Heart rate turbulence in patients with stable coronary artery disease and its relationship with the severity of the disease

Kararlı koroner arter hastalarında kalp hızı türbülansı ile koroner arter hastalığının ciddiyeti arasındaki ilişki

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ABSTRACT

Objective: Heart rate turbulence (HRT) indicates the impairment of cardiac autonomic function. With the literature containing insufficient information on HRT in stable coronary artery disease (CAD), this study aimed to investigate the role of HRT in patients with stable CAD.

Methods: The study included 58 patients (mean age: 58.9±10.0 years; 25 male) with documented CAD and demonstrating ventricular premature complexes on Holter monitoring, and a control group of 52 patients (mean age: 55.9±9.3 years; 36 male) with no history of CAD and demonstrating ventricular premature complexes. HRT parameters such as turbulence onset (TO) and slope (TS) were analyzed. Angiographic Gensini score were used to evaluate CAD severity.

Results: There was a significant difference in HRT parameters between the 2 groups. TO: 0.47±1.52% *vs.* -1.61±2.0% (p=0.001) and TS: 4.7±3.0 *vs.* 6.4±3.7 ms/RR (p=0.009) in patients with CAD and control group respectively. Given also that TO ≥0% and TS ≤2.5 ms/ RR values are considered abnormal, there was significant difference between the two groups; TO abnormal: 27 patients (46.6%) *vs.* 7 patients (13.5%), p=0.001, and TS abnormal: 15 patients (25.9%) *vs.* 4 patients (7.7%), (p=0.004) in CAD patients and control group respectively. A positive correlation was detected between TO and Gensini score (r=0.282, p=0.001) and a negative correlation detected between TS and Gensini score (r=-0.287, p=0.001).

Conclusion: The study demonstrated that HRT variables are impaired in patients with stable CAD when compared to those in the control group, and that these variables also correlate with severity of CAD.

ÖZET

Amaç: Kalp hızı türbülansı (KHT) ventriküler erken atımlara (VEA) yanıt olarak sinüs ritmi siklüsündeki fizyolojik değişimleri ifade eder ve anormal değerlerinin mortalite artışı ile iligili olduğu saptanmıştır. Çalışmamızda koroner arter hastalığında (KAH) KHT parametrelerini ve KAH'nin ciddiyeti ile arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Çalışmamıza Holter incelemesinde VEA saptanmış, KAH olan 58 hasta (ortalama 58.9±10.0 yıl; 25 erkek) ile kontrol grubu olarak koroner anjiyografide normal koroner arterler saptanan 52 olgu (ortalama yaş: 55.9±9.3 yaş; 36 erkek) alındı. Yirmi dört saatlik Holter kayıtlarından KHT parametreleri olan türbülans başlangıcı (TB), türbülans eğimi (TE) hesaplandı. Koroner arter hastalığının ciddiyeti Gensini skoru ile değerlendirildi.

Bulgular: İki grup arasında KHT parametreleri arasında anlamlı fark saptandı (sırasıyla, KAH ve kontrol grubu; TB: -%0.47±1.52 ve -%1.61±2.0, p=0.001; TE: 4.7±3.0 ve 6.4±3.7 ms/RR, p=0.009 TB), ayrıca TB ≥%0 ve TE ≤2.5 ms/RR değerleri patolojik olarak alındığında da KAH grubunda KHT parametreleri anlamlı olarak patolojik saptandı (sırasıyla, KAH ve kontrol grubu; TB anormal: 27 (%46.6) hasta ve 7 (%13.5) hasta, p=0.001; TE anormal: 15 (%25.9) hasta ve 4 (%7.7) hasta, p=0.004). Türbülans başlangıcı ile Gensini skoru arasında pozitif korelasyon (r=0.282, p=0.001) ve TE değerleriyle Gensini skoru arasında negatif korelasyon (r=-0.287, p=0.001) saptandı.

Sonuç: Çalışmamızda KHT parametreleri KAH grubunda, kontrol gurnuna göre anlamlı olarak patolojik saptandı. Ayrıca KHT parametreleriyle KAH ciddiyeti arasında korelasyon bulundu.

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Abbreviations:

CAD	*Coronary artery disease*
EF	*Ejection fraction*
HRT	*Heart rate turbulence*
TO	*Turbulence onset*
TS	*Turbulence slope*
VPCs	*Ventricular premature complexes*

Heart rate turbulence (HRT) is a recently coined phrase that describes short-term fluctuations in sinus cycle length that follows spontaneous ventricular premature complexes (VPCs).[1] Normally, sinus rate accelerates briefly and subsequently decelerates compared with the pre-VPC rate, before returning to baseline. These variations are believed to be mainly mediated by the cardiac autonomic nervous system. The pathophysiology is uncertain, but HRT has the same physiological mechanisms as ventriculophasic sinus arrhythmia, in which ventricular contractions influence the periods of sinus nodal discharges and arterial baroreflex responses are responsible for the fluctuations.[1] HRT is quantified by turbulence onset (TO) and turbulence slope (TS), TO referring to the amount of sinus acceleration following a VPC, and TS being the rate of sinus deceleration that follows the acceleration.[1] Various studies have shown that HRT impairment indicates cardiac autonomic dysfunction, especially impaired baroreflex sensitivity and reduced parasympathetic activity.[2–6] Moreover, a small number of studies have verified that an impairment of HRT reflects independent prognostic information in patients with post-myocardial infarction and congestive heart failure.[1,6–10] Nevertheless, there is insufficient information on HRT parameters in patients with stable coronary artery disease (CAD) and its relationship with severity of the disease.

This study aimed to investigate this issue by comparing HRT in a group of patients with stable CAD and frequent VPCs and a group of patients with no evidence of CAD or other structural cardiac abnormalities.

METHODS

The study comprised 58 patients with documented CAD who had ventricular premature complexes on 24-hour ambulatory Holter monitoring, normal ejection fraction (EF) and no history of myocardial infarction and revascularization (Group 1), and 52 patients with ventricular premature complexes, but with normal EF and coronary arteries (Group 2). Exclusion criteria were as follows: intraventricular conduction disorders, diseases known to impair the autonomic nervous system (Diabetes mellitus, hypertension), valvular heart disease, congestive heart failure and treatment with antiarrhythmic agents (Beta blockers etc.). The study was approved by the institutional review board.

Heart rate turbulence analysis

All subjects underwent 24 hour Holter monitoring using 3-channel tape recorders. Holter records were analyzed by cardiologists using the Holter device system (CardioScan Premier 12 Holter System, China). HRT analysis was assessed on sequences of sinus RR intervals related to VPCs showing the Schmidt criteria.[1] HRT was performed using standard parameters:[1] TO, early sinus acceleration after a VPC; and TS, a measure of the late sinus deceleration after a VPC. TO is obtained using the following formula: $[(RR_1 + RR_2) - (RR_{-2} + RR_{-1})]/RR_{-2} + RR_{-1}) \times 100$ and is expressed as a percentage. RR_1 and RR_2 are the first and the second sinus RR intervals after the VPC, and RR_{-1} and RR_{-2}

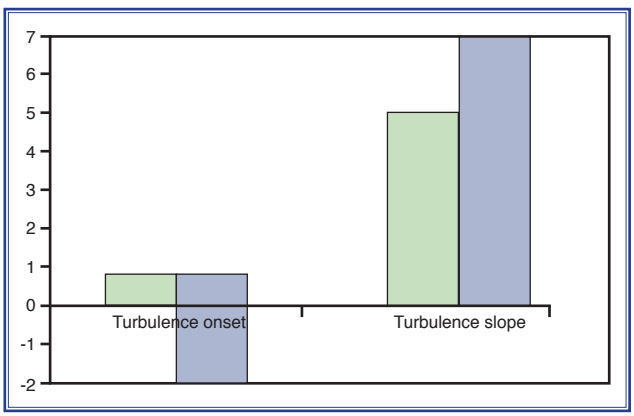

Figure 1. Results of heart rate turbulence analyses.

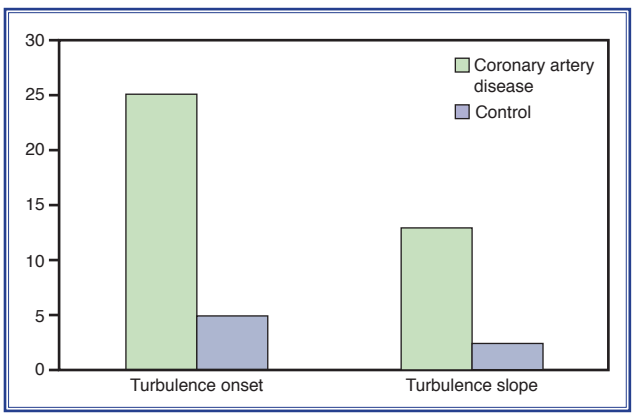

Figure 2. Heart rate turbulence parameters in patients with coronary artery disease and control group (Abnormal values were: Turbulence onset ≥0% and Turbulence slope ≤2.5 ms/ RR).

Table 1. Main clinical characteristics

	CAD group (n=58)			Control group (n=52)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age, years			58.9±10.0			55.9±9.3	NS
Men	25	48.1		36	62.1		NS
Hyperlipidemia	29	50		14	26.9		0.029
Smoker	17	29.3		12	23.0		NS
Family history	6	10.3		0	0		<0.001
Ejection fraction (%)			60.9±2.1			60.6±1.7	NS
Ventricular premature complexes/24 h			4.2±1.7			3.8± 1.4	NS
1 coronary artery disease narrowed >50%	28	48.2	–	–	–	–	–
2 coronary artery disease narrowed >50%	19	32.7	–	–	–	–	–
3 coronary artery disease narrowed >50%	11	19.1	–	–	–	–	–

CAD: Coronary artery disease; NS: Non significant. p<0.05 is statistically significant.

Table 2. Results of heart rate turbulence analyses

Heart rate turbulence	Coronary artery disease group			Control group			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Turbulence onset (%)			-0.47±1.52			-1.61±2.0	0.001
Turbulence slope (ms/RR)			4.7± 3.0			6.4±3.7	0.009
Patient with turbulence onset ≥0	27	46.6		7	3.5		0.001
Patient with turbulence slope ≤2.5	15	25.9		4	7.7		0.004

p<0.05 is statistically significant.

are the first and the second sinus RR intervals preceding the VPC. TS is calculated as the maximal positive slope among all slopes of a series of regression lines obtained from all sequences of 5 consecutive RR intervals included between the first and the 20th RR interval following the compensatory post-VPC pause, and is expressed as ms/RR. TO ≥0% and TS ≤2.5 ms values are considered abnormal.[1] Severity and extent of CAD were evaluated using Gensini score,[11] following which the relationship between the findings and HRT parameters was investigated.

Statistical analysis

Results are expressed as mean±SD. Continuous variables were compared by analysis of variance, and differences in HRT variables between the groups were adjusted for other clinical variables by multivariate analysis of variance. Comparisons of proportions were done by the chi-square test, while correlation analyses were performed by the Pearson rank test. Statistical significance was assumed at p<0.05. Statistical analysis was performed using SPSS for MS Windows, version 15.

RESULTS

There was no significant difference between the two groups in terms of age and gender. Furthermore, mean EF was 60% in both groups. Demographic characteristics of the groups are given in Table 1.

Heart rate turbulence

HRT parameters differed significantly between the groups. TO: -0.47±1.52% vs -1.61±2.0% (p=0.001) and TS: 4.7±3.0 vs 6.4±3.7 ms/RR (p=0.009) in Group 1 and Group 2 respectively. Also, given that turbulence onset ≥0% and turbulence slope ≤2.5 ms/ RR values are considered abnormal, there was significant

difference between the two groups; TO abnormal: 27 (46.6%) vs 7 patients (13.5%), p=0.001; TS abnormal: 15 (25.9%) vs 4 patients (7.7%), p=0.004 in Group 1 and 2 respectively (Figures 1, 2). In Group 1, the highest Gensini score was 165 and the lowest 4, with the average being 47.3±34.0. A positive correlation was detected between TO and Gensini score (r=0.282, p=0.001) and a negative correlation was detected between TS and Gensini score (r=-0.287, p=0.001). Patient HRT parameters are shown in Table 2.

DISCUSSION

In clinical terms, HRT is defined as a baroreflex-mediated biphasic reaction of heart rate in response to premature ventricular beats. Abnormal HRT shows patients with autonomic dysfunction or impaired baroreflex sensitivity due to a variety of disorders, but it may also reflect changes in the autonomic nervous system induced by different therapeutic modalities such as drugs, neural diseases (e.g. diabetes mellitus), or cardiac failure. More importantly, abnormal HRT has been shown to identify patients at high risk of all-cause mortality and sudden death, particularly post-infarction and congestive heart failure patients. It should be emphasized that abnormal HRT has a well-established role in risk stratification of post-infarction and heart failure patients.[1,6–8,13] Ongoing clinical trials may possibly indicate that HRT can be used as a guide for the implantation of cardioverter-defibrillators.[8,10]

In the present study, it was demonstrated that HRT variables are impaired in patients with stable CAD when compared to those in subjects without CAD. Furthermore, this impairment was found to be associated with severity of CAD, and that TO was positively and TS negatively correlated with Gensini score. Thus, the findings show a worsening of HRT parameters with increasing severity of CAD. HRT changes were independent predictors of the variables, such as left ventricular function and previous infarction. A small number of studies have verified that impairment of HRT reflects independent prognostic information in patients with post-myocardial infarction and congestive heart failure.[1,6–8,13] Only one study, that by Sestito et al.,[12] has investigated the role of HRT parameters in patients with stable CAD. They showed impaired HRT values in 29 CAD patients who had previous myocardial infarction and reduced EF, but they did not evaluate the relationship between severity of CAD and HRT parameters. The present study detected impaired HRT parameters in patients with hearts almost entirely normal structurally, and with no previous myocardial infarction.

This study also showed HRT parameters in patients with CAD with normal EF and no history of myocardial infarction and revascularization to be abnormal compared to the control group. Although the majority of these low-risk patients have a good prognosis, impaired HRT values can indicate increased mortality risk. Hence, these findings may be of assistance in treatment strategy decisions and patient follow-up. HRT has been included in the literature more recently, and we demonstrated impaired results in CAD patients. Thus, our findings suggest that using HRT in the clinic may be reliable. However, long-term multicenter studies are needed to validate the clinical availability of HRT in the diagnosis of CAD.

Conclusion

Impaired HRT results provide important information about the risk of overall mortality and sudden cardiac death. In previous studies, the relationship between HRT and several clinical forms of CAD has been demonstrated, but data is lacking on the issue of stable CAD. This study presented the impairment of HRT parameters in stable CAD and its relationship with CAD severity.

Study limitations

One limitation of our study is the inclusion of a relatively small number of patients. Secondly, long-term follow-up studies investigating the role of impaired HRT on the cardiovascular system are needed to evaluate the prognostic importance of our results.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. 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;353:1390–6. CrossRef
2. Davies LC, Francis DP, Ponikowski P, Piepoli MF, Coats AJ. Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure. Am J Cardiol 2001;87:737–42. CrossRef
3. Mrowka R, Persson PB, Theres H, Patzak A. Blunted arterial

baroreflex causes “pathological” heart rate turbulence. Am J Physiol Regul Integr Comp Physiol 2000;279:1171–5.

4. Watanabe MA, Marine JE, Sheldon R, Josephson ME. Effects of ventricular premature stimulus coupling interval on blood pressure and heart rate turbulence. Circulation 2002;106:325–30. CrossRef
5. Marine JE, Watanabe MA, Smith TW, Monahan KM. Effect of atropine on heart rate turbulence. Am J Cardiol 2002;89:767–9. CrossRef
6. Ghuran A, Reid F, La Rovere MT, Schmidt G, Bigger JT Jr, Camm AJ, et al. Heart rate turbulence-based predictors of fatal and nonfatal cardiac arrest (The Autonomic Tone and Reflexes After Myocardial Infarction substudy). Am J Cardiol 2002;89:184–90. CrossRef
7. Koyama J, Watanabe J, Yamada A, Koseki Y, Konno Y, Toda S, et al. Evaluation of heart-rate turbulence as a new prognostic marker in patients with chronic heart failure. Circ J 2002;66:902–7. CrossRef
8. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998;351:478–84. CrossRef
9. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84:482–92. CrossRef
10. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043–65.
11. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51:606. CrossRef
12. Sestito A, Valsecchi S, Infusino F, Sgueglia GA, Bellocci F, Zecchi P, et al. Differences in heart rate turbulence between patients with coronary artery disease and patients with ventricular arrhythmias but structurally normal hearts. Am J Cardiol 2004;93:1114–8. CrossRef
13. 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;21:474. CrossRef

Keywords: Coronary angiography; coronary artery disease; Gensini score; heart rate turbulence.

Anahtar sözcükler: Koroner anjiyografi; koroner arter hastalığı; Gensini skoru; kalp hızı türbülansı.