

# Relation between bradycardia dependent long QT syndrome and QT prolongation by disopyramide in humans

Hiroshi Furushima, Shinichi Niwano, Masaomi Chinushi, Kouji Ohhira, Akira Abe, Yoshifusa Aizawa

## Abstract

**Background**—Recent molecular biological investigations have identified abnormal genes in familial forms of long QT syndrome, but in bradycardia dependent acquired long QT syndrome, no such genetic abnormality has yet been identified.

**Objective**—To investigate the relation between the responses of QT interval to pacing change and to disopyramide.

**Methods**—This study included 13 patients with bradyarrhythmia who had undergone pacemaker implantation. The patients were divided into two groups: group I (n = 8), patients with QT prolongation (QT interval  $\geq$  500 ms) during bradycardia; group II (n = 5), patients without QT prolongation (QT interval < 500 ms) during bradycardia. The responses of QT interval caused by the change of pacing rate were determined and compared with the changes of the QT interval after disopyramide administration.

**Results**—The QT interval in group I was significantly longer than that in group II when the pacing rate was decreased from 110 to 50 beats/min: mean (SD) 451 (16) v 416 (17) ms at 90 beats/min (p = 0.0033), and 490 (19) v 432 (18) ms at 70 beats/min (p = 0.0002), respectively. The QT interval was prolonged significantly by disopyramide in both groups, but the change was more pronounced in group I than in group II: 78 (33) v 35 (10) ms (p < 0.05).

**Conclusions**—This study suggests that the patients showing bradycardia dependent

QT prolongation are also more markedly affected by disopyramide and that abnormal potassium channel may be the underlying mechanism.

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Keywords: bradycardia; long QT syndrome; disopyramide

In congenital long QT syndrome, recent molecular biological evidence has demonstrated abnormal genes related to potassium channel or sodium channel.<sup>1-3</sup> Torsades de pointes (TdP) is an important complication of bradyarrhythmias,<sup>4-6</sup> when it is associated with the QT prolongation but the mechanism of bradycardia induced QT prolongation is poorly understood. Whether bradycardia induced QT prolongation is caused by the abnormal potassium current remains to be determined.<sup>7-9</sup> In this study, the effect of disopyramide on the QT interval was studied in patients with bradycardia induced QT prolongation and compared with that in patients without this prolongation.

## Methods

### PATIENTS

The study included 13 patients (seven men and six women) with bradyarrhythmia (mean (SD) age 68 (14) years, range, 31 to 83). All had undergone pacemaker implantation. The diagnosis was sick sinus syndrome (n = 7) and complete atrioventricular block (n = 6). The patients were divided into two groups: eight patients (five men and three women) with QT interval  $\geq$  500 ms (group I) and five patients (two men and three women) with QT interval < 500 ms (group II) during bradycardia (38 (8), range 21 to 47 beats/min, no significant difference between groups). The two groups did not have a significant difference for any clinical background feature.

### STUDY PROTOCOL: QT INTERVAL RESPONSE TO PACING

Electrocardiograms were obtained on a six channel FX-4100 (Fukuda Denshi Inc, Japan) at a paper speed of 50 mm/s with a calibration of 10 mm/mV, and the QT interval was measured from the onset of the QRS in the sinus rhythm or from the pacing spike during pacing to the end of the T wave usually in lead II or V3-5. QTc was calculated according to Bazett's formula ( $QT_c = QT/\sqrt{RR}$ ).

The First Department of Internal Medicine, Niigata University School of Medicine, Niigata, 1-754 Asahi-machi, Niigata, 951 Japan

Correspondence to: Dr Furushima.

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Table 1 Relation between QT interval and heart rate

Patient number	QT interval (ms) at each heart rate (beats/min)			
	110	90	70	50
<b>Group I</b>				
1	420	460	500	520
2	400	440	480	—
3	420	460	500	—
4	400	440	480	—
5	420	460	500	520
6	390	420	460	480
7	440	460	480	500
8	440	470	520	550
Mean (SD)	416 (18)	451 (16)	490 (19)	—
<b>Group II</b>				
9	400	420	440	460
10	380	400	420	—
11	420	440	460	480
12	400	420	420	—
13	380	400	420	—
Mean (SD)	396 (17)	416 (17)	432 (18)	—

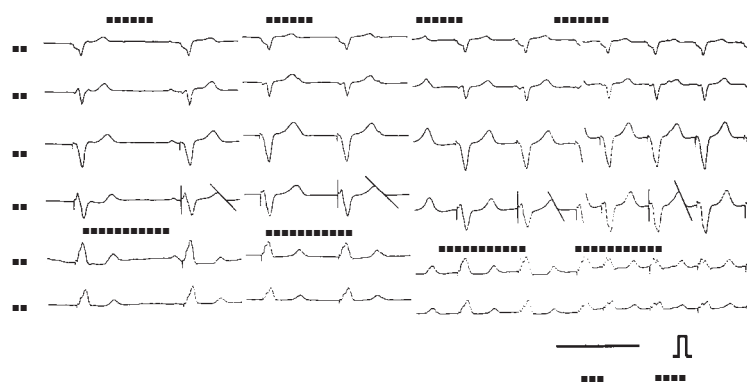


Figure 1 The QT interval responses to different pacing rates in a patient in group I. The pacing rate was decreased from 110 to 50 beats/min and the QT interval was measured, which was prolonged from 440 to 550 ms.

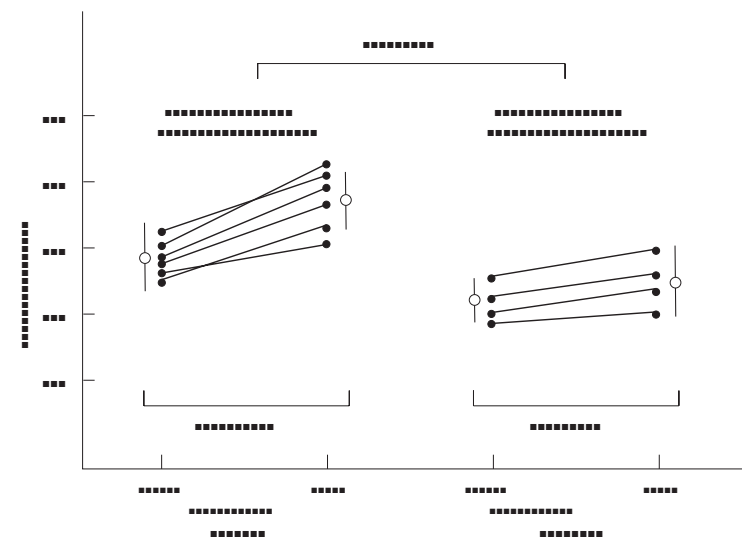


Figure 2 QT prolongation induced by disopyramide in each group. The QT interval was prolonged after disopyramide administration in both groups. The change of the QT interval induced by disopyramide was more pronounced in group I.

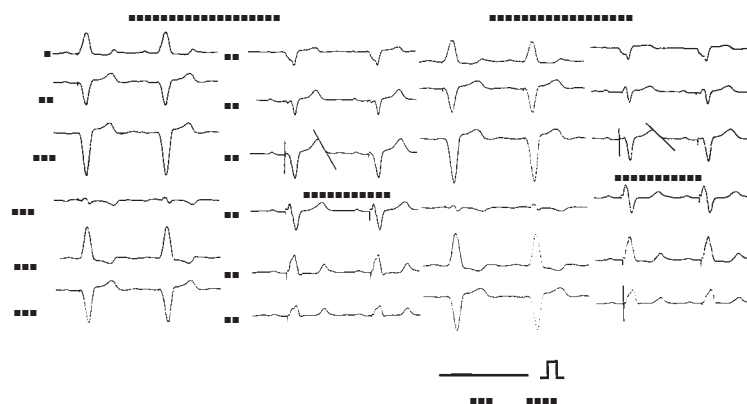


Figure 3 Change of the QT interval induced by disopyramide in patients with QT interval prolongation during bradycardia (group I). The net change of the QT interval is 90 ms.

We examined the QT interval at various heart rates and compared the intervals in group I with those in group II. Ventricular pacing at 110 beats/min was reduced in decrements of 20 beats/min to 50 beats/min. Pacing at each rate was continued for at least five minutes, and the QT interval was confirmed to be stabilised.

#### QT INTERVAL RESPONSE TO DISOPYRAMIDE

In five patients in group I and four patients in group II, disopyramide (50 mg) was given intravenously while the heart was paced at constant rate, and the QT interval was measured before and after the disopyramide administration. The responses in the two groups were compared. Blood pressure was measured during this part of the study.

#### STATISTICAL ANALYSIS

All data are expressed as mean (SD). The paired or unpaired Student's *t* test was used to compare the continuous data. A *p* value < 0.05 was considered significant.

### Results

#### PATIENT CHARACTERISTICS

No patient had organic heart disease except for one patient in group I who had cardiac sarcoidosis. The cardiac thoracic ratios were not significantly different in the two groups. No familial involvement of the QT interval could be demonstrated in either group.

#### QT INTERVAL RESPONSE TO VENTRICULAR RATE

Table 1 lists the responses of the QT interval to pacing rate. The QT intervals in group I were not significantly prolonged compared with those in group II at a pacing rate of 110 beat/min. However, the QT interval in group I was significantly prolonged compared with that in group II when the pacing rate was decreased to 70–90 beats/min, being 451 (16) *v* 416 (17) ms, respectively, at 90 beats/min (*p* = 0.0033), and 490 (19) *v* 432 (18) ms, respectively, at 70 beats/min (*p* = 0.0002). The QT interval was longer at low rates in group I than group II. Figure 1 shows a typical example of the QT interval changes in relation to heart rate in group I.

#### QT INTERVAL RESPONSE TO DISOPYRAMIDE

##### ADMINISTRATION

Figure 2 shows the responses of the QT interval to disopyramide. Before disopyramide administration the QT interval in group I (478 (29) ms) was slightly more prolonged than that in the group II (415 (34) ms) at the pacing rate of 63 (5) and 62 (6) beats/min, respectively (*p* < 0.05). The QT interval was prolonged by disopyramide administration, from 478 (29) ms to 533 (47) ms (*p* < 0.05) in group I, and from 415 (34) ms to 450 (42) ms (*p* < 0.05) in group II, and the change of the QT interval caused by disopyramide was significantly (*p* < 0.05) more pronounced in group I (78 (33) ms *v* 35 (10) ms, respectively). Figure 3 shows a representative example of the change in QT interval in a patient in group I.

#### RELATION BETWEEN THE PACING INDUCED VERSUS DISOPYRAMIDE INDUCED PROLONGATION OF THE QT INTERVAL

The changes of the QT interval provoked by the two interventions were fairly well correlated: *r* = 0.69, (*p* < 0.05).

## Discussion

Recently, genetic mutations have been identified in familial forms of long QT syndrome, and the existence was confirmed of at least three abnormal genes that encode either potassium channel<sup>6,10</sup> or sodium channel.<sup>11</sup> The defects are considered to delay the repolarisation and result in prolonged duration of the action potential and the QT interval. The mechanism of long QT syndrome, however, is still poorly understood. Recently we demonstrated that acetylcholine induced prolongation of the QT interval only in patients with long QT syndrome.<sup>12</sup>

Bradycardia is known to precipitate long QT syndrome and TdP,<sup>13-16</sup> and we sometimes observe a pronounced QT prolongation in some patients, but the mechanism of such bradycardia induced QT prolongation is not known.

Class Ia antiarrhythmic agents like quinidine, disopyramide, and procainamide have all been reported to induce long QT syndrome and TdP.<sup>7-9,17,18</sup> For quinidine and disopyramide, Jane *et al* reported a biphasic response in action potential duration: at low concentration, the QT interval is prolonged, particularly at slow rates (reverse rate dependence),<sup>19-20</sup> but it is shortened at higher drug concentration.<sup>15</sup> The QT prolongation is considered to result from the blocking effect of the potassium channel.<sup>21-23</sup>

In this study, the patients who had QT prolongation during bradycardia showed more prominent QT prolongation as heart rate decreased, as expected from the clinical findings. Furthermore, the QT interval was more markedly prolonged by disopyramide in these patients, and the changes caused to heart rate and those to disopyramide were well correlated ( $r = 0.69$ ). The mechanisms of these pronounced prolongations of QT interval at low rate and after disopyramide administration are unknown. Recently, Tao *et al*<sup>24</sup> suggested that IKr plays an important part in producing a reverse use dependence of action potential duration, but if bradycardia induced long QT syndrome is associated with abnormal IKr and if disopyramide induced QT prolongation shares the same potassium channel or not remain to be studied.

Our study shows that patients with QT interval prolongation during bradycardia display a pronounced rate dependency of the QT interval, and it seems possible to identify such patients using the class Ia agent disopyramide. Potential risk of developing TdP at slow rate might be screened by using disopyramide.

Two important limitations of this study were that the patient groups were not homogenous and the number of patients was small. However, most patients with sick sinus syndrome or atrioventricular block show normal QT interval, even at an extremely slow rate but the patients with QT interval prolongation during bradycardia seem to represent a distinct

subgroup with latent long QT syndrome. Data should be accumulated for a larger number of patients.

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