Abstract

Anxiety symptoms are associated with a marked increase in sudden cardiac death, suggesting an abnormality in the autonomic control of the heart. We examined the effects of sympathetic stimulation on QT interval variability in panic disorder patients by infusing the β-adrenergic agonist isoproterenol in 6 panic disorder patients and 11 normal subjects. The ECG signal was analysed before the infusion and after 5 min after the infusion was started. The outcome measures were the QT variability normalized for mean QT interval (QTvm) and the QT variability index (QTvi), a measure of QT variability normalized by the concomitant heart rate variability. Patients with panic disorder had more variability in QT interval duration than normal controls and this variability was increased further by sympathetic stimulation with isoproterenol. The isoproterenol-associated increase in QT interval occurred in controls in the absence of significant anxiety. However, on one of two measures, the increase in QT interval variability was greater in patients with panic disorder, suggesting a greater sensitivity to isoproterenol or to isoproterenol-induced anxiety.

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Introduction

Anxiety symptoms are associated with a 4- to 6-fold increase in sudden cardiac death (SCD) (Haines et al., 1987; Kawachi et al., 1994a,b), presumably because of some abnormality in the autonomic control of the heart. Autonomic mechanisms affect heart rate variability (HRV) and a number of anxiety disorders are associated with a decrease in HRV (Cohen et al., 1998; Friedman et al., 1993; Thayer et al., 1996; Yeragani et al., 1990, 1993, 1998). Reduced HRV predicts sudden death in both apparently healthy subjects (Fei et al., 1994; Molgaard et al., 1991) and patients with coronary heart disease (Kleiger et al., 1987; van Ravenswaaij-Arts et al., 1993).

Even anxiety measured by a simple eight-item self-rated scale, the Crown–Crisp index, is associated with decreased HRV and predicts sudden death (Kawachi et al., 1995). Findings from spectral analysis of heart rate in subjects with various types of anxiety are consistent with both increased sympathetic function (Cohen et al., 1997; Piccirillo et al., 1997, 1998; Yeragani et al., 1993, 1998) and diminished vagal function (Cohen et al., 1997; Friedman et al., 1993; Piccirillo et al., 1997; Thayer et al., 1996). Both of these changes in autonomic control of the heart are associated with cardiac arrhythmias (van Ravenswaaij-Arts et al., 1993).

A relatively new measure for studying autonomic control of the heart is QT interval variability. The QT interval reflects the time for repolarization of the ventricular myocardium; therefore QT variability is a measure of temporal repolarization lability. Conversely, an increase in QT variability is associated with severe ventricular abnormalities and sudden death (Atiga et al., 1998). Among patients referred for cardiac electrophysiological testing, QT variability normalized by concomitant HRV (QTvi) is a better predictor of SCD than HRV, spatial QT dispersion, and T-wave alternans (Atiga et al., 1998).

Unlike HRV, there are few studies of QT interval variability or of its autonomic control. However, we have recently shown that QT interval variability in normal controls is robustly increased by a change from supine to standing posture and by the β-adrenergic receptor agonist isoproterenol (Yeragani et al., 2000a). These increases are independent of respiration and suggest that QT interval variability is highly sensitive to sympathetic activity. In addition, we have recently found that QT interval variability is increased in both patients with panic disorder and patients with depression compared to healthy controls (Yeragani et al., 2000b).
In this study, we measured QT interval variability in patients with panic disorder and in normal controls before and after an intravenous infusion of isoproterenol. The objective of this study was to determine whether infusions of isoproterenol increase QT interval variability in panic disorder patients and to compare patients to controls.

Method

Eleven normal subjects (5 men and 6 women) and 6 panic disorder patients (2 men and 4 women) participated in this study. Subjects were diagnosed with a clinical interview using DSM-III-R criteria and were free of cardiac, endocrine, or other significant medical problems. Subjects were also free of psychotropic drugs, anti-histamines, and decongestants for at least 2 wk prior to the experiment. We have previously reported on the HRV in these same subjects (Yeragani et al., 1995) before the availability of a new algorithm that permits rapid and reliable measurement of QT variability (Berger et al., 1997). After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Wayne State University Human Investigation Committee. The age (mean ± s.d.) for the two groups was similar (25.1 ± 1.3 and 27.5 ± 4.8 yr, respectively). All subjects were physically healthy. Anxiety was assessed with the Panic Description Scale (PDS) (Rainey et al., 1984) both before and during the isoproterenol infusion. Isoproterenol was administered intravenously at a dose of 15 ng/kg.min over a 10-min period except for a shortened infusion of 6 min in a patient who experienced a panic attack.

The ECG signal was recorded at 500 Hz in lead II for 10 min before the infusions and for 10 min during the infusions while in a supine posture. The post-isoproterenol segments of data were taken 5 min after the beginning of the infusion. For these analyses, 256 s each of pre- and post-isoproterenol data were sampled after visual inspection of the data for artifacts.

Beat-to-beat quantification and analysis of QT intervals was performed using the method described by Berger et al. (1997) and has been described in detail in our previous studies (Yeragani et al., 2000a, In Press). There are two principal outcome measures in the study. The first is the QT variability normalized for mean QT interval (QTvm), calculated as the natural logarithm of detrended QT variance divided by the square of the mean QT interval. The second is the QT variability index (QTvi), a measure of QT variability normalized by the concomitant HRV. QTvi is the common logarithm of the ratio used to calculate QTvm divided by a similar ratio for HRV, namely HR variance divided by the mean HR squared.

The panic disorder and control groups were compared at baseline and after the isoproterenol infusion using two-tailed t tests. To determine whether isoproterenol had a larger effect on QT variability in the panic disorder group, the QT variability measures were compared using an ANCOVA with the baseline value as the covariate. In addition, Spearman rank correlations were performed between the total anxiety score on the PDS and QTvi.

Results

There were no differences in mean QT intervals between the panic disorder and control groups (Table 1). However, the panic disorder group had significantly greater QT interval variability as measured by both QTvm and QTvi both at baseline and after the isoproterenol infusion. Smaller negative values indicate higher QT interval variability (Table 1).

Isoproterenol infusions significantly increased QT variability in both groups. However, the panic disorder group experienced a greater increase in QTvm compared to the control groups (ANCOVA, F = 5.9; d.f. = 1.14;
QT vs was also higher in the panic disorder group, but this was not significantly different than the increase in controls (ANCOVA, $F = 2.3$, d.f. = 1,14; $p = 0.15$). The increase in PDS, a measure of panic symptoms, was negligible in the control subjects (from $0.09 \pm 0.3$ to $0.18 \pm 0.6$) while patients with panic disorder experienced robust increases in their PDS scores, from $3.3 \pm 4.9$ to $21.2 \pm 17.2$. For the entire group of subjects, there was a correlation between anxiety as measured by the PDS and QT vs. These correlations were more robust after the infusion of isoproterenol ($r = 0.80$, $p = 0.0001$) than at baseline ($r = 0.50$, $p = 0.04$). The correlations between PDS and QT vs were similar (post, $r = 0.69$, $p = 0.002$; pre, $r = 0.52$, $p = 0.04$). The patient who experienced a panic attack had the highest PDS score, 44, and the greatest QT interval variability ($QTvs = -0.29$).

Discussion

This study confirms previous findings that patients with panic disorder have greater QT interval variability than healthy controls (Yeragani et al., 2000b) and demonstrates that this variability is increased further by sympathetic stimulation with isoproterenol. The isoproterenol-associated increase in QT interval variability occurs without significant anxiety in healthy controls. However, on one of two measures, QT vs, the increase in QT interval variability is greater in the panic disorder group, suggesting a greater sensitivity to isoproterenol or to isoproterenol-induced anxiety. Isoproterenol infusions also increase QT vs in both groups, but the increase is not significantly greater in the patient group. This may be due to the small number of subjects or to differences between these measures.

The patient whose infusion was stopped early because of a panic attack had both the highest level of anxiety and the greatest amount of QT interval variability. Isoproterenol infusions induce panic attacks in panic disorder patients (Pohl et al., 1988, 1990) and it is possible that anxiety itself may increase QT interval variability. This would explain the higher baseline QT interval variability in panic disorder patients in this study and a previous study (Yeragani et al., 2000b), the greater increase in QT vs in panic disorder patients during an isoproterenol infusion, and the high QT interval variability seen in the panicking patient who received the shortest isoproterenol infusion. Like isoproterenol, anxiety may mediate increases in QT interval variability via adrenergic mechanisms. During a panic attack, the whole-body epinephrine spillover rate increases dramatically (Wilkinson et al., 1998). In the one patient in whom it was measured, there was a 16-fold increase in cardiac epinephrine spillover 10 min after a panic attack (Wilkinson et al., 1998).

These findings require replication given the small number of subjects and further work needs to be done to determine whether an increase in QT interval variability is found in other anxiety states. Variability in the QT interval appears to be a robust measure for the risk of sudden death. If an increase in QT variability is typical of patients with one or more anxiety disorders, it will be important to determine the effect of treatment on QT interval variability.

References


