# ORIGINAL ARTICLE

# Short-term effects of varenicline therapy on homogeneity of heart rate, atrioventricular conduction and ventricular repolarization

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**BACKGROUND:** The effects of varenicline, an effective drug for smoking cessation, on atrioventricular and ventricular conductance remain unknown.

**OBJECTIVE:** To evaluate the effects of varenicline on heart rate, PR interval, QT interval and QT dispersion (QTd).

**METHODS:** A total of 60 smokers were prospectively enrolled in the present study. Twelve-lead electrocardiogram recordings were obtained for all subjects before and on the 15th day of drug administration. Electrocardiograms were recorded at an amplitude of 20 mm/mV and a sweep speed of 50 mm/s.

**RESULTS:** The mean (± SD) age of the volunteers was 38±10 years. Thirty-four (57%) were male. Fourteen (23%) had hypertension, eight (13%) had diabetes and six (10%) had chronic obstructive pulmonary disease. The mean heart rate was 74.7±13.3 beats/min, and mean systolic and diastolic blood pressures on admission were 122.3±14.3 mmHg and 76.5±10.2 mmHg, respectively. Heart rate, and systolic and diastolic blood pressures did not change with varenicline treatment. Varenicline treatment resulted in limited prolongation in PR interval, which approached significance (163.5±18.3 ms versus 168.2±17.9 ms; P=0.053), while RR interval (796.3±117.4 ms versus 798.3±123.7 ms; P=0.926), QT interval (384.1±17.5 ms versus 383.4±20.9 ms; P=0.852) and QTd (52.6±14.9 ms versus 52.2±14.9 ms; P=0.919) were not significantly changed.

**CONCLUSION:** Varenicline had a limited effect on atrioventricular conduction, while it had no effect on heart rate, QT interval and QTd. Further studies are needed to prove the effects of varenicline on the conduction system of the heart, especially on PR interval.

**Key Words:** *PR interval; QT interval; QT dispersion; Smoking cessation; Varenicline*

Varenicline (Champix; Pfizer Inc, USA), which acts primarily as a partial agonist at the α4β2 nicotinic acetylcholine receptor (nAChR) (1), is an effective choice for smoking cessation and is widely used. There are several studies in the literature reporting a good cardiovascular safety profile for varenicline; the drug has been well tolerated and has not been associated with increases in cardiovascular events and deaths, or with any significant effects on blood pressure and heart rate (2). However, a recent systematic review (3) and several case reports (4) have raised concerns about the cardiovascular safety of varenicline. Moreover, a recent surveillance study has reported a total of 27 cases of arrhythmia, with unexplained cardiac death in two patients (5).

Cardiac arrhythmia can cause mortality. Sinus node dysfunction, atrioventricular block and ventricular tachycardia may also result in significant morbidity or mortality. The Framingham Heart Study (6) has demonstrated that even only first-degree atrioventricular block (PR interval >200 ms) is associated with a 1.44-fold risk for all-cause mortality and a 2.9-fold risk for pacemaker implantation. Prolonged QT interval and QT interval variability between the leads (QT dispersion [QTd]) are indicators of the heterogeneity of repolarization, which is known to be a predisposing factor for ventricular arrhythmias and sudden cardiac death (7). The standard 12-lead electrocardiogram (ECG), which provides information about the QT interval, is a representation of depolarization and repolarization of the ventricular myocytes. Thus, it is assumed that the increased QTd observed in cardiac diseases with heterogeneous ventricular recovery times reflects the disparity of ventricular recovery times (8,9). The QTd is a simple, inexpensive and noninvasive method to measure underlying dispersion recovery of ventricular excitability. QTd is an electrophysiological factor and may predispose toward ventricular arrhythmia and sudden cardiac death (10).

In the current literature, the effects of varenicline on PR and QT intervals and QTd have not yet been studied. The aim of the present study was to determine the effects of varenicline on PR and QT intervals and QTd in the smoker population.

## METHODS

### Study population and protocol
A total of 60 consecutive adult smokers who were admitted to the authors' smoking cessation outpatient clinic were prospectively enrolled in the present study. All volunteers fulfilled all of the following inclusion criteria: no use of drugs that would potentially influence PR and QT intervals, and QTd; no history of ischemic heart disease, congestive heart failure, renal insufficiency, atrial fibrillation, bundle branch block or abnormal serum electrolytes; normal resting ECG; and a good-quality ECG recording to measure the PR and QT intervals. The exclusion criteria were: moderate to severe valve diseases; congenital heart defects such as atrial septal defect; atrial fibrillation and other ECG abnormalities such as prolonged PR interval, bundle branch block and systolic left ventricular dysfunction (ejection fraction <50% or left ventricular end diastolic dimension >5.5 mm); unreliable identification of the beginning of the P wave and end of the T wave in the ECG; and uncontrolled hypertension, uncontrolled diabetes, renal dysfunction or coronary artery disease. Complete medical history, physical examination findings, blood chemistry profile (sodium, potassium, magnesium, calcium, blood urea nitrogen and creatinine levels), ECG and transthoracic echocardiography findings of all volunteers were recorded. The ECGs were numbered and presented to the analyzing investigator without name and date information. Approval from the institutional ethics committee was obtained for the study. Informed consent was obtained from all participants.

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## TABLE 1
### Demographic and clinical properties of volunteers (n=60)

| Variable | |
|---|---|
| Age, years, mean ± SD | 38±10 |
| Male sex | 34 (57) |
| Body mass index, kg/m$^2$, mean ± SD | 26.1±5.1 |
| Hypertension | 14 (23) |
| Diabetes mellitus | 8 (13) |
| Alcohol addiction/consumption | 0 (0) |
| Chronic obstructive pulmonary disease | 6 (10) |
| Heart rate, beats/min, mean ± SD | 74.7±13.3 |
| Systolic blood pressure, mmHg, mean ± SD | 122.3±14.3 |
| Diastolic blood pressure, mmHg, mean ± SD | 76.5±10.2 |

*Data presented as n (%) unless otherwise indicated*

### Electrocardiographic data acquisition

A baseline 12-lead ECG was obtained for all volunteers following a 15 min resting period in a supine position, at 20 mm/mV amplitude and 50 mm/s sweep speed with standard lead positions using a commercially available machine (Cardioline Delta 60 Plus CP/I version; Remco Italy Cardioline, Italy) before varenicline therapy. Control ECGs were taken five days after the maximum drug dose (on the 15th day after the beginning of the treatment). Using a magnifying glass, PR intervals were manually measured by two cardiologists who had no information about the patients or one another. The PR interval was measured as the distance from the crest of the P wave to the crest of the QRS complex. The QT interval was measured from the onset of the QRS complex to the end of the T wave. When U waves were present, the QT interval was measured to the nadir of the trough between the T and U waves. If the end of the T wave could not be identified, the lead was not included. Three consecutive QT intervals were measured with the aid of a magnifying glass and averages were calculated for each lead. Only ECG recordings with ≥8 different analyzable leads were accepted. The QTd was determined as the difference between the maximum and minimum values of QT interval duration in different leads (11). The RR intervals were measured at surface ECG lead V1 for three consecutive cycles and the average value used. Where an interobserver difference of 10 ms in an RR interval or 20 ms in a PR, QT or Tp-e interval was found, the recordings, still coded, were reanalyzed and a consensus was reached if possible. The interobserver correlations of variation of these PR and QT intervals were <10%. ECGs were evaluated separately by two of the authors, and readings were compared when differences in interpretation were found. They were resolved by consensus.

### Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous data are reported as mean (± SD) or median. Categorical variables are summarized as percentages. A paired *t* test was used to investigate the time-dependent variables. The relationship between durations-dispersions and parametric clinical variables were assessed using Pearson correlation analysis, and the Spearman correlation coefficient was used for nonparametric variables. A two-sided P<0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 17.0 (IBM Corporation, USA) for Windows (Microsoft Corporation, USA).

### RESULTS

The mean age of the volunteers was 38±10 years, and 34 (57%) were male. Fourteen (23%) had hypertension, eight (13%) had diabetes and six (10%) had chronic obstructive pulmonary disease (COPD). The mean heart rate was 74.7±13.3 beats/min, and systolic and diastolic blood pressures on admission were 122.3±14.3 mmHg and 76.5±10.2 mmHg, respectively (Table 1). Heart rate, and systolic and
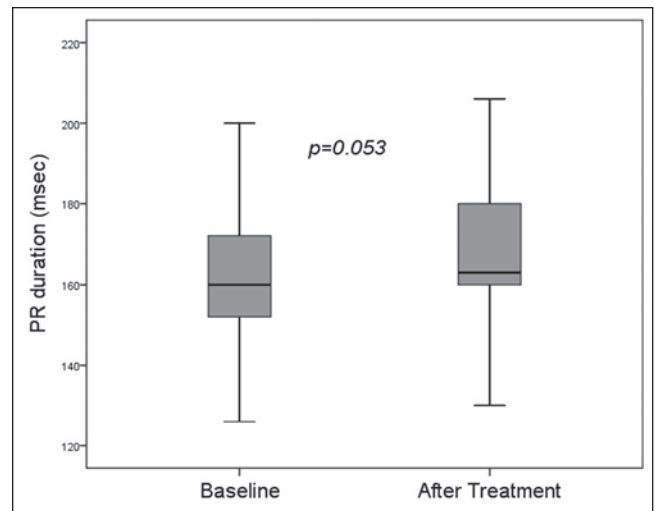


**Figure 1)** *Box-plot summarizing the comparison of baseline and postvarenicline PR intervals*

diastolic blood pressures did not change with varenicline treatment. The effects of varenicline treatment on ECG parameters were as follows: a limited prolongation in PR interval approached statistical significance (163.5±18.3 ms versus 168.2±17.9 ms; P=0.053) (Figure 1), while RR interval (796.3±117.4 ms versus 798.3±123.7 ms; P=0.926), QT interval (384.1±17.5 ms versus 383.4±20.9 ms; P=0.852) and QT dispersion (52.6±14.9 ms versus 52.2±14.9 ms; P=0.919) were unchanged (Table 2).

There was no correlation between PR prolongation and age, sex, hypertension, diabetes mellitus and COPD according to the correlation analysis (P>0.05 for all). Baseline PR interval was found to be weakly inversely correlated with PR prolongation (r=−0.381; P=0.038). Postvarenicline PR interval was strongly related to baseline PR interval (r=0.743; P<0.001), but weakly correlated with PR prolongation (r=0.353; P=0.045). No correlations were observed between postvarenicline PR interval and age, sex, hypertension, diabetes mellitus and COPD (P>0.05 for all). Postvarenicline QT interval was modestly correlated with baseline QT interval (r=0.500; P=0.005) but was not correlated with age, sex, hypertension, diabetes mellitus and COPD (P>0.05 for all), as well as postvarenicline QTd (P>0.05 for all).

### DISCUSSION

Although the use of varenicline caused a near-significant prolongation in PR interval in the present study, there were no effects on heart rate, QT interval and QT dispersion. Age, sex, hypertension, diabetes mellitus and COPD had no effect on time interval changes with varenicline administration.

Cigarette smoking is a common risk factor for cardiovascular diseases (12-14). Cardiovascular mortality has been shown to be reduced by 36% after cessation of smoking (15-17). Despite all the smoking cessation initiatives in Western society, the frequency of cigarette use has been reported to be 20%. In recent years, Turkey has won plaudits for tobacco control (18). With the recent launch of in-hospital smoking cessation initiatives for patients who had experienced a cardiovascular event, the cessation rates have been reported to have risen to 50% to 70% (19). However, the cessation rate has been reported to be only 4% to 7% for smokers who attempt to quit smoking without help (20). Therefore, medications that aid the cessation of smoking are important. There are three medical treatment options that have been shown to increase smoking cessation rates and have been approved for use: bupropion SR, varenicline and nicotine replacement (21). Varenicline has been reported to be 1.77- and 2.66-fold more effective in long-term cessation of smoking than

bupropion SR and placebo, respectively (22). However, information regarding side-effect profiles, particularly on the cardiovascular safety of varenicline, is limited (2-5).

As mentioned, varenicline is a partial agonist of the α4β2 nAChR. nAChRs increase heart rate, myocardial contractility and blood pressure, resulting in increased myocardial work and coronary vasoconstriction that reduces myocardial blood supply (23). It has been reported that varenicline affected the autonomous modulation by binding to this receptor and that the sympathomimetic cardiovascular effects of nicotine were mediated primarily by binding to α3β4 nAChR and α7 nAChR (24). Moreover, varenicline increases dopamine release and reinforcement behaviours to a lesser extent than does nicotine, suggesting that it may have a lower abuse potential than nicotine (25). However, the arrhythmogenic potential of varenicline has not been fully investigated. While single-dose varenicline has been reported to cause no change in heart rate variability in healthy smokers, it has increased the low frequency/high frequency ratio in healthy nonsmokers, which indicates increased sympathetic tonus (26). The elimination half-life of varenicline is approximately 24 h (27) and the peak concentration is reached in 3 h to 4 h after oral administration. The recommended dosage is 1 mg twice daily following a one-week titration: 0.5 mg once daily on days 1 to 3, and 0.5 mg twice daily on days 4 to 7 (28). In the present study, control ECGs were obtained five days after the maximum drug dose (on the 15th day after the beginning of treatment). While there was no change in heart rate and a limited increase in PR interval, it was clearly demonstrated that varenicline has no effect on QT interval and dispersion. Despite the autonomic system modulation by a nicotinic agonist may alter the homogeneity of ventricular repolarization (29), the lack of a significant change in QT interval and QTd after varenicline therapy was challenging in the present study.

Beta-blockers and calcium channel blockers, which are used to treat hypertension, prolong the PR interval. Moreover, several clinical conditions, including prolonged QT syndrome, cardiac arrhythmia, ischemic cardiac diseases, pulmonary disease, diabetes mellitus, uremia, and electrolyte and acid/base disorders, and the drugs used in their treatment, including antihypertensives, antidiabetics, antipsychotics, antidepressants and opioid drugs, are known to influence the QT interval (30). In our study, we excluded volunteers receiving such medications. The other variable that has a significant effect on QT is smoking. However, data regarding the effects of smoking on the QT interval and QT dispersion are conflicting. Although there are a number of studies reporting prolongation of the QT interval in smokers compared with nonsmokers (31-33), others have reported no significant differences (34), or even shorter QT intervals (35). However, because the volunteers in our study were smoking both at the beginning of the study and when the control ECGs were taken, the possible positive and negative effects of smoking on the results of the present study can be ignored. Heart rate is another variable that can affect PR and QT intervals. Changes in heart rate play a major role in variation of PR and QT intervals. Increased heart rate leads to shortening of PR and QT intervals, whereas bradycardia results in PR and QT prolongation. Therefore, the QT interval corrected for heart rate is commonly calculated. However, we did not calculate the corrected QT interval in the present study because previous studies have shown that the rate correction of parameters of repolarization dispersion is likely unnecessary and may even distort the values and diminish the predictive usefulness of QTd (36,37). In addition, due to the fact that there was no change in heart rate with the use of varenicline, the possible effects of heart rate on ECG were not observed.

**Limitations**

First, the present study was cross-sectional and did not evaluate the long-term effects of varenicline. In addition, the present study lacked ambulatory monitoring to investigate other factors such as heart rate variability. Second, patients who were at high risk for arrhythmia, including those with known heart failure, postmyocardial infarction, coronary artery disease or conduction abnormality, were excluded from

**TABLE 2**

**Electrocardiographic and clinical findings of volunteers at baseline and after varenicline therapy**

| Variable | Baseline | After treatment | P |
|---|---|---|---|
| Minimum QT interval, ms | 331.33±19.42 | 331.27±19.28 | 0.985 |
| Maximum QT interval, ms | 384.07±17.53 | 383.40±20.91 | 0.852 |
| QT dispersion, ms | 52.60±14.87 | 52.20±14.85 | 0.919 |
| Minimum PR interval, ms | 124.27±20.77 | 122.60±17.38 | 0.491 |
| Maximum PR interval, ms | 163.53±18.33 | 168.20±17.88 | 0.053 |
| RR interval, ms | 796.33±117.40 | 798.33±123.74 | 0.926 |
| Heart rate, beats/min | 74.7±13.3 | 74.3±12.8 | 0.844 |
| Systolic BP, mmHg | 122.3±14.3 | 121.6±14.1 | 0.885 |
| Diastolic BP, mmHg | 76.5±10.2 | 75.2±12.1 | 0.786 |

*Data presented as mean ± SD unless otherwise indicated. BP Blood pressure*

the study to evaluate only the effect of varenicline on the heart. Thus, our results are not representative of this group of patients. Finally, the present study included a relatively small number of cases.

**CONCLUSION**

Smoking cessation is an important component of cardiac rehabilitation. Varenicline, which is used as a smoking cessation aid, may have a limited effect on atrioventricular conduction; however, it showed no effect on heart rate, as well as on QT interval and QTd, indicators of ventricular depolarization and repolarization that are more important parameters for arrhythmia. We can conclude that varenicline is also safe for adverse effects on electrocardiographic parameters despite a borderline significant prolongation in PR interval; however, to provide certain additional information regarding this issue, further large-scale studies are needed.

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