Electrocardiograph QT lengthening associated with epileptiform EEG discharges—a role in sudden unexplained death in epilepsy?

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EEG with co-registered electrocardiography was recorded during at least two interictal epileptiform EEG discharges in each of 11 patients who later suffered from sudden unexpected death in epilepsy (SUDEP), and from another 11 age and sex matched patients, also with uncontrolled tonic-clonic seizures, drawn from the same centre who were still alive at the time of investigation (non-SUDEPs). A corrected QT interval for rate (QTc) was obtained and a mean value calculated for the period immediately prior to discharge, during discharge and immediately post discharge. Mean QTc was also obtained interictally without discharge. There was a significant ($P = 0.01$) increase in the mean QTc during discharge compared to that measured interictally without discharge for the whole population of SUDEPs and non-SUDEPs, and this was maintained for the SUDEPs alone ($P = 0.02$) but did not hold for the non-SUDEP group alone. Although reaching statistical significance, increases in mean QTc in SUDEP patients only exceeded currently accepted upper limits in one case, and then only marginally. The clinical significance of these findings merits further investigation.

Key words: epilepsy; sudden unexplained death; electrocardiography; QTc interval; interictal epileptiform discharge; EEG.

INTRODUCTION

Epilepsy carries an increased mortality risk of approximately two or three times the general population[1-3]. A proportion of these deaths may be due to suicide, accident, or convulsive status epilepticus[4-6]. However, there remains a group of people with epilepsy who die suddenly, in otherwise apparently good health, from a currently unknown cause or causes. This phenomenon is referred to as sudden unexplained death in epilepsy, or SUDEP[7,8]. A recent Canadian study found the annual incidence of death as a complication of seizures to be 2.68 in 100 000 population[9]. These deaths are typically associated with a tonic–clonic seizure, and are more likely to occur in patients who continue to have seizures despite treatment[6,10]. It is possible that a cardiac arrhythmia may be the terminal event in SUDEP[11-14]. Experimental evidence from animal models of epilepsy has shown that interictal EEG epileptiform discharges can be associated with changes in the electrocardiogram (ECG), including alteration in the length of the QT interval, and development of cardiac arrhythmia[12,15-18].

This study set out to test the hypothesis that patients who later suffer SUDEP have a transient increase in the QT interval during an EEG epileptiform discharge which predisposes them to ventricular fibrillation and sudden death[19]. This was tested by examining the QT interval, corrected for rate (QTc), before, during and immediately after interictal EEG epileptiform discharge in eleven cases of SUDEP on whom ambulatory EEG with co-registered ECG had been performed prior to death.

METHOD

Eleven cases of SUDEP occurring at the David Lewis Centre between 1989 and 1993 had previously had ambulatory EEG and co-registered ECG recordings. The diagnosis of

SUDEP was made on clinical grounds, confirmed by post-mortem findings where available (6/11 cases). The recordings dated from less than one to thirty one months prior to death (mean, 13 months).

In all 11 cases, two recordings of interictal EEG epileptiform discharges with co-registered ECG were examined. An 8-second interictal EEG and ECG record, without epileptiform discharge and at least 1 hour away from a discharge or seizure, was also examined for each case. The onset and end of the EEG epileptiform discharge were determined by an experienced EEG technician 'blind' to the proposed ECG analysis. The ECG recording, during EEG epileptiform discharge, was divided into three sections corresponding to immediately before, during and immediately after the discharge. The pre EEG epileptiform discharge ECG record comprised the three ECG complexes occurring immediately before the onset of the discharge (a period of about 2 seconds). The during EEG discharge record commenced with the first complete ECG complex (P wave, QRS complex and T wave) following the onset of EEG discharge and contained an average of eight ECG complexes (about 6 seconds). The post-EEG epileptiform discharge record consisted of a minimum of three ECG complexes occurring immediately after the end of the discharge. A corrected QT interval for rate (QTc) was obtained for each ECG complex by the method of Bazett[20] and a mean QTc value calculated for pre EEG discharge, during EEG discharge and post EEG discharge sections. QTc values and mean were also obtained for the eight second rhythm strip without EEG epileptiform activity.

A controlled sample matched for age, sex, presence of tonic–clonic seizures and uncontrolled epilepsy was drawn randomly from patients investigated at the David Lewis Centre who were still alive (the non-SUDEP group).

For each case and control the mean QTc was calculated for each of the four conditions (before, during, after and between discharges). Application of Shapiro-Wilk test for normality suggested that non-parametric statistical evaluation was appropriate, and so comparisons were tested for significance using the Wilcoxon signed rank test.

RESULTS

Table 1 shows the duration of the EEG discharge in SUDEPs and non-SUDEPs. There was no statistically significant difference between these two groups. Table 2 shows the mean and range of QTc values for the 11 SUDEPs without EEG epileptiform discharge, immediately pre, during and post EEG epileptiform discharge. Table 3 shows the same for the non-SUDEPs.

SUDEP and non-SUDEP data taken together showed a significant increase ($P = 0.01$) in QTc from between-discharge to during-discharge state. For the non-SUDEPs alone, however, although the mean QTc did increase during all three conditions, this was not statistically significant, whereas for the SUDEPs, mean QTc rose significantly (Wilcoxon 2-tailed $P = 0.02$) during an epileptiform discharge. Changes pre- and post discharge for SUDEPs were not significant, although there was a suggestion of a trend ($P = 0.07$) for increase from pre-discharge to during-discharge state (Table 4).

The change from between-discharge to during-discharge states for SUDEPs and non-SUDEPs is shown in Fig. 1. In this it will be seen that the SUDEPs include one outlier. Re-analysis excluding this outlier and its matched non-SUDEP control still gave a significant difference in the SUDEP group ($P = 0.03$) but not in the non-SUDEP group.

DISCUSSION

The cause, or causes if aetiologically heterogeneous, of SUDEP remains unknown. However a cardiac arrhythmia is considered to be a likely cause in at least some cases and for these, an increase in QTc may be a factor predisposing to arrhythmia. We have shown a small, but statistically significant, increase in the mean QTc during interictal EEG epileptiform discharge

Table 1: Duration of EEG epileptiform discharges (seconds)

	Mean	Standard deviation	Range
SUDEPs	6.38* (8 ECG complexes)	10.58	0.38–47.51
non-SUDEPs	5.65* (8 ECG complexes)	2.38	0.64–8.08

* Differences not significant both for duration of EEG discharge and number of ECG complexes.

Table 2: Mean and range of QTc (in seconds) for SUDEP cases

SUDEPs	No EEG discharge	Pre EEG discharge	During EEG discharge	Post EEG discharge
1 (female)	0.40 (0.36–0.42)	0.32 (0.30–0.32)	0.40 (0.36–0.42)	0.32 (0.30–0.34)
2 (female)	0.47 (0.44–0.50)	0.48 (0.46–0.49)	0.48 (0.41–0.54)	0.47 (0.43–0.50)
3 (female)	0.38 (0.36–0.40)	0.37 (0.34–0.40)	0.41 (0.37–0.45)	0.38 (0.35–0.45)
4 (male)	0.35 (0.35–0.38)	0.39 (0.37–0.42)	0.37 (0.36–0.39)	0.35 (0.34–0.36)
5 (male)	0.32 (0.29–0.35)	0.34 (0.30–0.38)	0.36 (0.33–0.38)	0.34 (0.31–0.36)
6 (male)	0.38 (0.37–0.40)	0.38 (0.35–0.42)	0.36 (0.34–0.40)	0.41 (0.37–0.45)
7 (male)	0.35 (0.32–0.37)	0.36 (0.34–0.39)	0.36 (0.35–0.38)	0.39 (0.37–0.42)
8 (female)	0.36 (0.33–0.37)	0.37 (0.35–0.40)	0.37 (0.29–0.45)	0.44 (0.41–0.47)
9 (female)	0.37 (0.36–0.40)	0.37 (0.34–0.39)	0.40 (0.35–0.42)	0.35 (0.35–0.36)
10 (female)	0.34 (0.32–0.36)	0.34 (0.33–0.35)	0.35 (0.34–0.38)	0.36 (0.34–0.37)
11 (female)	0.36 (0.35–0.36)	0.35 (0.32–0.39)	0.38 (0.33–0.44)	0.37 (0.33–0.42)

compared to a between discharge state in patients who later died of SUDEP. The change in an age and sex matched non-SUDEP group from the same centre still alive at the time of investigation, also with uncontrolled epilepsy was not significant. The currently accepted upper limit for QTc is 0.39 for males and 0.44 for females[20] and in only one of the cases (case 2) did the mean QTc value with and without EEG discharge exceed this.

Yet there are reasons why our data might underestimate the significance of QT changes in predisposition to SUDEP:

(1) Our non-SUDEP group consisted of people who happen to still be alive, but we do not know how many of them might be at risk of SUDEP in the future. If this group contains some potential SUDEPs then differences between SUDEP and non-SUDEP data might be minimised.

(2) SUDEP may well have a heterogeneous aetiology with only some cases being precipitated by an arrhythmia or being influenced by an increase in QTc so that our case data may be diluted.

(3) If EEG discharges only infrequently affect mean QTc significantly, as only two discharges per case were analysed, clinically significant change may have been missed by this study.

(4) Finally, the change in QTc may be typically

Table 3: Mean and range of QTc (in seconds) for non-SUDEPs

Non-SUDEPs	No EEG discharge	Pre EEG discharge	During EEG discharge	Post EEG discharge
1 (female)	0.37 –0.33–0.40)	0.37 (0.35–0.41)	0.40 (0.36–0.47)	0.43 (0.37–0.47)
2 (female)	0.41 (0.40–0.43)	0.41 (0.39–0.43)	0.41 (0.39–0.46)	0.43 (0.39–0.44)
3 (female)	0.34 (0.32–0.38)	0.35 (0.31–0.38)	0.34 (0.32–0.37)	0.33 (0.32–0.38)
4 (male)	0.39 (0.37–0.40)	0.39 (0.33–0.41)	0.38 (0.37–0.39)	0.39 (0.38–0.40)
5 (male)	0.34 (0.30–0.37)	0.35 (0.33–0.41)	0.35 (0.32–0.38)	0.35 (0.33–0.36)
6 (male)	0.33 (0.33–0.34)	0.40 (0.38–0.41)	0.40 (0.36–0.42)	0.39 (0.38–0.41)
7 (male)	0.35 (0.32–0.36)	0.34 (0.32–0.35)	0.34 (0.32–0.36)	0.34 (0.32–0.36)
8 (female)	0.38 (0.34–0.41)	0.35 (0.33–0.36)	0.34 (0.32–0.39)	0.34 (0.33–0.36)
9 (female)	0.37 (0.35–0.39)	0.39 (0.39)	0.40 (0.39–0.42)	0.42 (0.39–0.44)
10 (female)	0.35 (0.31–0.38)	0.41 (0.39–0.42)	0.38 (0.31–0.48)	0.34 (0.30–0.39)
11 (female)	0.41 (0.36–0.44)	0.43 (0.41–0.43)	0.42 (0.39–0.46)	0.42 (0.40–0.44)

Table 4: Probabilities (Wilcoxon 2-tailed)

	Pre-discharge	During discharge	Post-discharge
SUDEPs & non-SUDEPs combined			
Between discharge	NS	0.01	NS
Pre-discharge		NS	NS
During discharge			NS
SUDEPS only			
Between discharge	NS	0.02	NS
Pre-discharge		0.07	NS
During discharge			NS

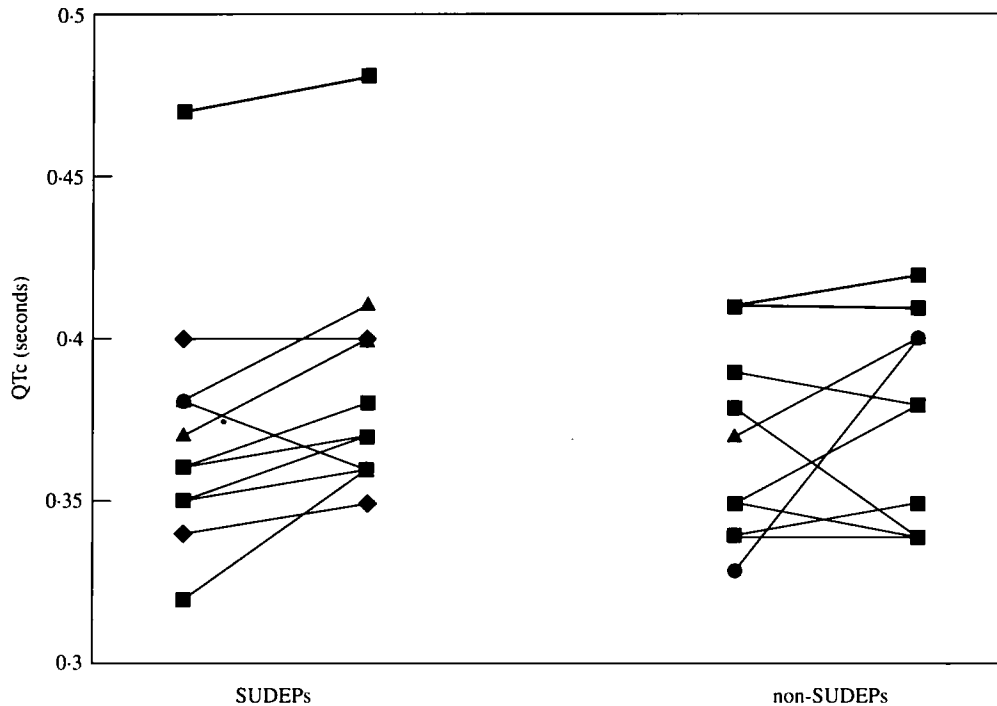All non-SUDEP alone comparisons were non-significant.

Fig. 1: QTc change during EEG epileptiform discharges.

small and either clinically insignificant or significant only in the presence of other factors which either prolong QTc, such as phenothiazines or hypokalaemia[21], or predispose to an arrhythmia, such as catecholamine release[22], as may occur during a seizure[14].

All these cases, both SUDEPs and non-SUDEPs, survived their epileptiform discharges at the time of recording, and we still know nothing of the events at the time of death. Given the propensity for QTc to increase during these non-fatal EEG discharges it is possible that on other occasions (perhaps associated with another intervening variable) QTc might increase further to a point where ventricular tachyarrhythmia could occur. These recordings were made using one-channel ECG approximating to standard lead II. A more accurate assessment of QT interval can be made using all 12 leads[23], but it has not been technically possible to obtain this information relating to ECG changes during these EEG discharges. We also lack any record to date of simultaneous EEG and ECG recording where SUDEP actually occurred.

These findings raise the issue of whether prophylactic anti-arrhythmic medication such as beta-blockers might act protectively in people identified as at risk by this method.

CONCLUSION

A statistically significant increase for QTc values during EEG epileptiform discharge has been demonstrated by this study for a group who subsequently died of sudden unexplained death, but not for a comparable group who are still alive. However the study population is relatively small so that the true clinical significance of this remains unclear. Given the potential heterogeneous aetiology of SUDEP and the possibility that not every EEG discharge significantly affects the QTc, to ascertain the true clinical significance of this finding, a larger study, using 12 lead ECG to look for QT dispersion and with greater numbers needs to be undertaken. In the meantime the question is tentatively raised that identification of at-risk subjects might enable use of prophylactic medication.

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