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Long-term smoking cessation and heart rate dynamics in an aging healthy cohort: Is it possible to fully recover?

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ABSTRACT

Aim: To evaluate the long-term influence of smoking cessation on the regulation of the autonomic cardiovascular system in an aging general population, using the subpopulation of lifelong non-smokers as control group.
Methods: We analyzed 1481 participants aged ≥ 50 years from the SAPALDIA cohort. In each participant, heart rate variability and heart rate dynamics were characterized by means of various quantitative analyzes of the inter-beat interval time series generated from 24-hour electrocardiogram recordings. Each parameter obtained was then used as the outcome variable in multivariable linear regression models in order to evaluate the association with smoking status and time elapsed since smoking cessation. The models were adjusted for known confounding factors and stratified by the time elapsed since smoking cessation.
Results: Our findings indicate that smoking triggers adverse changes in the regulation of the cardiovascular system, even at low levels of exposure since current light smokers exhibited significant changes as compared to lifelong non-smokers. Moreover, there was evidence for a dose–response effect. Indeed, the changes observed in current heavy smokers were more marked as compared to current light smokers. Furthermore, full recovery was achieved in former smokers (i.e., normalization to the level of lifelong non-smokers). However, while light smokers fully recovered within the 15 first years of cessation, heavy former smokers might need up to 15–25 years to fully recover.
Conclusion: This study supports the substantial benefits of smoking cessation, but also warns of important long-term alterations caused by heavy smoking.

1. Introduction

The risk of coronary heart disease in current smokers is increased by a factor of 2.5 to 4 compared to lifelong non-smokers (Negri et al., 1994; Novello, 1990; Office of the Surgeon General (US) and Office on Smoking and Health (US), 2004; Shaper et al., 1985; Shields and Wilkins, 2013; Teo et al., 2006; Wannamethee et al., 1995). Smoking cessation decreases cardiovascular morbidity and mortality and improves quality of life (Doll and Peto, 1976; Lightwood and Glantz, 1997; Novello, 1990; Ockene et al., 1990; Teo et al., 2006). However, the magnitude of the risk reduction and the length of cessation required remain poorly understood. While the risk seems to decrease immediately after smoking cessation (Dobson et al., 1991; Doll et al., 2004; Honjo et al., 2010; Mannan et al., 2010; Negri et al., 1994; Novello, 1990; Ockene et al., 1990; Office of the Surgeon General (US) and Office on Smoking and Health (US), 2004; Shields et al., 2013; Shields and Wilkins, 2013;

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Teo et al., 2006; Tverdal et al., 1993; Wannamethee et al., 1995), it is not clear when or even whether the risk reverts to that of lifelong non-smokers. While some studies have shown that the risk of coronary heart disease reverts to that of lifelong non-smokers within 3–5 years (Dobson et al., 1991; Mannan et al., 2010; Novello, 1990; Tverdal et al., 1993) or within 10–20 years (Honjo et al., 2010; Shields and Wilkins, 2013), other studies have identified a remaining risk in former smokers after 10 or even 20 years of continuous smoking cessation (Negri et al., 1994; Teo et al., 2006; Wannamethee et al., 1995). A remaining risk was exclusively identified in former heavy, but not in former light smokers. These findings led us to the hypothesis that repeated exposure to tobacco smoke over years could trigger an irreversible change in the regulation of the autonomic cardiovascular system.

Heart rate variability (HRV) is a useful non-invasive measure to assess the autonomic regulation of cardiac rhythm ("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," 1996). Lower HRV is associated with higher cardiovascular morbidity and mortality and has proved itself as an important prognostic tool for several cardiovascular conditions (Bigger et al., 1992; "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," 1996; Kleiger et al., 1987; Tsuji et al., 1996). HRV has been found to increase immediately after smoking cessation (Harte and Meston, 2014; Minami et al., 1999; Munjal et al., 2009; Yotsukura et al., 1998), to reach a peak after 2–7 days, and to gradually decline thereafter (Harte and Meston, 2014; Lewis et al., 2010; Minami et al., 1999; Yotsukura et al., 1998). The increase in HRV persisted 1 month after smoking cessation (Harte and Meston, 2014; Stein et al., 1996; Yotsukura et al., 1998). However, the long term evolution of HRV after smoking cessation has, to our best knowledge, only been investigated by Gać and Sobieszczańska (2014). Based on a cross-sectional study including 145 hypertensive subjects the authors reported that former smokers with cessation periods of over five years had increased HRV compared to those who actively smoked cigarettes, but decreased HRV compared to those who had never smoked. Therefore, a more thorough investigation in a larger sample from the general population, and for a longer period of time, is in order.

While HRV has traditionally been measured using time- and frequency-domain measures, there is increasing evidence that the regulation of the cardiovascular system involves nonlinear control mechanisms ("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," 1996; Rajendra Acharya et al., 2006). Thus, a quantitative assessment of the inter-beat interval time series generated from 24-hour electrocardiogram recordings, using nonlinear time series analysis techniques, appears promising (Goldberger and West, 1987; Meyer and Stiedl, 2003; Rajendra Acharya et al., 2006; Vandeput et al., 2012), and may help to unveil subtle, but important changes in the heart rate dynamics (Goldberger and West, 1987; Pikkujämsä et al., 2001; Pincus, 1991). Only one pilot study has so far examined the influence of smoking cessation over a 30-day period on heart rate dynamics using multifractal analysis (Lewis et al., 2010). Multifractality of cardiac time-series was found to be similar for smokers and non-smokers, and seemed unchanged by smoking abstinence or nicotine replacement therapy.

The objective of the present study was to evaluate the long-term influence of smoking cessation on the regulation of the autonomic cardiovascular system in an aging general population, using the subpopulation of lifelong non-smokers as control group. We investigated whether smoking cessation resulted in long-term normalization of the parameters describing the HRV and heart rate dynamics to the level of lifelong non-smokers, and whether this normalization was associated with the amount previously smoked.

2. Methods

2.1. Ethics statement

The study was approved by the central Ethics Committee of the Swiss Academy of Medical Sciences and the Cantonal Ethics Committees for each of the study areas. Each subject was informed in detail about the health examinations and signed an informed consent before any of the health examinations was conducted.

2.2. Study population

This study is part of the SAPALDIA (Swiss Cohort Study on Air Pollution and Lung and Heart Disease in Adults) study which was designed to assess the health effects from long-term exposure to air pollutants in the Swiss adult population. The study design has been described in detail elsewhere (Ackermann-Liebrich et al., 2005; Martin et al., 1997). In brief, the SAPALDIA cohort ($n=9651$) was enrolled in 1991, and consisted of a random sample of the Swiss population aged 18–60 years, recruited from the local registries of inhabitants in eight areas featuring distinct geographical and environmental conditions.

In 2002, the follow-up study included 8047 (83.4%) participants. A random sample of 1846 out of 4417 participants aged $\geq$ 50 years underwent a 24-hour electrocardiogram (ECG) Holter recording to assess HRV, as previously described in detail (Felber Dietrich et al., 2006). Exclusion criteria were general or spinal anesthesia within 8 days before the ECG recording ($n=5$), a myocardial infarction within 3 months prior to the examination ($n=2$), taking digitalis ($n=6$), and an artificial internal pacemaker ($n=0$). Participants with recordings showing atrial fibrillation ($n=12$), ECG duration lower than 18 hours ($n=73$), or of insufficient quality ($n=6$), non-valid data on HRV ($n=96$) were also excluded (Felber Dietrich et al., 2006). Participants who smoked pipe, cigars and/or cigarillos, but not cigarettes were excluded as well ($n=38$). Participants who smoked pipe, cigars and/or cigarillos in addition to cigarettes were not excluded. Finally, 127 subjects were excluded due to missing data on smoking status. Thus, the current study includes 1481 subjects.

2.3. Data collection

Data were collected using an electronic Case Report Form (eCRF) developed specifically for the SAPALDIA study. Information about the questionnaires and the measurements can be found in the Online Supplement.

2.4. Computational methods

Time series analysis parameters of heart rate variability were calculated for each individual time series of inter-beat intervals (RR series) generated from the 24-hour ECG recordings.

Traditional time and frequency domain measures were calculated in agreement with the standards of measurement proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology ("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