

ERECTILE DYSFUNCTION

Deterioration of Chronotropic Responses and Heart Rate Recovery Indices in Men With Erectile Dysfunction



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ABSTRACT

Introduction: Erectile dysfunction (ED) and cardiovascular (CV) diseases share common risk factors and ED has been accepted as an early manifestation of CV disease. Exercise stress testing (EST) is used to evaluate CV functions in men with ED. Low exercise workload, a slower heart rate recovery (HRR) after exercise, and inability to increase heart rate during EST (chronotropic incompetence) are independent negative predictors of adverse CV outcomes.

Aim: To assess the association among EST parameters, ED, and testosterone levels.

Methods: The study population consisted of 41 patients with ED and 40 controls. All participants underwent treadmill EST to assess cardiac autonomic functions. HRR indices were calculated by subtracting 1st (HRR1), 2nd (HRR2), and 3rd (HRR3) minute heart rates during the recovery period from maximal heart rate. Total exercise duration, exercise capacity and chronotropic response, and plasma testosterone levels were evaluated. Erectile functions were evaluated with the Sexual Health Inventory for Men. Patients were divided into sub-groups according to severity and duration of ED.

Main Outcome Measures: Mean HRR1 (30.6 ± 11.9 vs 36.9 ± 9.9 ; $P = .01$), HRR2 (44.9 ± 12.4 vs 54.9 ± 7.8 ; $P < .001$), and HRR3 (50.1 ± 11.7 vs 63.0 ± 7.9 ; $P < .001$) were significantly lower in the ED than in the control group. Total exercise duration (9.4 ± 1.9 vs 10.9 ± 1.7 minutes; $P < .001$), exercise capacity (12.5 ± 1.9 vs 13.6 ± 1.4 metabolic equivalents; $P = .004$), and chronotropic response (0.88 ± 0.1 vs 1.0 ± 0.1 ; $P < .001$) were worse in the ED group. However, we found no association between severity and duration of ED and EST parameters. In addition, serum testosterone levels were significantly correlated with HRR1 ($r = 0.36$, $P = .02$) in men with ED.

Conclusion: Our data suggested that cardiac autonomic functions are impaired in patients with ED. A weak correlation between cardiac autonomic dysfunction and low testosterone levels in patients with ED was noted. However, further studies are needed to elucidate the prognostic significance and clinical implications of impaired autonomic functions and testosterone replacement therapy in patients with ED. **Kucukdurmaz F, Agar G, Resim S. Deterioration of Chronotropic Responses and Heart Rate Recovery Indices in Men With Erectile Dysfunction. Sex Med 2018;6:8–14.**

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Key Words: Erectile Dysfunction; Heart Rate Recovery; Chronotropic Response; Testosterone

INTRODUCTION

Erectile dysfunction (ED) is described as the inability to attain and maintain an erection that is sufficient for satisfactory sexual

performance.¹ Epidemiologic studies have shown that prevalence rates vary from 20% to 50% in men 40 to 70 years old, with a steep age-related increase.^{2,3} ED can disturb physical and psychological health and result in significant lowering of quality-of-life scores of men and their partners.⁴ Moreover, increasing evidence shows that ED can be an early manifestation of coronary artery and peripheral vascular diseases. Therefore, it can be hypothesized that ED is not only a quality-of-life issue but also an early marker of cardiovascular (CV) diseases (CVDs).^{5,6} However, it is not affordable to evaluate all patients with ED for cardiac diseases. Priority for cardiac evaluation of patients with ED can be given to those who live in regions with prevalence toward CVD or share more than a few common risk factors for ED and CVD.

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ED and CVD share unmodifiable and modifiable common risk factors, such as obesity, diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome, smoking, and lack of exercise.^{7–9} In addition, autonomic nervous system (ANS) dysfunction is considered another common pathophysiologic mechanism linking the 2 diseases. The relation between ANS and erectile function is well known. In normal physiologic conditions, activation of the parasympathetic system is mandatory to provide penile erection. Studies have reported that ANS dysfunction can lead to ED.^{10,11}

The ANS has a pivotal role in the regulation of cardiac and vascular systems and its disruption can lead to CV events, which can result in morbidity and mortality.^{12,13} Cardiac autonomic functions can be evaluated by exercise stress testing (EST). Of EST parameters, heart rate (HR) recovery (HRR) index is important for investigating cardiac effects of ANS and is accepted as an indicator of parasympathetic reactivation.¹⁴ In addition, chronotropic responses (CRs) can reflect changes in ANS behavior.

In a previous study, younger patients with ED were found to have decreased functional capacity and CR compared with men without ED.¹⁵ More recently, Ioakeimidis et al¹⁶ reported that abnormal HRR and chronotropic incompetence (ChI) were associated with endothelial dysfunction and were lower in men with ED. Furthermore, severity of ED correlated with the worsening of those parameters. Ulucan et al¹⁷ also noted that HRR indices and effort capacity were remarkably decreased in patients with ED. These 2 studies suggest that these findings might indicate possible pathophysiologic links and could help predict CV risk in patients with ED.

Therefore, the aim of the present study was to further investigate the association of EST parameters with the presence, severity, and duration of ED. We also evaluated the relation between serum testosterone levels and EST parameters in men with ED.

METHODS

Study Populations

This case-control study was carried out in the cardiology and urology clinics of a tertiary university hospital in Kahramanmaraş, a province located at the intersection of the southeast and Mediterranean regions of Turkey, from December 2016 through February 2017. Patients admitted to the andrology outpatient clinic with the complaint of ED were referred to the cardiology department for EST to investigate cardiac autonomic functions. Participants were selected from those who were admitted to the hospital without considering their place of birth or ethnic or religious origins to provide a generalized study population. Initially, 59 men underwent EST. However, 18 were not enrolled in the study because of the following exclusion criteria: 6 used medications that could lead to arrhythmia, 4 had thyroid dysfunction, 3 had peripheral vascular disease, and 2 had bundle branch block. Also excluded were 3 patients who showed

ischemic changes during EST. Therefore, 41 men who were diagnosed with ED according to the 5-item International Index of Erectile Function (IIEF-5) participated in the study. 40 controls were recruited from the hospital staff. In the beginning, 65 men were selected for the control group. Those subjects were asked about previous cardiac events or presence of relatives with known cardiac diseases, history of ED, and use of erectogenic drugs or supplements including testosterone. Subsequently, 13 men were excluded owing to a history of angina and presence of first-degree relatives with known cardiac diseases. 5 and 7 patients were excluded owing to the use of erectogenic drugs and testosterone supplements, respectively. Inclusion criteria of cases were age older than 18 years and the diagnosis of ED. Exclusion criteria were the presence of diagnoses of coronary artery disease, peripheral vascular disease, ejection fraction less than 50%, atrial fibrillation, renal or liver dysfunction, chronic obstructive pulmonary disease, psychological diseases including depression and anxiety disorders, drug abuse, malignancy, moderate to severe valvular heart disease, bundle branch block and atrioventricular conduction abnormalities on electrocardiogram, thyroid dysfunction, anemia, electrolyte imbalance, use of medications that could lead to arrhythmia or ED, hormonal therapy for ED, pelvic surgery, or trauma. In addition, participants who showed ischemic changes during EST were excluded. Although we provided strict exclusion criteria to control for possible confounders, cases and controls could have had some unmeasured confounders such as stress, duration of smoking, dietary habits, and daily exercise patterns.

Clinical and laboratory characteristics of the participants including age and hematologic and biochemical parameters were obtained. All patients underwent a 12-lead electrocardiographic and transthoracic echocardiographic examination (Vivid 7 System, GE-Vingmed Ultrasound AS, Horten, Norway) to rule out rhythm disorders, heart failure, and valvular heart diseases. Written informed consent was obtained from each subject and the institutional ethics committee approved the study protocol.

Evaluation of Erectile Function

Participants' erectile function was evaluated according to comprehensive medical and sexual history, physical examination, IIEF-5 score, and morning testosterone levels. The IIEF-5 is a validated and widely used questionnaire in clinical settings and was used to evaluate sexual function within the past 6 months.¹⁸ Responses to each of the 5 items on the IIEF-5, 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 no higher than 21 might have evidence of ED. For men in a stable relationship (ie, men who had an opportunity for sexual activity), ED was categorized as mild (score = 12–21), moderate (score = 8–11), or severe (score = 1–7). We also classified duration of ED as shorter than 1 year, 1 to 5 years, or longer than 5 years.

Measurement of Testosterone

A non-fasting blood sample from each participant was obtained from 8:00 to 11:00 AM, which was regarded as consistent with the circadian rhythm of testosterone secretion. Serum testosterone levels were determined by electro-chemiluminescence immune assay (ADVIA Centaur XP Immunoassay System, Siemens Medical Solutions USA, Malvern, PA, USA). Level of testosterone was reported as nanograms per deciliter.

Exercise Testing

All participants enrolled in the study underwent treadmill EST under the standard Bruce protocol (Schiller Cardiovit AT-104, Reomed AG, Dietikon, Switzerland). They were asked to exercise until volitional fatigue in the absence of symptoms or indicators of ischemia. Medications, if used, were not changed or stopped before testing except for β -blockers or rate-limiting calcium channel blockers, which were stopped 72 hours before EST. Peak exercise time was recorded in minutes. The predicted peak HR was calculated as 220 beats/minute minus age and the aim of EST was to reach at least 85% of the age-predicted target HR. The end of exercise was flagged, and at least 3 minutes of postexercise HR was recorded with the subjects at rest. A qualified cardiologist prospectively collected physiologic and hemodynamic data during testing, including development of symptoms, HR, heart rhythm, blood pressure, and estimated functional capacity in metabolic equivalents (METs; where 1 MET = 3.5 mL/kg per minute of oxygen consumption).¹⁹ HRR indices were defined as decreases in HR from the rate at peak exercise to the rate at the 1st, 2nd, and 3rd minutes after the cessation of EST. These results were indicated as HRR1, HRR2 and HRR3, respectively. CR was assessed based on the proportion of HR reserve used at peak exercise ($[\text{peak HR} - \text{resting HR}]/[220 - \text{age} - \text{resting HR}]$); a value no higher than 0.80 was considered ChI. EST results were blind to the clinical and laboratory data of the patients and controls.

Statistical Analysis

SPSS 15.0 (SPSS Inc, Chicago, IL, USA) was used for the statistical study. Post hoc power analysis results of the variables were 21% to 100% when the significance level was set at 0.05.

All values were presented as mean \pm SD. Mean values of continuous variables were compared between groups using the Student t-test or Mann-Whitney U-test, according to whether they were normally distributed or not, as tested by the Kolmogorov-Smirnov test. The χ^2 test was used to assess differences between categorical variables. Pearson correlation coefficients were used to assess the strength of the relation between continuous variables. A *P* value less than .05 was considered significant.

RESULTS

Post hoc power analyses showed that only 3 variables in this study (resting HR, HRR1 < 18, and HRR1) had a power less

than 80%. The demographic and baseline characteristics of 41 patients with ED and 40 controls are presented in Table 1. Mean ages of the 2 groups were not statistically different. The 2 groups were homogeneous for hypertension, diabetes mellitus, hyperlipidemia, and smoking. C-reactive protein (CRP) levels were significantly higher in the ED than in the control group (*P* = 0.003). The ED group had lower total testosterone levels than the control group. Mean total testosterone level was 323.0 ± 132.2 ng/dL in patients with ED, and mean IIEF-5 ED score was 8.6 ± 4.9 .

All participants were in sinus rhythm and had normal 12-lead electrocardiographic results at rest. All subjects completed the EST without new-onset rhythm abnormalities, ischemic changes, or other complications. EST parameters including cardiac autonomic functions of the 2 groups are presented in Table 2. Resting HR was similar in the 2 groups. Peak HR, total exercise duration, and METs were significantly lower in the ED group. HRR indices were significantly impaired in the ED compared with the control group. Specifically, the 1st-, 2nd-, and 3rd-minute HRR indices were significantly lower in the ED than in the control group (30.6 ± 11.9 vs 36.9 ± 9.9 , *P* = .01; 44.9 ± 12.4 vs 54.9 ± 7.8 , *P* < .001; 50.1 ± 11.7 vs 63.0 ± 7.9 , *P* < .001, respectively).

The number of patients with HRR1 lower than 18 was larger in the ED than in the control group (12% vs 3%, odds ratio = 5.41, 95% CI = 0.604–48.608, *P* = .03). CRs were significantly lower in the ED than in the control group (0.88 ± 0.1 vs 1.0 ± 0.1 ; *P* < .001). ChI was encountered only in the ED group (29% vs 0%; *P* < .001).

In correlation analysis, HRR and CRs were not correlated with age, systolic or diastolic blood pressure, or left ventricular ejection fraction. A weak correlation between HRR1 and total testosterone level was established ($r = 0.36$, *P* = .02; Figure 1). There were no correlations between severity and duration of ED and EST parameters.

DISCUSSION

ED and CVD are considered the different clinical presentations of the same spectrum of disorders. The artery-size hypothesis, established by Montorsi et al,⁶ states that a larger vessel might better tolerate the same amount of atherosclerotic plaque as a small vessel. Because the diameter of penile arteries (1–2 mm) is narrower than that of coronary arteries (3–4 mm), it is reasonable to consider that symptoms are more likely to appear sooner in the penis. Therefore, ED was accepted as a surrogate and early marker of future CVDs. Many clinical studies have confirmed this hypothesis and ED was found to be preceded CVD by an average of 2 to 3 years.²⁰

Reported common pathophysiologic mechanisms that link ED and CVD are atherosclerosis, inflammation, endothelial dysfunction, hormonal abnormalities, and autonomic dysfunction.²¹ Of these mechanisms, proper ANS functioning is

Table 1. Demographic, clinical, and laboratory characteristic of study groups*

	Patients with erectile dysfunction (n = 41)	Controls (n = 40)	P value
Age (y)	46.8 ± 11.6	44.1 ± 9.2	.25
BMI (kg/m ²)	28.1 ± 3.5	28.2 ± 3.2	.85
BSA (m ²)	2.00 ± 0.15	1.97 ± 0.16	.40
Smoker	8 (19.5)	4 (10.0)	.35
Diabetes mellitus	11 (26.8)	5 (13.0)	.16
Hypertension	7 (17.0)	3 (8.0)	.20
LVEDD (mm)	48.0 ± 3.8	46.8 ± 3.3	.12
Ejection fraction (%)	66.8 ± 4.3	66.9 ± 2.7	.83
Left atrial diameter (mm)	36.1 ± 2.5	35.2 ± 2.3	.11
Creatinine (mg/dL)	0.9 ± 0.2	0.86 ± 0.1	.80
Total cholesterol (mg/dL)	172.5 ± 30.0	165.3 ± 30.0	.26
Triglycerides (mg/dL)	200.0 ± 123.3	184.3 ± 77.4	.09
LDL cholesterol (mg/dL)	99.2 ± 21.8	95.1 ± 25.2	.12
HDL cholesterol (mg/dL)	38.7 ± 6.9	40.4 ± 5.8	.23
GGT (mg/dL)	22.7 ± 10.8	18.1 ± 10.9	.06
Hemoglobin (g/dL)	13.5 ± 2.0	13.1 ± 1.8	.18
CRP (g/dL)	5.0 ± 2.0	3.8 ± 1.2	.003 [†]
Total testosterone (ng/dL)	323.0 ± 132.2	480.2 ± 125.5	.04 [†]

BMI = body mass index; BSA = body surface area; CRP = C-reactive protein; GGT = γ -glutamyl transferase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LVEDD = left ventricular end-diastolic diameter.

*Data are presented as mean ± SD or number (percentage).

[†]P < .05 statistically significant by Student t-test.

mandatory for penile erection and normal functioning of heart and valvular structures.^{22,23} EST is an important diagnostic tool for the identification of CV risk and mortality through investigation of maximal exercise capacity (eg, METs), autonomic disturbances, and risk stratification of patients with suspected or proven CVD. Of EST parameters, HRR (slowed recovery of HR after exercise) and ChI (an attenuated HR response to exercise) were believed to be related to autonomic dysfunction and shown to be associated with all-cause mortality and cardiac

events.^{24–26} Those parameters were found to be stronger predictors of CV risk than other traditional risk factors.²⁴ Previous studies have reported that HRR indices might represent parasympathetic activity and this increased activity with a decrease in sympathetic innervation occurs during the 1st minutes of the recovery phase.^{27,28} Changes in HRR indices have been evaluated in many other diseases and impairment of autonomic functions was found to be an independent predictor of CV mortality.^{23,24,29,30}

Table 2. Exercise stress testing measurements of participants with and without erectile dysfunction*

	Patients with erectile dysfunction (n = 41)	Controls (n = 40)	P value
Resting systolic BP (mm Hg)	127.3 ± 8.5	121.2 ± 7.4	.561
Resting diastolic BP (mm Hg)	79.1 ± 4.1	75.4 ± 3.8	.607
Resting heart rate (bpm)	80.0 ± 9.8	77.4 ± 10.4	.24
Peak heart rate (bpm)	161.1 ± 14.7	179.2 ± 8.1	<.001 [†]
Exercise duration (min)	9.4 ± 1.9	10.9 ± 1.7	<.001 [†]
Maximal systolic BP (mm Hg)	163.8 ± 7.1	158.5 ± 6.9	.23
Maximal diastolic BP (mm Hg)	85.6 ± 3.2	80.9 ± 3.1	.19
METs	12.5 ± 1.9	13.6 ± 1.4	.004 [†]
HRR1	30.6 ± 11.9	36.9 ± 9.9	.01 [†]
HRR2	44.9 ± 12.4	54.9 ± 7.8	<.001 [†]
HRR3	50.1 ± 11.7	63.0 ± 7.9	<.001 [†]
HRR1 < 18	5 (12)	1 (3)	.03 [†]
Chronotropic response	0.88 ± 0.1	1.0 ± 0.1	<.001 [†]
Chronotropic incompetence	12 (29)	0 (0)	<.001 [†]

BP = blood pressure; bpm = beats per minute; HRR = heart rate recovery; METs = metabolic equivalents.

*Data are presented as mean ± SD or number (percentage).

[†]P < .05 statistically significant by Student t-test.

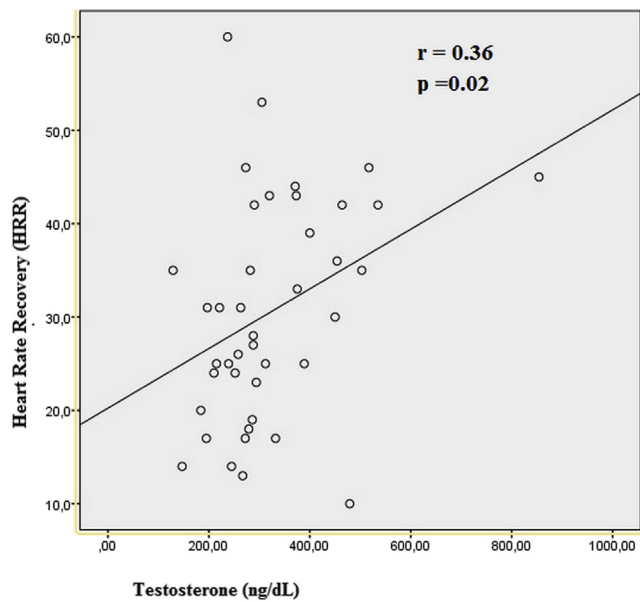


Figure 1. Representation of correlation analysis between heart rate recovery and total testosterone level.

The association between ED and cardiac functions has been investigated more meticulously in recent years. Dogru et al¹⁵ evaluated 65 men with ED and 70 control subjects by EST and reported that HRR1 was significantly lower in the ED population. They also found that patients with ED had significant ChI to exercise. A more recent study demonstrated that men with and without ED had similar HRR1 and HRR2 values after exercise. However, ChI was found to be associated with the presence and severity of ED, which means that the ChI of patients with severe ED was significantly lower than the ChI of patients with mild and moderate ED.¹⁶ Ulucan et al¹⁷ also reported that all HRR indices (1, 2, 3, and 5 minutes) and functional capacity were decreased in patients with ED. In addition, they defined HRR1 and HRR3 as independent risk factors for ED. Consistent with that report, our data showed that HRR1, HRR2, and HRR3 were lower in the ED group. Furthermore, we determined that CRs were lower in patients with ED and no ChI was noted in the control group. Therefore, it can be concluded that cardiac autonomic functions were impaired in patients with ED.

Although we demonstrated the correlation between ED and deterioration in HRR and CRs, we did not find any association between EST parameters and the severity and duration of ED. This could be due to the low post hoc power values for some variables and lack of data about the daily exercise patterns of the patient population. Also, lack of dose-response relations between exposure and outcome and inability to show casualty in case-control studies could be other reasons for this failure.

However, this study could have some important clinical implications. Functional capacity and METs have been correlated with IIEF scores.³¹ In addition, some studies have reported

that EST could play a critical role in the determination of ED management.^{31,32} EST also provides information about autonomic pathologies and future CVD risks. For this reason, investigation of EST parameters could be considered in men with ED after a taking a comprehensive history, clinical examination, and laboratory investigation including hormonal disturbances associated with ED, such as hypothyroidism, to define risks related to CVD.³³

As mentioned earlier, we found out that HRR indices were lower and that ChI was observed only in men with ED. Because HRR index decreases can be interpreted as the indicator of CV morbidity and mortality,³⁴ EST could have clinical implications in the identification of CV risks and prediction of mortality through the evaluation of autonomic pathologies in patients with ED. Those with ED with abnormal CRs and HRRs could be considered candidates for aggressive management of ED-related risk factors. Accurate management of these risk factors in patients with ED could help decrease CVD risk.^{25,26}

Low testosterone levels are another pathophysiologic mechanism linking ED to CVD.^{35,36} Testosterone plays a pivotal role in the regulation of sexual function and hypogonadism generally accompanies ED. Also, testosterone levels have been inversely correlated with the risk of having major adverse cardiac events and mortality.³⁷ Androgens can exert anti-inflammatory and antiapoptotic activities on endothelial cells by decreasing the expression of inflammatory and apoptotic mediators. Clinically insignificant chronic inflammation can lead to further impairment in endothelial functions, which could predispose to a prothrombotic status in the presence of hypogonadal state.³⁸ Recent large-scale cohort analyses have associated low testosterone levels with coronary artery diseases.^{39,40} A more recent study of 308 men with ED showed that low testosterone levels were associated with an increased risk of CVD and that high testosterone levels could decrease this risk.⁴¹

Previous studies have shown that EST parameters are not correlated with total testosterone and steroid hormone levels.^{15,42,43} In contrast to those reports, we determined that total testosterone levels were lower in men with ED and showed a weak correlation with HRR1. It can be hypothesized that increasing testosterone levels in men with ED could help correct cardiac autonomic functions and decrease CVD risk. However, further large-scale prospective studies should be conducted to evaluate the effects of testosterone replacement therapy on cardiac autonomic functions in men with ED.

Inflammation has been accepted as another pathophysiologic mechanism linking ED to CVD.²¹ Previous studies have reported that inflammatory markers and mediators including CRP are increased in men with ED.^{38,44} Moreover, expression of those mediators has been associated with the onset and severity of ED.^{44,45} Consistent with the literature, our data showed that CRP levels were higher in patients with ED compared with controls. However, we did not find any correlation between CRP levels and the severity and duration of ED.

Our study had some strengths and limitations. The main strength of the study was the correlation analysis between serum testosterone levels and EST parameters in patients with ED and control subjects. A major limitation of the study was the relatively small sample, which does not allow more complex statistics to investigate the relation between ED and autonomic dysfunction. Also, lack of randomization, inclusion of younger participants who could not address the research question properly, absence of nocturnal penile tumescence, and subdomain score evaluation of the IIEF, which could help differentiate organic and psychological causes of ED, can be stated as additional limitations of the study. Moreover, it should be remembered that there could be some unmeasured confounders, such as stress, duration of smoking, dietary habits, and daily exercise patterns of the cases and controls in the present study. Further clinical trials can help eliminate the effects of those confounders on the results. We also measured testosterone levels in the simplest way and disregarded some challenges in testosterone measurement, data interpretation, and methodologic appraisal.

CONCLUSION

Our results suggest that cardiac autonomic functions were impaired in men with ED. EST could have clinical implications in the identification of CV risks and mortality through evaluation of autonomic pathologies in patients with ED. In addition, low testosterone levels were associated with cardiac autonomic dysfunction. To support this hypothesis, further large-scale and prospective studies investigating the effect of testosterone replacement therapy on ED and cardiac autonomic functions should be conducted.

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