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## ORIGINAL RESEARCH

# Arrhythmic effects of Ivabradine in patients with coronary artery disease

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### Abstract

**Objectives:** Ivabradine is the first specific heart rate-lowering agent that has completed clinical development for stable angina pectoris. The aim of the present study was to investigate the effects of ivabradine therapy on P-wave duration, dispersion and QT duration, dispersion in coronary artery disease patients.

**Methods and Results:** The study population consisted of 21 patients with CAD who have confirmed by coronary angiography previously. Written informed consent was obtained in all patients. Twelve-lead electrocardiogram was recorded for each subject at a rate of 50mm/s on admission and repeated after 1 month ivabradine therapy. QT duration, QT dispersion, maximum and minimum QT duration calculated. Maximum and minimum P wave and P wave dispersion has been calculated. Heart rate was decreased after ivabradine therapy. ( $75 \pm 15$  and  $63 \pm 10$ ,  $P=0.02$ ). There was no difference between Pmax, Pmin and Pdis values before and after treatment. QTmax value was prolonged after treatment. ( $410 \pm 43$  and  $431 \pm 14$ ,  $P=0.005$ ) but there was no difference between cQTmax value. ( $455 \pm 38$  and  $439 \pm 21$ ) There was no difference between QTdis and cQTdis values before and after treatment. ( $44 \pm 18$  &  $49 \pm 14$ ; and  $49 \pm 22$  &  $48 \pm 15$ ). QTmax was prolonged after ivabradine therapy but cQTmax, Pdis, QTdis and cQTdis were not prolonged.

**Conclusion:** There is no relationship between ivabradine therapy and increased risk of ventricular and atrial arrhythmia in coronary artery disease patient.

Heart rate is an important predictor of cardiovascular mortality. Therefore, lowering heart rate is one of the most important therapeutic approaches in the treatment of stable angina pectoris. Heart rate is determined by spontaneous electrical pacemaker activity in the sinoatrial node controlled by the I(f) current. Ivabradine is the first specific heart rate-lowering agent that has completed clinical development for stable angina pectoris. It is selective for I(f) current, lowering heart rate at concentrations that do not affect other cardiac ionic currents. Specific heart-rate lowering with ivabradine reduces myocardial oxygen demand, simultaneously improving oxygen supply. Ivabradine has no negative inotropic or lusitropic effects, preserving ventricular contractility, and does not change any major electrophysiological parameters unrelated to heart rate.<sup>1-10</sup>

P wave dispersion has been defined as the difference between maximum and minimum P wave duration. Prolonged P wave duration and increased P wave dispersion have been reported to carry increased risk for atrial fibrillation. QT dispersion has been defined as the difference between maximum and minimum QT duration.<sup>11-13</sup> Several drugs can cause prolonged QT interval, as well as prolonged QT dispersion in ECG

TABLE 1.

	Men (n=16)	Women (n=5)
Mean Age (yr)	58 (39-77)	58(38-75)
HT(n)	8 (50 %)	5 (100 %)
DM	2 (12 %)	2 (40 %)
MI	3 (18 %)	1 (20 %)
LAD lesion	8 (50 %)	4 (80 %)
CX lesion	9 (56 %)	3 (60 %)
RCA lesion	9 (56 %)	3 (40 %)

recordings. QT dispersion may be a potentially sensitive marker of increased risk of ventricular arrhythmias<sup>16</sup>

The effects of some cardiac agents, such as beta blockers, on P-wave duration and dispersion in coronary artery disease patients have been studied<sup>16</sup>. The BEAUTIFUL study demonstrated the usefulness of ivabradine in patients with stable coronary artery disease, but there is no study that evaluates the arrhythmic effects of Ivabradine.<sup>5</sup> The aim of the present study was to investigate the effects of ivabradine therapy on P-wave duration, dispersion and QT duration, dispersion in coronary artery disease patients.

## Methods

The study was approved by the local ethics committee and written informed consent was obtained from all patients. Subjects consisted of 21 patients with CAD, confirmed by coronary angiography, who had stable angina that was not amenable to invasive revascularization and coronary bypass. Patients with beta blocker or calcium channel blocker therapy, acute coronary syndrome, NYHA class II or further class heart failure, low ejection fraction, hyperthyroidism, chronic obstructive lung disease, atrio-ventricular conduction defect, electrolyte imbalance or a history of arrhythmia were not enrolled. All patients underwent echocardiographic evaluation. A twelve-lead ECG was recorded for each subject at a rate of 50mm/s on admission and repeated after 1 month ivabradine therapy. QT duration was measured in all derivations. Interval QTc was calculated by the Bazetts formula. QT dis-

TABLE 2.

	Before therapy	After therapy	<i>P</i>
P max(ms)	116±15	119±15	05.06
P min	78±13	84±12	0.091
P disp	38±13	34±14	0.189
QT max	410±43	431±14	0.005
QT min	368±43	382±35	0.083
QT disp.	44±18	49±14	0.324
QTc max	455±38	439±21	0.059
QTc min	405±38	391±23	0.162
QTc disp.	49±22	48±15	0.805
Heart rate	75±15	63±10	0.002

persion has been defined as the difference between maximum and minimum QT duration. Maximum and minimum P wave duration was measured. Paired t-test was used to compare the mean ECG values recorded before and after treatment.  $P < 0, 05$  was considered statistically significant.

## Results

Twenty one patients were studied (16 men, 5 women, mean age: 58yr). 13 patients had HT (61%), four had DM (19%), four had previous MI (19%), one had LMCA lesion, 12 had LAD lesions (57%), 12 had CX lesion (57%) and 11 had RCA lesions (52%). Angiographic and clinical characteristics of patients are shown in Table 1. Heart rate was decreased after ivabradine therapy ( $P=0.005$ ). There was correlation between angiographic variables and ECG variables after treatment. Also, there was no difference between Pmax, Pmin and Pdis values before and after treatment. (Maximum P-wave duration; basal: 116±15ms vs. after ivabradine therapy: 119±15ms, PWD; basal: 38±13ms vs. after ivabradine therapy: 34±14ms). QTmax was prolonged after treatment. (Maximum QT duration; basal: 410±43ms vs. after therapy: 431±14,  $P=0,005$ ) but there was no difference between QTc value (Basal: 455±38 ms vs. after therapy: 439±21ms). There was no difference between QTdis and QTcdis values before and after treatment. (QTdis values; basal: 44±18ms vs. after ivabradine therapy:

49±14ms, QTcd values; basal: 49±22ms vs. after ivabradine therapy: 48±15ms). The ECG of patients before and after treatment, are shown in Table 2.

## Discussion

The major findings of this study are that patients who used ivabradine therapy had prolonged QTmax while QTcmax, QT dispersion, QTc dispersion and P dispersion measures were unchanged. This study makes two observations. First, ivabradine therapy has no association with increased risk of ventricular arrhythmias due to unchanged QTc and QTc dispersion even through the prolongation of QT interval. Second, ivabradine therapy has no association with increased risk of atrial fibrillation as assessed by P wave dispersion.

Prolongation of the QT interval and QT dispersion reflects the inhomogeneity of ventricular repolarization, leading to ventricular arrhythmias. Myocardial ischemia and fibrosis, left ventricular dysfunction, neurohormonal activation, electrolyte or metabolic imbalance, and various drugs lead to prolongation of the QTc and QTc dispersion. QTc and QTc dispersion have been studied by Camm AJ et al who evaluated the effects of a single intravenous administration of ivabradine on cardiac electrophysiological parameters in patients with normal baseline electrophysiology. They demonstrated that the mean heart rate decreased with ivabradine by 12.9 beats/min at 30 min and 14.1 beats/min at 1 hr and mean QT increased but QTc showed no change from baseline.<sup>1</sup> Zhang R et al evaluated the effects of ivabradine given primarily as a heart rate-lowering agent on allograft function and cardiopulmonary performance in heart transplant recipients with permanent sinus tachycardia. They found that, after 12 weeks of ivabradine treatment, corrected QT interval was reduced to normal.<sup>2</sup> Chaitman BR et al. studied ivabradine in treating chronic angina in chronic ischemic heart disease. They found a slight increase in QT interval (<10 ms on average) at the maximum approved dose of 1,000 mg twice daily. They suggested an ECG at baseline and during

follow-up, and that the drug should not be used in patients with QT prolongation or those who are receiving QT prolonging drugs unless longer term randomized outcome data demonstrates no excess risk.<sup>3</sup> Millez P and coworkers demonstrated that there were no effects of ivabradine on PR, QRS, or QT duration in severe, post-myocardial infarction, chronic heart failure patients.<sup>4</sup> The BEAUTIFUL study demonstrated the usefulness of ivabradine in patients with stable coronary artery disease and left ventricular systolic dysfunction.<sup>5</sup> We studied patients with stable coronary artery disease but with normal ejection fraction.

Ivabradine is a heart rate-lowering agent devoid of other direct cardiovascular effects. It has been approved for the treatment of patients with stable angina pectoris. Ivabradine selectively inhibits If in sinoatrial node cells, reducing diastolic depolarization rate and heart rate.<sup>5-9</sup> In this study, heart rate lowering with ivabradine was associated with increases in QTmax but no changes were observed in measures of QTcmax and QTc dispersion. These results demonstrate that the effects of ivabradine on QT interval are solely related to bradycardia with no evidence of any effect on repolarization. QTc and QTc dispersion are crude and approximate measure of abnormality of the complete course of repolarization in reality. Despite considerable literature, QT dispersion does not have a clear role in clinical practice. Therefore, in future studies we suggest the use of new methods for assessment and quantification of repolarization abnormalities in patients using ivabradine, such as principal components analysis of the T wave, T loop descriptors, T wave alternans and T wave morphology.<sup>10-14</sup>

The maximum P-wave duration and P dispersion are indicators of interatrial conduction disorder, and inhomogeneous atrial conduction, respectively. Prolonged P wave duration and P dispersion have been reported to represent an increased risk for atrial fibrillation in patients with no underlying heart disease.<sup>15, 16</sup> Increased P max and P dispersion are also related to stable angina pectoris<sup>17</sup>, acute coronary syndromes<sup>18</sup>,

coronary slow flow phenomenon<sup>19</sup> and those undergoing coronary artery bypass surgery.<sup>20</sup> Ivabradine has been approved for treatment of patients with stable angina pectoris. In our study, P wave dispersion, indicating increased risk for atrial fibrillation, was unchanged in patients receiving ivabradine – a novel finding. We calculated P-wave measurements, manually by magnifying lens instead of computer assisted P wave calculations. However, our method has been used in previous studies.<sup>21,22</sup> This study has limitations. In particular, the study has a small. Secondly, there is a lack of diversity of underlying pathology i.e. the only criterion was CAD.

Nevertheless, we conclude that ivabradine therapy is not associated with the risk of atrial fibrillation and ventricular arrhythmias.

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