies involving lifestyle advice and prescribed medications.

With heart rate holding such a prominent position in cardiovascular health, any factors which serve to

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raise heart rate above a normal, healthy and appropriate level should cause concern and prompt intervention. This review looks at the impact of nicotine in raising heart rate acutely and chronically and discusses the clinical implications of this relationship.

Chronic Effects of Long-term Elevated Resting Heart Rate

There is plausible physiological evidence to support the hypothesis that maintaining a low resting heart rate over a lifetime can increase longevity [12,13]. In support of this premise, epidemiological data on the long-term follow-up of healthy individuals have demonstrated that there is an independent association between chronic elevated heart rate and cardiovascular mortality and morbidity. Two large observational studies have demonstrated an increased risk of cardiac events in individuals whose resting heart rate has increased over time [14,15]. Although, a decreased risk of CVD in individuals whose heart rate has decreased over time was only demonstrated in one of these studies [14].

In the Framingham study (n = 5,070), there was a 30-year follow-up of healthy men and women. Although the increase in the overall mortality as a consequence of elevated resting heart rate was more marked among men, it was also found to be significant among women and in both younger and older individuals [16]. In another American study (n = 5,995), healthy subjects aged 25–74 years were followed for between 6 and 13 years. Elevated resting heart rate was found to be an independent risk factor for coronary artery disease (CAD) incidence or death among white and black men and women [17].

An elevated resting heart rate that develops or persists over a five year treatment period predicted greater likelihood of subsequent cardiovascular or all-cause mortality, independent of treatment modality, blood pressure lowering, and other variables [18]. In a sub-analysis of the LIFE (Losartan Intervention For Endpoint) study (n = 9,193), researchers discovered that a heart rate of 84 beats per minute (bpm) or greater, that either developed after initiation of treatment for hypertension or persisted during the study's average five-year follow-up, was linked to a 55% greater risk of cardiovascular death and a 79% greater risk of death from all causes. Although the participants had hypertension, researchers adjusted for this and other cardiovascular risk factors (including age, gender, race, diabetes, smoking, and history of heart disease) and found a strong association between persistent elevated heart rate and risk of death. Even incremental increases in heart rate were associated with increased risk of death. For example, every 10 bpm increase from baseline resting heart rate was associated with a 16% increased risk of death from cardiovascular disease and a 25% greater risk of all-cause mortality.

Tobacco use and cardiovascular disease

Tobacco products are made entirely or partly of leaf tobacco. These products are most commonly consumed through combustion, in which tobacco leaves are burned at high temperatures and the resulting smoke is inhaled (cigarettes, cigars, pipes). Tobacco may also be consumed via smokeless methods such as chewing, sucking, or snuffing. Tobacco is the single most preventable cause of death in the world today and is responsible for about one-in-ten deaths worldwide, equating to an estimated 5 million deaths each year [19].

Tobacco products are used by 1.1 billion people, representing up to one-third of the adult population [19]. The *World Health Organization* (WHO) only collects data on smoked tobacco and smoking has been studied more extensively than any other form of consumption. Rates of smoking have levelled off or declined in developed countries, but tobacco consumption continues to rise in developing countries [20]. According to data from 71 countries compiled by the *World Lung Foundation* and *American Cancer Society*, China is the world's largest overall consumer of cigarettes, accounting for 38% of the world market, followed by Russia with 6.5% and then the U.S. with 5%. However, Russia is in fourth place in terms of annual per capita consumption at 2,786 cigarettes per person (with China at 1,711, U.S. at 1,028, and U.K. at 750) [21].

Tobacco use is a major risk factor for several chronic diseases, including cancer, lung diseases, and cardiovascular diseases. Life expectancy is reduced in long-term smokers, with estimates ranging from 10 to 17.9 fewer years than non-smokers [22,23]. About one-half of long-term male smokers will die of illness due to smoking [23]. Male and female smokers lose an average of 13.2 and 14.5 years of life, respectively [24].

The harmful effects of tobacco consumption principally derive from three mechanisms. Firstly, thousands of different compounds are generated in tobacco smoke, many of which comprise chemical and radioactive carcinogens. There are over 45 known or suspected chemical carcinogens in cigarette smoke. These carcinogens can bind irreversibly to a cell's nuclear DNA, which may either kill the cell or cause a genetic

mutation [25]. If the mutation inhibits programmed cell death, the cell can survive to become a cancer cell.

Secondly, significant cardiovascular effects result from tobacco use. Inhalation of tobacco smoke causes several immediate responses. Within one minute, the heart rate begins to rise, increasing by as much as 30% during the first 10 minutes of smoking. Carbon monoxide in tobacco smoke exerts a negative effect on the heart by reducing the blood's ability to carry oxygen. Both of these conditions can become permanent with prolonged use of cigarettes. Smoking also increases blood pressure, vasoconstriction, and weakens blood vessels. Incidence of impotence is approximately 85% higher in male smokers compared to non-smokers and is a key factor causing erectile dysfunction. These effects increase the risk of smokers experiencing endothelial dysfunction and developing various forms of arteriosclerosis. Smoking increases blood cholesterol levels, negatively impacts on the ratio of high-density lipoprotein to low-density lipoprotein, raises the levels of fibrinogen, and increases platelet production. Indeed, cigarette smoking affects many aspects of atherogenesis and the spectrum of disease from atherosclerosis to angina and ultimately to acute coronary syndrome (ACS) has been extensively studied and reviewed [26].

The third mechanism by which tobacco use exerts a harmful effect is via the highly addictive alkaloid nicotine, which acts as a stimulant and can cause physical and psychological dependency.

Nicotine

Nicotine is a potent parasympathomimetic alkaloid found in the nightshade (Solanaceae) family of plants. It acts as a nicotinic acetylcholine receptor agonist, enhancing acetylcholine neurotransmission in the basal forebrain. It is produced in the roots and accumulates in the leaves of the plants. Nicotine is particularly prevalent in tobacco plants (Nicotiana), where is constitutes approximately 0.6–3.0% of the dry weight of tobacco leaves. Nicotine is present in various edible plants, including tomatoes, potatoes, aubergines, and peppers, with a mean daily dietary nicotine intake of approximately 1.4 μg/day in European and North American populations. By comparison, an average cigarette delivers 1–3 mg of absorbed nicotine and the typical pack-per-day smoker absorbs 20–40 mg of nicotine each day [27].

Transdermal nicotine patches are available in several different doses, and deliver between 5–22 mg of nicotine over a 16- or 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers. Nicotine lozenges and nicotine chewing gum are available in both 2 mg and 4 mg strengths. None of these nicotine replacement products deliver nicotine in the same quantity or as quickly as tobacco cigarettes. There is currently much debate over how much nicotine is delivered via an «electronic cigarette» with estimates varying widely, in part due to the variable efficacy and consistency of nicotine delivery within and between products. In electronic cigarettes that vaporize nicotine effectively, the amount inhaled from 15 puffs is lower compared with smoking a conventional cigarette, but some experienced users may be able to achieve cigarette-like increases in blood nicotine concentration (>10 ng/mL in 5 min) [28].

Nicotine is considered harmful to health, with the principal negative health effects deriving from two characteristics. Firstly, nicotine acts as a stimulant in mammals and this stimulant effect is likely to be a major contributing factor to the dependence-forming properties of tobacco use. Although the amount of nicotine inhaled with tobacco smoke is quite small, as most of the substance is destroyed by the heat, it is still sufficient to cause physical and/or psychological dependence. Nicotine addiction is one of the hardest addictions to break, with some studies suggesting that nicotine is more addictive than cannabis, caffeine, ethanol, cocaine and heroin when considering both somatic and psychological dependence. There is also the formation of harmane, a monoamine oxidase inhibitor (MAOI), from the acetaldehyde in cigarette smoke, which seems to play an important role in nicotine addiction, probably by facilitating dopamine release in the nucleus accumbens in response to nicotine stimuli. Evidence has shown that smoking tobacco increases the release of dopamine in the mesolimbic dopamine system, specifically in the mesolimbic pathway, the same neuro-reward circuit activated by drugs of abuse such as heroin and cocaine. This suggests nicotine consumption has a pleasurable effect that triggers positive reinforcement. It is worth noting that nicotine, although frequently implicated in producing tobacco addiction, is not significantly addictive when administered alone. The addictive potential manifests with the production of the MAOI harmane, which causes sensitization of the locomotor response, a measure of addictive potential [29].

Secondly, nicotine is a potent activator of the sympathetic nervous system and stimulates the body to produce adrenaline, which raises blood pressure, heart and respiration rate, thereby causing the heart to work harder. This may implicate nicotine in acute episodes of some diseases, such as stroke, impotence, and heart disease.

Nicotine may have some health benefit. Studies have shown that nicotine derived from smoking and other tobacco use may lower the risk of developing Parkinson's disease. A recent study showed that eating foods that contain naturally-occurring nicotine may also reduce the risk of Parkinson's disease. However, the negative health effects of nicotine appear to outweigh the positive.

Combustion is the most efficient method of delivering nicotine to the brain, with cigarette smoking being the most prevalent delivery system. Ingesting a compound by smoking is one of the most rapid and efficient methods of introducing it into the bloodstream, second only to injection, which allows for the rapid feedback that supports the smokers' ability to titrate their dosage. After inhaling on a cigarette, nicotine is delivered rapidly to the pulmonary venous circulation, from which it moves quickly to the left ventricle of the heart and to the systemic arterial circulation, taking about 10–20 seconds for the substance to reach the brain. The amount of nicotine absorbed by the body from smoking depends on many factors, including the type of tobacco, whether the smoke is inhaled, and whether a filter is used.

With recognition of the dangers inherent in combustible tobacco products, new non-combustible alternatives are on the rise. These products claim to reduce the toxic exposures caused by combustion and include non-combustible cigarettes (i.e. «smokeless» electronic cigarettes) and oral tobacco (e.g., lozenges, strips, snus, orbs), some of which are dissolvable. Electronic cigarettes, or e-cigarettes, are by far the fastest growing product, with an estimated 1.3 million users in the UK and more than 20% of adult smokers in the U.S. having tried an e-cigarette. This product aims to imitate conventional cigarettes whilst delivering nicotine in a toxin-free vapour. An electronic cigarette, also known as a personal vaporiser, consists of a plastic cartridge (which serves as a mouthpiece and contains a nicotine liquid), a battery and a heating element. When a consumer inhales through the device the liquid is heated and the resulting vapour is inhaled and absorbed principally through the mouth. When the user exhales, a plume of what appears to be smoke is emitted but which is actually largely water vapour. The liquid commonly contains glycerol, propylene glycol, flavourings, and nicotine. Most laboratory analyses have shown this liquid to contain no carcinogens and to be less toxic than regular cigarettes. However, the benefits and risks of electronic cigarette use remain uncertain and health organizations, including the *World Health Organization*, have called for urgent clinical studies on their effects on human health.

Nicotine and heart rate

The effects of consuming nicotine on the cardiovascular system can be detected almost immediately after a person starts to smoke a cigarette. Within one minute after smoking begins, the smoker's heart rate starts to increase: it may increase by as much as 30% during the first 10 minutes of smoking [30]. Even in habitual smokers, there can be a rise in heart rate of up to 37+4 bpm [31]. Blood pressure also increases when a person smokes a cigarette.

These increases are temporary but, as most smokers smoke cigarettes several times a day, these effects occur often and may cause a chronic problem that ultimately undermines longer-term health. This proposition has been tested. In one study, 10 normotensive smokers were asked to smoke one cigarette every 15 minutes for 1 hour. Blood pressure and heart rate were monitored continuously during the smoking period and during the preceding non-smoking hour. Six other normotensive smokers were asked to smoke two cigarettes per hour throughout the whole day, with blood pressure and heart rate being monitored non-invasively in ambulatory conditions every 10 minutes for 8 hours. In the first condition (four cigarettes over 1 hour), the first cigarette caused an immediate and marked increase in blood pressure and heart rate, and the peak blood pressure and heart rate achieved were similar for the remaining three cigarettes. In each instance, the hemodynamic effects were prolonged, with blood pressure and heart rate remaining persistently higher than during the non-smoking hour. In the second condition (two cigarettes per hour for 8 hours), daytime blood pressure and heart rate were also persistently higher during smoking than during non-smoking. The authors concluded that heavy smoking is associated with a persistent rise in blood pressure and heart rate [32].

Reductions in heart rate and blood pressure have been detected 20 minutes after ceasing to smoke. However, most research indicates that clinically meaningful reductions are only achievable after a full cessation of smoking. For example, one study found once subjects with angina stop smoking there is a decrease in heart rate and an improvement in ST segment changes provoked by exercise [33].

Studies have demonstrated a rise in heart rate in consumers of tobacco, both smoked and smokeless (chewed and snuffed). One study (n = 135), after adjusting for potentially confounding variables, found daytime ambulatory heart rates were significantly (P<0.05) elevated in both smokeless tobacco users and smokers compared with nonusers (69 ± 14 and 74

± 13 bpm, respectively, versus 63 ± 12 bpm). The authors conclude that the higher heart rates (and blood pressures) noted during the daytime in smokers and smokeless tobacco users were most likely due to the effects of nicotine [34]. A similarly conducted study, using 24-hour ambulatory blood pressure measurement to examine the effects of smoking in normoalbuminuric insulin-dependent diabetes mellitus patients found that the 24 smokers had significantly higher 24-hour heart rate that the 24 nonsmokers were matched for sex, age, and diabetes duration (80 ± 7.2 compared to 72 ± 9.2 bpm, P<0.001) [35].

Heart rate has been shown to increase as a consequence of passive smoking in healthy young females (n = 30). Heart rate measurements at 15th and 30th minute of exposure were higher than at baseline and 5th minute of exposure (88 ± 3.2 and 90 ± 3.7 vs. 76 ± 3.9 and 78 ± 4.5 bpm, P<0.05). Heart rate decreased notably at 15th minute and returned to baseline values at 30th minute after exposure (80 ± 1.2 and 76 ± 3.2 vs. 88 ± 4.5 bpm, P<0.05) [36].

It should be noted that elevations in heart rate are detected, not only in high-nicotine containing products like tobacco cigarettes, but also in low-nicotine containing products such as nicotine replacement products. Regarding electronic cigarettes, there is currently little evidence looking at the impact of nicotine contained in these products and the data that does exist may be unreliable due to the variable nicotine content in products, as discussed above. The studies that have explored the effects of e-cigarette use on heart rate are conflicting. In one study, 32 participants inhaled one e-cigarette cartridge per day for 4 weeks, but no abnormal changes in blood pressure or heart rate were observed [37]. Another small study (n = 42) used echocardiography to compare the cardiac function of 20 young smokers (aged 25 to 45 years of age) before and after smoking one tobacco cigarette to the cardiac function of 22 young e-cigarette smokers before and after using an e-cigarette for seven minutes, who were of a similar age. Results showed that smoking a tobacco cigarette had important hemodynamic consequences, with significant increases in blood pressure and heart rate (+8% systolic BP, +6% diastolic BP, and a 10% rise in heart rate). In contrast, e-cigarettes produced only a slight elevation in diastolic blood pressure (+4%). The authors concluded that, although nicotine is present in e-cigarettes, it is absorbed at a lower rate compared to regular cigarette smoking [38].

However, in contrast to these results, a recent study has reported that, relative to baseline, plasma nicotine and heart rate increased significantly within 5 minutes of first inhalation from an e-cigarette, and remained elevated throughout the ad lib puffing period [39]. This finding is supported with a qualitative article in which some e-cigarette users reported changes in heart rate and palpitations [40].

Regarding other nicotine replacement products, these do not appear to deliver high levels of nicotine when used as instructed. For example, regarding nicotine patches, despite increased nicotine concentration with concomitant use, the evidence from two studies, (n = 10) [41] and (n = 12) [42], suggests there are no increases in the incidence of side effects or significant changes in physiological parameters such as blood pressure and heart rate.

Discussion

Cigarette smoking has a considerable influence on cardiovascular risk and is one of the most significant modifiable risk factors for acute myocardial infarction [43]. Evidence outlined in this review points towards elevated resting heart rate being an important variable in cardiovascular disease. For example, high heart rate, among other things, is a marker of increased sympathetic nervous system activity, which itself is linked to increased heart ischemia, and is associated with promoting atherosclerosis and susceptibility to arrhythmia. Evidence also indicates that nicotine is a significant cause of an acute and often sustained rise in heart rate that, for the nicotine addict, effectively becomes a chronic elevated heart rate. With heart rate holding such a prominent position in cardiovascular health, any factors, especially modifiable, which serve to raise heart rate above a normal, healthy and appropriate level should cause concern and prompt intervention.

Heart rate is a measure not just of poor outcomes, but of the management of patients. Ensuring heart rate is within a healthy range is likely to become an increasingly important message for primary and secondary care. It is important for clinicians to remember that one problem in assessing patients consuming nicotine is that the acute effects of nicotine may escape clinic blood pressure measurement. Ambulatory monitoring may therefore be a more accurate way of assessing 16- or 24-hour heart rate (and blood pressure) in this population.

The link between nicotine and elevated heart rate is especially important at the current time. Although developed counties have seen a slow reduction in smoking and tobacco use over recent years, the issue of smoking remains a problem in both developed and

developing countries. The nicotine content of popular American-brand cigarettes has slowly increased over the years, and one study found that there was an average increase of 1.78% per year between the years of 1998 and 2005. This was found for all major market categories of cigarettes [44]. There are increasing calls to reduce the nicotine content in cigarettes to prevent children from becoming addicted smokers and giving people greater freedom to stop smoking if they decide to quit by reducing the addictiveness of cigarettes.

The debate over nicotine products as aids to smoking cession is complicated with the recent rise in electronic cigarettes and their potential to deliver high doses of nicotine, thereby perpetuating a nicotine addition, albeit using a less toxic delivery system. There is urgent need for research and possibly regulation of these products if they are found to deliver harmful levels of nicotine. Although the evidence currently suggests that up to half of the nicotine content may be exhaled in the vapour, there are also suggestions that nicotine replacement products such as e-cigarettes simply promote a slower absorption of nicotine.

In terms of the limitations of this review, the evidence contained herewith needs to be considered within the context of methodological shortcomings, such as the difficulties of comparing different nicotine delivery systems, and the paucity of data on newer nicotine products, such as electronic cigarettes.

Conclusion

Smoking cessation is fundamental to cardiovascular disease prevention, and it is associated with a significant reduction in risk of all-cause mortality in those with coronary heart disease. Inflammatory markers, which can indicate atherosclerotic disease, have been shown to return to baseline levels five years after quitting, suggesting that the inflammatory component of cardiovascular disease resulting from smoking is reversible with reduced tobacco exposure and smoking cessation [45]. With a greater understanding of the chronic impact of nicotine use on chronic resting heart rate, it is hoped that clinicians will take a long-term view and redouble their efforts to encourage and support abstinence from all forms of excess nicotine consumption.

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