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Erectile dysfunction as a predictor of two-year prognosis in acute myocardial infarction

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Abstract

Background: *Erectile dysfunction (ED) is a predictor or marker of coronary artery disease in patients at high risk of cardiovascular diseases. The aim of this study was to investigate the prevalence of ED in patients with acute myocardial infarction (AMI) and after 2 years of follow-up, and to determine the association between ED and the concentrations of the markers of inflammation, endothelial dysfunction and oxidative stress which were measured on the third day after hospital admission.*

Methods: *The study included 80 patients aged 62.25 ± 10.47 years. The primary endpoints of interest were re-hospitalization due to cardiovascular causes and death during the 2 year period after hospitalization. The Sexual Health Inventory for Men (SHIM) was assessed at the point of hospital discharge and 24 months thereafter.*

Results: *40.1% of patients had some degree of ED. The percentage of patients without ED increased (13.2%), while the percentage of patients with severe ED significantly decreased (14.7%) after 2 years. Patients with ED had significantly higher B-type natriuretic peptide (BNP) levels and decreased levels of nitric-oxide. During the 2 years of follow-up, 9 patients died (6.5% without ED, 68.6% with ED) ($\chi^2 = 7.19$, $p = 0.015$). During the same time period, 22 (27.5%) patients were re-hospitalized due to cardiovascular causes, of whom 59.1% had ED at hospital admission ($p < 0.05$).*

Conclusions: *Low levels of nitric-oxide were the best predictors of ED during AMI and after 2 years. ED predicted the worst outcomes of AMI: death and re-hospitalization. Lifestyle changes and nitric-oxide donors could assist in the treatment of ED and in the improvement of long-term prognosis for AMI.* (Cardiol J 2017; 24, 4: 393–402)

Key words: erectile dysfunction, acute myocardial infarction, prognosis, biomarker, nitric-oxide, endothelin-1, oxidative stress

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and maintain an erection sufficient to provide adequate sexual activity. ED is a common and important cause of poor quality of life and psychosocial morbidity in men. The Massachusetts male aging study was the first population study to address this issue, in which it was shown that the prevalence of ED was 52% in men aged 40–70 years [1].

The causes of ED can be predominantly organic, psychogenic or a combination of both. The most common organic causes are vascular, hormonal and neurogenic.

Penile erection is largely a vascular process and the penile endothelium and smooth muscle cells are very sensitive to structural and functional changes. Vasculogenic ED is caused by the impairment of the endothelium-dependent relaxation of the smooth muscles (functional vascular ED, the initial stage), by the occlusion of cavernous arte-

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ries due to atherosclerosis (structural vascular ED, later phase) or by a combination of both of these factors. New studies support the complex interdependence between endothelial dysfunction, inflammation and the subclinical deficiency of androgen hormones in ED etiology [2].

Erectile dysfunction is a predictor or marker of coronary artery disease (CAD) in patients at high risk of cardiovascular diseases (CVD). Subanalysis of the ONTARGET and TRANSCEND studies have shown that men with ED are at higher risk of cardiovascular (CV) mortality, myocardial infarction (MI), and all-cause mortality than men without ED [2, 3]. In a meta-analysis, Guo et al. [4] showed that men with ED have a 47% increased relative risk of CV events and a 41% increased relative risk of CVD compared to healthy people. Dong et al. [5] found in their meta-analysis that ED is associated with an increased risk of 48% for CVD, 46% for coronary heart disease (CHD), 35% for a stroke, and 19% for all-cause mortality. Vlachopoulos et al. [6] reported in a meta-analysis that ED is independently associated with a 44% increase in the risk of total CV events, a 62% increase for MI, a 39% increase for cerebrovascular events, and 25% for all-cause mortality [6].

The precise mechanism which could explain this connection has not yet been elucidated. There are a number of theories without extensive experimental validation. The most popular hypothesis explaining this association is the "artery size hypothesis" according to which the penile arteries are affected by atherosclerosis at the same time and in the same manner as coronary arteries, but since they have a smaller diameter, they show symptoms before heart vessels do. Therefore, ED precedes CHD and could be its early marker. Also, some authors have hypothesized that systolic hypertension and arterial stiffness lead to the degeneration of penile arterial walls in older age, and that those mechanisms are responsible for ED development. In addition, some studies associate mental depression with CHD and ED [4–6].

Newer studies recognize ED as a marker of a prothrombotic state. Therefore, the co-existence of ED and atrial fibrillation (AF) could be regarded as a consequence of a micro-thrombosis in AF patients, which could affect penile arteries and lead to ED, besides the other mechanisms involved in ED development such as endothelial dysfunction, inflammation and oxidative stress [7, 8].

Nitric-oxide (NO) is considered to be the link between ED and CVD. The initial damage to the endothelium-dependent vasodilatation may lead to a number of structural abnormalities in the vasculature and to atherosclerosis of the penile arteries, which reduces blood flow. Therefore, the penile vascular bed can be a sensitive indicator of systemic vascular disease. Subclinical inflammation affects the endothelial function, which may lead to a prothrombotic state. Several studies have shown that the development and severity of ED are associated with the increased expression of inflammatory markers. Inflammation may be responsible for the increased risk of coronary events in patients with ED even in the absence of obstructive lesions in the coronary blood vessels. The proinflammatory and prothrombotic state in ED causes a predisposition to the rupture of unstable, not necessarily obstructive, coronary plaques and consequently to the development of acute coronary events [2, 3].

Data suggest that endothelin-1 (ET-1) is a strong vasoconstrictor and could increase the oxidative stress in the penile arteries leading to endothelial dysfunction and to atherosclerosis [9].

The primary aim of this study was to determine the prevalence of ED in patients with acute MI (AMI) as measured on the third day after hospital admission and after 2 years of follow-up, as well as to test the association between ED and the concentrations of the markers of endothelial dysfunction, oxidative stress and inflammation. In previous studies, the markers of endothelial dysfunction (NO, ET-1 and albuminuria) showed the best predictive role for CV morbidity and mortality 72 h after AMI [10–12]. The second aim was to investigate the impact of therapy after AMI (nitric donors in particular and lifestyle changes) on erectile function.

Methods

A prospective study included 80 patients with AMI aged from 40 to 84 years (62.25 ± 10.47). Diagnosis and treatment of AMI was made according to the guidelines of the European Society of Cardiology [13]. All patients were Caucasian, had a minimum of elementary school education, had a stable financial income and were married. The estimated sample size for the 5% expected increase in the number of patients with ED, after 2 years, for a power of 0.8 was 87 participants. Patients excluded from the study were those with diabetes mellitus, chronic inflammatory diseases (e.g. chronic obstructive pulmonary disease, inflammatory bowel disease, connective tissue disorders, and rheumatoid arthritis), coagulopathy, and chronic renal and respiratory failure in which the markers

of inflammation, oxidative stress and endothelial dysfunction increase as part of the underlying disease. Also, patients treated for urogenital disorders were excluded. All participants gave written informed consent, and the study was conducted according to the Helsinki Declaration and local Ethics Committee. The participants were observed for 24 months and the endpoints of interest were re-hospitalization due to CV causes and death. Data were collected during scheduled clinical controls every 6 months. For those who died during the follow-up period, data were obtained from the family physician and death certificates. Blood samples for routine analysis were obtained on admission (including biochemical analysis, complete blood count, high-sensitivity troponin I (hsTnI) and B-type natriuretic peptide [BNP]). Concentrations of BNP, high-sensitivity C-reactive protein (hsCRP), and hsTnI were analyzed according to the description of the manufacturer (BNP [ARCHITECT ASSAY, Abbott, USA], hsCRP [BECKMAN COULTER, USA], hsTnI [ARCHITECT STAT High sensitive Troponin-I assay, Abbott Diagnostics, USA]).

The ELISA method, produced by a commercial test company R&D Systems, R&D Company, Minneapolis, USA, was used to determine the ET-1 level. Venous blood was collected in a potassium EDTA-coated vacutainer for the indirect measurement of NO by determining the concentration of nitrite/nitrate (NO2-/NO3-) in plasma. The plasma samples were stored at –20°C. The concentration of nitrate and nitrite was measured using a modified cadmium reduction method according to Navarro-Gonzalez et al. [14], based on the Griess-reaction. Moderately elevated albuminuria (formerly known as microalbuminuria) is defined as a urinary albumin-creatinine ratio (UACR) in the range from 3.4 mg/mmol to 34 mg/mmol [15]. The UACR was measured on the third day after admission to hospital in the first morning urine sample. The use of the initial morning urine specimen was recommended because, at that time, the influence of food intake and water, as well as physical activity on albuminuria is the weakest. Albumin in the urine was determined by a photometric color test with pyrogallol red on the Olympus AU 400 analyzer (Olympus, Tokyo, Japan).

An echocardiography examination was performed 24 h after admission to hospital. At hospital discharge and at the last clinical ambulatory control after 24 months, the Sexual Health Inventory for Men (SHIM), the Serbian version of the assessment of the existence of ED in the last 6 months, validated by the World Health Organization, was used as an assessment [16]. The questionnaire consisted of 5 questions and each question were scored on a 5-point ordinal scale in which lower values represent poorer sexual function. The response 0 for a question is considered the least functional, while the response 5 was considered the most functional. The possible scores for the questionnaire range from 1 to 25 (each question has a score of 1–5), and a score above 21 was considered as normal erectile function and at or below this cut-off point as ED. According to this scale, ED is classified into four categories based on the total score: severe (1–7), moderate (8–11), mild to moderate (12–16), mild (17–21), and no ED (22–25) [17].

Statistical analysis

All statistical calculations were performed using appropriate (non)parametric tests after verification of the distribution of the values in each group. All comparisons between (sub)groups were performed using the Mann-Whitney test, or ANOVA when appropriate. Spearman's rank correlation coefficient and the Pearson bivariate correlation analysis were used to investigate the relationship between two comparable variables; also, linear regression analysis was used to verify the level of the relationship examined. The biomarkers examined, together with the major risk factors for CVD, were included in the logistic regression analysis. To assess the ability of NO to predict ED incidence/ /prevalence, receiver-operator characteristic (ROC) curves were given with the area calculated under the curve (AUC), i.e. c-statistic. All data are presented as medians with the interquartile ranges, or when it was appropriate as means ± standard deviation. $P < 0.05$ was considered as significant. All statistical calculations were done using SPSS 17.0 for Windows (SPSS Inc., USA).

Results

The study included 61 men with a MI with ST--segment elevation (STEMI), 34.4% of whom had ED. Nineteen men had a MI without ST segment elevation (NSTEMI), among whom, 57.9% had ED which had lasted at least 6 months before AMI. Thus, 32 (40.1%) of the men with AMI had some degree of ED. There was no significant difference in the prevalence of ED among the patients with NSTEMI or STEMI.

A significant difference between the severity of ED at initial hospitalization and after 2 years was found. The percentage of patients without ED

Table 1. Presence and severity of erectile dysfunction (ED) in acute myocardial infarction (AMI) and after 2 years of follow-up.

Severity of ED	At hospitalization	2-years after AMI	χ^2 test/p
0 (without ED)	48 (60%)	52 (73.2%)	NS
1 (mild)	15 (18.8%)	9 (12.7%)	NS
2 (mild to moderate)	3 (3.8%)	5 (7%)	NS
3 (moderate)	–	3 (4.2%)	–
4 (severe)	14 (17.5%)	2 (2.8%)	$\chi^2 = 7.103$, $p < 0.01$
Total	80 (100%)	71 (100%)	

Table 2. Previous cardiovascular diseases and risk factors at admission in patients with and without erectile dysfunction (ED).

	Patients with ED at hospital admission	Patients without ED at hospital admission
Arterial hypertension	24 (75%)	36 (75%)
Angina pectoris	16 (50%)	18 (37.5%)
Previous myocardial infarction	9 (28.1%)	10 (20.8%)
Coronary artery bypass grafting	2 (6.3%)	1 (2.1%)
CVI/TIA	2 (6.3%)	3 (6.3%)
Newly diagnosed diabetes mellitus	4 (12.5%)	2 (4.2%)
Nonsmokers	6 (18.8%)	10 (20.8%)
Smokers	14 (43.8%)	26 (54.2%)
Ex-smokers	12 (37.5%)	12 (25%)
Dyslipidemia	10 (31.3%)	23 (47.9%)

CVI — cerebrovascular insult/stroke; TIA — transient ischemic attack

increased, while the percentage of patients with severe ED significantly decreased after 2 years (Table 1). There was no significant difference in the prevalence of CV risk factors or in the prevalence of previously diagnosed CVD among patients with/without ED assessed at hospital admission (Table 2).

The clinical and biochemical characteristics of patients with/without ED at admission are presented in Table 3. No significant difference was found between the parameters in patients with/without ED.

Among the clinical and biochemical parameters tested, we only found a significant difference in NO and BNP concentrations between patients without ED and those with severe ED (Table 4).

The levels of BNP and NO, measured 72 h after AMI were significantly different between patients with and without ED at hospital admission and between those with or without ED 2 years after AMI. An insignificantly higher percentage of patients with ED (during initial hospitalization and after the 2-year follow-up) had proteinuria (micro- or macroalbuminuria) (Table 4).

The age of the patient, left ventricular ejection fraction (LVEF), reduced LVEF (below 45%) and low levels of NO in the univariate model were associated with a higher risk of ED (Table 5). The multivariate model found NO, age and LVEF less than 45% to be independent predictors for ED. The use of NO donors, angiotensin converting enzyme (ACE) inhibitors/AT1 blockers, beta-blockers, statins and diuretics was not associated with higher risk of ED in the logistic regression analysis. In the ROC analysis it was revealed that concentrations of NO < 139.3 mmol/L (AUC = 0.676, 95% CI 0562–0677, p = 0.003) had a sensitivity of 75.0% and a specificity of 58.3% for the diagnosis of ED at hospital admission (Fig. 1). In the univariate model, it was found that with age, longer duration of hypertension, elevated BNP and fibrinogen concentrations, reduced NO levels, and with re-hospitalizations during the 2-year follow up, the probability of the existence/occurrence of

Table 3. Clinical characteristics and biochemical parameters in patients at hospital admission.

Clinical characteristic/ /biochemical parameter at hospital admission	Degree of ED assessed at hospital admission			
	0 (without ED)	1 (mild ED)	2 (mild to moderate ED)	4 (severe ED)
Age [years]	59.9 ± 10.03	64.2 ± 8.25	70.33 ± 11.59	66.5 ± 12.18
Systolic BP [mm Hg]	132.23 ± 26.14	133.33 ± 26.43	143.33 ± 20.81	137.79 ± 33.08
Diastolic BP [mm Hg]	82.87 ± 16.77	82.00 ± 13.20	83.33 ± 15.27	85.14 ± 19.06
BMI [kg/m^2]	27.72 ± 3.80	27.70 ± 4.75	27.89 ± 1.43	26.09 ± 3.43
LVEF [%]	53.67 ± 7.8	49.53 ± 12.92	52.0 ± 8.54	45.85 ± 13.85
LVEF > 45%	91.3%	53.3%	33.3%	38.5%
Duration of AH [years]	8.41 ± 6.9	8.1 ± 6.45	13.3 ± 7.6	11.6 ± 9.7
BNP [pg/mL]	245.90 (191.30–400.60)*	409.00 (366.50–455.30)	698.60 (387.40–1070.00)	2781.45 (562.90–5000.00)**
ET-1 [pg/mL]	2.86 (2.44–4.19)	3.07 (2.95–3.58)	3.68 (2.35–3.89)	8.47 (3.04–13.91)
NO [μmol/L]	155.20 (140.50–177.40)*	128.60 (123.60–167.40)	122.4 (110.3–148.1)	143.65 (102.40–184.90)**
hsTnI [ng/mL]	30.58 ± 53.79	31.14 ± 39.9	7.48 ± 10.87	51.42 ± 11.13
hsCRP [mg/L]	22.07 ± 34.32	22.38 ± 39.25	45.22 ± 38.77	34.39 ± 45.59
Fibrinogen [g/L]	5.94 ± 1.71	5.93 ± 1.43	6.7 ± 4.66	6.49 ± 2.23
UACR [mg/mmol]	3.39 ± 6.67	3.38 ± 5.56	0.66 ± 0.41	8.42 ± 21.99
Cholesterol [mmol/L]	5.29 ± 1.36	5.31 ± 1.56	5.97 ± 0.49	5.30 ± 1.23
LDL [mmol/L]	3.58 ± 1.01	3.93 ± 1.23	3.90 ± 0.98	3.36 ± 1.16
HDL [mmol/L]	1.19 ± 0.20	0.99 ± 0.18	1.37 ± 0.31	1.25 ± 0.27
Triglycerides [mmol/L]	1.62 ± 0.90	1.54 ± 0.54	1.49 ± 0.29	1.50 ± 0.87

*vs. **: $p < 0.05$; AH — arterial hypertension; BMI — body mass index; BNP — B-type natriuretic peptide; BP — blood pressure; ED — erectile dysfunction; ET-1 — endothelin-1; HDL — high density lipoprotein; hsCRP — high sensitivity C-reactive protein; hsTnI — high sensitivity troponin I; LDL — low density lipoprotein; LVEF — left ventricular ejection fraction; NO — nitric oxide degradation products; UACR — urinary albumin-creatinine ratio

Table 4. Biomarkers in patients with/without erectile dysfunction (ED) at hospital admission and after 2 years.

Biomarkers	Patients with vs. without ED during the initial hospitalization	Patients with vs. without ED 2 years after AMI
Albuminuria	24 (30%) vs. 21 (26.8%)	26 (37.5%) vs. 15 (21.7%)
BNP [pg/mL]	455.30 (387.75–630.75)* vs. 236.10 (162.60–400.60)**	562.90 (387.75–750.55)* vs. 236.10 (162.60–400.60)**
NO [μmol/L]	128.60 (115.50–149.60)* vs. 156.80 (141.10–179.30)**	131.80 (115.50–160.50* vs. 156.80 (140.50–181.80)**

*vs. **: $p < 0.05$; AMI — acute myocardial infarction; BNP — B-type natriuretic peptide; NO — nitric oxide degradation products

Table 5. Logistic regression analysis for diagnosis of erectile dysfunction at hospital admission.

Parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Nitric oxide degradation products	0.978	0.96120.995	0.010	0.976	0.956–0.995	0.016
LVEF	0.948	0.904–0.994	0.047			
LVEF category (< or ≥ 45%)	0.132	0.038–0.460	0.001	5.579	1.502–21.476	0.010
Age	1.060	1.011–1.112	0.016	1.057	1.002–1.117	0.049

CI — confidence interval; LVEF — left ventricular ejection fraction; OR — odds ratio

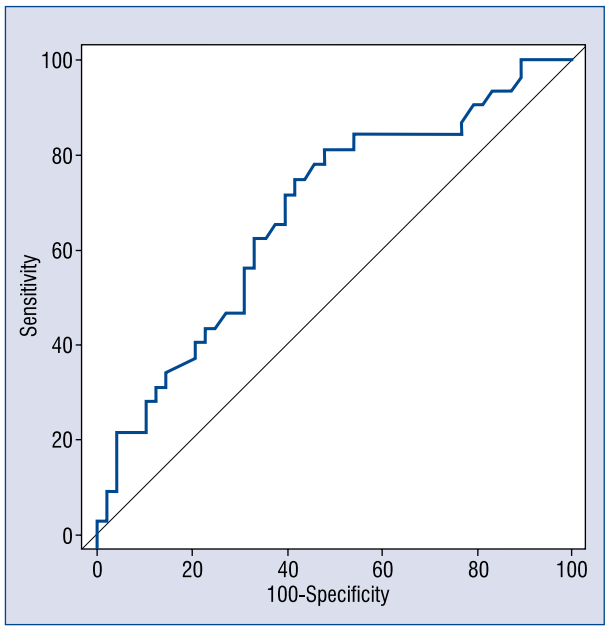

Figure 1. Receiver-operator characteristic (ROC) curve for nitric-oxide degradation products in predicting erectile dysfunction in patients with acute myocardial dysfunction.

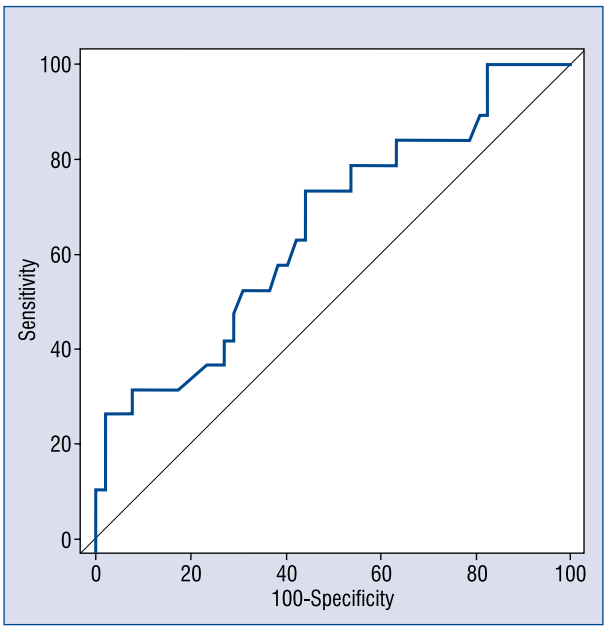

Figure 2. Receiver-operator characteristic (ROC) curve for nitric-oxide degradation products in predicting erectile dysfunction two years after myocardial infarction.

ED 2 years after the AMI had increased. In the multivariate model, increased age and decreased NO levels measured at hospital admission were independent predictors for the presence of ED 2 years after the AMI in our patients (Table 6). Using ROC analysis, we found that admission levels of NO < 134.9 (AUC = 0.658, 95% CI 0536–0767, p = 0.02) had a sensitivity of 73.68% and specificity of 55.77% for the ED diagnosis 2 years after MI (Fig. 2).

During the 2-years of follow-up, 9 patients died (6.5% without ED, 6.7% with mild ED, 33.3% with moderate to severe and 28.6% patients with severe ED) (χ^2 = 7.19, p = 0.015). During the same time period, 22 (27.5%) patients were re-hospitalized due to CV causes, of whom 59.1% had ED at hospital admission (p < 0.05).

After hospital discharge, 52.5% of these patients had NO donors in therapy (long-acting nitrates and molsidomine). 59.4% of the patients with ED and 47.9% of those without ED (p = NS) had NO donors in therapy. After 2 years, 52.6% of the patients with ED and 51.9% of those without ED (p = NS) had NO donors in therapy. Patients

Table 6. Logistic regression analysis of the risk factors for erectile dysfunction 2 years after acute myocardial infarction.

Parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Re-hospitalization	0.202	0.062–0.654	0.008			
Age	1.111	1.040–1.187	0.002	1.126	1.047–1.211	0.001
B-type natriuretic peptide	1.005	1.001–1.010	0.010			
Fibrinogen	1.452	1.021–2.066	0.038			
Nitric oxide degradation products	0.978	0.958–0.998	0.039	0.973	0.951–0.997	0.025
Duration of arterial hypertension	1.090	1.006–1.188	0.049			

CI — confidence interval; OR — odds ratio

with improved sexual function (ED at admission and with normal sexual function after 2 years — 15.7%), more frequently had NO donors in therapy (81.8% vs. 45.8%, p = 0.046), as opposed to those without changes in erectile functioning. There was no significant difference among patients without ED compared to those with ED in the frequency of the use of beta-blockers (79.2% vs. 81.3%), ACE inhibitors/AT1 blockers (81.3% vs. 81.3%), statins (93.8% vs. 93.8%) or diuretics (18.8% vs. 34.4%) at hospital discharge. None of our patients used type V phosphodiesterase (PDE) inhibitors during the 2 years.

Discussion

Forty percent of the patients with AMI had ED at hospital admission. After 2 years the number of patients with ED had significantly decreased (to 26.5%), and the percentage of patients with severe ED was significantly reduced (from 17.5% to 2.8%). This may also be the consequence of lifestyle changes and the use of medications.

Erectile dysfunction is now considered primarily as a vascular disease that shares the same risk factors as CAD [18]. ED and CVD are two different manifestations of the same systemic disturbance. The relationship between these pathological conditions lies in the interaction between CV risk factors, androgens, and chronic inflammation, which leads to arteriosclerosis and stenosis, which reduces arterial blood flow. Macroscopic non-visible changes, such as endothelial dysfunction or autonomic hyper-reactivity, may partially explain the complex relationship between ED and CVD. ED usually precedes CAD and its diagnosis provides an opportunity for risk assessment and the prevention of CHD. Also, prevention of CAD has a beneficial effect on erectile function [2, 3]. In the COBRA trial it was shown that in patients with chronic coronary disease with diffuse atherosclerosis, the ED is more severe than in those with the single vessel disease and acute coronary syndrome. Therefore, in patients with a higher atherosclerotic burden and more extensive endothelial dysfunction the ED is more severe [19].

A significant correlation was found between ED and the number of occluded coronary arteries during angiography. Also, in 16% of cases, patients with severe vascular ED (revealed by duplex sonography) had a severe or asymptomatic form of ischemic heart disease. Changes in the endothelial L-arginine-NO pathway are shown in the atherosclerotic coronary arteries and in penile and pelvic arteries in patients with ED. These studies support the concept of a reduction in the bioavailability of NO as an underlying cause of CVD and ED. Accordingly, vascular changes in the blood flow through the penis are a mirror of those that exist in the coronary blood vessels [18].

Patients with and without ED at hospital admission had no significant differences in the prevalence of CV risk factors or CVD. It is possible that testosterone deficiency in this group of patients had greater significance in the pathogenesis of ED than atherosclerosis and endothelial dysfunction [20]. Presumably, the treatment of patients with CVD or the risk factors could have had an influence on erectile function. There was no significant difference between the number of patients treated with NO donors, with and without ED, at the beginning or at the end of this study. Patients with improved sexual function more frequently had

Nitric oxide donors in therapy, which is not in line with previous studies. Burnett et al. [21] demonstrated that transdermal administration of nitroglycerin using a patch or plaster had only moderate and inconsistent efficacy in improving erectile function. It is possible that other drugs (ACE inhibitors or angiotensin [AT1] receptor antagonists, beta-blockers — nebivolol, antiaggregation therapy, statins) and physical activity with the adoption of a new, healthy lifestyle (quitting smoking and/or losing weight) also had an impact on improving erectile function after AMI. Depression is common in patients with AMI and ED. It is possible that lifestyle modifications after AMI improve the symptoms of depression and thus indirectly improve erectile functioning. Lemogne et al. [22] showed that in contrast to drugs, depressive mood is a better predictor for ED in logistic regression analysis.

There was a significant difference between the concentrations of NO and BNP measured at hospital admission in patients with/without ED during initial hospitalization and 2 years after the initial event. Patients with ED during AMI had elevated BNP levels and reduced NO values compared to those without ED. This finding supports the fact that left ventricular hemodynamic overload and consequent neurohumoral activation lead to the decreased bioavailability of NO in more severe forms of atherosclerosis, where penile arteries are also affected [23]. Oxidative stress is a key pathogenic factor in vascular diseases, such as hypertension and atherosclerosis, and it is found to be increased in ED [9]. Therefore in conditions

with increased oxidative stress, NO is involved in nitrosative stress.

A similar percentage of patients with ED during the initial event, and then after 2 years, had micro- or macroalbuminuria. This is not in line with previous studies in which albuminuria was found to be an indicator of systemic vascular permeability. Albuminuria in hypertensive patients, even below the lower referent value, is considered to be a significant predictor of CV events. A study with diabetic patients with ED and with angiographically proven coronary disease, in whom hypertension was very common, showed a significant association between microalbuminuria and CV events [23]. Microalbuminuria is a predictor of short and long term prognosis in AMI [12, 24].

In logistic regression analysis, as independent factors associated with an increased risk of ED we found NO below 139.3 mmol/L, the LVEF below 45% and older age. Independent predictors for ED, 2 years after the initial event, were older in age and had lower NO levels. The LVEF did not keep its independence as a predictor, which could be the consequence of an improved functional and possibly hormonal status after 2 years and the use of medications (beta-blockers, ACE inhibitors, statins and others). In fact, prior to the initial event a large percentage of patients had CVD or risk factors for it. We assume that after AMI patients carefully adhered to the recommendations involving lifestyle changes and regular use of therapy. In the univariate model, the risk of the existence of ED after 2 years was increased by re-hospitalizations during the follow-up period, a longer duration of hypertension, higher levels of BNP and fibrinogen. In patients who were re-hospitalized during the follow-up period, beside atherosclerosis, psychological factors could have had an effect on the impaired ED.

Aging, health status and gender affect sexual function. In population studies, men are more often sexually active and satisfied with a good sexual life than women [25]. Gender differences increase with age and are most prominent in the period from 75 to 85 years of age: approximately 39% of men vs. 17% of women are sexually active. Men and women with good health status are more sexually active than those with health problems. Although men remain sexually active, many of the changes associated with aging occur in sexual functioning, including delayed erection, decreased intensity and duration of orgasm, and ejaculation disorders [26]. All of these factors could have affected our study group.

Nitric oxide plays a major role in the physiology of penile erection. NO achieves these effects through the activation of guanylate cyclase and the subsequent production of cGMP. Reduction in the bioavailability of NO plays an important role in the pathogenesis of ED [18]. Accordingly we found that patients with more severe forms of ED had higher levels of NO degradation products, and presumably less available concentrations of NO. This "damaged activity of NO" could be similar to that found in other forms of vascular diseases in the presence of CV risk factors (e.g., smoking, dyslipidemia, diabetes, and hypertension) when the down-regulation of endothelial NO synthase is present. The development of type V PDE inhibitors that inhibit the breakdown of GMP has been revolutionary in the treatment of ED [18].

Although it would be expected that ET-1, as a strong vasoconstrictor, has an influence on the progression of ED, our results do not support previous research. ET-1 is also a significant inducer of oxidative stress, and experiments show that it can contribute to endothelial dysfunction in the penile arteries in states of insulin resistance. This confirms the key role of NADPH oxidase in vascular reactive oxygen species production in obese patients with insulin resistance. It has been shown that ET-B receptor antagonism reduces oxidative stress and endothelial dysfunction caused by ET-1 in the erectile tissue in obese patients with insulin resistance. The results of these studies suggest that the antagonism of ET-B receptors may be useful in the endothelial dysfunction associated with insulin ED-resistant conditions [9].

There is an ongoing debate regarding the use of ED as a risk factor in the primary and secondary risk assessment of CAD. Younger patients with ED and a moderate to severe CV risk are recommended taking further diagnostic procedures for detecting CAD. Besides biomarkers such as hsCRP, the glycosylated hemoglobin test (HbA1c), urinary albumin excretion, and lipoprotein-associated phospholipase A2, the procedures include non-invasive and invasive imaging. A positive stress test for inducible ischemia correlates with the presence of ED and with a decreased mean cavernous artery peak systolic velocity (< 35 cm/s). Also, increased carotid intima–media thickness and an increased coronary artery calcium score, quantified using non-contrast computerized tomography or electron beam scan, correlate with the presence of ED. It was shown that multi-detector computed tomography–coronary angiography (MDCT-CA) can better detect "silent" coronary artery plaques

in men with ED and lack of evidence for CAD than when detected with stress electrocardiogram [27]. This measurement of biomarkers is less expensive, less time-consuming, more available and easier to perform than imaging procedures in patients with ED. The "ideal" combination of biomarkers for risk stratification in patients with CV risk and ED remain to be determined.

Limitations of the study

Some study limitations need to be addressed. The major limitation is a relatively small sample size. Also, we did not have the serial measurements of the markers of endothelial dysfunction, oxidative stress and inflammation. The testosterone concentrations were not measured since it is not a routine marker measured during AMI. Its concentration decreases in AMI, and it was also expected in older patients, in agreement with this study. Further, the study design did not predict repeating measurements of the biomarkers.

Conclusions

Erectile dysfunction, alone, was a marker for poor prognosis after MI. Patients with ED prior to the AMI were at increased risk of 2-year mortality and re-hospitalization due to CVD. Older age and decreased NO concentration, measured on the third day after AMI, were independent predictors of ED prevalence and incidence even 2 years after AMI. Treatment of ED could improve the prognosis after AMI, principally by increasing the NO bioavailability and improvement in the quality of life.

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