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Original Article

Evolution of the QT interval in premature infants: a preliminary study

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Abstract *Background:* The association between long QT interval and sudden infant death syndrome has been clearly established. Several studies have been conducted to determine the evolution of the QT interval in childhood from birth, but only in full-term newborns. However, data on the QT interval in pre-term infants are extremely scarce. The objective was to describe the development of the QT interval in premature infants. *Material and methods:* In a prospective monocentric study in a neonatal intensive care unit, pre-term newborns born before 37 weeks of gestation without congenital heart disease, family history of long QT, unstable haemodynamic status, or administration of drugs inducing QT interval prolongation were included with parental consent. An electrocardiogram was recorded in similar conditions weekly until discharge in each child. The corrected QT was calculated with Bazett's formula. *Results:* In all, 309 echocardiograms were recorded in 87 children, with gestational age ranging from 24–36 weeks. QT first increased after birth in very premature infants – less than 30 weeks of gestation – and then started to decrease, whereas it only decreased in more mature infants. When plotted against postmenstrual age, QT first increased, and then decreased after 32 weeks. *Discussion:* Our data suggest that the QT interval varies with postmenstrual age in very premature infants, reaching a peak at 32 weeks. These developmental changes may induce specific vulnerability to QT-lengthening medications in premature infants. This study underlines the need for specific pharmacological studies in this population.

Keywords: Electrophysiology; electrocardiogram; paediatric cardiology

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The QT interval reflects ventricular repolarisation on an electrocardiogram. The association between QT prolongation and sudden death in infants has long been recognised.[1] This QT prolongation can be idiopathic, congenital, or result from drugs or electrolyte disorders.[2] The duration of the QT interval is highly variable, depending on factors such as heart rate, exercise, nycthemeral rhythm, autonomic imbalance, hysteresis, and age.[3–5] Several studies have reported the natural evolution of the QT interval in healthy children and full-term newborns.[6–10] During infancy, it has been shown that the QT progressively increases after birth, reaches a maximum value in the second month of life, and thereafter progressively decreases until 6 months of age to reach values similar to those of adults.[10]

Premature birth is a risk factor of sudden infant death syndrome. QT prolongation, spontaneous or drug induced, may play a role in this increased risk of sudden death. However, to our knowledge, there are very few data on the evolution of QT after birth in pre-term infants. In the foetus, magnetocardiography, using Superconducting Quantum Interference Device technology, enables to study cardiac electrical activity.[11–13] Horigome showed an increase in QT until the end of the 31st week of gestation followed by a decrease until term.[14] In the premature newborn, the few available data on QT evolution have been provided by Schwartz, who studied a group of

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premature and low birth weight infants. In contrast to full-term healthy infants, the QT of these children did not increase in the first 2 months of life.[10] However, in that study, all premature and low birth weight infants were pooled regardless of gestational age.

The aim of this observational, longitudinal, study was thus to assess the natural postnatal evolution of the QT interval in a cohort of premature infants, and to evaluate the respective influences of gestational, postmenstrual, and postnatal age.

Patients and methods

Patients

Premature infants hospitalised in our neonatal intensive care unit were included over a 6-month period – that is, from November, 2007 to April, 2008 – in this prospective monocentric study. Inclusion criteria were gestational age between 24 and 36 weeks and 6 days and postnatal age less than 48 hours.

Exclusion criteria included long QT congenital syndrome, congenital heart disease – except for haemodynamically significant patent ductus arteriosus – severe conduction disorder, major hypoxaemia, severe perinatal asphyxia, haemodynamic instability, significant arrhythmia or a notion of significant arrhythmias in the family, atrioventricular block of second or third degree, notion of sudden infant death or serious illness in the family, uncorrected electrolyte disorders, chromosomal disorder, congenital malformation, concomitant medication by a drug inducing QT modification, and parental refusal.

Informed and written parental consent was collected in the first 48 hours of life. Parents could remove their child from the protocol at any time thereafter. This study was approved by our local ethics committee.

Electrocardiogram measurements

Electrocardiograms were recorded first within the first 48 hours of life, and then once a week until discharge from the unit. When electrocardiogram recording was not possible because of clinical instability, the electrocardiogram was delayed for 24 hours or cancelled. All infants were placed on continuous bedside electrocardiogram and oxygen saturation monitoring, which is standard care in the neonatal intensive care unit during the entire hospitalisation. The electrocardiograms were recorded using the three leads of the Philips cardiorespiratory monitoring scope (IntelliVue) used in the unit, with a sampling rate of 500 Hertz. All recordings were made by the same technician in identical conditions: child awake, in supine position, calm, not during a feeding period. In order to limit the effect of physiological nycthemeral variability on QT duration, we tried, as much as possible, to perform electrocardiograms at the same hour for each child. All electrocardiograms were recorded in the morning. Once a week, three electrocardiograms were subsequently recorded over a time period of 20 minutes. The time values of the three electrocardiograms were averaged to provide a single value per recording. All the electrocardiograms were interpreted by the same investigator using the DII lead. Measurement of the QT interval was precisely achieved with the software of the monitoring device. QT interval was measured manually between the beginning of the QRS complex and the end of the T wave, which was defined as the intersection between the tangent to the downslope of the T wave and the isoelectric line. RR interval was measured between two R waves preceding the measured QT interval. QT interval was corrected using Bazett's formula ($QTc = QT/\sqrt{RR'}$).

Age, biometric data, cardiorespiratory variables – heart rate, respiratory rate, blood pressure, oxygen saturation – and electrolyte plasma concentrations were also collected. Electrolyte disorders were systematically corrected before the electrocardiogram recording.

Definitions

Gestational age defines the term of birth and is expressed in weeks of gestation. Postmenstrual age defines the time since conception, regardless of postnatal age, also in weeks of gestation. Postnatal age refers to age since birth and is expressed in weeks of life.

Statistical analysis

Data are expressed as mean plus or minus standard deviation. We divided the infants into three subgroups according to their gestational age – 24–29 weeks of gestation, 30–32 weeks of gestation, and 33–36 weeks of gestation – and, in each subgroup, we compared the corrected QT values at different postnatal ages with an analysis of variance. The variations of corrected QT according to postmenstrual age – time since conception, regardless of postnatal age – were also studied using an analysis of variance. p-Values less than 0.05 were considered statistically significant. The software used for the analysis was "SPSS 15.0 for windows".

Results

In all, 87 children were included in the study; 22 children were excluded from the study mainly because of the consequences of prematurity. None was

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Table 1. Characteristics of newborns.

Weeks of gestation	Number of children	Weight (grams)	Outborn	Caesarean delivery	Birth from multiple pregnancy	Exogenous surfactant therapy	Antenatal corticosteroids	Respiratory distress syndrome
24	2	684 (±105)	0	0	0	2	2	2
25	8	728 (±74)	0	4	6	6	8	8
26	1	1040	0	0	0	1	1	1
27	5	947 (±178)	1	5	5	4	3	4
28	6	1052 (±239)	0	5	5	4	6	4
29	3	1041 (±251)	0	3	3	0	3	0
30	8	1256 (±291)	1	4	1	4	7	4
31	6	1368 (±286)	1	3	0	1	6	1
32	14	1684 (±356)	1	11	6	0	12	0
33	12	1999 (±145)	1	8	7	0	11	0
34	11	2125 (±389)	1	5	3	2	6	2
35	8	2258 (±508)	1	5	2	0	3	0
36	3	2395 (±306)	1	2	2	0	0	0
Total	87	1573 (±605)	8	55	40	24	68	26

Weight is presented as mean plus or minus standard deviation

excluded for long QT congenital syndrome. The mean gestational age was 31 weeks plus or minus 3 weeks and 2 days, with a range from 24 weeks and 2 days to 36 weeks and 6 days. The sex ratio was 1:1, that is, 47 males/40 females. The characteristics of the newborns are reported in Table 1.

In all, 309 electrocardiograms were performed, most of them during the first 5 weeks of life. Regrettably, a significant number of infants could not be studied beyond 5 weeks of life because they were discharged home or transferred.

When analysed on all measurements pooled together, QT did not seem to vary significantly, nor follow a definite trend after birth (Fig 1). However, when we analysed the postnatal course of QT separately according to gestational age – 24–29 weeks of gestation, 30–32 weeks of gestation, and 33–36 weeks of gestation, we found out different trends (Fig 2). The QT of the most immature infants first increases, reaches a peak at 5 weeks of life, and then decreases (Fig 2a). The QT of more mature infants starts to decrease after 3 weeks of life (Fig 2b). The QT of even more mature infants decreases from birth (Fig 2c). The curve of postnatal evolution of QT seems to be shifting to the left as gestational age increases, suggesting that QT development follows a postmenstrual rather than a postnatal pattern.

We then focused on QT evolution according to postmenstrual age and defined four groups: under 29 weeks of gestation, 29–32 weeks of gestation, 33–35 weeks of gestation, and more than 35 weeks of gestation. To do so, we pooled weekly measurements made over 3- to 4-week periods, thereby obtaining more than one measurement by infant by period. We observed a two-phase corrected

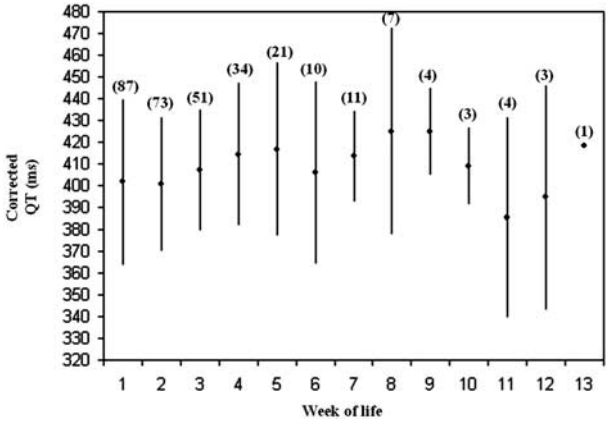

Figure 1.
Values of corrected QT according to the postnatal age. Results are presented as mean plus or minus standard deviation. Numbers in parentheses represent the number of children who had an electrocardiogram. Corrected QT is expressed in milliseconds (ms).

QT variation: first, corrected QT tended to increase with postmenstrual age up to 32 weeks of gestation. Then, corrected QT progressively decreased from 32 weeks of gestation of postmenstrual age up to full term (Fig 3).

During the hospitalisation, one child died from severe neurological damages due to prematurity. Owing to the fact that they were discharged home, all children were regularly followed up, for over 3 years. Only one patient had isolated episodes of bradycardia that lasted 3 months before disappearing. For this patient, the maximum value of corrected QT was 442 milliseconds at 32 weeks of gestation. No death or syncope was reported for the other patients.

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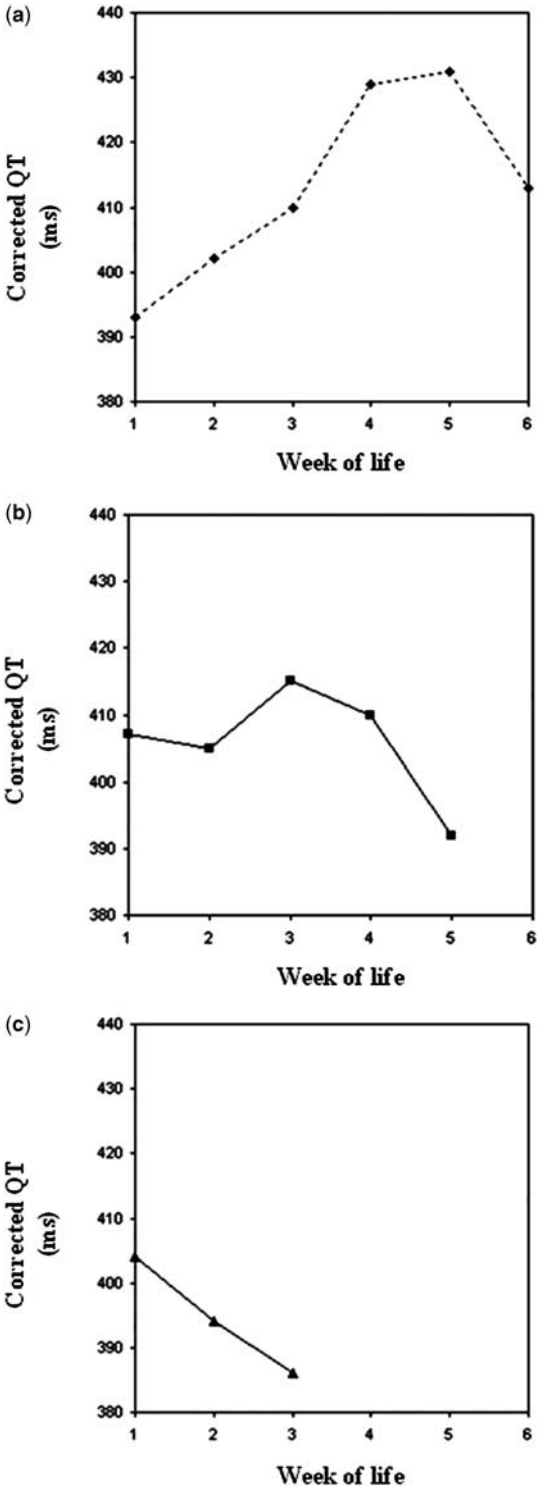

Figure 2.
Values of corrected QT according to the term of birth and to the postnatal age. (a) For the group of pre-term infants born between 24 and 29 weeks of gestation. (b) For the group of pre-term infants born between 30 and 32 weeks of gestation. (c) For the group of pre-term infants born between 33 and 36 weeks of gestation. Corrected QT is expressed in milliseconds (ms) and is presented in/as mean.

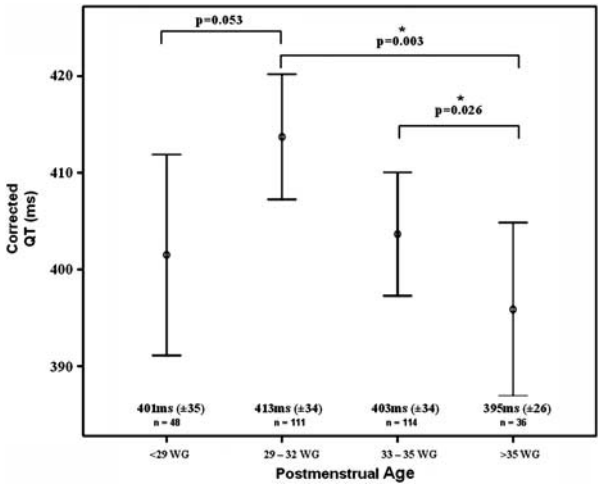

Figure 3.
Evolution of corrected QT according to the postmenstrual age. Postmenstrual age is expressed in/as weeks of gestation (WG). Corrected QT is expressed in milliseconds (ms). Circles represent means and vertical bars represent confidence intervals at 95%. The difference observed between the four groups is significant: $p = 0.012$ (analysis of variance).

Discussion

This prospective study is, to our knowledge, the first to evaluate the evolution of the QT interval specifically in the premature infant. The electrocardiograms were obtained in a population of preterm infants included very soon after birth, and then repeated at regular intervals during their hospitalisation, when the children's condition was stable. The QT intervals were all measured by a single observer. On the basis of these data, we demonstrated that its development depends on postmenstrual age rather than postnatal age. Our findings are very similar to those reported by in utero magnetocardiographic studies performed in the foetus: Horigome[14] noted an increase of corrected QT in utero between 20 and 26 weeks of gestation, followed by a decrease between 27 and 37–41 weeks of gestation. We observed only a tendency of increase between the less than 29 weeks of gestation and 29–32 weeks of gestation periods, but this failure to reach significance is probably due to a lack of power. In our study, the duration of corrected QT after 35 weeks of gestation postmenstrual age is very similar to that of full-term newborns.[10] These results suggest that the evolution of corrected QT is an ontogenic process that is not modified by premature birth. Further studies are required in order to evaluate the evolution of corrected QT in premature infants after the theoretical term and to determine whether this evolution is similar to that of full-term newborns or whether, like the parasympathetic activity, it still differs for several months.[15]

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Several mechanisms may underlie these variations. The changes in QT according to postmenstrual age may be due to developmental changes in repolarising potassium currents. Wang et al[16] demonstrated that the expression of cardiac transient outward current (I_{to}) and inwardly rectifying potassium current (I_{kr}) is age dependent in mice, resulting in longer action potential and repolarisation duration in newborn compared with adult mice. Similarly, developmental changes in action potential duration have been observed in guinea pig ventricular myocytes: action potential duration decreases between foetal and neonatal periods and increases between neonatal and adult periods.[17] These developmental changes were attributed to differences in the balance between I_{kr} and L-type calcium current (I_{caL}) densities. Generally speaking, all animal studies showed that the immature myocardium appears to have decreased repolarisation reserve, resulting in increased sensitivity to the prolonging effect of pharmacological agents.[18]

Another possible mechanism of QT developmental changes is the maturation of the autonomic nervous system. The duration of cardiac time intervals is influenced by the autonomic nervous system.[2,19] Indeed, the duration of the QT interval closely depends on the autonomic balance between sympathetic and parasympathetic activities, which can be roughly estimated by the measurement of heart rate variability.[20] It was well demonstrated that premature newborns have a lower parasympathetic activity than full-term newborns because the parasympathetic system development occurs late in gestation.[15,21,22] This depressed parasympathetic activity is associated with an increased risk of syncope and sudden death.[23] Only one study of the autonomic cardiac control in pre-term infants sought to evaluate the variations according to postmenstrual age, but the cohort was too small to yield significant differences between the groups.[22] In the postnatal period, the autonomic nervous system is the major factor regulating the development of cardiac ion channels involved in cardiac cell repolarisation.[24] Finally, an alternative explanation for the QT evolution in our population could be prematurity-related exogenous factors such as sepsis, bronchopulmonary dysplasia, cerebral damage, or even pharmacological treatment. However, this last hypothesis seems unlikely as the occurrence of these events in premature infants is highly dependent on gestational ages, whereas the evolution of QT in our infants was mainly dependent on postmenstrual age.

There are some limitations in our study. First, we were unable to obtain a lot of electrocardiograms after 5–6 weeks of postnatal age, even in the most premature infants, because they were either discharged home or transferred to another unit closer to home. Very few infants remained in the neonatal intensive care unit after 36 weeks of postmenstrual age. Therefore, we do not have information on the QT interval in these infants when they reach full term. The technical difficulties in determining the QT interval in premature infants, due to high heart rates and QT variability, should also be acknowledged. Electrocardiogram recordings obtained from the bedside electrocardiogram monitoring were easily feasible and minimally invasive, but were composed of only three leads, compared with a 12-lead regular electrocardiogram, with a sampling rate of 500 Hertz. Despite a strict reproduction of recording conditions for each child, hysteresis is, for example, difficult to control especially when a study is conducted in a care unit.[4,5] In the future, a study should use an electrocardiogram Holter, with a 24-hour recording, to control physiological nycthemeral variations.

Our data suggest that if premature newborns have to be exposed to potentially QT-lengthening drugs when they reach 30–32 weeks of gestation of postmenstrual age, electrocardiogram monitoring should be reinforced. Automated continuous QT interval monitoring, which has been recently reported in the setting of neonatal intensive care units, could be beneficial in this specific situation.[25]

We showed that corrected QT interval varies according to postmenstrual age in premature infants, increasing up to 32–33 weeks of gestation. Our results underline the need to better understand the development of the cardiac time intervals in premature newborns, to determine the patients at high risk of sudden death or serious arrhythmia. Knowledge of the physiological variations of QT interval is crucial for future neonatal pharmacological studies on the repolarisation-prolonging effect of drugs.

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References

1. Schwartz PJ, Stramba-Badiale M, Segantini A, et al. Prolongation of the QT interval and the sudden infant death syndrome. N Engl J Med 1998; 338: 1709–1714.
2. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. Prog Cardiovasc Dis 2001; 43: 1–45.
3. Ariagno RL, Mirmiran M, Adams MM, Saporito AG, Dubin AM, Baldwin RB. Effect of position on sleep, heart rate variability, and QT interval in preterm infants at 1 and 3 months' corrected age. Pediatrics 2003; 111: 622–625.
4. Sarma JS, Venkataraman SK, Samant DR, Gadgil U. Hysteresis in the human RR–QT relationship during exercise and recovery. Pacing Clin Electrophysiol 1987; 10: 485–491.

5. Lau CP, Freedman AR, Fleming S, Malik M, Camm AJ, Ward DE. Hysteresis of the ventricular paced QT interval in response to abrupt changes in pacing rate. Cardiovasc Res 1988; 22: 67–72.
6. Eberle T, Hessling G, Ulmer HE, Brockmeier K. Prediction of normal QT intervals in children. J Electrocardiol 1998; 31: 121–125.
7. Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for the paediatric electrocardiogram. Eur Heart J 2001; 22: 702–711.
8. Schwartz PJ, Garson A Jr, Paul T, Stramba-Badiale M, Vetter VL, Wren C. European Society of Cardiology. Guidelines for the interpretation of the neonatal electrocardiogram. A task force of the European Society of Cardiology. Eur Heart J 2002; 23: 1329–1344.
9. Semizel E, Oztürk B, Bostan OM, Cil E, Ediz B. The effect of age and gender on the electrocardiogram in children. Cardiol Young 2008; 18: 26–40.
10. Schwartz PJ, Montemerlo M, Facchini M, et al. The QT interval throughout the first 6 months of life: a prospective study. Circulation 1982; 66: 496–501.
11. Kähler C, Schleussner E, Grimm B, et al. Fetal magnetocardiography: development of the fetal cardiac time intervals. Prenat Diagn 2002; 22: 408–414.
12. Stinstra J, Golbach E, van Leeuwen P, et al. Multicentre study of fetal cardiac time intervals using magnetocardiography. BJOG 2002; 109: 1235–1243.
13. Van Leeuwen P, Lange S, Klein A, Geue D, Grönemeyer DH. Dependency of magnetocardiographically determined fetal cardiac time intervals on gestational age, gender and postnatal biometrics in healthy pregnancies. BMC Pregnancy Childbirth 2004; 4: 6.
14. Horigome H, Takahashi MI, Asaka M, Shigemitsu S, Kandori A, Tsukada K. Magnetocardiographic determination of the developmental changes in PQ, QRS and QT intervals in the foetus. Acta Paediatr 2000; 89: 64–67.
15. De Rogalski Landrot I, Roche F, Pichot V, et al. Autonomic nervous system activity in premature and full-term infants from theoretical term to 7 years. Auton Neurosci 2007; 136: 105–109.
16. Wang L, Feng ZP, Kondo CS, Sheldon RS, Duff HJ. Developmental changes in the delayed rectifier K+ channels in mouse heart. Circ Res 1996; 79: 79–85.
17. Kato Y, Masumiya H, Agata N, Tanaka H, Shigenobu K. Developmental changes in action potential and membrane currents in fetal, neonatal and adult guinea-pig ventricular myocytes. J Mol Cell Cardiol 1996; 28: 1515–1522.
18. Tanaka H, Namekata I, Nouchi H, Shigenobu K, Kawanishi T, Takahara A. New aspects for the treatment of cardiac diseases based on the diversity of functional controls on cardiac muscles: diversity in the excitation–contraction mechanisms of the heart. J Pharmacol Sci 2009; 109: 327–333.
19. Cuomo S, De Caprio L, Di Palma A, et al. Influence of autonomic tone on QT interval duration. Cardiologia 1997; 42: 1071–1076.
20. Pladys P, Beuchée A, Hernandez A, Carrault G. Heart rate variability in paediatrics: principles and applications. Arch Pediatr 2008; 15: 611–613.
21. Patural H, Barthelemy JC, Pichot V, et al. Birth prematurity determines prolonged autonomic nervous system immaturity. Clin Auton Res 2004; 14: 391–395.
22. Patural H, Pichot V, Jaziri F, et al. Autonomic cardiac control of very preterm newborns: a prolonged dysfunction. Early Hum Dev 2008; 84: 681–687.
23. Kahn A, Groswasser J, Franco P, et al. Sudden infant deaths: stress, arousal and SIDS. Early Hum Dev 2003; 75: 147–166.
24. Qu J, Robinson RB. Cardiac ion channel expression and regulation: the role of innervation. J Mol Cell Cardiol 2004; 37: 439–448.
25. Helfenbein ED, Ackerman MJ, Rautaharju PM, et al. An algorithm for QT interval monitoring in neonatal intensive care units. J Electrocardiol 2007; 40 (Suppl 6): S103–S110.