PROLONGATION OF THE QT INTERVAL AND THE SUDDEN INFANT DEATH SYNDROME

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ABSTRACT

Background   The sudden infant death syndrome (SIDS) is multifactorial in origin, but its causes remain unknown. We previously proposed that prolongation of the QT interval on the electrocardiogram, possibly resulting from a developmental abnormality in cardiac sympathetic innervation, may increase the risk of life-threatening ventricular arrhythmias and contribute to this devastating disorder. We prospectively tested this hypothesis.

Methods   Between 1976 and 1994, we recorded electrocardiograms on the third or fourth day of life in 34,442 newborns and followed them prospectively for one year. The QT interval was analyzed with and without correction for the heart rate.

Results   One-year follow-up data were available for 33,034 of the infants. There were 34 deaths, of which 24 were due to SIDS. The infants who died of SIDS had a longer corrected QT interval (QTc) than did the survivors (mean [±SD], 435±45 vs. 400±20 msec, P<0.01) and the infants who died from causes other than SIDS (393±24 msec, P<0.05). Moreover, 12 of the 24 SIDS victims but none of the other infants had a prolonged QTc (defined as a QTc greater than 440 msec). When the absolute QT interval was determined for similar cardiac-cycle lengths, it was found that 12 of the 24 infants who died of SIDS had a QT value exceeding the 97.5th percentile for the study group as a whole. The odds ratio for SIDS in infants with a prolonged QTc was 41.3 (95 percent confidence interval, 17.3 to 98.4).

Conclusions   Prolongation of the QT interval in the first week of life is strongly associated with SIDS. Neonatal electrocardiographic screening may permit the early identification of a substantial percentage of infants at risk for SIDS, and the institution of preventive measures may therefore be possible. (N Engl J Med 1998;338:1709-14.)

THE incidence of the sudden infant death syndrome (SIDS) has recently declined.[1] This trend followed the identification of several behavioral risk factors and their subsequent modification through public-education campaigns.[2] Nonetheless, SIDS remains the leading cause of death in the first year of life after the neonatal period, and effective preventive measures are still lacking because of the poor understanding of the mechanisms underlying the disorder. SIDS has devastating psychosocial consequences for the affected families.[3] There is a consensus that the cause of SIDS is multifactorial,[4] but despite the many hypotheses proposed,[5] none have yet been proved.

Most cases of SIDS probably result from a temporary defect in the neural control of either respiratory or cardiac function that may initiate a lethal sequence of events.[6] In 1976 one of us proposed that a developmental abnormality in cardiac sympathetic innervation may predispose some infants to lethal arrhythmias in the first year of life.[7] Specifically, it was suggested that an imbalance in the sympathetic nervous system may result in prolongation of the QT interval on the electrocardiogram and in potentially lethal ventricular arrhythmias.[8]

To test the hypothesis of a relation between prolongation of the QT interval and SIDS, we designed a multiyear, prospective study based on the recording of a standard electrocardiogram in three-to-four-day-old infants (the Multicenter Italian Study of Neonatal Electrocardiography and SIDS). Given the low incidence of SIDS (0.5 to 2 cases per 1000 live births), we prospectively collected neonatal electrocardiograms in a very large population of infants born in the period from 1976 through 1994 and followed the infants for one year to determine the incidence of death due to SIDS or to other causes. We now report the final results of this 19-year study.

METHODS

Study Population

Electrocardiograms were recorded in 34,442 neonates born in nine maternity hospitals (listed in the Appendix) between October 1976 and December 1994. Almost all the infants were healthy and born at full term, because most very premature and sick newborns were transferred to intensive care units before electrocardiography could be performed.

Electrocardiography

Twelve-lead electrocardiograms were recorded at a paper speed of 25 mm per second with Hewlett–Packard 1504 A and 1511 A recorders in the first part of the study and, since 1989, with a Marquette MAC PC recorder. All the recordings were made on the third or fourth day of life in order to avoid the variability of the QT interval that is maximal during the first two days of life.[9] RR and QT intervals were usually measured in lead II from five nonconsecutive beats, and the corrected QT interval (QTc) was calculated by dividing the QT interval by the square root of the RR interval (Bazett's formula).[10] We analyzed the electrocardiograms of all infants who died and those of a random sample of 9725 surviving infants (4867 boys and 4858 girls). Since the heart rate is elevated in the neonatal period, Bazett's formula may not be appropriate for correcting the QT interval for short cardiac-cycle lengths. Accordingly, we also divided the RR intervals into 17 categories with progressively increasing values (in increments of 20 msec); for each category we calculated the percentile distribution of the corresponding absolute values of the QT interval (from the 2.5th to the 97.5th percentile).

Follow-up

Information on survival at one year was obtained either by telephone or by mail through the census bureau for the cities where the infants' families resided. In cases of death, all the relevant records were analyzed. The diagnosis of SIDS was based on an adequate negative postmortem examination (i.e., on the absence of evidence of other causes of death) and on traditional criteria.[11]

Statistical Analysis

The distribution of values for the heart rate, QT interval, and QTc was assessed, and percentile values (from the 2.5th to the 97.5th percentile) were calculated. Differences in electrocardiographic measurements between groups were assessed by analysis of variance and Student's t-test with Bonferroni's correction, or by the Kruskal–Wallis test for non-normally distributed values. The frequency of outcomes was compared by means of chi-square analysis and Fisher's exact test. Odds ratios and 95 percent confidence intervals were calculated for all variables under study. A multiple logistic-regression analysis was performed, including the effects of sex, QTc, and heart rate. Data are presented as means ±SD. A two-sided P value below 0.05 was considered to indicate statistical significance.

RESULTS

Electrocardiographic Characteristics

Of the 34,442 infants enrolled, one-year follow-up data were available for 33,034 (96 percent; 16,538 boys and 16,496 girls). The remaining 1408 were lost to follow-up when their families moved.

The distribution of values for the heart rate, QT interval, and QTc was normal (P<0.001). The mean heart rate was 135±20 beats per minute, the mean PR interval was 113±23 msec, the duration of the QRS complex was 57±7 msec, and the QT interval was 274±28 msec. The mean QTc was 400±20 msec, confirming our earlier observation based on data on 3946 infants,[12] and it did not differ significantly between boys and girls (401±19 and 400±20 msec, respectively). The 97.5th percentile for the QTc among the infants was 440 msec, 2 SD above the mean. Consequently, we considered a QTc greater than 440 msec to be prolonged.

Incidence of Death Due to SIDS and Other Causes

During the one year of follow-up, there were 34 deaths: 24 due to SIDS and 10 due to other causes. The number of deaths from causes other than SIDS was low, probably because most of the infants who were sick at birth did not enter the study. The incidence of SIDS in this population was 0.7 per 1000, similar to that reported for Italy.[6]

Characteristics of Infants Who Died

Table 1 shows the characteristics of the infants who died of SIDS and those who died of other causes. The distribution of boys and girls was similar among survivors and infants who died of causes other than SIDS; the slight excess of boys among the infants who died of SIDS (15 of 24 infants [62 percent]) was not statistically significant (odds ratio for death among boys as compared with girls, 1.7; 95 percent confidence interval, 0.7 to 3.8). Most deaths due to SIDS (18 of 24 [75 percent]) occurred in the second or third month of life, as is typical of this disease, whereas other deaths occurred either during the first or after the third month of life. No victim of SIDS had a family history consistent with the long-QT syndrome.

Electrocardiographic Findings

The mean heart rate among the infants who died of SIDS was 136±20 beats per minute and did not differ from that among the infants who died of other causes (140±21 beats per minute, P not significant) or among the survivors (135±20 beats per minute, P not significant). The mean QTc was 435±45 msec in the group of infants who died of SIDS, significantly longer than that among the infants with other causes of death (393±24 msec, P<0.05) and that of the survivors (400±20 msec, P<0.01) (Fig. 1). More important, the analysis of the individual values for QTc in the two groups of infants who died (Fig. 1)

TABLE 1. CHARACTERISTICS OF THE INFANTS WHO DIED OF SIDS AND THOSE WHO DIED OF OTHER CAUSES.

PATIENT NO.	SEX	AGE AT DEATH (DAYS)	HEART RATE (BEATS/MIN)	QTc (MSEC)
Death due to SIDS				
1	M	8	130	477
2	M	18	150	448
3	M	20	147	444
4	M	32	95	563
5	F	43	128	451
6	M	49	115	514
7	M	56	110	399
8	F	57	112	381
9	F	58	148	408
10	F	58	106	380
11	M	62	145	368
12	M	63	143	435
13	M	64	171	403
14	F	68	129	460
15	M	69	127	407
16	M	80	136	394
17	M	84	149	391
18	M	89	132	456
19	F	90	166	473
20	F	90	166	433
21	F	92	154	448
22	F	120	150	412
23	M	135	115	444
24	M	258	155	456
Death due to other causes				
1	F	10	170	417
2	M	20	122	389
3	F	22	136	422
4	F	24	150	405
5	M	27	157	344
6	F	128	155	386
7	M	187	132	402
8	M	230	145	400
9	F	243	149	407
10	F	281	93	363

Figure 1. Mean QT Interval Corrected for Heart Rate (QTc) in 9725 Infants Who Were Alive at One Year, 24 Infants Who Died of SIDS, and 10 Infants Who Died of Other Causes.

The horizontal line represents the value of QTc at the 97.5th percentile for the entire study population. The circles represent individual values for QTc, and the bars indicate the SD. The mean QTc for the infants who died of SIDS was significantly longer than that for the infants who were alive at one year (P<0.01) and that of the infants who died of other causes (P<0.05).

showed that 12 of the 24 infants who died of SIDS (50 percent) had a QTc greater than 440 msec, whereas all the infants who died from other causes had a QTc shorter than 440 msec. Among the infants who died of SIDS, no significant difference was found in the duration of the QT interval between premature and full-term babies (439±26 and 433±50 msec, respectively). Furthermore, these findings were similar in our analysis of the relation between the absolute QT intervals and RR intervals. As Figure 2 shows, the individual values in 12 of the 24 infants who died of SIDS (50 percent) were at or above the 97.5th percentile, whereas all the values in the infants who died of other causes were below the 90th percentile.

The absolute risk of SIDS in infants with a normal QTc was 0.037 percent; by contrast, that of infants with a prolonged QTc was 1.53 percent (odds ratio, 41.3; 95 percent confidence interval, 17.3 to 98.4). Among the victims of SIDS, the incidence of a prol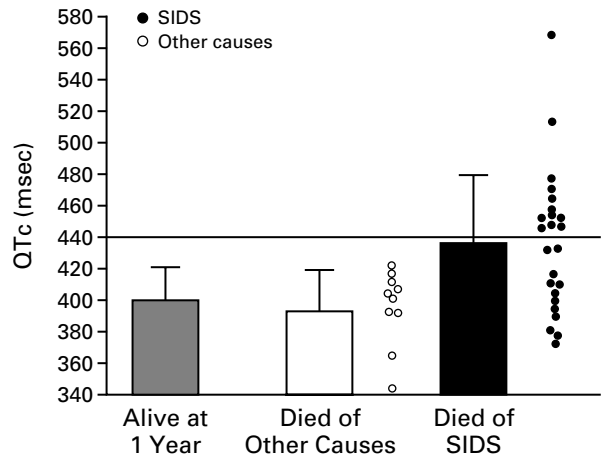onged QTc was similar in boys (8 of 15 infants [53 percent]) and girls (4 of 9 [44 percent]), despite a trend toward longer QTc values among boys (439±51 vs. 422±31 msec, P not significant). As compared with infants of the same sex with a normal QTc, boys with a QTc above 440 msec had an odds ratio for SIDS of 46.9 (95 percent confidence interval, 15.4 to 144.2), and girls with a QTc above 440 msec had an odds ratio of 33.0 (95 percent confidence interval, 7.4 to 141.7). Multiple logistic-regression analysis, including the effect of sex, heart rate, and QTc, showed that only the QTc was a significant predictor of SIDS (P<0.001).

DISCUSSION

This large, prospective study of more than 33,000 infants born during a 19-year period demonstrates that prolongation of the QT interval on the electrocardiogram is an important risk factor for SIDS. This finding points to pathogenetic mechanisms that may be involved in a large proportion of cases of SIDS and also suggests rational preventive strategies.

The "Normal" Neonatal Electrocardiogram

We collected a large body of electrocardiographic data recorded in the first week of life, which contribute to the definition of normal electrocardiographic standards for newborns. Most previous studies have been of older infants or have included fewer electrocardiograms.[9,13-15] In the study by Southall et al., which is an exception to this pattern,[16] most electrocardiograms were recorded before the third day, when
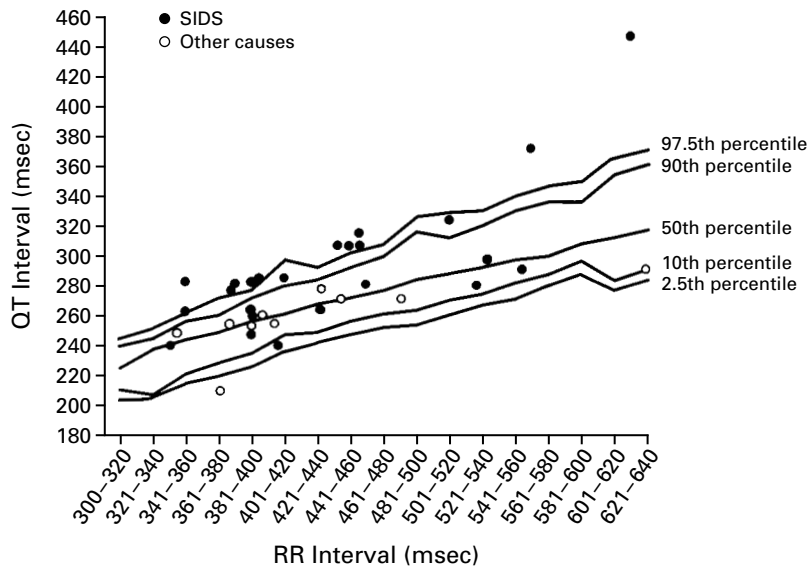
Figure 2. Relation between the Duration of the QT Interval and the Length of the Cardiac Cycle.
The curves represent the percentiles for uncorrected QT intervals at the corresponding range of values for the RR interval. The circles represent individual values for the 24 infants who died of SIDS and the 10 who died of other causes.

there is still marked variability in the QT interval in individual subjects.

The mean heart rate and QTc were similar to those previously reported during the first week of life.[9,13,14] Among adults, women have a longer QTc than men,[17] but in a previous study of neonates, we found no difference according to sex.[18] For newborns, unlike adults,[19] a QTc of 440 msec should be considered the upper limit of normal for both males and females.

Prolongation of the QT Interval and SIDS

Our results show that QTc measured on the third or fourth day of life is prolonged in infants who subsequently die of SIDS as compared with infants who survive for at least one year and also as compared with infants who die of other causes. The odds ratio for SIDS among infants with a QTc greater than 440 msec was approximately 41, and in boys it was approximately 47. Consequently, a prolonged QT interval in the first week of life represents an important risk factor, and this information may be useful in the early identification of infants at risk for SIDS. The other traditional risk factors, such as sleeping in a prone position, maternal smoking, and bed sharing, have odds ratios markedly lower than those we observed with prolongation of the QT interval.[20,21]

The original hypothesis that prolongation of the QT interval may have a role in the pathogenesis of SIDS was prematurely discarded on the basis of a series of apparently negative results.[16,22-25] However, most of those studies were performed in very small populations or focused on infants assumed to be at increased risk for SIDS, such as the siblings of SIDS victims[23,25] or infants who had had so-called near-miss or aborted SIDS.[22-24] As discussed in detail elsewhere,[4,26] conclusions drawn from these studies are not relevant to the assessment of the risk of SIDS associated with prolongation of the QT interval, for several reasons. Among the infants considered at risk for SIDS, even assuming that risk increases by a factor of 5 to 10, the probability of SIDS would approximate 10 per 1000, which would imply a 99 percent rate of false positives. In a population of infants most of whom will not die of SIDS, the absence of a prolonged QT interval obviously has no implications.

Southall et al.[16] prospectively studied 7254 infants, 15 of whom subsequently died of SIDS, and compared the mean values for QTc between those who died and the survivors. Even though they concluded that there was no significant difference between victims of SIDS and controls, 6 of the 15 infants who died of SIDS (40 percent) had a QTc exceeding the 90th percentile for the study population, with an odds ratio of 6. The combined results of the study by Southall et al.[16] and our study, which together involved more than 40,000 infants, suggest that even at a very conservative estimate, probably not less than 30 to 35 percent of infants who subsequently die of SIDS can be expected to have a prolonged QT interval in the first week of life.

The possibility that inadequate shortening of the QT interval during increases in the heart rate may be involved in SIDS was suggested by Sadeh et al.,[27]

on the basis of nighttime findings in 5 of 10 infants who subsequently died of SIDS. However, this finding was not confirmed when the analysis of the same infants was extended to the entire 24-hour period.[28]

Prolongation of the QT Interval and Susceptibility to Lethal Arrhythmias

Our finding of a strong association between SIDS and prolongation of the QT interval, a marker of reduced cardiac electrical stability,[29] suggests that some infants may have an increased susceptibility to life-threatening arrhythmias. Prolongation of the QT interval favors the occurrence of lethal arrhythmias and is associated with an increased risk of sudden death in several clinical conditions[30-32] and even in apparently healthy persons.[33] We have shown that the QTc increases during the second month of life and returns to the values recorded at birth by the sixth month.[12] These data agree with the epidemiologic observation that SIDS is rare during the first month of life, has a peak incidence during the second and third months, and declines after the fourth.[5,6] Thus, there is a tendency, which in some infants may become excessive, toward a reduction in cardiac electrical stability during the period when the incidence of SIDS is highest.

In the population we studied, the fact that many infants with prolonged QT intervals did not die of SIDS indicates that other factors in the postnatal period contribute to the lethal event. This assumption is consistent with the concept that prolongation of the QT interval acts as an arrhythmogenic substrate, which requires a trigger for the development of life-threatening arrhythmias. Prolongation of the QT interval, even in neonates,[34] is almost always associated with increased dispersion of ventricular repolarization, a factor that favors arrhythmias — particularly when sympathetic activity is augmented.[8] The likelihood that life-threatening arrhythmia will develop in an infant with an arrhythmogenic substrate — that is, with prolongation of the QT interval — depends on the presence of adequate triggers, such as the release of catecholamines or factors (such as drug therapy) that further prolong the QT interval.

Potential Causes of Prolongation of the QT Interval in Infants

Why is the QT interval prolonged in some newborns? Two mechanisms may be proposed. The first, based on the hypothesis proposed by one of us,[7] suggests that prolongation of the QT interval may depend on developmental alterations in cardiac sympathetic innervation.[35,36] The sympathetic innervation of the heart continues to develop after birth and becomes functionally complete by approximately the sixth month of life.[37] The right and left sympathetic nerves may occasionally develop at different rates and lead temporarily to a harmful imbalance.[8,36] A sudden increase in sympathetic activity may trig-

ger lethal arrhythmias in such electrically unstable hearts. Infants with these characteristics would be particularly vulnerable during the first year of life, and their higher risk of SIDS could be identified by the observation of a prolonged QT interval.

A second possibility involves a genetic abnormality. Some victims of SIDS may have a variant of the congenital long-QT syndrome. This disorder is characterized by prolongation of the QT interval and a high risk of sudden death, mostly under stressful conditions but also during sleep; it is usually familial but may be sporadic.[30,38] Four of the genes responsible for the long-QT syndrome have been identified, and they all encode sodium and potassium channels.[39] However, SIDS is not a familial disease. What is relevant to SIDS is that in sporadic cases of the long-QT syndrome, spontaneous mutations have been found. Infants with spontaneous mutations that affected one of the ionic currents controlling ventricular repolarization would also have a prolonged QT interval. Some of them might die because of ventricular fibrillation during the first few months of life,[40] and if no electrocardiogram were available, they would be labeled as having died of SIDS. Others might begin to have syncopal episodes during childhood and would then be diagnosed as having sporadic cases of the long-QT syndrome.

There is an additional genetic possibility. In some families with the long-QT syndrome, penetrance is so low that both parents and all siblings of clinically affected patients may have a completely normal QT interval and nonetheless be gene carriers.[41] In such a case, if the affected infant died suddenly without an electrocardiogram having been recorded, the examination of the family would reveal no prolongation of the QT interval. Without molecular diagnosis, the death would be ascribed to SIDS.

Clinical Implications

Our data, which document a significant association between prolongation of the QT interval and SIDS, also raise two further issues. One is the potential value of routine neonatal screening by electrocardiography; the other is the treatment strategy for the infants who are found to have a prolonged QTc. Screening may be warranted, because it is likely to identify some infants at high risk for SIDS. However, formal cost-effectiveness studies will be required before such a practice is implemented. Our study contains no data to justify new therapeutic recommendations. However, the identification of a mechanism that may be involved in the pathogenesis of SIDS allows some cautious speculation.

The lethal arrhythmias associated with prolongation of the QT interval are almost always torsade-de-pointes ventricular tachycardia due to early after-depolarizations and are usually triggered by sudden increases in sympathetic activity.[8] In the first year of

life, such an increase may be elicited often by a number of conditions, including sudden noise, exposure to cold, rapid-eye-movement sleep, apnea leading to a chemoreceptive reflex, and arousal.[5] In the long-QT syndrome, antiadrenergic interventions are quite beneficial.[30] It is plausible that infants with a prolonged QT interval, who are at high risk for SIDS on the basis of our data, could be protected by the careful administration of beta-blockers during the first year of life.

Even if our hypothesis were proved to be correct, however, such identification and treatment would not be a simple task. The low incidence of SIDS contributes to the low positive predictive value of QT-interval prolongation. Thus, not only would a large number of infants need to be screened to identify those with prolongation of the QT interval, but also 100 infants would have to be treated in order to save 2 lives. Additional information is needed to identify infants at risk for SIDS more precisely, so that preventive interventions can be targeted effectively.

APPENDIX

The following centers and investigators participated in the Multicenter Italian Study of Neonatal Electrocardiography and SIDS: *University of Milan, Milan (coordinating center)* — P.J. Schwartz, M. Stramba-Badiale, A. Segantini, F. Grancini, P. Careddu, V. Carnelli, M. Facchini, M. Montemerlo, M. Frediani, S. Guffanti, M. Negrini, F. Palla, N. Porta, P. Rusinenti, and T. Varisco; *Ospedale Regina Elena, Milan* — D. Rosti and P. Salice; *Ospedale Galmarini, Tradate* — R. Giorgetti and G. Poggio; *Ospedale Niguarda, Milan* — P. Austoni; *University of Ferrara, Ferrara* — G. Bosi; *University of Reggio Calabria, Catanzaro:* F. Perticone; *University of Rome, Rome* — S. Pelargonio; *University of Pavia, Pavia* — E.D. Marni; *Ospedale Regina Margherita, Turin* — M.G. Broveglio-Ferri; *University of Florence, Florence* — G. Mainardi.

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