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Interactive associations of depression and sleep apnea with adverse clinical outcomes after acute myocardial infarction

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Abstract

Objective—Depression and sleep apnea (SA) are common among patients after acute myocardial infarction (AMI), and both are associated with increased risk for adverse outcomes. We tested the hypothesis that there is an interaction between depression and SA in relation to prognosis in post-AMI patients.

Methods—Participants were 337 depressed and 379 nondepressed post-AMI patients who participated in a substudy of the Enhancing Recovery in Coronary Heart Disease (ENRICH) clinical trial. SA was identified from Holter ECG at the entry by an algorithm that detects cyclic variation of heart rate.

Results—During a median follow-up of 25 months, 43 (6.0%) of patients died and 83 (11.6%) either died or experienced a recurrent AMI. Among 94 patients with both depression and SA, these endpoints occurred in 20 (21.3%) and 25 (26.6%), the prevalence that was 6.9 and 3.9 times higher than predicted probabilities by ENRICH clinical risk scores ($P < .001$ for both). In the patients with depression alone, SA alone, or neither, the frequencies did not differ significantly from the predicted probability. Although both depression and SA predicted death and the combined endpoint, we observed depression by SA interactions ($P = .03$ and $.02$). SA independently predicted these endpoints in depressed ($P < .001$ and $P = .001$), but not in nondepressed patients ($P = .73$ and $.84$). Similarly, depression independently predicted these endpoints in SA ($P < .001$ for both), but not in non-SA patients ($P = .61$ and $.12$).

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COI disclosures: The algorithm of autocorrelated wave detection with adaptive threshold (ACAT) is installed in a Holter ECG scanner (Cardy Analyzer, Suzuken Company Limited, Nagoya, Japan). Dr. Hayano is a consultant of Suzuken Company Limited. Mr Kawai is an employee of Suzuken Company Limited. Dr Kodama is an advisor of Suzuken Company Limited. Other authors have reported that no potential conflicts of interest exist with any companies or organizations whose products or services may be discussed in this article.

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Conclusion—The combination of depression and SA estimated by CVHR is associated with long-term adverse clinical outcomes after AMI.

Keywords

Depression; Sleep apnea; Myocardial infarction; Mortality

INTRODUCTION

Depression and sleep apnea (SA) are prevalent among patients with a recent history of acute myocardial infarction (AMI), and both are associated with increased risk for adverse clinical outcomes (1-7). The point prevalence of depression in post-AMI patients ranges from 16 to 45% (2) and post-AMI depression is associated with a 2.0- to 2.5-fold increased risk for mortality and new cardiovascular events (1). The prevalence of SA also is high among post-AMI patients, ranging from 43 to 66% (3, 6, 7). SA predicts increased risk for adverse outcomes in stable CHD and following acute cardiac events (4, 5, 7-10). Due to the high prevalence of both conditions, the combination of depression and SA is common among post-AMI patients, and it may cause particularly deleterious effects. However, little is known about the prognostic impact of the comorbidity of these disorders.

Recently, we developed an ECG-based, automated SA detection algorithm called autocorrelated wave detection with adaptive threshold (ACAT) (11). This algorithm detects cyclic variation of heart rate (CVHR). CVHR is the characteristic pattern of heart rate that consists of bradycardia during apnea followed by abrupt recovery when normal breathing resumes (12). This pattern repeats throughout the night in patients with SA. The ACAT algorithm has been extensively studied and found to be a reliable, sensitive, and specific measure of SA (12-16). The ACAT algorithm was validated by overnight polysomnographic studies in 862 patients referred for the diagnosis of SA (11) and in a population of 162 male workers (11, 17), in which ACAT algorithm detected moderate-to-severe SA with 83 and 88% sensitivity and 88 and 97% specificity.

In the present study, we applied this algorithm to Holter ECG data from depressed and nondepressed post-AMI patients who participated in the Enhancing Recovery in Coronary Heart Disease (ENRICH) clinical trial (18) and in the ENRICH heart rate variability ancillary study (19). We assessed the mortality and morbidity risk associated with post-AMI depression and SA, and examined whether there is a prognostic interaction between them. To our knowledge, this is the first study to consider the prognostic significance of comorbid depression and SA in post-AMI patients.

METHODS

Participants

The study cohort consisted of 766 patients with a recent AMI; 358 (47%) of them were depressed, meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for either major or minor depression or dysthymia, and participated in the ENRICH clinical trial (18); 408 (53%) were otherwise eligible for ENRICH but had no prior episodes of major depression, current depression symptoms (Beck Depression Inventory (BDI) score <10), or low-perceived social support. All patients were recruited for this study from four of the trial's eight 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. Detailed information concerning recruitment and patient characteristics is available elsewhere (18, 19). This study was

approved by the Institutional Review Board of the Washington University School of Medicine (number, 96-0849) and written informed consent was provided by all participants.

Patients were excluded from this ancillary study if they: 1) had other life-threatening medical illnesses, cognitive impairment, or other major psychiatric disorders; 2) were too ill or logistically unable to participate; 3) showed sinus rhythm <80% of time in bed during the Holter ECG recording; 4) had atrial fibrillation, atrial flutter, or an implanted pacemaker; 5) were currently taking tricyclic or monoamine oxidase inhibitor antidepressants; or 6) refused to provide informed consent. None of the patients were receiving treatment for SA at the time of the Holter ECG recording. The depressed patients were participants in the ENRICHD clinical trial and were randomly allocated to receive usual care (UC) or usual care (UC) plus cognitive behavior therapy (CBT). However, there was no significant difference in event-free or overall survival between the groups (18). We therefore combined the UC only and UC plus CBT groups in the present study.

Baseline Measurements

At baseline, data on the participants' demographic characteristics, medical history, current medication use, and physical examination and laboratory test results were recorded, and the Beck Depression Inventory (BDI) (20) was administered. Holter ECG was recorded for 24 hours within 28 (median, 13; range 2-28) days after the index AMI.

ECG detection of SA

Data from the Holter ECG recording during patient-reported time in bed were used to identify SA. The ECG data were scanned on an SXP Laser scanner (Marquette Electronics). The labeled beat files were exported to a computer on which CVHR was detected by an automated ACAT algorithm (11). For the purpose of CVHR detection, the R-R interval time series were interpolated with a horizontal-step function using only N-N intervals and resampled at 2 Hz. The resampled R-R interval time series were smoothed by second-order polynomial fitting and submitted to the ACAT algorithm.

The ACAT algorithm detects transient tachycardia (dips in interbeat interval trend) as CVHR when they meet the following criteria: 1) width from 10 to 120 seconds, 2) depth-to-width ratio >0.7 ms/s, 3) depth >40% of the 90% CI of local interbeat interval variations, 4) cycle length (interdip interval) from 25 to 120 seconds, 5) similar waveforms among 5 consecutive dips (morphological correlation coefficients >0.4) and 6) three equivalent consecutive cycle lengths with a tolerance of 22% against the mean cycle length.

We calculated a CVHR index that was defined as the average number of CVHRs per hour during time in bed as estimated from the patient's diary during Holter ECG monitoring. Patients were considered to have SA if they had a CVHR index ≥ 15 per hour. This criterion was previously shown to be optimal for identifying patients with an apnea-hypopnea index (AHI) ≥ 15 per hour based on overnight polysomnography (11, 17).

Follow-up and endpoints

Patients were scheduled for follow-up 6 months after study enrollment and annually thereafter for up to 30 months. For the ENRICHD clinical trial, the primary endpoint was recurrent nonfatal AMI or death from any cause. These events were identified from follow-up visits, telephone calls, routine hospital surveillance, and contacts with the patients' physicians and family members. The records of every identified hospitalization were obtained for review and confirmation. The ENRICHD ECG core laboratory classified electrocardiograms obtained during hospitalizations by the Minnesota code using serial change rules. Death certificates were obtained for all reported deaths.

Statistical analysis

Chi-square tests and analysis of variance followed by Tukey's multiple comparison test were used to evaluate the differences in categorical and continuous variables between groups. The relationships between continuous variables were evaluated by Pearson's correlation coefficient. Cox proportional hazards regression analyses were used to determine the hazard ratio (HR) for depression, SA, and their interaction. In these analyses, the HR of depression and SA was evaluated in both categorical (the presence of depression and CVHR index ≥ 15 event/hr) and continuous (BDI score and CVHR index) values. When a significant interaction was observed, subgroup analyses were performed by stratifying the sample according to the presence of depression and SA. To examine whether the prognostic associations of SA and its combination with depression are independent of established risk factors for SA and adverse outcome after AMI, we took three different approaches. First, to determine demographic and clinical variables that were associated with depression and SA, patients' characteristics were compared with dividing patients into 4 groups (depression and SA, depression alone, SA alone, and neither). Second, using the ENRICHD risk scores that are weighted sums of all independent risk factors in the ENRICHD clinical trial ($n = 2481$) (21), we estimated the global risk levels and predicted probabilities for combined endpoint (death and recurrent nonfatal AMI) and all-cause death in each group. The ENRICHD clinical risk scores included age, diabetes, left ventricular ejection fraction $<40\%$, creatinine level ≥ 1.3 mg/dL, category of BDI score, prior AMI, history of pulmonary disease, prior transient ischemic attack or stroke, history of congestive heart failure, Killip class at the time of the index AMI, and medications. The predicted probabilities were compared with observed event rate to examine if SA and its combination with depression are additional risks that are not predicted by the other clinical risk factors. Finally, the Cox regression models were adjusted for gender, body mass index, treatment (UC or UC plus CBT), and the ENRICHD risk scores. Event-free (i.e., recurrent AMI-free) and overall survival curves in each group were generated by the Kaplan-Meier method and compared with the log rank test. The statistical power of the log rank test was estimated by the Power and Sample Size application of SAS version 9.2. We defined a P value <0.05 as statistically significant.

RESULTS

The Holter ECG data were analyzable for CVHR in 337 (94.1%) depressed and 379 (92.9%) nondepressed patients. One depressed and eight nondepressed patients were excluded due to atrial fibrillation and 20 depressed and 23 nondepressed patients were excluded due to $<80\%$ analyzable data. Among the 716 remaining patients, 94 (13%) had both depression and SA (CVHR index ≥ 15 per hour), 243 (34%) had depression alone, 132 (18%) had SA alone, and 247 (35%) had neither depression nor SA. The clinical and demographic characteristics of each group are shown in Table 1. Compared with the other patients, patients with both depression and SA were more likely to have diabetes, a left ventricular ejection fraction $<40\%$, histories of hypertension and congestive heart failure, and to be taking a vasodilator. The prevalence of SA did not differ between depressed and nondepressed patients (29% and 35%, $P = .15$) and there was no significant correlation between BDI scores and CVHR index in the entire cohort ($r = -0.07$). Among depressed patients, 146 (43%) received CBT.

During a median follow-up period of 25 months, the combined endpoint and deaths occurred in 83 (11.6%) and 43 (6.0%) out of 716 patients, respectively. In patients with both depression and SA ($n = 94$), these endpoints occurred in 25 (26.6%) and 20 (21.3%) patients, which were 3.9 and 6.9 times higher frequencies than the probabilities that were predicted from the ENRICHD risk scores in this group ($P < .001$ for both; Table 2). Although the observed event rates in depression alone and SA alone groups were from 1.5 to 1.9 times higher than the predicted probabilities, the differences were not statistically significant. In

the group of patients with neither depression nor SA, the event rates were comparable to the predicted probabilities.

As shown in Table 3, univariate Cox regression analysis revealed that both depression and SA were associated with increased risks for the combined endpoint ($P = .002$ and $P = .006$ for the BDI and SA, respectively) and for all-cause death ($P = .002$ and $P < .001$; univariate model). The multivariable analysis of depression and SA, however, revealed that there was a significant depression by SA interaction on the combined endpoint ($P = .02$) and on all-cause death ($P = .03$; multivariable model 1). Similar results were obtained for BDI score and the CVHR index. There were significant BDI-score by CVHR-index interactions on the combined endpoint ($P = .01$) and all-cause death ($P = .04$; multivariable model 2).

When the entire sample was divided into depressed and nondepressed patients, SA and CVHR index predicted the combined endpoint ($P = .001$ and $< .001$) and all-cause death ($P < .001$ for both) in the depressed subgroup, and their predictive power remained significant even after adjusting for gender, body mass index, treatment (UC or UC plus CBT), and the global risk scores (Table 3). In the nondepressed subgroup, there was no significant association of SA or CVHR index with either endpoint. When the entire sample was divided into SA and non-SA subgroups, depression diagnosis and BDI score predicted the combined endpoint ($P = .001$ and $< .001$) and all-cause death ($P < .001$ for both) only in the SA subgroup, and their predictive power remained significant even after adjusting for the clinical risk factors and treatment.

Figure 1 shows the Kaplan-Meier plots of event-free and overall survival rates. The survival curves in patients with comorbid depression and SA differed from the curves in patients with either depression or SA alone and in those with neither of them ($P < .001$ for both). In contrast, the survival curves in patients with either depression or SA alone did not differ significantly from the curves for patients with neither disorder. The statistical power for these log rank tests to detect 2.5-fold event rate difference was 0.84

DISCUSSION

To our knowledge, this is the first study to investigate the prognostic impact of comorbid depression and SA in post-AMI patients. We observed that patients with both depression and SA showed 3.9 and 6.9 times higher event rates of combined endpoint (death and recurrent nonfatal AMI) and all-cause death than the predicted probabilities from their clinical risk profile, while the event rates in the other patients (depression alone, SA alone, or neither) did not differ significantly from the predicted probabilities. Also, Cox regression analysis revealed significant depression by sleep apnea interactions on the combined endpoint and all-cause death. SA was an independent predictor of adverse outcomes in depressed patients but it was not a significant predictor in nondepressed patients. Likewise, depression was an independent predictor of adverse outcomes in SA patients but it was not a significant predictor in non-SA patients. These findings show that depression and SA combine to increase the risk for post-AMI morbidity and mortality.

We identified the presence of moderate-to-severe SA using the ACAT algorithm, an ECG-based CVHR detection technology (12-16). The ACAT algorithm that was used in this study is one of the best validated of these methods. In a previous study of 862 consecutive patients referred for standard, attended, overnight polysomnography (11), we demonstrated that the CVHR index derived by the ACAT algorithm closely correlates with polysomnographic AHI ($r = 0.84$), and that using a criterion of CVHR index ≥ 15 per hour, patients with moderate-to-severe SA (AHI ≥ 15 per hour) are identified with 83% sensitivity and 88% specificity. The validity of the algorithm was confirmed also in a polysomnographic

population survey of male workers (17), in which CVHR index ≥ 15 per hour detected individuals with moderate-to-severe SA (AHI ≥ 15 per hour) with 88% sensitivity and 97% specificity. We are therefore confident that the algorithm accurately detected SA in this study.

It is possible that depression might be more likely to be diagnosed in patients with SA due to the symptoms of poor concentration, disordered sleep, and fatigue. However, we found no significant association between depression and SA or correlation between BDI scores and CVHR index. On the other side, the ACAT algorithm that we used for assessing SA might have underestimated the prevalence of SA in depressed patients because depression is accompanied by high nighttime heart rate (22). This could have attenuated the bradycardia that ordinarily accompanies SA (23), making it more difficult to detect SA in the depressed patients.

Other cardiac risk factors in patients with depression and SA may have influenced the depression-SA relationship. However, the observed event rates of the combined endpoint and all-cause death in depression and SA group were 3.9 and 6.9 times higher than the predicted event probabilities by the ENRICH risk scores, which are composed of established risk factors for adverse outcomes after AMI. Also, both the relative risk associated with SA in the depressed patients and the risk associated with depression in the SA patients were significant even after adjustment for a number of potential confounders including gender, body mass index, and the ENRICH risk scores.

Several potential mechanisms might explain the interactions between depression and SA. Both depression and SA have been associated with increased sympathetic activation (19, 24, 25), impaired endothelial function (26-28), and systemic inflammation (25, 29). Thus, there may be synergistic effects of depression and SA on the development and/or promotion of hypertension, lethal arrhythmias, myocardial ischemia, thrombosis, and heart failure (30). Our observations indicate that the effects of depression and SA are more than additive, and that the risk increases geometrically when both are present.

Depression may interfere with respiratory responses to apneic events, which may worsen the deleterious effects of SA. There is evidence that depression is associated with a diminished hypercapnic ventilatory response (31-33) and reduced cerebral vasomotor reactivity to hypercapnia (34). These factors could prolong apnea/hypopnea episodes, leading to even greater sympathetic activation and cardiovascular strain during sleep. In a recent study (35), we conducted two nights of polysomnography in medically stable patients with coronary artery disease and major, minor, or no depression. Although the prevalence and severity of SA did not differ across the groups, the duration of apneic episodes was longer in patients with major depression than in those without depression.

Even if it is asymptomatic, central SA could have been present in some patients who developed left ventricular dysfunction after AMI (36). Because obstructive and central forms of SA are accompanied by similar CVHR (37), the ACAT algorithm can detect both forms of SA. Thus, the prognostic interaction of depression and SA may result partly from a harmful effect of depression in patients with subclinical left ventricular dysfunction (38).

The present study has several limitations. First, polysomnography is the gold standard for SA assessment; but we used CVHR to define SA. Although the ACAT algorithm is highly sensitive and specific for detecting moderate-to-severe SA as diagnosed by standard attended overnight polysomnography, the quantitative agreement between CVHR index and AHI is modest (11, 17). This may reflect less robust prognostic association of CVHR index compared with that of the dichotomized category, i.e., SA or non-SA (Table 3). Also, the validity of ACAT algorithm is not as well established in post-AMI or in depressed patients

as it is in other patients. Second, although the ACAT algorithm was developed to estimate AHI, it is unclear whether it is AHI (i.e., the frequency of apnea/hypopnea) or the severity of hypoxia that is associated with increased risk in post-AMI patients (39). This cannot be determined from this study. Third, the data from this study were obtained over ten years ago. It is possible that this relationship may not be present in current patients with an AMI, but there is no reason to think that would be the case. Fourth, patients with depression in this study participants in the ENRICHHD clinical trial and about half of them received CBT for depression. Although the prognostic associations of depression, SA, and their interaction were substantially unchanged even after adjusted for the possible treatment effects, we cannot completely ruled out its potential confounding interactions. Finally, the treatment of SA in patients with coronary artery disease has been reported to decrease cardiovascular events (40). To reveal the entire picture of the interaction between depression and SA as a post-AMI risk and as a therapeutic target, randomized clinical trials are needed to determine whether treatment of either depression or SA alone improves the prognosis in post-AMI patients with comorbid depression and SA.

CONCLUSIONS

This study finds that depression and SA as estimated by CVHR are interactively associated with adverse clinical outcomes after AMI. Thus, depression and sleep apnea may be a particularly high-risk form of comorbidity in post-AMI patients. This is of particular concern because both disorders are common in patients with CHD (2, 3, 6, 7), yet both generally go undetected. Major depression is not identified in over 70% of cases following an acute coronary syndrome (41, 42). Although there are few studies of SA in patients with a recent acute coronary syndrome, over 80% of cases of SA in adults escape clinical diagnosis (43, 44). More work is needed to elucidate the mechanisms for the high risk associated with the combination of these disorders, and to determine whether treating one or both disorders can reduce this risk in these patients.

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Abbreviations and Acronyms

ACAT	autocorrelated wave detection with adaptive threshold
AMI	acute myocardial infarction
AHI	apnea-hypopnea index
BDI	Beck Depression Inventory
CI	confidence interval
CVHR	cyclic variation of heart rate
ENRICHHD	Enhancing Recovery in Coronary Heart Disease
LVEF	left ventricular ejection fraction
HR	hazard ratio

SA sleep apnea

REFERENCES

1. van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, van den Brink RH, van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med*. 2004; 66:814–22. [PubMed: 15564344]
2. Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, Fauerbach JA, Bush DE, Ziegelstein RC. Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med*. 2006; 21:30–8. [PubMed: 16423120]
3. Lee CH, Khoo SM, Tai BC, Chong EY, Lau C, Than Y, Shi DX, Lee LC, Kailasam A, Low AF, Teo SG, Tan HC. Obstructive sleep apnea in patients admitted for acute myocardial infarction. Prevalence, predictors, and effect on microvascular perfusion. *Chest*. 2009; 135:1488–95. [PubMed: 19497895]
4. Peker Y, Hedner J, Kraiczi H, Loth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med*. 2000; 162:81–6. [PubMed: 10903224]
5. Moee T, Franklin KA, Holmstrom K, Rabben T, Wiklund U. Sleep-disordered breathing and coronary artery disease: long-term prognosis. *Am J Respir Crit Care Med*. 2001; 164:1910–3. [PubMed: 11734445]
6. Nakashima H, Katayama T, Takagi C, Amenomori K, Ishizaki M, Honda Y, Suzuki S. Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction. *Eur Heart J*. 2006; 27:2317–22. [PubMed: 16956914]
7. Yumino D, Tsurumi Y, Takagi A, Suzuki K, Kasanuki H. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. *Am J Cardiol*. 2007; 99:26–30. [PubMed: 17196456]
8. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005; 365:1046–53. [PubMed: 15781100]
9. Hagenah GC, Gueven E, Andreas S. Influence of obstructive sleep apnoea in coronary artery disease: A 10-year follow-up. *Respir Med*. 2006; 100:180–2. [PubMed: 16118049]
10. Gami AS, Rader S, Svatikova A, Wolk R, Herold DL, Huyber C, Winnicki M, Somers VK. Familial premature coronary artery disease mortality and obstructive sleep apnea. *Chest*. 2007; 131:118–21. [PubMed: 17218564]
11. Hayano J, Watanabe E, Saito Y, Sasaki F, Fujimoto K, Nomiyama T, Kawai K, Kodama I, Sakakibara H. Screening for obstructive sleep apnea by cyclic variation of heart rate. *Circ Arrhythm Electrophysiol*. 2011; 4:64–72. [PubMed: 21075771]
12. Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A. Cyclical variation of the heart rate in sleep apnoea syndrome. Mechanisms, and usefulness of 24 h electrocardiography as a screening technique. *Lancet*. 1984; 1:126–31. [PubMed: 6140442]
13. Penzel T, McNames J, Murray A, de Chazal P, Moody G, Raymond B. Systematic comparison of different algorithms for apnoea detection based on electrocardiogram recordings. *Med Biol Eng Comput*. 2002; 40:402–7. [PubMed: 12227626]
14. Khandoker AH, Palaniswami M, Karmakar CK. Support vector machines for automated recognition of obstructive sleep apnea syndrome from ECG recordings. *IEEE Trans Inf Technol Biomed*. 2009; 13:37–48. [PubMed: 19129022]
15. Mendez MO, Corthout J, Van Huffel S, Matteucci M, Penzel T, Cerutti S, Bianchi AM. Automatic screening of obstructive sleep apnea from the ECG based on empirical mode decomposition and wavelet analysis. *Physiol Meas*. 2010; 31:273–89. [PubMed: 20086277]
16. Roche F, Celle S, Pichot V, Barthelemy JC, Sforza E. Analysis of the interbeat interval increment to detect obstructive sleep apnoea/hypopnoea. *Eur Respir J*. 2007; 29:1206–11. [PubMed: 17301093]

17. Hayano J, Tsukahara T, Watanabe E, Sasaki F, Kawai K, Sakakibara H, Kodama I, Nomiyama T, Fujimoto K. Accuracy of ECG-based screening for sleep-disordered breathing: a survey of all male workers in a transport company. *Sleep Breath*. 2012
18. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) Randomized Trial. *JAMA*. 2003; 289:3106–16. [PubMed: 12813116]
19. Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, Czajkowski SM, O'Connor C, Stone PH, Freedland KE. Depression, heart rate variability, and acute myocardial infarction. *Circulation*. 2001; 104:2024–8. [PubMed: 11673340]
20. Beck, AT.; Rush, AJ.; Shaw, BF. Cognitive therapy of depression. Guilford Press; New York, NY: 1979.
21. Jaffe AS, Krumholz HM, Catellier DJ, Freedland KE, Bittner V, Blumenthal JA, Calvin JE, Norman J, Sequeira R, O'Connor C, Rich MW, Sheps D, Wu C. Prediction of medical morbidity and mortality after acute myocardial infarction in patients at increased psychosocial risk in the Enhancing Recovery in Coronary Heart Disease Patients (ENRICH) study. *Am Heart J*. 2006; 152:126–35. [PubMed: 16824842]
22. Carney RM, Steinmeyer B, Freedland KE, Blumenthal JA, Stein PK, Steinhoff WA, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Domitrovich PP, Burg MM, Hayano J, Jaffe AS. Nighttime heart rate and survival in depressed patients post acute myocardial infarction. *Psychosom Med*. 2008; 70:757–63. [PubMed: 18725430]
23. Douglas NJ, White DP, Pickett CK, Weil JV, Zvillich CW. Respiration during sleep in normal man. *Thorax*. 1982; 37:840–4. [PubMed: 7164002]
24. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995; 96:1897–904. [PubMed: 7560081]
25. Kop WJ, Stein PK, Tracy RP, Barzilay JI, Schulz R, Gottdiener JS. Autonomic Nervous System Dysfunction and Inflammation Contribute to the Increased Cardiovascular Mortality Risk Associated With Depression. *Psychosom Med*. 2010; 72:626–35. [PubMed: 20639389]
26. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, Somers VK. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation*. 2000; 102:2607–10. [PubMed: 11085964]
27. Sherwood A, Hinderliter AL, Watkins LL, Waugh RA, Blumenthal JA. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *J Am Coll Cardiol*. 2005; 46:656–9. [PubMed: 16098431]
28. Lavoie KL, Pelletier R, Arsenault A, Dupuis J, Bacon SL. Association between clinical depression and endothelial function measured by forearm hyperemic reactivity. *Psychosom Med*. 2010; 72:20–6. [PubMed: 19875632]
29. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T, Accurso V, Somers VK. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation*. 2002; 105:2462–4. [PubMed: 12034649]
30. Grippio AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress*. 2009; 12:1–21. [PubMed: 19116888]
31. Shershow JC, Kanarek DJ, Kazemi H. Ventilatory response to carbon dioxide inhalation in depression. *Psychosom Med*. 1976; 38:282–7. [PubMed: 940908]
32. Damas-Mora J, Jenner FA, Sneddon J, Addis WD. Ventilatory responses to carbon dioxide in syndromes of depression. *J Psychosom Res*. 1978; 22:473–6. [PubMed: 750657]
33. Mora JD, Grant L, Kenyon P, Patel MK, Jenner FA. Respiratory ventilation and carbon dioxide levels in syndromes of depression. *Br J Psychiatry*. 1976; 129:457–64. [PubMed: 990660]
34. Matsuo K, Onodera Y, Hamamoto T, Muraki K, Kato N, Kato T. Hypofrontality and microvascular dysregulation in remitted late-onset depression assessed by functional near-infrared spectroscopy. *NeuroImage*. 2005; 26:234–42. [PubMed: 15862223]

35. Carney RM, Howells WB, Freedland KE, Duntley SP, Stein PK, Rich MW, Miller GE. Depression and obstructive sleep apnea in patients with coronary heart disease. *Psychosom Med.* 2006; 68:443–8. [PubMed: 16738077]
36. Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. *Circulation.* 2003; 107:727–32. [PubMed: 12578876]
37. Thomas RJ, Mietus JE, Peng CK, Gilmartin G, Daly RW, Goldberger AL, Gottlieb DJ. Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. *Sleep.* 2007; 30:1756–69. [PubMed: 18246985]
38. Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O'Connor CM, Adams KF Jr, Dupree CS, Waugh RA, Bensimhon DR, Gaulden L, Christenson RH, Koch GG, Hinderliter AL. Relationship of depression to death or hospitalization in patients with heart failure. *Arch Intern Med.* 2007; 167:367–73. [PubMed: 17325298]
39. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, Somers VK. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol.* 2007; 49:565–71. [PubMed: 17276180]
40. Milleron O, Pilliere R, Foucher A, de Roquefeuil F, Aegerter P, Jondeau G, Raffestin BG, Dubourg O. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. *Eur Heart J.* 2004; 25:728–34. [PubMed: 15120882]
41. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med.* 2005; 67(Suppl 1):S29–33. [PubMed: 15953797]
42. Amin AA, Jones AM, Nugent K, Rumsfeld JS, Spertus JA. The prevalence of unrecognized depression in patients with acute coronary syndrome. *Am Heart J.* 2006; 152:928–34. [PubMed: 17070162]
43. Stoohs RA, Gingold J, Cohrs S, Harter R, Finlayson E, Guilleminault C. Sleep-disordered breathing and systemic hypertension in the older male. *J Am Geriatr Soc.* 1996; 44:1295–300. [PubMed: 8909343]
44. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep.* 1997; 20:705–6. [PubMed: 9406321]

FIGURE 1.

Kaplan-Meier plots of recurrent-AMI-free and overall survival curves in post-AMI patients grouped by the presences of SA and depression (DP). The numbers below each graph show the number of patients at risk in each group at respective times.

TABLE 1

Patient Characteristics

	Depression and SA N = 94	Depression alone N = 243	SA alone N = 132	Neither N = 247
Demographic				
Age, year	61 ± 11	55 ± 12	63 ± 9	60 ± 11
Women	34 (36)	129 (53)	31 (23)	92 (37)
Non-white	22 (23)	80 (33)	24 (18)	50 (20)
Clinical				
BDI score	17.5 ± 7.0 *	17.5 ± 7.2	3.6 ± 2.6	3.8 ± 2.5
CVHR index, episode/hr	29.1 ± 14.6 *	6.6 ± 6.2	31.3 ± 16.8	7.8 ± 4.1
Body mass index, kg/m ²	29.6 ± 6.9	30.1 ± 6.4	28.3 ± 5.2	28.7 ± 5.3
Systolic blood pressure, mm Hg	123 ± 23	124 ± 19	124 ± 19	122 ± 18
Diabetes mellitus	36 (38) *	73 (30)	33 (25)	55 (22)
Current smoker	35 (37)	105 (43)	27 (21)	70 (28)
Pulmonary disease	17 (18)	50 (21)	15 (11)	32 (13)
LVEF <40%	35 (37) *	44 (18)	39 (30)	49 (20)
Creatinine 1.3 mg/dL	25 (26)	35 (14)	39 (30)	48 (19)
History of hypertension	64 (68) *	134 (55)	73 (55)	124 (50)
Prior AMI	26 (27)	46 (19)	34 (26)	44 (18)
Prior coronary bypass surgery	11 (12)	26 (11)	16 (12)	22 (9)
Prior congestive heart failure	16 (17) *	32 (13)	11 (8)	10 (4)
Prior stroke/transient ischemia	10 (11)	24 (10)	9 (7)	12 (5)
Killip class III-IV	7 (8)	10 (4)	6 (5)	10 (4)
Non-Q-wave AMI	33 (35)	87 (36)	47 (36)	78 (32)
Anterior wall AMI	31 (32)	73 (30)	42 (32)	78 (32)
Treatment after AMI				
Thrombolytic therapy	24 (26)	73 (30)	41 (31)	79 (32)
Coronary bypass surgery	11 (12)	38 (16)	9 (7)	39 (16)
Coronary angioplasty	51 (54)	142 (58)	92 (70)	157 (64)
β-Blockers	79 (84)	191 (79)	106 (80)	212 (86)
ACE inhibitors	53 (56)	103 (42)	69 (52)	115 (47)
Ca channel blocker	13 (13)	41 (17)	20 (15)	29 (12)
Vasodilators	52 (55) *	120 (49)	57 (43)	96 (39)
CBT for depression	46 (49) *	100 (41)	0 (0)	0 (0)

ACE = angiotensin converting enzyme; AMI = acute myocardial infarction; BDI = Beck Depression Inventory; BCT = cognitive behavioral therapy; CVHR = cyclic variation of heart rate; LVEF = left ventricular ejection fraction; SA = sleep apnea.

* Significantly ($P < .05$) different from the other patients (either depression or SA alone or neither). Data are shown as mean ± SD or n (%) within groups.

TABLE 2

Predicted probabilities of events by ENRICHD risk scores and observed event rates

	Depression and SA N = 94	Depression alone N = 243	SA alone N = 132	Neither N = 247
Combined endpoint [*]				
ENRICHD risk score [†]	2.83 ± 0.76	2.42 ± 0.67	2.53 ± 0.65	2.39 ± 0.58
Predicted probability [†]	0.069	0.064	0.066	0.064
Observed event, n	25	27	13	18
Observed event rate	0.266	0.111	0.098	0.073
P(difference) [‡]	<.001	.10	.43	.93
All-cause death				
ENRICHD risk score [†]	4.02 ± 1.08	3.39 ± 0.94	3.82 ± 0.89	3.51 ± 0.84
Predicted probability [†]	0.031	0.026	0.028	0.026
Observed event, n	20	10	7	6
Observed event rate	0.213	0.041	0.053	0.024
P(difference) [‡]	<.001	.54	.54	.88

AMI = acute myocardial infarction; SA =sleep apnea.

^{*} All-cause death or recurrent nonfatal AMI[†] ENRICHD risk scores and predicted probability for each endpoint calculated according to the study of Jaffe et al (21).[‡] Significance of difference between predicted probability and observed event rate.

TABLE 3
Interactions between depression and SA on the risk for mortality and recurrent nonfatal AMI

	Combined endpoint (death or recurrent nonfatal AMI)			All-cause death		
	Unadjusted	Adjusted ^s	P	Unadjusted	Adjusted ^r	P
Entire cohort (n = 716)						
Univariate model *						
Depression, yes	2.02 (1.30-3.15)	2.65 (1.60-4.40)	<.001	2.77 (1.44-5.31)	4.14 (1.91-8.97)	<.001
SA, yes	1.83 (1.19-2.82)	1.71 (1.09-2.68)	.01	3.73 (2.01-6.93)	3.33 (1.70-6.52)	<.001
BDI score, per an increment of 5	1.23 (1.11-1.36)	1.29 (1.14-1.45)	<.001	1.29 (1.14-1.47)	1.32 (1.13-1.55)	<.001
CVHR index, per an increment of 15 /hr	1.52 (1.17-1.99)	1.23 (0.93-1.63)	.14	2.23 (1.57-3.16)	1.68 (1.16-2.43)	.006
Multivariable model 1						
Depression, yes	1.35 (0.73-2.52)	1.60 (0.83-3.10)	.16	1.28 (0.43-3.82)	1.17 (0.39-3.56)	.77
SA, yes	1.25 (0.60-2.60)	0.90 (0.43-1.89)	.78	1.88 (0.61-5.84)	1.14 (0.36-3.60)	.81
Interaction, yes [†]	2.77 (1.11-6.90)	2.86 (1.15-7.15)	.02	4.53 (1.11-18.6)	5.14 (1.25-21.3)	.02
Multivariable model 2						
BDI score, per an increment of 5	0.96 (0.75-1.22)	1.02 (0.79-1.33)	.84	0.97 (0.68-1.36)	0.93 (0.62-1.39)	.73
CVHR index, per an increment of 15/hr	1.00 (0.64-1.57)	0.85 (0.54-1.35)	.48	1.39 (0.77-2.52)	1.03 (0.55-1.91)	.93
Interaction [‡]	1.16 (1.03-1.30)	1.12 (1.00-1.26)	.04	1.16 (1.00-1.35)	1.16 (0.99-1.36)	.07
Depression (n = 337)						
SA, yes	2.43 (1.41-4.19)	2.58 (1.46-4.58)	.001	5.44 (2.55-11.6)	5.67 (2.38-13.5)	<.001
CVHR index, per an increment of 15/hr	1.87 (1.36-2.59)	1.55 (1.10-2.18)	.01	2.77 (1.84-4.17)	2.11 (1.38-3.24)	<.001
Nondepression (n = 379)						
SA, yes	1.36 (0.66-2.77)	0.93 (0.43-1.99)	.84	2.19 (0.74-6.51)	1.23 (0.38-4.00)	.73
CVHR index, per an increment of 15/hr	1.13 (0.70-1.84)	0.90 (0.54-1.50)	.68	1.41 (0.69-2.87)	1.02 (0.48-2.17)	.95
SA (n = 226)						
Depression, yes	2.94 (1.50-5.75)	4.61 (2.19-9.70)	<.001	4.30 (1.82-10.2)	7.20 (2.67-19.4)	<.001
BDI score, per an increment of 5	1.44 (1.24-1.66)	1.41 (1.21-1.63)	<.001	1.50 (1.28-1.76)	1.42 (1.20-1.69)	<.001
Non-SA (n = 490)						
Depression, yes	1.62 (0.89-2.94)	1.74 (0.86-3.53)	.12	1.84 (0.67-5.07)	1.42 (0.37-5.41)	.61

	Combined endpoint (death or recurrent nonfatal AMI)				All-cause death			
	Unadjusted		Adjusted [§]		Unadjusted		Adjusted [¶]	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
BDI score, per an increment of 5	1.09 (0.92-1.28)	.31	1.17 (0.97-1.42)	.10	1.03 (0.77-1.38)	.84	0.99 (0.66-1.48)	.97

AMI = acute myocardial infarction; BDI = Beck Depression Inventory; CI = confidence interval; CVHR = cyclic variation of heart rate; HR = hazard ratio; SA = sleep apnea.

^{*}In univariate model, depression and SA were analyzed separately.

[†]Interaction = depression × SA.

[‡]Interaction = BDI score × CVHR index.

[§]HR adjusted for gender, body mass index, treatment (UC or UC plus CBT), and the ENRICHD risk score for the combined endpoint (21).

[¶]HR adjusted for gender, body mass index, treatment (UC or UC plus CBT), and the ENRICHD risk score for all-cause death (21).