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The Effect of Divorce on Cardiac Autonomic Functions in Women: Relationship Between Hamilton Anxiety Score and Heart Rate Variability

Boşanmanın Kadınlarda Kardiyak Otonomik Fonksiyonlar Üzerine Etkisi: Kalp Hızı Değişkenliği ve Hamilton Anksiyete Değerlendirme Ölçeği Arasındaki İlişki

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This study was presented verbally at the European Congress of Cardiovascular Rehabilitation (June 14-15, 2016, Sophia Antipolis, France).

ABSTRACT Objective: The aim of this study was to evaluate the effects of divorce on cardiac autonomic functions by measuring heart rate variability (HRV) in women. **Material and Methods:** The study group consisted of 150 women who had been divorced in the past 12 months and the control group consisted of 50 age-matched married women, totally 200 women. Level of anxiety was assessed using Hamilton Anxiety Rating scale (HAM-A). Correlations between level of anxiety and HRV parameters were analyzed. **Results:** SDNN, SDANN index and SDNN index were significantly lower in the study group compared to the control group (129.8±31.8 vs 143.4±41.5 p=0.01, 119.0±30.6 vs 130.4±38.3 p=0.03 and 54.1±14.8 vs 59.9±18.0 p=0.02, respectively). rMSSD and pNN50 decreased in study group but not to a statistically significant degree (31.6±12.3 vs 35.8±17.7 p=0.06 and 11.0±8.0 vs 13.7±12.2 p=0.08, respectively). In study group, LF power and LF/HF ratio were significantly higher than those in control group (974.4±407.7 vs 822.1±429.4 p=0.03 and 4.14±4.54 vs 2.86±1.87 p=0.05, respectively). HAM-A score was negatively correlated with SDNN, SDANN, SDNN index, RMSSD, pNN50, HF power and positively correlated with LF power and LF/HF ratio. Nighttime SDNN and RMSSD were significantly lower in divorced women than those in married women (p=0.023 and p=0.046, respectively). According to multivariate logistic regression analysis, following factors were related to divorce: smoking, HAM-A score, SDANN and LF. **Conclusion:** Divorce has an unfavorable effect on cardiac autonomic functions. Cardiac autonomic dysfunction appear to parallel the level of anxiety. Divorce can increase cardiovascular disease risk in women.

Keywords: Divorce; anxiety; heart rate

ÖZET Amaç: Bu çalışmanın amacı boşanmanın kardiyak otonom fonksiyonlar üzerindeki etkisini kalp hızı değişkenliğini (KHD) ölçerek değerlendirmektir. **Gereç ve Yöntemler:** Çarpıntı şikayeti olan 200 kadın çalışmaya alınmıştır. Çalışma grubu son 12 ay içinde boşanmış 150 kadından, kontrol grubu ise 50 evli kadından oluşmuştur. Anksiyete seviyesi Hamilton Anksiyete Değerlendirme Ölçeği (HAM-A) kullanılarak ölçülmüştür. Anksiyete seviyesi ile KHD parametreleri arasındaki ilişki analiz edilmiştir. **Bulgular:** SDNN, SDANN indeks, SDNN indeks çalışma grubunda kontrol grubuna oranla anlamlı olarak düşük bulundu (sırası ile 129,8±31,8 vs 143,4±41,5 p=0.01, 119,0±30,6 vs 130,4±38,3 p=0,03 ve 54,1±14,8 vs 59,9±18,0 p=0,02). rMSSD ve pNN50 çalışma grubuna göre düşük saptandı ancak bu değerler istatistiksel anlamlılığa ulaşmadı (sırası ile 31,6±12,3 vs 35,8±17,7 p=0,06 ve 11,0±8,0 vs 13,7±12,2 p=0,08). Çalışma grubunda LF ve LF/HF oranı kontrol grubuna göre anlamlı olarak yüksek bulundu (sırası ile 974,4±407,7 vs 822,1±429,4 p=0,03 ve 4,14±4,54 vs 2,86±1,87 p=0,05). HAM-A puanı ile with SDNN, SDANN, SDNN indeksi, RMSSD, pNN50, HF arasında negatif, LF ve LF/HF oranı arasında pozitif bir korelasyon saptandı. Sirkadyan KHD analizinde gece dönemi SDNN ve RMSSD değerleri boşanmış kadınlarda evli kadınlara göre anlamlı olarak düşük bulundu. Multivaryant lojistik regresyon analizine göre sigara, HAM-A puanı, SDANN ve LF boşanma ile ilişkili bulundu. **Sonuç:** Çalışmamızın sonuçları boşanmanın kardiyak otonom fonksiyonlar üzerinde olumsuz etkileri olduğunu göstermektedir. Bu etki anksiyete seviyesi ile paralellik göstermektedir. Boşanma kadınlarda kardiyovasküler hastalık riskini artırıcı bir rol oynayabilir.

Anahtar Kelimeler: Boşanma; anksiyete; kalp hızı

Several studies have shown that marriage has protective effects against cardiovascular morbidity and mortality.[1-3] People who get divorced have increased risk of myocardial infarction and coronary heart disease.[4,5] Divorced couples have higher levels of stress hormones compared to the those of married couples.[6] Circulating stress hormones promotes an autonomic imbalance in favor of sympathetic nervous system. Autonomic nervous system plays a key role in the regulation of cardiovascular functions.[7] Impaired cardiac autonomic function is associated with coronary artery disease, myocardial infarction, congestive heart failure, ventricular fibrillation and increased cardiovascular mortality.[8-12] Although divorce is associated with an increased risk of cardiovascular diseases, its effects on cardiac autonomic function are not well known.

Heart rate variability (HRV) reflects the cardiac autonomic balance and indirectly measures sinoatrial node functions.[13] It is known that decrease in HRV is the earliest sign of cardiac autonomic dysfunction.[13-15] The aim of this study was to evaluate the effects of divorce on cardiac autonomic functions by measuring HRV in divorced women.

MATERIAL AND METHODS

STUDY POPULATION

Between April 2015 and January 2016, a total of 200 women within the age range of 18-40 years who complained of palpitations were enrolled in the study. The study group consisted of 150 women who had been divorced in the past 12 months and the control group consisted of 50 age-matched married women. The study was approved by the local ethics committee and was conducted in accord with the Helsinki declaration. The study was described to all subjects who gave informed consent before the beginning of the study.

Exclusion criteria were as follows: coronary artery disease, history of myocardial infarction or acute coronary syndrome, typical angina pectoris, dilated or hypertrophic cardiomyopathy, heart failure, nonsinus rhythm (e.g., atrial fibrillation), valvular disease, hyper or hypothyroidism, sustained or nonsustained ventricular tachycardia, and use of medicine such as β-blockers, antiarrhythmic, and antipsychotic drugs that may influence HRV parameters.

HRV

All subjects underwent 24 hour Holter monitoring using 3-channel tape recorders (CardioScan Premier 12 Holter System, China). Recordings lasting >22 hours and of sufficient quality for evaluation, were included in the analysis. For analysis of the data, 24-h recordings were split into daytime (06:00-22:00h) and nighttime (22:00-06:00h). Evaluations were performed by an experienced physicians. 24-hour ECG Holter recordings were used for HRV analysis Time domain HRV indexes were analyzed using a statistical method in which the square root of the mean squared differences of successive RR intervals (RMSSD), the standard deviation of all RR intervals (SDNN), the mean of the deviation of the 5 minute RR intervals over the entire recording (SDNN index), the standard deviation of the average RR intervals calculated over a 5 minute period of the entire recording (SDANN), and the proportion of adjacent RR intervals differing by >50 ms in the 24 hour recording (pNN50) were measured. Spectral analysis of HRV included total power which represents variability of the entire signal and is obtained by summing powers of each frequency band, high-frequency (HF) component (0,15-0,40 Hz): low frequency (LF) component (0,04-0,15 Hz). The low frequency power/ high frequency power (LF/HF) was calculated in all subjects. Time domain indices of HRV were also conducted during nighttime for all the participants. All measurements were performed according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[16]

Hamilton Anxiety Rating scale (HAM-A)

Level of anxiety was assessed using HAM-A, with a total score range of 0-56, where <17 indi-

cates mild, 18-24 mild to moderate, 25-30 moderate to severe and >30 severe anxiety.[17]

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as percentages. Statistical analyses were performed by using SPSS packed program (version 22 software, SPSS Inc., Chicago, Illinois, USA). Mean values for study and control patients were compared using the two sample t test. The correlations between the observed variables were examined by use of the Pearson's correlation test. Multivariate logistic regression analysis was performed to test associations between the divorce and patients' variables. P value < 0.05 was considered statistically significant.

RESULTS

The mean age of the study group was 30.3±8.1 years and the mean age of the control group was 31.0±8.0 years. There were no statistically significant differences between the two groups with respect to body mass index (BMI), alcohol consumption, blood pressure, ejection fraction, levels of fasting blood glucose, creatinine, hemoglobin, thyroid stimulating hormone. Smoking rate was significantly higher in divorce women compared to the married women. Compared to women who were married, lenght of marriage was shorter in divorced women (5.4±2.1 vs. 3.1±1.4 years p<0.001) (Table 1)

Average time elapsed after divorce was 7.8±3.5 months. HAM-A score was significantly higher in study group compared with the control group (29.5±9.5 and 15.5±6.2, p<0.0001, respectively). Minimum heart rate was similar in both groups, whereas maximum and average heart rate were significantly higher in study group when compared to control group. SDNN, SDANN SDNN index were significantly lower in the study group compared to the control group (p=0.01, p=0.03 and p=0.02, respectively). Likewise, RMSSD and pNN50 decreased in study group but not to a statistically significant degree (p=0.06 and 0.08 respectively). LF power and LF/HF ratio were significantly higher in the study group than those of the control group (Table 2).

TABLE 1: Clinical characteristics of the study and the control groups.

	Control group	Study group	P
Age (Years)	30.3±8.1	31.0±8.0	0.617
SBP (mmHg)	123±10.4	125.5±11.4	0.142
DBP (mmHg)	75.1±6.1	76.9±7.1	0.546
Alcohol consumption	3 (6)	14 (9.3)	0.464
Smoking, n (%)	4 (8)	26 (19.3)	0.044
BMI (kg/m²)	25.3±5.3	26.3±4.1	0.371
Fasting plasma glucose (mg/dl)	90.7±12.3	92.1±11.1	0.674
Creatinine (mg/dl)	0.79±0.8	0.81±0.22	0.605
Hemoglobin (g/dl)	12.9±2.1	12.2±3.4	0.562
TSH (µIU/ml)	1.92±0.8	1.87±0.9	0.723
EF (%)	62±5	63±7	0.875
Lenght of marriage (years)	5.4±2.1	3.1±1.4	<0.001

BMI: body mass index; **DBP:** diastolic blood pressure; **EF:** ejection fraction, **SBP:** systolic blood pressure, **TSH:** thyroid stiumulatiing hormone.

TABLE 2: HRV parameteres of the study and control groups.

	Control group	Study group	P
Hamilton anxiety score	15.5±6.2	29.5±9.5	<0.0001
Maximum HR	154.7±16.3	160.7±16.8	0.02
Minimum HR	49.6±8.9	48.6±8.8	0.48
Average HR	84.8±13.3	89.3±12.7	0.03
SDNN (ms)	143.4±41.5	129.8±31.8	0.01
SDANN (ms)	130.4±38.3	119.0±30.6	0.03
SDNN index (ms)	59.9±18.0	54.1±14.8	0.02
RMSSD (ms)	35.8±17.7	31.6±12.3	0.06
PNN50 (%)	13.7±12.2	11.0±8.0	0.08
LF	822.1±429.4	974.4±407.7	0.03
HF	461.1±437.4	376.4±276.5	0.11
LF/HF	2.86±1.87	4.14±4.54	0.05
Sympathetic (%)	89.4±5.5	91.4±3.8	0.02
Parasympathetic (%)	10.5±5.5	8.5±3.8	0.02
Ratio S/P	12.3±9.9	13.7±8.5	0.3

HF: high frequency; **HR:** heart rate, **LF:** low frequency, **pNN50:**The proportion of adjacent RR intervals differing by >50 ms in the 24 hour recording, **RMSSD:** The square root of the mean squared differences of successive normal to normal intervals, **SDANN:** The standard deviation of the average normal to normal intervals calculated over 5 minute period of the entire recording, **SDNN:** the standard deviation of all normal to normal intervals, **SDNN index:** the mean of the deviation of the 5 minute normal to normal intervals over the entire recording.

Divorced women had an increase of sympathetic activity and decrease of parasympathetic activity compared to the married women. There were significant negative correlation between HAM-A score and HRV parameters. HAM-A score was positively correlated with sympathetic activity and negatively correlated with parasympathetic activity (Table 3).

In circadian HRV analysis, we found that nighttime SDNN and RMSSD were significantly lower in divorced women than those in married women (Table 4). According to multivariate logistic regression analysis, following factors were related to divorce: smoking, HAM-A score, SDANN and LF (Table 5).

DISCUSSION

In this study, we compared the HRV parameters in divorced and married women with similar cardiovascular risk profile. Our results suggested that divorced women has increased sympathetic activity compared to the married women. Time domain markers such as SDNN, SDANN, SDNN index were found to be significantly lower in divorced women, which may reflect a predominant sympathetic stimulation of the heart. Compared with the married women, divorced women had significantly higher values for LF power and LF/HF ratio, indicating elevated sympathetic nerve activity. It appears that, parasympathetic function was less compromised in divorced women. RMSSD, pNN50 and HF power which reflect parasympathetic activity were not significantly affected when two groups were compared. Additionally, nocturnal HRV parameters including SDNN and RMSSD were significantly different in divorced women when compared to married women.

HAM-A scale was developed in 1959 by Max Hamilton. It consists of 14 items to evaluate the severity of a patients' anxiety.[17] In our study, we found relationship between HAM-A score and all HRV parameters. Subjects with higher HAM-A scores had significantly lower HRV parameters and had significantly greater reductions in HF power.

TABLE 3: Correlation between Hamilton anxiety score and HRV parameters.

Parameters	r	p
SDNN (ms)	-0.726	<0.0001
SDANN (ms)	-0.730	<0.0001
SDNN index (ms)	-0.533	<0.0001
RMSSD (ms)	-0.411	<0.0001
pNN50 (%)	-0.445	<0.0001
LF	0.225	0.001
HF	-0.399	<0.0001
LF/HF	0.267	<0.0001
Sympathetic	0.179	0.011
Parasympathetic	-0.179	0.011
Ratio S/P	0.114	0.108

HF: high frequency; **LF:** low frequency; **pNN50:** The proportion of adjacent RR intervals differing by >50 ms in the 24 hour recording; **RMSSD:** The square root of the mean squared differences of successive normal to normal intervals, **SDANN:** The standard deviation of the average normal to normal intervals calculated over 5 minute period of the entire recording,SDNN; the standard deviation of all normal to normal intervals, **SDNN index:** the mean of the deviation of the 5 minute normal to normal intervals over the entire recording.

TABLE 4: Circadian time domain analysis of HRV in study and control groups.

Asleep (22:00-6:00)	Control group	Study group	P
SDNN (ms)	105.6±32.1	96.1±22.8.	0.023
RMSSD (ms)	39.1±16.4	35.1±11.1	0.046
PNN50 (ms)	17.5±10.4	13.9±9.3	0.05

pNN50: The proportion of adjacent RR intervals differing by >50 ms in the 24 hour recording; **RMSSD:** The square root of the mean squared differences of successive normal to normal intervals; **SDNN:** the standard deviation of all normal to normal intervals.

TABLE 5: Multivariate regression analysis of variables.

Parameters	Odds ratio	95% C.I.	P
Smoking	0.047	0.004-0.623	0.020
Hamilton score	2.000	1.533-2.609	0.000
SDANN (ms)	1.095	1.095-1.013	0.022
SDNN (ms)	0.971	0.902-1.045	0.430
RMSSD (ms)	1.034	0.830-1.323	0.693
pNN50 (%)	1.034	0.778-1.372	0.820
HF	0.998	0.993-1.003	0.334
LF	1.005	1.002-1.008	0.003

HF: high frequency; **LF:** low frequency; **pNN50:** The proportion of adjacent RR intervals differing by >50 ms in the 24 hour recording, **RMSSD:** The square root of the mean squared differences of successive normal to normal intervals; **SDANN:** The standard deviation of the average normal to normal intervals calculated over 5 minute period of the entire recording; **SDNN:** the standard deviation of all normal to normal intervals.

These results suggested that divorced women with higher HAM-A scores have significantly greater reductions in parasympathetic activity and have significantly higher sympathetic activity.

Several studies have indicated that marriage has protective effects against cardiovascular disease.[1-4] Being married may protect a person against heart disease through several mechanisms; marriage is an important source of social support, presence of a spouse may result in more positive health-related behaviors, and increasing socioeconomic status may influence the use of health resources especially in women.[18,19] Negative life events like divorce could affect cardiovascular system. There are many factors that have major impact on cardiovascular system during the divorce process. It has been shown that divorced adults have significantly higher resting blood pressure and have a higher incidence of coronary artery disease.[4,20] A study by Engstrom et al. assessed the levels of inflammatory proteins and incidence of cardiovascular disease in healthy men. They found that the incidence of coronary events, and levels of inflammatory proteins were significantly increased in divorced men.[21] The MIDUS study evaluated the differences in HF-HRV by traditional marital status categories (married, divorced, widowed, and never married).[3] The study authors found that increases in marital satisfaction and support over 10 years were associated with higher HF-HRV.

Kriegbaum et al. found an association between broken partnership and MI. They showed that risk of MI was higher in the same year following broken partnership in women, whereas men has an excess risk of MI in the year following broken partnership.[5] Another study demonstrated stronger association between divorce and MI in women compared to men.[22] These results suggest that impacts of divorce on men and women may differ.

Kemp et al. investigated heart rate and HRV in 15105 participants who were recruited in ELSA-Brasil study. They reported that use of antidepressants was associated with increases in heart rate and decreases in HRV.[23] Levy measured HRV in patients with bipolar disorder. Their analysis indicated that bipolar disorder patients with high illness severity reported more symptoms of trait-anxiety and exhibited lower SDNN index and evaluated LF/HF ratio than patients with low illness severity.[24] Likewise, experiencing the anxiety of divorce might negatively affect the cardiovascular system.

Sinoatrial node is regulated by sympathetic and parasympathetic nervous system. Autonomic influences on the sinoatrial node can be measured by HRV.[1] Among HRV indices, SDNN, SDANN, LF reflect sympathetic activity, whereas RMSSD and pNN50 and HF reflect parasympathetic activity. HRV provides information about cardiovascular morbidity and mortality. HRV is reduced in patients with coronary artery disease, metabolic syndrome, obesity and hypertension and reduced.[8-11,25-27] HRV is associated with increased risk of malignant ventricular arrhythmias and mortality. In our study, divorced women showed lower level of HF power than the married women but the difference did not reach statistical significance. But we found a significant negative correlation between HF power and HAM-A score. These results indicate that parasympathetic activity was affected to a lesser degree than sympathetic activity at the same level of anxiety. Moreover, as the severity of anxiety increases, the impairment of the autonomic nervous system activity also rises, which is suggested by the correlation analysis.

Despite the consistent association between marriage and health, not all marriages has the same protective effects on health.[1-4,18,19] For example, people who have less satisfying marriages have higher risk of myocardial infarction and heart failure compared to those who have more satisfying marriages.[28,29] It has been shown that couples were less satisfied with their relationship when the female member of the couple was Type A rather than Type B.[30] Spouses who are Type A are more likely to respond with negative behavior when they are experiencing prolonged exposure to stress and

these behaviors may interfere with the formation of intimate relationship.[31,32] If a woman has type A personality or aggressive nature, which may cause for divorce, she may show a predominant sympathetic stimulation.[33] In the current study, we did not use personality tests. In order to better evaluate the influence of divorce on psychological status of the women, the study included only the women who had been divorced in the past 12 months. Because the subjects were only assessed once, no temporal conclusions can be drawn; it is not possible to know whether a woman has type A personality of aggressive nature, which may cause for divorce. Based on multivariate analysis, we found significant associations between divorce and HAM-A score, SDANN and LF.

We found higher smoking rates in the divorced women than in the married women. It is well established that smoking alters HRV parameters and after smoking cessation HRV parameters returns to normal.[34]

To the best of our knowledge, our study is the first study to investigate the effects of divorce on HRV parameters. Our findings suggest that divorce could be a risk factor of a predominant sympathetic stimulation of the heart and less compromised parasympathetic function. We found relationship between HAM-A score and HRV parameters. Subjects with high HAM-A scores have increased activation of the sympathetic nervous system.

CONCLUSION

The increase in divorce rate over the last decades is emerging as an public health problem. Divorce may have a negative impact on cardiovascular system. HRV is simple and inexpensive measure that can be used to assess early cardiac effects of divorce in women.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Abdülmelik Yıldız, Cennet Yıldız, Ahmet Karakurt;* ***Design:*** *Abdülmelik Yıldız, Cennet Yıldız, Ahmet Karakurt;* ***Control/Supervision:*** *Abdülmelik Yıldız;* ***Data Collection and/or Processing:*** *Abdülmelik Yıldız, Cennet Yıldız, Ahmet Karakurt;* ***Analysıs and/or Interpretatıon:*** *Abdülmelik Yıldız, Cennet Yıldız;* ***Literature Review:*** *Cennet Yıldız, Ahmet Karakurt;* ***Writing the Article:*** *Abdülmelik Yıldız, Cennet Yıldız, Ahmet Karakurt;* ***Critical Review:*** *Ahmet Karakurt;* ***References and Fundings:*** *Abdülmelik Yıldız;* ***Materials:*** *Abdülmelik Yıldız, Cennet Yıldız Ahmet Karakurt.*

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