International Journal of Cardiology 163 (2013) 109–115

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Effects of active and passive tobacco cigarette smoking on heart rate variability ☆

Petros C. Dinas [a], Yiannis Koutedakis [b,c], Andreas D. Flouris [a,d,*]

[a] FAME Laboratory, Institute of Human Performance and Rehabilitation, Centre for Research and Technology Thessaly, Greece
[b] Department of Exercise Sciences, University of Thessaly, Trikala, Greece
[c] School of Sport, Performing Arts and Leisure, University of Wolverhampton, Walshall, UK
[d] Department of Research and Technology Development, Biomnic Ltd., Trikala, Greece

ARTICLE INFO

Article history:
Received 4 May 2011
Received in revised form 21 October 2011
Accepted 30 October 2011
Available online 17 November 2011

Keywords:
Secondhand smoke
NN intervals
Autonomic nervous system
HRV
Environmental tobacco smoke

ABSTRACT

Given the widespread incidence of smoking as well as its deleterious health effects, it is crucial to examine practical and cost effective prognostic markers assessing its health impact. Heart rate variability (HRV) is a straightforward and cost effective technique to foresee health problems of cardiovascular nature and may be used to predict in advance smoking-induced health effects. In this review we evaluate the existing biological evidence regarding the effects of smoking on HRV and their associated cardiovascular consequences. In addition, we summarize fundamental information on the various HRV indicators and their diagnostic significance in relation to heart failure. An in depth analysis of the various HRV indices characterizing changes in the activation of the autonomic nervous system is provided together with a critical evaluation of all evidence published to date on the influence of chronic and acute active and passive smoking on HRV. Overall, the vast majority of published evidence suggests that acute and chronic active and passive smoking generate marked disruptions in the normal autonomic nervous system functioning characterized by increased sympathetic drive and reduced HRV and parasympathetic modulation. The proposed mechanisms that may generate this smoke-induced HRV reduction as well as its clinical implications are thoroughly evaluated.

1. Introduction

A vast number of studies have demonstrated that active smoking generates a number of unfavorable health effects, including an increased risk for stroke, multiple cancers, lung cancer, emphysema, and heart disease [1–3]. Based on recent evidence, there will be more than 8 million smoking-related deaths every year by 2030, while the total smoking-induced deaths during the 21st century will reach one billion [4]. This is because, despite the adoption of stricter antismoking campaigns in many countries, more people smoke today than during any other time in human history [estimated to >1.25 billion adults] [1,5]. Indeed, the prevalence rates of smoking are steadily increasing [1,6] primarily among young girls [7–9] and a further global expansion of the tobacco epidemic is projected in the near future [1].

Given the widespread incidence of smoking as well as its deleterious health effects, it is crucial to examine practical and cost effective prognostic markers assessing the impact of smoking on cardiovascular health. Heart rate variability (HRV) is a straightforward and cost effective technique to foresee health issues of cardiovascular nature and can be used to predict in advance smoking-induced health effects that may arise in the future [10]. Indeed, HRV abnormalities are linked with many cardiovascular diseases, including ischemic disease [11] and heart failure [12], and provide prognostic information for adverse outcomes [13]. However, to our knowledge the evidence linking smoking with changes in HRV and, in turn, cardiovascular abnormalities have not been critically reviewed. Therefore, the aim of this review is to critically evaluate the existing biological evidence regarding the effects of smoking (both active and passive) on HRV and their associated cardiovascular consequences. In addition, we summarize fundamental information on the various HRV indicators and their diagnostic significance. We envisage that the information provided will be valuable not only to physicians and scientists, but also to those interested in personal or public health, politics and economics. In order to achieve the above, a comprehensive search in PubMed was conducted using MeSH terms that are germane to active and passive smoking, HRV, autonomic function, and health effects (particularly of cardiovascular nature). The search also included the articles cited in the identified papers.

2. Heart rate variability (HRV)

HRV is calculated based on the time difference between repeated heart beats [3,14]. As such, it characterizes changes in the activation of the autonomic nervous system which comprises a neural network

☆ Grant support: This work was supported in part by funding from the European Union 7th Framework Program (FP7-PEOPLE-IRG-2008 grant no. 239521).

* Corresponding author at: FAME Laboratory, Institute of Human Performance and Rehabilitation, Centre for Research and Technology Thessaly, Karies, Trikala, 42100, Greece. Tel.: +30 24310 63190; fax: +30 24310 63191.
E-mail address: aflouris@cereteth.gr (A.D. Flouris).

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.10.140

that automatically controls a number of bodily actions (e.g., circulation, digestion) through a series of positive and negative feedback loops [14–16]. The autonomic nervous system is divided anatomically into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). A number of organs, including the heart, are innervated by both SNS and PNS, which generally have opposing actions. The transmitter substance at SNS nerve endings is norepinephrine, while some preganglionic sympathetic fibers pass directly to the adrenal medulla that can release epinephrine. Both norepinephrine and epinephrine activate effector organs by acting on α-, β_1-, or β_2-adrenoceptors [16]. On the other hand, the nerve endings of the PNS fibers release acetylcholine that acts on the different effector organs by activating muscarinic receptors [16]. The actions of SNS and PNS stimulation on a variety of organs are summarized in Fig. 1.

HRV describes the variations of the RR intervals (i.e., the time elapsing between two consecutive R waves in the electrocardiogram) and can be used as a trustworthy expression of the many physiological factors modulating the normal heart rhythm [3,14]. However, the relationship between different modalities of neural activity and HRV is not similar [17]. As shown in Fig. 1, the SNS acts to increase heart rate and plays an essential role in cardiovascular regulation in both health and disease [18]. On the other hand, the PNS acts to lower heart rate [16]. Based on this mechanism, the heart rate rhythm and the contraction strength of the cardiac muscle are a consequence of the opposing influences exerted by the SNS and the PNS [19]. At rest, the activation of the two systems must be comparable [15,19]. Increased SNS activation or decreased parasympathetic tone during periods of rest may suggest propensity to ventricular fibrillation as well as abnormalities such as hypertension, diabetes, cardiovascular diseases, or psychological problems [15,19,20] and have been proposed as mechanisms explaining the associations of reduced HRV with increased mortality [20–22]. On the other hand, increased PNS activation at rest is an indicator of physical prowess, overall health and young biological age. Furthermore, HRV may be age-dependent. For instance, HRV is reduced between ages 5 and 10 years after high SNS activity during infancy [19]. To the best of our knowledge there is only one study that examined the age dependent differences in HRV, in smokers. Hayano and colleagues reported that NN intervals were lower in moderate smokers and heavy smokers >30 years old than in moderate smokers and heavy smokers ≤30 years old. These results showed that HRV may be age dependent also in smokers [10]. Thus it is evident that HRV provides us with evidence that may predict heart abnormalities and it is linked with cardiovascular mortality [3,20–22].

Previous research has shown that active and passive smoking affect cardiovascular function by disrupting normal autonomic nervous system functioning [19].

Indeed, HRV measurements have shown that active [10] and passive [23] smoking generate both acute and chronic changes in autonomic cardiac control. Generally, active and passive smoking appear to decrease HRV and increase cardiac vulnerability [10,19,24] and arrhythmia susceptibility [25]. Furthermore, autonomic nervous system might alter by smoking via stimulation of pulmonary C-fibers in dogs [26] as well as via stimulation of capsaicin-sensitive lung vagal afferents, mainly C-fibers in rats [27]. Moreover, smoking via nicotine activity alters pulmonary sensory neurons [28].

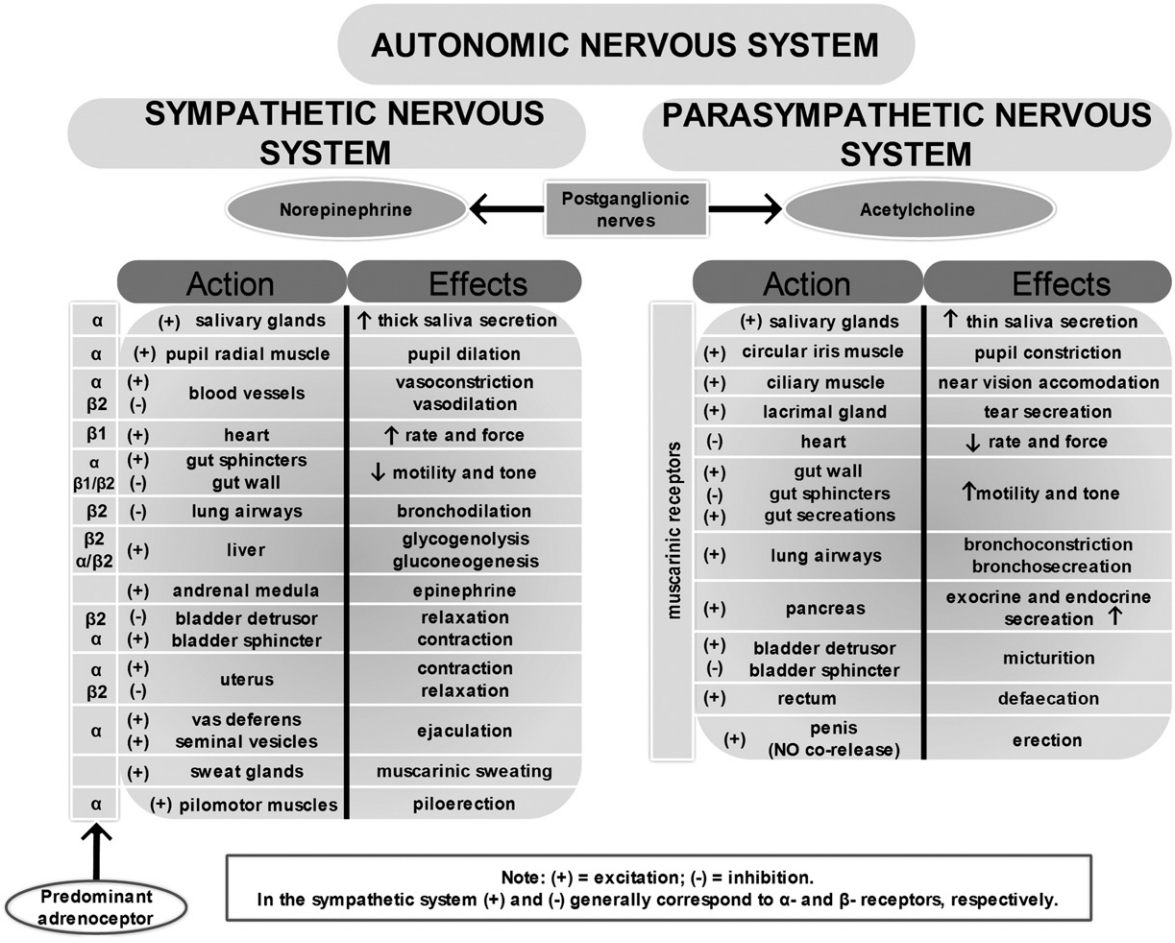

Fig. 1. Diagram of the autonomic nervous system and the actions of the sympathetic (SNS) and parasympathetic (PNS) subsystems stimulation on a variety of organs.

3. Indicators of HRV analysis

Wolf et al. [29] first recognized that reduced HRV is linked with an increased risk for postinfarction mortality. Consequently, power spectral analysis of heart rate fluctuations was introduced to quantitatively evaluate beat-to-beat cardiovascular control [30]. These analyses provided with indicators that enhanced knowledge regarding the autonomic background of RR interval fluctuations in the heart rate record [31,32]. At present, measurements of HRV are fundamentally composed of average, oscillatory, and non-linear components and are obtained usually through electrocardiography or specialized heart rate monitors [3,17,33–36]. HRV recording is performed by an algorithm counting system which provides indicators connected with the autonomic nervous system activity with regard to the activation of the SNS and PNS. The various indicators of HRV are based either on the calculation of time difference between successive RR intervals (i.e., time-domain methods) or on the distribution of power (variance) as a function of frequency of the time difference between successive RR intervals (i.e., frequency-domain methods).

3.1. Time-domain methods

Time-domain methods are the simplest form of HRV analysis and are based on determining either the heart rate at any point in time or on the intervals between successive normal complexes. Using a continuous electrocardiogram record, each QRS complex is detected and the normal-to-normal (NN) intervals (i.e., intervals between adjacent QRS complexes resulting from sinus node depolarizations) or the instantaneous heart rate is determined. The time-domain methods provide with a number of HRV indices that derive from statistical or geometric analyses.

3.2. Statistical indices

The statistical indices are based either on direct measurements of the NN intervals/instantaneous heart rate or on the differences between NN intervals. The most commonly used statistical indices include:

1. Standard deviation of the average NN intervals [SDANN; in milliseconds (ms)] calculated over successive short-period recordings with a normative SDANN value of 127 ± 35 ms [3,14]. Since SDANN is largely dependent on the duration of monitoring period, the common methodology used to derive SDANN values is to separate 24-h recordings into short term 5-min monitoring periods [3]. SDANN values reflect all the cyclic components responsible for variability in the period of recording and, if calculated based on 5-min recordings, it characterizes the long-term components of overall HRV activity [3,41].
2. SDNN, the standard deviation of the average NN intervals calculated over short-period recordings (usually 5 min) and it is driven by short-term components of overall HRV activity [3,41].
3. The root mean square of differences of successive NN intervals (RMSSD; in ms) with a normative value of 27 ± 12 ms is driven primarily by PNS activation [3,14,37].
4. Count number of pairs of NN intervals that differ more than 50 ms (NN50) indicating PNS activity [3,14].
5. The percentage value of pairs of NN intervals (pNN50%) that differ more than 50 ms characterizing the PNS component of autonomic function [3,14].

3.3. Geometric indices

The geometric indices derive from converting the time-domain series of NN intervals into a geometric pattern such as the sample density distribution of NN interval durations, sample density distribution of differences between adjacent NN intervals. Thereafter, the variability of the resulting pattern is assessed based on the geometric and/or graphic properties. The most commonly used geometric indices include:

1. The integral of the sample density distribution of NN intervals divided by the maximum of the density distribution (NN triangular index) with a normative value of 37 ± 15 ms [3,14]. This indicator characterizes overall HRV measured over 24 h and it is driven primarily by SNS but it is also influenced to some degree by the PNS [3].
2. Baseline width of the minimum square difference triangular interpolation of the maximum of the sample density distribution of NN intervals (TINN; in ms) that characterizes primarily the SNS but may be also influenced to some degree by the PNS [3].

3.4. Frequency-domain methods

The frequency-domain indicators of HRV are based on the distribution of power (variance) as a function of frequency of the time difference between successive NN intervals, also known as power spectral density. The methodologies used to estimate the latter are classified into parametric and nonparametric which, in most cases, provide comparable results. A detailed discussion of the advantages and disadvantages of parametric and nonparametric methods is beyond the scope of the present review and can be found elsewhere [3]. It is crucial to indicate that the VLF, LF, and HF power components are measured in absolute values of power (m^2). However, LF and HF may be measured by normalized units, which represent the relative value of each power component. This measurement may indicate the controlled and balanced behavior of the ANS [3]. The most commonly used frequency-domain indices distinguished in a spectrum calculated from short-term recordings of 2–5 min [30,32,38–40] are:

1. Very Low Frequency (VLF) in the range of 0.0033—0.04 Hz [14,41]. The physiological interpretation of VLF in relation to autonomic function warrants further elucidation.
2. Low Frequency (LF) band in the range of 0.04—0.15 Hz. It has been suggested that SNS activation is the main contributor of LF, particularly when LF is expressed in normalized units. There is some controversy, however, as others have suggested that LF is also influenced by PNS activity [3,14,41,42].
3. High Frequency (HF) band in the range of 0.15—0.40 Hz is suggested to be mainly driven by respiration and PNS activity [3,14,41].
4. The ratio of LF and HF frequency band powers (LF/HF), with normative values of 1.5–2.0 indicating the balance between SNS and PNS [3,14].
5. The total variance of all NN intervals, called total power, corresponds to the sum of all spectral bands (i.e., 0.0—0.5 Hz) [3,14,41].

It is important to note that frequency-domain indicators can be also used to analyze the sequence of NN intervals of the entire 24-hour period. In this case, however, the result also includes an ultra low frequency (ULF) band (in addition to VLF, LF, and HF components) between 0 and 0.0033 Hz [3].

4. Active smoking and HRV

4.1. Chronic effects

The influence of chronic active smoking on HRV has been studied extensively (Table 1). The first published evidence was provided by Penny and Mir [43] demonstrating a decreased HRV in chronic cigarette smokers compared to non-smokers. In the following years, a number of epidemiological studies were conducted, the vast majority of which confirmed that HRV is decreased in chronic active smokers. Specifically, Hayano and colleagues found a decreased vagal activation in heavy

Table 1
Acute and chronic effects of active smoking on HRV.

Study	History	Main Findings
Penny and Mir [43]; Eryonucu et al. [46]	Chronic	Lower HRV compared to non-smokers
Hayano et al. [10]	Chronic	Lower vagal activation in heavy smokers compared to non-smokers
Levin et al. [44]	Chronic	Lower HRV in heavy smokers (≥10 pack-years, >1 pack/day)
Kupari et al. [45]	Chronic	Lower HRV in smokers ≥10 cigarettes/day compared to non-smokers
Eryonucu et al. [46]; Xu and Wang [52]; Pope et al. [51]; Min et al. [50]	Chronic	Lower total HRV parameters compared to non-smokers
Alyan et al. [47]	Chronic	Higher LF, LF/HF and lower HF compared to healthy non-smokers
Fifer et al. [48]	Chronic	Decreased HRV during pregnancy
Thiriez et al. [49]	Chronic	Smoking during pregnancy associated with decreased offspring HRV
Minami et al. [53]	Chronic	Smoking cessation increased HRV within seven days
Yotsukura et al. [54]	Chronic	Smoking cessation increased HRV within seven days
Murata et al. [55]	Chronic	No relationship between current smoking status and HRV
Kageyama et al. [58]	Chronic	No relationship between current smoking status and HRV
Hayano et al. [10]	Acute	Decreased PNS modulation within three minutes after smoking
Niedermaier et al. [24]	Acute	Reduced PNS activity to the cardiac muscle due to smoking
Lucini et al. [57]	Acute	SNS dominance and reduced PNS modulation and overall HRV compared to non-smokers
Kobayashi et al. [58]	Acute	SNS activity increased and PNS activity decreased within five minutes after smoking one cigarette
Karakaya et al. [37]	Acute	Increased LF/HF and reduced mean NN interval, SDNN, and RMSSD within five minutes after smoking one cigarette

smokers compared to non smokers or moderate smokers [10]. Levin and colleagues found that the HRV of heavy smokers was significantly lower than that of non smokers [44]. Kupari and colleagues observed that HRV was lower in individuals who smoke ≥10 cigarettes/day compared to a nonsmokers or to smokers who smoke >10 cigarettes/day [45]. In line with these findings, Eryonucu et al. showed that the total HRV parameters were significantly lower in smokers than in non-smokers [46] which was confirmed by a recent study showing that regular healthy smokers demonstrate increased LF and LF/HF as well as decreased HF compared to healthy non-smokers [47]. Chronic active smoking has been also shown to reduce HRV during pregnancy of both the mother [48] and the offspring [49] with detrimental effects to the child's health [48]. The decrease in HRV caused by chronic active smoking has been also supported by studies showing that HRV is dramatically decreased in smokers but not in non-smokers when exposed to air pollution [50–52]. Further confirmation of the diminishing effect of chronic active smoking on HRV is provided by studies demonstrating that smoking cessation increases HRV within 7 days in chronic active habitual [53] as well as heavy [54] smokers.

It is important to mention that, although the majority of published evidence suggests that chronic active smoking is associated with decreased HRV, some studies failed to find such a relationship. Murata and colleagues did not observe an association between tobacco consumption and HRV in healthy male and female smokers [55]. Similarly, Kageyama did not find a link between current smoking status and HRV, although PNS modulation among heavy smokers tended to be lower than that among nonsmokers [56].

4.2. Acute effects

The literature presents with five studies investigating the acute effects of active smoking on HRV (Table 1). The first experiment was conducted by Hayano and colleagues who assessed HRV in smokers before smoking one cigarette as well as 3, 10, 17 and 24 min after smoking [10]. Results demonstrated a reduced PNS modulation within 3 min after smoking [10]. Similarly, Niedermaier and colleagues found that PNS activity to the cardiac muscle is reduced by active smoking [24]. Interestingly, this study also revealed that active smoking differentially affects SNS outflow to various target organs. Specifically, smoking was found to increase SNS traffic to the skin, heart, and adrenal glands but to reduce SNS traffic to the musculature [24]. A subsequent study also found that habitual smokers demonstrate a marked disturbance of the neural control of the heart as compared to non-smoking controls characterized by SNS predominance and reduced PNS modulation and overall HRV [57]. In line with these results, Kobayashi and colleagues found that SNS activity increases and PNS activity decreases within five minutes from smoking one cigarette in smoker taxi drivers during work [58]. Finally, Karakaya and colleagues measured HRV in 15 smokers 5 min before as well as 5, 10, 15, 20, 25, and 30 min after smoking one cigarette [37]. The results demonstrated that smoking reduced the LF/HF, the mean NN interval, the SDNN, and the RMSSD within the first 5 min [37].

5. Passive smoking and HRV

5.1. Chronic effects

To the best of our knowledge, only one study has assessed the chronic effects of passive smoking on HRV (Table 2). In this experiment, Felber Dietrich and colleagues measured HRV through 24-h electrocardiogram recordings in 1218 nonsmokers aged ≥50 years [42]. The results demonstrated that individuals who were passively exposed to smoke at home or at work for more than 2 h/day revealed decreased total power, LF and LF/HF as well as increased HF. These results suggest that chronic passive smoking at home and work is associated with lower HRV [42].

5.2. Acute effects

Until relatively recently, we were unaware of the acute influence of passive smoking on HRV. However, two germane experiments have been conducted during the past decade both showing that HRV is decreased by acute passive smoking (Table 2). Specifically, Pope and colleagues evaluated the effects of acute passive smoke exposure in a commercial airport on HRV in 16 adult nonsmokers via ambulatory electrocardiographic monitoring for 8-hr periods while participants alternated 2 h in nonsmoking and smoking areas [59]. Results demonstrated that acute exposure to passive smoke significantly reduced HRV as indicated by changes in VLF, LF, HF, triangular

Table 2
Acute and chronic effects of passive smoking on HRV.

Study	History	Main findings
Felber et al. [42]	Chronic	Two hours/day of smoke exposure decreased total power, LF and LF/HF and increased HF
Pope et al. [59]	Acute	Decreased HRV as indicated by changes in VLF, LF, HF, triangular index, and SDNN
Chen et al. [25]	Acute	Decreased HRV in mice during (3 days) and following (24 hours) passive smoking

index, and SDNN indices [59]. These findings were recently confirmed by a study in mice using a 6-hour exposure to passive smoke for three consecutive days [25]. The results demonstrated that the passive smoking exposure decreased HRV not only during but also beyond the exposure period. Moreover, acute passive smoking was associated with an increased susceptibility for arrhythmia [25].

6. Mechanisms

As observed in the previous sections, the vast majority of evidence provided to date suggests that acute and chronic active and passive smoking generate marked disruptions in the normal autonomic nervous system functioning characterized by increased SNS drive and reduced PNS modulation and overall HRV. Two main mechanistic pathways have been proposed to explain this smoking-induced effect on neurocardiovascular regulation. The principal biomarker in the first mechanism put forth is nicotine, the main constituent of tobacco smoke. Nicotine up-regulates catecholamine release generating potent acute and chronic effects on cardiovascular regulation mainly through SNS activation [37]. This is confirmed by evidence showing that plasma catecholamine levels increase within one minute after smoking a cigarette [60–64]. Interestingly, some evidence suggests that the smoking-induced adrenergic activation does not originate centrally and it is independent of ganglionic sympathetic transmission stimulation [63]. Indeed, smoking has been suggested to act on peripheral sympathetic sites to augment catecholamine release and/or to reduce its clearance at the neuroeffector junctions [63].

While much of the smoking-induced effects on autonomic function have been ascribed to the nicotinic pathway, research has shown that nicotine patches generate a much smaller reduction in HRV compared with smoking, suggesting the involvement of other factors [65]. In this light, a second mechanistic hypothesis has been proposed according to which respirable particles affect neural control of the heart [66]. Indeed, suspended particles resulting from the incomplete cigarette combustion may play an important role in the smoke-induced reduction in HRV [59]. While this notion requires further exploration, it is supported by several animal [67] and human [68–71] studies demonstrating that exposure to particulate matter, especially in the fine and ultrafine range, is linked with a decreased HRV.

7. Clinical implications

The mechanism(s) by which the smoking-induced reduction in autonomic function contributes to cardiovascular-related mortality is not well understood. A recent study in mice suggests that the smoking-induced reduction in autonomic function increases arrhythmia susceptibility (atrial fibrillation, ventricular fibrillation or tachycardia), abnormalities in cardiac electrical conduction, and AV block [25]. This may account for the findings in the epidemiological data linking active and passive tobacco smoking to cardiac arrhythmias and sudden cardiac death [2,72–77]. Lower HRV has also been associated with an increased risk for coronary heart disease, [8,18,78–80] cardiovascular morbidity and mortality [3,19,81–84] as well as ongoing subclinical inflammation [41,85].

Several studies report no relationship between ANS activity, as indicated by HRV, and inflammatory biomarkers [86,87]. There are, however, other published reports that indicate a relationship between HRV and tumor necrosis factor alpha following endotoxin exposure [88]. Thus, the issue remains controversial. Nevertheless, low HRV has been associated with disease [3,81] given its prognostic attributes in myocardial infarction [89] and heart failure conduction disturbances and ventricular dyssynchrony [90–92]. Moreover, increased SNS activity has been related to the development of hypertension, diabetes, and cardiovascular diseases [10,93]. Therefore, the reductions in HRV induced by both acute and chronic active and passive smoking supported in the majority of the published studies to date may have serious clinical implications characterized by marked disruptions in the normal autonomic nervous system functioning which, in turn, impair cardiac electrical conduction with confirmed detrimental long term effects.

8. Concluding remarks

This review attempts to critically evaluate the existing biological evidence regarding the effects of smoking (both active and passive) on HRV and their associated cardiovascular problems. Overall, the vast majority of published evidence suggests that acute and chronic active and passive smoking generate marked disruptions in the normal autonomic nervous system functioning characterized by increased SNS drive and reduced PNS modulation and overall HRV. This phenomenon is partly attributed to an up-regulation of catecholamine release by nicotine generating potent acute and chronic effects on cardiovascular regulation mainly through SNS activation [37]. In addition, suspended particles resulting from the incomplete cigarette combustion have been also hypothesized to play an important role in the SHS-induced reduction in HRV. The reductions in HRV similar to those induced by acute and chronic active and passive smoking are associated with an impaired cardiac electrical conduction with confirmed detrimental long term effects. Thus, it seems logical to postulate that the smoke-induced HRV reductions may account, at least in part, for the findings in the epidemiological data linking active and passive tobacco smoking to cardiac arrhythmias and sudden cardiac death.

Since the first study assessing the effects of tobacco smoke on HRV, research in this topic has spread into different areas and new scientific evidence continues to accumulate. However, many germane studies are inherently limited. For instance, a large number of epidemiological studies base tobacco smoke exposure on self-report without an objective measurement of exposure, they adopt a cross-sectional design, and they provide little data on the duration of the exposure or tobacco use. On the other hand, many mechanistic studies rely on animal models which are inherently limited, particularly in relation to the level and duration of tobacco exposure and use, as well as their relevance to humans. Nevertheless, the literature also contains outstanding experiments that have provided valuable evidence effects of tobacco smoke on cardiac autonomic regulation.

Notwithstanding the increased attention on the effects of tobacco smoke on HRV and the excitement for the continuously emerging discoveries in this area, we remain largely naive to issues as critical as the mechanisms causing the smoke-induced decrease in HRV. Furthermore, a standardization of the HRV indicators used in future research should be conducted, as studies thus far tended to evaluate different HRV indicators making their results difficult to compare. Finally, future research should address the effects of acute and chronic passive tobacco smoke on HRV given the dearth of published data on this topic.

Acknowledgments

This work was supported in part by funding from the European Union 7th Framework Program (FP7-PEOPLE-IRG-2008 grant no. 239521). The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010;144:1-2).

References

[1] World Health Organisation The tobacco atlas; 2002.
[2] Flouris AD, Vardavas CI, Metsios GS, Tsatsakis AM, Koutedakis Y. Biological evidence for the acute health effects of secondhand smoke exposure. Am J Physiol Lung Cell Mol Physiol Jan 2010;298(1):L3–L12.
[3] Anon. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation Mar 1 1996;93(5):1043–65.

[4] World Health Organization. WHO report on the global tobacco epidemic, 2008: The MPOWER package. Geneva: World Health Organization; 2008.
[5] WHO, Disease WHODoN. Tobacco Free Initiative. International Consultation on Environmental. Tobacco Smoke (ETS) and Child Health; 2009.
[6] Substance Abuse and Mental Health Services Administration. Results from the 2006 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-32, DHHS Publication No. SMA 07–4293). Rockville, MD; 2007.
[7] Warren CW, Jones NR, Peruga A, et al. Global youth tobacco surveillance, 2000–2007. MMWR Surveill Summ 2008;57:1–28.
[8] Flouris AD, Faught BE, Klentrou P. Cardiovascular disease risk in adolescent smokers: evidence of a 'smoker lifestyle'. J Child Health Care 2008;12(3):221–31.
[9] Metsios GS, Flouris AD, Angioi M, Koutedakis Y. Passive smoking and the development of cardiovascular disease in children: a systematic review. Cardiol Res Pract 2010;2011.
[10] Hayano J, Yamada M, Sakakibara Y, et al. Short- and long-term effects of cigarette smoking on heart rate variability. Am J Cardiol Jan. 1 1990;65(1):84–8.
[11] Camm AJ, Pratt CM, Schwartz PJ, et al. Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation Mar 2 2004;109(8):990–6.
[12] Bilchick KC, Fetics B, Djoukeng R, et al. Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). Am J Cardiol Jul 1 2002;90(1):24–8.
[13] Tapanainen JM, Thomsen PE, Kober L, et al. Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. Am J Cardiol Aug 15 2002;90(4):347–52.
[14] Niskanen JP, Tarvainen MP, Ranta-Aho PO, Karjalainen PA. Software for advanced HRV analysis. Comput Methods Programs Biomed Oct 2004;76(1):73–81.
[15] Kristal-Boneh E, Raifel M, Froom P, Ribak J. Heart rate variability in health and disease. Scand J Work Environ Health Apr 1995;21(2):85–95.
[16] Neal MJ. Medical pharmacology at a glance. 4th ed. London: Blackwell Science Ltd; 2002.
[17] Pagani M, Malliani A. Interpreting oscillations of muscle sympathetic nerve activity and heart rate variability. J Hypertens Dec 2000;18(12):1709–19.
[18] Sinski M, Lewandowski J, Abramczyk P, Narkiewicz K, Gaciong Z. Why study sympathetic nervous system? J Physiol Pharmacol Nov 2006;57(Suppl. 11):79–92.
[19] Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Biol Eng Comput 2006;44(12):1031–51.
[20] Tsuji H, Larson MG, Venditti Jr FJ, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation Dec 1 1996;94(11):2850–5.
[21] Kleiger RE, Miller JP, Bigger Jr JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59(4):256–62.
[22] Bigger Jr JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation Jan 1992;85(1):164–71.
[23] Zeskind PS, Gingras JL. Maternal cigarette-smoking during pregnancy disrupts rhythms in fetal heart rate. J Pediatr Psychol Jan–Feb 2006;31(1):5–14.
[24] Niedermaier ON, Smith ML, Beightol LA, Zukowska-Grojec Z, Goldstein DS, Eckberg DL. Influence of cigarette smoking on human autonomic function. Circulation Aug 1993;88(2):562–71.
[25] Chen CY, Chow D, Chiamvimonvat N, et al. Short-term secondhand smoke exposure decreases heart rate variability and increases arrhythmia susceptibility in mice. Am J Physiol Heart Circ Physiol Aug 2008;295(2):H632–9.
[26] Lee L, Kou Y, Frazier D, et al. Stimulation of vagal pulmonary C-fibers by a single breath of cigarette smoke in dogs. J Appl Physiol 1989;66(5):2032–8.
[27] Lin Y, Hsu C-C, Bien M-Y, Hsu H-C, Weng H-T, Kou Y. Activations of TRPA1 and P2X receptors are important in ROS-mediated stimulation of capsaicin-sensitive lung vagal afferents by cigarette smoke in rats. J Appl Physiol 2010;108:1293–303.
[28] Xu J, Yang W, Zhang G, Gu Q, Lee L-Y. Calcium transient evoked by nicotine in isolated rat vagal pulmonary sensory neurons. Am J Physiol Lung Cell Mol Physiol 2007;292:L54–61.
[29] Wolf MM, Varigos GA, Hunt D, JG S. Sinus arrhythmia in acute myocardial infarction. Med J Aust 1978;2:52–3.
[30] Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science Jul 10 1981;213(4504):220–2.
[31] Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol Jan 1985;248(1 Pt 2):H151–3.
[32] Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res Aug 1986;59(2):178–93.
[33] Gamelin FX, Berthoin S, Bosquet L. Validity of the polar S810 heart rate monitor to measure R–R intervals at rest. Med Sci Sports Exerc May 2006;38(5):887–93.
[34] Gamelin FX, Baquet G, Berthoin S, Bosquet L. Validity of the polar S810 to measure R–R intervals in children. Int J Sports Med Feb 2008;29(2):134–8.
[35] Nunan D, Jakovljevic DG, Donovan G, Hodges LD, Sandercock GR, Brodie DA. Levels of agreement for RR intervals and short-term heart rate variability obtained from the Polar S810 and an alternative system. Eur J Appl Physiol Jul 2008;103(5):529–37.
[36] Vanderlei LC, Silva RA, Pastre CM, Azevedo FM, Godoy MF. Comparison of the Polar S810i monitor and the ECG for the analysis of heart rate variability in the time and frequency domains. Braz J Med Biol Res Oct 2008;41(10):854–9.
[37] Karakaya O, Barutcu I, Kaya D, et al. Acute effect of cigarette smoking on heart rate variability. Angiology Oct–Nov 2007;58(5):620–4.
[38] Sayers B. Analysis of heart rate variability. Ergonomics 1973;16:17–32.
[39] Hirsh J. Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. Am J Physiol 1981;241:H620–9.
[40] Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation Aug 1991;84(2):482–92.
[41] Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. Psychoneuroendocrinology Nov 2008;33(10):1305–12.
[42] Felber Dietrich D, Schwartz J, Schindler C, et al. Int J Epidemiol Aug 2007;36(4):834–40.
[43] Penny WJ, Mir MA. Cardiorespiratory response to exercise before and after acute beta-adrenoreceptor blockade in nonsmokers and chronic smokers. Int J Cardiol Jun 1986;11(3):293–304.
[44] Levin FR, Levin HR, Nagoshi C. Autonomic functioning and cigarette smoking: heart rate spectral analysis. Biol Psychiatry Mar 15 1992;31(6):639–43.
[45] Kupari M, Virolainen J, Koskinen P, Tikkanen MJ. Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. Am J Cardiol Oct 15 1993;72(12):897–903.
[46] Eryonucu B, Bilge M, Guler N, Uzun K, Gencer M. Effects of cigarette smoking on the circadian rhythm of heart rate variability. Acta Cardiol Oct 2000;55(5):301–5.
[47] Alyan O, Kacmaz F, Ozdemir O, et al. Effects of cigarette smoking on heart rate variability and plasma N-terminal pro-B-type natriuretic peptide in healthy subjects: is there the relationship between both markers? Ann Noninvasive Electrocardiol Apr 2008;13(2):137–44.
[48] Fifer WP, Fingers ST, Youngman M, Gomez-Gribben E, Myers MM. Effects of alcohol and smoking during pregnancy on infant autonomic control. Dev Psychobiol Apr 2009;51(3):234–42.
[49] Thiriez G, Bouhaddi M, Mourot L, et al. Heart rate variability in preterm infants and maternal smoking during pregnancy. Clin Auton Res Jun 2009;19(3):149–56.
[50] Min JY, Min KB, Cho SI, Paek D. Combined effect of cigarette smoking and sulfur dioxide on heart rate variability. Int J Cardiol Mar 20 2009;133(1):119–21.
[51] Pope III CA, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation Jan 6 2004;109(1):71–7.
[52] Xu X, Wang L. Arch Environ Health Jan–Feb 1998;53:44–53.
[53] Minami J, Ishimitsu T, Matsuoka H. Effects of smoking cessation on blood pressure and heart rate variability in habitual smokers. Hypertension Jan 1999;33(1 Pt 2):586–90.
[54] Yotsukura M, Koide Y, Fujii K, et al. Heart rate variability during the first month of smoking cessation. Am Heart J Jun 1998;135(6 Pt 1):1004–9.
[55] Murata K, Landrigan PJ, Araki S. Effects of age, heart rate, gender, tobacco and alcohol ingestion on R–R interval variability in human ECG. J Auton Nerv Syst Mar 1992;37(3):199–206.
[56] Kageyama T, Nishikido N, Honda Y, et al. Effects of obesity, current smoking status, and alcohol consumption on heart rate variability in male white-collar workers. Int Arch Occup Environ Health 1997;69(6):447–54.
[57] Lucini D, Bertocchi F, Malliani A, Pagani M. A controlled study of the autonomic changes produced by habitual cigarette smoking in healthy subjects. Cardiovasc Res Apr 1996;31(4):633–9.
[58] Kobayashi F, Watanabe T, Akamatsu Y, et al. Acute effects of cigarette smoking on the heart rate variability of taxi drivers during work. Scand J Work Environ Health Oct 2005;31(5):360–6.
[59] Pope III CA, Eatough DJ, Gold DR, et al. Acute exposure to environmental tobacco smoke and heart rate variability. Environ Health Perspect Jul 2001;109(7):711–6.
[60] Trap-Jensen J, Carlsen JE, Svendsen TL, Christensen NJ. Cardiovascular and adrenergic effects of cigarette smoking during immediate non-selective and selective beta adrenoceptor blockade in humans. Eur J Clin Invest Jun 1979;9(3):181–3.
[61] Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med Sep 9 1976;295(11):573–7.
[62] Hill P, Wynder EL. Smoking and cardiovascular disease. Effect of nicotine on the serum epinephrine and corticoids. Am Heart J Apr 1974;87(4):491–6.
[63] Grassi G, Seravalle G, Calhoun DA, et al. Mechanisms responsible for sympathetic activation by cigarette smoking in humans. Circulation Jul 1994;90(1):248–53.
[64] Baer L, Radichevich I. Cigarette smoking in hypertensive patients. Blood pressure and endocrine responses. Am J Med Apr 1985;78(4):564–8.
[65] Lucini D, Bertocchi F, Malliani A, Pagani M. Autonomic effects of nicotine patch administration in habitual cigarette smokers: a double-blind, placebo-controlled study using spectral analysis of RR interval and systolic arterial pressure variabilities. J Cardiovasc Pharmacol May 1998;31(5):714–20.
[66] Stone PH, Godleski JJ. First steps toward understanding the pathophysiologic link between air pollution and cardiac mortality. Am Heart J Nov 1999;138(5 Pt 1):804–7.
[67] Godleski JJ. Cardiovascular responses to inhaled particles. In: Heinrich U, Mohr U, editors. Relationships between acute and chronic effects of air pollution. Washington, DC: ILSI Press; 2000. p. 141–55.
[68] Pope III CA, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc Jun 2006;56(6):709–42.
[69] Pope III CA, Verrier RL, Lovett EG, et al. Heart rate variability associated with particulate air pollution. Am Heart J Nov 1999;138(5 Pt 1):890–9.
[70] Gold DR, Litonjua A, Schwartz J, et al. Ambient pollution and heart rate variability. Circulation Mar 21 2000;101(11):1267–73.
[71] Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. Environ Health Perspect Jul 1999;107(7):521–5.
[72] Flouris AD, Metsios GS, Carrillo AE, et al. Acute and short-term effects of secondhand smoke on lung function and cytokine production. Am J Respir Crit Care Med 2009;179(11):1029–33.

[73] Barnoya J, Glantz SA. Cardiovascular effects of second-hand smoke help explain the benefits of smoke-free legislation on heart disease burden. J Cardiovasc Nurs Nov–Dec 2006;21(6):457–62.
[74] Bhatnagar A. Environmental cardiology: studying mechanistic links between pollution and heart disease. Circ Res Sep 29 2006;99(7):692–705.
[75] Kritz H, Schmid P, Sinzinger H. Passive smoking and cardiovascular risk. Arch Intern Med Oct 9 1995;155(18):1942–8.
[76] Flouris AD, Metsios GS, Jamurtas AZ, Koutedakis Y. Sexual dimorphism in the acute effects of secondhand smoke on thyroid hormone secretion, inflammatory markers and vascular function. Am J Physiol Endocrinol Metab Feb 2008;294(2): E456–62.
[77] Metsios GS, Flouris AD, Jamurtas AZ, et al. A brief exposure to moderate passive smoke increases metabolism and thyroid hormone secretion. J Clin Endocrinol Metab Jan 2007;92(1):208–11.
[78] Dekker JM, Crow RS, Folsom AR, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk In Communities. Circulation Sep 12 2000;102(11):1239–44.
[79] Flouris AD. Acute health effects of passive smoking. Inflamm Allergy Drug Targets Dec 2009;8(5):319–20.
[80] Flouris AD, Oikonomou DN. Electronic cigarettes: miracle or menace? BMJ 2010;340:c311.
[81] Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. Ann N Y Acad Sci Nov 2006;1088:361–72.
[82] Faught BE, Flouris AD, Cairney J. Epidemiological evidence associating secondhand smoke exposure with cardiovascular disease. Inflamm Allergy Drug Targets 2009;8(5):348–52.
[83] Metsios GS, Flouris AD, Koutedakis Y. Passive smoking, asthma and allergy in children. Inflamm Allergy Drug Targets 2009;8(5).
[84] Carrillo AE, Metsios GS, Flouris AD. Effects of secondhand smoke on thyroid function. Inflamm Allergy Drug Targets 2009;8(5).
[85] Lanza GA, Sgueglia GA, Cianflone D, et al. Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. Am J Cardiol Jun 15 2006;97(12):1702–6.
[86] Kox M, Ramakers BP, Pompe JC, van der Hoeven JG, Hoedemaekers CW, Pickkers P. Interplay between the acute inflammatory response and heart rate variability in healthy human volunteers. Shock Aug 2011;36(2):115–20.
[87] Lehrer P, Karavidas MK, Lu SE, et al. Voluntarily produced increases in heart rate variability modulate autonomic effects of endotoxin induced systemic inflammation: an exploratory study. Appl Psychophysiol Biofeedback Dec 2010;35(4): 303–15.
[88] Jan BU, Coyle SM, Macor MA, Reddell M, Calvano SE, Lowry SF. Relationship of basal heart rate variability to in vivo cytokine responses after endotoxin exposure. Shock Apr 2010;33(4):363–8.
[89] Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation Sep 1993;88(3):927–34.
[90] Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med May 20 2004;350(21):2140–50.
[91] Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol Jul 3 2002;40(1):111–8.
[92] La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation Feb 4 2003;107(4):565–70.
[93] Flouris AD, Scott JM. Heart rate variability responses to a psychologically challenging scuba dive. J Sports Med Phys Fitness Dec 2009;49(4):382–6.