Int.J. Behav. Med. (2014) 21:302–309
DOI 10.1007/s12529-013-9295-0

Effects of Smoking Cessation on Heart Rate Variability Among Long-Term Male Smokers

Christopher B. Harte · Cindy M. Meston

Published online: 9 February 2013

Abstract
Background Cigarette smoking has been shown to adversely affect heart rate variability (HRV), suggesting dysregulation of cardiac autonomic function. Conversely, smoking cessation is posited to improve cardiac regulation.
Purpose The aim of the present study was to examine the effects of smoking cessation on HRV among a community sample of chronic smokers.
Methods Sixty-two healthy male smokers enrolled in an 8-week smoking cessation program involving a nicotine transdermal patch treatment. Participants were assessed at baseline (while smoking regularly), at mid-treatment (while using a high-dose patch), and at follow-up, 4 weeks after patch discontinuation. Both time-domain (standard deviation of normal-to-normal (NN) intervals (SDNN), square root of the mean squared difference of successive NN intervals (RMSSD), and percent of NN intervals for which successive heartbeat intervals differed by at least 50 ms (pNN50)) and frequency-domain (low frequency (LF), high frequency (HF), LF/HF ratio) parameters of HRV were assessed at each visit.
Results Successful quitters (n=20), compared to those who relapsed (n=42), displayed significantly higher SDNN, RMSSD, pNN50, LF, and HF at follow-up, when both nicotine and smoke free.
Conclusions Smoking cessation significantly enhances HRV in chronic male smokers, indicating improved autonomic modulation of the heart. Results suggest that these findings may be primarily attributable to nicotine discontinuation rather than tobacco smoke discontinuation alone.

Keywords Smoking · Smoking cessation · Nicotine · Heart rate variability · Cardiac autonomic regulation · Autonomic nervous system

Introduction

Chronic tobacco use is the most preventable cause of morbidity and mortality in the world today [1] and introduces a variety of adverse health consequences such as cardiovascular diseases (CVD) [2], respiratory diseases [3], and cancer [4]. Smoking also increases the risk of ischemic heart disease and sudden cardiac death [5, 6], conditions which are believed to be, in part, mediated by smoking-induced autonomic imbalance (typically characterized by sympathetic hyperactivity) [7]. These adverse alterations in the autonomic nervous system have been associated with heart rate variability (HRV), which may play an important role in the relation between smoking and mortality [8]. HRV is an index of vagal tone and reflects the balance between parasympathetic and sympathetic maneuvers. Sympathetic nervous system activation accelerates heart rate (HR) thereby decreasing HRV, whereas parasympathetic nervous system activation decelerates HR and increases HRV. Elevations in HRV are a sign of healthy cardiac function, whereas reductions in HRV leave the heart vulnerable to arrhythmia and sudden death [9].

A growing body of cross-sectional data has shown that smokers, compared to nonsmokers, exhibit dysfunctional cardiac autonomic function, as evidenced by lower HRV indices. This has been shown to be the case when HRV is

C. B. Harte (✉)
Research Service, VA Boston Healthcare System, 150 S. Huntington Ave. (116-B4), Boston, MA 02130, USA
e-mail: christopher.harte@va.gov

C. B. Harte
Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA

C. M. Meston
Department of Psychology, University of Texas at Austin, Austin, TX, USA

measured in both the time domain (i.e., standard deviation of the normal inter-beat intervals) and the frequency domain (power spectrum data capturing high-frequency (HF) and low-frequency (LF) ranges) [8]. Additionally, duration of smoking has been found to be inversely associated with HRV [8].

Studies examining the temporal association between smoking and cardiac dysregulation have provided additional evidence supporting the adverse impact of tobacco on measures of HRV. Specifically, smoking appears to acutely instigate cardiac autonomic imbalance [10–12], and isolated nicotine intake acutely negatively affects HRV in a similar fashion [13]. A handful of studies have demonstrated the bidirectionality of this effect by examining the association between quitting smoking and cardiac functioning. In the first study to examine the effects of smoking cessation on HRV, Stein and colleagues [14] showed that, among chronic smokers motivated to quit, participants demonstrated enhancements in HRV as a result of quitting smoking and transitioning to a 21-mg nicotine patch, and continued improvements once they discontinued patch use and were completely abstinent. This suggests that both nicotine and tobacco smoke play a deleterious role in cardiac autonomic function. Two subsequent studies examining the relationship between quitting smoking cold turkey and HRV have provided additional evidence to this effect [15, 16].

The purpose of present study was to examine the effects of smoking cessation on HRV among a community sample of chronic male smokers, without a history of myocardial infarction (MI) or CVD. It was hypothesized that successful quitters, but not unsuccessful quitters, would display significant across-time enhancements in HRV. We additionally hypothesized that these differential changes in HRV would result in successful quitter showing significantly higher HRV parameters at follow-up, when both tobacco-free (i.e., cessation of smoking) and nicotine-free (successful completion of nicotine patch treatment), compared to unsuccessful quitters.

Method

Participants

Participants were adult male smokers recruited through both community and online advertisements. All data presented herein were taken from a nonrandomized intervention study examining the association between smoking cessation and sexual health indices in men [17]. Inclusionary criteria were comprised of being an adult between the ages of 23 and 60 years, and smoking at least 15 cigarettes per day for a minimum of five consecutive years. Exclusion criteria were as follows: (a) use of nicotine replacement therapies and/or non-nicotine smoking cessation medications within 3 months prior to enrollment (bupropion, varenicline); (b) use of non-cigarette tobacco products; (c) medical conditions that could make nicotine administration unsafe (e.g., history of MI, stroke, heart arrhythmias, angina, or uncontrolled hypotension or hypertension); (d) history of severe drug or alcohol abuse during the past 12 months (≥16 points on the Alcohol Use Disorders Identification Test (AUDIT) [18] and≥6 on the Drug Abuse Screening Test (DAST-10) [19]); and (e) a body mass index<18.5 kg/m^2 or>35 kg/m^2. Given the sexual nature of the parent study [17], other exclusion criteria included: use of medications or report of medical conditions known or believed to affect sexual or vascular functioning; self-report of a sexually transmitted infection; and not being currently sexually active. A detailed description of the participant flow can be found in Harte and Meston [17]. Of the 65 men who were enrolled in the original study, three individuals reporting CVD were removed, resulting in a total sample size of 62 participants for the current report.

HRV Measures

All cardiac data were measured using a three-channel electrocardiograph (ECG). Signals were collected at a rate of 80 samples/s, low-pass filtered (to 0.5 Hz), digitized (40 Hz), and recorded using a Model MP100WS data acquisition unit (BIOPAC Systems, Inc., Santa Barbara, CA, USA) and the software package AcqKnowledge III, Version 3.73 (BIOPAC Systems, Inc.). Normal-to-normal (NN) intervals were collected manually using the AcqKnowledge peak finder function, and artifacts were identified and removed manually. After cleaning ECG recordings, mean NN interval and mean HR were derived. Both time- and frequency-domain HRV indices were calculated using Kubios HRV Analysis Software (Biosignal Analysis and Medical Imaging Group, University of Kuopio, Kuopio, Finland). Time-domain measures included the standard deviation of NN intervals (SDNN), the square root of the mean squared difference of successive NN intervals (RMSSD), and the percent of NN intervals for which successive heartbeat intervals differed by at least 50 ms (pNN50). Frequency-domain parameters of HRV were calculated using fast Fourier transform to derive the spectral distribution. Indices included (in millisecond squared) LF power (0.04–0.15 Hz), HF power (0.15–0.40 Hz), and the ratio of these two indices (LF/HF), which reflected sympathovagal balance [20].

Procedure

For a full description of the procedure, we refer the reader to the parent study [17]. In brief, adult male smokers who expressed motivation and commitment to quit were recruited through both community and online advertisements. During

an initial telephone interview, prospective participants were screened for inclusion/exclusion criteria, and those meeting eligibility criteria were scheduled to present to the laboratory for three separate visits: at baseline while smoking regularly, 4 weeks later while using a high-dose nicotine transdermal patch (mid-treatment), and 4 weeks after completing the patch intervention (follow-up). All participants received an 8-week nicotine transdermal patch treatment administered in a step-down fashion and were monitored weekly via telephone for patch compliance and tobacco use. At the first visit, participants completed self-report questionnaires assessing socio-demographic information (age, education level, income, ethnicity, and marital status) medical history (e.g., medical condition(s) and current medications), current activity level (average number of days per week during the past month that a participant engaged in aerobic activity for≥30 min per occasion), substance use (per the AUDIT and DAST), affect (per the Positive and Negative Affect Schedule (PANAS [21]) and smoking characteristics (current smoking frequency, smoking duration, age when smoking was initiated, and nicotine dependence (assessed via the 6-item Fagerstrom Test for Nicotine Dependence [FTND; [22]])). At every visit, anthropometric (height, weight) indices, ECG data, blood pressure, and physiological and subjective sexual arousal responses were assessed. To bolster the validity of self-reported cigarette consumption, participants provided saliva samples and were spuriously told that these would be assayed for nicotine content. ECG data were collected during spontaneous breathing for all participants individually while sitting upright in a comfortable chair in a quiet, private, internally locked room. During data collection, participants were asked to watch a 3-min documentary film presented on a television screen approximately 10 ft in front of them. The ECG recordings were assessed between 11 a.m. and 3 p.m. in an attempt to reduce circadian variation of HRV parameters [23]. Three ECG limb leads were attached to disposable electrodes and were placed on the participant's upper right chest, lower left chest, and right ankle. ECG parameters were collected for 12 consecutive minutes, which consisted of an initial 3-min baseline period (documentary film presentation), immediately followed by an 8-min erotic film presentation designed to facilitate sexual arousal responses. For the purposes of the current study, only ECG data from the initial 3-min baseline period were examined.

All participants were asked to refrain from using any illicit substances and/or alcohol before entering the laboratory. Participants were allowed to enter the laboratory at their preferred nicotine levels; however, they were not allowed to smoke during the testing session. On average, participants reported smoking 7.19 cigarettes (SD=4.79; range=1–20) before the onset of the session, and reported an average duration of 29.50 min (SD=18.59; range=5–90) since smoking their last cigarette. At the completion of the third laboratory visit, participants were provided $30 and were mailed a detailed report of their laboratory assessments. All participants provided written, informed consent, and the protocol was approved by the university institutional review board.

Statistical Analysis

Smoking cessation efficacy was determined by using a 1-week point prevalence abstinence rate. Participants reporting 0 cigarettes and ≥1 cigarettes during the prior 7 days at follow-up were classified as successful quitters and unsuccessful quitters, respectively. Pack years were calculated by multiplying the number of packs of cigarettes smoked per day by the number of years smoked. Missing values for each HRV index were imputed using full information maximum likelihood estimation (FIML) [24], which produces more accurate parameter estimates compared to per protocol analyses or last observation carried forward techniques [25]. Total number of cigarettes smoked throughout the study, as well as number of cigarettes smoked at follow-up was estimated similarly; outcome status (successful quitter, unsuccessful quitter) was based on these imputed values. Successful and unsuccessful quitters were compared at each time point for all HRV parameters using general linear modeling (in the form of repeated measures ANCOVA models). For these analyses, the interaction effect of group×time was of primary interest. Statistically significant interaction effects were examined using planned comparison F tests for adjusted cell means to assess between-group differences at each time point. Baseline variables that differed between successful and unsuccessful quitters (i.e., drinking severity), as well as variables that differed between study completers and dropouts (i.e., race, smoking during enrollment), were entered as covariates in all analyses. Additionally, smoking status at second visit (smoke-free, relapsed) was entered as a covariate. Comparisons between successful and unsuccessful quitters at baseline, as well as comparisons between study completers and dropouts, were compared with t tests or Pearson χ^2 tests, as appropriate. All analyses were performed using SPSS statistical software version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Participant Characteristics

The total sample (N=62) ranged in age from 23 to 58 years with a mean age of 38.27 years (SD=10.62). The majority of the sample was White (88.7 %); breakdowns of other races/ethnicities were as follows: 3.2 % Black/African-American; 3.2 % Latino; 3.2 % Asian; and 1.6 % "other."

With respect to baseline smoking characteristics, participants reported a mean of 22.54 pack-years (SD=15.27), were smoking an average of 20.95 cigarettes per day (SD=7.31), and reported a moderate level of nicotine addiction as per the FTND (M=5.44; SD=1.96). Eight participants reported taking medications at the time of enrollment (mood stabilizer, n=3; antidepressant, n=1; anticonvulsants, n=1; benzodiazepine, n=1; serotonin modulator, n=1; H_2 blocker, n=1; antihistamine, n=2) and four participants reported a current psychiatric diagnosis (major depressive disorder, n=3; bipolar disorder, n=1). Neither medication use, $\chi^2(1)=.22$, $p=0.64$, $\varphi=0.06$, nor psychiatric diagnosis status, $\chi^2(1)=2.04$, $p=0.15$, $\varphi=.18$, differed between successful and unsuccessful quitters. No participants reported a history of MI or current CVD, and none were taking cardiac/cardiovascular medications.

Regarding participant flow, 17 participants dropped out after the initial visit, and an additional 12 after the second visit, resulting in a total of 33 participants who completed the study (53 % of the initial sample). Study completers versus those who discontinued treatment differed with respect to race and smoking throughout enrollment. Specifically, those who withdrew were more likely to be non-White, $\chi^2(1)=4.81$, $p=0.03$, $\varphi=.28$, and reported smoking more cigarettes throughout study enrollment, $t(60)=3.11$, $p=0.001$, $d=1.26$. Those who completed the study versus those who dropped out did not differ with respect to any HRV parameters. With respect to treatment efficacy, 36 % (22 of 65) and 68 % (42 of 65) of men were considered relapsed at mid-treatment and follow-up, respectively. Comparisons between successful (n=20) and unsuccessful (n=42) quitters indicated that these groups differed at baseline only with respect to drinking severity, with unsuccessful quitters reporting less alcohol use compared to successful quitters, $t(60)=3.00$, $p<0.001$, $d=0.82$. Additional baseline data can be found in Table 1.

Analyses of HRV

Results of the 2 (group: successful vs. unsuccessful quitter)×3 (time: baseline, mid-treatment, follow-up) repeated measures ANCOVAs revealed a significant group×time interaction effect for SDNN, $F(2,112)=3.92$, $p=0.02$, $\eta^2=0.07$; RMSSD, $F(2,112)=5.29$, $p=0.01$, $\eta^2=0.09$; pNN50, $F(2,112)=3.44$, $p=0.04$, $\eta^2=0.06$; LF power, $F(2,112)=2.97$, $p=0.05$, $\eta^2=0.05$; and HF power, $F(2,112)=5.20$, $p=0.01$, $\eta^2=0.09$. More detailed exploration of these interaction effects indicated that unsuccessful quitters did not demonstrate across-time changes with respect to these HRV parameters (SDNN, $F(2,76)=.79$, $p=0.46$, $\eta^2=0.03$; RMSSD, $F(2,76)=.47$, $p=0.63$, $\eta^2=0.02$; pNN50, $F(2,76)=1.64$, $p=0.20$, $\eta^2=0.06$; LF power, $F(2,76)=.66$, $p=0.52$, $\eta^2=0.02$; HF power, $F(2,76)=.46$, $p=0.63$, $\eta^2=0.63$), whereas successful quitters showed significant across-time increases in HRV (SDNN, $F(2,32)=2.96$, $p=0.05$, $\eta^2=.10$; RMSSD, $F(2,32)=.3.91$ $p=0.03$, $\eta^2=0.13$; pNN50, $F(2,32)=4.93$, $p=0.02$, $\eta^2=0.14$; LF power, $F(2,32)=.2.95$, $p=0.05$, $\eta^2=0.10$; HF power, $F(2,32)=5.58$, $p=0.01$, $\eta^2=0.17$). Additional post hoc tests of between-subjects contrasts revealed that SDNN, RMSSD, pNN50, LF, and HF were significantly higher among successful quitters compared to unsuccessful quitters at follow-up (SDNN, $p=0.05$, $d=.53$ (Fig. 1); RMSSD, $p=0.01$, $d=.68$ (Fig. 1); pNN50, $p=0.05$, $d=.50$ (Fig. 2); LF power, $p=0.05$, $d=0.51$ (Fig. 3); HF power, $p=0.01$, $d=.73$ (Fig. 3)), but not at baseline or mid-treatment (all p values>0.05).

Successful quitters, but not unsuccessful quitters, showed significant across-time changes in NN intervals and HRs. Specifically, successful quitters demonstrated larger NN intervals across time, $F(2,76)=3.20$, $p=0.05$, $\eta^2=0.10$, and lower HRs across time, $F(2,76)=3.49$, $p=0.04$, $\eta^2=0.11$; however, this did not result in group×time interaction effects, nor did successful and unsuccessful quitters differ on these measures at any of the three time points. Finally, there were neither main effects nor interaction effects with respect to LF/HF ratios.

Covariation Between Affect and HRV Parameters

Additionally, across-time covariation between changes in affect and HRV measures was examined to rule out the possibility that enhancements in cardiac tone were a byproduct of the alleviation of negative affectivity (a common feature of nicotine withdrawal). To this end, within-participants difference scores (baseline minus follow-up) were derived for all HRV measures, and for positive affect (PA) and negative affect (NA) scores of the PANAS, and then entered into separate regression models. Results indicated that there were no associations between either PA or NA change scores and any HRV parameter for either successful or unsuccessful quitters (all p values>0.05). This suggested that alterations in HRV were not epiphenomena of affect change as a result of cessation success.

Discussion

The current study examined changes in cardiac autonomic activity (assessed via HRV) as a function of quitting smoking among long-term male smokers without CVD. Results indicated that participants who successfully quit smoking, compared to those who did not, exhibited a graded pattern of improvement, characterized by increases in HRV parameters as a result of stopping smoking and transitioning to using a 21-mg nicotine patch, and further enhancements once patch use was discontinued and participants were fully abstinent from tobacco. Conversely, HRV indices of

Table 1 Characteristics of the participant sample

Characteristic	Successful quitters ($n=20$)		Unsuccessful quitters ($n=42$)		
	Mean (SD)	*n* (%)	Mean (SD)	*n* (%)	ES[a]
Age (years)	34.90 (9.65)		39.88 (10.80)		0.49
Education (years)[b]	15.47 (2.04)		14.46 (2.24)		0.47
Ethnicity					
White		19 (95.0)		36 (85.7)	
African-American		0 (0.0)		2 (4.8)	
Latino		0 (0.0)		2 (4.8)	
Asian		0 (0.0)		2 (4.8)	
Other		1 (5.0)		0 (0.0)	0.29
Marital status					
Single		13 (65.0)		19 (45.2)	
Married/cohabiting		4 (20.0)		17 (40.5)	
Divorced		3 (15.0)		6 (14.3)	0.21
Substance use measures					
Alcohol use[c]	6.85 (3.13)		4.24 (3.24)		0.82**
Drug use[d]	0.70 (0.98)		0.60 (0.80)		0.11
Smoking measures					
Age at smoking onset (years)[e]	16.05 (2.37)		16.65 (5.33)		0.15
Smoking duration (years)[e]	17.90 (10.03)		22.10 (11.15)		0.40
Pack years	18.18 (14.02)		21.67 (15.88)		0.23
Current smoking frequency (cigarettes/day)	19.00 (5.09)		21.88 (8.04)		0.43
Nicotine dependence level[e, f]	5.35 (1.84)		5.49 (2.04)		0.07
Current medication use		2 (10.0)		18 (90.0)	0.06
Psychiatric diagnosis		0 (0.0)		4 (9.5)	0.18
Aerobic activity≥30 min (days/week)[e]	4.45 (2.15)		3.80 (2.38)		0.29
BMI (kg/m^2)	25.86 (3.67)		25.75 (4.68)		0.03
Cardiac function					
Resting HR (bpm)	80.35 (14.55)		79.50 (12.25)		0.06
Systolic BP (mm Hg)[e]	124.85 (21.82)		131.50 (12.77)		0.37
Diastolic BP (mm Hg)[e]	85.65 (16.32)		84.52 (11.75)		0.08

BMI body mass index, *BP* blood pressure, *bpm* beats per min, *ES* effect size, *mm Hg* millimeters mercury, *HR* heart rate

[a] Effect sizes reported as Cohen's *d* and Cramer's φ for continuous and categorical variables, respectively

[b] Data missing for two participants

[c] Assessed with the Alcohol Use Disorders Identification Test [18]. Possible score range from 0 to 40, with higher scores reflecting increasing levels of problematic drinking

[d] Assessed with the Drug Abuse Screening Test, 10-item [19]. Possible score range from 0 to 10, with higher scores indicating greater substance abuse severity

[e] Data missing for one participant

[f] As per the Fagerström Test of Nicotine Dependence [22]. Possible score range from 0 to 10, with higher scores indicating greater dependency to nicotine

*$p<0.05$; **$p<0.01$

unsuccessful quitters remained generally unchanged across time. These differential across-time changes as a result of smoking status resulted in significantly higher SDNN, RMSSD, pNN50, LF, and HF among successful quitters at follow-up (approximately 4 weeks after nicotine patch discontinuation). Furthermore, successful quitters (but not unsuccessful quitters) showed increases in NN intervals and decreases in HRs across time; however, the magnitudes of these changes were not sufficient to result in group×time interaction effects. Taken together, these findings suggest that smoking cessation is associated with decreases in sympathetic tone and enhancements in autonomic cardiac

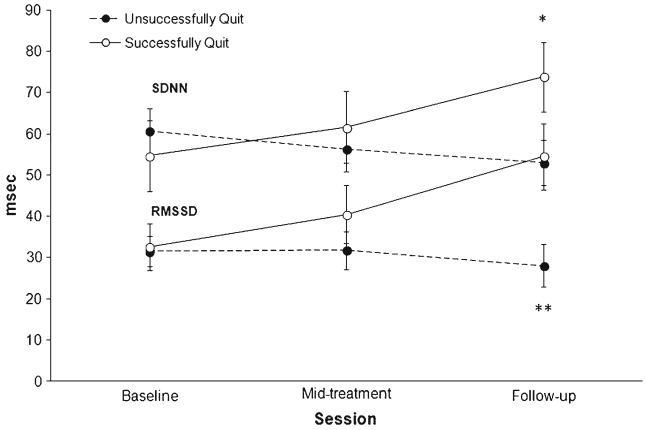

Fig. 1 Across-session changes in SDNN and RMSSD as a function of smoking status. *Upper and lower asterisks* represent significant results of between-group comparisons (successful versus unsuccessful quitters) at each time point for SDNN and RMSSD, respectively. *Error bars* represent standard errors of the means. Means have been adjusted for baseline drinking severity, race, total cigarettes smoked throughout enrollment, and smoking status at second visit. *SDNN* standard deviation of normal-to-normal intervals, *RMSSD* square root of the mean squared difference of successive normal-to-normal intervals, *HRV* heart rate variability. *$p<0.05$, **$p<0.01$

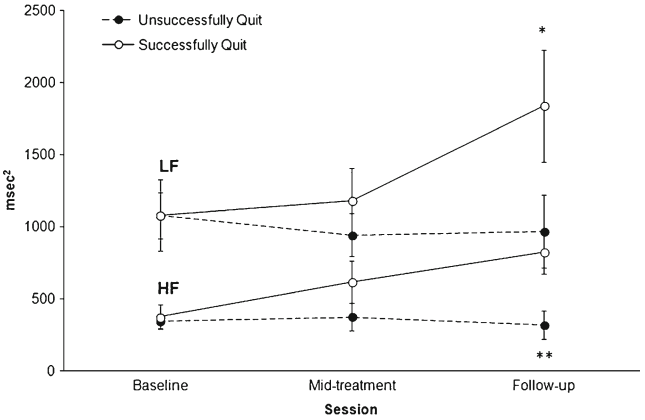

Fig. 3 Across-session changes in LF and HF among successful and unsuccessful quitters. *Upper and lower asterisks* represent significant results of between-group comparisons (successful versus unsuccessful quitters) at each time point for LF and HF, respectively. *Error bars* represent standard errors of the means. Means have been adjusted for baseline drinking severity, race, total cigarettes smoked throughout enrollment, and smoking status at visit 2. *LF* low-frequency power, *HF* high-frequency power, *HRV* heart rate variability. *$p<0.05$, **$p<0.01$

function. These findings are in concert with prior studies demonstrating increases in both time- and frequency-domain measures of HRV as a result of smoking cessation [14–16].

From a pharmacological standpoint, results may suggest that improvements in cardiac autonomic tone are chiefly attributable to nicotine discontinuation (as evidenced by between-group differences in HRV parameters at follow-up, when successful quitters were both nicotine-free and tobacco-free), rather than tobacco smoke discontinuation alone (i.e., lack of between-group differences at mid-treatment, when individuals ceased smoking and initiated nicotine patch treatment). These findings are consistent with a growing body of literature showing that isolated nicotine deleteriously affects HRV [13]. However, these interpretations are only speculative, given that there was no assessment of plasma nicotine concentrations. In fact, it has been shown that plasma nicotine levels during high-dose nicotine patch use are often only approximately half the levels generated by heavy cigarette smoking [26].

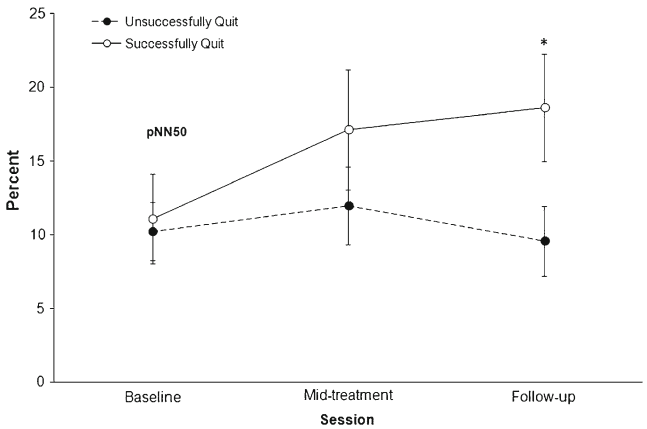

Fig. 2 Across-session changes in pNN50 among successful and unsuccessful quitters. *Asterisks* represent significant results of between-group comparisons (successful versus unsuccessful quitters) at each time point. *Error bars* represent standard errors of the means. Means have been adjusted for baseline drinking severity, race, total cigarettes smoked throughout enrollment, and smoking status at visit 2. *pNN50* percent of normal-to-normal intervals for which successive heartbeat intervals differed by at least 50 ms, *HRV* heart rate variability. *$p<0.05$, **$p<0.01$

There were several strengths inherent to the current study. First, to the authors' knowledge, this was the first longitudinal study examining the effects of transdermal nicotine patch use and smoking cessation on HRV parameters that incorporated a comparison quasi-control group (unsuccessful quitters), thereby enhancing internal validity. Additional strengths included: (a) multiple assessment points in order to gain a better understanding of the pharmacological effects of tobacco smoke and isolated nicotine on cardiac functioning; (b) examination of a variety of HRV parameters, both in the time and frequency domain; and (c) exclusion of individuals with a history of MI, CVD, and use of cardiovascular medication, all of which are conditions that have been associated with cardiac autonomic imbalance [27, 28].

Despite this investigation's novel findings, several study limitations warrant mention. First, this was not a randomized trial, and therefore results must be interpreted with caution. However, the present study did enable for between-group comparisons across time, whereby unsuccessful quitters served as a quasi-control group. Second, smoking status was assessed via self-report rather than via biochemical verification. However, at each visit, participants provided saliva

samples and were spuriously told that these would be assayed for nicotine content and cross-referenced with their self-report. This "bogus pipeline" technique has been shown to produce reliable and accurate estimates of smoking [29]. In fact, a meta-analysis of 36,830 participants showed that self-reported smoking behavior was highly concordant with biochemical verification of smoking activity [30]. Third, spontaneously breathing was not controlled for in the present study. It has been shown that breathing rate is associated with HRV via the respiratory sinus arrhythmia mechanism [31], and therefore the potential confounding covariation between smoke/nicotine cessation and changes in depth and/or rate of breathing could not be ascertained. A fourth limitation was the dropout rate before the follow-up session, a problem that is notorious in longitudinal smoking research [32]. Specifically, 53 % of the sample completed the 1-month follow-up. To enhance the reliability of the reported effects, data were imputed using FIML data estimation [24]. This technique produces more accurate parameter estimates compared to per protocol analyses or last observation carried forward techniques [25]. Additionally, it has been suggested that FIML methods can be reliably employed when up to 90 % of data are missing for a particular variable [24, 25, 33]. A final limitation was with respect to the sampling rate and digitization of the ECG data. Given that the current report comprised secondary analyses of available data from prior studies, ECG data were originally recorded at a rate (40 Hz) below what is recommended by the Society for Psychophysiological Research Committee on Impedance Cardiography [34] (500–1,000 Hz). It has been shown that frequency-domain measures of HRV are more strongly affected by digitization rate compared to time-domain measures [34]; however, the fact that *both* time- and frequency-domain indices showed significant across-time changes as a function of smoking status provides some tentative support to the possibility that sampling rate did not induce spurious results.

In conclusion, results of the present investigation indicated that quitting smoking significantly enhances cardiac autonomic function in chronic male smokers without a history of MI or CVD. These findings add to the growing body of literature demonstrating the variety of health benefits associated with smoking cessation. Cessation-induced improvements in HRV may explain the lower likelihood of adverse cardiac events among individuals who quit smoking compared to those who continue to smoke. However, it remains to be determined whether improvements in HRV indices resulting from quitting smoking are associated with reduced cardiac/cardiovascular risk in the long-term. Future research in the form of long-term follow-up designs is necessary to determine whether these immediate health benefits translate to reduced adverse health events.

Acknowledgments This project was supported by Award Number F31DA026276 from the National Institute on Drug Abuse (NIDA) to Christopher Harte. The contents of this work are solely the responsibility of the author and do not necessarily represent the official views of the NIDA or the National Institutes of Health. Portions of this work were also made possible by Grant Number 1 RO1 HD051676-01 A1 to Cindy M. Meston from the National Institute of Child Health and Human Development (NICHD). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NICHD. This project was also supported by the following fellowships/awards to the first author: The Sexual Medicine Society of North America Student Research Grant; two Graduate Dean's Prestigious Fellowship Supplements, and a College of Liberal Arts Graduate Research Fellowship, all from the University of Texas at Austin; the American Psychological Association Dissertation Research Award; and The Kinsey Institute Student Research Grant. The authors thank Tyler Watts, Hillary Perlman, Olivia Bentkowski, Alicia Whitaker, Gail Dalton, and Katy Siciliano for help with participant recruitment, screening, and data management.

Conflict of Interest The authors declare no conflict of interest.

References

1. Centers for Disease Control and Prevention. Annual smoking-attributable mortality, years of potential life lost, and economic costs—United States, 1995–1999. MMWR Morb Mortal Wkly Rep. 2002;51:300–3.
2. Campbell SC, Moffatt RJ, Stamford BA. Smoking and smoking cessation—the relationship between cardiovascular disease and lipoprotein metabolism: a review. Atherosclerosis. 2008;201:225–35.
3. Fagerström K. The epidemiology of smoking: health consequences and benefits of cessation. Drugs. 2002;62:1–9.
4. U.S. Department of Health and Human Services. The health consequences of smoking: a report of the surgeon general. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
5. Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. Nat Rev Cardiol. 2010;7:216–25.
6. US Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
7. 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. 1996;94:2850–5.
8. Barutcu I, Esen AM, Kaya D, et al. Cigarette smoking and heart rate variability: dynamic influence of parasympathetic and sympathetic maneuvers. Ann Noninvasive Electrocardiol. 2005;10:324–9.
9. 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. 2003;107:565–70.
10. Hayano J, Yamada M, Sakakibara Y, et al. Short-and long-term effects of cigarette smoking on heart rate variability. Am J Cardiol. 1990;65:84–8.
11. 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 Heal. 2005;31:360–6.

12. Karakaya O, Barutcu I, Kaya D, et al. Acute effect of cigarette smoking on heart rate variability. Angiology. 2007;58:620–4.
13. Sjoberg N, Saint DA. A single 4 mg dose of nicotine decreases heart rate variability in healthy nonsmokers: implications for smoking cessation programs. Nicotine Tob Res. 2011;13:369–72.
14. Stein PK, Rottman JN, Kleiger RE. Effect of 21 mg transdermal nicotine patches and smoking cessation on heart rate variability. Am J Cardiol. 1996;77:701–5.
15. Minami J, Ishimitsu T, Matsuoka H. Effects of smoking cessation on blood pressure and heart rate variability in habitual smokers. Hypertension. 1999;33:586–90.
16. Yotsukura M, Koide Y, Fujii K, et al. Heart rate variability during the first month of smoking cessation. Am Hear J. 1998;135:1004–9.
17. Harte CB, Meston CM. Association between smoking cessation and sexual health in men. BJU Int. 2012;109:888–96.
18. Saunders J, Aasland O, Babor T, de la Fuente J, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993;88:791–804.
19. Skinner HA. The Drug Abuse Screening Test. Addict Behav. 1982;7:363–71.
20. 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. 1986;59:178–93.
21. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Personal Soc Psychol. 1988;54:1063–70.
22. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: a revision of the Fagerstrom tolerance questionnaire. Br J Addict. 1991;86:1119–27.
23. Bonnemeier H, Wiegand UKH, Brandes A, et al. Circadian profile of cardiac autonomic nervous modulation in healthy subjects. J Cardiovasc Electrophysiol. 2003;14:791–9.
24. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd ed. Hoboken: Wiley-Interscience; 2002.
25. Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychol Methods. 2002;7:147–77.
26. Hurt RD, Dale LC, Offord KP, et al. Serum nicotine and cotinine levels during nicotine-patch therapy. Clin Pharmacol Ther. 1993;54:98–106.
27. Salo TM, Kantola I, Voipio-Pulkki LM, Pelttari L, Viikari JSA. The effect of four different antihypertensive medications on cardiovascular regulation in hypertensive sleep apneic patients—assessment by spectral analysis of heart rate and blood pressure variability. Eur J Clin Pharmacol. 1999;55:191–8.
28. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol. 2010;141:122–31.
29. Murray D, O'Connell C, Schmid L, Perry C. The validity of smoking self-reports by adolescents: a reexamination of the bogus pipeline procedure. Addict Behav. 1987;12:7–15.
30. Patrick D, Cheadle A, Thompson D, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. Am J Public Health. 1994;84:1086.
31. Grossman P, Karemaker J, Wieling W. Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: the need for respiratory control. Psychophysiology. 1991;28:201–16.
32. Lichtenstein E, Glasgow RE. Smoking cessation: what have we learned over the past decade? J Consult Clin Psychol. 1992;60:518–27.
33. Schafer JL. Analysis of incomplete multivariate data. Boca Raton: Chapman & Hall/CRC; 1997.
34. Berntson GG, Bigger JT, Eckberg DL, et al. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology. 1997;34:623–48.