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The Effect of Autonomic Neural Control on the Cardiovascular System in Patients with Depression

Depresyonlu Hastalarda Otonom Nöral Kontrolün Kardiyovasküler Sistem Üzerine Etkisi

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ABSTRACT

Purpose: In this study, we aimed to examine hearth rate recovery, systolic blood pressure response to exercise and heart rate variability to reveal the effect of autonomic autonomic neural control on the cardiovascular system in depressed individuals. **Methods**: A total of 151 patients; (49 out of 75 healthy controls and 54 out of 76 patients with depression were females) were associated to age, sex and physical activity. We examined the difference between heart rate at peak exercise and heart rate recovery at related minute. Systolic blood pressure at 2nd and 3rd min of recovery was divided into the systolic blood pressure at peak exercise in order to determine blood pressure recovery indices. **Results**: Heart rate recovery at first minute was significantly lower in the depression group compared to the control group ($p < 0.0001$). The resting systolic blood pressure was similar in both groups ($p = 0.762$). Systolic blood pressure during peak exercise was significantly higher in the depression group compared to the control group ($p < 0.0001$). In the depressive patient group, the systolic blood pressure recovery index was significantly higher at 2nd and 3rd minutes than the control group ($p < 0.0001$, $p = 0.015$). Time domain and frequency domain parameters significantly decreased compared to the controls. **Conclusion:** This study demonstrates that depression is characterized with decreased heart rate recovery, exaggerated systolic blood pressure response to exercise and attenuated heart rate variability. These results may also propose alterations in autonomic neuronal control of the cardiovascular system in depression.

Key words: Depression, hearth rate recovery

ÖZET

Amaç: Bu çalışmada, depresyonlu bireylerde otonomik nöral kontrolün kardiyovasküler sistem üzerindeki etkisini ortaya çıkarmak için, kalp atım hızı düzelmesini, egzersize verilen sistolik kan basıncı cevabını ve kalp hızı değişkenliğini incelemeyi amaçladık. **Yöntem:** Toplam 151 hasta (75 sağlıklı kontrolün 49'u ve depresyonlu 76 hastanın 54'ü kadın) yaş, cinsiyet ve fiziksel aktivite ile ilişkilendirildi. Pik egzersizde kalp atış hızı ile ilgili dakikada gerçekleşen kalp hızı toparlanması arasındaki farkı inceledik. Toparlanmanın 2. ve 3. dakikasındaki sistolik kan basıncı, pik egzersizdeki sistolik kan basıncına bölünerek kan basıncı toparlanma endeksleri belirlendi. **Bulgular:** Depresyon grubunda birinci dakikadaki kalp hızı toparlanması kontrol grubuna göre anlamlı derecede düşük bulundu ($p < 0.0001$). İstirahat sistolik kan basıncı her iki grupta da benzerdi ($p = 0.762$). Pik egzersiz sırasında sistolik kan basıncı depresyon grubunda kontrol grubuna göre anlamlı derecede yüksekti ($p < 0.0001$). Depresif hasta grubunda sistolik kan basıncının toparlanma indeksi kontrol grubuna göre 2. ve 3. dakikalarda daha yüksekti ($p < 0.0001$, $p = 0.015$). Zaman etki alanı ve frekans alanı parametreleri, kontrollere kıyasla önemli ölçüde azaldı. **Sonuç:** Bu çalışma, depresyonun azalmış kalp hızı toparlanması, egzersize abartılı sistolik kan basıncı cevabı ve azalmış kalp hızı değişkenliği ile karakterize olduğunu göstermektedir. Bu sonuçlar depresyonda kardiyovasküler sistemin otonomik nöral kontrolünde değişiklikler olabileceğini ön görmektedir.

Anahtar kelimeler: Depresyon, kalp hızı toparlanması

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INTRODUCTION

Cardiovascular diseases and depression are the most common causes of morbidity worldwide. It is usually observed in major depressive disorder with the development of cardiovascular disease.[1] In addition, it has been shown that the mortality increases in coronary artery disease, after myocardial infarction[2] and coronary artery bypass graft surgery.[3] On the other hand, mechanism of this action is still unknown.

Although there are several hypotheses to explain the possible correlation between depression and cardiac disorders, most emphasized ones for patients with post-cardiac depression include their having more cardiac risk factors such as diabetes, hypertension and smoking,[4] being less compatible in medical treatment,[5] having increased inflammatory processes and autonomic nervous system disorders.[6]

It has been shown that the association between cardiovascular mortality and the autonomic nervous system is significant.[7] The heart rate recovery (HRR) after exercise indicates parasympathetic activity[8] and the decay of parasympathetic activity is related to increased long-term mortality.[9] Studies have shown that delayed recovery of systolic blood pressure (SBP) after peak exercise is a diagnostic finding and is related to excessive sympathetic activity.[10] Also, the balance between sympathetic and parasympathetic nerve activities in heart has been shown through analyzing heart rate variations.[11] Hence, in this study we aimed to determine the autonomic neural activity by HRR, SBP after peak exercise and heart rate variability (HRV) in patients with depression.

METHODS

Study Population

This study was conducted in outpatient clinic of our University Hospital. A total of 151 patients were enrolled. Of these patients, 76 patients met the Diagnostic and Statistical Manual of Mental Disorders criteria for the diagnosis of depression. Seventy-five healthy subjects were enrolled as the control group. The Beck Depression Index-II was used to measure depressive symptoms. The diagnosis was made by the psychiatrist in charge. The groups were similar with regard to baseline age, body mass index and physical activity. The International Physical Activity Questionnaire (IPAQ) was used to match the physical activities of the groups. The patients with myocardial infarction or unstable angina or known coronary heart disease; hypertension or diabetes mellitus; heart failure or other known cardiomyopathies are excluded from the study. Patients with persistent laboratory abnormalities like kidney dysfunction, liver dysfunction or other significant non-cardiac diseases have not been included. Concomitant use of any antidepressant medications, reserpine, guanethidine, clonidine, methyldopa, anticonvulsants, neuroleptics, beta-blockers, calcium channel blockers ACE inhibitors or statins was another exclusion criteria. Psychiatric exclusion criteria included alcohol or substance abuse during the recent six months, psychotic symptoms, bipolar disorder, dementia, organic brain syndrome, risk of suicide, or psychotherapy support during the recent three months. Informed consent form was obtained from all participants and ethics committee approval was obtained from the Regional Ethics Committee prior to the study.

Heart Rate and Blood Pressure Recovery

The symptom-limited exercise tolerance test was performed in accordance with the modified Bruce protocol (using Quinton® treadmill system (Bothell, WA, USA)). SBP, heart rate and cardiac rhythm were examined during the each exercise phase and every minute after recovery for three minutes. After peak exercise, a 2-minute cool-down period at 1.5 mph at a 2.5% grade was tested. The gap between peak exercise heart rate and heart rate at the related minute of recovery was calculated and HRR obtained. In one example, 1st minute heart rate recovery (HRR1) was also calculated (at peak exercise HRR cool-down period 1 min). Metabolic parameters were calculated in accordance with Standard Normograma.[12]

For measuring blood pressure, we used mercury column of sphygmomanometer. SBP recovery indices were determined as the ratios of the SBP recovery 1st, 2nd and 3rd minutes of the peak exercise SBP.

Heart Rate Variability Analysis

The researcher was blinded to information about subjects obtained the HRV parameters from a 24-h electrocardiogram recordings and analyzed. The time domain indices were gathered as;

- SDNN: the standard deviation (SD) of R-R intervals.
- SDANN: the SD of the averages of R-R intervals at every 5-min in 24-h day
- pNN50: % R-R intervals more than 50 ms vary from each other
- RMSSD: the root mean square of successive differences
- SDNN index: mean of the SD of all R-R intervals at every 5-min parts of the 24-h recording

The frequency domain indices were obtained as;

- VLF: very low frequency (the power ≤0.04 Hz)

- LF: low frequency (the power between 0.04 to 0.15 Hz)
- HF: high frequency power (the power between 0.15 and 0.40 Hz)
- Total spectral power: the power between the 0.0 and 0.40 Hz.

The measurements of power components were shown in definite values of power (ms^2).

Physical Activity

The physical activity of the subjects was standardized by using the International Physical Activity Questionnaire (IPAQ). The short version of IPAQ includes seven questions to determine the frequency and duration of subjects in potent, moderate-intensity, walking activity and the sitting time during a day. Scores are calculated in minutes per week and the sum of these scores has given an indicator of total physical activity.Additionally, as an energy expense indicator the metabolic cost (MET)- minutes per week was calculated. We multiplied the minutes per week for moderate and walking activity by average metabolic costs (MET) for these activities. (the IPAQ executive committee suggests 4 and 3.3, respectively).[13]

Statistical Analysis

We used SPSS (version 9.0) a commercially available statistical software package (Chicago, Illinois, US) for data analysis. For continuous data, the results are presented as mean value ± standard deviations (SDs) and for categorical data as proportions. The Kolmogorov-Smirnov test was applied to verify whether the continuous variables showed a normal distribution. Unpaired t test was used for continuous variables with normal distribution and Mann-Whitney test was used for continuous variables with non-normal distribution. The power spectral measurements were converted to natural logarithms to actualize normal distribution in analysis when necessary. Chi-square or Fischer's exact test whichever appropriate were applied to analyze categorical parameters. Two-sided level of significance was set at p values <0.05.

RESULTS

Table 1 shows the baseline clinical characteristics of the depressed patient group and the control group. Both groups had similar characteristics in terms of age, body mass index and physical activity. Furthermore, when compared with respect to biochemical parameters, the depressed patient group and control subjects had comparable parameters.

Table 1. Baseline characteristics of the study population

Variable	Patients with Depression (n=76)	Controls (n=75)	p value
Age (yrs)	37 ± 5	36 ± 5	0.877
Females (n)	54	49	0.773
Body mass index (kg/m2)	26.2 ± 4.1	25.3 ± 4.4	0.267
Total cholesterol (mg/dl)	190.4 ± 22.3	180.7 ± 34.1	0.094
HDL cholesterol (mg/dl)	46.4 ± 13.0	52.1 ± 9.0	0.125
LDL cholesterol (mg/dl)	96.4 ± 33.2	85.9 ± 32.1	0.082
Triglyceride (mg/dl)	155.6 ± 27.2	145.3 ± 44	0.097
Blood glucose (mg/dl)	71.5 ± 10	67.6 ± 9.7	0.213
Physical Activity			
Total physical activity (MET-min/week)	1216 ± 1029	1342 ± 1070	0.620
Vigorous-intensity ~~v~~activity (MET-min/week)	NA	NA	
Moderate-intensity activity (MET-min/week)	200 ± 305	220 ± 420	0.650
Walking (MET-min/week)	962 ± 450	915 ± 418	0.753

HDL, high density lipoprotein; LDL, low density lipoprotein; MET, metabolic equivalent. NA, not applicable

The data given in Table 2 contains the exercise test findings of the study groups. The exercise test was negative for the diagnosis of ischemia for all subjects. When the heart rate at peak exercise was compared with the resting heart rate, both groups were similar (p = 0.855 and 0.333). The HRR1 values in the depressed patient group were significantly lower than the control group (p <0.001). This result was largely based on high heart rate in the first minutes of recovery of depressed patients. The SBP values of both groups were similar at rest, but peak exercise SBP values in the

depressed patient group were remained significantly increased (p <0.001). In addition, the SBP values measured at the first, second and third minutes of recovery were higher in the depressed patient group when compared to controls. (p <0.001 first, second and third separately). Furthermore, the systolic blood pressure recovery index (SBPRI) assessed at 2nd and 3rd minutes was significantly higher in the depressed patient group than the control group (p <0.01 and 0.019). This finding indicates a delayed improvement in SBP at peak exercise in depressive patients.

Table 3 represents the HRV measurements of the study groups. The time domain and frequency domain parameters of the depressed patients were significantly lower than the control group.

DISCUSSION

As a result of this study, it was observed that depressed patients had decreased HRR1, extreme SBP responded with delayed recovery and attenuated HRV.

Table 2. Exercise test findings of the study population

Variable	Patients with Depression (n=76)	Controls (n=75)	p value
Resting heart rate (BPM)	85 ± 13	82 ± 17	0.333
Peak heart rate (BPM)	180 ± 9	180 ± 11	0.855
Heart rate at 1.min of recovery (BPM)	157 ± 9	148 ± 12	0.012
Heart rate at 2.min of recovery (BPM)	139 ± 10	134 ± 15	0.295
Heart rate at 3.min of recovery (BPM)	126 ± 9	120 ± 10	0.085
Heart rate recovery at 1 min (BPM)	23 ± 5	32 ± 6	<0.0001
Heart rate recovery at 2 min (BPM)	40 ± 9	47 ± 8	0.059
Heart rate recovery at 3 min (BPM)	53 ± 6	59 ± 12	0.044
Resting systolic blood pressure (mmHg)	115 ± 8	114 ± 10	0.762
Peak systolic blood pressure (mmHg)	175 ± 15	155 ± 12	<0.0001
Systolic blood pressure at 1.min of recovery (mmHg)	170 ± 11	146 ± 11	<0.0001
Systolic blood pressure at 2.min of recovery (mmHg)	164 ± 13	132 ± 15	<0.0001
Systolic blood pressure at 3. min of recovery (mmHg)	150 ± 15	125 ± 10	<0.0001
Blood pressure recovery index at 1 minute	0.96 ± 0.05	0.94 ± 0.05	0.882
Blood pressure recovery index at 2 minute	0.92 ± 0.03	0.85 ± 0.05	<0.0001
Blood pressure recovery index at 3 minute	0.86 ± 0.06	0.80 ± 0.10	0.015
METs	10.2 ± 1.2	11.8 ± 1.7	0.178

BPM, beat per minute; METs, metabolic equivalents.

Table 3. Heart rate variability measures of the study population

Variable	Patients with Depression (n=76)	Controls (n=75)	p value
SDNN (msec)	120.5 ± 24.3	149.3 ± 30.5	0.003
SDANN (msec)	110.1 ± 23.2	135.6 ± 30.3	0.004
pNN50 (msec)	10.2 ± 8.0	18.0 ± 9.6	<0.001
RMSSD (msec)	30.3 ± 8.3	39.5 ± 12.3	0.003
SDNN index (msec)	50.3 ± 12.4	64.5 ± 10.1	< 0.001
HF power (msec^2)	300.2 ± 155. 5	470.3 ± 225.	0.005
LF power (msec^2)	670.1 ± 232.1	800.9 ± 256.3	0.022
VLF power (msec^2)	1510 ± 722	2276 ± 936	< 0.001
LF/HF	2.2 ± 0.8	1.7 ± 0.6	0.042
Total spectral power (msec^2)	2336.7 ± 1213.1	3513.7 ± 1084.3	< 0.001

SDNN, the standard deviation (SD) of all R-R intervals; SDANN, the SD of the avareages of R-R intervals during all 5-min periods that constitute the 24-h day; pNN50, percent of R-R intervals differing more than 50 ms from each other; RMSSD, the root mean square of

successive differences; SDNN index, mean of the standard deviations of all R-R intervals for all 5-min segments of the 24-h recording; HF, high frequency; LF, low frequency; VLF,very low frequency.

The increased heart rate during exercise develops partly due to decreased parasympathetic tonus. Heart rate recovery at the first minute during exercise is explained by the reactivation of vagal tone.[8] Therefore, HRR1 after treadmill exercise was accepted as a marker of parasympathetic activity; decreased HRR has been associated with increased mortality.[9] Markedly attenuated HRR1 in the depressed patients indicates reduced vagal activity in these patients.

The parameters affecting blood pressure; are left ventricular systolic function, heart rate and peripheral vascular resistance. Thus, the change in SBP during exercise is effected by the parasympathetic and sympathetic system and results in a cardiovascular response.[14] The first response to the exercise is an increase in heart rate due to a decrease in parasympathetic tone. Subsequently, metabolic products and local mediators of exercise increase sympathetic stimulation and effect arterial tone. The observation of an extreme SBP response in depressive patients may result from the changes in this inexplicable mechanism. On the other hand, this finding may be a predictor of hypertension.[15]

Termination of exercise causes a decrease in heart rate and systolic blood pressure. This was different in our patients with depression. The heart rate at 2nd and 3rd minutes was similar between depression and control groups. However, blood pressure recovery indices were significantly higher in depressive patients at this time. This may be in consequence of the continuation of the increased sympathetic stimulation that increases peripheral resistance. Also, the finding that delayed post-exercise blood pressure response is related to sympathetic hyperactivity was supported by others.[10] Long-term activation of the sympathetic nervous system has been suggested as a possible mechanism revealing the relation of depression with cardiovascular diseases.[16]

Decreased HRV is an indicative of sudden cardiac events and death, with an important determinant of many cardiac events such as coronary artery disease, stable angina pectoris, heart failure after myocardial infarction, and death.[17] HRV is also used to describe the differences in autonomic functions. Decreased HRV finding is an indicative of a change in autonomic function in depressed patients.[18] The reduced SDNN observed in this study was sugested to be an indicative of decreased parasympathetic and increased sympathetic activity in the sinus node.[19] In addition, the RMSSD and pNN50 indices are defined as a sensitive and specific predictor of parasympathetic activity, with reduced RMSSD and pNN50 in depressed patients, a decrease in vagal activity compared to controls.[20] In addition, a meta-analysis showed that high-frequency HRV was significantly lower in patients with major depressive disorder.[21] Because high-frequency HRV is a marker of vagal activity, these findings support that depression is associated with reduced vagal inhibition.

This is the first study that examined HRR in unmedicated depression patients and healthy controls who were crosschecked according to physical activity. To date, a few studies have examined relations between depression and heart rate recovery with mixed populations. Hughes et al showed that the relationship between depression and HRR remained significant even after adjustments for resting HR, peak HR and total test time.[22] Von Kanel et al suggested that HRR1 was not associated with depressed mood in chronic heart failure.[23] It was found that BDI-II scores were not predictive of recovery even though there was a significant effect of major depression on 1-minute HRR.[24] Our results indicate that the association between depression and delayed HRR cannot completely be attributed to lower fitness. The autonomic disorder in depression is probably characterized by sympathetic hyperactivity and vagal hypo activity; previously recommended by Thayer et al.[25]

The main limitation of this study is small sample size that limits the generalizability of the results. Also, methods used to determine autonomic nervous system activity until now cannot be considered as a 'gold standard' for assessment of adrenergic function. This study has some strengths like including patients who were not taking medications which could influence HRR and HRV.

In this study, we used a standard treadmill exercise test and heart rate variability analysis in patients with depression and healthy controls. These results may indicate the alterations in autonomic nervous system control of the cardiovascular system in depression patients.

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