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The Effect of beta Adrenergic Stimulation on QT and QTc Interval in Syncope Children with or without Coexisting Ventricular Arrhythmias

We investigated the effect of beta-adrenergic stimulation on the heart rate and QT interval in syncope children with or without coexisting ventricular arrhythmias (VA). Of the 24 children who presented with syncope or presyncope and showed negative tilt test, 13 were classified into a group with VA and the remaining 11 without VA. The provocative test was performed in bolus infusion and continuous infusion. RR, QT, and QTc intervals on routine 12-lead surface electrocardiogram were obtained during each stage of isoproterenol infusion. In all cases, malignant ventricular arrhythmia and syncope were not induced by isoproterenol provocative test. RR and QT intervals were shortened and QTc intervals were prolonged as the isoproterenol dose was increased in both groups and methods. The QTc interval reached its peak level after the bolus injection of 1.0 μg and during the continuous infusion of 0.03 μg/kg/min. The two groups showed no significant difference in the QTc interval change according to the infusion methods. This study indicates that changes in the heart rate and QT interval by beta-adrenergic stimulation were not different according to the coexisting ventricular arrhythmias in syncope children with negative head-up tilt test.

Key Words : *Electrocardiography; Arrhythmia; Adrenergic beta-Agonists; Isoproterenol; Syncope; Child*

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INTRODUCTION

In children and adolescents, syncope is a common problem. It has been reported that children with orthostatic positive neurocardiogenic syncope showed a different QT response to beta-adrenergic stimulation of isoproterenol (1). Autonomic dysfunction has been postulated as a possible underlying mechanism for syncopal episodes; cardiac and peripheral vascular autonomic control appeared to play a role (2-4).

Among the children who presented with syncope or presyncope, some showed ventricular arrhythmia on surface electrocardiogram or 24 Holter monitoring without positive findings on head-up tilt test. In those cases, it is important to define whether ventricular arrhythmias can become malignant and play a crucial role in the genesis of syncope or whether these ventricular arrhythmias are incidental findings. The variations in QT interval duration have been advocated as a marker of arrhythmogenicity, which is based on the evidence that increased heterogeneity of repolarization provides a substrate for malignant ventricular arrhythmias (5, 6). Therefore, the assessment of QT interval may help us predict the risk of ventricular arrhythmia.

In this study, we investigated the effect of beta-adrenergic stimulation on the heart rate and QT interval in children with syncope or presyncope. The purpose of this study was to examine whether there are different changes in response to isoproterenol between syncopal children with and without ventricular arrhythmias.

MATERIALS AND METHODS

After excluding the patients with a typical history of neurally mediated syncope or presyncope with positive head-up tilt test, 24 patients were enrolled in this study. The study was done primarily to evaluate the cause of syncope or presyncope. In all of these children, structural cardiac abnormalities were excluded by physical examination and noninvasive studies including echocardiography. The analyses of electrocardiograms at the basal state and during the provocative state with isoproterenol were performed to define the electrophysiological clues to the ventricular arrhythmia or syncope. Based on the presence of ventricular arrhythmias on ECG or 24-hr Holter monitoring, 13 children with ventricular arrhythmias were classified into the ventricular arrhythmia (VA) group, and the remaining 11 without ventricular arrhythmias into the syncope only (Syn) group. The VA group included children with significant ventricular arrhythmias (frequent monomorphic ventricular extrasystole; polymorphic ventricular arrhythmia; not suppressible during exercise test) and with a vague history of neurally mediated syncope. The Syn group included children with a vague history of neurally mediated syncope and with

negative head up tilt test. The average age of the study subjects at the time of the study was 127 months (range 41-197 months). They consisted of 15 males and 9 females.

The VA group consisted of 8 males and 5 females with an average age of 99±37 months (range, 41-161 months). Polymorphic ventricular extrasystole was noted in 3 cases and nonsustained monomorphic ventricular tachycardia in 2 cases. The Syn group consisted of 7 males and 4 females with an average age of 157±34 months (range, 82-196 months). Each subject did not have any evidence of congenital long QT syndrome or TU complex abnormalities. In all of these children, head-up tilt test was performed without inducing syncope or near syncope during the test.

We analyzed 12-lead electrocardiograms (ECG), which were obtained at the basal resting period and during the infusion of isoproterenol. The provocative test started with a bolus infusion of isoproterenol at a dose of 0.25 μg; the isoproterenol dose was increased to 0.5 μg and then to 1.0 μg five minutes after the preceding bolus infusion. ECG was recorded at 30 sec, 60 sec, 90 sec, 2 min, 3 min, and 5 min after each bolus infusion. The continuous infusion of isoproterenol was done 20 min after the completion of the bolus test. The test was performed at a dose of 0.01 μg/kg/min for 5 min, and then the dose was increased up to 0.04 μg/kg/min by an increment of 0.01 μg while obtaining the ECG at 30 sec, 60 sec, 90 sec, 2 min, 3 min, and 5 min. In all cases, malignant ventricular arrhythmia or syncope was not induced by isoproterenol provocative test.

The standard 12-lead ECG recordings were obtained at a paper speed of 50 mm/sec and a scale of 1 mV/10 mm. QT interval was measured from the lead II using calipers when the RR interval was maximally shortened at each stage of isoproterenol infusion. The measurements of QT were taken and averaged from at least three consecutive beats after each dose of isoproterenol at the point corresponding to the maximum heart rate effect. QT interval was defined as the interval between the beginning of QRS complex and the end of the T wave. The offset of the T wave was defined as the intersections of the isoelectric line and the tangent of the maximal slope on the down limbs of the T wave. Bazett's formula was used to obtain corrected QT intervals.

The data are expressed as mean plus standard deviation. The data were analyzed using the analysis of variance (ANOVA) for repeated measures. A value of $p<0.05$ was considered the limit for significance.

RESULTS

RR interval

The heart rate (RR interval) reached its peak level at 60-90 sec after bolus infusion and at 3-5 min during continuous infusion of isoproterenol (Fig. 1)

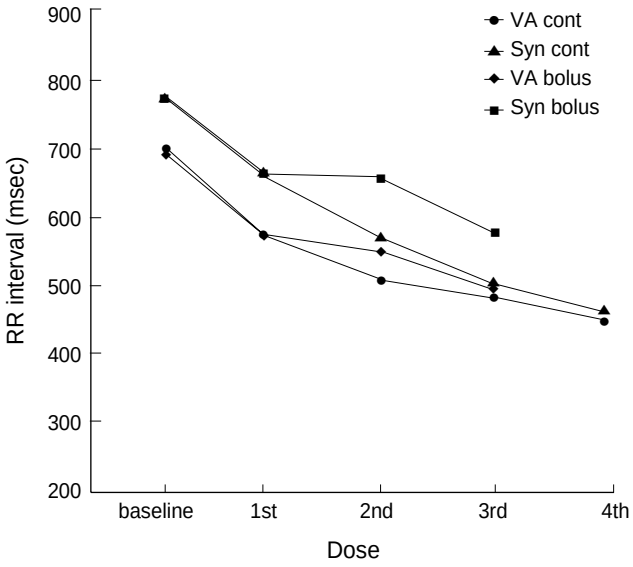

Fig. 1. The RR intervals in the VA group were shorter than those in the Syn group ($p>0.05$). The RR intervals are shortened as the isoproterenol dose is increased in both groups and methods ($p<0.05$). In bolus infusion, the first dose makes a greater change than the later doses ($p<0.05$). The two groups show no significant difference. VA, ventricular arrhythmia group; Syn, syncope only group; bolus, bolus infusion; cont, continuous infusion.

The baseline RR interval was 693±138 msec (range, 500-960 msec) in the VA group and 774±157 msec (range, 570-1,020 msec) in the Syn group.

At the bolus infusion of isoproterenol, the RR interval was shortened as the dose increased; 574±117, 543±110, and 496±106 msec at 0.25, 0.5, and 1.0 μg in the VA group and 639±103, 628±110, and 579±97 msec, respectively, in the Syn group.

During the continuous infusion, the RR interval was shortened; 574±90, 513±80, 480±63, and 436±54 msec at 0.01, 0.02, 0.03, and 0.04 μg/kg/min in the VA group and 640±119, 566±111, 515±84, and 460±60 msec, respectively, in the Syn group.

The RR intervals in the VA group were shorter than those in the Syn group, although the difference was statistically insignificant at any dose including the baseline. The RR intervals were shortened as the isoproterenol dose increased in both groups and methods. In bolus infusion, the first dose made a greater change in RR interval than the later doses. During continuous infusion, the amount of decrement of RR interval in continuous infusion decreased gradually. When the data from the two groups were compared, there was no significant difference in the change of RR interval in either methods of isoproterenol infusion.

QT interval

The baseline QT interval was 348±37 msec (range, 280-

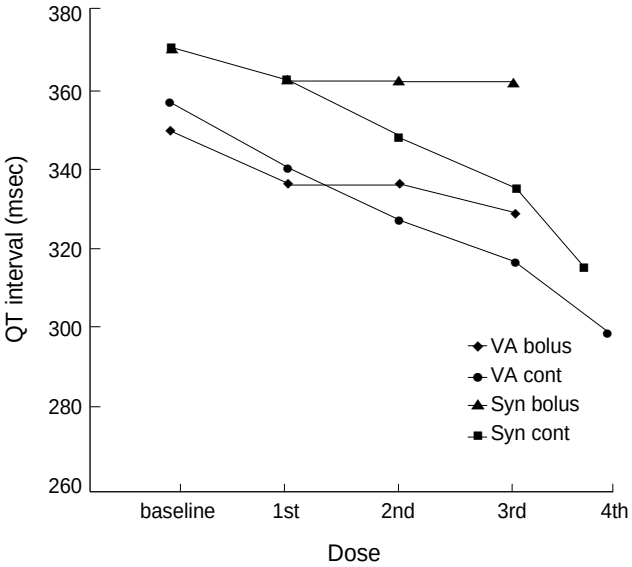

Fig. 2. The effect of isoproterenol on QT intervals. The QT interval is shortened gradually according to the increasing dose of isoproterenol in both groups and methods. The change of QT interval during continuous infusion shows a steeper decrease than in bolus infusion. The QT interval in the Syn group is longer than in the VA group by both methods (p<0.05). There is no significant difference in the change of RR interval in either methods of isoproterenol infusion between two groups (p>0.05). VA, ventricular arrhythmia group; Syn, syncope only group; bolus, bolus infusion; cont, continuous infusion.

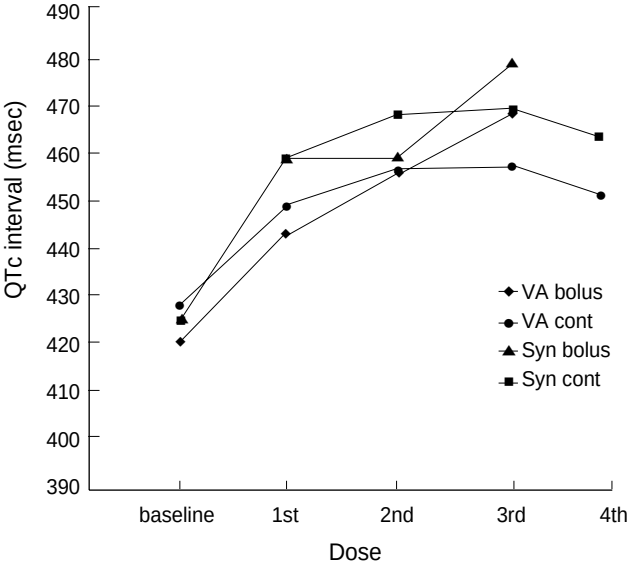

Fig. 3. The QTc interval is prolonged significantly as the dose increased in both methods (p<0.05). QTc interval reaches its peak level at the bolus dose of 1.0 μg and at the continuous dose of 0.03 (μg/kg/min. The two groups show no significant difference in the change of QTc interval. VA, ventricular arrhythmia group; Syn, syncope only group; bolus, bolus infusion; cont, continuous infusion.

420 msec) in the VA group and 370±28 msec (range, 320-400 msec) in the Syn group. QT intervals were measured after each dose of isoproterenol at the point corresponding to the maximum heart rate effect, that is, at the shortest RR intervals after each dose (Fig. 2).

After the bolus infusion of isoproterenol, the QT interval was shortened with the increase of dose; 335±46, 334±43, and 327±46 msec at 0.25, 0.5, 1.0 μg in the VA group, 363±23, 361±22, and 361±21 msec, respectively, in the Syn group.

During the continuous infusion, the QT interval was shortened gradually according to the increasing dose of isoproterenol in both groups; 340±33, 327±39, 317±38, 298±33 msec at 0.01, 0.02, 0.03, and 0.04 μg/kg/min in the VA group and 363±28, 349±27, 335±31, and 314±29 msec, respectively, in the Syn group.

The QT interval was shortened significantly in response to the increase of isoproterenol in both methods. However, the changes of QT interval after isoproterenol infusion were somewhat different by the method of infusion. Similar to the RR interval change after the bolus infusion, a greater or greatest change of QT interval appeared at the initial dose but the change was somewhat smaller at the later doses. The change of QT interval during continuous infusion showed a steeper decrease than in bolus infusion. The QT interval in the Syn group was longer than in the VA group by both methods (p<0.05). However, when the data from the two groups were compared, there was no significant difference in the change of QT interval in either methods of isoproterenol infusion.

QTc interval

The baseline QTc interval in the VA group was 420±27 msec (range, 396-429), and 423±33 msec (range, 396-462 msec) in the Syn group. QTc intervals were calculated using the Bazett's formula (Fig. 3).

At the bolus infusion of isoproterenol, the QTc interval was prolonged with the increase of dose; 444±27, 456±29, 467±33 msec at 0.25, 0.5, 1.0 μg in the VA group and 458±36, 460±36, and 479±35 msec, respectively, in the Syn group.

During the continuous infusion, the QTc interval was lengthened; 449±15, 456±27, 457±34, and 451±26 msec at 0.01, 0.02, 0.03, and 0.04 μg/kg/min in the VA group and 458±30, 467±32, 469±27, and 464±24 msec, respectively, in the Syn group.

The QTc interval was prolonged significantly as the dose of isoproterenol increased in both methods. In the bolus infusion, the QTc interval reached its peak level at the highest bolus dose of 1.0 μg and at a dose of 0.03 μg/kg/min of continuous infusion. In each stage of the two methods, there was no significant difference in the change of QTc interval between VA and Syn groups.

DISCUSSION

In this study, isoproterenol accelerated the heart rate, shortened the QT interval, and prolonged the QTc interval in both groups of the children. However, there was no significant difference in the change of RR and QT intervals whether ventricular arrhythmia was associated or not.

Children with neurocardiogenic syncope, proven by a positive head-up tilt test, have been shown to have beta-adrenergic hypersensitivity (2). Children with orthostatic positive neurocardiogenic syncope showed a significantly larger QT interval increment than the negative group after bolus injection of isoproterenol (1, 4). This supports the theory that altered beta-adrenergic sensitivity exists in children with neurocardiogenic syncope. In syncope patients who showed negative findings on head-up tilt test, QT interval was reportedly not prolonged by beta stimulation, and autonomic dysfunction such as beta-adrenergic hypersensitivity may not play a major role in syncope (1). Our results showed insignificant changes of QT interval in children with tilt negative syncope. Even though we did not compare the QT interval change between the tilt-positive and tilt-negative groups and thus cannot ascribe the syncope in these children to neurocardiogenic syncope, our results seemed to be concordant with previous reports.

If a child with complex ventricular arrhythmia or ventricular arrhythmia not suppressible during exercise suffers from syncope, it is very likely that ventricular arrhythmia is regarded as a cause of syncope particularly if the result of head-up tilt test is negative. We proposed that ventricular arrhythmia might be due to repolarization abnormality if related to syncopal episode, and isoproterenol could provoke the covert repolarization abnormality. We found that in some children, the later part of the TU complex became prominent after the infusion of isoproterenol without TU prolongation and was associated with ventricular arrhythmia. This finding might imply increased after-depolarization by isoproterenol. However, it needs further investigation.

Developmental imbalance in cardiac sympathetic innervation may predispose to ventricular fibrillation and may be associated with temporary prolongation of the QT interval (7). It is very important to understand the response of repolarization to sympathetic stimulation in children, which could be helpful for preventing life-threatening events caused by ventricular arrhythmias. Since the hearts of children continue to develop to maturity, we should not apply data from adults to children. In children, however, few data are available on the change of ventricular repolarization induced by beta-adrenergic stimulation (1, 2, 8, 9).

Assessment of repolarization change may help us predict the risk of ventricular arrhythmia and to guess the mechanism of syncope induced by ventricular arrhythmia. Beta-adrenergic stimulation increases the heart rate and shortens the QT interval in normal people (10). Abildskov showed in dogs that isoproterenol prolonged the QT interval when given as a bolus, but shortened it when given by continuous infusion (11). However, our results demonstrated a similar effect on QT interval when isoproterenol was given by bolus injection or continuous infusion. This may indicate that there are differences between species (human and dog) and/or specific diseases. Further study with isoproterenol is needed to elucidate the underlying mechanism.

Previous reports on the effect of alterations of the heart rate on the QT interval in adults have shown conflicting results (12, 13). In children and adolescents, the heart rate directly influences QT and QTc intervals on beta-adrenergic stimulation and atrial pacing. The QT is shortened, but QTc is prolonged. Reliance on the QTc alone could lead to an erroneous diagnosis of long QT syndrome. After beta-adrenergic stimulation, there is a far greater change in the denominator (RR) than in the numerator (QT) if one uses the Bazett's formula, and this leads to overcorrection that produces a spuriously high value. This could potentially lead to a false diagnosis of abnormal QT syndrome in these patients (14). In this study, because the mean age at the time of the study in the VA group was younger than that in the syncope only (Syn) group ($p<0.05$), RR and QT intervals in the VA group were shorter than in the Syn group ($p<0.05$). The continuous infusion of isoproterenol was found to be more effective than the bolus infusion in increasing the heart rate and QT interval. In the continuous infusion of isoproterenol, whereas RR and QT intervals continued to get shorter inversely with the increase of the isoproterenol dose, the QTc interval reached its peak level at the dose of 0.03 μg/kg/min. These data probably have resulted from the overcorrection using the Bazett's formula. In bolus infusion, the heart rate and QT interval changed less effectively on the second and third doses. But the QTc curve showed an increasing pattern according to the dose increment of isoproterenol because the change of RR interval (denominator) had some greater interval change than the QT interval (numerator). The two groups (VA and Syn) showed no significant difference in response to isoproterenol in either methods. However, the two methods of infusion of isoproterenol showed a different pattern. Because the dose of isoproterenol in bolus infusion is not based on the body weight, the effective drug level may not be achieved. Also the fluctuation of drug concentration in serum may contribute to the different patterns in both infusion methods. The ventricular muscle may need persistent and prolonged level of stimulation in order to change the repolarization homogeneity. This may suggest that ventricular repolarization inhomogeneity could be disclosed when enough dose of beta-adrenergic stimulation is given to a child with a normal heart. In children with normal heart, ventricular arrhythmia may not be associated with ventricular inhomogeneity unlike myocardial infarction. Although the abnormal QT interval change was not induced by beta stimulation, ventricular inhomogeneity and/or autonomic dysfunction may not be excluded

in the arrhythmogenesis.

In conclusion, beta-adrenergic stimulation may not be helpful for investigating the etiologic mechanism in syncope children who have negative tilt test with or without coexisting ventricular arrhythmia. Autonomic dysfunction and ventricular repolarization inhomogeneity are less likely to be involved in genesis of syncope.

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