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REVIEW

Smokeless tobacco, sport and the heart

Tabac non fumé, sport et cœur

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Summary Smokeless tobacco (snuff) is a finely ground or shredded tobacco that is sniffed through the nose or placed between the cheek and gum. Chewing tobacco is used by putting a wad of tobacco inside the cheek. Smokeless tobacco is widely used by young athletes to enhance performance because nicotine improves some aspects of physiology. However, smokeless tobacco has harmful health effects, including cardiovascular disorders, linked to nicotine physiological effects, mainly through catecholamine release. Nicotine decreases heart rate variability and the ventricular fibrillation threshold, and promotes the occurrence of various arrhythmias; it also impairs endothelial-dependent vasodilation and could therefore promote premature atherogenesis. At rest, heart rate, blood pressure, inotropism, cardiac output and myocardial oxygen consumption are increased by nicotine, leading to an imbalance between myocardial oxygen demand and supply. The same occurs at submaximal levels of exercise. These increases are accompanied by a rise in systemic resistances. At maximal exercise, heart rate, cardiac output and maximal oxygen uptake ($\dot{V}O_{2\,max}$) are unaffected by nicotine. Because endothelial dysfunction is promoted by nicotine, paradoxical coronary vasoconstriction may occur during exercise and recovery. Nicotine induces a decrease in muscular strength and impairs anaerobic performance. However, nicotine is used in sports as it diminishes anxiety, enhances concentration and agility, improves aerobic performance and favours weight control.

Abbreviations: SLT, smokeless tobacco; VO_{2max}, maximal oxygen uptake; WADA, World Anti-Doping Agency.

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Importantly, smokeless tobacco, similar to cigarette smoking, leads to nicotine dependence through dopaminergic pathways. Smokeless tobacco has harmful cardiovascular effects and is addictive: it fulfils all the criteria for inclusion in the World Anti-Doping Agency prohibited list as a doping product. Smokeless tobacco use in sporting activities must be discouraged.

MOTS CLÉS
Nicotine ;
Tabac non fumé ;
Sport ;
Dopage ;
Effets cardiovasculaires

Résumé Le tabac non fumé (TNF) est un tabac finement moulu ou broyé qui peut être placé soit dans le nez (*dry snuff*, tabac à priser) ou entre la joue et la gencive (*moist snuff*, *snus*, tabac à chiquer). Le TNF est utilisé couramment par les jeunes athlètes qui pensent ainsi pouvoir augmenter leur performance sportive, la nicotine améliorant certains paramètres physiologiques. Cependant, le TNF a des effets nocifs sur la santé, entraînant notamment des troubles cardiovasculaires, liés aux effets physiologiques de la nicotine, principalement via une libération de catécholamines. La nicotine diminue la variabilité de la fréquence cardiaque (FC), le seuil de fibrillation ventriculaire et favorise la survenue d'arythmies. Elle altère la vasodilatation dépendante de l'endothélium et pourrait donc favoriser le développement prématuré d'athérome. Au repos, la FC et la pression artérielle (PA), ainsi que l'inotropisme, le débit cardiaque et la consommation myocardique d'oxygène sont augmentées par la nicotine, conduisant à un déséquilibre entre la demande et l'apport en oxygène au niveau myocardique. Ceci est également constaté à des niveaux d'effort sous-maximal. Ces modifications sont accompagnées d'une élévation des résistances périphériques. À l'exercice maximal cependant, la FC, le débit cardiaque et à le $\dot{V}O_{2\,max}$ sont inchangés par la nicotine. Puisqu'un dysfonctionnement endothélial est favorisé par la nicotine, une vasoconstriction coronaire paradoxale peut survenir aussi bien pendant l'exercice que pendant la phase de récupération. La nicotine diminue la force musculaire et altère la capacité d'exercice anaérobie. Cependant, elle est consommée dans certains sports car elle diminue l'anxiété, renforce la concentration, améliore la performance aérobie et favorise le contrôle de la prise de poids. Il est important de savoir que le TNF, à l'instar du tabac fumé, entraîne une dépendance à la nicotine, relevant de mécanismes dopaminergiques. L'usage du TNF possède des effets cardiovasculaires nocifs, et induit une dépendance à la nicotine : le TNF remplit donc les critères pour être incorporé à la liste des produits dopants de l'Agence mondiale antidopage. L'utilisation du TNF doit donc être déconseillée dans le cadre de la pratique sportive.

Background

Over the past two decades, the use of alternative kinds of tobacco consumption, such as smokeless tobacco (SLT) in the form of 'snuff', chewing tobacco, snus or 'tabac à chiquer' in France, has increased in young athletes. SLT is chewed or sniffed but not smoked. Although the negative health effects of cigarette smoking have been largely documented, those of SLT remain controversial. SLT has been shown to be associated with an increased risk of oral or oropharyngeal cancer and cardiovascular diseases [1,2], leading to the strong discouragement of its use [3]. Although no firm association was found between SLT use and the risk of myocardial infarction in a pooled analysis of prospective observational studies [4], quitting snus, a humid form of powdered tobacco placed under the lip, after myocardial infarction has recently been associated with a better prognosis [5].

Current guidelines recommend that tobacco, including SLT, must be avoided for 2 hours before and after a sports session or practice [6]. However, given that SLT is mostly used by athletes and that intense physical exercise can induce acute cardiovascular events [7], it is important to determine whether the cardiovascular effects of nicotine can increase the risk of cardiovascular outcomes, especially during sports activities. Nicotine is currently under evaluation as a doping product by the World Anti-Doping Agency [8]. As nicotine contributes substantially to the cardiovascular effects of tobacco [9], the debate could be extended to e-cigarettes.

We aim to review current knowledge regarding SLT as a cardiovascular risk factor, considering patterns of consumption of SLT around the world, the pharmacological properties of SLT, the context of SLT use by athletes and SLT safety data. Finally, we review the main findings on the cardiovascular impact of SLT and discuss whether SLT can be classified as a doping agent.

Worldwide consumption patterns

Few data are available on the real use of SLT across the world. In the USA, SLT use is frequent among athletes, especially baseball players [1,10]. In Scandinavia, SLT use is common both in the community and among athletes [1,11], and often starts early in life; more than 15% of

boys aged between 14 and 15 years were found to have used snuff [12]. SLT use is even more frequent among individuals participating in sports club activities, especially team sports, such as ice hockey [11]. In Sweden, the only European Union country where the sale of snuff is allowed, SLT represents almost 50% of total tobacco consumption [13]. Cigarette smoking in Sweden is much lower than that in neighbouring countries, and tobacco-related mortality is about 50% lower than in other European countries [13]. However, the interplay between SLT and cigarette smoking is complex. Switching patterns exist in both directions and both types of consumption can be concomitant [1]. The consumption of snus and chewing tobacco is much lower among young Swiss men [14].

In France, epidemiological data are controversial. Among 920 students from the Alpine region, 11.2% had tried chewing tobacco [15]. However, SLT use has been reported in French ice hockey players and skiers [16]. In France, as in other European countries (except Sweden and Norway), the sale of snuff is prohibited. SLT can be purchased via the Internet or brought in by relatives or friends travelling from countries such as the USA, Norway or Sweden, where the sale of SLT is allowed. In France, the snuff-provider role of team partners and coaches travelling from such countries must not be underestimated. Moreover, chewing tobacco is sold legally in France, which explains why some athletes use it.

Analysis of urine from 2185 athletes worldwide suggests that nicotine is used for reasons other than recreational purposes [17], especially in certain sports, such as American football, ice hockey and wrestling.

Pharmacology

SLT includes chewing tobacco, spit tobacco, dry snuff, which is sniffed into the nose, and moist snuff (snus), which is placed in the mouth between cheek and gum. Quantitatively, nicotine is the most abundant alkaloid component of tobacco; it is thus assumed that nicotine is one of the major causes of the pharmacological effects of tobacco [9]. The concentration of nicotine in snuff is approximately twice that in chewing tobacco.

Pharmacokinetics

After ingestion of SLT, nicotine absorption by the oral mucosa is rapid and massive [18,19], and is increased in some preparations by the adjunction of very small particles of glass. Plasma nicotine concentration shows a peak that is nearly as high as that obtained by cigarette smoking, with a time to peak after snuff intake of about 30 minutes. This peak is then followed by a plateau phase, which lasts about 2 hours, and is thus much longer than with cigarette smoking. Interestingly, nicotine absorption lasts for 1 hour after the SLT has been removed from the mouth. For these reasons, exposure to nicotine after snuff intake is nearly twice that after cigarette smoking. The half-life of nicotine is about 2 hours. Nicotine is mostly metabolized by the liver; the main metabolite, cotinine, is inactive and has a much longer half-life (about 16 hours) than nicotine. Cotinine is found in the blood and urine; this issue is important for biological assessments of consumption.

Pharmacodynamics

Most of the effects of SLT are attributable to nicotine [9]. This alkaloid binds to nicotinic receptors, which are located in the brain, the autonomic ganglia, the adrenals and neuromuscular junctions. The stimulation of these receptors by nicotine induces the release of neuromediators (e.g. norepinephrine, epinephrine, acetylcholine, dopamine, serotonin, vasopressin, nitric oxide, etc.). Most cardiovascular effects are due to the secretion of catecholamines: either norepinephrine by sympathetic nerve terminals or epinephrine by the adrenomedulla [9]. Direct effects can also occur, independently of nicotinic cholinergic receptors and catecholamine release [20]; nicotine can block ionic channels [21] at nicotine concentrations that are achieved after SLT use [20]. Nicotine may increase carotid and aortic chemoreceptor sensitivity [22]. Some authors have suggested that the sympathetic response may be attributable to a reaction induced by parasympathetic effects [22]. These mechanisms could explain the polyphasic and dose-dependent response to nicotine. The cognitive and addictive effects are mainly caused by dopaminergic stimulation, especially in the nucleus accumbens and prefrontal area [23].

The tolerance phenomenon is a key issue for the effects of nicotine, as it occurs very early after nicotine exposure. If the blood nicotine peak is progressive, as is the case with nicotine gum or patches, tolerance effects induce less intense cardiovascular effects than other means of administration, such as intravenous infusion, snuff dipping or cigarette smoking.

Use in athletes

Athletes have different motivations for SLT consumption, including enhanced concentration, help with relaxation or for ritual reasons [10]; sometimes they use SLT for weight control [24]. Athletes also think that SLT can enhance their performance [16,24]; however, this belief was not reported in baseball players who answered anonymous questionnaires [10].

It has been suggested that SLT provides the 'beneficial' effects of nicotine without the negative effects of smoke, especially on the respiratory tract. During the 2009 Ice Hockey World Championship, nicotine and its metabolites were detectable in nearly 50% of 72 urine samples, suggesting active tobacco consumption. Moreover, two athletes had quite elevated concentrations, which is highly suggestive of SLT use for doping purposes [25].

Baseball players use SLT more often during the baseball season than during the off-season [10]. However, long-term SLT use failed to improve physical performance in middle-aged men [26]. Moreover, in this cohort of 144 Swedish firemen, maximal oxygen uptake ($\dot{V}O_{2\,max}$) and maximal workload during a bicycle stress test were similar in SLT users and nonusers of tobacco, but higher than in cigarette smokers. Data from a meta-analysis on the effects of nicotine found that nicotine significantly improved fine motor

abilities, alerting attention-accuracy and response time, and orienting attention-response time [27]. However, reaction and movement times were similar in SLT users and nonusers after nicotine absorption [28,29]. Moreover, anticipation time was also similar in both groups. In contrast, the abilities to face cognitively challenging tasks and to manage stressful situations were better in SLT users, and the anxiety-scale response during tests was lower. Interestingly, with the intake of increasing amounts of SLT [29], no dose-response effect was found regarding performance and self-reported anxiety. Although some beneficial effects are observed, caution must be taken, given that these tests have major limitations: as tests are often performed in current users during a withdrawal period, it is sometimes difficult to separate what is due to the beneficial effects of the SLT from what is due to correction as a result of withdrawal [27].

The scoring performances of baseball players were similar for users and nonusers [30]. SLT use induced a decrease in the muscular strength of athletes [31]. In contrast, participation in brief high-intensity exercise (such as the Wingate anaerobic test) was unchanged after SLT [24]. SLT can impair anaerobic performance [32]. In some studies, maximal effort was not improved [32,33] and lactate accumulation occurred earlier [32]; this could be deleterious for exercise, with an earlier anaerobic threshold [32]. $\dot{V}O_{2\,max}$ was found to be similar with and without SLT [32].

Interestingly, transdermal nicotine administration was found to increase performance during aerobic exercise, probably through delayed central perception of fatigue. Also, nicotine increases pain tolerance; it also reduces appetite and enhances lipolysis [6,34], thus promoting weight loss. The potential effects of nicotine on performance are summarized in Table 1.

Cardiovascular effects

The cardiovascular effects of nicotine have been studied in acute and chronic conditions [9]. Discrepancies are found in experimental data, and are probably linked to the different species used (rat, swine, dog, calf), the conditions (whether anaesthetized or not) and the nicotine doses; discrepancies are also found between animal and human studies. Moreover, results may also vary between usual SLT users and nonusers, because of the tolerance effect. However, in humans, as nicotine was most often tested in usual SLT users, some results could be affected by suppression of withdrawal effects [22].

Arrhythmia

Nicotine has been shown to induce many proarrhythmic, dose-dependent and polyphasic effects, which are partly mediated through catecholamine release. Nicotine acts by prolonging action potentials and membrane depolarization [21], thereby promoting arrhythmia.

Nicotine has multiple direct effects on ionic channels, via blockade of many types of potassium channels [20,21]. Nicotine decreases heart rate variability by acting on the autonomic nervous system [22]. The ventricular fibrillation threshold was found to be decreased [5,6]. In anaesthetized dogs, low doses of nicotine (equivalent to < 1 cigarette) did not induce significant changes in the electrocardiogram, but higher doses had significant effects, ranging from ectopic premature beats to ventricular fibrillation [35]. Interestingly, the response to nicotine was triphasic and included immediate bradycardia, with or without atrioventricular block (probably linked to the Bezold-Jarish

Table 1 Factors of performance potentially affected by nicotine.

Target	Nicotine effect	Nicotine administration	
		SLT	Other than SLT
Aerobic endurance	Improved		[34]
Weight control	Improved		[34]
Anxiety	Diminished	[29]	
Ability to face complex situation	Improved	[29]	
Fine motor abilities	Improved	[27]	
Reaction time	Improved Unaffected	[27] [28,29,31]	
Anticipation time	Unaffected	[29]	
Movement time	Unaffected	[28]	
Anaerobic maximal performance	Unaffected	[24]	
$\dot{V}O_{2\,max}$	Unaffected	[32]	
Thermoregulation	Possibly impaired		[34]
Anaerobic thresholds	Impaired	[32]	
Strength	Impaired	[31]	

SLT: smokeless tobacco; $\dot{V}O_{2\,max}$: maximal oxygen uptake.

Table 2 Cardiovascular effects of nicotine at rest.

Target	Nicotine effect	Nicotine administration	
		SLT	Other than SLT
Ventricular fibrillation threshold	Lowered		[6]
Heart rate variability	Impaired	[22]	
Arrhythmia	Increased		[35]
Heart rate	Increased	[18,32,41,42]	
Blood pressure	Increased	[18,32,41,42]	
Stroke volume	Impaired	[32,33]	
	Increased		[43]
Cardiac output	Unaffected	[32]	
	Increased		[43]
Systemic vascular resistance	Increased	[41]	[43]
Coronary vasoconstriction	Increased		[3,46]
Coronary blood flow	Impaired		[45,46]
Myocardial oxygen consumption	Increased		[43]
Endothelial function	Impaired	[37]	[38]
Angiogenesis	Increased		[50]
Atherogenesis	Accelerated		[50]

SLT: smokeless tobacco.

reflex), followed by a parasympathetic response (bradycardia, atrial arrhythmia) and then a sympathetic response (sinus tachycardia, atrial and ventricular arrhythmia including ventricular tachycardia). The underlying mechanisms are complex, through both the direct effect of nicotine and the autonomic nervous system. These effects may be aggravated by free fatty acid release [3] or myocardial ischaemia.

Endothelial dysfunction

Endothelial dysfunction plays a major role as an early marker of cardiovascular risk, and there is a close relationship between endothelial function in human coronary and peripheral circulation [36]. Endothelial-dependent vasodilation is impaired by nicotine use [37,38], through catecholamine release and oxidative stress [39]. In humans, most studies have been conducted in chronic SLT users or cigarette smokers [37,38]. SLT users have the same endothelial dysfunction as smokers [37].

During strenuous exercise, oxidative stress, the procoagulant state and platelet activity are increased [7,40]. In contrast, although nicotine has no effect on platelet activation [3], it aggravates oxidative stress and the procoagulant state [6,39]. These effects can have a dramatic impact during effort and at recovery.

Haemodynamic effects

At rest

The haemodynamic effects of nicotine have been well documented (Table 2). In dogs and humans, the use of oral SLT increases resting heart rate and blood pressure [18,32,33,41] through sympathetic stimulation [18,32,33,42], in both SLT users and nonusers [41]. Haemodynamic modifications are related to epinephrine release [42]. In dogs, inotropism and myocardial oxygen consumption are markedly increased [43], with no major involvement of the baroreflex. The blood pressure rise that accompanies tachycardia is rather related to nicotine-induced stimulation of the central sympathetic nerve system and the local release of catecholamines from cardiac sympathetic nerve terminals. After the administration of a 4 mg nicotine tablet, there was an increase in muscle sympathetic nerve activity [44]. Some authors further observed a biphasic response, with a short initial phase in which the baroreflex could be involved [43]. Cardiac output and stroke volume are elevated in dogs [43], but only mildly so, and are reduced in humans [33]. In addition, an animal study showed that nicotine could induce post-ischaemic myocardial dysfunction, probably via a mechanism involving increased oxidative stress [9].

Nicotine has controversial effects on vascular resistance, ranging from a lack of any effect [42] to vasoconstriction [43]. Impaired coronary blood flow is partly mediated through alpha-adrenergic vasoconstriction [3] and other mechanisms, as shown after adrenergic blockade [45]. Coronary blood flow decreases with impaired coronary flow reserve after nicotine absorption in dogs [41,43]. Nicotine induces an imbalance between myocardial oxygen demand and supply [46]; these authors suggested that coronary blood flow could be decreased via coronary vasoconstriction and the elevation of intramyocardial pressure. Nicotine

Table 3 Haemodynamic effects of nicotine during exercise.

Condition	Target	Nicotine effect	Nicotine administration	
			SLT	Other than SLT
Submaximal exercise	Heart rate	Increased	[32]	
	Blood pressure	Increased	[48]	
	Stroke volume	Diminished	[32]	
	Cardiac output	Increased	[32]	
	Systemic vascular resistance	Increased		[49]
	Myocardial oxygen consumption	Increased		[49]
	Myocardial blood flow	Increased		[46,49]
Maximal exercise	Heart rate	Unaffected	[32]	
	$\dot{V}O_{2\,max}$	Unaffected	[32]	
Recovery	Heart rate	Increased	[33,48]	
	Blood pressure	Unaffected	[33,48]	

SLT: smokeless tobacco; $\dot{V}O_{2\,max}$: maximal oxygen uptake.

use has been reported to stimulate muscarinic receptors, giving a biphasic response that first consists of vasoconstriction followed by vasodilation. Interestingly, this effect was observed with nicotine blood levels close to those reached by SLT users [47].

Vasoconstriction has been documented in anaesthetized dogs under nicotine [45]. Nicotine can induce vasoconstriction of skin vasculature [34]; this can be deleterious during prolonged exercise by compromising thermoregulation.

During exercise

Data on the effect of nicotine during exercise are shown in Table 3; potential deleterious interferences can be seen on Fig. 1. At maximal exercise, heart rate and $\dot{V}O_{2\,max}$ were not modified by nicotine; however, at submaximal levels, these variables and cardiac output were higher [32]. Increasingly higher heart rates and blood pressure were observed with increasing levels of exercise intensity [48]; however, whether such an effect is cumulative with the intense sympathetic stimulation due to physical exertion is difficult to establish [24]. In swine, higher plasma catecholamine levels are associated with nicotine infusion during exercise [49]; this elevation was less pronounced than that observed at rest. A lower response to stimulus when catecholamine levels are high, as in exercise conditions, could explain this effect. Stroke volume is reduced at submaximal exercise [32]. In anaesthetized swine, rate $\times$ pressure product (reflecting myocardial oxygen consumption) and systemic resistances during exercise were raised after nicotine absorption [49]; however these modifications were lower when nicotine was infused during exercise than at rest. Myocardial blood flow was increased to a lesser extent than expected from studies with high levels of myocardial work [49]. Nicotine was found to limit the increase in myocardial blood flow during heart pacing in healthy nonsmokers [46]; this suggests that coronary vasoconstriction by nicotine, which could be relevant in the situation of a high heart rate encountered during exercise or recovery. Because endothelial dysfunction can be induced by nicotine, paradoxical coronary vasoconstriction can occur during exercise [7]. Splanchnic vasoconstriction and the subsequent decrease in blood flow induced by exercise could also impair hepatic nicotine clearance and therefore prolong the effects of nicotine [32].

Heart rate at recovery remains elevated after nicotine intake [33,48]. Acetylcholine induces coronary vasoconstriction in the presence of endothelial dysfunction [36]. This can occur during recovery, with a vagal hypertonic state after the end of exercise. Moreover, nicotine can elicit a direct coronary vasoconstrictive response [47]. This is of importance, as the effects of nicotine may be enhanced and prolonged by exercise [32]. The significant effects of SLT taken before a sports session could therefore occur after exercise, more precisely during the recovery period. Nevertheless, whether or not parasympathetic stimulation has an additive effect on vascular tone remains to be determined.

Long-term effects

Long-term cardiovascular risk associated with SLT remains a matter of debate. SLT is a gateway to cigarette smoking and, like cigarette smoking, can induce addiction [3]. Moreover, as SLT use begins at an early age [10,12,15] (often before the age of 15 years), it may promote premature atherogenesis, particularly through endothelial dysfunction [50].

Can smokeless tobacco be considered as a doping agent?

Many effects of nicotine are deleterious during exercise. Haemodynamic modifications can compromise myocardial and muscular vascularization, muscular strength can be impaired and anaerobic threshold is reached earlier. However, athletes often think SLT improves their performance. This obviously raises the debate about doping.

To be included in the forbidden list of the World Anti-Doping Agency (WADA), a substance or method must fulfil at

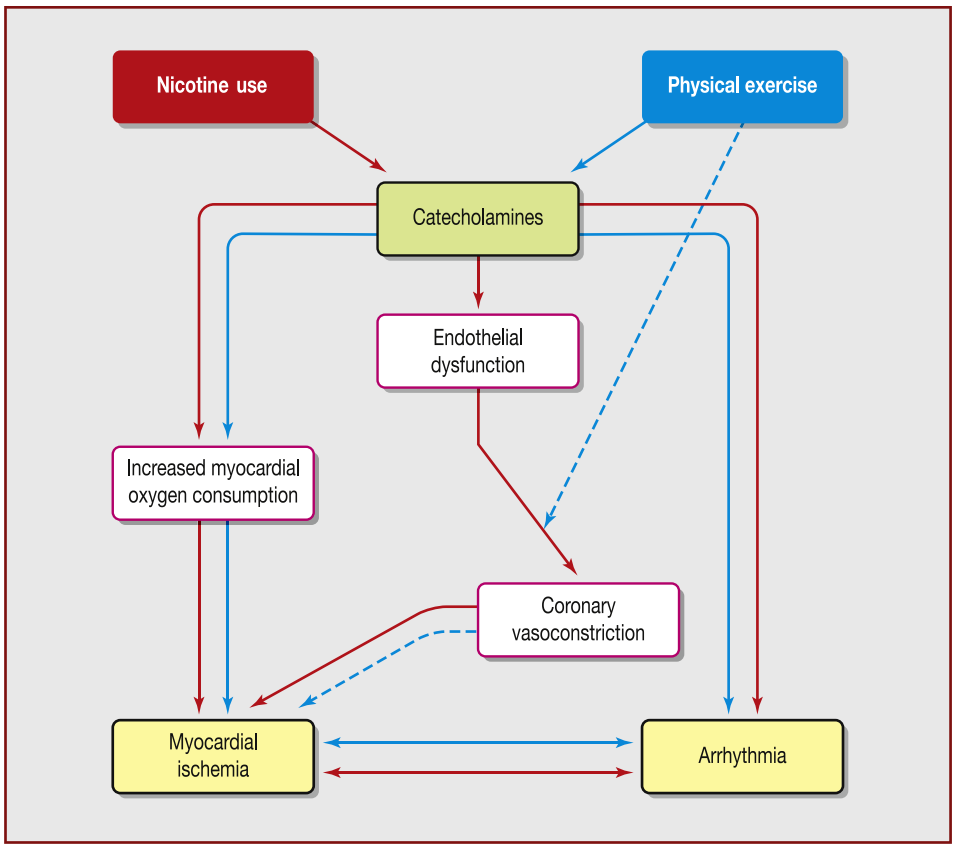

Figure 1. Schema of the cardiovascular effects of nicotine and physical exercise. Red: nicotine effects; blue: physical exercise effects; dotted arrows: in case of endothelial dysfunction.

least two of the following criteria: enhances performance; induces health risk; and does not respect the spirit of sport [51].

First, nicotine can improve some aspects of performance, by enhancing concentration and reactivity, facilitating movement precision and reducing anxiety; such properties can be useful in many sports. The weight-reducing effect is relevant in sports where there are weight categories. Improvement of pain tolerance can be beneficial in some sports, such as fighting sports. Moreover, delaying perception of fatigue could be of value in endurance sports.

Second, SLT has deleterious effects on health and is dangerous for the cardiovascular system during or after exercise.

Third, as SLT use can be addictive and considered as a gateway to cigarette smoking, it does not respect the spirit of sport.

Therefore, as SLT fulfils the three WADA criteria, SLT may be considered as a doping agent.

Conclusion

Current data in the literature strongly suggest that SLT has deleterious effects on human health, including the cardiovascular system. SLT is used extensively in the sports community worldwide and, more precisely, in snow sports in Europe. Nicotine use is reported in the monitoring program and is under current consideration by the WADA. Nicotine use, including SLT, fulfils all the WADA criteria [51] for inclusion in the WADA prohibited list as a doping product. Hence, chewing and spit tobacco, as well as dry and moist snuff, must therefore be discouraged, particularly when sports activities are considered.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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