A new approach to the measurement of heart rate in patients with chronic heart failure-Heart rate performance index: an observational study

Kalp yetersizliği olan hastalarda kalp hızına yeni bir yaklaşım-Kalp hızı verim göstergesi: Gözlemsel bir çalışma

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Abstract

Objective: In order to evaluate the utility of the heart rate performance index (HRPI), which is obtained by dividing HR mean by the difference of HR max and HR min in the context of Holter monitoring, we sought to determine whether there was any correlation or relationship between the HRPI and LVEF values as determined by echocardiography and to compare the HRPI between the study and control groups.

Methods: This study is a cross-sectional, controlled observational study. Thirty-two patients with symptomatic or asymptomatic left ventricular systolic dysfunction (LVEF <45%) were included as study group and 32 subjects without chronic heart failure (CHF) were included as a control group. In the study group, 10 patients were in NYHA class I (31.2%), 12 - were in NYHA class II (37.6%) and 10 - were in NYHA class III (31.2%). Heart rate analysis was measured using 24-hour Holter ambulatory electrocardiography. To determine the HRPI, the difference between maximum (HR max) and minimum heart rate (HR min) was divided by mean heart rate (HR mean) (beats/minute): HRPI=(HR max-HR min) / HR mean. Statistical analysis was performed using t-test for independent samples, Mann-Whitney U test, Chi-square test, Kruskal-Wallis test, Pearson's correlation and linear regression analyses.

Results: The HRPI index value was markedly decreased [0.83 (0.58-1.1) and 1.10 (0.74-1.3), p<0.001] in the study group as compared to the control group. The data collected for the study group and the control group (n=64) demonstrated a positive correlation between the HRPI and LVEF (r=0.62, p<0.001) as well as a negative correlation between the HR mean and LVEF (r=-0.39, p<0.003). The HR mean was higher (80.2±11.3 and 75.2±6.7, p<0.007) and HR max-HR min (67.9±11.6 and 83.3±14.3, p<0.001) were lower in the study group as compared to the control group. Linear regression analysis demonstrated no significant relationship between LVEF and HRPI and other heart rate derivatives (unstandardized β=42.43 95% CI: 21.98-50.51, p=0.231).

Conclusion: According to our findings, patients with CHF exhibited higher HR mean values, reduced HR max-min values and significantly decreased HRPI values. There is a positive correlation between HRPI and LVEF, a decreased HRPI is associated with a decreased LVEF, but there is no relationship between these two variables. Therefore HRPI values may represent a viable option for assessing daily exercise activity and potentially sympathetic activation in patients with CHF. The assessment of HRPI may be helpful the evaluation of CHF patients, as well as resting HR. *(Anadolu Kardiyol Derg 2013; 13: 215-20)*

Key words: Congestive heart failure, ambulatory electrocardiography, heart rates, ventricular ejection fraction, regression analysis

Özet

Amaç: Yirmi dört saatlik Holter EKG incelemede kalp hızı verim göstergesi (KHVG), en yüksek kalp hızı ile en düşük kalp hızı arasındaki farkın ortalama kalp hızına bölünmesi ile elde edildi. KHVG çalışma ve kontrol grupları arasında karşılaştırıldı ve ekokardiyografi ile ölçülen sol ventrikül fırlatma yüzdesi arasında bir ilişki olup olmadığını araştırıldı.

Yöntemler: Bu çalışma kesitsel ve gözlemsel bir çalışmadır. Kapak hastalığı olmayan 32 kalp yetersizliği hastası ile birlikte, kalp yetersizliği olmayan 32 kişi alındı. KHVG'ni tespit etmek için Holter EKG de ölçülen en yüksek kalp hızı ile en düşük kalp hızı arasındaki fark (EYKH-EDKH) ortalama kalp hızına (OKH) bölündü. KHVG=(EYKH-EDKH) / OKH (vuru/dk).Istatistiksel analizde eşleştirilmemiş t-testi, Mann-Whitney U testi, Ki-kare testi, Kruskal-Wallis testi, Pearson korelasyon ve lineer regresyon analizleri kullanıldı.

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Bulgular: Konjestif kalp yetersizliği (KKY) hastalarında OKH daha yüksek (80.2±11.3 ve 75.2±6.7, p<0.007) iken, EYKH ve EDKH arasındaki farkı ise daha az (67.9±11.6 ve 83.3±14.3, p<0.001) bulundu. KHVG kontrol grubuna göre KKY grubunda azalmıştı [0.83 (0.58- 1.1) ve 1.10 (0.74-1.3), p<0.001]. KKY ve kontrol grubu verileri birlikte analiz edildiğinde KHVG ve SVFY arasında pozitif bir korelasyon vardı (r=0.62, p<0.001). Lineer regresyon analizinde SVFY ve KHVG arasında ilişki bulunmadı (β=42.43 95% CI: 21.98-50.51, p=0.231).

Sonuç: KKY hastalarında KKY olmayanlara göre OKH değerleri daha yüksek iken EYKH ile EDKH değerleri arasındaki fark ise daha azdır ve KHVG değerleri daha düşüktür. KHVG ve SVFY arasında pozitif yönde korelasyon vardır, fakat ilişki yoktur. KHVG, KKY hastalarının günlük egzersiz aktivitelerinin ve olasılıkla sempatik aktivasyonlarının değerlendirilmesinde kullanılabilir. KKY hastalarında SVFY ve KHVG'nin istirahat kalp hızının yanısıra kullanılması faydalı olabilir. *(Anadolu Kardiyol Derg 2013; 13: 215-20)*

Anahtar kelimeler: Konjestif kalp yetersizliği, ambulatuvar elektrokardiyografi, kalp hızları, ventrikül ejeksiyon fraksiyonu, regresyon analizi

Introduction

An increased resting heart rate (HR) is an independent risk factor in patients with coronary artery disease (CAD) and chronic heart failure (CHF). The accurate measurement of resting HR is therefore of elevated importance in patients with CHF and CAD (1, 2). One of the most important adaptations in patients with CHF is activation of the sympathetic nervous system, which occurs early in the course of CHF (3). The changes of HR mean, HR max and HR min is expected in CHF patients due to a decreased capacity for exercise and an increased sympathetic tone.

Ambulatory Holter electrocardiogram monitoring (H-ECG) has been routinely used to determine the analysis HR derivatives such as HR min, HR max and HR mean, as well as arrhythmias, heart rate variability (HRV), heart rate turbulence, QT dispersion, T-wave alternans, signal-averaged ECG and late potentials (4-10).Various H-ECG methods have been proposed to predict mortality in patients with CHF, but only left ventricular ejection fraction (LVEF) and resting HR are practical for using in CHF patients.

The measurement of resting HR and LVEF is very simple and also important in predicting of mortality, but up to now studies are very limited to show whether a relationship between the resting HR and LVEF or between the HR max-HR min and LVEF. HR mean indicates a variety of resting HR, is a predictor of mortality in CHF, and HR max-HR min reflects a kind of heart rate reserve which is known as the difference of HR baseline and HR max on treadmill exercise testing and shows a chronotropic insufficiency (11).

Dividing HR mean by HR max and HR min yields a new index, which here is denoted as the heart rate performance index: HRPI=(HR max-HR min)/HR mean. We want to investigate whether a correlation or relationship between LVEF and heart rate derivatives.

In the present study, we sought to determine whether there was any correlation or relationship between the HRPI and LVEF values as determined by echocardiography and to compare the HRPI between the study and control groups.

Methods

Study design

Study was designed as a cross-sectional observational controlled study.

Study population

The study was conducted in our cardiology clinic. Participants enrolled in the study were selected among patients not requiring hospitalization and subjects from January 2011 to June 2011. We selected the patients who had undergone routine clinical and laboratory examinations, including H-ECG, transthoracic echocardiography and routine blood tests.

The inclusion criteria for the CHF were as follows: New York Heart Association (NYHA) Class I-II and III, the patients with low LVEF, and Holter-ECG for 24 hours. Exclusion criteria were defined as the following: presence of atrial fibrillation or flutter, acute coronary syndromes, moderate -severe valvular disease, severe CAD, or any systemic disease as well as those on beta-blocker (BB) medication, digoxin and ivabradine. Ten of them were hypertensive, 3 of them were smoking, and 8 of them have CAD. They were using only diuretics, Angiotensin II receptor blockers (ARB) and/or angiotensin-converting-enzyme inhibitors (ACEI).

Subjects in control group were not taking digoxin or BB medication and nine of them were using diuretics, ARB and/or ACEI due to hypertension. They were selected among the subjects who had no cardiac any arrhythmias, CAD, CHF and any valvular heart disease.

Diabetes mellitus, hyperlipidemia, any congenital or pericardial disease, any thyroid disease, stroke, malignancies, pulmonary embolism or any systemic disease were the other exclusion criteria for the both groups.

All patients gave oral and written informed consent. The study was approved by the local ethics committee and was conducted according to the Helsinki declaration.

Study protocol

Our study included 32 patients (15 female) with mild-moderate non-valvular CHF (LVEF <45%) in sinus rhythm as study group and 32 subjects (14 female) without heart failure and CAD as control group. First, we planned to compare the values of HR mean, HR max-min and HRPI between the subjects without CHF and the patients with CHF. Second, we planned to combine the two groups' data for better observation the correlation or relationship between LVEF and HR derivatives.

Study variables

The clinical variables including age, gender, body mass index (BMI), and major risk factors for CAD, functional capacity according to NYHA and medication variables are summarized in Table 1.

Predictor variable was presence of CHF: the subjects with LVEF <45% were accepted as those with CHF. The outcome variables of study were HR mean, HR max-min and HRPI. Confounding factors were: age, gender, BMI, smoking, hypertension, and CAD. The subgroup analysis was performed according to NYHA functional class, treatment with ARB, ACEI and diuretics.

Holter monitoring and HRPI

Twenty four-hour Holter ECG was performed without hospitalization and analyzed using a three-channel ambulatory recorder (MT-101, Schiller AG, Baar, Switzerland). Since, the number of RR intervals taken from the calculation of the maximal and the minimal heart rate is generally optional and very important, recordings were analyzed by two independent investigators utilizing a 24 h two-channel full disclosure. Finally, the analysis was performed by deleting ECG signal artifacts in the calculation of HR min, HR max and HR mean. Dividing HR mean by the difference of HR max and HR min yields an HRPI, which here is denoted as the heart rate performance index: HRPI=(HR max-HR min)/HR mean.

Echocardiography

Transthoracic echocardiographic examinations were performed using commercially available instruments in combination with a cardiac probe (2.5-3.5 MHz) (Esaote, My Lab 50, Florence, Italy). Echocardiograms were obtained in standard parasternal long-axis and short-axis views as well as apical two-, four-, and five-chamber views. LVEF estimations were performed using the modified Simpson's method (12). Two cardiologists agreed upon a diagnosis of CHF based upon an LVEF <45%.

Statistical analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Categorical variables were reported as numbers (n) and percentages (%), whereas continuous variables were expressed as mean and standard deviation (SD) and median and minimum-maximum where appropriate. Student's t-test, Mann-Whitney U test and Chi-square test were used to compare differences between two groups. Kruskal-Wallis test was performed for comparing ejection fraction and HR derivatives in the study group's subgroups. Correlations between the HR derivatives and LVEF were analyzed using Pearson's test. Linear regression analysis was performed to find whether the relationship between HRPI and LVEF, HR mean and LVEF, HR max-mean and LVEF, respectively. A p<0.05 was considered significant.

Results

Baseline characteristics of the population and heart rate derivatives

The study group included 17 male (53.1%) and 15 female (46.9%) subjects with systolic CHF, while the control group consisted of 18 male (56.2%) and 14 female (43.8%) without CHF. The study group did not differ significantly from the control group with regard to age, sex, smoking, hypertension, blood pressure, or BMI. Ten patients were classified as having NYHA class I (31.2%), 12 patients were classified as NYHA class II (37.6%), and 10 patients were classified as NYHA Class III (31.2%). Eight patients had CAD (25%), and 24 patients (75%) had non-ischemic heart failure. The characteristics of the two groups are summarized in Table 1.

In a subgroup analysis, there were differences between NYHA class I-III subgroups in LVEF, HR mean, HR max, HR min, HR max-min and HRPI, respectively, (p=0.020; p=0.030, p=0.011, p=0.041, p=0.028 and p=0.025) (Table 2).

HR mean was higher (p<0.007) and the difference between HR max and HR min was lower in the study group as compared to control group (p<0.001). HRPI values were markedly decreased in patients with CHF compared to control group [0.83 (0.58-1.1) and 1.10 (0.74-1.3), p<0.001] (Table 3). The study and control groups were similar in terms of HR max and HR min (p<0.759 and p<0.287).

Relationship between HRPI and LVEF

When the two groups were analyzed together (n=64), there was a positive correlation between the HR max-min and LVEF (r=0.42, p<0.01) and a negative correlation between HR mean and LVEF (r=- 0.39, p<0.003) (Fig. 1, 2). A significant positive correlation was observed between the HRPI and LVEF (r=0.62, p<0.001) (Fig. 3).

Table 1. The demographics and baseline characteristics of the study participants

Variables	Study group (n=32)	Control group (n=32)	*p
Age, years	60±12	57±9	0.956
Male, n (%)	17 (53.1)	18 (56.2)	0.568
Female, n (%)	15 (46.9)	14 (43.8)	0.789
CAD, n (%)	8 (25)	0	<0.01
Smoking, n (%)	3 (9.3)	4 (12.5)	0.232
Hypertension, n (%)	10 (31.2)	9 (28.1)	0.453
SBP, mmHg	123.2±16.6	139.6±20.4	0.080
DBP, mmHg	81±9.3	85.2±9.4	0.569
BMI, kg/m^2	27.2±2.87	28.7±4.65	0.678
Medication, n (%)			
ARB/ACEI	29 (90.6)	9 (28.1)	<0.05
Loop diuretic	12 (37.5)	5 (15.6)	<0.01
Spironolactone	10 (31.2)	1 (3.1)	<0.01
Acetylsalicylic acid	25 (78.1)	7 (21.8)	0.765
NYHA functional capacity, n (%)			
Class I	10 (31.2)	0	<0.01
Class II	12 (37.6)	0	<0.01
Class III	10 (31.2)	0	<0.01

Data are presented as number (percentage) and mean±SD
* Unpaired Student t-test and Chi-square test.
ACEI - angiotensin-converting-enzyme inhibitors, ARB - angiotensin II receptor blockers, BMI - body mass index, CAD - coronary artery disease, DBP - diastolic blood pressure, EF - ejection fraction, SBP - systolic blood pressure

Table 2. Ejection fraction and HR derivatives in NYHA class subgroups

Variables	NYHA I (n=10)	NYHA II (n=12)	NYHA III (n=10)	*Chi-square	*p
Age, years	58 (33-74)	60 (35-76)	61 (38-78)	0.84	0.216
LVEF, %	40 (36-44)[a,b]	34 (30-38)[c]	28 (22-34)	26.8	0.020
HR mean, beats/min	74±12[a,b]	79±5[c]	89±8	7.43	0.030
HR max, beats/min	114±13[b]	122±9	130±8	5.1	0.011
HR min, beats/min	50±6[b]	52±6[c]	62±9	10.3	0.041
HR max-HR min, beats/min	70±11[a]	67±19	67±15	0.09	0.028
HRPI	0.85 (0.68-1.1)[a,b]	0.88 (0.64-1.02)[c]	0.75 (0.58-1.1)	6.5	0.025

Data are presented as mean ±SD and median (minimum-maximum) values.
*Kruskal-Wallis test, Mann-Whitney U test for the comparison between the groups: [a]between NYHA I vs. NYHA II, [b]between NYHA I vs. NYHA III, [c]between NYHA II vs. NYHA III; p<0.05
HR mean - mean heart rate, HR max - maximal heart rate, HR min-minimal heart rate, HR max-min- the difference value between HR max and HR min, HRPI - heart rate performance index (maximum heart rate-minimum heart rate) /mean heart rate (beat per minute), LVEF - left ventricular ejection fraction

Table 3. 24- hour ambulatory electrocardiographic measurements in study and control groups

Variables	Study group (n=32)	Control group (n=32)	*p
Ejection fraction, %	34±6	59±5	0.018
HR mean, beats/min	80.2±11.3	75.2±6.7	0.007
HR max, beats/min	120.3±12.5	136.2±14.1	0.087
HR min, beats/min	32.4±7.6	53.6±9.3	0.759
HR max-HR min, beats/min	67.9±11.6	83.3±14.3	0.001
HRPI	0.83 (0.58-1.1)	1.10 (0.74-1.3)	0.001

Data are presented as number and mean±SD. and median (minimum-maximum) values
*Student t-test and Mann-Whitney U test.
HR mean-mean heart rate, HR max -maximal heart rate, HR min-minimal heart rate, HR max -min-the difference value between HR max and HR min, HRPI - heart rate performance index (maximum heart rate -minimum heart rate) /mean heart rate (beat per minute), LVEF - left ventricular ejection fraction

Table 4. Linear regression analysis of LVEF association with HR variables

Variables	Beta coefficient	95% confidence interval	*p
HR mean	-0.60	-1.30-0.86	0.084
HR max-mean	-0.46	-1.67-0.74	0.445
HRPI	31.59	-20.64-83.83	0.231

*Linear regression analysis
HR mean-heart rate mean, HRPI-heart rate performance index (Maximum Heart Rate-Minimum Heart Rate) /Mean Heart Rate (beat per minute), LVEF - left ventricular ejection fraction

However, in linear regression analysis we did not find a relationship between LVEF and HRPI (unstandardized β=42, 43, 95% CI: 21.98-50.51, p=0.231), as well as there was no statistically a relationship between LVEF and HR mean, LVEF and HR max-min, respectively, (unstandardized β=-0.22, 95% CI: -0.52 -0.73, p=0.225 and unstandardized β=-0.46, 95% CI -1.66-0.73, p=0.411) (Table 4).

Discussion

In our study, we present the novel use of one aspect of heart rate as determined by H-ECG in the evaluation of patients with CHF. This parameter is denoted here as HRPI and correlates with LVEF in patients with CHF. Notably, we observed a greater difference between HR max and HR min among control subjects as opposed to CHF patients due to the former's increased capacity for exercise. HR mean was elevated in the CHF. We found that the HR mean was higher and the difference between HR max and HR min was lower in the study group as compared to control group. There was a positive correlation between the HRPI and LVEF (r=0.62, p<0.001) as well as a negative correlation between HR mean and LVEF (r=-0.39, p<0.003). There was no a relationship between LVEF and HRPI in linear regression (β=42, 43 95% CI: 21.98-50.51, p=0.231). The results of the investigation showed us that HRPI is a simple practical marker of daily exercise activity and potentially sympathetic activation.

The resting HR and LVEF are practical methods in the assessment of CHF patient, but the studies investigating a relationship between them are very limited. Improved tools will reduce the variability of these analyses and facilitate the evaluation of patients with CHF, particularly with respect to estimates of LVEF. Various heart rate parameters have been used to establish a relationship between autonomic tone and CHF. There is still a need in a new Holter ECG parameter, which could better show the relation between HR and clinical status of the patient. Some heart rate parameters such as heart rate turbulence and HRV are more useful in stratifying cardiovascular risk than in evaluating a given patient's clinical status (13, 14). Although some publications in the past demonstrated the predictive power of the resting heart rate (15, 16), this finding was largely buried beneath the wealth of data on HRV (5, 6, 17).

The increased HRPI values may be an alternative to a decreased resting HR as a target parameter in the assessment in patients with CHF who are only taking only ACEI, ARB or diuretics. The suppression of diurnal heart rate fluctuations in CHF patients results in reduced differences between minimal and maximal HR values as well as an increase in resting heart rate (3, 18). Numerous studies (CIBIS-II, MERIT-HF, COMET and SHIFT) have demonstrated a relationship among increased resting heart rate, mortality and health-related quality of life (2, 19-22). Specifically, the magnitude of HR reduction in patients with HF is associated with a reduction in mortality. Patients with HF and HR>70 beats/min have a significantly greater rate of cardiovascular mortality and risk of hospital admission than those with HR<70 beats/min, and the discrimination by HR is even more accurate in predicting coronary-related vascular outcomes (15). The target heart rate in the treatment of patients with heart failure is typically about 60-70 beats/ min (2, 22). Heart rate can be easily determined during physical examination of the patient and therefore allows a simple hint on the prognosis and efficiency of therapy (23).

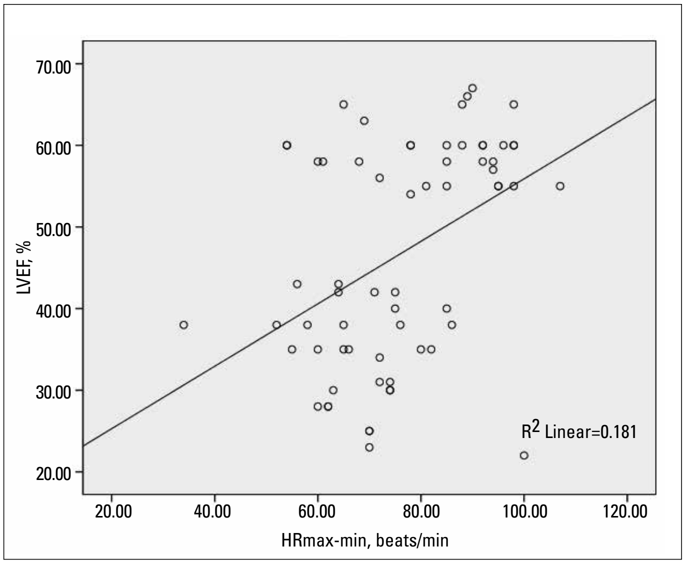

Figure 1. Correlation between HR max-mean and LVEF (Pearson's coefficient r= 0.42, p<0.01)

HR max - maximum heart rate during 24 hours, HR min - minimum heart rate during 24 hours, LVEF - left ventricular ejection fraction

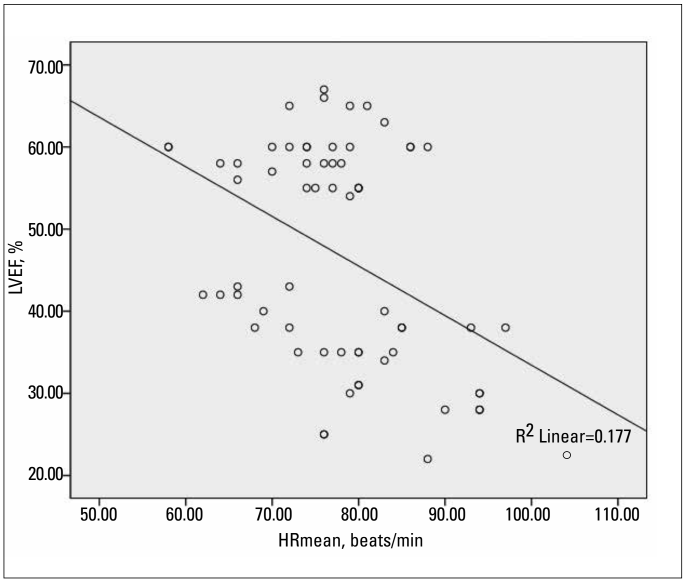

Figure 2. Correlation between HR mean and LVEF (%) (Pearson's coefficient r=- 0.39, p<0.003)

HR mean- averaged heart rate during 24 hours, LVEF - left ventricular ejection fraction

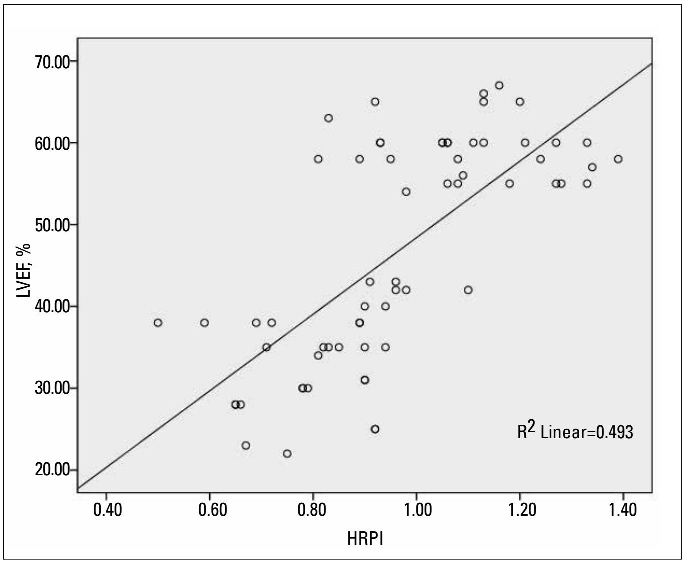

Figure 3. Correlation between HRPI and LVEF (%) (Pearson's coefficient r=0.62, p<0.001)

HRPI - heart rate performance index: HR max-HR min / HR mean, LVEF - left ventricular ejection fraction

The first disadvantage of HRPI, the measurement of HR mean and HR max-min is not routinely very practical, because the true HR min values can be usually obtained in the sleeping phase and the true HR mean value needs during 24 hours recording. But it may be useful in some clinics with no optional commercial Holter ECG tools such as HRV, heart rate turbulence. The analysis of cardiac tone in bedside monitoring with memory capacity can be obtained by the HRPI method, especially in the clinics with the capabilities of ECG monitor having memory capacity and lack of Holter ECG tools. The second disadvantage of HRPI seems to be affected with medication BB, digoxin or ivabradine.

Relatively small number of the study group is the first limitation of the study. We could not find enough new untreated NYHA Class IV patients, especially with no medication on BB, digoxin or ivabradine, and also NYHA Class IV patients were excluded from the study for ethical reasons. Second, all CHF patients were taking medications such as ARB, ACEI and/or diuretics and some subjects of the control were hypertensive and have CAD. Finally, some authors concluded that HR parameters are affected by smoking, gender, physical inactivity and advanced age (24), but we did not take into account these mentioned factors.

Conclusion

We found that there is a positive correlation between LVEF and HRPI, which may be a new approach of the assessment of heart rate in patients with CHF. Our study shows that HRPI may potentially represent a valuable approach in assessing the daily exercise activity and potentially sympathetic activation among CHF patients examined by 24-hour Holter ECG analysis.

HRPI may also be better an alternative method to HR mean or resting HR for using as an indicator of the quality of autonomic cardiac function. The assessment of LVEF and HRPI together may facilitate the evaluation of CHF patients, as well as resting HR. Further studies will be necessary to confirm the utility of this clinical parameter in predicting autonomic activation or in supposing the clinical situation and LVEF in patients with CHF.

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A.A., Ş.A., D.Ç.A.; Analysis &/or interpretation - A.A., N.G.; Literature search - A.A., Ş.A., D.Ç.A.; Writing - A.A.; Critical review - A.A., N.G., Ş.A., D.Ç.A.

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