INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2006; **21**: 147–150.
Published online 16 January 2006 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1439

Differences in heart rate variability between depressed and non-depressed elderly

Koen G. van der Kooy[1], Hein P. J. van Hout[1],* Harm W. J. van Marwijk[1], Marten de Haan[1], Coen D. A. Stehouwer[2] and Aartjan T. F. Beekman[3]

[1]*Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands*
[2]*Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands*
[3]*Valeriuskliniek GGZ Buitenamstel, VU University Medical Center, Amsterdam, The Netherlands*

SUMMARY

Objective To determine whether older primary care patients with a Major Depressive Disorder (MDD) have lower heart rate variability (HRV) compared to non-depressed patients. HRV is a measure of cardiac autonomic functioning.
Method A cross-sectional comparison of 136 elderly persons with MDD and 136 non-depressed controls (matched for age and gender) recruited in family practices in the Netherlands. Depression was determined according to the DSM–IV criteria using the PRIME–MD. HRV was measured with an electrocardiogram (ECG) during a 5-minute supine rest.
Results Multivariate analyses showed statistically significant decrease in HRV in MDD patients compared with controls.
Conclusion Older primary care patients with MDD have a reduced HRV. This may explain why depression is a risk factor for cardiovascular disease and mortality. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — major depression; heart rate variability; autonomic nervous system; primary care

INTRODUCTION

Depressive disorders are associated with increased cardiovascular morbidity and mortality (Wulsin and Singal, 2003). One of the explanations is that depressive disorders cause a deregulation in the autonomic nervous system (ANS). The ANS modulates the electrical and contractile activity of the myocardium through the collaboration of sympathetic and parasympathetic (vagal) outflow. ANS deregulation consists of increased sympathetic activity and reduced vagal activity, which are strongly involved in the pathophysiology of arrhythmogenesis, sudden cardiac death, myocardial infarction, congestive heart failure and diabetic neuropathy (Stein and Kleiger, 1999). Measurement of HRV represents a non-invasive and highly sensitive procedure for investigating cardiac ANS function (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Reduced HRV points to a disturbed balance between the sympathetic and vagal branches of the ANS. In population studies, decreased HRV is predictive for cardiac events and cardiac mortality among healthy adults (Dekker *et al*., 2000).

Studies on depression and HRV, mostly performed in psychiatric inpatients, have revealed conflicting results. Several studies reported a reduction of HRV (Dalack and Roose, 1990; Rechlin *et al*., 1994; Guinjoan *et al*., 1995; Tulen *et al*., 1996; Stein *et al*., 2000; Agelink *et al*., 2002; Nahshoni *et al*., 2004;) where other studies reported no HRV difference (Yeragani *et al*., 1991; Moser *et al*., 1998; Bar *et al*., 2004) in depressed patients compared with non-depressed controls. This inconsistency may be due to methodological or population differences. It is unknown whether a reduced HRV is present in depressed primary care patients, who constitute the majority of all major depressive disorder (MDD)

*Correspondence to: H. P. J. van Hout, Institute for Research in Extramural Medicine, VU University Medical Center, PO Box 2941, 1000 SN, Amsterdam, The Netherlands. Tel: +31 20 4449678. Fax: +31 20 4448361.
E-mail: hpj.vanhout@vumc.nl

Contract/grant sponsor: The Netherlands Heart Foundation, The Hague, The Netherlands; contract/grant number: 2000 B 038.

Received 11 April 2005
Accepted 21 July 2005

patients. In this study we compared the HRV between elderly primary care patients with and without a MDD.

METHODS

In this case-control study we recruited older (55 years and over) patients in waiting rooms of 14 family practices in the Netherlands. Six thousand seven hundred and nineteen persons were screened for depressive symptoms using the Geriatric Depression Scale 15-item questionnaire (GDS-15) (Burke *et al*., 1991). All persons who scored 5 points or more were asked to participate in a diagnostic interview by a trained interviewer, using the Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer *et al*., 1994). Exclusion criteria were antidepressant treatment (drugs or psychotherapy) in the last six months, alcohol dependence, psychosis or cognitive impairment. The participating MDD patients were matched on sex and age to a person with a negative GDS-15 score. All participants gave their written informed consent prior to inclusion for the study. The ethical committee of the VU University Medical Center approved the study. One week prior to the physical examination the severity of the depressive symptoms was measured with the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Controls who scored 10 or higher ($n = 11$) on the MADRS and MDD patients who scored under 10 ($n = 8$) were excluded from the comparison.

Measurements of HRV using ECG took place at the VU University medical research centers in Amsterdam and Hoorn. All examinations took place in the morning between 8.00 and 11.00 am. The subjects were asked not to drink caffeine or smoke before the examination. During the five-minute supine rest a 12-lead ECG and software of CardioPerfect© were used. The following ECG variables were calculated as indicators of ANS function. Time domain variables including: (a) the Standard Deviation of all NN intervals (SDNN) as an estimate of overall HRV and (b) the Root Mean Square Successive Differences of NN intervals (rMSSD), which indicate mostly parasympathic activity (Kleiger *et al*., 1992). Power spectral analysis was done by a Fast-Fourier transformation, whereby three frequency bands were automatically separated: (c) High Frequency band (HF; 0.15–0.4 Hz); (d) Low Frequency band (LF; 0.04–0.15 Hz); (e) Very Low Frequency band (VLF; 0.003–0.04 Hz), The short 5-min analysis period precludes a conclusive interpretation of the VLF. The LF-band is associated with both sympathetic and parasympathetic activity, while the HF-band reflects the respiratory sinus rhythm resulting from centrally mediated cardiac vagal control (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Blood pressure was measured manually using a cuff fixed on the left arm. Height and weight were measured to calculate the Body Mass Index (BMI). The Hospital Anxiety and Depression Scale subscale for Anxiety (HADS-A) (Zigmond and Snaith, 1983) was used to measure co-morbid anxiety symptoms.

The HRV measures were log transformed to produce normal distributions. Univariate regression analyses were used to determine whether the HRV measures differed between the MDD and the control group. We explored potential confounding and effect-modification on the relation between depression and HRV. No confounding and effect-modification was found. In a multivariate analysis we adjusted for age, sex, smoking, diabetes and heart medicine (beta blocking agents and calcium channel blockers). These variables have previously been associated with HRV measures and depression (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Carney *et al*., 2001). Associations were expressed in regression coefficients (B) with 95% confidence intervals (CI).

RESULTS

The screening revealed 187 eligible patients of which 63% participated in our study. The non-participants had a comparable gender distribution (66.7% *vs* 64.0% female), but were older (71.55 *vs* 67.59 years), and had on average a lower PRIME-MD score (5.86 *vs* 6.37) with the participating patients. Table 1 shows the characteristics of 124 of 136 eligible MDD participants that were matched with a control because 12 male patients dropped-out before the physical examination. The MDD patients had a higher anxiety score on the HADS-A ($t = -12.52$, $\mathrm{df} = 256$, $p < 0.01$), had more self-reported cardiovascular diseases ($\chi^2 = 5.41$, $\mathrm{df} = 1$, $p = 0.02$), were more often diabetic ($\chi^2 = 5.82$, $\mathrm{df} = 1$, $p = 0.02$), had more chronic diseases ($t = -2.59$, $\mathrm{df} = 258$, $p = 0.01$) and used more prescription medications ($\chi^2 = 5.82$, $\mathrm{df} = 1$, $p = 0.02$). Women with MDD had a higher mean BMI. Other general characteristics of the depressed group and the controls did not differ significantly.

Univariate analyses of HRV characteristics show that MDD patients had significantly lower SDNN

Table 1. General characteristics of the MDD and the control group

General characteristics	Major depression		Controls	
	$n = 124$	SD	$n = 136$	SD
Mean age (years)	67.28	(8.28)	67.58	(7.6)
Female sex (%)	88	(71)	87	(64)
MADRS**	19.57	(7.83)	2.75	(3.93)
HADS-A**	10.10	(2.28)	5.96	(2.47)
Smoking (%)	24	(19.4)	17	(12.5)
BMI (kg/m^2)*	28.17	(5.12)	26.76	(4.16)
SBP (mmHg)	146.25	(17.88)	142.44	(18.56)
DBP (mmHg)	83.62	(9.41)	83.72	(8.18)
CHD (%)*	31	(25.6)	19	(14.1)
Diabetic (%)*	14	(11.6)	5	(3.7)
Other chronic diseases*	5.05	(2.63)	4.01	(2.48)
Heart Medication[a] (%)*	54	(43.5)	41	(30.1)

Variables are presented as means with standard deviation or as n with the percentage when marked (%); MADRS = Montgomery Asberg Depression Rating Scale; HADS-A = Hospital Anxiety and Depression Scale subscale for Anxiety; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; CHD = coronary heart diseases.
[a]Beta blocking agents and Calcium channel blockers.
*$p < 0.05$.
**$p < 0.01$.

($F = 6.70$, $p = 0.01$), rMSSD ($F = 4.19$, $p = 0.04$) and LF-power ($F = 6.08$, $p = 0.01$), whereas HF-power also tended to be lower ($F = 3.08$, $p = 0.08$). Table 2 shows the regression coefficient (B) of depression for the univariate and multivariate analysis. After adjusting for age, sex, smoking, diabetes and heart medication (beta blocking agents and calcium channel blockers), the log transformed HRV measures; SDNN (B = −0.09, 95% CI = −0.15–0.02) rMSSD (B = −0.10, 95% CI = −0.18–0.01) LF power (B = −0.16, 95% CI = −0.31–0.02) and HF power (B = −0.18, 95% CI = −0.36–0.01) remained significantly lower for the MDD group compared with the control group. The severity of depression, expressed by the MADRS score, did not add to difference in the HRV measures between the MDD patients and the control group in multivariate analysis. The HADS-A score was highly correlated with the MADRS score ($r = 0.63$, $p < 0.01$). Anxiety, demographic or medical variables did not display interaction between depression and HRV measures.

DISCUSSION

Our study showed an impaired HRV among older primary care patients with MDD. MDD patients had a reduced overall HRV (SDNN) and an inhibited vagal tone (rMSSD, HF-power). This is the first HRV study among a large group of older depressed patients in primary care, who were diagnosed using an established diagnostic instrument and for whom it was possible to adjust for potential confounders and modifiers. The study supports the hypothesis that deregulation of cardiac ANS control is a mechanism

Table 2. Mean heart rate and mean log-transformed time and frequency domain indices of HRV for the MDD and the control group

HRV characteristics	Major depression		Controls		B	95% CIs	B[a]	95% CIs
	$n = 116$	SD	$n = 125$	SD				
HR (bpm)	67.27	(9.81)	66.06	(13.60)	1.21	(−1.86, 4.29)	1.66	(−1.55, 4.86)
log SDNN (ms)	1.49	(0.25)	1.57	(0.24)	−0.08*	(−0.15, −0.02)	−0.09*	(−0.15, −0.02)
log rMSSD (ms)	1.38	(0.33)	1.46	(0.34)	−0.09	(−0.17, 0.00)	−0.10*	(−0.18, −0.01)
log LF power (ms^2)	2.25	(0.55)	2.43	(0.57)	−0.18	(−0.33, −0.04)	−0.16*	(−0.31, −0.02)
log HF power (ms^2)	2.26	(0.66)	2.41	(0.67)	−0.15*	(−0.32, −0.02)	−0.18*	(−0.36, −0.01)

Variables are presented as means with standard deviation; B = unstandardized regression coefficient; CI = confidence interval; HR = average heart rate in beats per minute; rMSSD = root mean square of successive differences; LF = low frequency (0.04–0.15 Hz); HF = high frequency (0.15–0.4 Hz).
[a]Adjusted for: age, sex, smoking, diabetes and heart medication (beta blocking agents and calcium channel blockers).
*$p < 0.05$.

that links depression to an increased cardiovascular morbidity and mortality as found in epidemiological cohort studies (Rugulies, 2002; Wulsin and Singal, 2003). So far HRV differences have been reported only among psychiatric inpatients with MDD compared to healthy controls (Tulen *et al*., 1996; Agelink *et al*., 2002; Nahshoni *et al*., 2004).

The cross-sectional design of our study limited the insight in the dynamics of the relation between depression and HRV. Future research should investigate if changes in depression over time result in HRV alterations. Another fruitful area for future research would be to test whether integrating cardiovascular and affective treatment strategies would help to reduce the cardiovascular sequel of affective disorders in older patients.

ACKNOWLEDGMENTS

This study was funded by the Netherlands Heart Foundation, the Hague, the Netherlands. (Grant number: 2000 B 038).

REFERENCES

Agelink MW, Boz C, Ullrich H, Andrich J. 2002. Relationship between major depression and heart rate variability: clinical consequences and implications for antidepressive treatment. *Psychiatry Res* **113**: 139–149.

Bar KJ, Greiner W, Jochum T, Friedrich M, Wagner G, Sauer H. 2004. The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters. *J Affect Disord* **82**: 245–252.

Burke WJ, Roccaforte WH, Wengel SP. 1991. The short form of the Geriatric Depression Scale: a comparison with the 30-item form. *J Geriatr Psychiatry Neurol* **4**: 173–178.

Carney RM, Blumenthal JA, Stein PK, *et al*. 2001. Depression, heart rate variability, and acute myocardial infarction. *Circulation* **104**: 2024–2028.

Dalack GW, Roose SP. 1990. Perspectives on the relationship between cardiovascular disease and affective disorder. *J Clin Psychiatry* **51**(Suppl.): 4–9.

Dekker JM, Crow RS, Folsom AR, *et al*. 2000. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk In Communities. *Circulation* **102**: 1239–1244.

Guinjoan SM, Bernabo JL, Cardinali DP. 1995. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. *J Neurol Neurosurg Psychiatry* **59**: 299–302.

Kleiger RE, Stein PK, Bosner MS, Rottman JN. 1992. Time domain measurements of heart rate variability. *Cardiol Clin* **10**: 487–498.

Montgomery SA, Asberg M. 1979. New Depression Scale Designed to be Sensitive to Change. *Br J Psychiatry* **134**: 382–389.

Moser M, Lehofer M, Hoehn-Saric R, *et al*. 1998. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *J Affect Disord* **48**: 115–124.

Nahshoni E, Aravot D, Aizenberg D, *et al*. 2004. Heart rate variability in patients with major depression. *Psychosomat* **45**: 129–134.

Rechlin T, Weis M, Spitzer A, Kaschka WP. 1994. Are affective disorders associated with alterations of heart rate variability? *J Affect Disord* **32**: 271–275.

Rugulies R. 2002. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med* **23**: 51–61.

Spitzer RL, Williams JB, Kroenke K, *et al*. 1994. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA* **272**: 1749–1756.

Stein PK, Carney RM, Freedland KE, *et al*. 2000. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *J Psychosom Res* **48**: 493–500.

Stein PK, Kleiger RE. 1999. Insights from the study of heart rate variability. *Ann Rev Med* **50**: 249–261.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996. Heart rate variability—standards of measurement, physiological interpretation, and clinical use. *Circulation* **93**: 1043–1065.

Tulen JH, Bruijn JA, de Man KJ, Pepplinkhuizen L, van den Meiracker AH, Man in 't Veld AJ. 1996. Cardiovascular variability in major depressive disorder and effects of imipramine or mirtazapine (Org 3770). *J Clin Psychopharmacol* **16**: 135–145.

Wulsin LR, Singal BM. 2003. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosomat Med* **65**: 201–210.

Yeragani VK, Pohl R, Balon R, *et al*. 1991. Heart rate variability in patients with major depression. *Psychiatry Res* **37**: 35–46.

Zigmond AS, Snaith RP. 1983. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scand* **67**: 361–370.

