# QT interval measurements before sudden infant death syndrome

D P SOUTHALL, W A ARROWSMITH, V STEBBENS, AND J R ALEXANDER

*Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London, Doncaster Royal Infirmary, Doncaster, South Yorkshire, and Department of Mathematics, Statistics and Computing, Thames Polytechnic, London*

SUMMARY    Standard electrocardiogram recordings were performed on a total of 7254 newly born infants from two maternity hospitals. Fifteen recordings were obtained on 15 infants who subsequently suffered sudden infant death syndrome. None showed lengthening of QT intervals sufficient to warrant the description of 'long QT syndrome'.

When the QT intervals corrected for heart rate of cases with sudden infant death syndrome were compared with controls in age matched groups or after individual matching for postnatal age, hospital of birth, and weight at birth, no significant differences could be identified.

Lengthening of the QT interval and an associated vulnerability to ventricular arrhythmias and sudden death is an attractive hypothesis put forward to explain some examples of sudden infant death syndrome.[1] Unfortunately, studies on infants believed to be at high risk, namely 'near miss' cases,[2 3] subsequent siblings of victims of sudden infant death syndrome,[4] or other relatives of cases with the syndrome[5 6] have yielded conflicting results that have failed to substantiate or to reject the hypothesis.

In 1979 we reported an infant with the long QT syndrome, which was undiagnosed before sudden death without abnormal findings detected at the postmortem examination.[7] A coroner labelled this death as sudden infant death syndrome, and it clearly became important to know how often a prolongation of the QT interval was escaping detection and contributing to the pathogenesis of sudden infant death syndrome.

In our large prospective study involving 24 hour tape recordings of electrocardiograms (ECG) in the newborn period on 29 infants who subsequently suffered sudden infant death syndrome, none showed a major lengthening of the QT interval, and there were no apparent differences between the QT intervals of cases and controls.[8] However, the amplifiers within individual 24 hour tape recorders had slightly differing frequency responses, and it was considered that, although these results excluded gross prolongation of the QT interval, less clear cut differences in the distribution of QT measurements

in cases with the syndrome might have been masked by differences between recorders.

In 1982 Schwartz *et al* published QT interval measurements on a population of 4205 infants.[9] Three of this sample subsequently died suddenly and unexpectedly. Although details of postmortem examinations were not given and therefore the diagnosis of sudden infant death syndrome was not established, these three infants showed lengthening of the QT interval compared with controls.

In this paper we present two prospective studies involving standard ECG recordings on over 7000 infants, yielding recordings on 15 infants who subsequently suffered sudden infant death syndrome. The diagnosis of sudden infant death syndrome was made only after a full postmortem examination, including histological and microbiological investigations.

We also report an analysis of the reproducibility of QT interval measurement from the standard ECG recording.

## Patients and methods

Two populations were studied.

**(1) Doncaster study.** From September 1982 to August 1983 infants born at the Doncaster Royal Infirmary, a hospital that caters for all deliveries in the area (except for a small number born at home), underwent a standard ECG recording before discharge from hospital (majority ≤3 days of age). If

Table 1   Clinical details of the 15 infants with sudden infant death syndrome

| Case No | Age at recording (days) | Sex | Pregnancy complications | Mother's age (years) | Smoking during pregnancy | Birth weight (g) | Gestation (clinical weeks) | Delivery | Apgar score at 1 and 5 minutes | Postnatal illnesses | Feeding history | Age at death (days) | Postmortem examination |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Doncaster:* | | | | | | | | | | | | | |
| 1 | 29 | F | Triplet number 1 | 25 | No record | 1200 | 31 | Breech with forceps | 2, 4 | Small ventricular septal defect | Bottle | 96 | Sudden infant death syndrome + small ventricular septal defect |
| 2 | 2 | M | Threatened abortion | 23 | No record | 3350 | 40 | Normal | 8, 10 | None | Bottle | 52 | Sudden infant death syndrome |
| 3 | 1 | M | Pre-eclamptic toxaemia | 27 | Yes | 3490 | 38 | Normal | 8, 10 | None | Breast→bottle | 143 | Sudden infant death syndrome |
| 4 | 2 | M | Hyperemesis | 20 | No record | 3320 | 38 | Normal | 6, 10 | Upper respiratory tract infection 14 and 39 days | Bottle | 44 | Initial resuscitation 24 hours sudden infant death syndrome |
| 5 | 3 | M | Shirodkhar suture | 25 | No record | 3120 | 39 | Normal | 9, 10 | Bronchiolitis 8 weeks | Bottle | 161 | Sudden infant death syndrome |
| 6 | 3 | F | None | 19 | None | 4030 | 40 | Normal | 9, 10 | None | Breast | 29 | Sudden infant death syndrome |
| 7 | 1 | F | None | 23 | Yes | 2920 | 40 | Normal | 8, 10 | None | Bottle | 286 | Sudden infant death syndrome |
| 8 | 2 | F | Premature labour; salbutamol, dexamethasone | 19 | None | 2920 | 32 | Forceps | 9, 10 | None | Bottle | 191 | Sudden infant death syndrome |
| *Dorset:* | | | | | | | | | | | | | |
| 9 | 7 | M | Thyrotoxicosis; propranolol, carbimazole | 24 | None | 2860 | 38 | Normal | 9, 10 | None | Bottle | 69 | Sudden infant death syndrome + upper respiratory tract infection |
| 10 | 1 | M | None | 20 | No record | 3750 | 38 | Normal | 8, 10 | None | Bottle | 59 | Sudden infant death syndrome + upper respiratory tract infection |
| 11 | 5 | M | Twin 1 | 19 | No record | 2650 | 38 | Normal | 8, 9 | Upper respiratory tract infection day 10 | Breast | 117 | Sudden infant death syndrome + upper respiratory tract infection |
| 12 | 1 | F | Premature rupture of membranes at 33 weeks | 26 | No record | 1960 | 35 | Normal | 8, 10 | Urinary tract infection day 23 | Breast | 88 | Sudden infant death syndrome + upper respiratory tract infection |
| 13 | 8 | F | None | 21 | No record | 3600 | 40 | Normal | 9, 10 | None | Bottle | 59 | Sudden infant death syndrome |
| 14 | 28 | M | Premature labour | 25 | Yes | 1450 | 32 | Normal | 5, 2 (oxygen bag and mask) | Mild respiratory distress syndrome, patent ductus arteriosus 28–32 days | Breast | 85 | Sudden infant death syndrome |
| 15 | 8 | M | Asthma; salbutamol, chlorphenira-mine, choline theophyllinate, beclomethasone | 25 | None | 4430 | 40 | Vacuum | 9, 10 | Lower respiratory tract infection day 76, jittery day 2 | Bottle | 125 | Sudden infant death syndrome + upper respiratory tract infection |

the infant was discharged before the recording could be completed a research assistant went to the home during the subsequent week and made the recording. All home deliveries were also included. There were no refusals, but roughly 40 infants born during this period were not studied because of technical difficulties. A total of 3871 underwent recordings, including eight who subsequently suffered sudden infant death syndrome (Table 1). Two of these eight infants (cases 1 and 8) were preterm (31 and 32 weeks). Their post conceptional ages at recording were 35 and 33 weeks. Roughly 7% of the controls were recorded at a similar post conceptional age.

**(2) Dorset study.** Details of this project have already been reported.[10–12] Of 3383 infants who underwent standard ECG recordings in the neonatal period, seven subsequently suffered sudden infant death syndrome (seven recordings) (Table 1). These seven recordings were mixed with 956 randomly selected, postnatal age matched controls and measurements made blind by the technicians in Doncaster who performed the study described above. Two of the seven infants (cases 12 and 14) were preterm (35 weeks and 32 weeks). Their post conceptional ages at recording were 35 weeks and 36 weeks, respectively. Roughly 6% of the controls were recorded at post conceptional ages of 35 and 36 weeks.

**Methods of recording.** In Doncaster recordings were made with the infant lying as quietly as possible, either sucking a sterile teat or asleep. The aim was to avoid recordings at high heart rates (>150 bpm) where measurements of QT intervals had been found to be difficult and poorly reproducible.

In Dorset no attempt was made to control whether the infant was awake or asleep or to obtain heart rates <150 bpm when recordings were undertaken.

Informed consent was obtained from one of the parents in all cases studied.

In Doncaster recordings were made with a Cambridge Instruments portable ECG machine (VS550). Only the standard limb leads and V1 chest lead were recorded. In the Dorset study recordings were made with a Hewlett Packard 1504B portable ECG machine. All limb and chest leads were recorded.

Roughly five ECG complexes/lead were recorded, and in every case a two minute rhythm strip of lead II was included.

**Group matched, single measurement analysis.** In Doncaster measurements were made on the day of recording. To improve the reproducibility the interval with the most clear cut end to the T wave was selected by one of two technicians. The QT interval, its immediately preceding RR interval, and the

QTc ($QTc=QT/\sqrt{RR}$) were calculated. All three measurements were logged together with infant name, number, and age. Intervals containing U waves were rarely identified and were not included in these measurements. The Dorset cases with the syndrome and controls were similarly measured blind by the same two technicians.

The values for the 15 cases with the syndrome were compared with their respective control populations by age group, using the Van Elteren modified Wilcoxon rank sum test,[13] which takes account of stratification by age group.

**Matched control, multiple measurement analysis.** To control for the effect of birth weight and to include measurements on all possible QRS complexes in the ECG recording, a group of 10 controls was selected for each of the 15 cases with the syndrome, matched closely on recording age, birth weight, and hospital of birth. With the exception of two low birthweight infants, the mean birth weight of the matched controls was within roughly 5% of the weight of the infant with the syndrome. In almost all cases the age at recording was matched exactly, with the exception of one baby recorded at 28 days. Although it was necessary to select from a wide age range to obtain the controls for this infant, the mean recording age of the selected controls was 27·2 days. For all of these controls and the cases with the syndrome repeated measurements of QT were obtained whenever the end of the T wave could be identified and for every heart beat in which there was a preceding RR interval. The number of measurements for each case or control varied from four to 82.

For each beat measured QTc was calculated using Bazett's formula [$QTc=QT/\sqrt{RR}$], and the mean, median, and quartiles of the QTc measurements for each case with the syndrome compared with the mean of the corresponding statistics for controls using the Wilcoxon signed rank test.

Because the QTc formula may over compensate for the effect of heart rate on QT interval duration additional methods of standardising QT were also employed, and the mean standardised values for each case with the syndrome compared with the mean of its controls using the same statistical methods. The two additional methods of standardising QT were (a) fitting a linear regression for each control subject of QT on RR and interpolating for each control subject the value for the QT interval at the mean RR interval for the measurement made on their matching case with the syndrome, and (b) fitting a linear regression for each control of QTc on RR and interpolating as above for each control subject the value for the QTc at the mean RR

interval for the measurements made on their matching case with the syndrome. The latter two methods follow a suggestion of Wynne (Wynne V. Personal communication). The median and quartile values for cases and controls were also obtained for these QTc interval measurements corrected for heart rate and, like the mean values (see above), compared using the Wilcoxon signed rank test (as above).

**Assessment of ECG machines.** To assess the inter-machine variability of QT interval recordings made on the two different ECG recorders, a 1 Hz square wave signal at 1 mV peak to peak was injected into the two machines. The 1 Hz signal was measured using a counter timer to within $\pm0.1\%$. A section of 25 cm of recording was obtained at a chart speed of 25 mm/sec and the intervals between square waves measured.

**Inter-rater reproducibility of QT interval measurement.** To test the reproducibility of measurement, 100 ECGs from the Dorset study were presented to seven doctors, who were asked to measure RR and QT intervals and calculate QTc on every ECG complex within each recording that showed a satisfactory end to the T wave.

### Results

**Population distribution of QTc in control infants.** Mean and standard deviations for QT intervals corrected for heart rate by age are shown in Table 2 for the two populations. Figures 1 and 2 show the centiles by age for QTc measurements in controls and the individual QTc values for infants who subsequently suffered sudden infant death syndrome.

The population distribution of QTc is symmetrical in all age groups but is not normal. There is a tendency towards excess kurtosis (that is, an excess of extreme values compared to the normal distribution), which is pronounced in the first 2 days of life and persists through to 2 weeks and beyond.
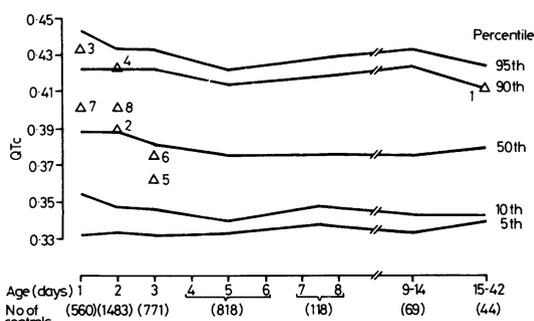


Fig. 1    *The position of QT interval measurements corrected for heart rate (calculated using Bazett's formula) on the eight cases with sudden infant death syndrome (numbered as in Table 1) from the Doncaster study plotted against postnatal age. The percentile lines illustrate values for the controls at the median age of each age group.*
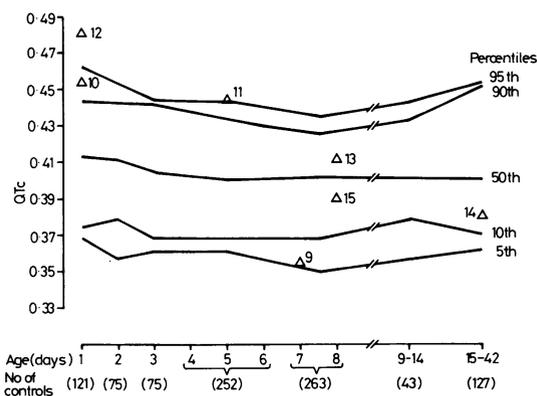


Fig. 2    *The position of QT interval measurements corrected for heart rate (calculated using Bazett's formula) on the seven cases with sudden infant death syndrome (numbered as in Table 1) from the Dorset study plotted against postnatal age. The percentile lines illustrate values for the controls at the median age of each age group.*

Table 2    *Summary of QTc intervals in Doncaster and Dorset*

| Age at recording (days) | Doncaster | | Dorset | |
|---|---|---|---|---|
| | No of recordings | Mean (SD) QTc | No of recordings | Mean (SD) QTc |
| 1 | 560 | 0·388 (0·033) | 121 | 0·411 (0·028) |
| 2 | 1483 | 0·385 (0·031) | 75 | 0·411 (0·028) |
| 3 | 771 | 0·382 (0·031) | 75 | 0·402 (0·026) |
| 4–6 | 818 | 0·376 (0·029) | 252 | 0·401 (0·026) |
| 7–8 | 118 | 0·382 (0·028) | 263 | 0·403 (0·029) |
| 9–14 | 69 | 0·378 (0·035) | 43 | 0·406 (0·027) |
| 15–42 | 44 | 0·379 (0·027) | 127 | 0·409 (0·029) |

The median QTc in the control populations can be seen to fall by around 2% in the first week of life and remain fairly stable for the next 3 weeks (Figures 1 and 2). Data are available from one of our centres to 3 months and beyond, and this indicates that the median QTc rises by around 5% during the second and third months of life.

**Differences between the results for the two control populations.** The differences in location and scale between the distributions in the two populations might be accounted for by differences in machine speed and machine variability as well as differences in the way infants were recorded.

The recorder speeds both differed from 25 mm/sec. The bias was −4·8% in the Cambridge chart speed and +4·4% in the Hewlett Packard chart speed. We have not made any adjustments to the data presented in this paper to compensate for these biases.

The mean recorded RR interval for the Dorset population, retrospectively measured by the technicians, was shorter than that for the Doncaster infants, and the standard deviation was also lower. This probably arose as a result of attempts in Doncaster to record the infants at heart rates below 150 bpm.

**Inter-rater reproducibility.** Systematic inter-rater variability between the seven doctors was highly significant (p<0·001, analysis of variance), the raters' mean scores for the one hundred recordings differing by a maximum of 0·018 seconds, or around 4·5%.

The standard deviation of QTc measurements between different assessments of the same recording with the same rater can be estimated from the analysis of variance as 0·027, or around 7%. This gives a 95% confidence band of ±0·05 seconds for a single observation.

**Group matched, single measurement analysis.** Figures 1 and 2 show the QTc measurement for 15 recordings on the 15 infants with the syndrome plotted onto the percentile charts for Doncaster and Dorset, respectively.

The values for the 15 infants, when compared with their respective control populations by age group, using a Van Elteren modified Wilcoxon rank sum test, did not show more than marginal evidence
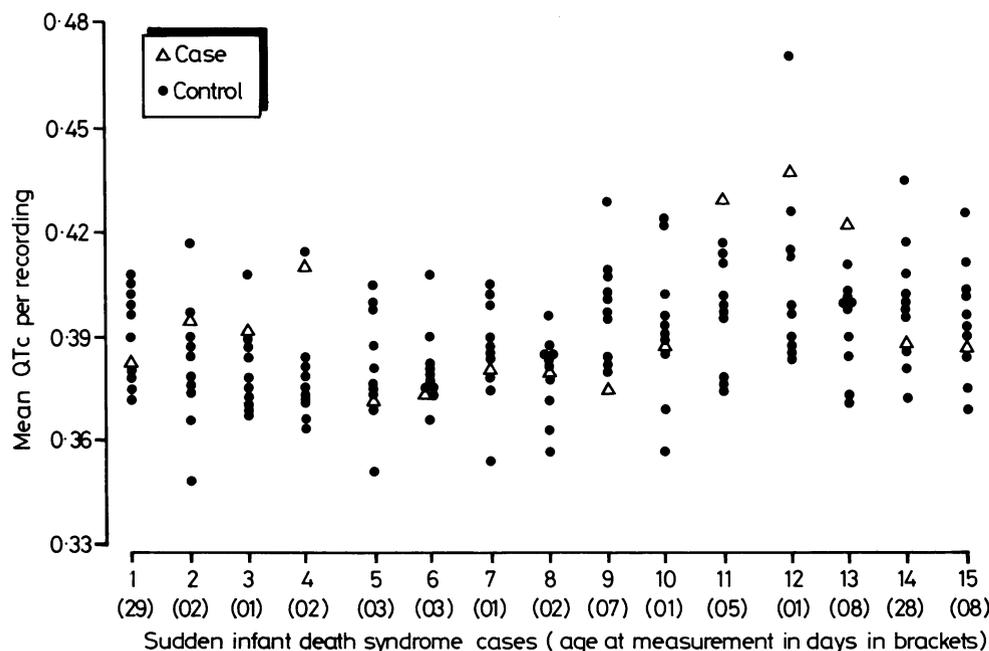


Fig. 3   *The position of QT interval (from Bazett's formula) measurements corrected for heart rate for each of the 15 cases with sudden infant death syndrome (numbered as in Table 1) and each of its 10 controls matched for birth weight, postnatal age at recording, and hospital of birth.*

of a tendency to a raised distribution of QTc levels among the infants with the syndrome (p=0·14, two sided test).

**QT and QT indices corrected for heart rate in cases with the syndrome and individually matched controls (multiple measurement analysis).** None of the measurements adjusted for heart rate of QT intervals showed any significant difference between cases and controls (p>0·05) (Fig. 3 for the mean QTc per recording).

## Discussion

The most important finding of this study is that QT interval measurements on a neonatal electrocardiogram cannot be used in isolation to identify the infant at risk of sudden infant death syndrome. Although two of the 15 cases with the syndrome showed values above the 95th centile in controls matched only on age and hospital of birth, only one infant with the syndrome had a QT interval that exceeded the range in its controls matched for age, birth weight, and hospital of birth (Fig. 3). Nevertheless, it is important to remember that disordered sympathetic innervation of the heart with a predisposition to ventricular tachyarrhythmias may be present without prolongation of the QT interval on the ECG.[14]

The epidemiological characteristics of the 15 cases with the syndrome conform to those reported from larger studies (see Merritt and Valdes-Dapena[15] for summary), suggesting that our findings are probably applicable to most cases with the syndrome. Nevertheless, the fairly small sample of cases examined must be borne in mind.

Measurements of QT intervals from the standard electrocardiogram are known to be poorly reproducible.[16 17] In this study we found that differences in the paper speed of ECG machines and in inter- and intraobserver variability can all contribute considerably to errors in measurement. These problems should not influence the identification of the long QT syndrome but are relevant to the findings presented in this and other studies. It is important to mention the fact that both ECG machines were working within the manufacturers' specification. The intraobserver reproducibility problem will probably have been reduced by the individually matched analysis where an attempt was made to measure as many ECG complexes as possible for each recording. In the group matched analysis the observation of a smaller standard deviation in the presence of higher mean values for QTc in the Dorset compared with the Doncaster controls (Table 2) cannot be adequately explained but may

have arisen from interactions between the choice of the QT intervals measured and the way in which the QT intervals were corrected to heart rate. Also, although it was not quantified, there were possibly more variations in paper speed in the Doncaster study. These differences between centres do not invalidate the comparison of cases and controls, but the possibility of paper speed variabilities may have made it less likely that any real difference would be detected.

In conclusion, it is not possible from these data to assert that there is no relation between disordered sympathetic innervation of the heart and sudden infant death syndrome (the 'QT hypothesis'). If, however, there is such an association it can be concluded that it is of little value to try to identify infants at risk by measuring QT intervals on a neonatal electrocardiogram.

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Correspondence and requests for reprints to Dr D P Southall, Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3 6HP.