ORIGINAL ARTICLE

Chronotropic Incompetence and Dynamic Postexercise Autonomic Dysfunction Are Associated with the Presence and Severity of Erectile Dysfunction

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Background: Exercise stress testing (EST) is crucial to determine cardiovascular (CV) risk in men with erectile dysfunction (ED). Low exercise workload, a slower rate of recovery following exercise, and an impaired capacity to increase heart rate (HR) during exercise testing (chronotropic incompetence) are independent predictors of adverse CV outcomes. Aim of this study was to investigate the association between ED and EST parameters.

Methods: A total of 180 ED patients and 50 men without ED underwent maximal EST. Exercise parameters including exercise capacity (metabolic equivalents, METS), peak exercise time, HR at six METS, peak exercise, HR recovery (HRR) at 1 and 2 minutes and chronotropic index (CI) were evaluated in all individuals. Endothelial function was evaluated with flow-mediated dilatation (FMD) of the brachial artery.

Results: ED patients had lower peak exercise time and thus lower calculated exercise capacity ($P < 0.001$) and reduced CI ($P < 0.01$) compared to men without ED. There was a significant association of ED severity with duration of exercise, peak workload, HRR 2 minutes after exercise, and CI (all $P < 0.05$). There also was a positive relation of HRR and CI with FMD (all $P < 0.05$).

Conclusions: This study shows interrelationships between exercise capacity, HRR, CI, and ED. Abnormal HRR and CI are associated with systemic endothelial dysfunction. These findings imply pathophysiological links and may have important implications for the estimation of cardiovascular risk in ED patients.

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exercise stress test; erectile dysfunction; exercise capacity; chronotropic index; heart rate recovery

The standard exercise stress test (EST) is one of the most powerful tools for risk stratification of patients suspected of having, or with cardiovascular disease (CVD).[1] Although symptoms, the electrocardiographic response, and exercise tolerance have been traditionally used to investigate patients who may, or may not have clinical evidence of coronary artery disease (CAD), and to estimate risk for cardiovascular (CV) events and mortality,[2] recent studies have observed that heart rate (HR) EST parameters related to autonomic balance provide both independent

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and complementary information for estimating prognosis.[3,4] Both an attenuated HR response to exercise [termed chronotropic incompetence (CI)] and slowed recovery of HR following exercise (termed heart rate recovery (HRR]) have been associated with all-cause mortality and cardiac events.[5,6]

Erectile dysfunction (ED) is a highly prevalent disorder that affects, to a varying severity, almost one out of two men aged 40–70 years.[7] Importantly, ED is considered an early manifestation of a generalized vascular disease[8,9] and predicts all-cause mortality and cardiovascular (CV) events.[10] Despite its limitations in detecting CAD without significant stenosis,[11] EST (with or without imaging) can further define the cardiovascular risk in patients with ED and no overt CAD.[12] Furthermore, EST is crucial to the assessment of ED patients before the initiation of ED therapy in all men with no overt CAD regardless of cardiovascular risk.[13,14]

A previous study in younger ED patients without risk factors reported a decreased functional capacity and chronotropic incompetence as compared to men with normal erectile function.[15] However, to date, no data exist regarding HR response to exercise and recovery in individuals with risk factors and ED. Therefore, the aim of this study was to investigate the association between these EST parameters with the presence and severity of ED. Furthermore, an additional objective of our investigation was to assess whether EST parameters are related to endothelial dysfunction, a feature of principal pathophysiological importance.

MATERIALS AND METHODS

Population Study

From January 2008 to June 2013, we enrolled consecutive men who were referred to the Cardiovascular Diseases and Sexual Health Unit of our Department for evaluation of ED. These patients had ED symptoms of recent onset but they were neither symptomatic of CVD nor had they documented CVD disease. Initially, 212 men underwent maximal EST. Thirty-two ED patients with clinical and electrocardiographic evidence of myocardial ischemia during EST and recovery were excluded from this study. Finally, 180 men with ED were analyzed in this study. In addition, 50 men with negative EST who had normal erectile function matched for traditional risk factors were recruited from a large cohort followed in our Department for Arterial Function studies. The study complies with the Declaration of Helsinki and the protocol was approved by our Institutional Research Ethics Committee. All subjects gave written informed consent.

Evaluation of ED

ED was diagnosed according to comprehensive medical and sexual history, score of the 5-item form of the International Index of Erectile Function,[16] the Sexual Health Inventory for Men (SHIM), physical examination, and hormonal testing (total testosterone and prolactin). The SHIM is widely used as a screening measure in clinical practice settings and is intended to gauge sexual function over the past 6 months. In addition, the SHIM has been adopted as a standard diagnostic aid for office screening of ED. Responses to each of the five items on the SHIM, which are based on a rating scale from 0 to 5 or from 1 to 5 (depending on the item), are summed to arrive at a total score that can range from 1 to 25, with higher scores indicating better sexual health. Patients with a score of 21 or less may have evidence of ED. Among men in a stable relationship (i.e., men who had an opportunity for sexual activity), classification of ED is partitioned into three severity grades: mild (12–21), moderate (8–11), and severe ED (1–7).

Through these evaluations, patients were excluded if their ED was secondary to hormonal, psychological, neurological, or anatomic abnormalities, pelvic surgery, or trauma.

Exercise Stress Test

All participants underwent maximal EST under the standard Bruce protocol. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or indicators of ischemia. Medications were not changed or stopped before testing except for β-blockers or rate-limiting calcium channel blockers that were stopped 72 hours prior to the EST.

Peak exercise time was recorded in seconds. Peak workload was estimated as metabolic equivalents (METs). One MET is defined as the energy expended at rest, which is equivalent to an oxygen consumption of 3.5 mL/kg of body weight per minute.[17] Age-predicted peak exercise heart rate was determined based on standardized methods.

Heart rate (HR) values were computed at one-third total exercise capacity, at six METs, at peak exercise, and at 1 and 2 minutes of recovery (HRR). Chronotropic index (CI) was calculated as $[(HR_{peak} - HR_{rest})/(220 - age - HR_{rest})]$. The CI was considered abnormal when ≤0.8 in patients not taking β-blockers.[4]

Evaluation of Endothelial Function

Flow-mediated dilatation (FMD) of the brachial artery is predominantly dependent on endothelial nitric oxide release and can be used as an estimate of endothelial function.[18] Before (resting) and after 5 min of ischemia induced by forearm arterial flow occlusion (postocclusion) arterial diameters and flows, reactive hyperemia (the stimulus for the postocclusion diameter response) and FMD of the conduit brachial artery were determined as previously described,[19] by using a high-resolution, linear-array ultrasonic transducer of 7.5–10.5 MHz (Sonos 5500; Hewlett-Packard, Andover, MA, USA). The longitudinal image of the artery was recorded continuously from 30 seconds before up to 2 minutes after cuff deflation. The post-occlusion diameter was measured at 60 seconds after cuff deflation. FMD was calculated as the percent change of brachial artery diameter from baseline: FMD (%) = [(postocclusion diameter − resting diameter)/resting diameter] × 100. All subjects were tested before performing the exercise testing.

Statistical Analysis

Continuous variables are expressed as mean value ± standard deviation. Normality was tested using the Kolmogorov–Smirnov criterion. Skewed variables are expressed as the median value (interquartile range). Between ED and no ED groups, the Student's *t*-test for unpaired measures or the Mann-Whitney U-test was used to compare normally distributed and skewed continuous variables, respectively. Categorical variables were compared using the chi-square test.

To evaluate severity of ED associated with EST parameters, we next categorized ED patients into three groups according to SHIM (mild, moderate, severe). The analysis of variance (ANOVA) or the chi-square test was used to compare data for these groups. Post hoc (Bonferoni correction) was used for multiple comparisons of the data obtained regarding EST variables. Analysis of covariance was performed in order to detect significant differences in EST parameters between men with ED and subjects without ED as well as between ED subgroups after adjustment for confounders that were significantly different in initial comparisons. Correlations between brachial FMD and EST parameters were evaluated by calculation of the Pearson correlation coefficient.

Exact P values of less than 0.05 were considered statistically significant. Data analysis was performed using SPSS software, version 14.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Relation to Presence of ED

The baseline clinical characteristics of the 180 ED patients and 50 controls are given in Table 1. ED patients were older ($P = 0.005$) and they had higher cholesterol ($P = 0.04$) and C-reactive protein (CRP) levels ($P = 0.02$) compared to non-ED subjects. The two groups had similar prevalence of hypertension, diabetes, hypercholesterolemia, and smoking. β-Blocker use was not significantly different between groups.

Table 2 shows EST parameters of the two study groups. Compared to controls, ED patients had significantly lower peak exercise time and thus lower calculated exercise capacity (all $P < 0.001$). There were no significant differences in median values of HR at six METs and peak exercise. ED and controls also had similar HR decrease 1 and 2 minutes after exercise. Interestingly, ED patients had a substantially reduced CI ($P<0.01$, Table 1) and a higher prevalence of abnormal CI (≤0.8) than that of non-ED subjects (42% vs. 21%, $P < 0.01$).

Among subjects with arterial hypertension, men with ED ($n = 115$) had statistically significant lower peak exercise time and lower calculated exercise capacity (10.6 ± 2.5 vs. 11.5 ± 2.7 and 543 ± 135 vs. 606 ± 121 seconds) and a reduced CI (0.83 ± 0.16 vs. 0.91 ± 0.20) compared to non-ED ($n = 31$) individuals (all $P < 0.05$). Interestingly, compared to non-ED subjects, hypertensive individuals with ED had a lower HRR 2 minutes after exercise (45 ± 12 vs. 51 ± 16 bpm, $P = 0.017$). Importantly, the differences in peak exercise time, calculated exercise capacity and HRR remained significant after adjustment for age ($F = 3.56$, $F = 3.85$, $F = 4.14$, respectively, all $P < 0.05$).

Table 1. Baseline Characteristics of ED and Non-ED (controls) Individuals

	Non-ED, n = 50	ED, n = 180	P Value
Age (years)	54 ± 11	57 ± 6	0.005
BMI (kg/m²)	28 ± 4	29 ± 4	0.26
Hypertension (n, %)	31(62)	115 (64)	0.72
Dyslipidemia (n, %)	28 (56)	104 (58)	0.56
Diabetes (n, %)	18 (36)	61 (34)	0.31
Smoking (n, %)	23 (46)	70 (39)	0.22
β-Blockers (n, %)	3 (6)	8 (4)	0.55
Total cholesterol (mg/dL)	193 ± 35	207 ± 36	0.04
Triglycerides (mg/dL)	116 (82–151)	116 (81–153)	0.53
HDL (mg/dL)	43 ± 8	43 ± 8	0.41
CRP (mg/L)	0.2 ± 0.1	0.6 ± 0.2	0.02
FMD (%)	7.6 ± 2.0	5.7 ± 1.9	<0.001

Categorical variables are presented as absolute (relative) frequencies; continuous variables, as mean ± SD or median (interquartile range).
Abbreviations as in text.

Table 2. Exercise Stress Test (EST) Parameters of ED and Non-ED (Controls) Individuals

Exercise Parameters	Non-ED, n = 50	ED, n = 180	P Value
Systolic BP base (mm Hg)	130 ± 13	127 ± 15	0.18
Diastolic BP base (mm Hg)	82 ± 10	80 ± 9	0.22
HR base (bpm)	80 ± 10	76 ± 13	0.10
Maximal systolic BP (mm Hg)	187 ± 28	180 ± 25	0.15
Maximal diastolic BP (mm Hg)	86 ± 11	85 ± 10	0.34
Maximal HR (bpm)	157 ± 18	153 ± 16	0.07
HR at six METS (bpm)	119 ± 14	117 ± 15	0.28
dHR (peak exercise) (bpm)	78 ± 18	73 ± 20	0.03
HRR, 1 minute (bpm)	29 ± 4	26 ± 5	0.55
HRR, 2 minutes (bpm)	49 ± 15	46 ± 15	0.32
CI	0.90 ± 0.19	0.83 ± 0.19	0.008
Exercise duration (seconds)	613 ± 140	545 ± 120	<0.001
METs	11.8 ± 2.4	10.7 ± 2.3	<0.001

Data are expressed as mean ± SD.
Abbreviations as in text.

Relation to the Severity of ED

ED patients were divided into three groups according to SHIM (mild = 62, moderate = 92, severe = 26). The three subgroups did not differ with regard to age, risk factors, and biochemical characteristics. Table 3 shows the baseline EST parameters of the three subgroups. Systolic, diastolic blood pressure (BP), and HR at baseline were similar between the three subgroups. There was a progressive increase in systolic BP level at peak exercise with increasing severity of ED ($P < 0.001$), whereas the diastolic BP responses at peak exercise were similar. As Table 3 shows, there was a significant association of ED severity with duration of exercise ($P < 0.001$), peak workload (METs; $P < 0.001$), HR decrease 2 minutes after exercise ($P < 0.001$) and CI ($P < 0.001$). On post hoc analysis, METs, HRR 2 minutes after exercise and CI of patients with severe ED were significantly lower compared with the values of subjects with mild and moderate ED. The prevalence of abnormal CI was significantly higher in men with severe ED.

Relation to Peripheral Endothelial Dysfunction

Brachial FMD was positively correlated with HRR,2 minutes after exercise ($r = 0.204$, $P = 0.011$) and CI ($r = 0.284$, $P = 0.006$) suggesting a decrease in HR response to exercise and a decrease in HR recovery in ED patients with impaired systemic endothelial function. The associations remained significant after adjustment for age and baseline systolic BP (all $P < 0.05$).

Table 3. Exercise Stress Testing Parameters and FMD in the ED Population

Exercise Parameters	Mild, n = 62	Moderate, n = 92	Severe, n = 26	P Value
Systolic BP base (mm Hg)	125 ± 15	126 ± 16	129 ± 16	0.51
Diastolic BP base (mm Hg)	80 ± 10	80 ± 9	78 ± 9	0.50
HR (bpm)	75 ± 11	77 ± 10	72 ± 12	0.15
Maximal systolic BP (mm Hg)	175 ± 23	180 ± 22	189 ± 28	<0.001
Maximal diastolic BP (mm Hg)	83 ± 10	84 ± 10	85 ± 11	0.55
dHR (peak exercise) (bpm)	73 ± 20	75 ± 18	70 ± 18	0.03
HRR, 1 minute (bpm)	27.8 ± 13.8	27.2 ± 12.7	21.8 ± 9.9	<0.01
HRR, 2 minutes (bpm)	48.7 ± 16	47.4 ± 15	42.1 ± 13	<0.001
CI	0.87 ± 0.17	0.85 ± 0.17	0.68 ± 0.20	<0.001
Exercise duration (seconds)	651 ± 112	526 ± 95	361 ± 117	<0.001
METs	12.6 ± 2.2	10.4 ± 1.6	7.5 ± 1.9	<0.001
FMD (%)	5.9 ± 2.4	5.7 ± 2.0	5.4 ± 2.2	0.04

Data are expressed as mean ± SD
Abbreviations as in text.

DISCUSSION

This is the first study, to the best of our knowledge, to show abnormal HR changes during EST and recovery in patients with ED and risk factors. Our data are also in line with other studies showing that ED is associated with reduced exercise capacity.[15,20] These parameters correlate with the presence and severity of ED independently of age and risk factors. Men with chronotropic incompetence and slower rate of recovery following exercise had significantly decreased brachial FMD. These observations highlight the role of EST to further characterize CV risk of ED patients and imply a pathophysiologic contribution of endothelial dysfunction to processes associated with autonomic imbalance and ED.

Clinical Implications

This study may have important implications. ED shares common risk factors with CAD, such as age, hypertension, diabetes, hyperlipidemia and smoking, and the risk that this condition carries for future CV events is on top of that conferred by these factors.[10] In men with ED, exercise testing, while principally important to detect CAD (e.g., exercise-induced myocardial ischemia, arrhythmias),[21–24] it is also essential to define CV risk and mortality through evaluation of maximal exercise capacity (e.g., METs)[25] and autonomic pathologies (e.g., chronotropic incompetence, HRR after exercise test).[26] Peak exercise capacity, which is defined as the maximum ability of the cardiovascular system to deliver oxygen to exercising skeletal muscle and of the exercising muscle to extract oxygen from the blood, is one of the strongest and most consistent prognostic markers identified in EST.[1] Chronotropic incompetence and HRR, which reflect dynamic autonomic response to exercise and the postexercise period respectively, are stronger predictors of CV risk than pretest clinical data and traditional risk markers.[3]

ED patients with decreased exercise capacity, chronotropic incompetence, and abnormal HRR are candidates of aggressive management of ED-related risk factors. Management of these factors alleviates ED and may decrease the CVD risk associated with ED.[13,14] This risk reduction may be mediated, at least in part, by effects on exercise capacity and chronotropic incompetence.[27] Indeed, lifestyle modification has been shown to enhance exercise capacity and counterbalance chronotropic incompetence and delayed HRR.[28] Exercise training, and particularly 3–6 months of endurance training, may attenuate dysautonomia in patients with CVD.[28,29] Smokers who have abstained for 3 years have better exercise capacity and HR parameters during EST than continuing smokers.[30] The increase in HRR has been significantly correlated with decreases in body weight, body mass index (BMI) and waist circumference in obese men.[31] Further studies concentrated to men with ED are necessary to evaluate whether this holds true for such patients.

An interesting finding of our analysis is the significant and independent positive association of ED severity, as indicated by SHIM, with exercise capacity, CI and HRR. In other words, men with severe ED have lower exercise capacity, lower HR reserve, and a blunted exercise HR response

compared to men with mild or moderate ED. This is particularly important taking into consideration that not only ED but also evaluation of severity of ED based on validated questionnaires has been associated with greater risk of CV events,[32] CAD,[33] and extent of CAD.[34]

MECHANISMS

The results of this study, taken together with those of previous studies,[15,35] suggest that a generalized imbalance of the autonomic function in men accounts partly for ED in such patients. Indeed, penile erection is a neurovascular event and increased sympathetic activity and/or diminished parasympathetic activity is a well-known pathophysiologic mechanism of ED,[36] although in most cases endothelial dysfunction goes to the fore.[37] The impact of treatment with β-blockers in the HR observations was not significant.

Strength of our data is that we measured brachial FMD, which is the most widely used technique in the evaluation of macrovascular endothelial function.[38] Endothelial dysfunction is the main pathophysiologic mechanism of ED, and numerous studies have consistently shown blunted brachial artery FMD in patients with ED.[37,39] The significant association of impaired HR responses during exercise and recovery with brachial FMD reflects the interrelationship of endothelial dysfunction, exercise capacity, and HR responses[40] and may allow inferences on the role of the nitric oxide availability as potential mediator of the exercise-induced autonomic modulation in men with ED.[41] However, the nature of our study does not substantiate a causal relationship. However, although low androgen levels have been shown to be associated with ED, no correlations between EST parameters and steroid hormone levels have been found.[15]

LIMITATIONS

We should acknowledge that we do not have data regarding daily exercise training, which is also a risk factor for ED.[42] This important parameter may have shed further light on whether ED presence and severity is directly or indirectly related to EST chronotropic incompetence and delayed HRR since it may influence both ED and EST.

CONCLUSIONS

Chronotropic incompetence and dynamic post-exercise autonomic dysfunction correlate with presence and severity of ED independent of age and risk factors. This condition may reflect impaired systemic endothelial function in these patients. While further research is warranted, these findings have important clinical implications given the increasing prevalence of ED in middle-aged men and the higher risk for CV events that ED confers.

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