Effects of Depression on QT Interval Variability After Myocardial Infarction

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Objectives: Clinical depression is a risk factor for cardiac mortality in patients with coronary heart disease. High QT interval variability is a risk factor for arrhythmic events, including sudden cardiac death. The purpose of this study was to determine whether depression is associated with increased QT variability in patients recovering from myocardial infarction. **Methods:** Twenty patients with major depression recovering from a recent myocardial infarction were matched with 20 nondepressed post–myocardial infarction patients on age and sex, and all underwent 24-hour Holter monitoring. **Results:** There were no differences between groups on average heart rate, heart rate variability, or other electrocardiographic measures. However, the QT interval showed significantly greater variability in the depressed than in the nondepressed group, especially at midnight and at 6:00 AM. **Conclusions:** Depressed post–myocardial infarction patients may be at greater risk for sudden cardiac death as a result of abnormalities in ventricular repolarization. More work is needed to determine the clinical and prognostic significance of QT variability in these patients. **Key words:** psychiatric depression, myocardial infarction, QT interval.

ANOVA = analysis of variance; BDI = Beck Depression Inventory; CHD = coronary heart disease; DISH = Depression Interview and Structured Hamilton; ECG = electrocardiographic; ENRICHD = Enhancing Recovery in Coronary Heart Disease; HR = heart rate; HRm = mean heart rate; HRv = detrended heart rate variance; HRV = heart rate variability; MI = myocardial infarction; PVC = premature ventricular contraction; QTm = mean QT interval; QTv = detrended QT variance; QTvi = heart rate–corrected QT variability index; QTvm = QT variance corrected for mean QT.

INTRODUCTION

Clinical depression is an independent risk factor for cardiac mortality in patients with coronary heart disease (CHD) (1–4). Patients who are already at high risk for sudden cardiac death may be particularly vulnerable to the effects of depression (1–3, 5). For example, Frasure-Smith et al. (5) found that depressed patients who had ≥10 premature ventricular contractions (PVCs) per hour after a myocardial infarction (MI) were at considerably higher risk for mortality than were depressed post-MI patients without PVCs and nondepressed post-MI patients with ≥10 PVCs per hour.

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Low heart rate variability (HRV), an indicator of altered cardiac autonomic function, is common in depressed patients with CHD (6–9). Low HRV predicts mortality after MI (10–12), and it may therefore be one of the mechanisms linking depression to increased risk for mortality in patients with CHD.

Recent studies have shown that QT variability also predicts arrhythmic events and sudden cardiac death (13–17). The QT interval is the electrocardiographic (ECG) signature of ventricular repolarization time. Therefore, QT interval variability reflects beat-to-beat fluctuations in myocardial recovery time. Postural challenge and isoproterenol infusion greatly increase QT interval variability (18), which suggests that ventricular repolarization is modulated by the sympathetic nervous system. Recent studies have found higher QT variability in medically well psychiatric patients with panic disorder and depression (19).

These findings suggest the possibility that depression might increase the risk of mortality after MI by contributing to dysregulation of ventricular repolarization. The purpose of this study was therefore to determine whether depression is associated with increased QT variability in patients recovering from MI as it is in medically well patients.

METHODS

Subjects

The 20 depressed subjects of this study were participants in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial (20). The 20 nondepressed control subjects, matched on age, gender, and body weight, were participants in an ENRICHD ancillary study of depression and HRV after MI (9). The methods of the ENRICHD study and of the HRV ancillary study were reported previously (20, 9). Briefly, patients were screened for eligibility for both studies within 28 days of an acute MI. The MI was documented by cardiac enzymes and by either chest pain compatible with acute MI or characteristic evolutionary ST-T changes or new Q waves. Patients were excluded from both studies if they 1) had other life-threatening medical illnesses, cognitive impairment, or other major psychiatric disorders; 2) were too ill or logistically unable to partic-

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ipate; 3) were currently taking tricyclic or monoamine oxidase inhibitor antidepressants; 4) had atrial fibrillation, atrial flutter, or an implanted pacemaker; or 6) refused to participate.

Depression Assessment

Patients not excluded by the above criteria were eligible for the ENRICHD study if they met the DSM-IV diagnostic criteria for major or minor depression. The criteria were modified for patients with a prior history of major depression (20). These patients were eligible for enrollment if they met the symptom criteria for a major or minor depressive episode for at least 7 (instead of the usual 14) days. Whether or not there was a prior episode of depression, the onset of symptoms of the current episode could have occurred either before or after the onset of the MI.

Depression Interview and Structured Hamilton. The DISH (21) is a semistructured interview developed for the ENRICHD study to diagnose current depressive episodes in cardiac patients according to the DSM-IV criteria and to screen for other psychiatric disorders. Patients meeting the modified DSM-IV criteria for either major or minor depression or dysthymia were classified as "depressed."

Beck Depression Inventory. The BDI (22) is a 21-item measure of the self-reported severity of depression symptoms. BDI scores can range from 0 to 64; the standard BDI cutoff for clinically significant depression is a score of 10 or higher (23).

Enrollment

Depressed subjects. All patients with major depression who were enrolled in either the intervention or the usual care arm of ENRICHD were eligible for participation in this study if their BDI score was 10 or higher. Holter monitor data were acquired after randomization, but before treatment was initiated (in the intervention arm). Tapes from twenty subjects with major depression recruited from the St. Louis site were randomly selected for the present study.

Nondepressed control subjects. Patients who were otherwise eligible for ENRICHD but who did not meet the ENRICHD depression or social isolation criteria (20), had no prior episodes of major depression, and scored 9 or below on the BDI were eligible for enrollment in this study as nondepressed control subjects. Enrollment of control subjects continued at the same rate throughout the recruitment period but was capped at 120% of the depressed sample. Control patients from the St. Louis site were matched with the 20 patients with major depression on age and sex.

Medical Assessments

Medical information. Medical records were reviewed to ascertain the patients' medical history, current medications, medical comorbidity, and CHD risk factors.

Ambulatory ECG monitoring. Marquette model 8500 monitors were used to record two analog data channels and a 32-Hz digital timing signal channel, which was also used for marking patient events. The electrodes were placed using a standard configuration. A 12-lead ECG was obtained to check ECG signal quality for each patient. All recordings were completed between 5 and 10 days after the MI.

QT variability. Eight 5-minute segments were sampled from the 24-hour ECG recording with one sample taken every 3 hours. The resulting data were digitalized for QT variability analysis at a sampling rate of 1000 Hz.

The algorithm used for QT analysis has been described in detail by Berger et al. (13) and has been used in previous studies (13–15, 19). The analyses were performed by one of the investigators (V.K.Y.) on a desktop PC with a graphic interface, using Solaris Desktop Unix software (Sunsoft, Mountainview, CA). R waves were identified by a peak detection algorithm. The operator identifies the beginning and the end of the QT wave template, and the algorithm then finds the QT interval for each beat using the time-stretch model. If the operator chooses a longer QT template, the error is consistent for all subsequent measurements and therefore poses no risk of bias in estimating QT variability.

The heart rate (beats per minute, or bpm) time series was sampled at 4 Hz using the technique described by Berger et al. (13). All tapes were manually edited for exclusion of artifacts. Only HR time series that were free of ventricular premature beats and noise were used. Temporal trends for HR and QT were removed (detrended) before the spectral analyses by using the best-fit line and subtracting the slope from each data point.

The mean HR (HRm), detrended HR variance (HRv), mean QT interval (QTm), detrended QT variance (QTv), and QT variance corrected for mean QT ($QTv/QTm^2 = QTvm$) were calculated from the instantaneous HR and QT time series of 1024 points (256 seconds).

A normalized, HR-corrected QT variability index was calculated as described by Berger et al (13): $QTvi = Log_{10}[(QTv/QTm^2)/(HRv/HRm^2)]$. This index represents the log-ratio between the QT interval and the HR variabilities, each normalized for the corresponding mean.

Statistical Analyses

The Fisher exact test, two-tailed *t* tests, and Pearson correlations were used to determine whether the demographic and medical variables differed between depressed and nondepressed patients, and two-tailed *t* tests were used to compare HRm, HRv, QTm, QTv, and QTvm. Repeated-measures ANOVA was used to determine whether QTv differed between depressed and nondepressed patients over time during the 24-hour recording period. Post hoc analyses were completed to determine the time intervals in which the groups differed.

RESULTS

Four tapes, two from depressed and two from nondepressed subjects, could not be analyzed because of excessive artifacts. Thus, data for 18 depressed and 18 control subjects are reported. A comparison of selected demographic and medical variables is presented in Table 1. There were no significant differences between depressed patients and the control subjects on any of these variables except the BDI scores, which were higher in the depressed patients.

The results of the analyses of HRm, HRv, QTm, QTv, and QTv corrected for QTm (QTv/QTm^2), and QTvi are presented in Table 2. As can be seen from the table, only QTvi was significantly different between depressed and nondepressed patients (group: $F = 4.8$; $df = 1,34$; $p = .035$; time: $F = 1.37$; $df = 7$; $p = .22$; group-by-time: $F = 1.40$; $df = 7,238$; $p = .21$). As can be seen from Table 3, mean QTvi was higher in depressed patients for each epoch tested. Moreover, post hoc analyses of the eight 5-minute epochs presented

TABLE 1. Medical and Demographic Characteristics by Depression Status[a]

Characteristic	Depressed (N = 18)	Nondepressed (N = 18)	p
Age (y)	60 ± 10.5	61 ± 9.8	.68
BDI score	18.2 ± 5.9	4.0 ± 2.6	< .001
Gender (female)	50% (9)	56% (10)	1.00
Systolic blood pressure (mm Hg)	124 ± 14	125 ± 19	.85
Killip class III–IV	11% (2)	11% (2)	1.00
Q wave	22% (4)	39% (7)	.13
Prior MI	22% (4)	29% (5)	.71
Diabetes	50% (9)	56% (10)	1.00
Current/former smoker	72% (13)	67% (12)	1.00
Left ventricular ejection fraction <45%	44% (8)	33% (6)	.85
β-Blockers	78% (14)	61% (11)	.47
Calcium channel blockers	28% (5)	22% (4)	1.00

[a] Continuous variables are reported as mean ± SD. Categorical variables are listed as column-wise percentage (N).

TABLE 2. ECG Indices by Depression Status[a]

Index	Depressed	Nondepressed	p
HRm	83.5 ± 15.1	82.1 ± 11.4	.76
HRv (detrended)	7.8 ± 8.3	13.4 ± 11.5	.10
QTm	409 ± 46	433 ± 63	.20
QTv (detrended)	63.4 ± 37.5	53.7 ± 35.1	.43
QTvm (ln)	−8.4 ± 0.7	−8.2 ± 0.6	.36
QTvi	−0.28 ± 0.5	−0.64 ± 0.5	.04

[a] Units: HR is in bpm; HRv is in bpm^2; QT is in milliseconds; QTv is in milliseconds squared; QTvm = log-transformed QTv/QTm^2.

show significant differences at two of the eight time points: midnight ($p < .03$) and 6:00 AM ($p < .02$).

DISCUSSION

QT interval variability was significantly higher in the depressed post-MI patients than in the age- and gender-matched nondepressed control subjects. QT variability was consistently higher in the depressed patients at each of the eight sampling times over the 24-hour period, but the difference was significant only at midnight and at 6:00 AM

There is evidence that the sympathetic nervous system may be instrumental in increasing QT variability. Yerigani et al. have shown that postural challenge and infusions of isoproterenol result in highly significant increases in QT variability in normal subjects (18). They have also found higher QT variability in medically well psychiatric patients with panic disorder and depression (19). This is consistent with studies that have found evidence for altered sympathetic function in depressed psychiatric patients as evidenced by elevations in urine and plasma levels of catecholamines and their metabolites (23–28).

QT interval variability has been shown to predict arrhythmic events, including sudden cardiac death, in patients with CHD (14–17). Sudden cardiac death has been shown to have a circadian variability with a peak incidence in the early morning hours (29). The difference between depressed and nondepressed patients in QT variability was greatest in the early morning, just after 6:00 AM. This may reflect an even greater increased risk for arrhythmias and sudden death for depressed patients during this high risk time.

Although heart rate variability, a risk factor for sudden cardiac death, did not differ significantly between depressed and nondepressed patients in this study, it has been found to be lower in depressed CHD patients in larger studies (6–9). Taken together, those results and the results of the present study suggest that depressed patients with CHD may be at greater risk for sudden cardiac death than nondepressed patients as a result of abnormalities in ventricular repolarization

TABLE 3. 24-Hour QT Variability[a]

Depres	6:00 PM	9:00 PM	Midnight	3:00 AM	6:00 AM	9:00 AM	Noon	3:00 PM
QTvi								
Depressed	−0.34 ± 0.18	−0.26 ± 0.52	−0.27 ± 0.66	−0.33 ± 0.56	−0.29 ± 0.56	−0.28 ± 0.66	−0.23 ± 0.61	−0.27 ± 0.52
Nondepressed	−0.64 ± 0.58	−0.60 ± 0.59	−0.74 ± 0.62[b]	−0.63 ± 0.68	−0.74 ± 0.58[c]	−0.53 ± 0.56	−0.62 ± 0.65	−0.60 ± 0.52

[a] ANOVA: group: $F = 4.5$; $df = 1,34$; $p \leq .04$; time: $F = 1.37$; $df = 7$; $p < .22$; group by time: $F = 1.40$, $df = 7,238$; p = .21.
[b] Post hoc analysis: midnight, $p \leq .03$.
[c] Post hoc analysis: 6:00 AM, $p \leq .02$.

that are possibly related to increased sympathetic activity.

The major limitation of the study is the small sample size. Although none of the medical variables thought to contribute to QT variability differed between groups, not all of the determinants of QT variability are known. Thus, it is unclear whether the groups were truly equivalent in all relevant factors. More study is needed to determine the medical parameters affecting QT interval variability, and future studies comparing QT interval in depressed and nondepressed patients should use larger samples. Finally, more work is needed to determine the clinical and prognostic significance of QT interval variability in relation to sudden cardiac death in depressed patients with cardiac disease.

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