The QT Interval Throughout the First 6 Months of Life: A Prospective Study

Peter J. Schwartz, M.D., Massimo Montemero, M.D., Mario Facchini, M.D., Patrizia Salice, M.D., Dario Rosti, M.D., Gianluigi Poggio, M.D., and Roberto Giorgetti, M.D.

SUMMARY A prospective electrocardiographic study was designed to establish baseline values for electrocardiographic measurements, with specific reference to the QT interval during infancy, and to test the "QT hypothesis" for the sudden infant death syndrome (SIDS). In this ongoing study, ECGs are recorded on the fourth day of life and in the second, fourth and sixth months. The state of health at 1 year is ascertained by a phone call. So far, 4205 newborns have been enrolled. The mean QTc (QT interval corrected for heart rate) was 397 ± 18 msec (± SD) at the fourth day, 409 ± 15 msec (p < 0.0001) at the second month, and 406 ± 15 msec at the fourth month; by the sixth month, it returned to 400 ± 14 msec. In 88 newborns, the QTc increased by over 40 msec at the second month. Among the 2000 infants checked at 1 year, there have been three sudden and unexpected deaths. The QTc of one of the victims at the fourth day was 563 msec, which exceeded the mean by more than 9 standard deviations, while the QTc of the other SIDS victims exceeded the mean by more than 2 and 3 standard deviations. These results are consistent with the "QT hypothesis," but more data are necessary before any conclusion on the potential relationship between QT interval prolongation and SIDS can be drawn. This study provides definitive waking normal values for QT interval in infancy and indicates that the QT interval lengthens physiologically and temporarily during the first months of life. In some infants, this lengthening may transiently impair cardiac electrical stability.

DELAYED ventricular repolarization, usually measured as prolongation of the QT interval, is closely associated with an increased incidence of sudden death.1 This is true not only when the prolongation of the QT interval is idiopathic, as in the long QT syndrome,2-4 but also when it is secondary to treatment with various drugs5-8 or to coronary artery disease, as in patients9 and in animals10 with myocardial infarction.

Careful examination of the QT interval may allow early identification of patients at high risk for sudden cardiac death.11 Furthermore, the QT interval is largely affected by manipulations of the autonomic nervous system, as shown by studies in animals12,13 and in man.14,15 Thus, prolongation of the QT interval seems to be a counterpart of a specific imbalance in the cardiac sympathetic innervation characterized by dominance of left-sided nerves. This kind of imbalance reduces cardiac electrical stability and favors the development of ventricular fibrillation.16-18

Sudden death is by no means limited to adulthood; it represents a major and tragic problem in infancy, particularly at a time of important developmental changes in the cardiac sympathetic innervation.19 There is almost a consensus that the sudden infant death syndrome (SIDS) depends on a respiratory defect; nonetheless, the possibility that part of SIDS may depend on a cardiac abnormality is logically tenable20 and has not yet been discounted. These and other considerations led Schwartz to hypothesize that in at least some of the SIDS victims, a developmental imbalance in the cardiac sympathetic innervation may predispose to ventricular fibrillation and may be associated with temporary lengthening of the QT interval.21 Henceforth, this hypothesis will be referred to as the "QT hypothesis".

The data on the QT interval in normal infants22-25 are extremely limited in absolute numbers and do not provide sufficiently detailed longitudinal information. We undertook a large prospective study to provide a data base on the QT interval during infancy and to test the QT hypothesis.

The information acquired on over 4200 newborns already enrolled in the still ongoing prospective study provides sufficient data to draw conclusions regarding baseline values for QT interval and its fluctuations during infancy. The data do not yet allow any inference on the relationship between prolongation of the QT interval and SIDS.

Preliminary data have been presented.26

Methods

Since October 1976, 4205 newborns have been enrolled in the study. Standard ECGs are recorded (Hewlett-Packard 1504 A and 1511 A) on the fourth day of life to avoid the variability of the QT interval that is maximal during the first 3 days of life. During the recording on the fourth day, most babies appear to be asleep, but they are awake at the subsequent observations. The purpose of the study is explained to the mothers and they are invited to bring their babies for
additional visits at the second, fourth and sixth months of life. Initially, only the second month control was planned. A card indicating the dates for subsequent visits and listing the names and phone numbers of the investigating physicians for possible contacts is given to the mothers as a reminder. Two weeks before each scheduled visit, a standard letter is mailed to the families as a further reminder. If a baby is not brought in, a telephone contact is usually attempted. Not all of these measures were initially used. Phone calls are made periodically to check if the 1-year-old babies are alive and well. The infants were classified into one of three groups: normal or healthy babies; babies with various illnesses, such as respiratory distress, hyperbilirubinemia, congenital heart disease and various malformations; and premature babies or babies small for gestational age.

No data were available on the incidence of SIDS in Italy. Therefore, we used the surrogate method described by Peterson et al.,27 using the data relative to 121,000 live births in Milan in the years 1971–1976, to estimate the incidence of SIDS in the same area in which our prospective study was to be performed.

Blood tests for calcium levels were performed only when the QT interval was obviously prolonged. In most instances, the time interval between ECG recording and analysis prevented the feasibility of these tests before discharge from hospital.

The QT interval was always measured by the same investigator to avoid individual variability in measurements. It was calculated as \( \frac{Q - T}{R - R} \) in at least five nonconsecutive beats, using lead II, and five or more values were then averaged. We define prolonged QT intervals as those that exceed the mean by 3 standard deviations, although probably values greater than 2 standard deviations might be considered the upper limit of normal. These values are 451 msec on the fourth day, 454 at the second month, 451 at the fourth month and 442 at the sixth month.

Statistical analysis was performed using the \( t \) test for paired and unpaired observations. Values are reported as mean ± SD.

Results

As of March 1, 1982, 4205 newborns were enrolled in the study. The QTc values are listed in table 1.

Among the normal babies, the mean QTc at the fourth day (n = 3946) was 397 ± 18 msec, at the second month (n = 2418) 409 ± 15 msec (p < 0.0001), at the fourth month (n = 351) 406 ± 15 msec and at the sixth month (n = 234) it returns to 400 ± 14 msec (fig. 1). Since the increase in QTc at the second month might have been due to the difference in the number of newborns attending the four visits, an internal control study was performed for babies who did attend all the visits. The changes observed were exactly the same as those in the entire population under study.

In babies with various disease states, the QTc at the fourth day (n = 141) was 396 ± 22 msec and at the second month (n = 51) 398 ± 18 msec. In the group of premature babies, the QTc at the fourth day (n = 118) was 401 ± 24 msec and at the second month (n = 60) 400 ± 17 msec. In both of these groups, the number of babies observed after the second month is too small to provide meaningful information.

Thirty-five babies had a QTc that exceeded the mean by more than 3 standard deviations on at least one of the visits (table 2). Three of these babies were lost to follow-up despite extensive search. Two of the 35 had documented hypocalcemia, two died because of SIDS, one has to return for the second visit and all the others

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### Table 1. QT Interval (QTc) Throughout the First 6 Months of Life

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal infants</th>
<th>Premature or small infants*</th>
<th>Sick infants†</th>
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<td>QTc (msec)</td>
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*Includes infants small for gestational age.
†Includes infants admitted to the intensive care unit for any reason.
TABLE 2. Infants with Prolonged QT Interval: Changes with Time in QT Interval (msec)

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Italicized values exceed the mean by more than 3 SD.

*SID at 1 month.
†Documented hypocalcemia.
‡Lost to follow-up.
§Alive at 9 months.
6SID at 2 months.
**Twin of MC.

had a normalization of QTc at some time during their development. In the majority of the babies who had a normalization of QTc by the second month, hypocalcemia cannot be excluded because blood tests were performed only in a small minority of cases in which prolongation of the QTc interval was recognized at the time of ECG recording. In one infant the QTc was still

prolonged at 1 year, but became normal by the third year of life. At age 3 years, however, this child had episodes of atrioventricular nodal tachycardia.

Of the 2000 babies checked at 1 year, five died. Three were considered typical SIDS cases. The first had a QTc of 563 msec (which exceeded the mean by more than 9 standard deviations) and normal levels of calcium and potassium, and died at 1 month of life a few minutes after having been put to sleep for an afternoon nap (fig. 2). The second was found dead in his crib at the third month of life. His QTc was 417 msec at the fourth day and 440 msec at the second month (2 standard deviations over mean). The third SIDS victim was found dead at midnight when she was 2 months old. Her QTc on the fourth day was 460 msec. This

FIGURE 2. ECG of patient GS, a victim of sudden infant death syndrome, taken when he was 4 days old. Simultaneous recordings of leads D1, D2 and V1, as well as lead V2, are shown. The QTc is 563 msec. The heart rate fluctuates between 90 and 100 beats/min. A lower-than-normal heart rate is consistent with incomplete function of right-sided cardiac sympathetic nerves.
baby was born prematurely and had a twin whose QTc was even longer, 469 msec; the twin is now 3 months old and her QTc at the second month has returned to normal (420 msec). A fourth infant died at age 3 months because of bronchitis; his QTc at the first two controls was 407 and 413 msec, respectively. A fifth infant died at 4 months because of aortic stenosis; her QTc was 407 and 386 msec at the first two controls.

The incidence of SIDS in Milan, based on retrospective information relative to 121,000 births, was found to be 2.6 per 1000 live babies. This figure is similar to that reported in many countries.

Discussion

The present prospective study, based on over 4200 newborns, provides sufficient data to establish the normal values for the QT interval in infants and to demonstrate conclusively that it lengthens physiologically and temporarily during the first months of life.

**QT Interval**

Prolongation of the QT interval has attracted increasing attention, mostly because of its association with sudden death and with abnormalities in the sympathetic innervation of the heart. The incidence of sudden death is abnormally high in patients who show prolongation of the QT interval, whether idiopathic (long QT syndrome) or in association with ischemic heart disease or with various drugs such as quinidine, pentothal, disopyramide, sotalol and others.

There is an inverse relationship between length of the QT interval and cardiac electrical stability. Prolongation of the QT interval may occur in the absence of any cardiac abnormality as a direct result of an imbalance between right and left components of cardiac sympathetic innervation with a left dominance. This important effect was first demonstrated in anesthetized dogs and has since been observed in conscious cats and in man. Thus, prolongation of the QT interval may constitute the marker of an imbalance in cardiac sympathetic innervation with dominance of the left-sided nerves, which have recently been found to be highly arrhythmogenic. The possibility that a neurogenic prolongation of the QT interval, either congenital or developmental, may identify some of the future victims of SIDS has in part stimulated our study.

The lengthening of the QT interval at or before the second month of life and its return by 6 months to the values present at birth are important.

This observation has already been made partially by other investigators. Alimurung et al. compared two small groups of babies, ages 0–1 and 1–4 months, and found that the latter had a longer QT interval. Haddad et al. and Steinschneider, in studies on the effect of sleep stages on QT interval, also found that the QT interval prolonged after birth. On the other hand, Ziegler observed an opposite trend in his small series (28 and 38 babies at the first week and the second month, respectively), and this confirms the limited value of such observations. The study by Steinschneider, in which the QT interval at the first and fourth weeks of life was compared, suggests that lengthening may already occur during the first month of life.

The natural lengthening of the QT interval is important, certainly not because of the absolute difference between the means (12 msec) (although highly significant statistically, this would have no clinical relevance), but because it indicates a trend that occurs physiologically and temporarily. Some infants may "overshoot" and the modest and physiologic increase in QT interval may reach levels that impair the electrical stability of the heart for a limited period. As a matter of fact, 88 newborns (3.6%) increased their QT interval at the second month by more than 40 msec, 21 of them by more than 50 msec and two by more than 90 msec. These babies may thus be temporarily at risk of life-threatening arrhythmias if sympathetic activity is suddenly increased by any cause, such as an episode of prolonged apnea.

This finding indicates that in about 4% of babies, as suggested by the lengthening of the QT interval, cardiac electrical stability decreases transiently at the time when SIDS reaches its peak and, quite suggestively, returns to normal by the sixth month of life, after which time the incidence of SIDS becomes extremely low. Any hypothesis for SIDS must account for its characteristic age distribution, and our results show that the QT hypothesis is not at variance with the epidemiologic data.

The fact that among our premature infants, the lengthening of QT interval is not evident at the second month may be of interest, but their small number (n = 118) calls for caution. More data are needed before this finding can be interpreted.

Neonatal hypocalcemia may have contributed to the number of infants with prolonged QTc on the fourth day of life. One may assume that many, or most, of the infants who had a normalization of QTc at the second month may have been hypocalcemic at the time of the first ECG. This problem may be avoided by repeating an ECG 2 weeks after birth in all infants who initially had a prolonged QTc.

Kralios and Millar contributed important information about the development of cardiac sympathetic innervation, which is relevant to the QT hypothesis and to the data presented here. They found evidence in puppies for a nonuniform maturation of cardiac nerves and, more specifically, observed that at the third week of life there is a predominance of left-sided nerves. This may represent the explanation for the temporary prolongation of QT interval observed in normal babies and may provide the physiologic substrate for a time-limited decrease in electrical stability of the heart that favors life-threatening arrhythmias, as previously postulated.

**Limitations of the Study**

This study has shortcomings. The number of babies studied at the fourth and sixth months is small because in the original protocol, only the first two controls were planned, according to the
hypothesis that a prolonged QT interval might have been found in the "at risk" babies either at birth or during development. Only after we realized that at the second month the QT was significantly longer did we decide to explore its subsequent behavior. Also, in one of the two hospitals involved, logistic problems limited the study to the first two controls.

In prospective studies, parents of healthy babies are less likely to bring the babies for follow-up visits. Of the first 500 babies enrolled, only 25% were brought for the second month control. After institution of more aggressive recruitment, follow-up visits are currently almost 70%. Among the factors that contribute to this difficult problem are: the size of Milan, a city with almost 3 million inhabitants; the high number of non-stable immigrants; and a surprisingly high incidence of families without a telephone.

Not all babies in the participating hospitals have been enrolled, since the protocol required the recording to be made on fourth day of life. Infants born on Wednesdays and Thursdays were excluded because of technical problems in data acquisition.

Relationships with SIDS

Since its presentation, the QT hypothesis has generated a controversy. Our data do not yet allow relating QT prolongation to SIDS. Even the marked prolongation of QT interval in two of the victims must be viewed at most as an interesting anecdote. However, since the QT hypothesis has been proposed, two other cases of SIDS with QT prolongation manifest at birth have been reported and a similar one has not been published (McCormick: personal communication).

Although the general attitude toward a relationship between QT prolongation and SIDS is skeptical, the question is still entirely open because current views rest on the unchallenged conclusions of a few studies not critically analyzed. A detailed analysis of this controversy has been published.

The question of the role of a prolonged QT interval in part of SIDS can be answered only by the difficult and time-consuming acquisition and examination of the ECGs of a large number of SIDS victims. The continuation of our study should provide such an answer.

Acknowledgment

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