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QT INTERVAL PROLONGATION IN FUTURE SIDS VICTIMS: A POLYSOMNOGRAPHIC STUDY

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Short title: QT intervals in future SIDS victims

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ABSTRACT

Objective: Previous data have suggested that a prolonged QTc interval during the first days of life can be associated with some cases of Sudden Infant Death Syndrome (SIDS). Analysis of heart rate variability during sleep in future SIDS victims has shown findings compatible with an imbalance in autonomic tone. We hypothesized that some future SIDS infants could have longer QTc intervals during sleep compared with healthy control infants, and that this difference would correlate with the autonomic imbalance already found in these infants.

Methods: QTc intervals and a heart rate autoregressive power spectral analysis were calculated during the same periods in the polysomnographic sleep recordings of 18 infants who eventually died of SIDS and of 18 control infants. The control infants were matched for sex, gestational age, postnatal age, birth weight and sleep position. The median postnatal age was 8 weeks.

Results: Compared with control infants, future SIDS victims were characterized by longer QTc intervals during total sleep ($p = 0.019$), REM ($p = 0.045$) and NREM sleep ($p = 0.029$). When the night was divided into three equal parts, this difference was always present, but was most marked during the last part of the night. There was, respectively, a negative and a positive correlation between parasympathetic activity and sympathovagal balance and median and maximum QTc interval values.

Conclusion: Compared with matched control infants, QTc intervals were increased in future SIDS victims. Such a prolongation could be related to the autonomic dysfunction already reported in these patients.

ABBREVIATIONS

ANS: autonomic nervous system

HF: high frequency

HR: heart rate

HRSA: heart rate power spectral analysis

LF: low frequency

LF/HF: low frequency to high frequency power ratio

QTc: Corrected QT interval

NREM: Non Rapid Eye Movement sleep

REM: Rapid Eye Movement sleep

SIDS: Sudden Infant Death Syndrome

INTRODUCTION

Sudden infant death syndrome (SIDS) is defined as the sudden death of an infant under the age of one year that remains unexplained after a complete postmortem examination, including an investigation of the death scene and a review of the case history. Such deaths occur during sleep, which may be a daytime nap or a night sleep[1]. Despite extensive research, the etiology of SIDS is still unknown. Cardiac mechanisms, including life-threatening arrhythmias, have been suspected of causing a proportion of SIDS cases[2]. A large prospective cohort study provided evidence of an association between neonatal QT prolongation recorded on ECG during the first days of life and the subsequent occurrence of SIDS[3]. Various mechanisms could be implicated in the association between SIDS and QT prolongation. In the late 70's, Schwartz et al. suggested that abnormal development of cardiac sympathetic innervation could occur with a difference in the timing of the maturation between left and right cardiac sympathetic innervation during the first months of life[2]. Such QT prolongation could also be an early manifestation of congenital long QT syndrome[2,4]. Long QT syndrome is a primary cardiac channelopathy with 7 cardiac ion channel genes currently implicated: KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CAV3[5]. Potentially lethal cardiac ion channel gene mutations have been found in 9.5% of SIDS infants suggesting that *de novo* mutations in cardiac ion channels could provide a lethal arrhythmogenic substrate in some infants at risk for SIDS[5]. Another possibility is that prolongation of the QTc intervals could be related to the autonomic dysfunction already reported in some of these patients[6-8]. In a previous study, following analysis of night polygraphic recordings of 18 infants who died some weeks later of SIDS compared with those of matched control infants, we reported a higher sympathetic activity in SIDS infants, especially at the end of the night when most cases of SIDS occur[9]. In Schwartz's prospective study of QT values[3], an ECG was obtained in the first week of life when transitional QT prolongation is a relatively common finding. The purpose of the present

study was to determine if certain future SIDS victims recorded at 2-3 months of age could also present prolongations of QTc intervals compared with matched control infants and if this QTc prolongation was related to sleep stages, time of night and autonomic nervous system activity.

METHODS

1. Patients

Diverse sleep research programs on sleep maturation in infants were initiated in Belgium during the 1980's. Parents could have a polysomnographic night recording of their infant during the first year of life to relieve anxiety about SIDS. The indications were very broad and were based on personal and family history (multiple births, prematurity, maternal smoking, inappropriate weight for gestational age, sibling of a SIDS victim, ..), but also on clinical signs (apparent life-threatening events, breath-holding spells, episodes of fatigue during feeding, profuse sweating, snoring or noisy breathing during sleep,..).[10]. More than 45,000 sleep studies have been recorded in the last 25 years. The prevalence of SIDS during this period was 0.8/1000 live births. Forty infants eventually died some days or weeks after their recordings[11]. The recordings of the 18 controls were consecutively selected when matching and technical criteria were found. For each SIDS recording, one recording of a control infant was selected. Control and SIDS infants were matched for sex, gestational age, postnatal age, birth weight and sleep position. All control infants were healthy, had no family history of SIDS and survived the first year of life. Only polysomnographic recordings with digitized ECG signals sampled at 300 Hz were used for the autonomic nervous system studies (Morpheus system, Medatec, Belgium). This system has been available since 1992. All of the recordings of these SIDS and control infants were performed during the same period from 1992 to 1995. Following the SIDS prevention campaign in 1994, the number of SIDS victims decreased abruptly[12]. The 18 recordings of future SIDS victims and matched control infants

were analyzed and the results on autonomic controls have been published[9,13]. In this population of 18 SIDS victims, 13 were males and 6 were preterm. Two of the preterm infants had inappropriate weights for their gestational ages. One infant was a sibling of a SIDS victim. At the time of recording, no infant had signs of infection. No infant was being monitored at the time of death. The 18 deaths were unexpected, and remained unexplained despite complete postmortem studies. Data on the children's histories and usual behavior were collected using a standard questionnaire before sleep monitoring was undertaken. The questionnaires were coded and analyzed together with the sleep recordings. Treatment by cisapride was noted since this prokinetic agent, which facilitates gastrointestinal motility, was widely used for treatment of gastroesophageal reflux disease in the 1990's[14]. Cisapride was subsequently reported to prolong QT intervals and to induce ventricular arrhythmia[15, 16]. The aims and methodology of the present study were approved by the university ethics committee.

2. Polygraphic recordings

The infants were admitted for a night monitoring session that lasted 8 to 9 h. The data were collected on a computerized polygraph recording system (Morpheus system, Medatec, Belgium). The following variables were recorded simultaneously: 8 EEGs, 2 electrooculograms, digastric electromyography, ECG (DII), thoracic and abdominal respiratory movements by inductive plethysmography, and airflow by means of thermistors taped under each nostril and on the side of the mouth. Oxygen saturation was continuously recorded using a transcutaneous sensor (Ohmeda Box, USA).

3. Data analysis

3.1. Sleep stages

Each recording was allocated a random code number. The code was disclosed after completion of the analysis. Two independent scorers analyzed the sleep recordings to ensure reliability. The two scorers, who had not taken part in the collection of the data, analyzed the coded recordings without knowing the patient's identity. Conflicting data were discussed, and after consensus, subsequently-agreed codes were used for analysis of the data. Each thirty-second period of the recordings was analyzed and categorized as either non-rapid eye movement sleep (NREM), rapid eye movement sleep (REM), and movement or wakefulness according to the guidelines in the literature[17]. NREM refers to NREM II and III stages. Sleep efficiency was defined as the ratio of the total sleep time divided by the total recording time, expressed as a percentage. Movement time represents gross body movements detected by movement sensors or seen as movement artifact in the somatic channels (ECG, EEG, respiratory parameters) for less than 15 seconds and reported as a percentage of total recording time.

3.2. Cardiorespiratory parameters

Sleep apneas were scored only if they lasted 3 seconds or more. A central apnea was scored when flat tracings were obtained simultaneously from thoracic/abdominal movements and thermistors. An obstructive apnea was scored when continuous deflections were obtained from thoracic movements, while a flat tracing was recorded from thermistors. To avoid artificial scoring due to thermistor displacement, obstructive apneas preceded by body movements, crying, or sighs were rejected. Mixed apneas were defined as central apneas followed directly by obstructive episodes, and were scored with obstructive apneas.

3.3. QT intervals

QT and preceding RR intervals were manually measured on the screen using electronic calipers in 3 consecutive heart cycles in each successive REM and NREM sleep stage throughout the night. In order to ensure signal stability, QT intervals were always measured 5 minutes after the onset of REM and NREM sleep. Care was taken to exclude episodes of desaturation, obstructive and central apnea. QT was measured from the onset of Q wave to the end of the T wave, at its point of return to the isoelectric line. The computer "zoom in" feature made it possible to enlarge the P-QRS-T complex, which provided accurate measurement of the end of the T wave[18]. The QT interval was corrected for heart rate with Bazett's formula[19]. The median, minimal and maximal values of QTc intervals were calculated for total sleep, NREM and REM sleep. Recordings were divided into three periods (9:00 p.m. to 12:00 p.m., 12:01 p.m. to 3:00 a.m., and 3:01 a.m. to 6:00 a.m.) in order to evaluate QTc values throughout the night.

3.4. Heart rate spectral analysis

Heart rate spectral analysis (HRSA) was obtained as follows: digitized ECG signals were sampled at 300 Hz. Premature ventricular contractions, or artifactual RR intervals due to gross body movements or arousals were eliminated by visual analysis of the HR data before HRSA was performed. HRSA was computed for periods of 256 successive RR intervals. QT intervals and HRSA were selected at the same time during the night. An HRSA of the trendgram was calculated for each period according to the method proposed in references 20 and 21 and the Task Force recommendations[22]. The trendgram was defined by the RR time according to the index of the cardiac beat. The autoregressive analysis was directly applied to this time series. The frequencies were expressed in Hzeq to point out the approximation

involved in this procedure. The validity of this approach has been extensively demonstrated [8,13,,20,21,22].

Two major peaks were recognizable: a low-frequency component (LF) defined by a center frequency of 0.1 Hzeq (0.04-0.15 Hzeq) related to sympathetic and parasympathetic activities and a high-frequency component (HF) defined by a center frequency of 0.4 Hzeq (> 0.15-2 Hzeq), reflecting parasympathetic tone[20]. Respiratory frequency during the selected period was measured manually after being printed. For each 256 RR interval period, the major component in the LF band of the HR spectrum was related to the major component in the HF band, corresponding to the mean respiratory frequency as determined by analysis of breath-to-breath intervals. The LF/HF power ratio for each episode was calculated as an index of the sympathovagal interaction[23]. Spectral components were represented as the RR intervals (in ms), power (in $msec^2$), bandwidth (in Hzeq)[20,21], and normalized power obtained by dividing the power of the period by the total power component (in %), after subtraction of the direct current component[24].

3.5. Statistical analysis

Wilcoxon matched-paired signed rank test was used to compare the SIDS cases with the matched control subjects and to compare QTc values during the three periods of the night and between REM and NREM sleep. Spearman correlation coefficient was used to describe the relationship between QT intervals and the HRSA data and the frequency of obstructive apnea. The results were considered as being significant at $p < 0.05$.

RESULTS

The general characteristics of the infants studied are reported in Table 1. Due to the study design, no differences were noted between the future SIDS victims and the control subjects, except than mothers of future SIDS victims were younger (p = 0.038). Only one infant died after 6 months of life, at the age of 36 weeks. Two SIDS infants and three control infants were receiving cisapride at the recommended pediatric dosage. At the time of recording, no infant was receiving other medication.

1. Sleep characteristics

No significant differences were noted between the two groups of infants for the main sleep variables (Table 2). As previously reported[13], future SIDS victims had more obstructive and mixed apnea episodes than their matched control subjects (p = 0.004).

2. QTc values

There were no significant differences between the two groups for the frequency of studied periods for QT analyses in total sleep (224 in future SIDS victims versus 219 in control infants, in NREM sleep (103 in future SIDS victims versus 102 in control infants) and in REM sleep (121 in future SIDS victims versus 117 in control infants).

As shown in Table 3, compared with the control infants, future SIDS victims were characterized by longer median QTc intervals during total sleep (p = 0.019), NREM (p = 0.029) and REM sleep (p = 0.045). Max QTc intervals were longer during total sleep (p = 0.022) and NREM sleep (p = 0.023) in future SIDS victims. There were no significant

differences between REM and NREM sleep for QTc intervals in both SIDS and control infants (Table 3). Only one SIDS infant, but no control infants had median QTc intervals values greater than 440 ms (Table 4). The sibling of the SIDS infant had normal QTc values. There was no significant correlation between the frequency of obstructive apnea and QTc intervals.

3. Nycthemeral variations of QTc values

Differences in median QTc intervals between the two groups of infants were found throughout the night (Table 5, Fig 1). Max QTc intervals tended to differ between future SIDS victims and control infants in the last part of the night ($p = 0.05$). These differences were noted when QTc interval values during REM and NREM sleep were considered together. There were no significant differences when the values in REM and NREM were considered separately.

4. Short-term heart rate spectral analysis

Table 6 provides a summary of the short-term spectral analysis in REM and NREM sleep. Compared with control subjects, SIDS infants were characterized by lower HF powers and HF normalized powers, and higher LF/HF power ratios in total sleep and NREM sleep. The results were the same in both groups for REM sleep concerning HF powers and LF/HF ratios. There were no significant differences in RR intervals, total power of the spectrum, LF values in REM and NREM sleep between the two populations.

5. Correlation between short-term heart rate spectral analysis and QTc values

For the control infants, there was a negative correlation between parasympathetic tonus and the median and maximum duration of QTc intervals (respectively r = -0.48, p = 0.048 and r = -0.55, p = 0.023) in NREM sleep. In REM sleep, there tended to be a correlation between median QTc intervals and parasympathetic tonus (r = -0.45). For SIDS victims, there was a positive correlation between sympathovagal balance and the minimum of QTc intervals (r = 0.36, p = 0.048) in total sleep. When the data of control and SIDS victims were considered together, there was a negative correlation between parasympathetic tonus and the median and maximum QTc intervals (respectively r = -0.25, p = 0.043 and r = -0.25, p = 0.045). There was also a positive correlation with sympathovagal tonus and median, minimum and maximum QTc intervals (respectively r = 0.26, p = 0.033; r = 0.28, p = 0.024; r = 0.301, p = 0.016).

No significant differences were found between infants receiving cisapride and those without treatment in both SIDS and control infants. Prone position was not associated with significant differences in QTc interval duration in both groups of infants.

DISCUSSION

Schwartz and colleagues have already suggested in a prospective study of more than 33,000 infants that prolongation of the QT interval on the electrocardiogram recorded in the first week of life is strongly associated with SIDS[3]. Our study demonstrated that a few weeks before death, SIDS victims had longer QT intervals than control infants throughout the night in REM and NREM sleep. This was especially observed in the late hours of the night when most SIDS occur[25, 26]. QT intervals were significantly correlated to other aspects of autonomic

regulation, showing, respectively, a negative and a positive correlation between parasympathetic tonus and sympathovagal balance.

The QT interval represents repolarization of the ventricular myocardial cells[27]. If ventricular repolarization is prolonged, there is a risk of torsades de pointes when a ventricular extra beat occurs, leading to ventricular fibrillation with sudden death as a terminal event [28]. QT prolongation can occur from a genetic abnormality or acquired factors. The inherited forms of long QT syndrome are mostly secondary to a dysfunction in the transport of potassium and sodium ions through channels across the myocardial cell membranes [29]. Seven genotypes of long QT syndrome have been identified in families with long QT syndrome [30]. The three commonest types are KCNQ1, KCNH2 and SCN5A. Mutations in cardiac ion channels, responsible for the long QT syndrome, were identified in cases initially diagnosed as SIDS [30,31]. In the first genetic analysis of the LQT genes in SIDS victims, SCN5A defects were reported in 5% of a prospective SIDS population-based cohort[4]. Recently, Arnestad et al. found 9.4% of the mutations as likely contributors to sudden death in over 200 cases of SIDS[5]. We found that most of the QTc values were longer than those of the control infants but were usually within the normal ranges. In our study, only one SIDS infant but no control infants, had a markedly long QTc interval with a QTc max at 480 ms. It is very probable that this infant had LQTS.

The QT interval is influenced by many factors including medications (such as cisapride), myocardial disease, biochemical factors (particularly hypokalemia) and physiological factors (autonomic nervous system, sleep...)[14,32-39]. The autonomic nervous system can modify the QT interval by its parasympathetic and sympathetic influences on the sinoatrial node by modulating cardiac rhythm or directly through its sympathetic ventricular innervation[34-37]. A

circadian modulation of the QT-RR relationship by the sympathetic-vagal balance has shown prolongation of the QT interval during sleep independent of heart rate in normal subjects[38,39]. QT and QTc intervals reach their peaks during the early waking hours, which could reflect the increased autonomic instability at this time of increased vulnerability to ventricular tachycardia and sudden cardiac death[39].

Cerebral injury at all ages can cause QT prolongation [40]. Pathological and immunohistochemical studies in SIDS infants have demonstrated diffuse lesions within different nuclei of the central nervous system, especially at the brainstem level[41-43], but also in the cerebellum[44-45]. Serotonergic neuron abnormalities have been reported in the ventral medulla of SIDS victims, in brainstem structures associated with respiratory, cardiovascular and arousal control [46,47]. Dysregulation in the autonomic nervous system has recently been recorded in a future SIDS victim whose postmortem investigation later demonstrated brainstem serotoninergic abnormalities [48]. Otherwise, the cerebellum may play a critical role in compensatory responses particularly to autonomic challenges and mediate failure mechanisms in SIDS[49].

Evidence of changes in cardiac autonomic controls such as higher heart rate[6], decreased heart rate variability, profuse night sweating, lower parasympathetic tone or higher sympathovagal balance[7,8,11] has been observed in infants who eventually died of SIDS. The obstructive sleep apneas found in future SIDS victims could also be associated with abnormal autonomic control of the upper airways[9,12,50].

The correlation between QT interval values and autonomic control found in this study confirmed the relation between QT prolongation and autonomic imbalance. The most marked difference in QT intervals between SIDS and control infants was found during the last part of

the night when a high desynchronized sympathetic peak appears in SIDS victims[9]. QT prolongation could act as an arrhythmogenic substrate which requires a trigger, such as a stress condition for the development of life-threatening arrhythmias. Infants could be exposed to several conditions that increase cardiac electrical instability: REM sleep with bursts of vagal and sympathetic activation, minor upper respiratory tract infections that in infants, easily induce hypoxemia and trigger chemoreceptive reflexes, and environmental risk conditions which increase sympathetic activity such as the prone position[51], maternal smoking[52], high ambient room temperature, sleep deprivation. The factors reported to be protective for SIDS such as the use of a pacifier[53] and sleeping supine in a swaddled condition have an inverse effect on the autonomic system, increasing parasympathetic tonus and/or decreasing sympathetic activation. The increase in sympathetic activity could reduce the electrical stability of the heart and precipitate ventricular fibrillation and sudden cardiac death[54].

Moreover, most deaths from SIDS occur in the first 6 months of life, with a specific peak between 2 and 4 months of age which coincides with the period when the QTc interval tends to be longest after the first week of life[55]. It has been postulated that this QT prolongation represents a transient development imbalance between the innervation by the right and left sympathetic nerves[2,55]. In agreement with other authors, we did not find statistical differences in QT intervals between the prone and supine positions in 2-3 month-old infants[56,57]. Ariagno et al. found longer QTc in the prone position only in preterm infants at 1 month but not at 3 months corrected age[57].

We must admit that there were several limitations on our study. Firstly, because of the limited number of SIDS subjects available for analysis, this report was restricted to the description of QTc and heart rate spectral analysis. No multiple analyses were performed on the various

infant characteristics that could have led to the identification of determinant factors in QTc interval prolongation. It can also not be excluded that some biases exist in the selection of these infants in the general population. However, there were no significant differences between the two analyzed groups (Table 1). All control infants were healthy and survived the first year of life. Secondly, it is of interest to note that there are no official guidelines on QT interval measurement in childhood. There is no consensus on the number of successive RR intervals required for an accurate evaluation of the QTc. With the advent of modern technology, clinicians have at their disposal various measurement procedures, including digital automatic, manual measurement with calipers or rulers, application of a digitizing board with or without magnification, on-screen measurement with electronic calipers...[58]. The digital manual method in our study could be more accurate than manual measurement. QT interval is often corrected for heart rate. In pediatric practice, Bazett's formula is a widely used method for QT heart rate correction[18]. Some investigators have questioned the appropriateness of this formula for correction of the QT interval. More specifically, Bazett's formula overadjusts the QT interval at high heart rates[17]. In our study, there were no statistical differences in heart rate values between SIDS and control infants. We cannot exclude the possibility that application of Bazett's formula influenced QT values. Such a bias would, however, affect the infants in both groups. In figure 2, we show HR and non-corrected QT values on scatter plots. More SIDS infants had higher median and max non-corrected QT values than control infants in total sleep, NREM and REM sleep. Thirdly, as for heart rate spectral analysis, cross-spectral analysis of respiration and HR changes were not evaluated[7]. Our previous studies comparing future SIDS victims with control infants have provided results[11] that are similar to those reported by authors using cross-spectral analysis of respiration and heart rate changes[7]. Moreover, the LF/HF ratio must be interpreted with care[22,59]. While it is generally accepted that in the high-frequency band, the respiratory peak is

principally vagally mediated and can be used as a measure of parasympathetic activity[22,60]; within the low frequency range, HR fluctuations depend on both sympathetic and parasympathetic controls[22]. Vasomotor or thermal influences can be observed under 0.09 Hz[61], and baroreceptor controls contribute to changes in the 0.1 to 0.15 Hz frequency band[62]. With these restrictions in mind, the ratio of LF/HF powers is usually considered as an index of sympathovagal interaction[22,23,59]. Finally, genetic analysis of the implicated cardiac ion channel genes could not be performed in this retrospective study.

To conclude, SIDS victims as a group had longer QTc intervals than control infants. This prolongation could be related to the autonomic dysfunction already reported in these patients. In our study, one infant probably had LQTS. The concept of systematic ECG screening in newborns to prevent SIDS is still being debated[28]. SIDS is a multifactorial disease. The huge body of epidemiological and physiological data would appear to suggest that a deficit in cardio-respiratory control of arousal could be implicated as a determinant key cause of SIDS [63]. Schwartz and al. propose ECG screening as a cost effective program to prevent all LQTS-related deaths, and in particular, early LQTS SIDS labeled deaths[64,65]. We have asked ourselves if the death of the infant with the QTc of 480 ms and who was probably affected by LQTS could have been prevented by using a beta-blocker treatment. This study advances our comprehension of the mechanisms favoring the unexpected death of an infant during sleep and provides additional data for subsequent discussion of the benefit of newborn ECG screening programs[66].

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1. **TABLE 1: Major characteristics of the infants studied**

	SIDS INFANTS	CONTROL INFANTS
No.	18	18
Gender (M/F)	13/5	13/5
Gestational age (weeks)	38 (27-41)	38 (27-41)
Birth weight (g)	2.925 (0.96-3.98)	2.790 (1.090-3.840)
Age at sleep study (weeks)	8 (5-19)	8 (5-19)
Weight at sleep study (g)	4.380 (2.220-5.900)	4.845 (2.000-6.400)
Sleep position (prone/supine)	9/9	9/9
Age at death (weeks)	13.5 (10-36)	-
Maternal age (years)*	24 (20-29)	27 (21-36)
History:		
Sibling of SIDS cases	1	0
Preterm infants	6	6
Inappropriate weight for gestational age	2	2
Maternal smoking	5	1
Multiple births	3	3
Cyanosis episode during the first day of life	1	0
Noisy breathing or snoring during sleep	3	4
Breath-holding spells	1	2
Feeding difficulties (fatigue, choking.)	2	5
Regurgitations	5	5
Cisapride therapy (0.80 mg/kg/day)	2	3

The figures represent absolute, median and range values.

*Wilcoxon matched-paired test between SIDS cases and controls, $p < 0.05$.

Table 2: Sleep and cardiorespiratory characteristics of SIDS victims and control infants

	FUTURE SIDS INFANTS	CONTROL INFANTS	*P*
Total Recording Time (min)	480 (330-510)	480 (290-510)	NS
Total Sleep Time (min)	347 (228-480)	370 (198-440)	NS
Sleep Efficiency (%)	80.2 (48-100)	77.3 (56.3-91.7)	NS
NREM sleep (%)	29.9 (16.6-43.1)	32.6 (10.4-40.7)	NS
REM sleep (%)	46.1 (24.4-69.8)	42.6 (25.2-61.6)	NS
Mvt (%)	4.65 (0-15.5)	4 (0.1-10.7)	NS
Central apnea frequency (/h sleep)	4.8 (0.7-19.4)	6.4 (3.2-15.4)	NS
Central apnea duration (s)	7.8 (5.1-10.2)	7.4 (4.3-10.1)	NS
Obstructive events frequency (/h)	0.88 (0-4.85)	0.22 (0-1.91)	0.004
Obstructive events duration (s)	8.1 (4.1-18.9)	7 (4-9.1)	NS
Basal Heart Rate (bpm) NREM	133 (105-147)	125.5 (109-150)	NS
Basal Heart Rate (bpm) REM	136 (109-156)	131 (111-155)	NS
Basal Breathing Rate (bpm) NREM	39 (21-45)	31 (19-39)	NS
Basal Breathing Rate (bpm) REM	43 (24-48)	36 (20-40.5)	NS
Oxygen saturation values (%)	93.7 (86.5-98.6)	95.8 (88.5-97.3)	NS

The figures represent median and range values. Statistical analyses were performed with Wilcoxon matched-paired test between SIDS cases and controls, $p < 0.05$.

TABLE 3: QTc values of SIDS and matched control infants during total sleep time, REM and NREM sleep.

QTc VALUES (ms)	FUTURE SIDS INFANTS	CONTROL INFANTS	*P*
Total Sleep			
Median	396.2 (342.5-452)	373 (327.5-409)	0.019
Max	405 (358-480)	392.5 (335-428)	0.022
NREM sleep			
Median	393.5 (340-451)	375.25 (413)	0.029
Max	401 (349-459)	387 (334-428)	0.023
REM sleep			
Median	387.2 (345-466)	371 (328.5-408)	0.045
Max	398 (354-480)	386.5 (333-428)	NS
NREM sleep/REM sleep			
Median	NS	NS	
Max	NS	NS	

The figures represent absolute, median and range values. Statistical analyses were performed with Wilcoxon matched-paired test between SIDS cases and controls, $p < 0.05$.

Table 4: Individual mean Heart Rate (HR), mean and max QTc values for SIDS and control infants

	SIDS Infants			Control infants		
	Mean HR	Mean QTc	Max QTc	Mean HR	Mean QTc	Max QTc
1	104	342.5	358	105	327.5	335
2	100.5	353	367	112.5	350.5	365
3	89	400	420	103	406	409
4	106	374	392	105.5	372	381
5	103	452	480	123	333	407
6	114	420	444	109	388	401
7	111	400	412	89	409	428
8	92.5	357	372	93	371	392
9	109.5	397	425	87.5	377.5	398
10	105	390	398	94	384	392
11	82.5	409.5	417	94	364	386
12	99	384	401	92	379	400
13	84	378	391	84	371.5	394
14	109	352	362	94	364	387
15	103	396	407	94	387.5	401
16	101	402	415	96	380	393
17	96.5	396.5	408	95	374	386
18	108	399	403	93	360	375

The figures represent median HR, median and max QTc values in total sleep time.

TABLE 5: QTc values of SIDS and matched control infants throughout the night.

QTc VALUES (ms)	FUTURE SIDS INFANTS	CONTROL INFANTS	*P*
Median values			
21:00-00:00 h	387.5 (344-413)	375 (350-399)	0.019
00:01-03:00 h	390.5 (354-466)	375 (349.5-422)	0.016
03:01-06:00 h	391 (343.5-457.5)	372.5 (346-423)	0.010
Max values			
21:00-00:00 h	394 (344-425)	380 (354-400)	NS
00:01-03:00 h	396 (354-480)	384 (350-428)	NS
03:01-06:00 h	394 (343.5-467)	378 (351-428)	0.050

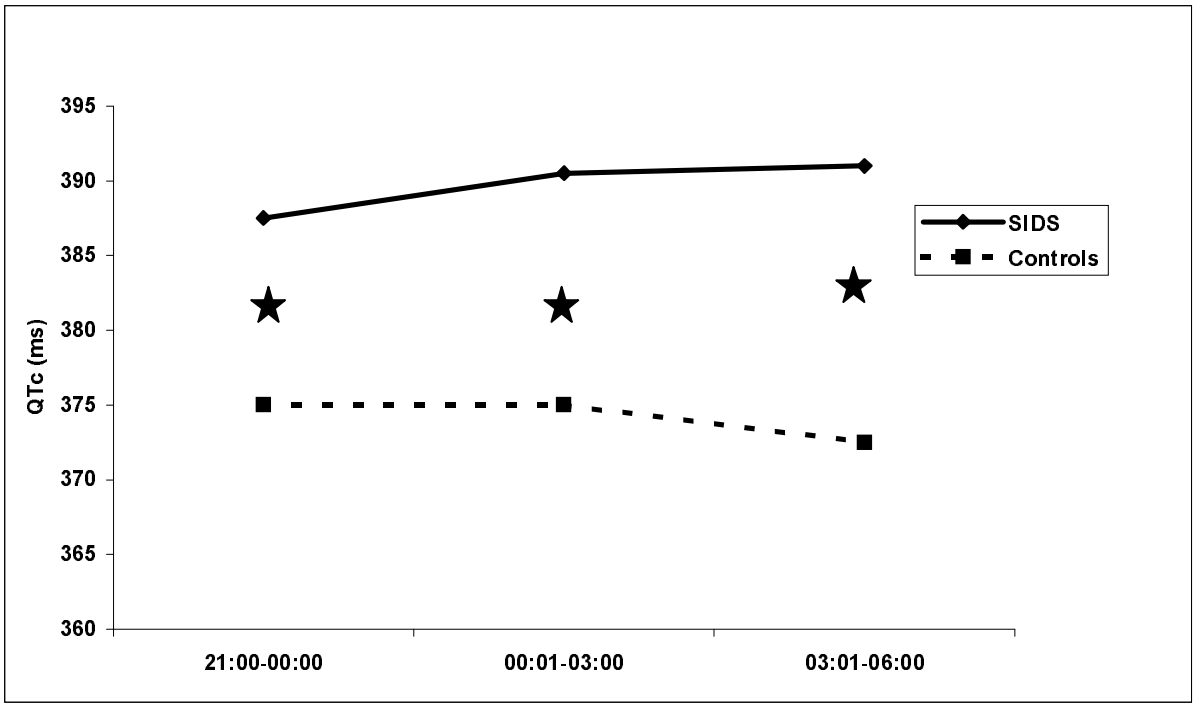
The figures represent absolute, median and range values. Statistical analyses were performed with Wilcoxon matched-paired test between SIDS cases and controls, $p < 0.05$.

TABLE 6: Short-term spectral analysis in SIDS and control infants

	FUTURE SIDS INFANTS	CONTROL INFANTS	*P*
Total Sleep			
HF Power (ms^2)	13.07 (5.06-98)	31.64 (3.56-174.61)	<0.001
HF Normalized Power (%)	6.25 (2.5-23.60)	13.10 (2.45-54.50)	0.002
LF/HF power ratio (%)	8.99 (1.38-24.24)	5.04 (0.71-18.82)	0.005
NREM Sleep			
HF Power (ms^2)	10.63 (5.06-46.94)	36.59 (3.56-167.68)	0.006
HF Normalized Power (%)	10.20 (5-17.3)	21.75 (4.5-54.5)	0.008
LF/HF power ratio (%)	6.65 (2.06-13.98)	1.96 (0.71-18.82)	0.050
REM sleep			
HF Power (ms^2)	14.09 (5.6-98)	29.99 (11.91-174.61)	0.027
Normalized Power (%)	5.4 (2.5-23.6)	7.68 (2.45-14.9)	NS
LF/HF power ratio (%)	9.53 (1.38-24.24)	5.33 (2.52-17.44)	0.046

The figures represent absolute, median and range values. Statistical analyses were performed with Wilcoxon matched-paired test between SIDS cases and controls, $p < 0.05$.

Figure 1: Nycthemeral variations of median QTc values in SIDS and matched control infants. Statistically significant (✯).



The figures represent median values.

Figure 2. Individual non-corrected median and max QT values presented according to their heart rate values in total sleep time, NREM and REM sleep.