

Association Between Erectile Dysfunction and Asymptomatic Cardiovascular Damage in Middle-Aged Men

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Key Words: metabolic syndrome; pulse wave velocity; carotid artery intima media thickness; left ventricular mass index; erectile dysfunction.

Summary. *Background and Objective.* It has been proposed that the same cardiovascular risk (CV) factors predispose middle-aged men to the development of both coronary artery disease and erectile dysfunction (ED). Moreover, several recently published studies have identified ED as a possible early marker of CV disease. The aim of this particular study was to evaluate the association between ED and early asymptomatic heart and vascular damage in middle-aged men with CV risk factors.

Material and Methods. In this case-control study, the International Index of Erectile Function (IIEF) questionnaire was employed to assess the erectile function of the study participants and to allocate them either into the ED group ($N=21$; mean IIEF score, 18.15 [SD, 2.54]; mean age, 48.2 years [SD, 4.4]) or the control group ($N=24$; mean IIEF score, 23.45 [SD, 0.99]; mean age, 46.8 years [SD, 3.1]). Additionally, pulse wave velocity, augmentation index, pulse pressure, carotid intima media thickness (IMT), and atherosclerotic plaque count were determined, and echocardiography was performed in every subject.

Results. The mean IMT and left ventricular mass index (LVMI) of both carotid arteries in the ED group were significantly higher when compared with controls (598.57 vs. 535.54 $\text{mm}\cdot 10^{-3}$, $P=0.03$, and 107.26 vs. 98.67 g/m^2 , $P=0.04$, respectively). Using multiple regression analysis, an independent association between the IIEF score and the LVMI was found ($P=0.002$). No significant differences in the results of pulse wave velocity, atherosclerotic plaque count, and other laboratory tests were found between the 2 study groups.

Conclusions. The study suggests that ED is associated with a higher LVMI and may be an early marker of CV disease.

Introduction

Erectile dysfunction (ED) is a well-recognized condition in men, with a prevalence of 30%–70% within the age group from 40 to 70 years (1, 2). Multiple factors including depression, hormonal imbalances, and vascular or neurological changes after surgery and/or trauma are known to contribute to the development of ED (3). However, by far the most common etiological cause of ED is related to the impaired neuromyovascular phenomenon, which is determined by the nitric oxide (NO) release from the endothelial cells.

Erection occurs in the corpora cavernosum of the man's penis and is governed by the NO/cGMP pathway. The stimulation of the parasympathetic nervous system causes the secretion of NO from the nerve endings and the endothelial cells, which in turn induces the relaxation of the penile vascular smooth muscle. In a normal physiological state, this

leads to an increased perfusion of the corpora cavernosum culminating in simultaneous enlargement and hardening of the penis. On the other hand, the diminished NO production and release, which is often due to endothelial dysfunction, lead to an insufficient perfusion of the cavernosal sinusoids resulting in ED (4, 5). Therefore, factors such as high blood pressure and/or high blood glucose levels damaging the endothelium may also have a negative impact on the erectile function. Interestingly, an association between ED and vascular diseases, such as hypertension, heart disease, and diabetes, has been reported by a large population-based random sample in the Massachusetts Male Aging Study (6, 7). Similarly, a greater prevalence of ED has been noted in patients with the metabolic syndrome (MS), defined as a constellation of an increased abdominal circumference, high blood pressure (BP), elevated blood triglycerides (TG), and low high-density lipoprotein cholesterol (HDL-C) levels (8–10).

Most of the traditional cardiovascular risk factors, such as smoking, diabetes, obesity and others,

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initiate the pathophysiological processes of atherosclerosis that modify the structure of arteries. Alterations in the vascular structure manifest in the loss of elasticity and increased arterial wall thickness and stiffness and are significant independent predictors of adverse cardiovascular outcomes (11, 12). Interestingly, the effect of atherosclerosis on smaller penile arteries (1–2 mm in diameter) becomes evident much earlier than on larger coronary (3–4 mm) or carotid (5–7 mm) arteries (13). Shared risk factors for coronary artery disease (CAD) and ED have also been documented, and the degree of ED was found to correlate with the severity and the number of these risk factors (14, 15).

However, only few studies have assessed the association between the vascular parameters and the development of ED rendering the relationship inconclusive (16, 17). The aim of our study was to evaluate whether ED was associated with early asymptomatic heart and vascular damage in middle-aged men with cardiovascular risk factors.

Material and Methods

Study Participants. The study participants were 45 Caucasian men (mean age, 47.5 years; SD, 3.4) recruited from the outpatient Preventive Cardiology Unit of Vilnius University Hospital Santariškių Clinics. The inclusion criteria were based on the presence of cardiovascular risk factors and the ability to read and understand informed consent of the study. Only the patients who stated that they were

either married or were currently in a stable relationship with a partner and were sexually active were enrolled. The frequency or the kind of sexual activity was not part of the inclusion or exclusion criteria, nor was the sexual orientation.

All the study participants gave informed consent to take part in the study and subsequently had their demographic data collected as well as complete medical, surgical, and psychosexual histories taken. They also underwent a detailed physical examination, which included biochemical tests measuring HbA1c, fasting glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, TG, C-reactive protein (CRP), and testosterone. The International Index of Erectile Function (IIEF) questionnaire was used to evaluate the erectile function. The participants were assigned to either of the 2 study groups based on the IIEF scores (Table 1). ED corresponding to the IIEF score of <21 was diagnosed in 21 study participants (46.7%), whereas 24 patients with the IIEF score of >21 entered the control group.

Study Design. In this case-control study, all the measurements were collected in the morning between 8:00 and 11:00 AM. The participants were requested to abstain from tobacco, coffee, and food for at least 12 hours. The administration of vasoactive medications was discontinued at least 24 hours before the study.

Height, weight, and waist circumferences were measured in all the participants. The waist circumference was measured with a measuring tape at the

Table 1. Baseline Patients' Characteristics

Characteristic	ED+ N=21	ED- N=24	P
Age, years (SD)	46.80 (3.12)	48.2 (4.41)	0.233
BMI, kg/m ² (SD)	31.79 (5.56)	29.58 (4.93)	0.165
WC, cm (SD)	110.61 (14.31)	104.58 (14.12)	0.016
Abdominal obesity, %	66.7	50	0.259
Smoking	42.9	29.2	0.338
Metabolic syndrome, %	66.7	41.7	0.094
Hypertension, %	95	71	0.051
Systolic blood pressure, mm Hg	158.09 (18.45)	149.70 (20.59)	0.160
Diastolic blood pressure, mm Hg	107.26 (13.43)	97.67 (12.15)	0.004
MAP, mm Hg	104.19 (5.52)	104.30 (9.07)	0.468
HOMA, %	28.13 (12.94)	37.50 (27.16)	0.238
HbA1c, %	6.2 (1.15)	6.2 (0.55)	0.9
Fasting glucose, mmol/L	6.58 (1.63)	6.0 (0.79)	0.125
Total cholesterol, mmol/L	6.8 (1.37)	6.81 (1.04)	0.974
LDL-C, mmol/L	4.11 (1.35)	4.15 (1.31)	0.930
HDL-C, mmol/L	1.09 (0.214)	1.11 (0.285)	0.712
Triglyceride, mmol/L	3.47 (1.75)	3.84 (4.7)	0.731
CRP, mg/L	3.2 (2.8)	5.94 (11.47)	0.293
Testosterone, ng/L	16.9 (7.36)	17.9 (10.7)	0.745
Peripheral pulse pressure, mm Hg	56.80 (11.44)	53.37 (10.95)	0.310
IIEF score	18.15 (2.54)	23.45 (0.99)	0.0001

Values are mean (standard deviation). ED, erectile dysfunction; BMI, body mass index; WC, waist circumference; HbA1c, glycosylated hemoglobin; MAP, mean arterial pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, c-reactive protein; HOMA, homeostasis model assessment.

midpoint between the bottom of the rib cage and the top of the iliac crest, in the standing position, with the subject breathing normally. Body mass index was calculated as body weight (kg)/height (m²).

BP measurements were performed with the subjects in a seated position, following the resting period of 10 minutes. Thus, 2 consecutive measurements of BP and the heart rate were obtained, and the mean value was recorded. Fasting glucose and lipids, i.e., TC, HDL-C, TG, CRP, insulin, and total testosterone were quantified by commercially available laboratory kits. The LDL-C level was calculated using the Friedewald formula: $LDL-C = TC - HDL-C - TG/2.2$. All the patients regardless of their fasting basal glucose levels underwent a 2-hour 75-g oral glucose tolerance test (OGTT), adhering to the World Health Organization criteria. The homeostasis model assessment (HOMA) was calculated using the following formula: $serum\ glucose \times insulin/21$.

Information about the traditional cardiovascular risk factors was also obtained. Hypertension was defined as any systolic BP of ≥ 140 and/or diastolic BP of ≥ 90 mm Hg or a history of antihypertensive medication use. Current cigarette smoking was defined as any cigarette smoking during the past month.

The study was approved by the Vilnius Regional Biomedical Research Ethics Committee.

Diagnosis of Metabolic Syndrome. The diagnosis of the MS was based on the NCEP (ATP III modifications in 2005) criteria. In fact, 3 or more of the following factors had to be present: hypertension, waist circumference of >102 cm for men or >88 cm for women, serum triglycerides of >1.7 mmol/L, HDL-C of <1 mmol/L for men or <1.2 mmol/L for women, and fasting glucose of >5.6 mmol/L.

International Index of Erectile Function. The patients were screened for the presence of ED using the validated IIEF questionnaire. The erectile function domain consists of 5 questions with 5 possible answers, each scoring from 1 to 5. A score of <21 (out of 25 points in total) was used as a threshold value for the diagnosis of ED. At this cutoff point, the test has a sensitivity of 98% and a specificity of 88% (18).

Analysis of Aortic Elastic Properties. Arterial stiffness parameters were assessed using 2 techniques: applanation tonometry and the cardio-ankle vascular index (CAVI).

Applanation Tonometry. Arterial stiffness was assessed by a noninvasive measurement of the augmentation index (Aix) and brachial and aortic pulse wave velocity (PWV) with a validated noninvasive device (SphygmoCor ArtCor Medical v10., Australia) (19). The Aix was defined as the difference between the first (P1) and the second (P2) peak of the central arterial waveform, expressed as a percentage of the pulse pressure, and ejection duration

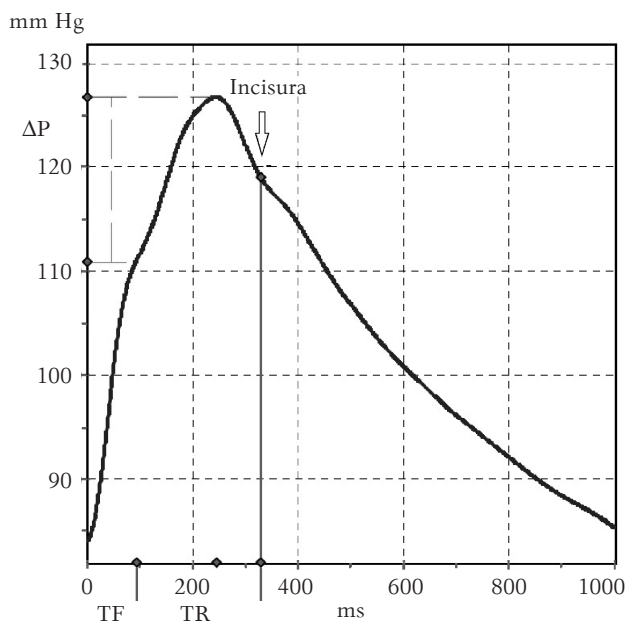


Fig 1. A central aortic pressure wave of a 50-year-old man (derived from the ascending portion of the aortic pressure waveform)

Two systolic peaks, P1 and P2, are seen, the latter becoming more prominent after the age of 35 years. The augmentation index is calculated as a difference between P2 and P1 (ΔP) expressed as a percentage of the pulse pressure (PP). Ejection duration is calculated as the time between the foot of the wave (TF) and the incisura, and TR is defined as the time between TF and the inflection point.

as the time from the foot of the pressure wave to the incisura (Fig. 1). Given a strong relationship between the Aix and the HR, the measured Aix was normalized to a HR of 75 bpm (19). The PWV was assessed quantifying the sequential carotid and radial artery pressure waveforms. Then, these waveforms were synchronized using the R wave on the simultaneously recorded electrocardiogram. The PWV was determined by the calculation of the difference in the carotid to the radial or the femoral path length (Δx) divided by the difference in the R wave to waveform foot times (Δt): $PWV = \Delta x / \Delta t$.

The PWV was measured over 10 consecutive heartbeats to cover the complete respiratory cycle.

Assessment of Cardio-Ankle Vascular Index. The subject was instructed to assume a supine position for simultaneous BP, electrocardiographic, and cardiac phonographic monitoring. The VaSera VS-1000® panel (Fukuda Denshi, Tokyo, Japan) (Software Version 08-01) to obtain the 4-limb plethysmograms was utilized. The measurements were generated with plethysmography cuffs placed on the upper arms and both ankles, ECG leads on the wrists, and phonocardiography (PCG) sensors at the right sternal border in the second intercostal space. All the limbs were rested onto the cushions in order to prevent any contact with hard surfaces and to minimize the reading discrepancies. The CAVI

and stiffness parameter β were automatically computed from the continuous ECG, PCG, and ankle-brachial waveform readings.

Carotid Ultrasound Imaging. Following a 15-minute recumbent rest, ultrasound of the common carotid artery and measurements of arterial stiffness were performed in every subject by 2 physicians trained and certified in vascular echography. The ART.LAB[®] (Esaote, Italy) system based on high-resolution echo tracking technology (WallTrack system) using a 128-RF line multi-array was utilized to make the measurements. This unique technology allows measuring the intima media thickness (IMT) at a resolution of 21 μm . Both the right and left common carotid arteries were examined with the head tilted upwards but maintained in the midline. The image was magnified in order to achieve higher resolution. Plaque was defined as a focal structure that either encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-to-media wall thickness or demonstrates a 1.5-mm thickness as measured from the media-adventitia to the intima-lumen interfaces.

Echocardiographic Examination. The study participants were kept supine and turned on the left side by 30° for echocardiographic investigation. A commercially available echocardiographic machine (GE Systems, Oslo, Norway) with a 2.5-MHz transducer was utilized to obtain 2-dimensional guided M-Mode echocardiograms at the chord level just below the mitral valves. Septal and posterior wall thickness and left ventricular chamber dimensions were measured following the American Society of Echocardiography (ASE) guidelines. The left ventricular mass index (LVMI) was calculated using the ASE-recommended formula:

$$\text{LVMI (g/m}^2\text{)} = (1.04 [(IVST + \text{LVID} + \text{PWT})^3 - \text{LVID}^3] - 13.6) / \text{body surface area}$$

Left ventricular hypertrophy was defined as a LVMI of $\geq 95 \text{ g/m}^2$ and $\geq 115 \text{ g/m}^2$ in women and men, respectively.

Statistical Analysis. The data were analyzed using the SPSS 16.0 (version for Windows) statistical software package. The values of quantitative variables are expressed as frequencies or means and standard deviation (SD).

The differences in normally distributed continuous variables were tested by the unpaired *t* test, while the Mann-Whitney test was used to compare nonnormally distributed continuous variables. The categorical data were compared using the chi-square test. The Pearson correlation was used to associate the baseline characteristics with the IIEF score.

The forward model of linear multiple regression was applied to test the association between ED severity and early asymptomatic organ damage. The IIEF score was a dependent variable, whereas femoral and brachial PVW, Aix, CAVI, carotid artery

IMT, and LVMI were used as independent variables. In all the tests, a *P* value of <0.05 was considered to be statistically significant.

Results

In total, 21 patients scored <21 in the IIEF questionnaire and were assigned to the ED group, while 24 participants (IIEF score >21) entered the control group. The baseline characteristics of both groups are shown in Table 1. The 2 groups did not have differences regarding the primary risk factors. The men with ED did not have a significantly higher prevalence of hypertension than the men without ED (95% vs. 71%, $P=0.051$) (Table 1). No significant differences were found between the groups regarding abdominal obesity (66.7% vs. 50%, $P=0.259$), smoking (42.9% vs. 29.2%, $P=0.338$), and diabetes mellitus (23.8% vs. 20.8%, $P=0.813$). Similarly, there was no significant difference between the groups with respect to the results of laboratory tests such as fasting glucose, HbA1c, and CRP levels.

The ATP III criteria for the diagnosis of the MS were met by 66.7% of the patients with ED vs. 41.7% of the patients without ED ($P=0.001$). No significant differences in the testosterone levels were identified between the patients with and without ED (16.99 [SD, 7.36] vs. 17.90 [SD, 10.70] ng/L, $P=0.745$).

The differences in the cardiovascular data are summarized in Table 2. The mean IMT and LVMI of both carotid arteries in the ED group were significantly higher than the control groups (598.57 vs. 535.54 $\text{mm}\cdot 10^{-3}$, $P=0.03$, and 107.26 vs. 98.67 g/m^2 , $P=0.04$, respectively). On the other hand, there were no significant difference in the PWV, the CAVI, and the incidence of atherosclerotic plaques between the groups.

Multiple linear regression analysis models were constructed to evaluate the independent contributions of early asymptomatic organ damage to the severity of ED. Our multivariate model consisted of the IIEF score as the dependent variable and femoral and brachial PVW, Aix, CAVI, carotid artery IMT, and LVMI as independent variables. Only LVMI was recognized as an independent risk factor for ED severity (Table 3).

Additionally, a negative association between the IIEF score and blood glucose levels ($r=-0.32$, $P=0.031$), the pulse pressure ($r=-0.35$, $P=0.019$), and the LVMI ($r=-0.40$, $P=0.008$) was found (Fig. 2). A positive association between the IIEF score and the MS ($r=0.309$, $P=0.039$) was also observed (data not shown).

Discussion

ED is a well-recognized disorder often impairing the quality of life of men. In this study, we investigated an association between various cardio-

Table 2. Echocardiographic and Arterial Stiffness Data Associated With Erectile Dysfunction

	ED+ N=21	ED- N=24	P
Radial-carotid a. PWV, m/s	9.8 (1.06)	10.03 (1.14)	0.54
Carotid-femoral a. PWV, m/s	8.74 (0.92)	9.0 (1.67)	0.59
CAVI, m/s	8.1 (1.34)	8.0 (1.5)	0.88
cIMT, mm·10 ⁻³	598.57 (120.88)	535.54 (64.24)	0.03
Plaques, %	9.5	8.3	0.73
LVMI, g/m ²	107.26 (13.44)	98.67 (12.15)	0.04
Central pulse pressure, mm Hg	54.29 (11.07)	54.93 (10.35)	0.86
HR, beats/min	67.38 (15.23)	65.66 (11.64)	0.67
Aix, %	28.58 (4.31)	28.40 (7.98)	0.95
Aix/HR, %	18.31 (7.13)	16.0 (7.9)	0.39

Values are mean (standard deviation).

PWV, pulse wave velocity; LVMI, left ventricular mass index; CAVI, cardio-ankle vascular index; cIMT, carotid intima media thickness; HR, heart rate; Aix, augmentation index.

Table 3. Multiple Linear Regressions Model for International Index of Erectile Function (Last Set)

Model Summary	Model	Unstandardized Coefficients β	Standardized Coefficients β	P
IIEF score (Model R=0.433; R square=0.188; adjusted R square=0.158; model P _{ANOVA} =0.019, predictors: constant, LVMI)	Constant LVMI	31.654 -0.114	-0.433	<0.001 0.019

Only those variables that remained significant after stepwise elimination are shown; multivariate model included Aix, CAVI, cIMT, LVMI, carotid-femoral and radial-carotid PWV.

IIEF, International Index of Erectile Function; LVMI, left ventricular mass index, cIMT, carotid intima media thickness.

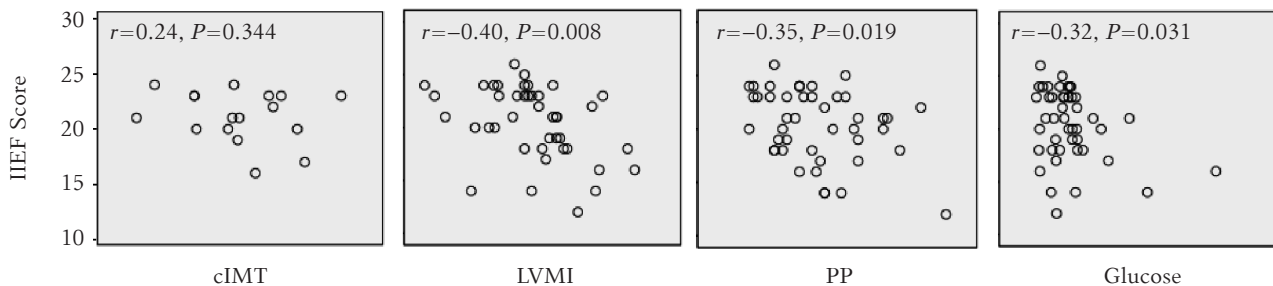


Fig. 2. The scatterplot matrix of International Index of Erectile Function (IIEF) score against left ventricular mass index (LVMI), carotid intima media thickness (cIMT), pulse pressure (PP), and glucose level

vascular risk factors and ED. Our data indicate that ED was present in 46.7% of the study participants. Seftel et al. studied the incidence of treatable cardiovascular risk factors among 272 325 patients with ED and found that 42% of the patients had arterial hypertension (20). In our study, the prevalence of hypertension among the ED participants was 95%. This disagreement on the frequencies of hypertension between our observations and the published literature most likely is due to the fact that our study participants were recruited from the clinical setting rather than from the general population. Arterial hypertension is always associated with an increased risk of coronary disease (21). Al-

though the underlying mechanism of the relationship between arterial hypertension and ED remains unknown, one theory of how these diseases are interrelated is suggested: increased production of reactive oxygen species (ROS) and vasoconstricting eicosanoids can counteract the vasodilating and vasoprotective effects of NO (22). The increased generation of superoxide is responsible for the degradation of NO because it mediates the uncoupling of NO synthase and inactivates NO via peroxynitrite formation. Since endothelial dysfunction is a systemic process, the NO inactivation is thought to occur in ED and hypertension (23).

Most studies have shown that the MS is associ-

ated with a 2-fold increase in the incidence of cardiovascular diseases and a 5-fold increase in the risk of developing type 2 diabetes mellitus (24). Using the NCEP ATP III modified criteria, we did not find that the men with ED were more likely to have the MS than those with a normal erectile function. Many previous studies have demonstrated that the MS is directly related to ED (25). Furthermore, Demir et al. found the MS to be a risk factor for ED (26). Similarly, our patients with ED and the MS had a worse erectile function when compared with the patients without the MS (IIEF score 17.7 [SD, 3.1] vs. 18.8 [SD, 2.7]) (data not shown). The MS is characterized by a collection of cardiovascular risk factors, many of which manifest in endothelial dysfunction. As penile erection strongly relies on the release of NO from the endothelial cells, we speculate that endothelial dysfunction is the pathophysiological link between ED and the MS.

Glucose metabolism disorders are an integral part of the MS. Our study confirmed that the erectile function negatively correlated with the increasing levels of fasting glucose, suggesting that the presence of diabetes mellitus predisposes men to the development of ED (24).

Contrary to the findings of Shing-Tai Chang et al. where PWV correlated with the degree of ED, we showed that ED in our patients was not related to small or large artery stiffness (16). However, all of our study participants had various numbers of cardiovascular risk factors, which could have masked the true relationship between PWV and ED. It has also been demonstrated that PWV more closely correlates with the systolic BP, whereas our study participants predominantly exhibited an elevated diastolic BP (27). The elevated systolic BP increases pulsation in arteries and damages elastic membrane, thus, contributing to arterial stiffening.

In our study, we employed a pressure-independent arterial stiffness measure (CAVI) to examine the relationship between ED and the stiffness of either aorta, femoral, or tibial arteries. However, we did not observe any difference in the CAVI between the 2 experimental groups. To our best knowledge, the CAVI is a useful diagnostic marker for the progression of coronary or carotid atherosclerosis (28). Being a validated BP-independent parameter for assessing arterial stiffness, the CAVI has served as a valuable tool in validity testing of novel methodologies for arterial stiffness measurement and cardiovascular risk evaluation (28–30). However, further studies are needed to delineate the value of the CAVI in this particular clinical setting.

Our observations indicate that ED is closely linked to the LVMI and carotid IMT. Increased arterial stiffness is believed to shift the time of pressure wave reflection from diastole to systole, thus,

further augmenting the systolic pressure. This elevation of the systolic pressure reinforces the left ventricle (LV) pulsatile load and eventually results in LV hypertrophy leading to the thickening of the intima media layer and the appearance of atherosclerotic plaques. An increase in carotid IMT is a cumulative result of diverse etiology, one of which is simple aging of the arteries. An increased IMT strongly correlates with various vascular risk factors, such as diabetes mellitus, dyslipidemia, and hypertension, and is associated with CAD. It has also been suggested that an elevated carotid IMT could be used to predict cardiovascular events (11). The conventional risk factors (e.g., hypertension, hyperlipidemia, diabetes, and smoking) were found to account for as much as 70% of developed carotid IMT (11). In our study, significantly lower carotid IMT values were recorded in the control group than in the men with ED. These findings suggest that in patients bearing a specific set of cardiovascular risk factors, ED may be an early marker of an adverse cardiovascular outcome. Interestingly, the incidence of atherosclerotic plaques did not reveal any association with ED. Although we are unable to provide an evidence-based explanation for this observation, the number of the patients included in the study may have been insufficient to uncover more subtle variations.

Finally, the study design does not allow us to draw any conclusions about causality. Moreover, our study was not community-based and, thus, likely is not reflective of the general population.

Conclusions

The results of this study suggest that a significant proportion of men with ED exhibit target organ damage, such as left ventricular hypertrophy and thicker carotid intima media. Regression analysis showed that the erectile function changes predicted left ventricular hypertrophy. This suggests that the risk factors for atherosclerosis, namely hypertension, hyperlipidemia, and diabetes, are all associated with ED. The control of these risk factors might be expected to reduce the risk of ED. In addition, when men do present with ED, it is important to identify these risk factors not only to potentially improve ED but also to try to prevent other future cardiovascular sequelae.

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Statement of Conflict of Interest

The authors state no conflict of interest.

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