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Ischemia-Induced Reflex Sympathoexcitation during the Recovery Period after Maximal Treadmill Exercise Testing

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Summary

Background: Heart rate variability (HRV) analysis is problematic during maximal treadmill exercise testing (ET) due to rapidly changing heart rate.

Hypothesis: The aim of this study was to assess HRV spectral components during treadmill ET in patients with coronary artery disease (CAD) and in healthy controls, and to search for possible differences between the two groups.

Methods: Thirty patients with CAD and 30 age-matched healthy controls underwent symptom-limited ET and continuous electrocardiographic monitoring. For adequate assessment of HRV during maximal ET, we calculated the HRV measures [normalized units (NU)]—low-frequency (0.040–0.150 Hz) power (LF), high-frequency (0.150–0.400 Hz) power (HF), and the LF/HF ratio—from all the sequential stages of the ET with limited changes (20 beats/min) in heart rate (stress 80–100, 100–120, 120–140, 140–160, 160–180/recovery 180–160, 160–140, 140–120, 120–100, 100–80).

Results: Both LF and HF were found to decrease gradually during ET and to increase during the recovery period in both patients and controls ($p<0.001$). LF values were higher during the recovery period than during the respective stages of exercise time in both patients and controls, and LF/HF ratio was higher during recovery in patients only.

Conclusions: During maximal ET (1) vagal tone withdraws during the exercise time and increases during the recovery period; (2) the sympathetic activity predominates during the recovery period, especially in patients with CAD and exercise-induced myocardial ischemia. This finding raises the possibility of ischemia-induced cardiocardiac sympathetic excitatory reflexes.

Key words: reflex sympathoexcitation, myocardial ischemia, exercise testing, heart rate variability

Introduction

Analysis of heart rate variability (HRV) has provided a valuable noninvasive tool for the investigation of autonomic effects on the heart.[1–3]

Exercise heart rate has already been studied by spectral analysis of HRV.[4–11] Previous studies on the mechanism of heart rate regulation during exercise have utilized autonomic blocking drugs to deduce the relative roles of the sympathetic and parasympathetic activities. These studies have led to the conclusion that during mild levels of exercise heart rate is increased primarily by withdrawal of vagal activity, whereas during maximal exercise heart rate augmentation is due to increased sympathetic tone.[5,12] The use of autonomic blocking drugs has led to the conclusion that during recovery from exercise sympathetic activity decreases gradually and vagal tone recovers.[13]

It is well known that HRV spectral analysis is problematic during maximal treadmill exercise testing (ET) due to the rapidly changing heart rate. The aim of this study was to calculate HRV spectral components in patients with coronary artery disease and in healthy controls, from sequential stages of the exercise time and of the recovery period with rather limited changes in heart rate, and to search for possible differences between the two groups.

Methods

Study Population

We studied 30 patients (22 men and 8 women, mean age 57 ± 9 years, range 40–75 years) with angiographically proven coronary artery disease (> 70% narrowing of the luminal diameter in at least one major coronary artery), known to have angina on effort. The patients' characteristics are shown in

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Table I. Exclusion criteria were unstable angina pectoris, hypertension, previous myocardial infarction, clinically overt heart failure [New York Heart Association (NYHA) classes II–IV], atrial fibrillation, atrioventricular block, left or right bundle-branch block, left or right ventricular hypertrophy, sick sinus syndrome, prior pacemaker implantation, ventricular preexcitation, frequent (> 10/h) ectopic beats, diabetes mellitus, and significant renal failure. We also excluded patients with valvular heart disease or nonischemic cardiomyopathy.

Thirty healthy subjects (22 men and 8 women) were used as controls. All normal subjects had a complete physical examination and history that revealed no significant cardiovascular disease, no risk factors for coronary artery disease, and no medication usage. All healthy controls had normal 12-lead electrocardiogram, echocardiogram, and negative previous treadmill ET.

All patients and healthy controls underwent maximal treadmill ET and ambulatory ECG monitoring simultaneously. The study was approved by the Ethics Committee of Hippokration Athens University Hospital, and all participants gave written informed consent for participation in the study.

Exercise Testing

All patients and healthy controls performed exercise on a Quinton 5000 treadmill (Quinton Instruments Co., Seattle Wash.) according to the multistage Bruce protocol. Blood pressure was measured by sphygmomanometry every 2 min during exercise. Electrocardiographic leads V_1, aVF, and V_5 were continuously monitored on the oscilloscope, and the ECG was recorded every minute during exercise and for 10 min during the recovery period. Exercise was terminated because of severe angina, fatigue, or shortness of breath. In the absence of symptoms, each test was terminated at the occurrence of 3 mm ST-segment depression or frequent premature ventricular beats, or a decrease in systolic blood pressure >20 mmHg. The patients' medications were discontinued at least five half-lives before the ET. Ischemic exercise-induced ST-segment changes were considered if there was (1) a > 1 mm horizontal or downsloping ST-segment depression; (2) a slowly rising ST segment with at least a 1.5 mm depression 80 ms after the J point; or (3) an additional 2 mm of ST-segment depression in the presence of ST-segment depression at rest.

Patients or controls who terminated exercise because of fatigue at a heart rate of < 85% of the predicted maximal heart rate aborted the study. Using a magnifying lens, exercise ECG measurements were performed by investigators who were blinded to the HRV data. Intra- and interobserver variability for the ST-segment depression was 0.08 ± 0.06 and 0.09 ± 0.05 mm, respectively.

Ambulatory Electrocardiographic Monitoring

Ambulatory ECG recording was performed using 2-channel Oxford Medilog II TM MR45 (Oxford Med. Instruments, Abingdon, Oxon, UK) recorders. Heart rate variability analysis was performed using previously described methods.[14]

TABLE I Patient characteristics

Age (years)	57 ± 9
Males/females	22/8
Coronary vessel disease (No.)	
1 (%)	12 (40)
2 (%)	10 (33)
3 (%)	8 (27)

Power spectrum analysis (using parametric autoregressive modeling) was automatically calculated by our analysis system (Oxford Medilog Excel TM 2 version).

Since physiologic changes (as in heart rate) that occur during maximal exercise protocols are inherently nonstationary, we decided to divide the exercise time as well as the recovery period into five sequential stages with limited changes in heart rate (20 beats/min) (stress 80–100, 100–120, 120–140, 140–160, 160–180/recovery 180–160, 160–140, 140–120, 120–100, 100–80). The duration of each stage of the exercise time ranged from 2 to 3 min, and of the recovery period from 1 to 2 min. Sequential stages with smaller changes (< 20 beats/min) in heart rate were not selected in order to obtain stages with duration sufficient to perform autoregressive spectral analysis.

Heart rate variability spectral components—low frequency (LF) power at 0.040 to 0.150 Hz, high frequency (HF) power at 0.150 to 0.400 Hz, and LF/HF ratio—were calculated for all the sequential stages of the exercise time and the recovery period in each one of the patients and the healthy controls. Low and high frequency were measured in normalized units (NU). Normalized units were calculated using previously described methods.[16]

Statistical Analysis

Data are presented as mean values ± standard deviation (SD). Comparisons between the HRV spectral components of the two groups were made using the Student's *t*-test. Two-way analysis of variance was used for comparisons among the HRV values of the sequential stages of the exercise time and the recovery period within the two study groups. All statistical calculations were performed using commercially available computer software. Statistical significance was assumed at $p<0.05$.

Results

All 30 patients and none of the healthy controls had positive ET results. Of the 30 patients, 25 showed exercise-induced ST-segment depression, and all of these complained of exercise-induced angina pectoris. Exercise was terminated in the patients group because of severe angina or ST-segment depression. None of the healthy controls showed exercise-induced ST-segment depression or complained of angina-like symptoms during ET. They all completed the exercise pro-

TABLE II Exercise test parameters

	Patients (n = 30)	Healthy controls (n = 30)
Duration (s)	421.5 ± 149.3	622.2 ± 158.4
Max HR	142.2 ± 20.4	169.1 ± 14
Max SBP	184.3 ± 23.5	181 ± 13.4
Max DP	26125 ± 4302	30349 ± 2735
Angina (No.)	30	0
ST depression (No.)	25	0
Max ST depression (mm)	2.25 ± 0.82	—

Abbreviations: DP = double product, HR = heart rate, SBP = systolic blood pressure.

tocol or stopped exercise because of fatigue after having achieved more than 85% of the predicted maximal heart rate. The ET parameters for both the study groups are shown in Table II.

Three (10%) patients completed all five stages of the exercise time (and of the recovery period), 9 (30%) patients completed four stages, 11 (37%) completed three stages, and 7 (23%) patients completed only two stages. On the other hand, 13 (43%) healthy control subjects completed five stages of the exercise time, 15 (50%) completed four stages, and 2 (7%) completed three stages.

Low-frequency values (NU) showed a progressive decrease during the sequential stages of ET and gradual recovery during the recovery time in both patients and healthy controls (between the groups $F = 5.86$, $p < 0.001$; among the exercise stages $F = 69.86$, $p < 0.001$).

High-frequency normalized values increased gradually during the exercise time and decreased during the recovery period in both study groups (between the groups $F = 1.83$, $p < 0.001$; among the exercise stages $F = 10.71$, $p < 0.001$). On the other hand, the LF/HF value also showed significant changes during the sequential stages of the exercise time and the recovery period in both study groups (between the groups $F = 2.23$, $p < 0.001$; among the exercise stages $F = 3.18$, $p < 0.001$).

Spectral components of HRV were not found to be significantly different between patients and healthy controls with the exception of the initial stages of the exercise time (Fig. 1).

Low-frequency values were found to be higher during the recovery stages than during the exercise time stages, with the same (in opposite direction) change in heart rate, in both patients and controls (Tables III, IV). Only in the patient group (Table III) was the LF/HF ratio found to be higher during the recovery stages than during the exercise time stages, with the same (in opposite direction) change in heart rate.

Discussion

The principal findings of this study are that in both patients with coronary artery disease and in healthy controls the parasympathetic activity is significantly decreased during the exercise time and is increased during the recovery period of maximal ET. In addition, the sympathetic tone predominates during the recovery period of maximal treadmill ET (Fig. 2 A,B). This sympathetic predominance during the recovery period is more pronounced in patients with coronary artery disease than in healthy controls. This sympathetic overactivity during the recovery period in patients may be due to an ischemia-induced cardiocardiac sympathetic reflex.

Heart Rate Variability Analysis during Exercise Testing

Heart rate variability spectral analysis is commonly used to evaluate the autonomic control of heart rate during ET.[4–11]

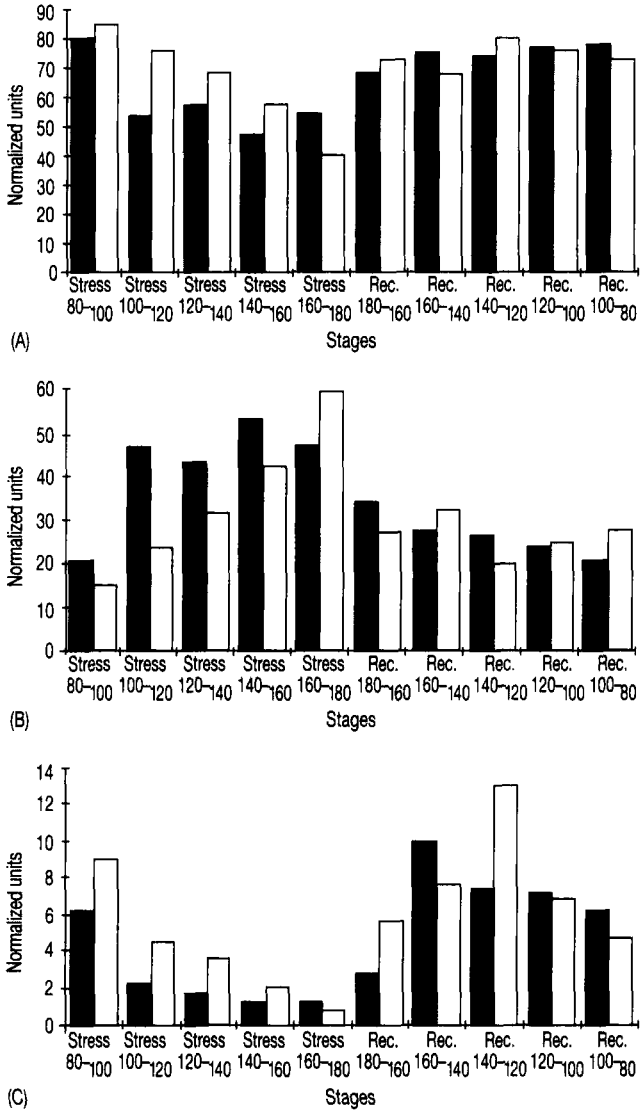

FIG. 1 Heart rate variability spectral components during the sequential stages of treadmill exercise testing in patients with coronary artery disease and in healthy controls: (A) Low frequency spectral component (LF), (B) high frequency spectral component (HF), (C) ratio of LF to HF. Rec. = recovery, ■ = patients, □ = controls.

TABLE III Comparisons between the heart rate variability spectral values of the exercise time and the recovery period stages with the same (in opposite direction) change in heart rate in the patient group

	LF		HF		LF/HF	
	t Value	p Value	t Value	p Value	t Value	p Value
Stress 80/100 vs. recovery 100/80	0.624	NS	−0.090	NS	−0.021	NS
Stress 100/120 vs. recovery 120/100	−6.375	<0.001	6.385	<0.001	−3.331	<0.01
Stress 120/140 vs. recovery 140/120	−4.204	<0.001	4.223	<0.001	−3.138	<0.01
Stress 140/160 vs. recovery 160/140	−6.399	<0.001	6.385	<0.001	−2.885	<0.05
Stress 160/180 vs. recovery 180/160	−0.956	NS	0.881	NS	−0.901	NS

Abbreviations: HF = high frequency spectral component, LF = low frequency spectral component, LF/HF = ratio of LF to HF, NS = nonsignificant.

Previous studies on the autonomic control of heart rate during exercise have led to the conclusion that, during mild levels of exercise, heart rate is increased primarily by withdrawal of vagal activity. Thus, HF spectral power is significantly decreased during ET.[4–6, 8, 10, 11] During maximal exercise, heart rate augmentation is also due to increased sympathetic nervous system activity.[5, 11, 12] This is consistent with the finding of increased circulating catecholamines during ET.[17–19] However, LF spectral power was found to be reduced during ET,[4, 5, 8, 10] possibly due to the reduction of its vagal component.

During recovery from exercise, sympathetic nervous system activation decreases gradually and vagal tone recovers.[13] Previous studies[4, 6] have shown that during the early recovery from exercise all spectral components (HF, LF, LF/HF) augment because of the fast increase of vagal activity and the quite persistent sympathetic excitation.[20]

In this study we confirmed the results of the previously mentioned studies. LF, HF (absolute values), and LF/HF were found to decrease gradually during treadmill maximal ET and to increase during the recovery period in patients with coronary artery disease and in healthy controls. Our study population consisted of patients known to have angina on effort, and treadmill ET reproduced their symptoms. In most of them myocardial ischemia was also confirmed with exercise-induced ST-segment depression. On the other hand, healthy subjects completed maximal ET without any signs of myocardial ischemia. Although patients and controls achieved different levels of maximal heart rate and blood pressure, or possibly had different maximal respiratory rates, they showed similar decrease of high and low frequency HRV spectral components during exercise time and increase during the recovery period. This finding is in accordance with the previously mentioned studies, which suggested a complete withdrawal of vagal activity during maximal ET followed by an increase of parasympathetic activity during recovery from exercise.

Low frequency values were found to be significantly higher during the recovery stages than during the exercise time stages with the same (in opposite direction) change in heart rate in both patients and controls. This is probably due to a sympathetic overactivity as an early after effect of exercise which has already been described by previous studies.[4, 6, 20, 21] In addition, the LF/HF ratio, which is considered by many investigators to reflect the sympathetic modulations or the sympathovagal balance,[15] was found to be significantly higher during the recovery stages than during the respective exercise time stages only in the patient group. We believe that this LF/HF predominance during the recovery period in patients with coronary artery disease is due to ischemia-induced cardiocardiac sympathetic reflexes. Several other studies have also dealt with ischemia-induced autonomic tone alterations and have already proposed the presence of an ischemia-induced reflex sympathoexcitation.[22–25] We believe that this is the first study to report ischemia-induced reflex sympathoexcitation during the recovery period of maximal treadmill ET. We suggest that the sympathetic activity, which predominates during the recovery after exercise-induced myocardial ischemia in patients with coronary artery disease, is due to ischemia-induced reflex sympathoexcitation and may constitute

TABLE IV Comparisons between the heart rate variability spectral values of the exercise time and the recovery period stages with the same (in opposite direction) change in heart rate in the control group

	LF		HF		LF/HF	
	t Value	p Value	t Value	p Value	t Value	p Value
Stress 80/100 vs. recovery 100/80	2.969	<0.01	−2.970	<0.01	2.086	NS
Stress 100/120 vs. recovery 120/100	0.161	NS	−0.165	NS	−1.013	NS
Stress 120/140 vs. recovery 140/120	−2.093	<0.05	2.069	NS	−1.908	NS
Stress 140/160 vs. recovery 160/140	−1.886	NS	−1.885	NS	−2.03	NS
Stress 160/180 vs. recovery 180/160	−4.889	<0.01	4.890	<0.01	−1.869	NS

Abbreviations as in Table III.

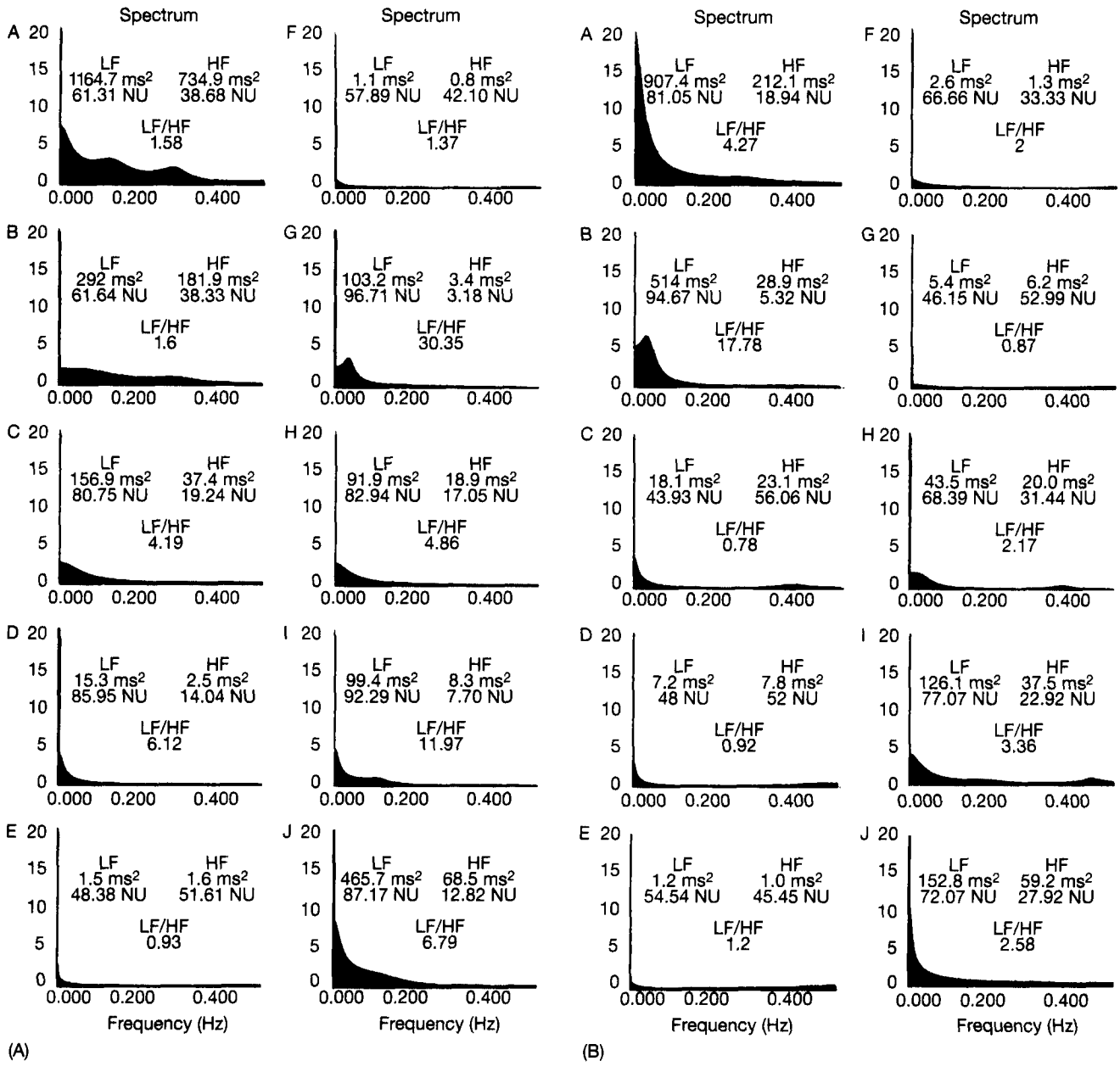

FIG. 2 Heart rate variability spectral analysis during the sequential stages of treadmill exercise testing in (A) a patient with coronary artery disease and exercise-induced myocardial ischemia, and (B) a healthy control. A = stress 80–100; B = stress 100–120; C = stress 120–140; D = stress 140–160; E = stress 160–180; F = recovery 180–160; G = recovery 160–140; H = recovery 140–120; I = recovery 120–100; J = recovery 100–80. HF = high frequency spectral component, LF = low frequency spectral component, LF/HF = the ratio of LF to HF, NU = normalized units.

one of the principal mechanisms provoking the well-known recovery-related arrhythmias.

Study Limitations

It is known that the HRVs at the respiratory frequency (HF power) are due to the modulation of vagal activity that occurs with respiration. Previous studies[26, 27] have demonstrated that respiratory rate and tidal volume alter the amplitude of respiratory sinus arrhythmia, decreasing respiratory sinus arrhythmia as respiratory frequency increases and increasing respiratory sinus arrhythmia as tidal volume increases. In this study we have not normalized respiratory-related sinus arrhythmia for changes in respiratory frequency and tidal volume. We believe that this had no significant effect on our results because of the offsetting effects of increased respiratory frequency and tidal volume that occur in combination during exercise. It has already been proposed[5] that it is not important to apply the correction for changes in breathing parameters to HRV spectra obtained in exercise.

In addition, analysis of arterial pressure fluctuations during maximal treadmill ET in order to evaluate the baroreflex control of heart rate was not performed in this study.

Another possible limitation of this study is the relatively small number of patients and healthy subjects who participated. We must emphasize the difficulties in recruiting ambulatory ECG recordings during treadmill ET with enough limited noise and artifacts to obtain valuable HRV spectral results. In any case, our study cohort was sufficient to draw statistically significant results.

Conclusions

It is concluded that vagal withdrawal during the exercise time and increase during the recovery period are found during maximal ET both in patients with coronary artery disease and in healthy controls. The sympathetic predominance found during the recovery period of maximal ET both in patients and controls seems to be more pronounced in the former group. Therefore, it is possible that exercise-induced myocardial ischemia is responsible for cardiocardiac sympathetic excitatory reflexes observed in the recovery period of maximal treadmill ET. This reflex sympathoexcitation may increase the likelihood of malignant arrhythmias in the recovery period after maximal ET.

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