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

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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.

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. 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 al1 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”. In contrast our own 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. 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 In brief, electrocardiograms from the Medilog recorder together with the simultaneously recorded 60 Hz calibration signals were

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<th>Age (days)</th>
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<td>61</td>
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*Same infant.
Normal cardiac repolarisation in sudden infant death syndrome

Figure 1. An example of two electrocardiographic complexes from one of the controls. RT, RTA, RTB, and RTc behave in a similar fashion to the QT interval with changes in the immediately preceding RR interval. RT 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. 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 (RR 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 (RTmax), (b) the point where the T wave crossed the baseline value (RTx), (c) the point of minimum amplitude of the T wave (RTmin), and (d) the point where the T wave crosses the baseline again (RTend). Previous investigations have shown that all four measurements vary in similar fashion with changes in the RR interval. 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 interval were much reduced compared with those of the remaining three measurements. The RT 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 RTx and RTend 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 RTx. Linear regression analysis was used to fit equations to plots of RT against RR and plots of RT against RR from data obtained in the previously reported study. The mean (SEM) slopes and intercepts respectively were 0-35 (0-03) and 57 (12) ms for RT against RR and 0-37 (0-03) and 70 (12) ms for RT against RR. If it is assumed that RT and QT are directly proportional the following equation can be written:

\[ \log_2(\text{RT}) = b \log_2(\text{RR}) + k \] (equation 1)

where k is the intercept and where b is a constant that relates the RT 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. 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 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 and 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 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 latter 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, 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 rate and heart rate variability 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. 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. Sadeh et al.'s report was published before we...
had completed an analysis of our data with
exacting attention to several technical and
mathematical artefacts that could easily in-
validate conclusions about the association be-
 tween 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.45 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 value of the time-series relation be-
 tween 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 hypoth-
esis 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 higher (0.20)
than values found by Sadeh et al3 (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 al3 in suggesting
that Bazett’s formula4 (where b = 0.50)
provides an inappropriate method for correct-
ing 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/RRb, 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 inter-
 vals 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 al3
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 al3
(0·13 (0·04) (SD)). The small remaining differ-
ence between the control values of b is possibly
a result of the two different methods by which
each study chose to compensate for the diffi-
culties 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 al3 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 in-
crease. Therefore, with higher heart rates con-
taining 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 fre-
quency 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 Meding PB2 system is
0·5–70 Hz. Nevertheless, as previously reported by us,5
the frequency re-
sponse of the original cassette tape recording
system is not ideal for low frequency signals
such as the T wave (diagnostic electrocardio-
gram recordings have bandwidths from 0·05 to
100 Hz).

A third reason for the discrepancy be-
 tween these present results and those of Sadeh et al
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 cases8
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 “sig-
nificantly different from zero at P = 0·002” for
their plot of mean RR intervals against mean
values of b in their control group.5 In our
analysis no such linear relation was seen be-
 tween 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\textsuperscript{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,\textsuperscript{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.

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