

## Original Article

# Utility of Exercise Electrocardiographic Stress Test for Assessment of Cardiac Autonomic Function in Hypertensive Patients

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**ABSTRACT**

**Objective:** To evaluate the usefulness of recovery time after a treadmill exercise ECG test for assessment of autonomic function in hypertensive patients using Holter-based heart rate variability as a reference.

**Methods:** One hundred untreated hypertensive patients were included in the study. Echocardiography was done to assess left ventricular mass index and function. Exercise ECG test was done in all patients. The heart rate recovery was calculated as the reduction in heart rate from its peak value to one minute of the recovery time. A cut off value of 12 beats/minute or less was considered abnormal. The patients were classified into two groups; Group I: included 70 patients with impaired heart rate variability and Group II: included 30 patients with normal heart rate variability. Holter 24 - hour ECG monitoring was done in all patients for assessment of heart rate variability.

**Results:** There was a significant impaired heart rate variability in hypertensive patients, with impaired heart

rate recovery than in those with normal heart rate recovery ( $p < 0.05$ ). Predictive indices of heart rate recovery after exercise ECG test, for assessment of cardiac autonomic function revealed a sensitivity of 74%, specificity of 83.3%, positive predictive value of 91.5 %, negative predictive value of 58.2 % and an accuracy of 77%. Stepwise logistic analysis revealed a significant relation between the maximal heart rate during exercise test, time-domain heart rate variability variables (r-MSSD & p-NN50) and impaired heart rate recovery after exercise ECG test in hypertensive patients ( $p < 0.05$ ). There was a significant correlation between Holter based vagal dependent r-MSSD and the heart rate recovery after exercise test ( $p < 0.05$ ).

**Conclusion:** Incorporation of heart rate recovery after exercise may eventually be considered an useful diagnostic test for assessment of autonomic nervous system function in hypertensive patients.

KEY WORDS : autonomic function, cardiac, heart rate recovery, holter monitor

**INTRODUCTION**

The increase in heart rate during exercise is thought to be due to a combination of parasympathetic withdrawal and sympathetic activation. However, the reduction in heart rate immediately after exercise is mainly thought to be a function of a reactivation of the parasympathetic nervous system<sup>[1]</sup>. It has been shown in a large study of subjects undergoing a symptom-limited exercise test for diagnostic purposes that the reduction in heart rate from peak exercise to one minute after termination was a powerful predictor of death during a follow-up period of six years. Similar findings have also been reported in other cohorts of patients and in healthy subjects<sup>[2]</sup>. Heart rate variability (HRV), either evaluated in the time domain or in the frequency domain, is considered a valid tool for investigating the influence of the autonomic nervous system on the heart. It has repeatedly been shown that both measurements in the time domain and in the frequency domain,

especially in the low frequency part, are powerful predictors of subsequent cardiovascular events and mortality in patients with coronary artery disease or congestive heart failure and in a sample population<sup>[3]</sup>. Pitzalis *et al*<sup>[4]</sup> reported that hypertensive patients show impaired baroreflex heart rate response and that this is particularly evident in those with functional and anatomic involvement.

The aim of this study was to evaluate the utility of recovery time after treadmill exercise ECG test to assess autonomic function in hypertensive patients.

**PATIENTS AND METHODS****Study patients:**

The study included one hundred pharmacologically untreated hypertensive patients (80 male and 20 female). All patients were evaluated clinically by looking at the history, physical examination, 12-lead ECG, routine laboratory investigations, echocardiography and Doppler study.

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**Table 1**

Clinical and echocardiographic data in both groups

Variables	Group I	Group II	p- value
Age (years) M ± SD	48.216 ± 3.18	47.42 ± 4.29	NS
Male n (%)	58 (82.86)	22 (73.33)	NS
Female n (%)	12 (17.14)	8 (26.67)	NS
LVMi (gm/m <sup>2</sup> )	33.41 ± 11.54	49.16 ± 12.23	NS
E/Aratio	0.81 ± 0.11	1.32 ± 0.21	<0.05

LVMi = left ventricular mass index, M = mean, n = number, SD = standard deviation, NS = not significant

**Table 2**

Stepwise logistic multivariate analysis of patients with impaired heart rate recovery as regards their resting heart rate, resting systolic and diastolic blood pressure, maximal heart rate and maximal systolic blood pressure during exercise

Variables	R	SE	p- value	95% CI
Resting HR	0.0522	0.0178	NS	0.854 ---- 1.731
Resting SBP	0.0258	0.0789	NS	0.923 ---- 1.176
Resting DBP	0.0632	0.0649	NS	0.976 ---- 1.023
Maximal HR	0.1143	0.0974	<0.05	1.061 ---- 1.892
Maximal SBP	0.0678	0.0378	NS	0.654 ---- 1.531

CI = confidence interval, HR = heart rate, DBP= diastolic blood pressure, R = regression coefficient, SBP = systolic blood pressure, SE = standard error, NS = not significant

Exclusion criteria included patients with diabetes mellitus, cerebrovascular disease, significant valvular disease, irritability, anxiety, chronic obstructive lung disease and history of heart failure. Exclusion was based on medical history, physical examination, routine biochemical tests, and echocardiography to avoid confounding factors.

#### Echocardiographic study:

Two-dimensional and M-mode echocardiography were performed in all patients in the study using HP Sonos 1000 and a 3.5 MHZ phased array transducer. Left ventricular dimensions were measured at or immediately below the tips of the mitral leaflets and were averaged over 5 heart cycles. Left ventricular mass and left ventricular mass index were calculated.

#### Twenty-four hour Holter monitor and heart rate variability:

All subjects and patients of the study underwent continuous ambulatory 3 - channel Holter monitoring for 24 hours. Time domain measures that were determined from normal to normal sinus beats included the mean R-R interval and its SD (SDNN), the percentage of successive R-R intervals that deviated by >50% from the prior RR interval (p-NN50), the root mean square of successive RR interval differences (r MMD) and the SD of the

**Table 3**

Agreement of the Holter - based heart rate variability and heart rate recovery after exercise

	Impaired HRV	Normal HRV
Impaired HRR	52	5
Normal HRR	18	25
Total	70	30

Kappa coefficient value = 0.786

HRR=heart rate recovery; HRV = heart rate variability; Sensitivity = 74%; Specificity = 83.3%; Positive predictive value = 91.5%; Negative predictive value = 58.2%; Accuracy = 77%

**Table 4**

Stepwise logistic multivariate analysis of patients with impaired heart rate recovery as regards the ambulatory 24-hour Holter-based frequency domain heart rate variability variables

Variables	R	SE	p- value	95% CI
Total power	0.0522	0.0978	NS	0.454 ---- 1.240
LF power	0.1258	0.0789	<0.05	1.229 ---- 1.976
HF power	0.0632	0.0649	NS	0.976 ---- 1.023
LF/HF power ratio	0.0143	0.0174	NS	0.761 ---- 0.892

CI = confidence interval, HR = heart rate, DBP= diastolic blood pressure, R = regression coefficient, SBP = systolic blood pressure, SE = standard error, NS = not significant

average of RR intervals in all 5-minutes segments of the 24-hour recording (SDANN)<sup>[5]</sup>.

#### Treadmill exercise ECG test protocol:

All patients in the study underwent exercise ECG test using standard or modified Bruce models as a baseline. Resting blood pressure (measured manually by arm-cuff sphygmomanometer) was measured in supine and standing positions before the test. Patients with orthostatic hypotension (defined as a decrease of >20 mmHg in systolic blood pressure (SBP) after standing) were excluded. Resting ECG was done for all patients to exclude patients with significant ST segment changes, left bundle branch block or tachyarrhythmias.

#### Recovery after exercise:

After achieving peak workload, the treadmill was stopped and blood pressure, heart rate, rhythm and symptoms were recorded immediately with the patient in the standing position (no cool down period). The same data were also recorded at one minute into recovery in the supine position. Heart rate recovery was calculated as reduction in heart rate from the peak to one minute of the recovery time and a cut off value of 12 beats/minute or less was considered abnormal<sup>[6]</sup>. Monitoring was terminated at six minutes into the recovery unless warranted by symptoms or electrocardiographic changes.

**Table 5**

Stepwise logistic multivariate analysis of patients with impaired heart rate recovery as regards the ambulatory 24-hour Holter-based time domain heart rate variability variables

Variables	R	SE	p-value	95% CI
Mean RR	0.0621	0.0775	NS	0.251 — 1.131
SDNN	0.0351	0.0769	NS	0.829 — 1.071
SDANN	0.0538	0.0547	NS	0.676 — 1.073
r-MSSD	0.1341	0.1199	<0.05	1.261 — 1.652
p-NN50	0.1628	0.1944	<0.05	1.054 — 1.831

p-NN50 = proportion of adjacent RR >50 ms difference, r-MSSD = root mean square of difference of successive RRs, RR = RR-interval, SDANN = standard deviation of 5-minute mean RR-interval, SDNN = mean of all 5-minute standard deviation of RRs, NS = not significant

### Predictive Indices:

The following indices were calculated - True positive (TP), true negative (TN), false positive (FP) and false negative (FN), sensitivity = TP / (TP+FN), specificity = TN / (TN+FP), positive predictive value = TP / (TP+FP), negative predictive value = TN / (TN+FN) and accuracy = (TP+TN) / (TP+TN+FP+FN).

### Statistical analysis:

Continuous variables are summarized as mean  $\pm$  standard deviation (SD). Comparison between two groups was performed with t-test for continuous variables and chi-square test for categorical variables. A p-value <0.05 was considered statistically significant and a p-value <0.01 was considered highly significant. A stepwise multivariate regression model was used to identify possible independent variables associated with impaired heart rate recovery after exercise in hypertensive patients. The strength of the association with impaired heart rate recovery is presented as 95% confidence intervals. Potential confounding of clinical variables was entered as independent variables.

The validity of the exercise ECG stress test was assessed by estimating the predictive indices and Kappa coefficient to determine its overall agreement with the data obtained from the 24-hour Holter- ECG monitoring.

The Kappa coefficient value (k) = (Observed frequency of agreement - Expected frequency of agreement) / (Total observed - Expected frequency of agreement).

## RESULTS

There were two groups :

- Group I: included 70 hypertensive patients with impaired heart rate variability.
- Group II: included 30 hypertensive patients

with normal heart rate variability.

Clinical characteristics: Both groups were well matched as regards their demographic data (p = NS) (Table 1). There was no significant difference between both groups as regards the percentage of patients with history of smoking, hypercholesterolemia, lipid lowering drugs use and history of prior myocardial infarction (30 (42.86%) versus 16 (53.33 %), p = NS, 20 (28.57 %) versus 10 (33.33 %) patients, p = NS, 15 (21.42 %) versus 7 (23.33 %), and 28 (40%) versus 10 (33.33 %), p = NS) respectively. There was no significant difference regarding the resting heart rate between both groups ( $87.35 \pm 6.92$  versus  $79.8 \pm 8.92$  beat/minute, respectively, p = NS), but there was a significant increase in systolic and diastolic blood pressure in the hypertensive patients with impaired heart rate recovery after exercise than those with normal heart rate recovery ( $179.5 \pm 12.41$  versus  $162.35 \pm 8.11$  mmHg, and  $109.8 \pm 5.32$  versus  $96.84 \pm 6.18$  mmHg, respectively, p<0.05).

### Echocardiographic findings:

There were no significant differences between patients with normal heart rate recovery and those with impaired heart rate recovery after exercise as regards the LVMI and EF ( $127.3 \pm 5.47$  versus  $126.53 \pm 4.28$  gm/m<sup>2</sup>, p = NS and  $60.61 \pm 4.22$  versus  $62.52 \pm 3.22\%$ , p = NS) respectively but there was a significantly decreased E/Aratio in the hypertensives with impaired heart rate recovery than those with normal heart rate recovery ( $0.81 \pm 0.11$  versus  $1.32 \pm 0.21$ , respectively, p<0.05), Table 1.

### Exercise ECG test:

There was an insignificant difference between both groups as regards the peak heart rate during exercise ( $165.8 \pm 7.66$  versus  $158.4 \pm 9.21$  beats/minute, respectively, p = NS) but there was a significant increase in peak blood pressure and a significant decrease in the duration of the exercise test in hypertensives with impaired heart rate recovery after exercise than those with normal heart rate recovery (p<0.05).

There was a significant decrease in the variables of Holter-based vagal dependent heart rate variability (p-NN50 and r-MSSD) in hypertensive patients with impaired heart rate recovery after exercise than those with normal heart rate recovery after exercise (p<0.01), Fig. 1&2. There was a significant correlation between Holter-based vagal dependent heart rate variability parameter r-MSSD and the heart rate recovery after exercise ( $y = 7.5 + 0.12x$ ,  $r = 0.875$ , p<0.05), Fig. 3.

Stepwise logistic multivariate analysis revealed that there was no significant relationship between the age of the patients, gender, smoking, left

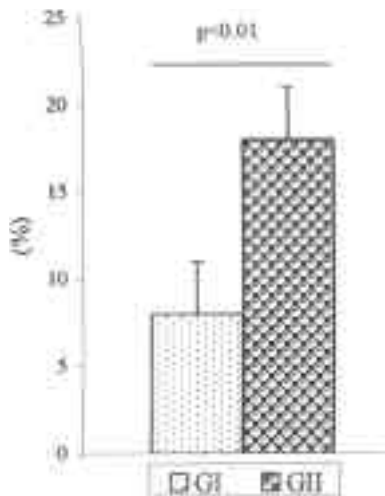


Fig. 1: Significant difference was observed in regards of p-NN 50 in hypertensive groups of the study

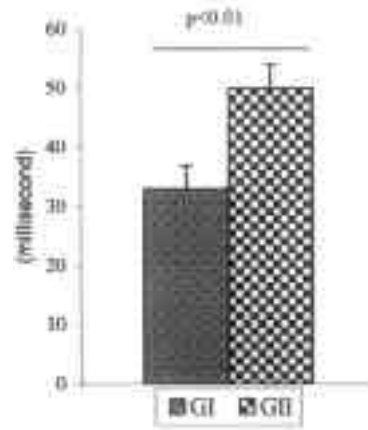


Fig. 2: Significant difference was observed in regards of r-MSSD in hypertensive groups of the study

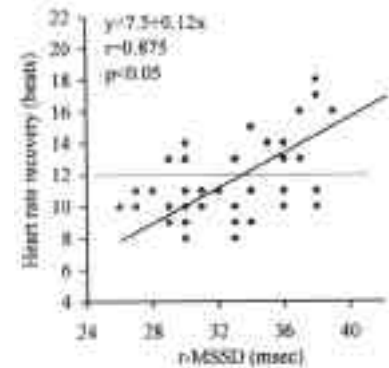


Fig. 3: Correlation between Holter vagal dependent parameter and heart rate recovery after exercise

ventricle mass index, left ventricular diastolic dysfunction, ST- segment depression during or after exercise and impaired heart rate recovery after exercise in hypertensive patients ( $p = \text{NS}$ ). There was a significant relationship between the maximal heart rate during exercise ECG test and the impaired heart rate recovery after exercise ( $p < 0.05$ ), but no significant relationship between the resting heart rate, resting SBP, maximal SBP during exercise test and the impaired heart rate recovery after exercise test ( $p = \text{NS}$ ), Table 2.

The calculated predictive indices were as follows: sensitivity = 74%, specificity = 83.3%, positive predictive value = 67.5%, negative predictive value = 32.5% and accuracy = 77%, Table 3. Stepwise logistic multivariate analysis revealed a significant relationship between the Holter-based frequency domain heart rate variability parameter low frequency (LF) power and the heart rate recovery after exercise test ( $p < 0.05$ ) but there was no significant relationship between total power, high frequency (HF) power, LF/HF power ratio and the heart rate recovery after exercise test ( $p = \text{NS}$ ), Table 4. There was a significant relationship between the Holter-based time domain heart rate variability parameters r-MSSD, p-NN50 and the heart rate recovery after exercise test ( $p < 0.05$ ) but there was no significant relationship between mean RR, SDNN, SDANN and the heart rate recovery ( $p = \text{NS}$ ), Table 5.

## DISCUSSION

Clinicians caring for hypertensive patients with known or suspected coronary artery disease often refer patients for exercise testing or non-invasive imaging for the purpose of detecting stress-induced ischemia and identifying those who might be

appropriate candidates for revascularization. Although ischemia is a known marker of increased risk and revascularization does improve prognosis in some patient subsets, other pathophysiological findings have emerged as possibly more important predictors of risk. These include left ventricular systolic dysfunction, inflammation, endothelial dysfunction, insulin resistance and autonomic imbalance<sup>[7]</sup>.

Until recently, researchers primarily used sophisticated measures of heart rate variability, baroreceptor reflexes and heart rate turbulence to detect disturbance of autonomic function. Sympathetic over-activity and /or parasympathetic under-activity are powerful and independent predictors of death among patients with and without coronary artery disease<sup>[8]</sup>.

In 1994, Imai *et al*<sup>[9]</sup> performed a careful investigation of heart rate dynamics during the first few minutes after vigorous exercise. Because vagal tone is thought to protect against potentially fatal arrhythmias, it was subsequently hypothesized that an attenuated heart rate recovery would be predictive of mortality<sup>[10]</sup>. Studies of tens of thousands of patients in different institutions have confirmed this hypothesis. Heart rate recovery is predictive of all-cause death, even after accounting for exercise capacity, left ventricular systolic function, imaging evidence of myocardial ischemia, the chronotropic response during exercise and angiographic severity of coronary disease<sup>[11]</sup>.

Out of the 70 patients who had impaired heart rate variability as detected by Holter monitor, there were 52 patients who had impaired heart rate recovery after exercise test. However, there were 18 patients with impaired heart rate variability and normal heart rate recovery after exercise ECG test

(i.e. Holter monitor appears to identify more patients with impaired autonomic cardiac function than exercise ECG test). The findings by Lind and Andren<sup>[12]</sup> provide additional support to the autonomic hypothesis of cardiovascular disease. Laboratory investigations have yielded evidence that altered autonomic tone in the skeletal muscle periphery may directly contribute to decreased insulin sensitivity. Other phenomena in which autonomic abnormalities have been implicated as possibly causative in cardiac disease include sudden death after acute coronary artery occlusion and the deterioration of myocardial function in chronic heart failure<sup>[13]</sup>.

This seemingly very simple measurement of heart rate recovery during the first minute after exercise makes it possible to easily assess pathologically and prognostically, important abnormalities of autonomic function in routine clinical practice. But what are clinicians supposed to do with this information? First, by combining heart rate recovery with functional capacity, arguably the most powerful prognostic measure made during stress testing, one can easily identify patients at low risk of death without having to worry about ST segments and use of  $\beta$ -blockers. Patients with preserved functional capacity and a normal heart rate recovery are at very low risk of death, even when left ventricular dysfunction, ischemia or both are present. Second, patients with abnormalities of heart rate recovery, functional capacity, or both might be appropriate candidates for further testing, aggressive medical therapy or both<sup>[14]</sup>. The optimal treatment of autonomic dysfunction as manifested by an abnormal heart rate recovery is not yet known. In any case, the exercise laboratory, now considered to be an autonomic function center rather than an ischemia center, is once again emerging as a clinically relevant and exciting area of cardiovascular care and research<sup>[15]</sup>.

#### Limitations of the study:

1. Coronary angiography was not done for all patients in this study to determine whether they had coronary artery disease.

2. Blood pressure recovery after exercise was not a part this study. Further prospective studies are needed to evaluate the clinical significance of blood pressure recovery.

#### CONCLUSION

Treadmill exercise ECG test is a feasible and valid tool for assessment of autonomic cardiac function in hypertensive patients. Incorporation of

heart rate recovery into the routine evaluation of the hypertensive patients may help in their pharmacological management.

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