Normal relation between heart rate and cardiac repolarisation in sudden infant death syndrome

Vernon T Wynn, David P Southall

Abstract

Objective—To determine whether there was a difference in the relation between heart rate and RT intervals in infants who later died of sudden infant death syndrome (SIDS) and controls.

Design—A blinded, computer analysis of prospectively acquired physiological data on SIDS cases and controls.

Setting—Physiological data obtained from infants at home (collaborative analysis National Heart and Lung Institute and Exeter University).

Participants—Nine fullterm infants who subsequently died of SIDS and 10 surviving controls matched for age and birth weight.

Interventions—24 hour tape recordings of the electrocardiogram at home between three and 11 weeks of age.

Main outcome measures—Mean value of the constant b, which relates by linear regression the log of each RT interval to the log of its preceding RR interval, and any difference between SIDS cases and controls.

Results—The mean (2SEM) values for b were 0.20 (0.03) for the 10 controls and 0.19 (0.03) for the nine SIDS infants. Cyclical correlations between RT and RR intervals of varying strength were identified in both SIDS infants and controls.

Conclusions—Infants who subsequently died of SIDS did not show an impaired ability to modify RT intervals in response to change in heart rate.

analysis of the same data has produced different results. In the light of potentially harmful preventive therapies, we consider it important to describe our own analysis. We then discuss the possible reasons for this evident conflict between our findings and those of Sadeh *et al.*³

Patients and methods

We analysed segments from ten 24-hour cassette tape recordings of electrocardiograms obtained prospectively on nine full term victims of SIDS aged 16–63 days at the time of recording (birth weights from 2.35 to 4.79 kg) (table 1). Ten similar recordings on 10 surviving fullterm controls matched for postnatal age (21–75 days) and birth weight (2.64–4.00 kg) were similarly studied (table 1). We examined the same recordings from SIDS cases as Sadeh *et al.*³ However, Sadeh *et al* included only data from midnight to 6 am; we intentionally used complete data from the entire 24 hour period to include daytime and night time activity.

The waveforms in the prospective study yielding these data¹ were obtained from two electrodes on the chest wall. The frequency content of the resulting signals was 0.5–70 Hz after processing through the tape replay system (Oxford Medilog PB2). Details of the technique have been previously reported in detail.^{4,5} In brief, electrocardiograms from the Medilog recorder together with the simultaneously recorded 60 Hz calibration signals were

In our previous prospective studies of electrocardiograms from infants who died of sudden infant death syndrome (SIDS) we did not find any predictive lengthening of the QT interval.^{1,2} The purpose of this present analysis was to evaluate the response of the QT interval to variations in heart rate. We hypothesised that a defect in this response might indicate a vulnerability to dangerous ventricular arrhythmias. A similar analysis has been reported by Sadeh *et al*³ of 24 hour electrocardiographic recordings collected by us¹ from 10 infants who subsequently died of SIDS. The ability to shorten their QT interval in response to an increasing heart rate was reported to be impaired in five of their 10 cases. As a result of their findings Sadeh *et al* argued that “sudden death in these cases may have resulted from defective modulation of cardiac repolarisation”.³ In contrast our own

Table Details of recordings and infants

Age (days)	Birth weight (g)	Gestation (wk)
SIDS cases		
16	2780	39
24*	3770	40
63*	3770	40
30	2350	40
40	3030	40
40	3960	41
41	4790	40
47	2920	40
52	2810	39
61	2980	40
Controls		
21	3660	42
36	3700	42
75	2640	38
37	3740	38
39	3690	40
42	3300	40
42	3230	39
42	3950	40
55	3800	40
61	4000	38

*Same infant.

Department of
Physics, University of
Exeter, Exeter
V T Wynn
The National Heart
and Lung Institute,
Royal Brompton
Hospital, London
D P Southall
Correspondence to
Dr David P Southall,
National Heart and Lung
Institute, Royal Brompton
Hospital, Sydney Street,
London SW3 6NP.
Accepted for publication
10 September 1991

Figure 1 An example of two electrocardiographic complexes from one of the controls. RT_{max} , RT_x , RT_{min} , and RT_{end} behave in a similar fashion to the QT interval with changes in the immediately preceding RR interval. RT_x was chosen to represent ventricular repolarisation time.

played back from an FM tape recorder at real time speed (SE Labs 8-4, frequency response DC to 625 Hz). Sections of the original tape recordings were chosen to cover as wide a range of RR intervals as possible in every subject. Any fluctuations in the tape speed produced by the tape recorders or their tape replay system were detected and compensated by a specially made correction device.⁶ Slowed down re-recordings were digitised at approximately 4 kHz, the sampling rate being dependent on the frequency of the calibration signal. Waveforms were analysed by a microprocessor-based computer system.

Each RR interval was measured from the rapidly rising part of the R wave at a level just above that of the height of the P wave. We obtained a baseline from which to make measurement of ventricular repolarisation time (RT interval) by averaging 64 data points from the flat portion of the PR interval. The Q wave was not included, preference being given to the more consistent and sharper R wave deflection. Measurements were made (fig 1) of the times from the rapidly rising part of the R wave to (a) the point of maximum amplitude of the T wave (RT_{max}), (b) the point where the T wave crossed the baseline value (RT_x), (c) the point of minimum amplitude of the T wave (RT_{min}), and (d) the point where the T wave crosses the baseline again (RT_{end}). Previous investigations have shown that all four measurements vary in similar fashion with changes in the RR interval.^{4,5} The similarity between the four measurements existed over the full range of RR intervals. However, these latter studies also showed that the random variations in the RT_x intervals were much reduced compared with those of the remaining three measurements. The RT_x interval also had the advantage of being less affected by those electrocardiographic waves that were so short that the P wave was mixed in with the end of the T wave.

The small size of the QR interval and the close relation between changes in the preceding RR intervals and both RT_x and RT_{end} indicated that a good estimate of the relation between QT and RR intervals could be obtained by assuming that QT interval duration is directly

proportional to RT_x . (Linear regression analysis was used to fit equations to plots of RT_{end} against RR and plots of RT_x against RR from data obtained in the previously reported study.^{4,5} The mean (SEM) slopes and intercepts respectively were 0.35 (0.03) and 57 (12) ms for RT_x against RR and 0.37 (0.03) and 70 (12) ms for RT_{end} against RR).

If it is assumed that RT_x and QT are directly proportional the following equation can be written:

$$\log_e(RT_x) = b \log_e(RR) + k \quad \text{equation 1}$$

where k is the intercept and where b is a constant that relates the RT_x to the RR according to a power law.

From each 24 hour tape recording of SIDS cases and controls, a technician who did not know whether the data originated from a SIDS case or a control selected 8–10 segments using the data collected in the earlier study.^{4,5} Each segment consisted of 63 consecutive cardiac cycles with a high signal to noise ratio. The number of segments was chosen to ensure statistical significance for each measurement of b and k. The number of cardiac cycles per segment (63) was chosen to match the program within the eight-bit microprocessor and was consistently large enough to include several short-term cycles in heart rate variability. The segments from each infant, whether a control or SIDS case, were chosen so as to provide as wide and evenly spaced a range of RR intervals as possible. The computer data were in the form of approximately 1000 numerical tables, each table consisting of 63 pairs of consecutive RR and RT_x values. Only those tables that showed no trace of artefact (low noise) when observed on an oscilloscope as they were being loaded into the computer were selected by the independent technician.

The RR interval range for each of the segments of 63 heart beats in the controls varied from 14 to 288 ms; that is, in one segment the RR interval varied by only 14 ms over the 63 beats while at the other extreme the RR interval varied by 288 ms over the 63 beats. The overall range for the SIDS cases varied from 8 to 294 ms.

Correlation coefficients and values of b were obtained by fitting equation 1 to the RT_x values and their corresponding RR values by linear regression analysis for both SIDS cases and controls (fig 2A, B, and C). These values of b were also plotted against the individual ranges of RR intervals within each 63 beat segment for all recordings in both controls and SIDS cases (fig 3). Time series plots of successive RR and RT_x intervals were then obtained for each 63 beat segment analysed.

Results

The mean (2 SEM) value of b for the SIDS cases was 0.20 (0.02) when all 10 SIDS recordings were used and 0.19 (0.03) when analysis was limited to the later of two recordings on one of the SIDS cases. For the surviving controls the mean value of b was 0.20 (0.03). The time series plots of RR and RT_x intervals behaved in

such a similar fashion for both controls and SIDS cases that they could not be distinguished by statistical analysis. Periodicities of varying amplitude and correlation were frequently seen in the different segments from each infant, irrespective of whether they were victims or controls. Figure 2A shows the data for the nine cases of SIDS (10 recordings) and 10 controls, constructed by plotting the mean RR interval for all segments on each infant against the mean value of *b* for the same segments. The numbers set against the SIDS patients indicate those infants in whom heart rate⁷ and heart rate variability⁸ were measured in earlier studies. Figure 2A clearly shows that it is not possible to distinguish SIDS cases from their controls by the value of *b*. The range of the mean values of *b* in both SIDS cases and controls is 0.11 to 0.25.

Figure 2B shows the variability in terms of standard deviation from the mean for the values of both *b* and RR intervals for all recorded segments from infants dying suddenly. Values in the controls were virtually identical (fig 2C).

Figure 3 shows the mean values of *b* for both SIDS cases and controls plotted against the mean RR interval ranges. The mean value of *b* for the RR range of 212 ms is the mean of seven points. All the other mean values have been calculated by grouping the values of *b* and their respective RR ranges into sets of at least 10. There was no significant difference between the SIDS group and the controls in this graph. As the range of RR intervals increased the value of *b* fell.

Cyclical behaviour in the relation between RT and RR intervals was as common in the controls as in the SIDS cases.

Discussion

Prospective identification of infants at risk of sudden death is a desirable objective on which to base preventive care. However, incorrect predictors may prompt harmful intervention, especially if cardioactive treatment is being considered. This is why the results presented by Sadeh *et al*,³ with their implications concerning prediction, must be confirmed or rejected. Unfortunately, only one prospective data base is available on which these results can be checked and that is the original 24 hour electrocardiograms obtained by our group.¹ Sadeh *et al*'s report was published before we

Figure 3 Plot of mean values of *b* for both SIDS cases and controls against the mean RR interval ranges. The value of *b* at the RR interval range of 212 ms is the mean of seven points. All of the other mean values were calculated by grouping the values of *b* and their respective RR ranges into sets of at least 10. The horizontal and vertical lines are SEMs.

had completed an analysis of our data with exacting attention to several technical and mathematical artefacts that could easily invalidate conclusions about the association between ventricular electrical activity and the incidence of sudden infant death. This analysis is now complete and unlike Sadeh *et al* we found no consistent differences between SIDS cases and controls.

The analysis in this paper differs from that carried out previously by our group.^{4,5} Earlier work was based on mean values of the intervals in the electrocardiogram obtained by simply averaging over 63 consecutive heart beats. In the present study we undertook the more difficult investigation of the relation between individual RT ventricular repolarisation times and each preceding RR interval (fig 1).

This analysis of the time-series relation between RT and RR intervals did not show any difference between recordings from SIDS infants and their surviving controls. These results do not, therefore, support the hypothesis that a disordered relation, as measured from the surface electrocardiogram, between ventricular repolarisation time and heart rate influences subsequent sudden unexplained infant death. Moreover, within each infant's recording, whether they were SIDS cases or controls, some segments were found to show a strong cyclical correlation between RT and RR intervals while others showed no such relation. Sadeh *et al* inferred that unlike SIDS cases the controls always showed this strong correlation.

The spread of values for the constant *b* (which relates by linear regression the log of each RT interval to the log of its preceding RR interval) in both controls and SIDS cases in this present study was less (0.11–0.25) and the mean value of *b* for controls was greater (0.20) than values found by Sadeh *et al*³ (their range was 0.05–0.25, and their mean for controls was 0.13). These present findings, however, do accord with those of Sadeh *et al*³ in suggesting that Bazett's formula⁹ (where $b = 0.50$) provides an inappropriate method for correcting the QT interval for heart rate in this age group.

The following differences between SIDS cases and controls were reported by Sadeh *et al*.³ Firstly, according to the equation $QT = C(RR)^b$, their mean (1 SD) values for *b* were 0.096 (0.032) in the SIDS cases and 0.134 (0.043) in controls ($p < 0.02$). Secondly, their illustrated time series of QT intervals plotted against the immediately preceding RR intervals from 500 consecutive heart beats showed, in a single control recording, highly correlated cyclical variations in both intervals. There was a much smaller correlation in a similar plot from a single time series from a SIDS case. Presumably these two plots were included to lend weight to differences that they concluded existed between the controls and five of the SIDS subjects. Finally, in their plot of *b* against mean RR intervals for each segment of the recording analysed for the 10 SIDS cases and 29 controls, five of the 10 sudden death values for *b* fell outside the 95% confidence interval for the controls.

There are several possible explanations for the differences between our results and those of Sadeh *et al*.³ Firstly, to "improve the reliability of their statistical comparisons" Sadeh *et al*³ selected their segments on the basis that the RR intervals within each segment varied by more than 100 ms. As shown in fig 3, this could result in lower values of *b*. If values of *b* in this present report are limited to those segments where the RR interval range is > 100 ms (> 45 sets of points), mean (2 SEM) values of *b* are 0.16 (0.03) for controls and 0.17 (0.02) for SIDS cases. These values are reasonably close to the control measurements of Sadeh *et al*³ (0.13 (0.04) (SD)). The small remaining difference between the control values of *b* is possibly a result of the two different methods by which each study chose to compensate for the difficulties in estimating the end of ventricular repolarisation. A second possible explanation for the different results is the high pass (10 Hz cut-off) filter used by Sadeh *et al*³ before the measurement of QT and RR intervals. This filter produces a phase difference between input and output signals which decreases as the frequency components of the input signal increase. Therefore, with higher heart rates containing correspondingly higher frequencies, there would be a smaller timing error between the true QT and their measured QT interval. This would result in the changes in duration of the QT interval appearing to be smaller in response to changes in RR interval at the higher heart rates. For this reason we did not use a highpass filter but rather a high quality frequency modulated tape copy directly from the original 24 hour cassette recordings. Contrary to the statement made by Sadeh *et al*,³ the frequency response of the signals after replay through the Oxford Medilog PB2 system is 0.5–70 Hz not 10–100 Hz. Nevertheless, as previously reported by us,¹ the frequency response of the original cassette tape recording system is not ideal for low frequency signals such as the T wave (diagnostic electrocardiogram recordings have bandwidths from 0.05 to 100 Hz).

A third reason for the discrepancy between these present results and those of Sadeh *et al*³ concerns the comparability of heart rates analysed in the SIDS cases and their controls. Figure 5 of their study showed that the five recordings from SIDS cases that showed the lowest values for *b* also had higher average heart rates than controls. In the present study we compensated for the significantly higher heart rates previously reported to be present in these particular recordings from SIDS cases^{7,8} by selecting segments in both controls and SIDS cases where the range of heart rates was as wide as possible (for example, by including data from the whole 24 hour period) and by matching our controls for birth weight and postnatal age.

Sadeh *et al* reported a linear relation "significantly different from zero at $P = 0.0002$ " for their plot of mean RR intervals against mean values of *b* in their control group.³ In our analysis no such linear relation was seen between mean *b* and mean RR for our controls (see

fig 2A), thus supporting our use of a power equation. It is difficult to understand how Sadeh *et al*³ can reconcile their findings of a linear relation and continue to use the original power law equation where b is assumed to be constant with respect to RR.

In conclusion, as in our earlier reports,^{1,2} we found no evidence to support the hypothesis that a defect in ventricular repolarisation time or its relation to heart rate are predictive for sudden and unexplained infant deaths. We can rule out neither the unlikely possibility that a serious repolarisation abnormality was present that could not be detected by surface electrocardiogram nor the possibility that a subsequent defect in repolarisation developed closer to the time of death.

We thank Mrs Joyce Lamb for her help in preparing these data for analysis, Dr A J Wilson for his early suggestions on apparent heart rate effects on QT intervals resulting from the inherent phase response of high pass filters, and to Dr W New and Professor R H Anderson for their expert advice on this paper.

This project and DPS were funded by Nellcor and the National Heart and Chest Hospitals.

- 1 Southall DP, Richards JM, de Swiet M, Arrowsmith WA, Cree JE, Fleming PJ, *et al*. Identification of infants destined to die unexpectedly during infancy: evaluation of predictive importance of prolonged apnoea and disorders of cardiac rhythm or conduction. First report of a multi-centred prospective study into the sudden infant death syndrome. *BMJ* 1983;286:1092-6.
- 2 Southall DP, Arrowsmith WA, Stebbens V, Alexander JR. QT interval measurements before sudden infant death syndrome. *Arch Dis Child* 1986;61:327-33.
- 3 Sadeh D, Shannon DC, Abboud S, Saul JP, Akselrod S, Cohen RJ. Altered cardiac repolarization in some victims of sudden infant death syndrome. *N Engl J Med* 1987;317:1501-5.
- 4 Wynn VT. Heart rate dependence of the RT interval in the first month of life. *Clin Phys Physiol Meas* 1986;7:369-73.
- 5 Wynn VT. Measurement and analysis of RT and RR intervals in 72 infants in the age range 2 to 75 days. In: Copeland K, ed. *Progress reports on electronics in medicine and biology*. The Institution of Electronic and Radio Engineers, 1986:331-6. ISBN 0903748657.
- 6 Bundy K, Wynn VT. ECG tape-speed error compensator. *Med Biol Eng Comput* 1985;23:607-9.
- 7 Wilson AJ, Stevens V, Franks CI, Alexander JR, Southall DP. Respiratory and heart rate patterns in infants destined to die of the sudden infant death syndrome. *BMJ* 1984;290:497-501.
- 8 Southall DP, Stevens V, Franks CI, Newcombe RG, Wilson AJ. Sinus tachycardia in term infants preceding sudden infant death syndrome. *Eur J Pediatr* 1987;147:74-8.
- 9 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353-70.