Heart Rate Turbulence, Depression, and Survival After Acute Myocardial Infarction

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Objective: Depression is a risk factor for mortality after acute myocardial infarction (AMI), possibly as a result of altered autonomic nervous system (ANS) modulation of heart rate (HR) and rhythm. The purposes of this study were to determine: a) whether depressed patients are more likely to have an abnormal HR response (i.e., abnormal turbulence) to premature ventricular contractions (VPCs), and b) whether abnormal HR turbulence accounts for the effect of depression on increased mortality after AMI. **Methods:** Ambulatory electrocardiographic data were obtained from 666 (316 depressed, 350 nondepressed) patients with a recent AMI; 498 had VPCs with measurable HR turbulence. Of these, 260 had normal, 152 had equivocal, and 86 had abnormal HR turbulence. Patients were followed for up to 30 (median = 24) months. **Results:** Depressed patients were more likely to have abnormal HR turbulence (risk factor adjusted odds ratio = 1.8; 95% confidence interval [CI] = 1.0–3.0; $p = .03$) and have worse survival (odds ratio = 2.4; 95% CI = 1.2–4.6; $p = .02$) than nondepressed patients. When HR turbulence was added to the model, the adjusted hazard ratio for depression decreased to 1.9 (95% CI = 0.9–3.8; $p = .08$), and to 1.6 (95% CI = 0.8–3.4; $p = .18$) when a measure of HR variability (LnVLF) was added. The hazard was found to differ over time with depression posing little risk for mortality in year 1 but greater risk in years 2 and 3 of the follow up. **Conclusion:** ANS dysregulation may partially mediate the increased risk for mortality in depressed patients with frequent VPCs after an AMI. **Key words:** depression, acute myocardial infarction, survival, heart rate turbulence.

ANS = autonomic nervous system; **HR** = heart rate; **VPC** = premature ventricular contraction; **AECG** = ambulatory electrocardiography; **AMI** = acute myocardial infarction; **LnVLF** = natural log of very low frequency; **LVEF** = left ventricular ejection fraction; **TO** = turbulence onset; **TS** = turbulence slope.

INTRODUCTION

Depression is a risk factor for increased mortality after acute myocardial infarction (AMI) (1–4). One of the leading candidate mechanisms that may underlie this heightened risk is autonomic nervous system (ANS) dysfunction (5,6). Heart rate (HR) variability analysis has been used to study cardiovascular ANS functioning (7). Low HR variability reflects excessive sympathetic and/or inadequate parasympathetic modulation of HR (7), and it is an independent predictor of post-MI mortality (8–10). In a recent study, low values for the natural log of very low frequency (LnVLF) power, an index of HR variability, explained 27% of the mortality risk associated with post-MI depression during a 2-year follow up (11).

ANS dysfunction can increase the risk for ventricular arrhythmias and sudden cardiac death after AMI (12,13). There is evidence that depression may potentiate the risk of mortality that is associated with ventricular arrhythmias. For example, Frasure-Smith and her colleagues (14) found that depressed patients who had 10 or more ventricular premature contractions (VPCs) per hour after an AMI were at considerably higher risk for mortality than were depressed post-MI patients without VPCs or nondepressed post-AMI patients with 10 or more VPCs per hour. One interpretation of these data is that depressed patients may be at greater risk for death as a result of an abnormal response to VPCs or other arrhythmias.

HR turbulence is an index of HR response to VPCs. Ordinarily, HR first accelerates and then decelerates after a VPC. This response pattern is thought to be regulated by baroreceptor reflexes and the parasympathetic nervous system (15,16). HR responses that deviate from this pattern have been found to be better predictors of post-AMI mortality than traditional measures of HR variability and as predictive of mortality as low left ventricular ejection fraction (LVEF) (17–19).

The primary aims of this study were to determine whether there is an association between depression and abnormal HR turbulence in response to VPCs and whether abnormal HR turbulence may help to account for differences in survival between depressed and nondepressed post-MI patients. A secondary aim was to determine whether HR turbulence and VLF have additive effects on the risk of mortality in depressed patients.

METHODS

Subjects

Three hundred fifty-eight depressed patients with a recent AMI who participated in the ENRICHD clinical trial and 408 patients with a recent AMI who were free of depression but otherwise eligible for ENRICHD were recruited for this study from four of the trial's clinical sites (Washington University, St. Louis, MO; Duke University, Durham, NC; Harvard Univer-

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sity, Boston, MA; and Yale University, New Haven, CT) between October 1997 and January 2000. All of the depressed patients scored 10 or higher on the Beck Depression Inventory (BDI) (20); 163 met modified Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for major depression and 195 met the criteria for minor depression or dysthymia. The nondepressed patients reported adequate social support, scored less than 10 on the BDI, and had no previous episodes of major depression. Detailed accounts of recruitment, enrollment, and the demographic and medical characteristics of the participants in this study and in the ENRICHD trial are available elsewhere (21–24).

Procedure

Ambulatory Electrocardiographic Monitoring

All patients underwent ambulatory electrocardiographic (AECG) monitoring with Marquette Model 8500 recorders within 24 hours of study enrollment. The AECG tapes were scanned at the HR variability core laboratory at Washington University, St. Louis, on a Marquette SXP Laser scanner with software version 5.8 (Marquette Electronics, Milwaukee, WI).

Heart Rate Turbulence

HR turbulence indices quantify the HR response to VPCs (19). Ordinarily, there is a brief period of HR acceleration immediately after a VPC. Turbulence onset (TO) quantifies the magnitude of change in HR as the percent change in N-N interval two beats after the VPC compared with the two beats before. Turbulence slope (TS) quantifies the oscillation in HR (tachycardia, then bradycardia, followed by a return to baseline) that follows a VPC as the largest fitted slope of the N-N intervals between any five beats within 15 beats of the VPC. The combination of abnormal TO and TS is associated with a high risk for mortality (17–19). TO and TS require a minimum of five VPCs for calculation and are expressed as an average of the responses to all of the VPCs during the time of the recording. Details of the measurement of HR turbulence can be found elsewhere (17–19).

Consistent with previous studies, abnormal TO was defined as no change or a decrease in HR after a VPC. Abnormal TS was defined as ≤2.5 ms/beat reflecting a diminished or absent oscillatory response (15). Patients were initially categorized as having: a) fewer than five VPCs in 24 hours; b) five or more VPCs but unclassified turbulence resulting from excessive artifact, lack of sufficient eligible beats, or other technical problems; c) normal turbulence (both TO and TS were normal); d) equivocal turbulence (either abnormal TO or abnormal TS but not both); or e) abnormal turbulence (both TO and TS were abnormal). Patients in the first two categories were excluded from further analysis. The remaining three categories comprised an ordinal turbulence index (0 = normal, 1 = equivocal, 2 = abnormal).

Follow Up

Patients were followed for up to 30 months (median = 24 months) after the index MI. The primary end point was time to death from any cause. Death certificates were obtained to confirm all reported deaths.

Statistical Analyses

Synthesizing concepts from a number of disciplines and extending work by Baron and Kenny (25), Kraemer et al. (26) proposed five ways that risk factors can work together to affect outcomes: mediation, moderation, independence, overlapping, and proxy. The differences among them depend on three characteristics of the risk factor relationship: temporal precedence, correlation, and potency. The aim of this study was to determine whether abnormal HR turbulence mediates the effect of depression on survival. According to Kraemer et al., the mediation hypothesis would be supported if depression precedes abnormal HR turbulence in time, abnormal HR turbulence is correlated with depression, and the effect of HR turbulence totally or partially dominates that of depression in predicting outcome. These elements are illustrated in the path diagram in Figure 1. Although a mediation hypothesis implies a causal model, the results do not prove causality because such models depend on assumptions that are rarely met (27). Most notably, observational studies cannot demonstrate temporal precedence even if, like in the present study, there are strong arguments in its favor. Furthermore,

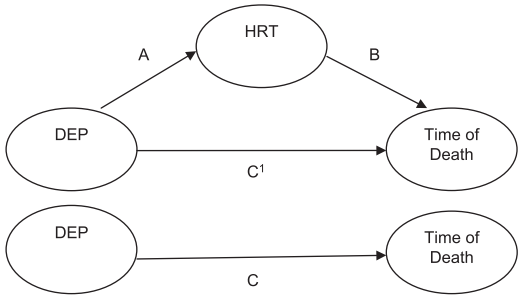

Figure 1. Mediation model of the effect of depression on time to death through heart rate turbulence.

Kraemer et al. stress that risk factors be robust to measurement error. A further condition is that there should be no interaction between the risk factors, because interactions are characteristic of moderators rather than mediators. The following analysis is intended to support the correlation and potency aspects of mediation. It begins with the common approach of testing a mediation hypothesis by fitting two regression models, one with and one without the putative mediator. Then, the potency of the risk factor relationship is quantified by the "proportion-mediated" statistic defined in terms of Figure 1 as (C–C′)/C (28) where C and C′ are the unexponentiated coefficients from the Cox regression model (29) of survival on depression (path C) and the Cox regression model of survival on depression adjusted for HR turbulence (path C′). The association between depression and HR turbulence (normal, equivocal, and abnormal) is determined by a proportional odds model (path A).

Path C′ is referred to as the direct effect of depression and the pathway through paths A and B is called the indirect or mediated effect of depression. Robins and Greenland (30) showed that to disentangle the direct and indirect effects in a mediation model, the causal pathways must not be confounded by other variables. To address this issue, a global risk score was included as a covariate in all models computed as a weighted sum of risk factors present in the final prediction model of all-cause mortality in the ENRICHD trial (31), including age, diabetes, LVEF, creatinine level, prior AMI, history of pulmonary disease, prior transient ischemic attack or stroke, history of congestive heart failure, Killip class at time of index AMI, and treatment with vasodilators.

A secondary hypothesis that HR turbulence and VLF jointly mediate the effect of depression on the risk of mortality was tested in the same framework. In the secondary Cox regression model, LnVLF was standardized to mean ± standard deviation of 0 ± 1.

A multiple imputation procedure (SAS Proc MI) was used to impute missing data in the subset of patients with HR turbulence data. LVEF was missing in approximately 10% of cases. No other variable had more than 3% missing data. Survival outcomes were not included in the imputation model. All analyses were performed on 50 completed data sets in which missing values were replaced with values estimated from other observed variables. The resulting model estimates were then combined for statistical inference. SAS 9.1.3 software (SAS Institute, Inc., Raleigh, NC) was used to perform all statistical analyses.

RESULTS

AECG data were available for 740 (97%) of the 766 participants, including 344 depressed and 396 nondepressed patients. HR turbulence could not be calculated in 100 cases as a result of artifact or other technical difficulties. These patients were more likely to have diabetes and less likely to be current smokers than the patients who had usable AECG data, but there were no other medical or demographic differences between these groups.

Of the remaining 666 patients (316 depressed and 350 nondepressed), 81 (26%) depressed and 87 (25%) nondepressed patients ($p > .05$) had fewer than five VPCs during the AECG recording period, so HR turbulence was not calculated in these cases. Table 1 reports the results of HR turbulence

TABLE 1. Turbulence Category by Depression Status[a]

Variable	Depressed (*N* = 235)	Nondepressed (*N* = 263)
Normal turbulence (normal TO and TS)	113 (48%)	147 (56%)
Equivocal turbulence (abnormal TO *or* TS)	73 (31%)	79 (30%)
Abnormal turbulence (abnormal TO *and* TS)	49 (21%)	37 (14%)

[a] N (column %).
TO = turbulence onset; TS = turbulence slope.

by depression status in the 498 cases with turbulence data. The depressed patients had a mean of 890 ± 2553 VPCs compared with 826 ± 2249 for the nondepressed patients ($p = .77$).

With regard to path A of the mediation model, depressed patients were more likely than the nondepressed patients to have equivocal or abnormal turbulence (adjusted odds ratio [OR] = 1.4; 95% confidence interval [CI] = 1.03–2.03; $p = .04$). In secondary analyses, depressed patients were not more likely to have equivocal turbulence (adjusted OR = 1.2; 95% CI = 0.8–1.9; $p = .29$) but were more likely to have abnormal turbulence (adjusted OR = 1.8; 95% CI = 1.1–3.0; $p = .03$).

TABLE 2. Medical and Demographic Characteristics by Depression Status[a]

Characteristic	Depressed (*n* = 235)	Nondepressed (*n* = 263)	*p*
Age (years)	58.6 ± 12.2	62.4 ± 10.4	.0002
Beck Depression Inventory	17.1 ± 7.4	4.0 ± 3.1	.0001
Women	45.1%	33.8%	.01
Nonwhite	27.7%	19.0%	.03
Body mass index (kg/m^2)	29.5 ± 6.0	28.3 ± 5.0	.02
Systolic blood pressure	123.4 ± 20.0	123.0 ± 18.3	.83
Diabetes mellitus	32.0%	21.3%	.008
Cigarette smoker (ever)	77.3%	71.4%	.15
Left ventricular ejection fraction (<40%)	28.6%	28.9%	.99
Killip class III–IV	7.6%	5.6%	.46
Non-Q-wave AMI	38.3%	30.9%	.12
Anterior wall AMI	32.1%	34.9%	.56
Creatinine (mg/dL)	1.1 ± 0.8	1.2 ± 0.9	.54
Prior AMI	25.3%	24.3%	.83
Thrombolytic therapy	29.8%	32.2%	.62
Beta blocker	79.8%	84.1%	.18
Angiotensin converting enzyme inhibitor	47.8%	51.2%	.47
Aspirin	89.1%	90.9%	.54
Coronary bypass post-AMI	15.2%	16.4%	.80
Coronary angioplasty <24 hr	56.8%	64.6%	.09

[a] Continuous variables are reported as means ± standard deviations; categorical variables are listed as percentage of subjects with the characteristic.
AMI = acute myocardial infarction.

Table 2 compares the 235 depressed and 263 nondepressed patients with HR turbulence on prespecified medical and demographic variables. Several variables differed between the depressed and nondepressed patients. None of these variables have been established in previous studies as potential confounders of the relationship between depression and abnormal HR turbulence. However, the fact that they differ between the groups raises the possibility that they might be confounders. Consequently, a series of exploratory regression analyses were performed to investigate this question. The initial model included only depression and age. Likelihood ratio tests (32) were then used to determine whether there was a significant change in goodness of fit when individual candidate covariables were added. Gender ($\chi^2 = 6.60, p = .01$), diabetes ($\chi^2 = 32.22, p < .001$), and beta blockers ($\chi^2 = 7.01, p = .008$) affected the model goodness of fit, but depression remained a significant predictor of abnormal HR turbulence after adjusting for gender and beta blockers and marginally significant ($\chi^2 = 3.62, p = .06$) after adjusting for diabetes.

With respect to path B of the model, using normal turbulence as the reference category, abnormal turbulence was associated with decreased survival after adjusting for risk score and depression status (hazard ratio [HR] = 2.3; 95% CI = 1.1–4.9; $p = .03$). Equivocal turbulence was not associated with decreased survival (HR = 0.5, 95% CI = 0.2–1.2; $p = .11$).

For path C, the hazard ratio for depression was 2.4 (95% CI = 1.2–4.6; $p = .01$). When abnormal HR turbulence was added to the model, the adjusted hazard ratio for depression (path C′) was reduced to 1.9 (95% CI = 1.2–4.6; $p = .01$). Twenty-eight percent of the mortality risk of depression was attributable to abnormal HR turbulence. Finally, when both turbulence and LnVLF were included in the model, the hazard ratio for depression dropped to 1.6 (95% CI = 0.9–3.8; $p = .08$) accounting for 47% of the mortality risk associated with depression.

On further inspection, it was noted that the hazard of depression varied during the course of follow up with a relatively low hazard immediately after the AMI and a much higher hazard during the end of the follow-up period. To correct for this violation of the proportional hazards assumption of the Cox model, hazard ratios were calculated separately for two time periods: year 1 and years 2 to 3. The hazard ratio for depression for year 1 was 0.94 (95% CI = 0.4–2.4; $p = .90$) and 5.9 (95% CI = 2.0–17.6; $p = .001$) for years 2 to 3. When abnormal HR turbulence was added to the depression model, the adjusted hazard ratio for depression (path C′) was nearly unchanged (HR = 0.7; 95% CI = 0.3–2.0; $p = .55$) for year 1 but dropped from 5.9 to 4.5 (95% CI = 1.5–13.5; $p = .008$) for years 2 to 3.

When LnVLF was added to the model with depression and abnormal turbulence, the hazard ratio for depression dropped to 0.6 (95% CI = 0.18–1.8; $p=.35$) for year 1 and to 4.0 (95% CI = 1.3–12.3; $p = .02$) for years 2 to 3. The results of the path C analyses are summarized in Table 3.

TABLE 3. Cox Models[a] of Time to Death for Total Follow-Up Period and With Separate Estimates for Year 1 and Years 2 to 3

Variable	Hazard Ratio	*p*
Total follow-up period		
Major/minor depression	2.4 (CI = 1.2–4.6)	.02
Major/minor depression adjusted for abnormal turbulence	1.9 (CI = 0.9–3.8)	.08
Major/minor depression, adjusted for abnormal turbulence and lnVLF	1.6 (CI = 0.8–3.4)	.18
Year 1		
Major/minor depression	0.9 (CI = 0.4–2.4)	.90
Major/minor depression adjusted for abnormal turbulence	0.7 (CI = 0.3–2.0)	.55
Major/minor depression, adjusted for abnormal turbulence and lnVLF	0.7 (CI = 0.2–1.9)	.43
Years 2–3		
Major/minor depression	5.9 (CI = 2.0–17.6)	.001
Major/minor depression adjusted for abnormal turbulence	4.5 (CI = 1.5–13.5)	.008
Major/minor depression adjusted for abnormal turbulence and lnVLF	4.0 (CI = 1.3–12.3)	.02

[a] All models adjusted for other predictors of mortality.
CI = confidence interval; LnVLF = natural log of very low frequency.

DISCUSSION

Depressed patients are more likely to have an abnormal HR response (i.e., abnormal turbulence) to VPCs than are nondepressed patients. That is, depressed patients are more likely to show either no change or decreases in HR and diminished or absent oscillatory responses to VPCs. In this study, depression was found to be associated with decreased survival after controlling for other risk factors. Adding abnormal HR turbulence to the risk score-adjusted depression model reduced the effect of depression on survival and accounted for 28% of the risk. These findings are consistent with the possibility that abnormal HR turbulence partially mediates the effect of depression on mortality.

Abnormal HR response to VPCs is thought to be the result of abnormal vagal activity and inadequate baroreceptor response to change in arterial blood pressure (15,16). Additional evidence for abnormal ANS functioning in depressed patients has been found in studies of HR variability. VLF power, an index of HR variability, reflects changes in HR at a cycle length of 20 seconds to 5 minutes. VLF power is unaffected by beta blockade but nearly abolished by atropine, suggesting that the parasympathetic nervous system is the predominant determinant of VLF (33). Low VLF is associated with depression (21), and it has been shown to be an independent risk factor for mortality (8–10). In this study, when the natural log of VLF was added to the model along with depression and HR turbulence, the effect of depression on survival was further reduced. This suggests that altered ANS modulation of HR affects survival of depressed patients through other pathways in addition to HR turbulence. The combination of abnormal HR turbulence and low VLF accounted for nearly one half of the relationship of depression to decreased survival.

Neither depression nor HR turbulence predicted survival in the first year after AMI, but both were highly predictive in the second and third years. The significance of this finding is not immediately clear. Although previous studies have not revealed any differences in early versus late effects of depression on survival after an AMI, it is possible that the proportional hazards assumption was violated but the assumption was not assessed for the Cox models that were used in these studies. Thus, the effect may have been present but undetected in at least some of the earlier studies. In addition, most of the previous studies were completed before the ENRICHD clinical trial. It is possible that the early negative effects of depression and abnormal baroreceptor response and vagal modulation of heart rate and rhythm are offset by the protective effects of the aggressive strategies for treating AMI and for minimizing early post-AMI risk that have been widely implemented in recent years (34). If so, this may help explain the failure of studies with relatively brief follow-up periods to find an effect for depression on survival after an acute MI.

In addition to the findings of this study, there is other more indirect evidence that depression may increase the risk of post-AMI mortality through proarrhythmic pathways. As described earlier, Frasure-Smith and her colleagues (14) found that depressed patients who had ≥10 VPCs per hour after an AMI were at greater risk for dying than were depressed patients without VPCs or nondepressed patients with or without VPCs. Irvine and her colleagues found that depression predicted mortality in a group of patients at high risk for sudden cardiac death who were taking part in a trial of an antiarrhythmic drug (amiodarone), but only in the placebo arm (35). Among those who received the active drug, depressed patients were not at increased risk for mortality, but actually tended to be at lower risk of death than nondepressed patients. In another study, a series of patients undergoing treatment for ventricular tachyarrhythmias or syncope of unknown origin were significantly more likely to die during the course of the follow-up period if they were depressed at the time of the initial assessment (36). Finally, in a sample of medically stable patients with coronary heart disease with normal ventricular function, depressed patients had more frequent and longer runs of ventricular tachycardia than the nondepressed patients (38).

Although abnormal HR turbulence and low LnVLF account for approximately one half of the effect of depression on survival, this leaves much of the effect unexplained. Thus, other mediators may also participate in this relationship. Depression has also been associated with other risk factors for mortality, including procoagulant and proinflammatory processes and behavioral risk factors such as poor adherence to medical treatment regimens (5). These and other potential mediators require further investigation. A better understanding of the mechanisms through which depression reduces survival is needed to plan clinical trials. Treatments are needed that not only decrease depression, but that also modify the pathways

that link depression to cardiac mortality. There is already some evidence that successful psychotherapeutic or pharmacological treatment of depression may reduce HR and improve HR variability in depressed patients with coronary heart disease (37). Research is needed to determine the effects of treating depression on HR turbulence as well as on other potential pathways linking depression to increased risk for mortality.

This study has several limitations. First, the results may not generalize to the entire population of post-AMI patients because those who were too sick or debilitated to participate in the ENRICHD clinical trial were excluded. Patients in atrial fibrillation/flutter or who were pacemaker-dependent were also excluded from this study. In addition, patients were excluded from the present analysis if their 24-hour AECG data could not be used to calculate HR turbulence and VLF as a result of artifact or other technical problems with the recording.

Furthermore, although the survival analyses were adjusted for known predictors of mortality, there is always the possibility that an unknown, uncontrolled confounder may influence the effect of depression on survival or the relationship between depression and turbulence. No potential confounders of the relationship between depression and abnormal HR turbulence had been identified in previous studies, so we adjusted only for a composite risk score composed of previously established predictors of post-MI mortality. Exploratory analyses showed that gender, diabetes, and beta blocker use are plausible candidate confounders that should be taken into account in future studies. However, depression remained significantly associated with HR turbulence when gender and beta blockers were added to the model with depression and age and marginally significant when diabetes was added. Diabetes was part of the risk score that was included as a covariate in the primary analysis. More work is needed to identify other possible confounders between depression and turbulence.

Depressed and nondepressed patients were classified into one of five groups based on the presence of VLF and their HR responses. This produced relatively small subgroups and low statistical power for some of the analyses. The relatively small number of deaths ($n = 43$) during the follow-up period also affected statistical power, especially in the separate analyses for year 1 versus years 2 to 3. In addition, arrhythmic deaths could not be reliably identified in the ENRICHD cohort. Whether abnormal HR turbulence and low VLF would have accounted for a different proportion of the effect of depression on arrhythmic deaths is unknown.

Finally, the statistical methods for testing hypotheses about mediators of the effects of risk factors on survival outcomes are controversial, and mediation analyses have been criticized for not meeting model assumptions (39,40). An important assumption of these models is the temporal precedence of the risk factor to the mediator. In this case, depression must predate abnormal turbulence. Although the depressed patients were depressed for 7 days or longer before HR turbulence was assessed, and although most had one or more prior episodes of major depression before their AMI (22), it cannot be said with certainty that the onset of depression invariably preceded the development of abnormal HR turbulence. That is, some patients may have had abnormal HR turbulence even before the AMI and possibly before they were depressed.

In conclusion, the results of the study suggest that abnormal HR turbulence may partially mediate the effect of depression on survival after an AMI, accounting for approximately one fourth of the total risk. The addition of low LnVLF increased the proportion to approximately one half of the total risk. Other factors associated with depression may also increase the risk for mortality. More research is needed to identify these mechanisms as well as to develop treatments for depression that will improve both depression and survival after an AMI.

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