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Nighttime Heart Rate and Survival In Depressed Patients Following Acute Myocardial Infarction

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Abstract

Background—Depression is a risk factor for mortality following acute myocardial infarction (AMI). It is also associated with sleep disturbances, and with elevated heart rate (HR), which may be more pronounced at night. Resting and 24 hour HR have been found to predict mortality in patient and community samples.

Objective—The purpose of this study was to determine: 1) whether depressed patients with a recent AMI have higher nighttime HR than nondepressed patients, and 2) whether elevated nighttime HR is associated with decreased survival following AMI.

Methods—Ambulatory ECG data were obtained from 333 depressed and 383 nondepressed patients with a recent AMI. They were followed for up to 30 (median = 24) months.

Results—Depressed patients had higher nighttime (70.7 $\pm$.7 versus 67.7 $\pm$.6 bpm; $p=.001$), and daytime (76.4 $\pm$.7 versus 74.2 $\pm$.6 bpm; $p=.02$) HR than nondepressed patients, even after adjusting for potential confounds. Depression (H.R. = 2.19; $p=.02$) and nighttime (H.R. = 1.03; $p=.004$), but not daytime HR, predicted survival after adjusting for other major predictors and for each other.

Conclusions—Mean day and nighttime HRs are higher in depressed than in nondepressed patients following an AMI, and both depression and nighttime HR are independent predictors of mortality in these patients. Although depressed patients have a higher nighttime HR than nondepressed patients, elevated nighttime HR predicts mortality independent of depression status.

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Keywords

Depression; heart rate; nighttime; acute myocardial infarction; mortality

Introduction

Depression is an independent risk factor for cardiac morbidity and cardiac and all-cause mortality following an acute myocardial infarction (AMI).(1-4) The mechanisms that account for this risk are yet to be determined. However, depression is associated with behavioral and physiological abnormalities that may help to explain this relationship. One of these abnormalities is elevated heart rate (HR). Compared to nondepressed controls, depressed psychiatric patients and depressed patients with CHD tend to have higher resting and 24-hour HRs.(5-14) Elevated resting and 24-hour HR predict mortality and cardiac morbidity, both in patients with known cardiovascular disease(15-20) and in community residents.(21-28)

Most individuals show diurnal variation in HR, with HR being higher during the day than at night. This is primarily due to the relative dominance of the sympathetic nervous system during daytime activities and of the parasympathetic nervous system at night, especially during sleep.(29) There is evidence that not only do depressed but otherwise medically well psychiatric patients have higher 24-hour HR than nondepressed comparison groups, but the difference in HR between depressed and nondepressed patients is more pronounced at night than during the day.(30-32) Sleep disturbance is a common symptom of depression(33, 34), and it may help to explain the higher nighttime HR in depressed patients.(30) Polysomnographic studies have found differences in sleep architecture, as well as more frequent arousals and poorer sleep efficiency, in depressed psychiatric patients compared to controls.(35-37) Frequent arousals and poor sleep efficiency may reduce parasympathetic control and interfere with the restorative functions of sleep. The purpose of this study is to determine whether nighttime HR is higher in depressed compared to nondepressed patients with a recent AMI, and whether nighttime HR predicts survival in these patients.

Methods

Subjects

Three hundred fifty-eight depressed patients with a recent AMI who participated in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial, and 408 post-AMI patients who were free of depression but otherwise eligible for ENRICHD, were recruited for this study from four clinical sites (Washington University, St. Louis, MO; Duke University, Durham, NC; Harvard University, Boston, MA; Yale University, New Haven, CT) between October 1997 and January 2000. The ENRICHD study was a multicenter, randomized, controlled clinical trial designed to determine whether treating depression and low perceived social support following acute MI reduces the risk of recurrent infarction and death.(38)

All of the depressed patients scored 10 or higher on the Beck Depression Inventory (BDI) (39); 163 met modified DSM-IV criteria for major depression(40), 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. More detailed information concerning the methods of recruitment and enrollment, as well as the demographic and medical characteristics of the participants, is available elsewhere.(38, 41-43)

Procedure

Ambulatory Electrocardiographic Monitoring—All patients underwent 24-hour ambulatory electrocardiographic (ECG) monitoring with Marquette Model 8500 recorders within 24 hours of study enrollment. To ensure standardization of ECG recordings, the same ambulatory ECG recorder model (Marquette Model 8500) was used at all four sites. The Marquette Holter recorder continuously records two analog data channels in addition to a 32 Hz digital timing signal channel. Signal quality was checked with a 12-lead ECG prior to each 24-hour recording.

The tapes were scanned on a Marquette SXP Laser scanner with software version 5.8 (Marquette Electronics, Milwaukee, Wisconsin, USA) using standard Holter analysis procedures. The longest and shortest true normal-to-normal intervals were identified and carefully edited for each recording. Daytime was defined as between 8:00 AM and 8:00 PM and nighttime between midnight and 6:00 AM. These times were selected in order to capture representative wake and sleep segments for HR estimation. HR in beats per minute (bpm) was determined by first calculating the mean heart period from N to N in milliseconds for the specified recording time, and then multiplying the reciprocal of that number by 60,000.

Follow-up—Patients were followed for up to 30 months (median = 24 months) after the index AMI. The primary endpoint for the study was time to death from any cause. Standardized, group-masked classification of cause of death was performed by the ENRICHD endpoint classification committee. This committee was composed of experienced cardiologists who remained masked to depression status and to clinical trial group assignment.

Statistical Analyses—Chi-square tests and two-tailed t-tests were used to determine whether demographic and medical variables differed between depressed and nondepressed patients. Analysis of covariance (ANCOVA) was used to compare the nighttime, daytime, and 24 hour HRs of the depressed and nondepressed patients. For each time period, the first model examined the univariate effect of depression on HR. The second model examined the effect of depression after controlling for the ENRICHD risk score. This score is a weighted sum of all independent risk factors for all-cause mortality in the ENRICHD trial.⁽⁴⁴⁾ Potential risk factors that were considered included factors such as smoking, and medications, including beta blockers. The final risk score included 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. The third model adjusted for the risk score, beta blockers, gender, diabetes, and current smoking, based on their association in prior studies with depression and HR.

The effects of nighttime, daytime, and 24 hour HR on patient survival were each analyzed in separate Cox proportional hazards regression models.⁽⁴⁵⁾ For each of these candidate predictors (e.g., nighttime HR), the univariate effect of HR was fitted first. In the second step, the HR model was adjusted for the ENRICHD global risk score. In the third step, depression was added to the model. Finally, a depression by HR interaction term was added to determine whether depression moderates the effects of elevated HR on survival. Schoenfeld⁽⁴⁶⁾ and Martingale residuals⁽⁴⁷⁾ were used to test the Cox model assumptions of proportional odds and linearity of continuous covariates, respectively. In addition, overall goodness-of-fit was ascertained.⁽⁴⁸⁾ Survival curves were generated by the Kaplan-Meier method and were then compared with the log rank statistic.

Multiple imputation (SAS Proc MI) was used to impute missing data.⁽⁴⁹⁾ 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 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

Twenty four-hour ambulatory ECG data were available for 716 (93%) of the 766 participants, including 333 depressed and 383 nondepressed patients ($p > 0.05$). The ambulatory monitoring was completed a mean of 18.9 ± 0.37 days following the AMI for the depressed patients, and 18.1 ± 0.42 days for the nondepressed patients ($p = 0.11$). A comparison of selected demographic and medical variables for the depressed and nondepressed participants is presented in Table 1. The groups differed with respect to age, gender, diabetes, current cigarette smoking, and beta blocker use. These variables were included as covariates in the adjusted analyses comparing day and nighttime HR between depressed and nondepressed patients.

The depressed patients had significantly higher nighttime HRs compared to nondepressed patients (68.4 ± 0.7 versus 64.1 ± 0.6 bpm, $F = 22.27$; $p < .0001$). Patients with major depression had the highest mean nighttime HR (69.4 ± 1.1 bpm), followed by those with minor depression (67.6 ± 0.9 bpm). Similar differences between depressed and nondepressed patients were found for daytime (73.5 ± 0.7 versus 70.1 ± 0.6 , $F = 13.75$; $p = .0002$) and 24 hour HR ($71.6 \pm .7$ versus $68.0 \pm .6$, $F = 18.11$; $p < .0001$). After adjusting for the risk score, and current smoking, gender, and use of beta blockers, the depressed patients continued to have a significantly higher mean nighttime heart rate than their nondepressed counterparts (70.7 ± 0.7 versus 67.7 ± 0.8 ; $t = 3.30$; $p = .001$). Daytime ($76.4 \pm .7$ versus 74.2 ± 0.8 bpm; $t = 2.41$; $p = .016$) and 24 hour HR (74.4 ± 0.7 versus 71.9 ± 0.8 bpm; $t = 2.86$; $p = .004$) also continued to differ between depressed and nondepressed patients.

Although not available for the total sample, HR data were analyzed from the subset of the sample ($n = 631$) who recorded the times at which they went to bed and they awakened. The mean number of hours in bed for this subset did not differ between the depressed (8.6 ± 2.4) and nondepressed patients (8.5 ± 1.9 ; $p > 0.05$). The unadjusted HRs were nearly identical in this subset of patients and in the total sample (depressed, 68.5 ± 0.7 ; nondepressed, 64.2 ± 0.6 bpm).

Thirty three depressed patients (9.9%) and 14 (3.7%) nondepressed patients died during follow-up. Twenty four (73%) of the deaths among the depressed patients were classified as likely due to cardiovascular causes, compared to 10 (71%) deaths among the nondepressed patients ($p = 0.93$). Hazard ratios (Haz R) were first estimated from unadjusted models for depression, and nighttime, daytime, and 24 hour HR (Table 3). Depression (Haz R = 2.90; $95\% \text{ CI} = 1.108$; $p = .0009$), nighttime HR (Haz R = 1.03; $95\% \text{ CI} = 1.318$; $p = .0003$), 24 hour HR (Haz R = 1.02; $95\% \text{ CI} = 4.01$; $p = .045$), but not daytime HR (Haz R = 1.01; $95\% \text{ CI} = .84$; $p = .356$), were significantly associated with survival. Depression (Haz R = 2.54; $95\% \text{ CI} = 8.29$; $p = .004$), nighttime HR (Haz R = 1.04; $95\% \text{ CI} = 11.70$; $p = .0007$), and 24 hour HR (Haz R = 1.03; $95\% \text{ CI} = 5.20$; $p = .023$) remained predictive of survival when adjusted for the ENRICH mortality risk score (Table 2). As in the unadjusted model, daytime HR was not a significant predictor of survival (Haz R = 1.02; $95\% \text{ CI} = 1.90$; $p = .167$).

The final Cox model included both depression and HR (night, day and 24 hour) in order to examine the joint contribution of these variables to mortality after controlling for the ENRICH risk score (3rd row in Table 2). While daytime (Haz R = 1.01; $95\% \text{ CI} = 1.17$; $p = .28$) and 24 hour HRs (Haz R = 1.02; $95\% \text{ CI} = 3.53$; $p = .06$) were no longer significantly related to long-term survival, nighttime HR (Haz R = 1.03; $95\% \text{ CI} = 8.18$; $p = .004$) remained a significant

predictor. Depression was also highly predictive of mortality in each of the models that included HR (nighttime: Haz R = 2.19; $\text{CI} = 1.02, 5.66$; $p = .02$, daytime: Haz R = 2.45; $\text{CI} = 1.02, 7.62$; $p = .006$, 24 hour: Haz R = 2.36; $\text{CI} = 1.02, 6.86$; $p = .009$). The interaction between nighttime HR and depression was included in the final Cox model. The interaction term approached, but did not achieve, significance ($\text{CI} = 0.99, 2.99$; $p = .08$).

The hazard ratios reported for the analyses of HR refer to the effects on survival of increasing HR by one beat per minute. The adjusted hazard ratios for increases of 5, 10 and 15 bpm are presented in Table 3. To further illustrate the relationship between elevated nighttime HR and survival, risk score-adjusted survival curves for the depressed and nondepressed patients within the lowest (< 57.2 bpm) and highest (> 73.5 bpm) mean nighttime HR quartiles ($n = 358$) (Figure 1). The omnibus test of differences in survival among these groups was significant (log-rank test: $\chi^2 = 12.10$; $p = .007$). Nondepressed patients with low HR had the best survival, and depressed patients with high HR had the worst.

Although the quality of sleep during the night of ambulatory ECG monitoring was not assessed, depressed patients were more likely to report sleep problems during the previous seven days (77%) than were the nondepressed patients (33%) ($p < 0.001$).

Discussion

Depressed patients had higher nighttime and daytime HRs compared to nondepressed patients even after adjusting for potential confounders, including beta blocker use, age, gender, diabetes, and smoking. Both depression and nighttime HR, but not daytime HR, were significantly associated with survival, before and after adjusting for other risk factors and each other. Depression was associated with poor survival, even after adjusting for HR. However, the interaction between depression and nighttime HR on survival approached statistical significance ($p = 0.08$). There were only 47 deaths during the follow-up, and it is possible that the interaction would have achieved significance with a larger sample or with more events. Thus, elevated nighttime HR may be a greater risk factor for mortality in depressed than in nondepressed patients. However, patients with elevated HR at night, regardless of depression status, are at greater risk for dying following an AMI than those with lower nighttime HR. For example, after adjusting for the ENRICH risk score and depression, the hazard ratio for mortality increases nearly 40% (27% - 53% : 95% CI) for every ten beats per minute in nighttime HR.

Both 24 hour HR and resting HR have been shown to be elevated in depressed psychiatric and cardiac patients compared to controls (5-14), and elevated resting HR is a risk factor for ventricular arrhythmias and sudden cardiac death (50), progression of atherosclerosis (20, 51), myocardial ischemia (19), and plaque disruption in acute coronary syndromes (17). Studies of CHD patients have reported mean resting and 24 hour HRs of between 4 to 11 bpm higher in depressed compared to nondepressed patients (5-7). The mean difference in nighttime HR between depressed and nondepressed patients in the present study was at the lower end of this range. To our knowledge, this is the first study to examine HR in depressed patients with a recent AMI, and it is possible that HR differences may be less pronounced in depressed patients with an acute event than in medically stable or healthy depressed individuals. It is also possible that HR overall was lower because most patients in this study were receiving beta blockers, and this may have narrowed the difference between depressed and nondepressed patients.

We have previously shown that 24 hour HR variability is lower in these and in other depressed patients with CHD, compared to nondepressed patients (42). Low HR variability

suggests excessive sympathetic or reduced parasympathetic modulation of HR and rhythm. (52) Most(53), although not all(54) studies of HRV and depressed patients with CHD have reported similar findings. Low HR at night may reflect high sympathetic and/or low parasympathetic nervous system modulation activity even during a time of relative rest.

Disturbed sleep, frequently reported in patients with depression(33, 34), may also help explain why nighttime HR is associated with survival. Although the quality of sleep was not assessed during the night of ambulatory ECG monitoring, the depressed patients in this study were more than twice as likely to report sleep problems during the previous seven days than were the nondepressed patients. There is evidence that arousals from sleep that are associated with increased HR may provoke ischemic events(55), arrhythmias(56), and QT interval prolongation(57) in patients with CHD. Elevated HR may also reflect obstructive sleep apnea/hypopnea syndrome (OSAHS.) OSAHS is common in patients with CHD, and often goes undetected.(58-61) HR usually decreases and then dramatically increases during the course of apneic episodes.(62) These episodes can thus trigger nocturnal myocardial ischemia, heart rhythms characteristic of cardiac sympathetic predominance, and a heightened risk of myocardial infarction.(63-66) In a recent study, we found no evidence of a higher prevalence of OSAHS in depressed patients with medically stable CHD, but we did find that patients with major depression tended to have longer episodes of sleep apnea than nondepressed patients, and that depressed men had more frequent episodes than did the nondepressed men.(67) Thus, arousals from sleep, either secondary to sleep apnea or due to other causes, are associated with increased HR and also may predispose depressed and nondepressed patients to cardiac events.

Clinical trials have shown that HR reduction is an important mechanism in the reduction in mortality associated with drugs such as beta blockers following AMI, chronic heart failure, or in stable CHD.(16) Whether treating depression reduces resting or 24 hour HR is a clinically important question. The tricyclic antidepressants increase HR due to their anticholinergic side-effects.(68) Fortunately, they are not generally recommended for the treatment of depression in patients with heart disease. The selective serotonin reuptake inhibitors (SSRIs) do not seem to have a direct effect on HR(69), but the relationship between change in depression and HR in patients treated with SSRIs has not been well studied. There has been only one study of the effects of a psychotherapeutic intervention on HR. Fifty patients with stable CHD and comorbid major depression were given up to 16 sessions of cognitive behavior therapy (CBT), a recognized psychotherapeutic treatment for depression.(39) Following successful treatment, the average 24 hour HR decreased by 5 bpm, compared to a decrease of less than 1 bpm in the controls. A decrease of 5 bpm is roughly half of what has been reported in patients receiving beta blockers in major clinical trials(70), and was the difference between the patients with major depression and the nondepressed controls in the present study. It is possible that a decrease of this magnitude could have a significant impact on survival. Larger, better controlled studies are needed to determine the effects of various treatments for depression on resting, mean nighttime, and 24 hour heart rate. Future studies should also examine the relationship between elevated HR and various sleep parameters to clarify the causes of elevated nighttime HR.

This study has several limitations. First, HR was determined for nighttime and daytime periods, rather than actual sleep vs. wake periods. Daytime napping and interruptions during nighttime sleep were not recorded by the participants, and therefore were not considered in the analysis. Sleep time HR data were analyzed from the subset of the sample (n= 631) who recorded the times at which they went to bed and when they awakened. The mean HR for both depressed and nondepressed subjects, and the hazards associated with depression and awake/sleep time HRs, were nearly identical to those reported for the daytime vs. nighttime analyses.

Although being prescribed beta blockers was included as a covariate in the analyses, data concerning the dosages were not available. It is possible that depressed patients may have been prescribed a lower dose of beta blockers or other drugs on average than the non depressed patients. However, that seems unlikely as the depressed patients were recruited at the same time, from the same hospitals, and had the same cardiologists, as the nondepressed patients.

The results may not generalize to the population of post-AMI patients because those who were too sick or debilitated to participate in the ENRICHD clinical trial were excluded. Also excluded were patients in atrial fibrillation/flutter, and those who were pacemaker-dependent, had missing ECG data during the specified recording periods, or had more than 20% ectopic beats.

In summary, mean nighttime and daytime HR was higher in the depressed than in nondepressed patients with a recent AMI. Both depression and nighttime HR independently predicted survival, although there was some evidence that elevated nighttime HR may be a more significant predictor of survival in the depressed patients. Future studies should determine the reasons for elevated nighttime HR, and whether addressing the causes would improve survival in these patients.

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Figure 1.

Risk score adjusted nighttime heart rate survival curves. Curves depict lowest (Mean < 57 bpm) and highest (Mean > 73.5 bpm) HR quartiles for both depressed (DEP) and nondepressed (ND) groups.

Table 1

Medical and demographic characteristics by depression status (N=716) *

Characteristic	Depressed (n=333)	Nondepressed (n=383)	P-value
Age (years)	57.2 ∓ 12.4	61.1 ∓ 10.6	<.0001
Beck Depression Inventory	17.4 ∓ 7.5	3.9 ∓ 2.9	<.0001
Women	48.7%	32.1%	<.0001
Systolic blood pressure	123.6 ∓ 20.0	122.3 ∓ 18.3	.37
Diabetes mellitus	34.2%	22.2%	.0004
Cigarette smoker (current)	40.1%	26.0%	<.0001
LVEF (<40%)	24.5%	23.8%	.84
Killip class III-IV	5.7%	4.4%	.43
Creatinine (mg/dl)	1.14 ∓ 0.84	1.15 ∓ 0.81	.98
Prior AMI	22.6%	20.5%	.50
Coronary bypass post MI	14.0%	13.1%	.57
Thrombolytic therapy	27.6%	33.6%	.09
Beta blocker	80.3%	85.2%	.04
ACE inhibitor	46.6%	50.1%	.35
Aspirin	88.8%	90.5%	.47

* Continuous variables are reported as (mean ∓ SD); categorical variables are percentage of subjects with the characteristic

Table 2

Effect of Night, Day and 24 Hour Heart Rate / Depression on Mortality

Cox Model Parameter	Haz R	(N=716) (95% CI)	P-value
Heart Rate ¹ (bpm)			
Nighttime (00:00 B 06:00)	1.03	(1.02, 1.05)	.0003
Daytime (08:00 B 20:00)	1.01	(0.99, 1.03)	.36
24 Hour (00:00 B 24:00)	1.02	(1.00, 1.05)	.05
Depression ²	2.90	(1.55, 5.42)	.0009
Heart Rate ³			
Nighttime (00:00 B 06:00)	1.04	(1.02, 1.06)	.0007
Daytime (08:00 B 20:00)	1.02	(0.99, 1.04)	.17
24 Hour (00:00 B 24:00)	1.03	(1.00, 1.05)	.02
Depression ⁴	2.54	(1.34, 4.79)	.004
Heart Rate and Depression ⁵			
Nighttime (00:00 B 06:00)	1.03	(1.01, 1.05)	.004
Depression	2.19	(1.15, 4.19)	.018
Daytime (08:00 B 20:00)	1.01	(0.99, 1.04)	.28
Depression	2.45	(1.30, 4.65)	.006
24 Hour (00:00 B 24:00)	1.02	(0.99, 1.05)	.06
Depression	2.36	(1.24, 4.47)	.009

Abbreviations: Haz R = estimated hazard ratio; bpm = beats per minute

¹ univariate effect of day/night heart rate (1 bpm) on patient survival² univariate effect of depression on survival³ effect of night/day/24hr heart rate on survival, controlling for the ENRICH risk score⁴ effect of depression on patient survival, controlling for the risk score⁵ effect of night/day/24hr heart rate AND depression on patient survival, controlling for the risk score

Table 3

Effect of Nighttime Heart Rate on Mortality for Select, Clinically Meaningful Increases (N=716)

Nighttime Heart Rate Increase (bpm)	Haz R* (95% CI)
1 beat	1.03 (1.02, 1.04)
5 beats	1.17 (1.11, 1.24)
10 beats	1.37 (1.23, 1.53)
15 beats	1.60 (1.36, 1.89)

Keywords: Haz R = estimated hazard ratio; bpm = beats per minute

*
adjusted for the ENRICH risk score and depression