

## Increased QT dispersion in breath-holding spells

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**Aim:** Breath-holding spells are common in infancy and early childhood, and patients are frequently referred to paediatric cardiology clinics for exclusion of heart disease. Recent data reveal subsequent development of epilepsy and neurocardiogenic syncope. Autonomic dysregulation and increased vagal stimulation leading to cardiac arrest and cerebral ischaemia is considered as the cause. Iron deficiency anaemia may be associated with these spells. We studied QT dispersion for the assessment of ventricular repolarization in these patients. **Methods:** The study group consisted of 19 girls and 24 boys between 3 and 108 mo of age (mean  $\pm$  SD =  $22.7 \pm 17.7$  mo); and the control group consisted of 13 girls and 12 boys between 3 and 57 mo of age (mean  $\pm$  SD =  $22.9 \pm 15.1$  mo). QT interval was measured; corrected QT interval (QTc), QT dispersion (QTd) and QTc dispersion (QTcd) were calculated from 12-lead surface electrocardiograms of the patients and the control group. **Results:** There was no statistically significant difference in terms of QT and QTc intervals between patient and control groups, while QTd and QTcd values were significantly increased in patients with breath-holding spells compared to the healthy children. QT dispersion was  $59.5 \pm 35.9$  ms and  $44.8 \pm 11.9$  ms, respectively, in patients and controls ( $p < 0.05$ ). QTc dispersion was  $102.1 \pm 41.9$  ms and  $79.6 \pm 24.6$  ms, respectively ( $p < 0.01$ ). The presence of iron deficiency did not effect the QT and QTc dispersion.

**Conclusion:** QT dispersion is increased in patients with breath-holding spells, and this finding justifies further investigation for rhythm abnormalities and autonomic dysfunction in this patient group.

**Key words:** Breath-holding spell, dysrhythmia, QT dispersion, syncope

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**Abbreviations:** QTc: Corrected QT; QTd: QT dispersion; QTcd: Corrected QT dispersion; ECG: electrocardiography; EEG: electroencephalography; SD: standard deviation; Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume

Breath-holding spell is a frequently observed clinical entity in infancy and early childhood. Affected children are usually referred to paediatric cardiology and neurology clinics for exclusion of heart disease or epileptic seizures (1). The diagnosis is possible by observation of typical attacks following minor trauma or emotional stress. The attacks are characterized by a crying period, followed by a noiseless state of expiration accompanied by colour change in the skin as paleness or cyanosis, and finally loss of consciousness and postural tone. Convulsive movements may be seen in severe attacks following the crying period (2, 3). Two types are defined as pallid and cyanotic based on the colour change during the spells. Some children may have mixed type attacks. Although the aetiology is not known, autonomic dysfunction and increased vagal tonus leading to cardiac arrest and cerebral anoxia are

considered to play a role (4). Previously, these attacks were considered as benign and they were thought to resolve spontaneously with maturation of the autonomic nervous system; however, recent prospective studies have shown presence of patients with syncopal attacks later in life (2). Long QT syndromes and paroxysmal rhythm abnormalities must be considered in the differential diagnosis of these attacks (2). An association with iron deficiency anaemia is reported (5).

QT dispersion is a simple method which is helpful for non-invasive assessment of the heterogeneity of repolarization within the ventricular myocardium using the surface electrocardiogram. Increased QT dispersion has been found to indicate an increased risk of dysrhythmia and sudden death in various disease states including cardiomyopathies, mitral valve prolapse, ischaemic heart disease and renal failure (6, 7). QT dispersion is also found to be increased in children with ion channel defects causing ventricular dysrhythmia and long QT syndrome (8). In this study, we studied QT dispersion of the children with breath-holding spells and searched for abnormal ventricular repolarization in this patient group.

## Materials and methods

The study was conducted between January 1999 and December 2002, and the study group included patients referred to the paediatric cardiology and pediatric neurology clinics of Marmara University Hospital due to cyanotic attacks and/or fainting, and diagnosed to have breath-holding spells by observation of the typical attacks during examination or by obtaining the typical history. These were patients with moderate to severe attacks referred for cardiac or neurological consultation. Oral consent of the children's parents was obtained before the study. The study protocol was approved by the ethical committee of our hospital. Both a paediatric cardiologist and a paediatric neurologist had evaluated the patients, and any cardiac or neurological disease was excluded. Chest roentgenogram, 12-lead electrocardiography (ECG), echocardiography and electroencephalography (EEG) were performed for exclusion of organic disease. In order to study the relation of breath-holding spells with iron deficiency anaemia, complete blood count and serum ferritin levels were studied in all patients. The control group consisted of the healthy children in the same age group followed-up in our healthy child clinics during visits for routine check-up or vaccination. 12-lead electrocardiograms were obtained in the control group.

The 12-lead surface electrocardiograms of all the patients and the control group were obtained using a single channel Nihon-Kohden electrocardiography machine. The measurements were performed by hand, by a single observer. The heart rate, RR interval, RR variability, PR interval, amplitude and duration of P wave, QRS interval, QRS axis, and QT interval were measured, and corrected QT (QTc), QT dispersion (QTd), QTc dispersion (QTcd) were calculated from all the electrocardiograms.

The QT interval was accepted as the interval between the beginning of the QRS complex and the end of the T wave. We accepted the end of the T wave as the point the wave returns to the isoelectric line. In the presence of the U wave, the nadir of the T wave was identified as the termination of the T wave. The Bazett formula was used for calculation of QTc (9). At least three QT intervals and QTc intervals were calculated in each derivation, and the QT dispersion was calculated as the difference between the longest QT interval in any derivation and the shortest QT interval in any derivation. QTc dispersion was also calculated in a similar way by subtracting the shortest QTc from the longest QTc in any derivation.

According to their haemoglobin, haematocrit, mean corpuscular volume and ferritin levels, the patient group was divided into two groups. Haemoglobin, haematocrit and serum ferritin levels below the reference values (10) according to the age of the child were considered as iron deficiency. The first group included patients with iron deficiency and the second group included patients

without iron deficiency. The differences in terms of QT, QTc, QTd and QTcd were also studied between these two groups. In addition, QT, QTc, QTd and QTcd values were compared between the patients with pallid or mixed spells and the patients with cyanotic spells.

The statistical difference for all the ECG parameters was investigated using the unpaired Student's *t*-test and Mann-Whitney U-test.

## Results

The patient group consisted of 43 children (24 boys and 19 girls) between the ages of 3 and 108 mo (mean  $\pm$  SD =  $22.7 \pm 17.7$ , median = 18 mo); the control group consisted of 25 healthy children (12 boys and 13 girls) between the ages of 3 and 57 mo (mean  $\pm$  SD =  $22.9 \pm 15.1$ , median = 18 mo). There was no statistically significant difference in terms of age and gender between the two groups. The patients had been suffering from these attacks for  $12.2 \pm 15.8$  mo. Eight of the patients had pallid spells, while four of them had mixed and the remainder (32 patients) cyanotic-type spells.

During the haematological evaluation of the patients, 16 patients had low haemoglobin (Hb) values and 20 patients had low haematocrit (Hct) values compared to normal reference values (10). In addition, four patients had decreased mean corpuscular volume (MCV), and six patients had low levels of serum ferritin despite normal Hb and Hct values. According to their Hb, Hct, MCV and ferritin levels, 28 patients were decided to have iron deficiency with or without anaemia. A summary of the haematological findings is given in Table 1.

There was no statistical difference in terms of the electrocardiographic parameters such as heart rate, RR interval, PR interval, QRS axis and duration between the patients and the control group. The difference between the two groups regarding the QT and QTc intervals was not statistically significant either. On the other hand, QT dispersion and QTc dispersion were significantly increased in patients with breath-holding spells compared to the healthy children ( $p < 0.05$  and  $p < 0.01$ , respectively). The electrocardiographic par-

Table 1. Haematological parameters in patients with breath-holding spells.

<i>n</i> = 43	Mean $\pm$ SD	Range
Age (mo)	$22.8 \pm 17.7$	(3–108)
Haemoglobin (g/dl)	$10.6 \pm 1.1$	(7.4–12.1)
Haematocrit (%)	$32.3 \pm 2.9$	(25.4–35.8)
MCV ( $\mu$ l)	$73.2 \pm 7.3$	(58.4–85.5)
Ferritin (g)	$21.3 \pm 27.7$	(1.5–124.9)

SD: standard deviation.

Table 2. Electrocardiographic parameters compared between patients with breath-holding spells and the control group.

	Breath-holding spell group	Control group	<i>p</i> -value
<i>n</i>	43	25	
Heart rate (bpm)	126.6 ± 24.9	120.1 ± 23.0	>0.05
RR (ms)	500 ± 111.4	502.9 ± 101.1	>0.05
PR (s)	0.1 ± 0.02	0.1 ± 0.01	>0.05
QRS (s)	0.068 ± 0.01	0.065 ± 0.09	>0.05
QT interval (ms)	285.6 ± 29.7	287.8 ± 23.8	>0.05
QTc (ms)	412.7 ± 24.2	403.3 ± 20.1	>0.05
QT dispersion (ms)	59.5 ± 35.9	44.8 ± 11.9	<0.05
QTc dispersion (ms)	102.1 ± 41.9	79.6 ± 24.6	<0.05

QTc: corrected QT; QTd: QT dispersion; QTcd: QTc dispersion.

ameters in patients and the control group are given in Table 2.

When we compared the patients with iron deficiency and without iron deficiency, there was no statistically significant difference in terms of QT, QTc, QTd and QTcd between the two groups, despite slightly higher QTd and QTcd values in the patients without iron deficiency. The ECG parameters of the patients with and without iron deficiency are shown in Table 3.

In comparison of the patients with cyanotic attacks to the patients with pallid or mixed attacks, there was no difference in terms of QT and QTc values. QT dispersion was increased in the pallid/mixed group compared to the cyanotic group; however, this difference did not reach a statistically significant level. On the other hand, dispersion of corrected QT values was significantly higher in patients with pallid/mixed attacks compared to the patients with cyanotic attacks. The electrocardiographic values of the patients with pallid/mixed spells and cyanotic spells are shown in the Table 4.

## Discussion

Breath-holding spell is an involuntary, non-volitional, reflexic, non-epileptic phenomenon of childhood. Incidence is reported to be between 0.1% and 4.6% (2). When simple spells in a healthy-child population are included, the incidence may be as high as 27% (2). The attacks usually begin during the first 6 to 12 mo of life and resolve at 4 y of age; although rare cases lasting until 7 y old are also present (1, 2). A familial penetrance is known, and autosomal-dominant inheritance is suggested (11). Children with breath-holding spells are frequently mislabelled as having behavioral disorder rather than a medical problem. Ultimately, the personality of children with breath-holding spells and their mothers was not found to differ from other children. However, the mothers of the patients with breath-holding spells are under a greater degree of emotional stress (13, 14).

Iron deficiency is common in patients with breath-holding spells and is thought to play a role in the

pathogenesis (5, 15). Mocan et al. (5) have found iron deficiency anaemia in 63 of 91 patients with breath-holding spells, and 84% of them responded to iron treatment. We found iron deficiency in 65% of our patients, which is consistent with previous reports, but this is a higher incidence than the normal population in our country, in which incidence has been reported to be about 20–40% in this particular age group (16). The mechanism—how iron deficiency causes the attacks—is not clear. Iron is thought to play a role in catecholamine metabolism and neurotransmitter function. The decreased oxygen-carrying capacity due to iron deficiency anaemia and decreased cerebral oxygenation is another suggested mechanism (5, 14). It can be speculated that myocardial oxygenation may also be affected in a similar way, causing increased QT dispersion. However, we could not find any significant difference between patients with iron deficiency and patients without iron deficiency in our study. Increased QT dispersion has been found in patients with protein-energy malnutrition (17). However, no study concerning the ventricular repolarization in iron deficiency is found in our literature survey. Even if there is a relation between these two situations, it is difficult to explain the breath-holding spells in patients without iron deficiency. Although statistically not significant, the average heart rate of the children without iron deficiency was higher than the patients with iron deficiency, although tachycardia due to anaemia was the expected finding. However, the ages of the patients without iron deficiency were also slightly younger than the others. An inaccuracy in the evaluation of QT dispersion due to this difference is unlikely, since QT and QTc dispersion are not dependent on heart rate, while QT interval is dependent on heart rate.

QT dispersion is an easy and non-invasive method for assessment of the risk for serious ventricular arrhythmia and sudden cardiac death. Increased QT dispersion indicates non-homogeneous ventricular repolarization within the myocardium which causes the rhythm abnormalities (7). Increased QT dispersion has been demonstrated to be related to increased risk of arrhythmia and sudden death in various patient groups, such as dilated and hypertrophic cardiomyopathy,

Table 3. Electrocardiographic parameters compared between patients with and without iron deficiency

	Iron deficiency (+)	Iron deficiency (–)	<i>p</i> -value
<i>n</i>	28	15	
Age (mo)	24.64 ± 20.7	19.30 ± 9.82	>0.05
Heart rate (bpm)	124.5 ± 22.3	135.7 ± 26.4	>0.05
QT interval (ms)	288.0 ± 28.6	281.0 ± 32.1	>0.05
QTc (ms)	413.2 ± 22.6	411.9 ± 27.8	>0.05
QT dispersion (ms)	52.9 ± 19.0	72 ± 53.9	>0.05
QTcd dispersion (ms)	97.5 ± 26.8	110.5 ± 61.3	>0.05

QTc: corrected QT; QTd: QT dispersion; QTcd: QTc dispersion.

ischaemic myocardial disease and long QT syndrome; and this increase has a prognostic value (16). QT dispersion reflects the difference of the durations of action potentials in different localizations within the myocardium. The region with long repolarization time is resistant to electrical conduction and provides a substrate for re-entry (7). To our knowledge, this is the first study evaluating QT dispersion in patients with breath-holding spells.

In the adult population, normal values of QT dispersion range between 25 and 50 ms; the highest values are found in patients with long QT syndrome and may be as high as 150–200 ms. QT dispersion over 80–90 ms is accepted to indicate a high risk for dysrhythmia (12). There are still problems about the standardization and reproducibility of QT dispersion in childhood. Vialle et al. (18) have studied normal values of QT dispersion in paediatric patients. Our QTd values, both in the patients with breath-holding spells and in the control group, are slightly higher than their values. However, inter-observer variability is high in measurement of QT dispersion. Another issue is the difficulty in correction of the QT interval according to heart rate. The Bazett formula is not actually ideal for correction in spite of its common use. Furthermore, in the presence of respiratory sinus arrhythmia, calculation of corrected QT values may cause significant variations. Tutar et al. (19) did not recommend using corrected QT dispersion in childhood. Since respiratory sinus arrhythmia may be more prominent in patients with breath-holding spells, differences in corrected values may be expected. In our patients, QT dispersion ranged between 20 and 220 ms (mean = 59.53 ± 35.85 ms) and QTc dispersion ranged between 28 and 250 ms (mean = 102.1 ± 41.9). There

was a wide variation in the values, and QT and QTc dispersion in six and 32 patients, respectively, were over reported critical values. Additionally, the mean values were significantly higher than our age-matched control group. Even if this may not be an indication of increased risk for dysrhythmia, further investigation is needed in order to clarify the aetiology of abnormal ventricular repolarization in this patient group.

The incidence of arrhythmia and sudden death was not studied extensively in patients with breath-holding spells. On the other hand, respiratory sinus arrhythmia was found to be more common in pallid spells (12). In addition, in patients with breath-holding spells, severe bradycardia and asystole may occur and even permanent pacemaker implantation may be required (21).

Autonomic nervous system dysregulation is thought to be the primary abnormality in the pathophysiology of breath-holding spells. These children have an exaggerated oculocardiac reflex. Increased parasympathetic tone and decreased sympathetic activity may prolong the QTc interval. However, its effects on QT dispersion are controversial (6). Autonomic dysfunction is found to affect QT dispersion in diabetic patients and patients with primary autonomic disorders (22, 23). The reason for increased QT and QTc dispersion in breath-holding spells may be this abnormal autonomic nervous system function. On the other hand, since there is no increase in QT and QTc values, it is not easy to attribute increased QT dispersion to autonomic dysfunction. Cyanotic attacks are mediated by hypersympathetic effects, and pallid spells are mediated by hyperparasympathetic autonomic effects. Both sympathetic and parasympathetic stimulation may affect QT interval and QT dispersion (24, 25). Our data also show a difference in terms of QTc dispersion between the two groups. QT dispersion was increased in patients with pallid/mixed attacks compared to patients with cyanotic attacks. This finding may have clinical importance and may indicate a more serious autonomic dysfunction. The relation of this finding with rhythm abnormalities needs to be clarified.

There is increasing knowledge about ion channel disorders causing paroxysmal symptoms in various systems due to impaired electrical activity. These findings have provided a new insight to many disease states which were previously defined as idiopathic or

Table 4. Electrocardiographic parameters compared between the patients with cyanotic spells and pallid or mixed-type spells.

Type of spell	Pallid/mixed	Cyanotic	Level of significance
<i>n</i>	10	33	
QT (ms)	286.8 ± 27.9	285.2 ± 30.6	0.899
QTc (ms)	412 ± 20.6	412.9 ± 25.5	0.944
QTd (ms)	74 ± 52.5	55.2 ± 28.7	0.194
QTcd (ms)	128.8 ± 49.3	93.9 ± 36.5	0.005

QTc: corrected QT; QTd: QT dispersion; QTcd: QTc dispersion.

cryptogenic (26). Our data are not sufficient to speculate about the presence of a milder type of ion channel mutation in patients with breath-holding spells. However, further studies in this field would be helpful for understanding the aetiology and mechanism causing these attacks.

Breath-holding spells were previously thought to be self-limited, benign disorders which resolve spontaneously. However, Di Mario et al. (2) followed 95 children with this disorder prospectively and found hypoxic convulsions in 15, syncopal attacks in 12 and learning difficulties in four children. The frequency of complications and increased QT dispersion indicate the need for further investigation into arrhythmia and autonomic dysfunction in this patient group.

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