

Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease

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Abstract

Objective: The purpose of this study was to investigate the relationship between depression and heart rate variability in cardiac patients. **Methods:** Heart rate variability was measured during 24-hour ambulatory electrocardiographic (ECG) monitoring in 40 medically stable out-patients with documented coronary heart disease meeting current diagnostic criteria for major depression, and 32 nondepressed, but otherwise comparable, patients. Patients discontinued β -blockers and antidepressant medications at the time of study. Depressed patients were classified as mildly ($n = 21$) or moderately-to-severely depressed ($n = 19$) on the basis of Beck Depression Inventory scores. **Results:** There were no significant differences among the groups in age, gender, blood pressure, history of myocar-

dial infarction, diabetes, or smoking. Heart rates were higher and nearly all indices of heart rate variability were significantly reduced in the moderately-to-severely versus the nondepressed group. Heart rates were also higher and mean values for heart rate variability lower in the mildly depressed group compared with the nondepressed group, but these differences did not attain statistical significance. **Conclusion:** The association of moderate to severe depression with reduced heart rate variability in patients with stable coronary heart disease may reflect altered cardiac autonomic modulation and may explain their increased risk for mortality. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Depression; Autonomic nervous system; Coronary heart disease

Introduction

There is considerable evidence that clinical depression is a risk factor for cardiac morbidity and mortality in patients with coronary heart disease; that is, heart disease resulting from coronary atherosclerosis [1–8]. Moreover, relatively severe forms of depression are associated with a greater risk for cardiac events; for example, myocardial infarction, need for balloon angioplasty, coronary artery bypass surgery, or other cardiac-related hospitalizations. L  sperance et al. [9], for instance, found that 40% of acute myocardial infarction patients with both a history of major depression and major depression at the time of their myocardial infarction (MI) died in the year following the myocardial infarction, compared with 10% of patients who were depressed for

the first time with relatively mild depression. Similarly, Barefoot et al. [2] found that patients with documented coronary heart disease who had moderate to severe depression had an 84% greater risk for mortality, and those with mild depression had a 57% greater risk, than did nondepressed patients with coronary disease.

These adverse effects of depression in coronary heart disease patients are believed to be due, at least in part, to dysregulation of the autonomic nervous system. Autonomic dysregulation, that is, a predominance of adrenergic activation and/or lack of parasympathetic modulation, has been found in medically well patients with major depressive disorder, as evidenced by elevated plasma and urinary catecholamines and their metabolites [10–15], altered cardiac autonomic balance as measured by elevated resting heart rate [4,16,17], and decreased heart rate variability [18–22].

Attenuated heart rate variability is a well-known independent risk factor for mortality after myocardial infarction [23,24]. Decreased heart rate variability has

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been shown to predict subsequent mortality even when it is measured in stable patients 1 year after myocardial infarction [25] and in unselected consecutive patients without any recent cardiac events involving cardiac catheterization [26]. We have previously shown that heart rate variability is significantly lower in depressed patients with newly diagnosed coronary disease than in otherwise comparable nondepressed patients [18]. Although there were no significant differences between the depressed and nondepressed groups with respect to prescribed medications, the fact that some patients were taking cardiac medications, such as β -blockers, may have affected the heart rate variability results in the sample as a whole. Furthermore, the sample was too small to determine whether heart rate variability was lower in more severely depressed patients than in mildly depressed ones. Thus, the purpose of the present study was to determine whether moderately-to-severely depressed, unmedicated patients with stable coronary heart disease have lower heart rate variability than comparable mildly depressed or nondepressed patients.

Methods

Subjects

Medically stable patients with angiographically documented coronary disease were eligible to participate if they were ≤ 75 years old and had no history or current evidence of congestive heart failure (the inability of the heart to pump sufficient blood to meet the needs of the body), a recent (within 6 months) myocardial infarction (heart attack), severe systemic illness, a noncardiac medical illness that could influence autonomic function, recent coronary artery bypass surgery or angioplasty, cardiomyopathy, valvular heart disease other than mitral value prolapse, substance abuse, or a significant psychiatric disorder other than depression. Patients were excluded if they were scheduled for revascularization procedures, not on a stable medication regimen, or unable to temporarily discontinue any medications that could affect cardiac autonomic tone.

Both depressed and nondepressed subjects were recruited from cardiac rehabilitation centers and through newspaper advertisements. The depressed patients were offered free treatment for depression, and both the depressed and nondepressed subjects were paid \$100 for their participation.

Procedure

Psychiatric interview. A modified version of the National Institutes of Mental Health Diagnostic Interview Schedule [27] was administered to determine the presence of depression and to identify other psychiatric disorders. The interview was modified to assess the duration of current depressive symptoms. The interviewer

had extensive training and prior experience with psychiatric interviewing. The diagnosis of major depression, as defined by the 1994 edition of the American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM-IV), was derived from the interview. Patients who could not be clearly characterized as either depressed or not depressed were excluded from the study.

Severity of depression. The Beck Depression Inventory (BDI) [28], a 21-item questionnaire, was administered to assess subjects' self-reported severity of depression. The BDI is one of the most widely used instruments for assessing the severity of depression in both research and in clinical settings. Depression was classified as mild for a BDI score of 10–19, or moderate to severe for a score of ≥ 20 .

Medications. To eliminate the effects of medications on heart rate variability (HRV), participating patients, with the consent of their physicians, were asked to discontinue β -adrenergic antagonists and antidepressants for 3 days or five half-lives (whichever was longer) prior to the assessment of heart rate variability. Patients who could not, in the judgment of their physicians, temporarily withdraw from these medications without minimal risk were excluded from this study.

Heart rate variability measurement. Twenty-four-hour ambulatory electrocardiographic (ECG) recordings were obtained on an out-patient basis using Marquette Series 8500 Holter monitors and analyzed on a Marquette SXP Holter laser scanner (software version 5.8) with standard Holter analysis techniques to accurately label beats and artifact. Patients were excluded if they were not in predominantly regular sinus rhythm or if they had sustained atrial arrhythmias such as atrial fibrillation or $>10\%$ ectopic complexes. Beat-stream files, representing the time and classification of each QRS complex, were transferred to a Sun Sparc station computer for heart rate variability analysis procedures using validated techniques [29,30].

Time domain heart rate variability indices. Twenty-four-hour time domain indices of heart rate variability included: AVGHR (average heart rate reflecting normal-to-normal intervals, in beats/minute); SDNN (standard deviation of normal-to-normal intervals, in milliseconds); SDANN (standard deviation of 5-minute mean values of normal-to-normal intervals for each 5-minute interval, in milliseconds); SDNNIDX (average of standard deviations of normal-to-normal intervals for each 5-minute interval, in milliseconds); rMSSD (root-mean-square successive difference of normal-to-normal intervals, in milliseconds); and pNN50 (the proportion of successive normal-to-normal interval differences >50 ms, in percent). RMSSD and pNN50 primarily reflect parasympathetically mediated changes in heart rate [31]. The other time domain variables reflect a mixture of parasympathetic, sympathetic, and other physiologic influences [31].

Frequency domain heart rate variability indices. The following standard frequency domain components of heart rate variability, measured in milliseconds squared, were computed: high-frequency power, the respiration-mediated component of the total variance in heart period between 0.15 and 0.40 Hz, which primarily reflects vagal modulation of heart rate [32]; low-frequency power, the component between 0.04 and 0.15 Hz, which reflects both sympathetic and parasympathetic modulation of heart rate [32]; very low-frequency power, the component between 0.0033 and 0.04 Hz, which may represent the influence of the thermoregulatory [33] or renin–angiotensin systems [32]; and ultra-low-frequency power, the component between 1.15×10^{-5} and 0.00335 Hz, which primarily reflects circadian variation in heart rate. Total power (1.15×10^{-5} – 0.40 Hz) for the total 24-hour cycle was also determined. The ratio of low- to high-frequency power, which has been proposed by some to be a marker of sympathetic:parasympathetic balance, was also calculated [34].

The methods used for spectral analysis have been described previously [30]. Briefly, the sequence of normal-to-normal intervals was resampled and filtered to provide a uniformly spaced time series. Segments missing because of excessive artifact, weak signal, or failure of the scanner to detect the onset of a beat were replaced by linear interpolation from the surrounding signal. The average normal-to-normal interval was subtracted from the time series and fast Fourier transforms were performed to determine the frequency components underlying the cyclic activity in the time series. Measurements of ultra-low and very low-frequency power were based on *en bloc* analysis of the entire 24-hour period. Other power spectral indices reported here reflect the average of 5-minute segments in which $\geq 80\%$ of the beats were normal.

Frequency domain indices of heart rate variability have a highly skewed distribution. Therefore, these indices were log transformed to produce an approximately normal distribution for the purpose of statistical analysis.

Statistical analysis

Fisher's exact test was used to test univariate associations between categorical variables. Multivariate analyses of variance (MANOVA) with the Hotelling–Lawrence trace multivariate test of significance was used to compare the heart rate variability indices and other continuous variables for the nondepressed, mildly, and moderately-to-severely depressed groups. Analysis of covariance adjusted for any significant difference in baseline characteristics. The α -level was set at 0.05 per comparison.

Results

Of the 54 depressed and 40 nondepressed patients recruited for the study, 40 depressed and 30 nonde-

pressed patients had recordings that were adequate for 24-hour heart rate variability analysis. As can be seen in Table 1, the groups were similar with respect to demographic and medical characteristics, except for a significantly greater pack-year smoking history among the severely depressed. The mean Beck Depression Inventory score for the moderately-to-severely depressed subjects was 28.2 ± 6.4 , compared with 18.9 ± 3.5 for the mildly depressed subjects, and 2.7 ± 2.3 for the nondepressed subjects. There was no difference between the groups on discontinuance of β -blocking agents prior to the recording (three nondepressed, two mildly depressed, and three moderately-to-severely depressed). Nine depressed patients were discontinued from antidepressant medications prior to their recording, three in the mild and six in the moderate-to-severe group. History of depression was found in 43.8% of nondepressed, 71.4% of mildly, and 79% of moderately-to-severely depressed patients.

MANOVA was used to compare time-domain indices of HRV between groups. Because time domain HRV is completely described by one HRV index from each of three domains (long-term, intermediate-term, and short-term HRV), we selected one variable from each group for inclusion in the MANOVA. SDANN reflects long-term HRV, SDNNIDX reflects intermediate-term HRV, and rMSSD reflects short-term HRV. To permit parametric statistical comparisons, rMSSD was log transformed to provide a normal distribution. Average heart rate was also included in the model. Results are shown in Table 2 and in Figs. 1 and 2. The MANOVA was significant (Hotelling–Lawley $F = 2.30$, $p = 0.03$). Post hoc testing revealed differences between both nondepressed and mildly depressed patients compared with moderately-to-severely depressed patients for heart rate and all indices of heart rate variability except rMSSD, which was different only between the nondepressed and moderately-to-severely depressed subjects. Although the mean values for heart rate and heart rate variability for the mildly depressed patients were intermediate between those for the nondepressed and moderately-to-severely depressed patients, these differences were small and none attained statistical significance. The results were unchanged when these comparisons were adjusted for smoking history in pack-years. Both the main effects of gender and diabetes and the interactions between these variables and depression were tested, but none of these effects were significant.

A MANOVA was conducted to compare heart rate variability in the frequency domain in nondepressed and mildly and moderately-to-severely depressed coronary heart disease patients. Because the entire heart rate power spectrum is described by the combination of ultra-low, very low, low- and high-frequency power, all of these log-transformed frequency domain indices of heart rate variability were entered in the model. The MANOVA was significant (Hotelling–Lawley $F = 2.87$, $p < 0.01$).

Table 1

Demographic comparisons between nondepressed, mildly depressed and moderately-to-severely depressed CHD patients ($\alpha = 0.05$)

	Nondepressed (N = 30)	Mildly depressed (N = 20)	Moderately-to- severely depressed (N = 20)	Omnibus <i>p</i> -value	Significant comparisons
Age (years)	62.4 \pm 8.9	60.2 \pm 8.1	60.5 \pm 9.1	NS	
Gender	21 M, 9 F	11 M, 9 F	10 M, 10 F	NS	
BDI score	2.8 \pm 2.3	15.3 \pm 3.5	28.2 \pm 6.4	<0.01	All
Resting SBP (mm Hg)	131 \pm 20	129 \pm 22	133 \pm 21	NS	
Resting DBP (mm Hg)	75 \pm 9	76 \pm 9	78 \pm 10	NS	
Pack-years of smoking	21.6 \pm 26.9	19.5 \pm 24.8	40.8 \pm 38.7	0.05	No vs. severe Mild vs. severe
History of MI	50.0%	60.0%	70.0%	NS	
Diabetes	20.0%	35.0%	25.0%	NS	

NS, nonsignificant.

Post hoc testing revealed that, consistent with the time-domain results, HRV was significantly lower in the moderately-to-severely depressed patients compared with both the mildly depressed and the nondepressed groups (Table 3 and Fig. 3), but the difference for the logarithm of high-frequency power attained statistical significance only for the moderately-to-severely depressed versus the nondepressed groups. As in the time domain, mean heart rate variability values for the mildly depressed patients were intermediate between those of the nondepressed and moderately-to-severely depressed groups, but no statistically significant differences were found. The low-frequency:high-frequency power ratio was not significantly different among the groups.

Discussion

In a previous study, we found that heart rate variability was lower in depressed than in nondepressed patients

with newly diagnosed coronary disease, some of whom were taking cardiac medications such as β -blockers [9,18]. The present study extends this finding by documenting reduced heart rate variability in clinically depressed patients with stable coronary heart disease who had temporarily discontinued all cardiac medications. Although it is possible that there was a rebound effect on heart rate variability from the discontinuance of β -blockers, there was no difference in the prevalence of β -blocker use across groups, so any rebound effect would not affect our results. The results also suggest that the differences in heart rate variability that have been found between depressed and nondepressed patients with coronary heart disease are due to markedly reduced heart rate variability among patients with comparatively severe depression.

Previous prognostic studies have found that mildly depressed patients are at increased risk for mortality, although less so than are more severely depressed pa-

Table 2

Twenty-four-hour time domain indices of heart rate variability for nondepressed, mildly depressed and moderately-to-severely depressed CHD patients ($\alpha = 0.05$)

	Nondepressed (N = 30)	Mildly depressed (N = 20)	Moderately-to- severely depressed (N = 20)	Omnibus <i>p</i> -value	Significant comparisons
Average HR	74 \pm 9	78 \pm 9	83 \pm 11	<0.01	Nondepressed vs. severe
SDNN (ms)	119 \pm 20	117 \pm 30	99 \pm 21	NA	Not determined
SDANN (ms)	109 \pm 19	107 \pm 28	93 \pm 19	0.04	Nondepressed vs. severe
SDNNIDX (ms)	46 \pm 13	43 \pm 14	33 \pm 10	<0.01	Nondepressed vs. severe
rMSSD (ms)	24 \pm 8	23 \pm 9	19 \pm 8	0.09 ^a	Mild vs. severe Nondepressed vs. severe
pNN50 (%)	5.1 \pm 4.5	4.8 \pm 5.3	3.0 \pm 4.5	NA	Not determined

AVGHR, average heart rate in beats/minute; SDNN, standard deviation of normal-to-normal interbeat intervals; SDANN, standard deviation of 5-min mean values of normal-to-normal interbeat intervals for each 5-min period; SDNNIDX, the average of standard deviations of normal-to-normal interbeat intervals for each 5-min period; rMSSD, the root-mean-square successive difference of normal-to-normal interbeat intervals; pNN50, the proportion of successive normal-to-normal differences in interbeat intervals >50 milliseconds (in percent).

^a *F*-statistic based on ln rMSSD.

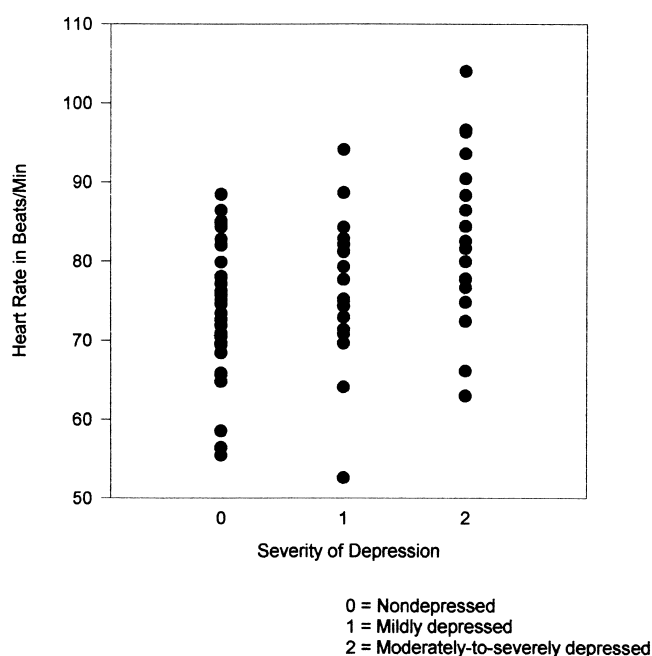


Fig. 1. Comparison of heart rates in beats/minute for nondepressed, mildly depressed, and moderately-to-severely depressed stable CHD patients.

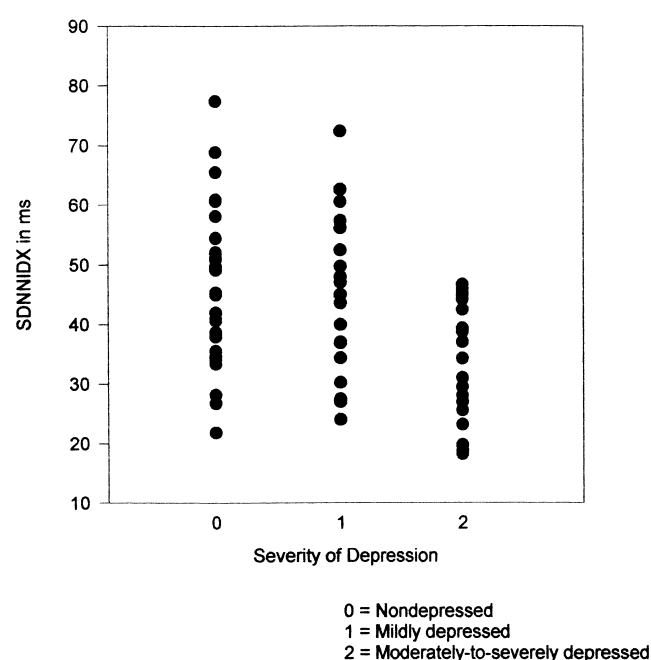


Fig. 2. Comparison of SDNN (in milliseconds) for nondepressed, mildly depressed, and moderately-to-severely depressed stable CHD patients.

tients [2,9]. Although indices of heart rate variability in the mildly depressed group did not differ significantly from heart rate variability in the nondepressed patients, they were in the expected direction. Thus, the results of our study are consistent with the findings of prognostic studies.

In the present study, 65% of the moderately-to-severely depressed patients with coronary heart disease had a previous myocardial infarction, as did 50% of the nondepressed patients. Although the predictive value of attenuated heart rate variability for mortality was most clearly validated in patients with a recent acute myocardial infarction, it has also been shown to predict subsequent mortality even when measured 1 year after myocardial infarction when postinfarction recovery of HRV is complete [25], and in unselected coronary patients without any recent cardiac events [26]. This suggests that decreased HRV remained a risk factor for mortality in the cardiac patients studied here.

Various heart rate variability criteria have been advanced to identify those at highest risk for mortality. The best known is SDNN <50 ms in patients within 2 weeks following an acute myocardial infarction [23]. However, heart rate variability is known to increase in the 3 months following acute myocardial infarction [35]. The Cardiac Arrhythmia Pilot Study (CAPS) criterion is probably more relevant for identifying those at highest risk in our study. CAPS assessed heart rate variability 1 year after myocardial infarction [25]. Although all indices of heart rate variability were strong predictors of mortality, very low-frequency power, <600 ms² (In

very low frequency power <6.4), identified patients at a 4.4 relative risk of mortality over the next 2 years. Forty-seven percent of the moderately-to-severely depressed, 29% of the mildly depressed, and 13% of the nondepressed group in the present study had very low-frequency power below this cutpoint (Fig. 3). This difference was statistically significant between the nondepressed and the moderately-to-severely depressed groups ($p = 0.02$). Thus, the lower heart rate variability seen in the moderately-to-severely depressed patients may have prognostic significance.

In addition to altered cardiac autonomic tone, other mechanisms for increased mortality in depressed patients have been proposed. For example, depressed patients have been found to be less adherent to medical treatment regimens than nondepressed patients [36,37]. Nevertheless, the results of this study strongly suggest that altered cardiac autonomic tone could explain much of this increased risk.

A substantial proportion of depressed patients smoke or have a history of smoking [38]. Current smoking clearly depresses heart rate variability and, even among those who have recently quit and have no clinical evidence of heart disease, heart rate variability remains lower compared with that of normal nonsmokers [39]. There were only eight current smokers in our study, five depressed and three nondepressed, and we did not observe any difference in heart rate variability between former smokers and those who had never smoked. Although not an influential factor in this study, smoking must be taken into account in any study of the effect

Table 3

Twenty-four-hour frequency domain indices of heart rate variability for nondepressed, mildly depressed and moderately-to-severely depressed CHD patients ($\alpha = 0.05$)

	Nondepressed (N = 30)	Mildly depressed (N = 20)	Moderately-to-severely depressed (N = 20)	Omnibus <i>p</i> -value	Significant comparisons
ln TP	9.60 \pm 0.45	9.46 \pm 0.50	9.18 \pm 0.46	NA	Not determined
ln ULF	9.40 \pm 0.37	9.33 \pm 0.52	9.04 \pm 0.47	0.02	Nondepressed vs. severe
ln VLF	7.03 \pm 0.63	6.84 \pm 0.67	6.25 \pm 0.78	<0.01	Mild vs. severe Nondepressed vs. severe
ln LF	6.07 \pm 0.75	5.83 \pm 0.70	5.16 \pm 0.75	<0.01	Mild vs. severe Nondepressed vs. severe
ln HF	4.81 \pm 0.83	4.63 \pm 1.07	4.24 \pm 0.95	0.12	Mild vs. severe Nondepressed vs. severe
LF/HF ratio	3.96 \pm 1.96	3.90 \pm 2.17	3.15 \pm 2.10	0.36	None

TP, total power ($1.15 \times 10^{-5} - 0.40$ Hz) for the total 24-hour cycle; ULF, ultra-low-frequency power, the component between 1.15×10^{-5} Hz; VLF, very low frequency power, the component between 0.0033 and 0.04 Hz; LF, low-frequency power, the component between 0.04 and 0.15 Hz; HF, high-frequency power, the component between 0.15 and 0.40 Hz; LF/HF ratio, the ratio of low- to high-frequency power.

of depression on heart rate variability that involves a substantial number of current smokers.

All of the patients in the study had coronary disease documented by cardiac catheterization and angiography. However, recent angiograms were not available for some of the patients. Although one study found no relationship between any index of heart rate variability and the severity of coronary heart disease [40], another,

which measured short-term (200 to 300 RR interval) HRV in response to controlled respiration, reported a significant correlation between a vagally modulated index of heart rate variability (the power associated with respiratory sinus arrhythmia adjusted for heart rate) and disease severity [41]. Thus, the relationship between severity of coronary disease and heart rate variability is unclear. However, although it is possible that there was a difference in the severity of atherosclerosis between the depressed and nondepressed patients, there were no other medical or demographic differences, including history of myocardial infarction or revascularization procedures, that would suggest that was the case.

Nine patients, seven of whom were moderately to severely depressed, temporarily discontinued their antidepressant medications for this study. All were on selective serotonin reuptake inhibitors (SSRIs), which have been shown either to have no effect on heart rate variability [42], or to increase it slightly [43,44]. Increasing heart rate variability in the depressed patients would, in fact, have *reduced* the effect reported in this study. However, there was no difference in heart rate variability between the depressed patients who were not on SSRIs and those who discontinued their use, nor was there any difference in heart rate variability between patients with a past history of depression and those experiencing their first episode.

The patients in our study were recruited from a variety of settings, and not from a single source in a sequential series. Although this may affect the generalizability of our findings, it is difficult to imagine how this selection procedure would affect the relationship between depression and heart rate variability. Also, heart rate variability was measured only after specific medications

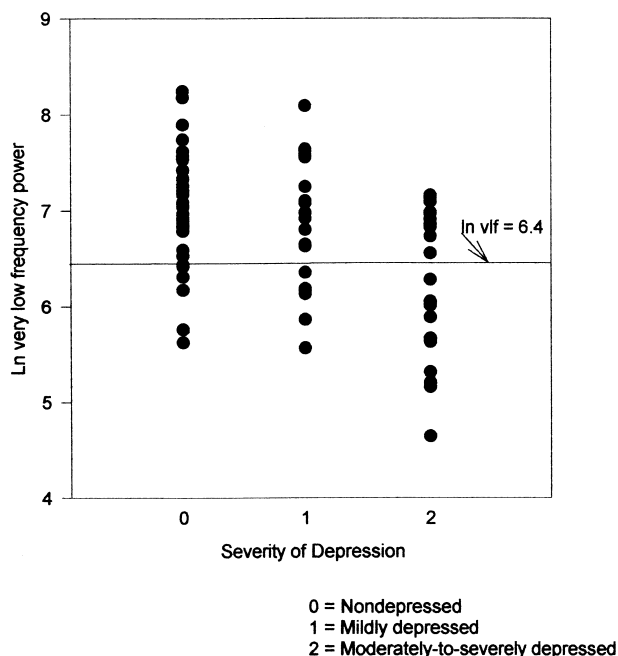


Fig. 3. Comparison of ln (very low-frequency power) for nondepressed, mildly depressed, and moderately-to-severely depressed stable CHD patients. Horizontal line indicates cutpoint for a 4.4 times relative risk of mortality.

were discontinued and, therefore, the generalizability of our results to patients on usual therapy cannot be determined from our data. Although not addressed here, the HRV effect of discontinuance of medications deserves further study.

We conclude that stable coronary heart disease patients with moderate-to-severe depression have markedly reduced heart rate variability compared with less severely depressed and nondepressed patients, and that this may reflect the autonomic derangements associated with depression. Heart rate variability analysis as a technique for the assessment of cardiac autonomic modulation may yield insights into factors underlying increased mortality in severely depressed cardiac patients.

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