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Research paper

Nighttime heart rate predicts response to depression treatment in patients with coronary heart disease

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ABSTRACT

Background: Previous studies suggest that patients with coronary heart disease (CHD) who do not respond to treatment for depression are at higher risk of mortality than are treatment responders. The purpose of this study was to determine whether elevated nighttime heart rate (HR) and low heart rate variability (HRV), both of which have been associated with depression and with cardiac events in patients with CHD, predict poor response to depression treatment in patients with CHD.
Methods: Patients with stable CHD and a current major depressive episode completed 24 h ambulatory ECG monitoring and were then treated for up to 16 weeks with cognitive behavior therapy (CBT), either alone or in combination with an antidepressant. Pre-treatment HR and HRV were calculated for 124 patients who had continuous ECG from early evening to mid-morning.
Results: Following treatment, 64 of the 124 patients (52%) met study criteria for remission (Hamilton Rating Scale for Depression score ≤ 7). Prior to treatment, non-remitters had higher nighttime HR ($p=0.03$) and lower nighttime HRV ($p=0.01$) than did the remitters, even after adjusting for potential confounds.
Limitations: Polysomnography would have provided information about objective sleep characteristics and sleep disorders. More CBT sessions and higher doses of antidepressants may have resulted in more participants in remission.
Conclusions: High nighttime HR and low nighttime HRV predict a poor response to treatment of major depression in patients with stable CHD. These findings may help explain why patients with CHD who do not respond to treatment are at higher risk for mortality.

1. Introduction

Depression is a common comorbidity and a significant risk factor for cardiac morbidity and mortality in patients with coronary heart disease (CHD) (Lichtman et al., 2014). Although the mechanisms of this risk are unclear, depression is associated with other risk factors for cardiac events including elevated heart rate (HR) and low heart rate variability (HRV) (Carney et al., 2005b; Kemp et al., 2010), dysfunctional sleep (Buysse et al., 1998; Ford and Kamerow, 1989), and blunted circadian HR rhythm (Stampfer, 1998; Taillard et al., 1990). Following an acute myocardial infarction (MI), for example, compared to non-depressed patients those with depression have higher nighttime HRs (Carney et al., 2008), lower heart rate variability (Carney et al., 2001), and a greater likelihood of having little or no decrease in nighttime HR relative to daytime levels (nocturnal dip) (Carney et al., 2014). All of these characteristics predicted mortality after adjusting for potential confounders.

Clinical trials that have examined whether treating depression can improve outcomes in cardiac patients have been limited by small numbers of cardiac endpoints and small post-treatment differences in depression between the intervention and control groups, and none have shown an effect on cardiac morbidity or mortality. However, secondary analyses of these trials have found

Abbreviations: ACS, acute coronary syndrome; ANCOVA, analysis of covariance; BAI, Beck Depression Anxiety Inventory; BDI-II, Beck Depression Inventory 2; CABG, coronary artery bypass graft; CBT, cognitive behavior therapy; CHD, coronary heart disease; FDA, functional data analysis; HAM-D-17, Hamilton Depression Inventory-17 items; HRV, heart rate variability; lnVLF, log of Very Low Frequency; MI, myocardial infarction; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; SSRI, Selective Serotonin reuptake inhibitor

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that the risk for cardiac morbidity and mortality is elevated in patients who have minimal or no response to depression treatment (Carney et al., 2004; Carney and Freedland, 2009). Cardiac patients who do not respond to depression treatment may remain at high risk for cardiac events simply because they continue to be depressed. However, it is also possible that these patients are at higher risk than those who do respond even before they are treated. That is, the factor(s) that place them at high risk for morbidity and mortality may also predict a poor response to depression treatment. Although little is known about predictors of treatment response in depressed patients with CHD, dysfunctional sleep and blunted circadian rhythms have predicted treatment response in depressed psychiatric patients (Buysse et al., 1999; Szuba et al., 2001) and mortality in patients with CHD (Laugsand et al., 2011).

The purpose of this study was to determine whether patients with stable CHD and major depression who failed to remit following treatment had higher nighttime HR and lower nighttime HRV before treatment than patients whose depression remitted.

2. Methods

2.1. Eligibility screening and recruitment

Patients were recruited between May 2009 and August 2013 at cardiology offices and diagnostic laboratories affiliated with Washington University School of Medicine and Barnes-Jewish Hospital of St. Louis. Consenting patients with CHD documented by coronary angiography, a history of coronary revascularization or hospitalization for an acute coronary syndrome (ACS), completed the Patient Health Questionnaire (PHQ-9) (Spitzer et al., 1999). Patients were excluded from the study if they had significant cognitive impairment, psychotic features, a comorbid psychiatric disorder other than an anxiety disorder, a high risk of suicide, current substance abuse, hospitalization for ACS or coronary artery bypass graft (CABG) surgery within the previous two months, advanced malignancy, a disability that would affect compliance with the study protocol, or physician or patient refusal. Patients who had been taking a guideline-recommended dose of an approved selective serotonin reuptake inhibitor (SSRI) antidepressant for at least 30 days were eligible to participate as long as all of the other eligibility criteria were met. Patients who were not excluded and who screened positive for depression on the PHQ-9 (total score ≥ 10) were scheduled for a structured clinical interview. Those who met the DSM-IV criteria for a major depressive episode on the interview, scored ≥ 16 on the Beck Depression Inventory (BDI-II), and gave written informed consent were enrolled. The study was approved by the Human Research Protection Office at Washington University School of Medicine in St. Louis.

2.2. Psychiatric assessments

2.2.1. Depression Interview and Structured Hamilton (DISH)

The DISH (Freedland et al., 2002) was administered at baseline and at 16 weeks to diagnose major depression according to the DSM-IV criteria and to measure the severity of depression on an embedded version of the Hamilton Rating Scale for Depression (HAM-D-17). The DISH includes a screen for exclusionary psychiatric conditions, and assesses psychiatric history including previous major depressive episodes, psychiatric treatment, and family psychiatric history.

2.2.2. Beck Depression Inventory-II

The 21-item BDI-assesses the self-reported severity of depression symptoms (Beck et al., 1996). It was administered at baseline and 16-week evaluations.

2.2.3. Beck Depression Anxiety Inventory (BAI)

The 21-item BAI measures the self-reported severity of anxiety symptoms (Beck et al., 1988). It was administered at the baseline and 16-week evaluations.

2.2.4. Pittsburgh Sleep Quality Index (PSQI)

The PSQI (Buysse et al., 1989) assesses sleep quality including sleeping habits and specific sleep complaints during the past month. The PSQI global score was used as the primary index of sleep quality for this study, and was administered at the baseline and 16-week evaluations.

2.3. Laboratory assessments

A blood specimen was drawn for standard laboratory tests after the patient rested supine on an examination table for 15 min. The patient was then fitted with an ambulatory ECG monitor for a 24 h recording. The details of the blood testing and results are available elsewhere (Carney et al., 2016).

2.4. Ambulatory electrocardiographic monitoring

The ECG recordings were scanned at the HRV Core Laboratory at Washington University on a Cardioscan Holter scanner (Version 52a, DMS Holter, Stateside, NV) and analyzed with MARS Holter scanning software (Version 7.01, GE Medical Systems, Milwaukee, WI). The labeled beat-to-beat file was exported to a Sun workstation (Sun Microsystems, Palo Alto, CA) for advanced HRV analysis. HRs were derived from at least three continuous normal-to-normal N-N intervals and averaged in 5-min epochs. The interval between 7:00 pm and 9:00 am was chosen for analysis in order to sample HR activity before, during, and after typical periods of sleep.

The log of Very Low Frequency (ln VLF) power (0.0033–0.04 hz in ms^2) was chosen *à priori* as the index of HRV for this study based on evidence that it is lower in depressed compared to nondepressed patients with CHD, (Carney et al., 2001) and that it partially mediates the effect of depression on survival in these patients (Carney et al., 2005a). The methods used for spectral analysis of ambulatory ECG data have been described previously (Rottman et al., 1990).

All study personnel who had contact with the participants, including the CBT therapists, the psychiatrist, and the interviewers, were blinded to the results of all assessments.

2.5. Treatment

All participants received up to 12 sessions of CBT over four months. Telephone contacts by the therapist were permitted as needed during this time. The general principles and therapeutic techniques of the intervention were guided by published treatment manuals (Beck, 1995). Some of the standard cognitive-behavioral techniques were modified for use in cardiac patients, such as adapting behavioral activation plans to address medical safety concerns. More details of the CBT intervention are available elsewhere (Carney et al., 2016).

Participants who were receiving a therapeutic dose of an SSRI antidepressant for at least four weeks prior to enrollment received CBT while remaining on the same antidepressant for the duration of the study. Those who were not taking an antidepressant at enrollment initially received only CBT. However, if their BDI-II score did not decrease $\geq 30\%$ by the 5th week of treatment, or $\geq 50\%$ by the 8th week, they were prescribed a maximum dose of 100 mg of sertraline per day until the end of the 16-week treatment period. Sertraline has been shown to be safe in depressed cardiac patients. However, higher doses of sertraline were not prescribed as they only marginally increase response rates while