5 ISSN:2149-455X
Makale / Article

Heart Rate Recovery Index Was Deteriorated In Diastolic Dysfunction

Muhammed Necati Murat Aksoy[1]* Harun Kilic[1] Ugur Saygisunar[2]
Munevver Sari[3] Mehmet Ayturk[3] Mustafa Gokhan Vural[1] Ekrem Yeter[4] Ramazan Akdemir[1]

[1] Sakarya University School of Medicine Departmet of Cardiology, Sakarya, Turkey
[2] Ministry of Health Giresun State Hospital, Department of Cardiology, Giresun, Turkey
[3] Ministry of Health Kartal Kosuyolu Training and Research Hospital, Department of Cardiology, İstanbul, Turkey
[4] Ministry of Health Diskapi Training and Research Hospital, Department of Cardiology, Ankara, Turkey

Özet

Amaç Daha önce diyastolik kalp yetmezliği dahil çok çeşitli kardiak hastalık grubuyla ilişkisi gösterilen KHTI nin asemptomatik sol ventrikül diyastolik disfonksiyonu olan bireylerle normal diyastolik fizyolojiye sahip bireyler arasındaki farkını inceledik.

Metod: Çalışmamıza normal diyastolik fonksiyonlu, Evre 1 DDF ve Evre 2 DDF gruplarına ayrılan 71 hasta dahil edildi. Diyastolik fonksiyon değerlendirmesi transtorasik ekokardiyografi ile yapılırken, tüm hastalar eforlu EKG testinde yaşa göre belirlenmiş maksimal kalp hızına çıkarıldıktan sonra egzersiz bitiminde 1. ve 2. dakikadaki KHTI ölçümleri alındı.

Bulgular: Gruplara göre ortalama HRR1 değerleri arasındaki fark değerlendirildiğinde, Evre 1 ile Normal DF grupları arasındaki fark istatiksel olarak anlamlı ve Evre 1 grubunda HRR1 değerleri daha düşük izlenirken, bu fark Evre 1 ile Evre 2 grubu arasında ve Evre 2 ile Normal DF grubu arasında izlenmemiştir ancak Evre 2 grubu HRR1 değerlerinde azalmaya yönelik bir eğilim de dikkati çekmiştir. (Normal DF, Evre 1 ve Evre 2 değerleri sırasıyla 36,6±9,7 25,1±11,1 ve 29,0±10,2 p:0,003). Gruplara göre HRR2 değerleri arasında ise benzer sonuçlar elde edilmiştir. Evre 1 DDF grubunda Normal DDF grubuna göre anlamlı olarak daha düşük izlenen HRR1 değeri diğer demografik kriterlere göre regresyon analizi ile düzeltme yapıldığında yine anlamlı olarak düşük bulunmuş olup, aralarında bağımsız bir ilişki izlenmiştir.

Sonuç: Evre 1 DDF olan bireylerde yaş, cinsiyet, BKİ, DM, HT ve sigara öyküsünden bağımsız olarak KHTI normal bireylere göre düşük izlenmiştir. Bu bulgu asemptomatik diyastolik disfonksiyonu olan hasta grubunda, otonomik bozukluğun semptomların başlamasından daha önce bozulduğunun ve artmış mortalitenın göstergesi olabilir

Anahtar Kelimeler: Kalp hızı toparlanma indeksi, Diyastolik disfonksiyon, Ekokardiyografi

Abstract

Aim: *To investigate Heart Rate Recovery (HRR) in asymptomatic diastolic dysfunction patients.*

Methods: *We enrolled 71 patients, which were divided into 3 groups. Both Grade 1 and Grade 2 diastolic dysfunction and normal diastolic function patients were evaluated by transthoracic Doppler echocardiography. Heart rate recovery measured at 1st (HRR1) and 2nd (HRR2) minutes after cessation of exercise without a cool down period.*

Results: *HRR1 values in Grade 1 diastolic dysfunction group were significantly lower than normal diastolic functions group. Although mean HRR1 values of group 2 showed a trend towards lower than controls, it did not reach any statistical significance comparing with Grade 1 diastolic dysfunction and control group. (Normal, Grade 1 and Grade 2 HRR1 values were 36,6±9,7 25,1±11,1 and 29,0±10,2 p:0, 003). There was no significant difference in HRR2 values between groups. Regression analysis showed that the difference of HRR1 values between Grade 1 DDF and Normal DF groups was independent from the presence of other epidemiologic variables (age, sex, DM, HT, smoking).*

Conclusion: *These findings suggest that HRR index as a marker of autonomic functions was deteriorated in asymptomatic diastolic dysfunction patients.*

Keywords: *Heart rate recovery, Diastolic dysfunction, Echocardiography*

Corr. Author: **M. N. Murat AKSOY, MD**
Sakarya University School of Medicine, Department of Cardiology Adapazari 54000, Sakarya, Turkey
GSM: **0 532 702 00 71** E-mail: **draxoy@gmail.com**

Introduction

Although systolic dysfunction has been the main concern for describing heart failure for many years, it has been shown that almost half of the patients with typical heart failure symptoms have normal or near-normal systolic functions[1-3]. This specific subgroup of heart failure syndrome is named as heart failure with preserved ejection fraction and we know that the key pathophysiological mechanism is diastolic dysfunction for heart failure symptoms in this patient population. In fact, most of the people with altered diastolic properties on echocardiography have little or no symptoms in terms of heart failure.
Treadmill test is a non-invasive method to detect the presence and the severity of coronary artery disease for many years. Previously it has been also shown that the data, which is derived from these tests, can be used as a measure of autonomic nerve system functions[3-7]. Heart rate recovery index (HRRI) is described as the amount of fall in the heart rate count during a prespecified time period right after the end of the exercise protocol in treadmill test[8].

HRRI is an indirect measure of vagal tone and independent predictor of cardiovascular mortality[9,10].

Heart rate and myocardial contractility are two key determining factors for diastolic functions, which is a product of sympathetic and parasympathetic nerve system activity. The aim of the present study is to investigate the HRRI in patients with diastolic dysfunction.

METHODS

The study patients were selected among our cardiology outpatient clinic population who underwent echocardiography evaluation.

Patients with systolic and diastolic heart failure, coronary and peripheral artery disease, congenital heart disease or more than mild degree valvular heart disease were excluded. Patients with grade III diastolic dysfunction were also excluded. Patients who are on medication, which affects heart rate (Beta blockers, Ca channel blockers, digoxin, other anti-arrhythmic agents) and patients without sinus rhythm on baseline ECG are also excluded

Echocardiography and Treadmill Test

Echocardiography was performed by Philips iE33 Diagnostic Ultrasound System (Bothell, Washington, USA). Conventional echocardiography and Doppler evaluation was performed in left lateral decubit position. Early and late mitral inflow velocities of E and A waves, Em and Am values were measured using mitral annular TDI velocities for each patient respectively. Patients were classified as grade 1 diastolic dysfunction (DD), grade 2 DD and normal diastolic function (DF). All measurements were taken according to the related guideline of the American Society of Echocardiography[11].

All patients completed treadmill test with modified Bruce protocol, and exercise times on treadmill were modified for each patient until the patient's heart rate reaches to the calculated submaximal heart rate (85 % of the age dependent maximal heart rate). All patients in the study managed to reach the calculated target heart rates. The exercise of each patient was stopped abruptly without a cool down period and heart rate values at the end of 1st and 2nd minutes after the exercise were noted. These values were subtracted from each patient's recorded maximal heart rate during the exercise and these values are noted as HRR1 and HRR2 for each patient.

Statistical Analysis

Data analysis was made on SPSS for Windows 11.5. Shapiro Wilk test is used to determine whether continuous variable distribution is close to normal or not. Defining statistics was shown as mean ± standard deviation or median values for continuous variables and as number of patients and percentage for categorical variables.

Student's t test was used to establish the significance of the average difference between groups when the number of group was two. When there were more than two groups One Way Analysis of Variance was used. Kruskal Wallis Test was used to establish the significance of median value difference between groups.

Spearman's Correlation Test was used to determine if there is a statistically significant correlation between continuous variables or not. Linear Regression Analysis was used on HRR1 values. Regression coefficient and %95 confidence interval

for every variable was calculated. p<0,05 was accepted as statistically significant.

RESULTS

A total of 51 patients were assigned in the study (32 male and 19 female) (Table 1). There was no statistically significant difference between groups in terms of sex distribution [(male/female) 13/6 normal DF, 9/6 grade 1 DD and 10/7 grade 2 DD, p:0, 810]. Mean age of patients was 43,3±14,0. Mean age of patients in the grade 1 DD and grade 2 DD groups was significantly higher than the normal DF group (normal DF: 29,3±8,4 grade 1 DD: 54,5±7,9 grade 2 DD: 49,2±9,7 p<0,001) but there was no statistical difference between grade 1 and grade 2 DD groups (Table 2).

Table 1 Demographics

	n=51
Age	43,3±14,0
Gender	
Male	32 (%62,7)
Female	19 (%37,3)
Body Mass Index	27,1±2,7
DM	7 (%13,7)
HT	15 (%29,4)
Smokers	24 (%47,1)
Diastolic Dysfunction Grade	
Grade 0 (normal)	19 (%37,3)
Grade I	15 (%29,4)
Grade II	17 (%33,3)

Body mass index (BMI) of patients in the grade 1 DD and grade 2 DD groups were significantly higher than the normal DF group but there was no difference between two groups. (BMI Normal DF: 25,2± 3,4 grade 1 DD: 28,5±1,5 grade 2 27,9±1,1 p<0,001) (Table 2).

The ratio of diabetics among all patients was %13,7. There was a significant difference of diabetic patients between the Normal DF group and grade 2 DD group [Normal DF:0 patients (%0), grade 1: 2 patients (%13,3) and grade 2: 5 patients (%29,4) p:0, 015] (Table 2).

Table 2 Demographic and Clinical Variables Among Groups

	Grade 0	Grade I	Grade II	p-value
Age	29,3±8,4[a,b]	54,5±7,9[a]	49,2±9,7[b]	<0,001
Gender				0,810
Male	13 (%68,4)	9 (%60,0)	10 (%58,8)	
Female	6 (%31,6)	6 (%40,0)	7 (%41,2)	
Body Mass Index	25,2±3,4[a,b]	28,5±1,5[a]	27,9±1,1[b]	<0,001
DM	0 (%0)[b]	2 (%13,3)	5 (%29,4)[b]	0,015
HT	1 (%5,3)[a,b]	7 (%46,7)[a]	7 (%41,2)[b]	0,013
Smoker	6 (%31,6)[b]	6 (%40,0)	12 (%70,6)[b]	0,052
E/E'	7,2 (4,8-9,4)[a,b]	8,7 (5,1-10,9)[a,c]	11,2 (9,1-23,4)[b,c]	<0,001
HRR 1	36,6±9,7a	25,1±11,1[a]	29,0±7,5	0,003
HRR2	48,2±9,4	38,2±13,0	44,6±10,2	0,062

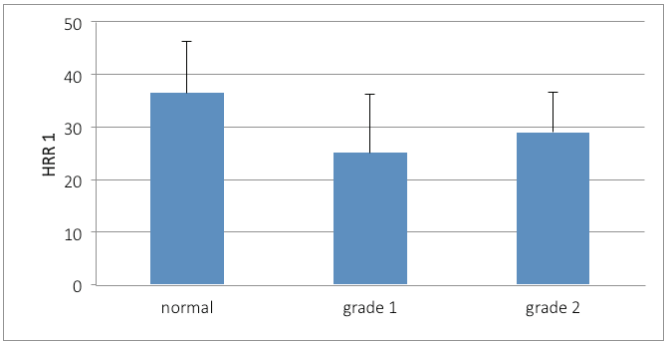

Figure 1 HRR1 Values Among Groups

The number of hypertensive patients was higher both in grade 1 and grade 2 groups than the Normal DF patients but there was not a significant difference between two DD group of patients. [Normal: 1(%5,3) grade 1: 7(%46,7) grade 2: 7(%41,2) p:0, 013] (Table 2).

In the analysis of mean HRR1 values among all groups, there was a significant difference between grade 1 DD group and normal DF group. Although there was no statistical difference between grade 1 DD and grade 2 DD groups and also between grade 2 DD and normal DF groups, there were lower HRR1 values in the grade 2 DD patients than the Normal DF patients (Normal DF, grade 1 and grade 2 values were 36,6±9,7 25,1±11,1 and 29,0±10,2 respectively p:0, 003). HRR2 values among all groups were not different statistically (Table 2 and Figure 1).

In the correlation analysis between HRR1 values and age, BMI and E/Em values, the only significant difference was between age and HRR1 values (r:-0, 384, p:0, 005) (Table 3).

Table 3 Correlation Coefficient and p Values Between HRR1 Values with Age, Body Mass Index and E/E' Values

	Correlation Coefficient	p-value
Age	-0,384	0,005
Body Mass Index	-0,153	0,282
E/E'	-0,183	0,200

The significant lower values of HRR1 in the grade 1 DD group comparing to Normal DF group was corrected with regression analysis according to the demographic criteria. HRR1 values were still statistically lower suggesting that there is an independent relationship between diastolic dysfunction and mean HRR1 values (Table 4).

Table 4 After Correction Using Linear Regression Analysis for Age, HT, DM, Smoking History and BMI, the Affect of Grade 1 and Grade 2 DD over HRR1 Values Comparing to Normal DF

	Regression Coefficient	p-value	%95 Confidence Interval	
			Lower Limit	Upper Limit
Grade 1	-12,921	0,021	-23,826	-2,016
Grade 2	-6,706	0,166	-16,306	2,894
AGE	0,010	0,954	-0,327	0,346
HT	-2,063	0,596	-9,854	5,727
DM	-2,485	0,580	-11,469	6,498
SMOKER	-4,569	0,134	-10,608	1,470
BMI	0,851	0,189	-0,436	2,138

DISCUSSION

The degenerated autonomic control of heart rate in individuals with primarily systolic dysfunction was well documented in previous studies[12-14]. The primary mechanism for this degeneration in patients with systolic dysfunction was suggested as decreased vagal activity[13,15]. Phan et al.[16] has documented that heart rate recovery index (HRRI) of patients with heart failure with preserved ejection fraction is statistically lower than the control group in a previous study.

Previous studies has already documented that both in heart failure patients with and without systolic dysfunction, HRRI is abnormal and this finding is a sign of degenerated autonomic tone, especially vagal activity. In this study, the HRRI at the 1st minute for the patients with asymptomatic left ventricular diastolic dysfunction were significantly lower than the healthy control group. This finding might be explained as the deterioration of vagal activity starts even before the beginning of heart failure symptoms in patients with left ventricular diastolic dysfunction. The clinical significance of this finding is unknown on the other hand.

This significantly impaired HRR1 values in grade 1 diastolic dysfunction patients might let us create a hypothesis that worsening diastolic dysfunction is going to lead more impairment of HRR1 values, but although HRR1 values of grade 2 DD patients tends to be lower, it is not significant in statistical analysis. This might be explained with the lesser number of patients in the grade 2 DD group and we still think that with larger number of patients, one might find the same significant difference of HRR1 values as in grade 1 DD patients comparing to control group.

Since diabetes is a well known disease which affects the autonomic nerves and causes autonomic dysfunction, one might predict that, in demographic subgroup analysis of this study diabetic patients would have significantly lower HRR1 values comparing to non diabetics. But we were not able to document such finding and this again, might be explained with the relatively small number of patients with diabetes in the whole patient population (e.g. 7 patient, 13% of all patients).

Considering the whole study population, the number of individuals with history of smoking, diabetes and hypertension were significantly higher in the total diastolic dysfunction group than the controls as expected. The mean BMI values of patients were significantly higher in patients with diastolic dysfunction and this relationship of obesity and diastolic dysfunction is described in a previous study[17].

Analyze of the relationship between HRR1 values and all of the demographic subgroups, only age have shown a significant negative correlation with HRR1 values. This might be

interpreted, as aging is a destructive process on autonomic functions independent of all other systemic diseases, which has destructive effects on autonomic nervous system. But we need more studies with larger number of patients to reach at such conclusion.

In the previous study Cole et al. has published, they have set up a threshold value for the HRRI, so the patients with the values under this threshold was considered abnormal dividing the study population into two groups. The subgroup with abnormal HRR values had statistically larger number of patients with hypertension and diabetes. Since we haven't set up such a threshold analyzing this kind of a relationship is impossible. But the presence of diabetes, hypertension and smoking history doesn't have a significant correlation with HRR1 values in this study. This lack of correlation might be explained with small patient population again. On the other hand in a previously published study Phan et al.[16] has divided their control group into two groups as hypertensives and normotensives and compared two groups in terms of HRR values. These two groups didn't have a significant difference either. We think that there is a need for specifically designed studies about this matter to reach more definitive conclusions.

The correlation of higher mortality with lower HRR values has been well documented by Cole et al.[18] In a study by Halley CM et al.19 it has been documented that the mortality rates of medium and severe diastolic dysfunction patients were significantly higher than normal patients, independent of all other risk factors in a retrospective single center study. Combining the data we provided with these studies, we think there might be a higher mortality risk with disrupted vagal activity especially in asymptomatic grade 1 DD patient group comparing to normal individuals.

CONCLUSION

Asymptomatic grade 1 DD patients has significantly lower HRR1 values than the patients with normal diastolic function which reflects an autonomic function deterioration.

This difference is independent from age, presence of diabetes and hypertension, smoking history and BMI values.

LIMITATIONS

The number of patients for each group was very low to reach a more definitive conclusion for the results of the study. Especially lack of enough patient number in the grade 2 DD group might have affected the statistics. Larger number of patients for each group is needed to reach more definite conclusions.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Lopez AD, Mathers CD, Ezzati M et al. (eds): Global Burden of Disease and Risk Factors, Oxford, England, Oxford University Press and Washington, DC, The World Bank, 2006
2. Yancy CW, Lopatin M, Stevenson LW et al. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006; 47:76.
3. Vanoli E, De Ferrari G, Stramba-Badiale M et al. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res 1991; 68:1471– 81.
4. Olsson G, Wikstrand J, Warnold I et al. Metoprolol-induced reduction in mortality: pooled results from five double-blind randomized trials. Eur Heart J 1992;13:28 –32.
5. Frishman W, Furberg C, Friedewald W. Beta-Adrenergic blockade for survivors of acute myocardial infarction. N Engl J Med 1984; 310: 830 –7.
6. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomized trial. Lancet 1999;353: 9 –13.
7. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.
8. Shetler K, Marcus R, Froelicher VF et al. Heart rate recovery: Validation and Methodologic Issues J Am Coll Cardiol.2001;38: 1980-7.
9. Cole C, Foody J, Blackstone E et al. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardio- vascularly healthy cohort. Ann Intern Med 2000;132:552–5.
10. Hao S, Chai A, Kligfield P. Heart rate recovery response to symptom-limited treadmill exercise after cardiac rehabilitation in patients with coronary artery disease with and without recent events. Am J Cardiol 2002;90:763–5.
11. Rakowski H, Appleton C, Chan KL et al. Canadian consensus recomendations for the measurement and reporting of diastolic dysfunction by echocardiography. J Am Soc Echocardiogr 1996;9:736-760
12. Frennaux MP.Autonomic changes in patients with heart failure and in post myocardial infarction patients.BMJ.2004;90:1248-1255
13. Eckberg DL ,Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease.N Engl J M.1971;285:877-883
14. Ungerer M, Bohm M, Elce JS et al. Altered expression of beta-adrenergic receptor kinase and beta-1 adrenergic receptors in the failing human heart. Circulation,1993;87:454-463
15. Colucci WS, Ribeiro JP, Rocco MB et al. Impaired chronotropic response to exercise in patients with congestive heart failure. Circulation.1989;80:314-323
16. Phan TT, Shivu GN, Abozguia K. et al. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. Circ Heart Fail. 2010;3:29-34
17. Russo C, Jin Z, Homma S et al. J Am Coll Cardiol. 2011 Mar 22;57(12):1368-74. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort.
18. Cole C, Blackstone E, Pashkow F et al. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351–7.
19. Halley CM, Houghtaling PL, Khalil MK et al. Mortality rate in patients with diastolic dysfunction and normal systolic function. Arch Intern Med 2011; 171: 1082- 1087