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The Effect of Smoking on the Baroregulatory System; Heart Rate Turbulence

Sigara Alışkanlığının Baroregülatuvar Sisteme Olan Etkisi; Kalp Hızı Türbülansı

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ABSTRACT

Introduction: *Smoking has been known to cause various adverse cardiovascular reactions. Our study was conducted to demonstrate the chronic effects of smoking on baroregulatory function by using heart rate turbulence (HRT) parameters among asymptomatic smokers.*

Materials and Methods: *Sixty four smokers with histories of incessant smoking for at least one year (group 1) and 30 non-smokers (group 2) were enrolled in this study. Addiction of smoking was graded according to the modified Fagerström test for nicotine dependence (m-FNDT). Each smoker was conferred a nicotine dependence index (NDI) according to the m-FNDT. The values of HRT (TO: Turbulence onset, TS: Turbulence slope) were compared between two groups along with basic clinical, echocardiographic and Holter parameters. And the relationship between HRT and m-FDT was analyzed.*

Results: *There was no significant difference the basic clinical and echocardiographic features ($p> 0.05$). The mean value of TO was higher significantly ($p< 0.05$) in group 1 than group 2, the mean values of TS was not different significantly between the two groups. The value of NDI was positively correlated with the value of TO ($p< 0.05$).*

Conclusion: *Smoking impaired baroregulatory function especially in TO, even in asymptomatic smokers.*

Key Words: *Smoking; heart rate; nicotine; tobacco use disorder.*

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ÖZET

Giriş: *Sigaranın kardiyovasküler sisteme olan zararlı etkileri bilinmektedir. Çalışmamızın amacı sigara içiminin baroregülatuvar mekanizmaya olan etkilerini, kalp hızı türbülansını kullanarak normal kişilerle karşılaştırmaktır.*

Materyal ve Metod: *En az bir yıldır sigara içme öyküsü olan asemptomatik 64 kişi grup 1 olarak kabul edildi. Aynı klinik özelliklere sahip asemptomatik sigara alışkanlığı olmayan 30 kişi grup 2*

olarak düzenlendi. Çalışmaya alınan grup 1'deki sigara içicilerinin nikotin bağımlılık indeksi (NBİ) modifiye-Fagerström Nikotin bağımlılık testi (m-FNBT) kullanılarak hesaplandı. Tüm gruplardaki hastalara 24 saatlik elektrokardiyografi Holter takılarak, tamamının HRT (TO, total onset ve TS, total slope) ile bazal ekokardiyografik parametreleri hesaplandı.

Bulgular: *Gruplar arasında taşıdıkları demografik, klinik ve ekokardiyografik özellikler açısından istatistiksel olarak anlamlı bir fark saptanmadı (p> 0.05). Grup 1'de ortalama TO değeri anlamlı olarak yüksek iken (p< 0.05), ortalama TS değerleri arasında iki grup arasında istatistiksel olarak anlamlı bir fark saptanmadı (p> 0.05). Grup 1'de hesaplanan NBİ değeri ile ortalama TO arasında pozitif korelasyon saptandı (p< 0.05).*

Sonuç: *Kronik sigara içicisi olanlarda, aynı özelliklere sahip içmeyen gruba oranla baroregülatuvar mekanizmada (özellikle TO) bozulma olduğu saptandı.*

Anahtar Kelimeler: *Sigara içme; kalp hızı; nikotin; tütün kullanımı.*

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INTRODUCTION

Cigarette smoking is an important and independent risk factor for cardiovascular morbidity and mortality[1]. Some studies suggest that smokers have a sympathetic hyperactivity compared with non-smokers[2,3]. Smoking increases plasma catecholamines and cardiac norepinephrine spillover and results in an increase in blood pressure, heart rate, ventricular precystole (VPC) and sympathetic outflow that all of them are potentially arrhythmogenic[4]. Several studies indicate an association between smoking and autonomic dysfunction[5,6]. Also these studies suggested that baroreflex function is impaired in normal person with smoking. Impaired cardiac autonomic function has been associated with cardiac vulnerability and may represent an important pathophysiologic mechanism linking cigarette smoking and risk of cardiac mortality. It has been shown that smoking as a independent risk factor for recurrence of sudden cardiac death (SCD)[7]. SCD from arrhythmia is a major cause of mortality.

Risk stratification for ventricular arrhythmias and sudden cardiac death (SCD) is enormous importance for the health care community. The major problem in risk stratification is the relative low positive predictive value of most tests such as heart rate variability parameters, QT dispersion, late potentials or programmed stimulation. Heart rate turbulence (HRT) is a relatively new parameter used as a tool for evaluating cardiac autonomic tone. Abnormal HRT reflects increased sympathetic tone and abnormal baroreflex sensitivity, both facilitate ventricular arrhythmias[8,9]. Also these studies showed that HRT is a valuable tool in the setting of risk stratification. Furthermore, it is easy to perform without the need for additional time-consuming tests or procedures[10]. Our study was conducted to demonstrate the chronic effects of smoking on baroregulatory function by using HRT parameters among asymptomatic smokers.

MATERIALS and METHODS

Patients

Sixty four smokers with histories of incessant smoking for at least 1 year (group 1, 35 males and 29 females; mean age, 29.9 ± 6.6 years) and thirty non-smokers (group 2, hospital staff; 16 males and 14 females; mean age, 29.0 ± 6.1 years) were enrolled in this study. A complete physical and echocardiographic examination was performed before the study. Routine 12-lead electrocardiography (ECG) of the patients was also evaluated prior to the ambulatory rhythm monitoring. All study subjects were free from the other risk factors for coronary artery disease (hypertension, diabetes mellitus, etc.), and no subject was receiving any medication. Informed consent was obtained from all patients and the protocol was approved by the ethics committee. All participants were asked to refrain from alcohol and caffeine-containing beverages and strenuous exercise for 24 hours prior to study and during 24 hours holter recording. All smokers were also asked not to smoke cigarettes for at least 8 hours before the study and during holter recording.

Fagerström Test for Nicotine Dependence

Addiction of smoking was graded according to the modified Fagerström test for nicotine dependence (m-FNDT) [11]. Each smoker was conferred a nicotine dependence index (NDI) according to the m-FNDT.

Measurement of Heart Rate Turbulence

24-hour Holter recordings of all patients were analyzed to obtain the HRT parameters of TO and TS. Recordings

were performed with a GE Marquette SEER system digitizing at 125 samples per second (GE Marquette, Milwaukee, WI). QRS detection, morphology classification (normal, aberrant, premature aberrant) and measurement of the RR interval were automatically performed by the system. All Holter files were reviewed and manually corrected.

HRT analysis was performed on sequences of sinus RR intervals after VPB. The evaluated sinus rhythm immediately before and after the VPB was free from any arrhythmia or other artifacts. HRT after a VPB comprises two parameters: TO, which represents the initial acceleration (shortening of R-R intervals); and TS, which represents the subsequent deceleration (prolongation of R-R intervals)[12]. In mathematical terms, TO (%) (normal < 0) is the difference between the sum of the first two R-R intervals after the compensatory pause following a VPB and the sum of the last two R-R intervals preceding the VPB, divided by the sum of the last two R-R intervals preceding the VPB. TS (normal > 2.5 ms/R-R interval number) was accepted as the steepest regression line between the R-R interval count and the duration. The average of HRT values measured for all convenient VPBs was accepted as the final HRT value to characterize the patient.

For the risk stratification HRT values are classified into three categories:

1. Category 0; TO and TS are normal,
2. Category 1; 1 of TO or TS is abnormal,
3. Category 2; both TO and TS are abnormal.

If HRT cannot be calculated because no or too few suitable VPC tachograms are found in the recording, patients who are otherwise in sinus rhythm are classified as HRT category 0[9,10,13].

The presence of potential causes of impaired HRT including CHF, moderate or severe degrees of any valvular regurgitation or co-existent valvular stenosis, previous MI, angina or angina-like symptoms, diabetes mellitus and obstructive sleep apnea, were accepted as exclusion criteria. Those patients with pacemaker rhythm, atrial fibrillation (AF), left bundle branch block, right bundle branch block, any sign of ischemia on the initial ECG and echocardiographic evidence of LV hypertrophy, systolic dysfunction, wall motion abnormalities or pericardial disease were also excluded from the study.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using student t-test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. Pearson correlation coefficients examined the degree of association between examined variables. p value < 0.05 was considered as significant. The variables for which the unadjusted p value was < 0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. p value < 0.05 was considered as significant and confidence interval (CI) was 95%. All statistical analyses were performed with the SPSS version 15 (SPSS, Inc., Chicago, Illinois).

RESULTS

Clinical characteristics of both groups are shown in Table 1. There was no significant difference between two groups in demographics of age, blood pressure, and body mass index (p> 0.05). On physical examination, no clinically significant disorder was detected in any of the study subjects. Echocardiographic examination revealed no significant cardiac disorder. All study subjects had sinus rhythm. The 24 hour baseline heart rate tended to be significantly higher in smokers than in non-smokers (76.25 ± 6.67 vs. 71.87 ± 7.44 beats/min, p< 0.001). Between the Holter parameters, group 1 patients had a significantly higher mean TO value than group 2 (group 1: 0.89 ± 0.5, group 2: 0.08 ± 0.06; p< 0.001), whereas mean TS values was smaller in group 1 than group 2, but not significantly (group 1: 2.41 ± 3.06, group 2: 3.14 ± 2.33; p= 0.212). In heart rate turbulence analyses, turbulence onset values was > 0% in 48 patient in Group 1, and six patient in Group 2 (p< 0.05), turbulence slope values was < 2.5 ms/RRI 20 patient in Group 1, and four patient in Group 2 (p< 0.05). When HRT parameters were compared to the risk stratification categories, there were significant differences between smokers and non-smokers for all categories (category 0= group 1 21.9% n= 14, group 2 73.3% n= 22 p< 0.05; category 1= group 1 50% n= 32, group 2 20% n= 6 p< 0.001; category 2= group 1 28.1% n= 18, group 2 6.3% n= 6.7 p< 0.001, respectively) (Figure 1). The mean value of m-FNDT score in smoking group was found to be 4.61 ± 2.28, while the mean value of smoking duration was 3.81 ± 2.08 years. In the risk stratification categories analyses, m-FNDT score was 2.14 ± 1.08 in category 0, 4.31 ± 1. 51 in category 1 and 7.06 ± 1.70 in category 0. A significant relationship

Table 1. The comparison of general features, echocardiographic and Holter parameters between group 1 (smoking) and group 2 (non-smoking) patients

	Smokers (n= 64)	Non-smokers (n= 30)	p value
Age (years)*	29.9 ± 6.6	29.0 ± 6.1	NS
Sex (male) %*	54.7%	53.3%	NS
BMI (kg/m^2)*	23.54 ± 3.17	23.86 ± 3.22	NS
Systolic blood pressure (mmHg)*	110.17 ± 14.14	105.50 ± 11.32	NS
Diastolic blood pressure (mmHg)*	65.70 ± 9.18	65.33 ± 6.68	NS
Heart rate (bpm)*	76.25 ± 6.67	71.87 ± 7.44	p= 0.008
LVEF (%)*	61.32 ± 5.23	61.92 ± 5.68	NS
LVEDD (cm)*	4.32 ± 0.31	4.28 ± 0.33	NS
TO (%)*	0.89 ± 0.5	0.08 ± 0.06	p< 0.001
TS (ms/beat)*	2.41 ± 3.06	3.14 ± 2.33	NS (p= 0.212)
Cigarettes/day	16.22 ± 8.45		
Years of smoking	3.81 ± 2.08		

* Values are mean ± SD.

LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; BMI: Body mass Index; NS: Non-significant; TO: Turbulence onset; TS: Turbulence slope.

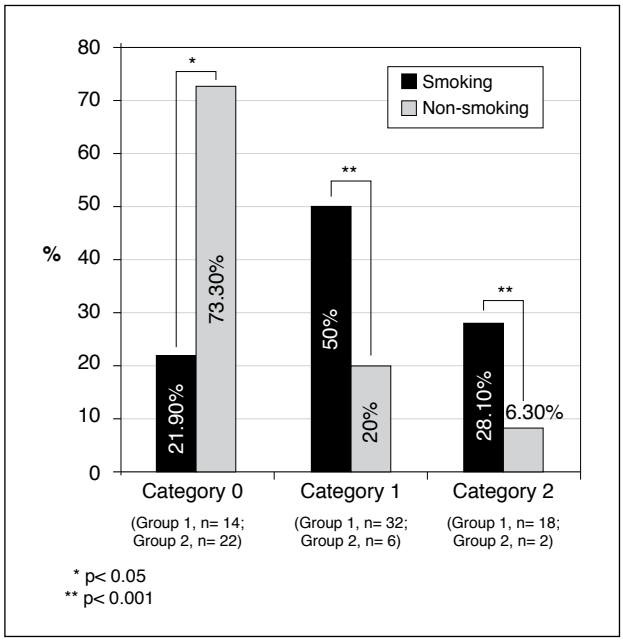

Figure 1. Heart rate turbulence groups values of the two study groups.

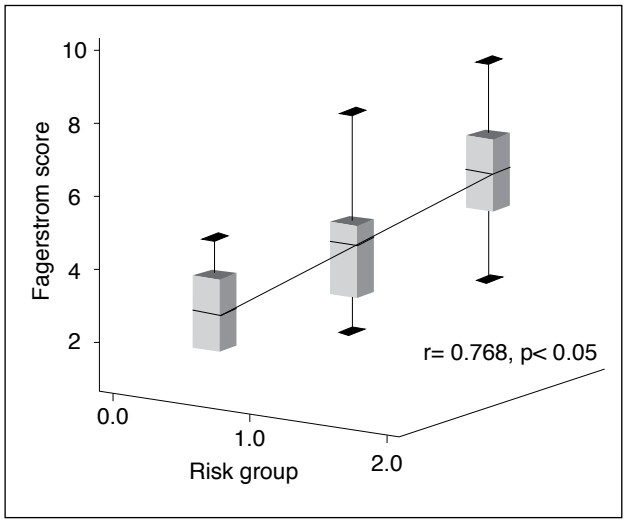

Figure 2. Correlation between risk groups and Fagerstrom score.

was observed at the value of the m-FNDT score and the risk stratification categories (r= 0.768, p< 0.05, Figure 2). A strong positive correlation was also found between the value of NDI and the value of TO (r= 0.845, p< 0.001).

DISCUSSION

The principal findings of our study are;

I. Smoking group had a significantly higher mean TO value when compared to non-smokers;

II. When HRT parameters were compared to the risk stratification categories, there were significant differences between smokers and non-smokers;

III. A significant relationship was observed at the value of the m-FNDT score and the smoking group risk stratification categories;

IV. The NDI of the cigarette smoking group is positively correlated with the value of TO;

V. For an abnormal TO value (≥ 0), the number of patients in smoking group were statistically higher than non-smoking group;

VI. For an abnormal TS value (< 2.5 ms/R-R), the number of patients in smoking group were statistically higher than non-smoking group;

VII. The 24 hour baseline heart rate tended to be significantly higher in smokers than in non-smokers.

Cigarette smoking is a major and an independent risk factor for cardiovascular morbidity and mortality. Previous reports suggested that chronic smokers have a higher pulse rate and blood pressure compared with non-smokers[3,14,15]. Smoking has some adverse effects to the neurocardiovascular regulation. These effects have been attributed to the nicotine, the main constituent of cigarette[16]. In addition to nicotine, tobacco smokers inhale over four thousand chemicals that have possible pharmacological and toxicological effects. Some investigators showed the mechanism of increasing blood pressure and heart rate by nicotine; activation of the sympathetic nervous system with a release of norepinephrine and epinephrine, vasopressin release or by direct effects on endothelial function[17,19]. Nicotine has a wide spectrum of cardiac rhythm disorders, including transient sinus arrest and/or bradycardia, sinus tachycardia, atrial fibrillation, sinoatrial block, AV block, and ventricular tachyarrhythmias[20-22]. Impaired HRT is associated with an increased risk of mortality and susceptibility to life threatening arrhythmias[8-10]. In our study we found a strong correlation between smoking and impaired HRT. The common point of the underlying reason is mostly cardiac autonomic system dysfunction. Our findings suggested that as the smoking dependence gets worse, the cardiac rhythm disorders get more. Several previous studies have focused on the effect of cigarette smoking on cardiac autonomic system. Several investigators have reported that reduced heart rate variability (HRV) in smoking subjects, is a strong indicator for autonomic disturbances that may be involved in the mechanism promoting arrhythmias and sudden death in smoking subjects[23-26]. Previous studies showed that there is a strong correlation between HRT and HRV[27,28]. Yap et al., found that TS and TO has significant correlation with almost all heart rate variability time domain parameters[28]. Our study support that there is a close relation between our results and previous HRV studies for smoking. Interestingly Rosamond et al., found that smoking-associated CVD risk appears to be the greatest among younger smokers[29]. Together with the previous results, our findings suggest that impairment of cardiovascular autonomic system in healthy long-term adult smokers may be a possible component of deleterious effect of smoking.

Studies in normal populations suggested that the 24 hours baseline heart rate measured by ambulatory monitoring, might be a predictor of total, cardiovascular and non-cardiovascular mortality[30-35]. In our results, the 24 hour baseline heart rate tended to be significantly higher in healthy young smokers than in non-smokers. Previous studies clearly showed the effect of the nicotine on the heart rate[15,17,22].

The main limitation of our study seems to be the small sample size. Because the small sample size results in low statistical power for equivalency testing, negative results may be simply due to chance. However, it should be taken into account that establishing a smoking group without co-morbidities (e.g. diabetes mellitus, hypertension, cardiovascular and renal disorders) is difficult. Secondly, we did not make subgroup analysis in our study according to the smoking grade because the classification of patients according to NDI would decrease the sample size in subgroups. In this situation, the statistical power of these subgroups would decrease, too. Also we did not check the impact of circadian variation. Diurnal fluctuations in autonomic tone suggest one value for HRT in 24 hours. This may also influence the results.

Our study demonstrated that the autonomic modulation of the heart is reduced in smokers and it becomes apparent particularly during parasympathetic manoeuvre and that the impaired autonomic cardiac control may in part explain the mechanism promoting arrhythmias and sudden death in smoking subjects. To achieve a meaningful reduction in the societal burden of coronary heart disease, cigarette smoking in young adults must be targeted for reduction.

REFERENCES

1. *World Health Organization. The World Health Report, 2002. Reducing Risks, Promoting Healthy Life. Geneva (Switzerland): World Health Organization, 2002.*
2. *Gidding SS, Xie X, Liu K, Manolio T, Flack JM, Gardin JM. Cardiac function in smokers and non-smokers: the CARDIA study. J Am Coll Cardiol 1995;26:211-6.*

3. *Hill P, Wynder EL. Smoking and cardiovascular disease: effect of nicotine on the serum epinephrine and corticoids. Am Heart J 1974;87:491-6.*
4. *Narkiewicz K, van de Borne PJ, Hausberg M, Cooley RL, Winniford MD, Davison DE, et al. Cigarette smoking increases sympathetic outflow in humans. Circulation 1998;98:528-34.*
5. *Goldenberg I, Moss AJ, McNitt S, Zareba W, Daubert JP, Hall WJ, et al. Cigarette smoking and the risk of supraventricular and ventricular tachyarrhythmias in high-risk cardiac patients with implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 2006;17:931-6.*
6. *Zhu B, Parmley WW. Hemodynamic and vascular effects of active and passive smoking. Am Heart J 1995;130:1270-5.*
7. *Hallstrom AP, Cobb LA, Ray R. Smoking as a risk factor for recurrence of sudden cardiac arrest. N Engl J Med 1986;314:271-5.*
8. *Mrowka R, Persson PB, Theres H, Patzak A. Blunted arterial baroreflex causes "pathological" heart rate turbulence. Am J Physiol Regul Integr Comp Physiol 2000;279:R1171-5.*
9. *Yap YG, Camm AJ, Schmidt G, Malik M. Heart rate turbulence is influenced by heart rate, age, LVEF, NYHA class, diabetes, drugs and frequency of ventricular ectopics in patients after acute myocardial infarction-EMIAT substudy (abstr). J Am Coll Cardiol 2001;37(Suppl A):133A.*
10. *Barthel P, Schneider R, Bauer A, Ulm K, Schmitt C, Schömig A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 2003;108:1221-6.*
11. *Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nictoine dependence: a revision of the Fagerstrom tolerance questionnaire. British Journal of Addictions 1991;86:1119-27.*
12. *Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;9162:1390-6.*
13. *Exner DW, Kavanagh KM, Slawnych MP, Mitchell LB, Aggarwal SG, Aggarwal SG, et al. On behalf of REFINE Investigators. Noninvasive risk assessment early after a myocardial infarction the REFINE study. J Am Coll Cardiol 2007;50:2275-84.*
14. *Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976;296:573-7.*
15. *Niedermaier ON, Smith ML, Beightol LA, Zukowska-Grojec Z, Goldstein DS, Eckberg DL. Influence of cigarette smoking on human autonomic function. Circulation 1993;88:562-71.*
16. *Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: Implications for nicotine replacement therapy. J Am Coll Cardiol 1997;29:1422-31.*
17. *Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smokingassociated hemodynamic and metabolic events. N Engl J Med 1976;295:573-7.*
18. *Waeber B, Schaller MD, Nussberger J, Bussien JP, Hofbauer KG, Brunner HR. Skin blood flow reduction induced by cigarette smoking: role of vasopressin. Am J Physiol 1984;247:895-901.*
19. *Celermajer DS, Sorensen KE, Georgeakopoulos D, Bull C, Thomas O, Robinson J, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation 1993;88: 2149-55.*
20. *Benowitz N. Drug therapy: pharmacologic aspects of cigarette smoking and nicotine addiction. N Engl J Med 1988;319:1318-30.*
21. *Escobedo LG, Zack MM. Comparison of sudden death and nonsudden coronary death in the United States. Circulation 1996;93:2033-6.*
22. *Stewart PM, Catterall JR. Chronic nicotine ingestion and atrial fibrillation. Br Heart J 1985;54:222-3.*
23. *Eryonucu B, Bilge M, Güler N, Uzun K, Gencer M. Effects of cigarette smoking on the circadian rhythm of heart rate variability. Acta Cardiol 2000;55:301-5.*
24. *Kupari M, Virolainen J, Koskinen P, Tikkanen MJ. Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. Am J Cardiol 1993;72:897-903.*
25. *Barutcu I, Esen AM, Kaya D, Turkmen M, Karakaya O, Melek M, et al. Cigarette smoking and heart rate variability: dynamic influence of parasympathetic and sympathetic maneuvers. Ann Noninvasive Electrocardiol 2005;10:324-9.*
26. *Levin FR, Levin HR, Nagoshi C. Autonomic functioning and cigarette smoking: heart rate spectral analysis. Biol Physchiatry 1992;31:639-43.*
27. *Watanabe MA. Heart rate turbulence: a review. Indian Pacing and Electrophysiology Journal (ISSN 0972-6292) 2003;3:10-22.*
28. *Yap YG, Camm AJ, Schmidt G, Malik M. Heart rate turbulence is influenced by sympathovagal balance in patients after myocardial infarction-EMIAT substudy. Eur Heart J 2000;21(Suppl.):474.*
29. *Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics 2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25-146.*
30. *Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Blunted heart rate dip during sleep and all-cause mortality. Arc Intern Med 2007;167:2116-21.*
31. *Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. Am Heart J 1987;113:1489-94.*
32. *Benetos A, Rudnichi A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a French population. Role of age, gender, and blood pressure. Hypertension 1999;33:44-52.*
33. *Reunanen A, Karjalainen J, Ristola P, Heliovaara M, Knekt P, Aromaa A. Heart rate and mortality. J Intern Med 2000;247:231-9.*
34. *Greenland P, Daviglius ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and non-cardiovascular mortality. Am J Epidemiol 1999;149:853-62.*
35. *Kristal-Boneh E, Silber H, Harari G, Froom P. The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight year follow-up of 3527 male Israeli employees (the CORDIS Study). Eur Heart J 2000;21:116-24.*