Correlation of Chronotropic Index and Heart Rate Recovery to Heart Rate Variability and Diastolic Function Values in Men

M Dogru, S Gunaydin, V Simsek, M Tulmac, M Guneri

Citation

M Dogru, S Gunaydin, V Simsek, M Tulmac, M Guneri. *Correlation of Chronotropic Index and Heart Rate Recovery to Heart Rate Variability and Diastolic Function Values in Men*. The Internet Journal of Cardiology. 2006 Volume 4 Number 2.

Abstract

Introduction: Correlation between heart rate recovery (HRR), chronotropic index (CI) values and autonomic and diastolic function data has importance in predicting the pathologic states that coincide with each other in clinical assessment. The aim of the study is to show the relationship of autonomic system and HRR, CI and diastolic functions of the heart.

Method: Fifty-eight healthy asymptomatic men were included in the study. History, physical examination, routine biochemistry, ECG, 24-hour Holter monitoring, color Doppler echocardiography, tissue Doppler echocardiography and exercise stress test were applied to all

Results: While there was a positive correlation between HRR values and logarithmic low frequency (LogLF) and high frequency (LogHF) values (p=.010, p=0.002 respectively); there was a negative correlation with Log LF/LogHF (p=0.034). Comparison of groups having CI below and over 0.8 showed that E/A ratio of transmitral flow was high in low CI subjects (p=0.035,Z : 2109)

Conclusion: HRR and CI showed strong positive correlation with parasympathetic tone as well as diastolic function measurements.

INTRODUCTION

Men are in a higher risk group than women for having hypertension[1,2,3], coronary artery disease[3], stroke[3], sudden cardiac death[4].

Higher sympathetic tone in men particularly before 60 years of age than women [5,6] may increase cardiovascular morbidity and mortality[7]. Heart rate recovery (HRR) and chronotropic index (CI) values have been shown to predict cardiovascular morbidity and mortality [7,26]. Thereby, showing the effects of autonomic balance that could be determinative for replying inner or outer stress factors, on HRR, CI and diastolic functions of the heart is valuable for addressing of autonomic effects on cardiac morbidity and mortality. This study aims at assessing the relationship between HRR, CI, diastolic functions and demonstrating how changes on autonomic balance could affect these factors in the group of healthy asymptomatic men

PATIENTS AND METHODS

Following ethical approval of institutional board and obtaining informed consent, fifty-eight healthy asymptomatic men. Age, height, weight, body mass index, waist and hip circumference, waist/hip ratio were recorded. History, physical examination, routine biochemical tests, complete blood count, thyroid function tests, 12 lead ECG and 24 hour Holter examination (Delmar –Impresario, General Electric, USA) were obtained. Chest X-ray, color Doppler echocardiography (GE-Vivid 7 Pro, General Electric, Florida-USA) and exercise stress test (Quinton 4500 treadmill, Seattle, ABD) were applied to the subjects for differential diagnosis when required. All the tests for each were completed in 15 days.

24 HOUR HOLTER MONITORING, HEART RATE VARIABILITY MEASUREMENTS

Heart rate variability measurements are examined from the records that have no artifacts. Fast Fourier transformation system is used for the evaluation of heart rate variability.

The following parameters were measured:

LF: (Low Frequency) (0.04-0.15 Hz) (msn^2): LF band reflects both sympathetic and parasympathetic activity and is associated with baroreflex activity.

HF: (High Frequency) (0.15-0.4 Hz.) (msn^2): HF band is associated with respiratory frequency and respiration related heart rate changes (respiratory sinus arrhythmia) and reflects cardiac vagal tonus.

LF/HF: LF/HF ratio is believed to reflect sympathetic/parasympathetic activity ratio by some authors.

Normalized LF (LFn): [LF/(LF+HF)] ratio

Normalized HF (HFn) : [HF/(LF+HF)] ratio

Normalized LF (LFn) and Normalized HF (HFn)

Normalized LF and normalized HF are the percentage of each parameter to total power.

Total power (msn^2): It is the total band width consisting of VLF,LF,HF and VHF. [8]

pNN50 (%): percent of differences between adjacent normal RR intervals that are greater than 50 ms over the entire 24 hour recording.

RMSSD (root mean square of successive differences): the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24 hour recording. It is an important marker of parasympathetic activity. [8].

As the results are more valuable logarithmic transformations of LF, HF and LF/HF values are also used in the study[15].

TRANSTHORACIC COLOR DOPPLER ECHOCARDIOGRAPHY

Transthoracic color Doppler echocardiography was done to all of the participants included in the study. Transmitral Doppler flow measurements are taken from the tips of the mitral valve leaflets in apical four chamber view if the patient has normal chamber sizes, no morphologic abnormality, segmental wall motion disorder, hypertrophy or dilatation. E wave velocity, A wave velocity, E/A ratio, mitral E wave deceleration time, isovolumic relaxation time(IVRT), isovolumic contraction time (IVCT), mitral flow period (the period from the beginning of E wave to end of A wave), diastolic period (IVRT + Diastolic filling period :DFP), were measured.

By using tissue Doppler echocardiography Ea, Aa and Ea/Aa ratios were measured. Mainly we used the criteria for evaluation and definition of vary types of diastolic dysfunction that shown in table 6. [9,10,11] Additionally E/Ea ratio which gives an idea about left ventricular filling pressure is measured and the correlation between other variables is determined [9,11]

Table 6: Definitions of some data used in article and diastolic dysfunction criteria

Figure 1

DATA	DEFİNİTİON	RANGES
BMI (kg/m2)	Body mass index	Normal : 18-26
HRR	Heart rate recovery	Normal : >12
CI	Chronotropic index	Normal : >0.8
E/A	Transmitral echo E wave velocity /A Wave velocity ratio	Normal : >1 Relaxative Type-diastolic dysfunction <1 Restrictive Type-diastolic dysfunction >2
IVRT(msn)	Isovolumetric relaxation time	Normal : <100 msn Relaxative Type-diastolic dysfunction >100 msn Restrictive Type-diastolic dysfunction < 60 msn
DECELERATION TIME (DT)(msn)	Transmitral echo E wave deceleration time	Normal :<220 msn Relaxative Type-diastolic dysfunction >220 msn Restrictive Type-diastolic dysfunction <150 msn
Ea (cm/sec.)	Tissue Doppler echo E wave velocity	Normal : >8 Relaxative Type-diastolic dysfunction <8 Restrictive Type-diastolic dysfunction <8
Ea/Aa	Tissue Doppler echo E wave velocity /A Wave velocity ratio	Normal : >1 Relaxative Type-diastolic dysfunction <1 Restrictive Type-diastolic dysfunction <1
E/Ea	Transmitral echo E wave velocity / Tissue Doppler echo E wave velocity ratio	Normal : <8 If E/Ea > 10 , pulmonary capillary wedge pressure greater than 15 mmHg[32]. If E/Ea > 15 , Left ventricular diastolic pressure greater than 12 mmHg[33].

EXERCISE STRESS TEST

All of the participants were tested using Bruce Protocol between 14:00 and 16:00 in daytime. A light lunch and a 30 minute rest were applied. In the case of excessive tea ,alcohol, and coffee intake and excessive physical activity the test was delayed. Getting target heart rate, symptoms about angina or equivalents, ischemic electrocardiographic changes during the test are accepted as positive test criteria and the participant's request were indications to terminate the test [12].After terminating the test, heart rate was recorded in the cool down period's first and third minutes

Heart Rate Recovery (HRR) was calculated as [HRR= HR_{peak} – HR 1.minute rest].

Chronotropic index (CI) was calculated as [(HR_{peak} –HR_{rest})/ (220– age– HR_{rest})]

The participants were grouped according to HRR value's being below 12 and above 12, chronotropic index being below 0.8 and above 0.8. and the differences between these groups were examined. [7,12]

STATISTICAL ANALYSIS

SPSS 11.5 for Windows was used for statistical analysis. The correlation between the data were analyzed by Pearson and Spearman tests. The factors to have an influence on results like age, weight, body mass index, waist circumference hip circumference and waist/hip ratio were controlled by 2 way partial correlation. Partial correlation analysis results are shown in tables. Mann-Whitney U test was used for the comparisons of CI data as the data were not normally distributed. The results were shown in tables as mean± Standard deviation (SD) and Z values. P value less than 0.05 was defined as statistically significant.

RESULTS

Table 1 demonstrates the baseline data of all the participants. In the tables about correlation data, the partial correlation analysis results are shown in order to eliminate the possible effects of age, weight, body mass index, and waist/hip ratio. The positive and negative signs shown before the p values points out the direction of the correlation.

Figure 2

Table 1: Patient characteristics

N=58	Minimum	Maximum	mean±SD
Age (years)	29	59	46.02±6.75
Height (cm)	160.00	185.00	171.74±5.76
Weight (kg)	65.00	120.00	81.55±10.53
Body Mass Index (BMI) (kg/m²)	22.04	38.97	27.67±3.50
Waist circumference (cm)	80.00	124.00	98.65±8.54
Hip circumference(cm)	80.00	120.00	92.22±6.86
Waist hip ratio(m)	0.95	1.20	1.04±0.064

Table 2 reveals the HRR and chronotropic index data obtained after exercise stress testing and heart rate variability data. HRR was negatively correlated both minimal and mean heart rate that determined 24 hour holter monitoring (p=0.028 and p=0.002 respectively). Otherwise HRR was positively correlated with both the HRR parameters Log LF and Log HF(p=0.01 and p=0.002 respectively) and time based parameters pNN50 and RMSSD(p=0.022 and p=0.032 respectively).HRR was negatively correlated with as a sympathetic tone marker LogLF/LogHF ratio (p=0.034 and p=0.028 respectively)

Figure 3

Table 2: Heart rate variability data, HRR and CI correlations

Heart rate variability data 24 hours	HRR		CHRONOTROPİC İNDEX	
	C	p	C	P
Minimum heart rate.	–	0.028*	+	N
Maximum heart rate.	–	N	+	N
Mean heart rate	–	0.002¶	+	N
Log LF	+	0.010*	+	0.019*
Log HF	+	0.002¶	+	N
Log TOTAL	+	0.013*	+	0.006¶
Log LF/HF	–	0.034*	–	N
LFn	–	N	–	N
HFn	+	N	+	N
PNN50	+	0.022*	+	N
RMSSD	+	0.032*	+	N
SDNN	+	0.046*	+	N
SDNN index	+	0.009*	+	N

P< 0.05 is significant, N : P>0.05 , * : P< 0.05 , ¶: P<0.01, #: P<0.001

C: (–): Negative correlation , (+) : Positive Correlation

Table 2 shows the partial correlations between HRR,CI and HRR.

Chronotropic index was also positively correlated with LogLF (P=0.019).Both HRR and CI was positively correlated with total power (p=0.013 and p=0.006 respectively)

Although not being the main purpose of our study HRR data were compared with transmitral flow patterns and tissue Doppler data (Table 3).While autonomic tone values were not correlated with transmitral flow patterns, there was a close correlation with tissue Doppler data. As a sympathetic tone marker, LFn were negatively correlated with Ea and Ea/Aa (p<0.001 and p=0.001 respectively) whereas positively correlated with E/Ea (p=0.037)which is suggested to be positively correlated with diastolic filling pressure([9,10,11]).These correlations were exactly the opposite for the parasympathetic tone marker HFn (table 3). As a symphatetic tone marker, LFn/ HFn mainly correlated same way by LFn with echocardiographic data. LFn/ HFn was negatively correlated with Ea and Ea/Aa (p<0.001 and p<0.001 respectively); positively correlated with E/Ea (p=0.004)

Figure 4

Table 3: The correlations between transmitral and tissue Doppler data and some significant heart rate variability data.

	LFn Sympathetic tonus marker		HFn Parasympathetic tonus marker		LF/ HF Sympathetic tonus marker	
	K	P	K	P	K	P
E	–	0.793	+	0.793	–	0.989
A	+	0.300	–	0.300	+	0.668
E/A	–	0.137	+	0.137	–	0.447
Ea	–	<0.001#	+	<0.001#	–	<0.001#
Aa	–	0.299	+	0.299	–	0.691
Ea/Aa	–	0.001¶	+	0.001¶	–	<0.001#
E/Ea	+	0.037*	–	0.037*	+	0.004¶

P< 0.05 is significant. N : P> 0.05 , * : P< 0.05 , ¶: P<0.01, #: P<0.001

C: (–): Negative correlation , (+) : Positive correlation

HRR and CI were significantly correlated with echocardiographic and autonomic values.

HRR,CI and diastolic function relations were also examined in our study.(Table 4)which shows the partial correlation results demonstrates the parasympathetic tone marker HRR([7]) was positively correlated with diastolic period and mitral flow period and negatively correlated with systolic/diastolic period(p=0.002,p=0.025 and p=0.005 respectively). HRR and CI likewise heart rate variability measures were not correlated with transmitral flow patterns (only E/A ratio is correlated with HRR. p=0.048) but correlated with tissue Doppler data. HRR was positively correlated with Ea and Ea/Aa (p=0.050 and p=0.001 respectively) whereas negatively correlated with Aa and E/Ea (p=0.012 and p=0.024 respectively).But the correlation between CI and tissue Doppler data was more significant. CI was positively correlated with Ea and Ea/Aa (p=0.002 and p=0.001 respectively) and negatively correlated with E/Ea (p<0.001)

Figure 5

Table 4: Echocardiographic data, HRR and CI correlations

Echocardiographic data	HRR		CHRONOTROPİC İNDEX	
	C	p	C	p
E	+	N	–	N
A	–	N	+	N
EA	+	0.048*	–	N
IVCT	–	N	+	N
IVRT	+	N	+	N
DECELERATİON TIME	–	N	–	N
MİTRAL FLOW PERIOD	+	0.025*	–	N
DİASTOLE	+	0.002¶	–	N
Ea	+	0.050*	+	0.002¶
Aa	–	0.012*	+	N
Ea/Aa	+	0.001¶	+	0.001¶
E/Ea	–	0.024*	–	<0.001#

P< 0.05 is significant. N : P> 0.05 , * : P< 0.05 , ¶: P<0.01, #: P<0.001
C: (–): Negative correlation , (+) : Positive correlation

After performing the exercise stress test the chronotropic indexes were calculated and the participants were divided into two subgroups according to having a CI value of less than or equal to 0.8 or above 0.8. Comparisons about these two subgroups are shown in table 5. As only 4 of 58 participants had the pathologic value of less than 12/minute subgroup analysis was not done. The subgroup having a CI index of less than 0.8 has decreased HF(parasympathetic tone) , total power and SDNN (p=0.023, Z:2.271; p=0.013, Z:2.471; P=0.042, Z: 2.035 respectively), and increased transmitral E/A ratio and E/Ea (p=0.035 Z:2.109; p<0.001 Z:4.625 respectively) decreased Ea wave and Ea/Aa (p<0.001 Z:3.646 ; p<0.001 Z:3.835 respectively)

Figure 6

Table 5: Echocardiographic and heart rate variability data with respect to chronotropic index

MANN- WHİTNEY U Test	CHRONOTROPIC İNDEX >0.8(A) mean± SD n=44	CHRONOTROPIC INDEX <0.8 (B) mean± SD n=14	Z	P
MAXIMUM HEART RATE	124.11±11.18	120.61±13.72	1.000	0.317
MINIMUM HEART RATE	52.34±6.64	56.15±7.01	1.925	0.054
MEAN HEART RATE	73.93±8.32	75.53±7.03	0.719	0.472
ECHOCARDIOGRAPHIC DATA				
E	0.74±0.14	0.84± 0.21	1.837	0.660
A	0.72± 0.17	0.70±0.14	0.232	0.788
E/A	1.05± 0.23	1.21±0.28	**2.109**	**0.035**
IVCT	72.19±20.36	68.53±34.49	1.295	0.195
IVRT	92.91±24.74	88.04±23.95	0.915	0.360
DECELERATION TIME	206.90±71.77	238.62±60.37	1.835	0.066
MITRAL FLOW PERIOD	419.54±140.23	462.96±134.50	1.265	0.206
DIASTOLE	515.33±148.72	551.00±138.16	1.075	0.282
Ea	0.71±0.22	0.45±0.06	**3.646**	**<0.001**
Aa	0.75±0.13	0.78±0.18	0.173	0.863
Ea/Aa	0,94±0.23	0.62±0.21	**3.835**	**<0.001**
E/Ea	1.13±0.39	1.93±0.50	**4.625**	**<0.001**
HEART RATE VARİABİLİTY DATA				
LF	408.60±237.66	298.42±211.11	1.763	0.078
HF	196.27±208.69	89.48±67.38	**2.271**	**0.023**
TOTAL	1309.49±726.26	806.65±449.76	**2.471**	**0.013**
LF/HF	3.19±1.90	4.16±2.17	1.654	0.098
LFn	0.71±0.13	0.76±0.123	1.635	0.102
HFn	0.28±0.13	0.23±0.12	1.635	0.102
PNN50	8.31±8.17	5.76±6.47	1.236	0.217
RMSSD	37.80±19.04	28.46±9.72	1.699	0.089
SDNN	153.01±36.51	129.62±29.79	**2.035**	**0.042**
SDNN index	48.17±13.58	40.77±10.47	1.826	0.068

A: CHRONOTROPIC İNDEX >0.8 , B: CHRONOTROPIC İNDEX <0.8
Mann- Whitnev U Test. P< 0.05 is significant.

DISCUSSION

HRR and chronotropic index both as an autonomic tone marker and having prognostic significance has been the subject of many studies recently[7].Previous studies have shown that HRR is a good marker of parasympathetic activity[7,13,14]. The close relation between HRR and heart rate variability and the parasympathetic tonus marker HF is well documented[14,15].Our study stated a significant positive correlation between HRR and all the parameters of parasympathetic tone .The correlation between HF and HRR was present also after eliminating the effect of age, weight, waist and hip circumferences (table 2).

Not only the HF parameter but also the LF values were positively correlated with HRR. LF value generally defined as a sympathetic tonus marker [8,16,17] is thought to be related with both sympathetic and parasympathetic tonus, sympathetic and parasympathetic efferent modulation of baroreflex activity, sympathetic modulation of vasomotor activity and increases during the reflex activities with the changes in blood pressure[7,16,17,18,19]. There are studies that LF component is not solely related with sympathetic activity[19,28].Previous studies has not examined the relation of HRR and LF values in detail. The significant negative correlation between LF and HRR determined by Evrengul et al[21] was not noted in our study. But contrarily to our study that study was executed on a population of coronary artery disease. HRR which is an important marker of parasympathetic activity[7] not only had positive correlation with parasympathetic tonus parameters but also with the LF values indicating that the vagal control mechanism is not free from LF value. Martinmaki et al stated decrement of LF and total power besides the HF value after complete vagal blockade [22].LF value is believed to reflect not only sympathetic but also the parasympathetic activity [7, 19, 22]. These results can explain the correlation between HRR and LF values found in our study. The sympathovagal balance marker LF/HF showed a strong negative correlation with HRR as usual. The increase in sympathetic tone results in shortening of the sinoatrial node recovery time. In addition to these HRR is positively correlated with SDNN values which have predictive value for cardiovascular mortality[7]. As the predictive value of HRR for cardiovascular morbidity has already been known, it is not surprising for HRR to be correlated with other predictive factors.

There was a significant correlation between HRR and diastolic function data. Autonomic system is suggested to be the factor that relates this group of data. The presence of positive correlation with Ea and Ea/Aa and the negative correlation with E/Ea with both HRR and CI suggested that the increase in sympathetic tonus shows the same effect on ventricular muscle and sinus node. Previous studies have emphasized on the close relationship between tissue Doppler data and autonomic tonus.[23].Obtained data suggested that the increase in sympathetic tonus decreased the compliance of ventricular myocardium besides decreasing HRR and CI by the effect on sinus node. While there was not a significant correlation between HRR and transmitral flow values, there was a significant correlation between HRR and tissue Doppler data. This may be related to the fact that transmitral flow is highly dependent on other factors affecting volume and transmitral flow[10].This study also revealed the significant correlation between tissue Doppler data and autonomic tonus. A decrease in Ea wave and an increase in Aa wave is seen with the increase in sympathetic tonus while the increase in parasympathetic tonus is correlated with the increase in Ea wave. This situation can be explained with the increased sympathetic tone but it is surprising to see this finding in asymptomatic men. This demonstrates that the decrease in ventricular compliance due to sympathetic tonus does not have to occur in a pathologic state. The correlation between the diastolic functions obtained by tissue Doppler and heart rate variability has been demonstrated in previous studies, but this is beyond our study purpose. The strong correlation between HRR and diastolic period that is affected by parasympathetic tonus is an expected result. As it is known, E/Ea is correlated with left ventricular filling pressure. [9,11]HRR is negatively correlated E/Ea in our study. The increase in sympathetic tonus increases left ventricular filling pressure besides decreasing HRR.

Chronotropic index also predicts cardiovascular morbidity and mortality like HRR [20,21,22]. CI was positively correlated with LF like HRR. But the insufficiency of the chronotropic adaptability can not be explained with the presence of the parasympathetic component of LF. This partially contrary state may be related with the positive correlation of LF seen with adrenalin but not with noradrenalin [28].Colucci et al. stated desensitization to noradrenalin after a long term sympathetic activation [27].The desensitization formed against beta1 receptors can be bypassed with adrenalin which also stimulates beta2 receptors. The effect of beta2 receptors on the control of heart rate has been documented [27]. Adrenalin is thought to control the heart rate by beta2 receptor stimulation when noradrenalin increase in response to exercise [28,30]has less effect on heart rate control due to down-regulated beta1 receptors under chronic stimulation [27,29]. Adrenalin forms the escape pathway of chronotropic response by the help of desensitized beta2 receptors [29,30,31].At this point of view, the positive correlation of LF value with increased adrenalin and chronotropic index is an expected result. But the study design and the results are not sufficient to comment. Further studies with larger group of subjects are warranted.

The autonomic tonus changes that explains the relation between HRR and tissue Doppler data is also responsible for the same relation between CI and tissue Doppler data. The comparison of the two subgroups of CI grouped according to having values less or equal to 0.8 or greater than 0.8, supports our other results.

The decrease in Ea/Aa ratio which is a marker of the decrease in CI and ventricular compliance and the increase in E/Ea ratio which is related with increased ventricular filling pressure are the results of possible increased sympathetic tonus particularly under the effect of noradrenalin. Although not being tested noradrenalin levels are expected to be high in the group of low CI values [7,27]. . Another interesting result that took attention, contradictory negative correlation was determined transmitral flow E/A ratio and CI. It was interpreted that this result depended on flow dependency of transmitral echocardiographic values. Also it was considered us, increased end diastolic pressure of left ventricle and more restrictive response accompanied increased sympathetic tone even though the group is healthy.

CONCLUSION

HRR and chronotropic index values which have important predictive value for cardiac morbidity and mortality are associated with the changes in sympathetic tonus and these changes parallels with the diastolic function changes.

CORRESPONDENCE TO

Dr. M .Tolga DOGRU, University of Kirkkale, Kirikkale-Turkey 7100 Tel:+90-3182252485 , +90-5554727096 Fax +90-3182252819 E-mail: mtolgadogru@superonline.com

References

1. Burt VL, Whelton P, Roccella EJ, et al. 1995 Prevalence of hypertension in the U.S. adult population: results of the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension 1995; 25:305-313.
2. August P.Hypertension in men.J Clin Endocrinol Metab 1999; 84(10):3451-4.
3. The Heart, Hurst's, Chapter 2, The burden of increasing worldwide cardiovascular disease. Pages 19-37, Mc Graw Hill, 11. ed , 2004.
4. The Heart, Hurst's, Chapter 41, Sudden Cardiac Death. Page 1053, 11. ed., Mc Graw Hill, 2004.
5. Fagard RH, Pardaens K, Staessen JA. Influence of demographic, anthropometric and lifestyle characteristics on Heart rate and its variability in the population. J Hypertens 1999 Nov;17(11):1589-99.
6. Kuo TB, Lin T, Yang CC, Li CL, Chen CF, Chou P. Effect of aging on gender differences in neural control of heart rate.AmJ Physiol 1999 Dec;277(6 Pt 2):H2233-9.
7. Textbook of cardiovascular medicine, Eric J Topol, chapter 77 , clinical assesment of the autonomic nervous system. Pages1615-27. 2. ed., Lippincott Williams& Wilkins, 2002.
8. Camm AJ, Malik M, Bigger J et al. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996; 93: 1043-1065
9. Feigenbaum's echocardiography , chapter 6 , Evaluation of diastolic function. Pages 169-179. 6. ed, Lippincott Williams& Wilkins, 2005.
10. Restrictive cardiomyopathy. Thamilarasan M., Klein A. In: The Practice of Clinical Echocardiography, Catherine M Otto. Second ed. Chapter 28. Pages 619-620. WB.Saunders. Philedephia 2002.
11. Left Ventricular Diastolic Function. Smith DM. In: The Practice of Clinical Echocardiography, Catherine M Otto. Second ed. Chapter 6. Pages 135-136. WB.Saunders. Philedephia 2002.
12. Braunwald's Heart Disease, chapter 10, exercise stres testing, Pages 155-165. 7. ed. Elsevier Saunders, 2005.
13. Imai K, Sato H, Hori M et al. Vagally mediated heart rate recovery after exercise is accelerated in athletesbut blunted in subjects with chronic heart failure.J Am Coll Cardiol 1994 Nov; 24(6):1529-35.
14. Arai Y, Saul JP, Albrecht P, Hartley LH, Lilly LS, Cohen RJ, Colucci WS. Modulation of cardiac autonomic activity during and immediately after exercise.Am J Physiol 1989; 256(1 Pt 2):H132-41.
15. Ohuchi H, Suzuki H, Yasuda K, Arakaki Y, Echigo S, Kamiya T. Heart rate recovery after exercise and cardiac autonomic nervous activity inchildren. Pediatr Res 2000 Mar;47(3):329-35.
16. Kamath MV, Fallen EL. Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. Crit Rev Biomed Eng 1993;21(3):245-311.
17. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain.Circulation. 1991 Aug; 84(2):482-92.
18. Pagani M, Lombardi F, Guzzetti S et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986 Aug; 59(2):178-93.
19. Hopf HB, Skyschally A, Heusch G, Peters J. Low-frequency spectral power of heart rate variability is not a specific marker of cardiac sympathetic modulation. Anesthesiology 1995 Mar;82(3):609-19.
20. Bilchick KC, Berger RD. Heart rate variability. J Cardiovasc Electrophysiol 2006 Jun;17(6):691-4.
21. Evrengul H, Tanriverdi H, Kose S, Amasyali B, Kilic A, Celik T, Turhan H. The relationship between heart rate recovery and heart rate variability in coronary artery disease.Ann Noninvasive Electrocardiol 2006 Apr;11(2):154-62.
22. Martinmaki K, Rusko H, Kooistra L, Kettunen J, Saalasti S.Intraindividual validation of heart rate variability indexes to measure vagaleffects on hearts.Am J Physiol Heart Circ Physiol 2006 Feb;290(2):H640-7.
23. Skaluba SJ, Litwin SE. Doppler-derived left ventricular filling pressures and the regulation of heartrate recovery after exercise in subjects with suspected coronary artery disease. Am J Cardiol 2005 Apr; 95(7):832-7.
24. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic

implications ofchronotropic incompetence in the Framingham Heart Study. Circulation. 1996 Apr; 93(8):1520-6.
25. Brener SJ, Pashkow FJ, Harvey SA, Marwick TH, Thomas JD, Lauer MS. Chronotropic response to exercise predicts angiographic severity in subjects with suspected or stable coronary artery disease. Am J Cardiol. 1995 Dec;76(17):1228-32.
26. Dresing TJ, Blackstone EH, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. Am J Cardiol 2000 Sep ; 86(6):602-9.
27. Colucci WS, Ribeiro JP, Rocco MB et al. Impaired chronotropic response to exercise in subjects with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization.Circulation 1989; 80(2):314-23.
28. Sloan RP, Shapiro PA, Bagiella E, Bigger JT Jr, Lo ES, Gorman JM. Relationships between circulating catecholamines and low frequency heart period variability as indices of cardiac sympathetic activity during mental stress. Psychosom Med 1996; 58(1):25-31.
29. Leenen FH, Davies RA, Fourney A. Catecholamines and heart function in heart transplant subjects: effects of beta1- versus nonselective beta-blockade.Clin Pharmacol Ther 1998; 64(5):522-35.
30. Leenen FH, Davies RA, Fourney A.Role of cardiac beta 2-receptors in cardiac responses to exercise in cardiactransplant subjects.Circulation 1995; 91(3):685-90.
31. Omodani H, Kinugawa T, Ogino K et al. Augmented exercise plasma noradrenaline with impaired chronotropic responsiveness in subjects with hypertrophic cardiomyopathy.Clin Exp Pharmacol Physiol 1998;25(12):1018-23.
32. Nagueh SF, Middleton KJ, Kopelen HA, et al. : Doppler tissue imaging :A noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527.
33. Ommen SR, Nishimura RA, Appleton CP, et al: Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular pressures: A Comparative simultaneous Doppler - Catheterization study. Circulation 2000; 102:1788.

Author Information

M. Tolga Dogru
Department of Cardiology, Kirikkale University

Serdar Gunaydin
Department of Cardiovascular Surgery, Kirikkale University

Vedat Simsek
Demet Hospital

Murat Tulmac
Department of Cardiology, Kirikkale University

Mahmut Guneri
Department of Cardiology, Kirikkale University