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Microvascular endothelial dysfunction predicts the development of erectile dysfunction in men with coronary atherosclerosis without critical stenoses

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Abstract

Background—Erectile dysfunction (ED) is associated with an increased risk for cardiovascular (CV) disease, stroke and all-cause mortality, independent of conventional CV risk factors.

Coronary endothelial dysfunction is independently associated with ED in men with early coronary atherosclerosis. We aimed to investigate if coronary microvascular dysfunction predicts development of ED in patients presenting with coronary atherosclerosis without critical stenoses.

Methods—Coronary microvascular function was evaluated in 130 men with coronary atherosclerosis without critical stenoses by administration of intracoronary acetylcholine at the time of diagnostic study. After a mean follow-up of 8.4 years, patients were assessed for the development of ED by administration of a questionnaire.

Results—68 (50%) of the men had microvascular endothelial dysfunction at baseline. 35 (51%) of men with microvascular endothelial dysfunction developed ED on follow-up compared to 19 (31%) of men without microvascular endothelial dysfunction. Men who developed ED had a lower CBF response (% CBF) compared to men who did not develop ED; mean $\pm$ SD 25.4 ± 71.3 vs. 81.7 ± 120 $p=0.003$ In univariate analysis, microvascular endothelial dysfunction was a predictor for the development of ED; relative risk 2.4 (1.2 to 4.9) $p=0.016$. In multivariate logistic regression adjusting for traditional CV risk factors (age, hypertension, hyperlipidemia, diabetes, vascular disease and family history of CAD), only microvascular endothelial dysfunction $p=0.027$ and age $p=0.044$ remained significant predictors of development of ED.

Conclusion—Coronary microvascular dysfunction is a predictor of the development of ED in men with coronary atherosclerosis without critical stenoses. This study underscores the systemic involvement of the endothelial function in vascular disease.

Keywords

Endothelium; Erectile dysfunction; prognosis

Introduction

Erectile dysfunction (ED) has a high prevalence worldwide, affecting 40% of men over 40 years¹ with considerable impact on the quality of life of middle aged and elderly men. It is estimated that there are over 150 million men with ED worldwide and the number is projected to increase to 320 million by the year 2025.²

ED was formerly thought of as a psychological condition but it is now known to be predominantly a vascular disease of penile circulation.³ It shares many of the risk factors of cardiovascular disease (CVD)^{4, 5} and is itself an independent marker of increased risk for CVD, coronary heart disease, stroke and all cause mortality.^{6, 7} Indeed ED is thought to precede cardiovascular (CV) events by 3-5 years⁸⁻¹⁰ and its early identification provides an opportunity for CV risk reduction.¹¹

Endothelial dysfunction is the initial stage of the atherosclerotic process involving multiple vascular beds, including the penile^{12, 13} and coronary circulation.¹⁴ Previous studies have shown increased risk of future CV events in patients with both coronary and systemic endothelial dysfunction.¹⁵⁻¹⁸ Markers of endothelial dysfunction are increased in patients with ED compared to controls.^{19, 20} We have also recently shown that coronary endothelial dysfunction is independently associated with ED in men with early coronary atherosclerosis.²¹

However, the temporal relationship between endothelial dysfunction and risk of developing ED is not known. Therefore this study tested the hypothesis that coronary epicardial and microvascular endothelial function precede and predict the development of ED in middle-aged men.

Methods

Study Design

This study is a prospective single center cohort study. The Mayo Clinic Institutional Review Board approved the study and informed consent was obtained from all patients.

Study Population

The study group consisted of 130 men with coronary atherosclerosis without critical stenoses and free from ED at baseline who were referred to the cardiac catheterization laboratory for evaluation of coronary artery disease, found to have non-obstructive disease, and had comprehensive coronary physiology study, including the assessment of endothelial function and non-endothelium-independent coronary flow reserve (CFR).²²⁻²⁵

Exclusion criteria included: significant coronary artery stenosis (>40%), ejection fraction <45%, unstable angina, previous myocardial infarction, use of radiographic contrast agents

within 12 hours and significant systemic disease. Medications that may affect cardiovascular hemodynamics were discontinued for at least 48 hours before the study.

Study Protocol

At baseline, diagnostic coronary angiography and determination of endothelium-dependent changes in blood flow (CBF) and endothelium-independent coronary flow reserve were performed as previously described.^{24, 26, 27} A Doppler guide wire (0.014-in diameter, FloWire, Volcano Incorporated) within a 2.2F coronary infusion catheter (Ultrafuse, SciMed Life System) was advanced and positioned in the middle portion of the left anterior descending coronary artery (LAD). Intracoronary bolus injections of incremental doses (18 to 36 µg) of adenosine (Fujisawa), an endothelium-independent vasodilator (primarily of the microcirculation),²⁸ were administered into the guiding catheter until maximal hyperemia was achieved.

Assessment of the endothelium-dependent changes in CBF was performed by selective infusion of ACh into the LAD. ACh (Iolab Pharmaceuticals) 10^{-6} , 10^{-5} , and 10^{-4} mol/L, was infused at 1 mL/min for 3 minutes.^{26, 29} Hemodynamic data (heart rate and mean arterial pressure), Doppler measurements, and coronary angiography were obtained after each infusion. Endothelium-independent epicardial vasodilation was assessed with an intracoronary bolus injection of nitroglycerin (200 µg, Abbott Laboratories).³⁰

Quantitative Coronary Angiography (QCA)

Coronary artery diameter was analyzed by QCA from digital images with modification of a previously described technique from our institution.^{24, 26, 27} LAD was divided into proximal, middle, and distal segments. For each segment, the measurements were performed in the region showing the greatest change during the ACh infusion. An angiographically smooth segment of the proximal, middle, and distal LAD, free of any overlapping branch vessels, was identified in each patient and served as the reference diameter for calculation of diameter stenosis. End-diastolic cine frames that best showed the segment were selected, and calibration of the video and cine images was done, identifying the diameter of the guide catheter. Quantitative measurements of the coronary arteries were obtained using a computer-based image analysis system. Segment diameters were determined at baseline and after both ACh and nitroglycerin administration. The proximal segment, which was not exposed to ACh, served a control segment.

Assessment of Coronary Blood Flow

Doppler flow velocity spectra was analyzed online to determine the time-averaged peak velocity. Volumetric CBF was determined from the following relation: $CBF = \text{cross-sectional area} \times \text{average peak velocity} \times 0.5$.³¹ Endothelium-dependent microvascular function was calculated as % CBF in response to ACh as previously described.³²

Microvascular endothelial dysfunction

As in previous studies microvascular endothelial dysfunction was defined as 50% increase in coronary blood flow (CBF) in response to the maximal dose of ACh compared with baseline CBF.^{21, 22, 33}

Follow-Up

Long-term follow-up was performed by a questionnaire asking the patients about the development of ED since their coronary vascular study. The questionnaire asked about any incident ED (new diagnosis) that developed after the comprehensive coronary vascular reactivity study.

Statistical analysis

Data are displayed as means $\pm$ SD or counts and percentages as appropriate. Variables with heavily skewed distribution are reported as medians with first and third quartiles in parenthesis. Comparison of demographic and baseline clinical data between the groups was performed using the Student's t test for continuous data and the Pearson's chi-squared test for categorical data.

Results

We studied 130 men of whom 68 (52%) had microvascular endothelial dysfunction at baseline. The mean age at baseline was 50 ± 11 . History of hypertension was present in 44%, hyperlipidemia in 64%, diabetes in 10% and family history of CAD in 60% of patients enrolled. Mean duration of follow-up was 8.4 ± 4.7 years.

Coronary microvascular function and ED

The study population was divided into two groups: those with microvascular endothelial dysfunction (% CBF to ACh $\leq 50\%$, n=68), and those with normal microvascular endothelial function (% CBF to ACh $>50\%$, n=62).

Baseline Characteristics

The baseline characteristics and use of CV medications at the time of functional angiogram were similar between the two groups except for family history of coronary artery disease and smoking history. Patients with microvascular endothelial dysfunction had a higher incidence of ED at follow-up compared to patients with normal endothelial function 50 % vs. 30% ($P = 0.016$).

During the follow-up period, 54 patients (40%) developed ED. Patients who developed ED were older 54 ± 9.7 vs. 47 ± 11.7 years ($P = 0.0011$) and had a higher prevalence of diabetes 20% vs. 4% ($P = 0.0017$) compared to those who did not develop ED. CBF, and CFR was lower in patients who developed ED compared to those who did not (Table 2)(Figure 1 and 2) but there was no difference in the percent change of CAD (Figure 3).

Univariate and adjusted models

Univariate analysis identified the presence of microvascular endothelial dysfunction (OR 2.4 CI 1.18 to 4.99 $P = 0.016$), diabetes (OR 6.74 CI 1.98 to 31 $P = 0.0017$), hs CRP ($P = 0.0047$) and increasing age (OR 1.6 for 10 year increase (1.2 to 2.5 $P = 0.019$) as significant predictors for development of ED (Table 3).

In multivariate analysis adjusting for traditional CV risk factors (age, bmi, hypertension, diabetes, hyperlipidemia, family history of coronary artery disease and smoking) only microvascular endothelial dysfunction (OR, 2.67; 95% CI 1.13 to 6.6 P=0.024) and age (P=0.0458) were independent predictors of development of ED.

Coronary flow reserve and Coronary epicardial function

In univariate analysis CFR (P=0.0374) was a predictor of development of ED but this was not so in multivariate analysis adjusting for traditional risk factors. % CAD was not a predictor of development of ED in univariate analysis.

Discussion

The present study demonstrates that the presence of coronary microvascular endothelial dysfunction is an independent marker of ED in middle-aged men without coronary artery disease. Of the traditional risk factors for atherosclerosis only diabetes and age were predictive of the development of ED in univariate analysis. In multivariate analysis however, only microvascular endothelial dysfunction and increasing age predicted the development on ED. Thus, the current study supports an important role for microcirculatory dysfunction as a potential mechanism and marker for ED.

Endothelial dysfunction is associated with most CV risk factors and is considered a key event in the initiation, progression and complications of atherosclerosis.^{34, 35}. Indeed the effect of age and diabetes on development of ED observed in this study may be mediated via the microcirculation.³⁶ ED shares many of the modifiable risk factors with CVD. Both endothelial dysfunction and ED have also been shown to be independent markers of increased risk for CVD.^{67, 17}

Several studies have shown an association between endothelial function (both in coronary and systemic circulation), ED and CVD.^{16, 19, 20} We have previously shown that endothelial function measured peripherally using PAT predicts adverse events in the coronary circulation³⁷ and endothelial dysfunction in the coronary bed predicts the development of strokes.¹⁸ We have also demonstrated that coronary microvascular disease is associated with abnormal glomerular filtration rate.³⁸ In this study we further extended this link by showing that coronary microvascular endothelial dysfunction is an independent marker for increased risk of developing ED in middle aged men with higher predictive value than conventional CV risk factors.

Endothelial dysfunction represents an integrated index of both the overall traditional and novel CV risk factor burden and the sum of all vasculoprotective factors in an individual.^{35, 39} Endothelial dysfunction is a systemic disorder affecting vascular beds in different regions and its detection in one vascular bed could phenotypically manifest itself as a clinical abnormality in a different vascular region.

Penile erection occurs in response to sexual stimulation and the subsequent release of nitric oxide (NO) from autonomic nerves and endothelial cells in the corpus cavernosum. Microvascular dysfunction within the pelvic organs would have a negative effect on the

perfusion and oxygenation of these organs and their autonomic nerves. Traditional risk factors are associated with erectile dysfunction and cause endothelial dysfunction in the penile vascular system. Endothelial dysfunction and hypoxia within the corpus cavernosum are known to be important in the pathophysiology of erectile dysfunction.⁴⁰ ED is an independent risk factor for CVD and its diagnosis precedes cardiac events by about 3 to 5 years.⁸⁻¹⁰ The recent consensus conference on the management of ED and CVD recommended CV risk assessments in men with ED and lifestyle changes to reduce CV risk and improve erectile function.⁴¹ A recent study also demonstrated that treatment with phosphodiesterase inhibitor improved endothelial function in patients with diabetes⁴² underscoring the link between ED and endothelial function.

In this study we have shown that endothelial dysfunction is predictive of the development of ED. Hence the discovery of endothelial dysfunction in any vascular bed should be taken into consideration and appropriate management of CV risk factors instituted. The increased risk of developing ED in men with endothelial dysfunction could serve as an added impetus for the less motivated men to undertake life style modification for CV risk reduction. In addition the use of phosphodiesterase inhibitors for management of ED may also improve systemic endothelial function⁴² although more studies are needed to determine if this therapy positively impacts CV disease.

Study limitations

There are several limitations to be mentioned. First development of ED was determined by questionnaires that were filled by the patients and thus maybe underestimated. Patients self reported a new diagnosis of ED that occurred after the coronary endothelial function testing. We did not use a validated questionnaire to assess ED in the cohort. We were thus limited in verifying the diagnosis of ED. There is also the risk of recall bias from patients who were diagnosed with ED or were embarrassed to report such a diagnosis.

Second, we considered all diagnosis of ED and did not differentiate between vasculogenic ED and ED from other causes. We would speculate that the association is strongest for vasculogenic ED and performance of penile Doppler US studies would have made the study stronger.

Third, our study was not designed to measure if improvement in endothelial function had an impact on the diagnosis of ED. Patients diagnosed with endothelial dysfunction were provided with treatment and this may have led to improved endothelial function and led to regression to the mean of our results.

Conclusion

We demonstrated that coronary microvascular endothelial dysfunction is a marker of increased risk of developing ED in middle-aged men without coronary artery disease independent of traditional CV risk factors. The current study further supports the role of the microcirculation as a mechanism and potentially therapeutic target in CV disease.

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Figure 1.
Percent change in Coronary Blood Flow, by erectile dysfunction (ED) (mean $\pm$ SD).

Figure 2.
Percent change in Coronary Flow Reserve by erectile dysfunction (ED) (mean $\pm$ SD).

Figure 3.
Percent change in Coronary Artery Diameter by erectile dysfunction (ED) (mean $\pm$ SD).

Table 1
Baseline Patient Characteristics

	Normal Endothelial Function (n=62)	Microvascular Dysfunction (n=68)	P
Age, Y	49 ± 12.4	51 ± 10.5	0.27
BMI, kg/m ²	27.7 ± 4.6	29.1 ± 5.6	0.12
Hypertension, n (%)	25 (40)	33 (49)	0.33
Diabetes, n (%)	4 (6)	10 (14)	0.12
Hypercholesterolemia, n (%)	42 (68)	44 (66)	0.71
Family history CAD, n (%)	28 (47)	48 (75)	0.0012
Smoking			0.0308
Former	25 (40)	31 (46)	
Current	12 (19)	3 (4)	
Testosterone	399 ± 187	418 ± 139	0.81
CRP	1.69 ± 3.4	1.34 ± 1.90	0.55
Aspirin, n (%)	33 (53)	45 (66)	0.13
ACE inhibitor, n (%)	13 (21)	13 (19)	0.79
B- blockers, n (%)	17 (27)	23 (34)	0.43
Ca ²⁺ Channel blocker, n (%)	19 (31)	30 (44)	0.13
Lipid lowering, n (%)	25 (40)	35 (51)	0.20
Oral hypoglycemic, n (%)	3 (5)	7 (10)	0.93
Diuretics	5 (8)	6 (9)	0.88
% CBF	135.8 ± 102	-12.3 ± 40.3	--
% CAD	28.2 ± 22.7	-7.6 ± 16.1	<0.001
CFR	3.3 ± 0.83	3.0 ± 0.72	0.049

Values are mean ± SD or n (%). BMI indicates body mass index, % CBF indicates percent change in coronary blood flow to acetylcholine, % CAD indicates percent change in coronary artery diameter to acetylcholine, and CFR indicates coronary flow reserve.

Table 2
Patient Characteristics by Erectile dysfunction (ED)

	No ED (n=76)	ED (n=54)	P
Age, Y	47.7 ± 12	54 ± 9.7	0.002
BMI, kg/m ²	27.8 ± 5.6	29.5 ± 4.4	0.06
Hypertension, n (%)	31 (41)	27 (50)	0.33
Diabetes, n (%)	3 (4)	11 (20)	0.0029
Hypercholesterolemia, n (%)	46 (61)	40 (74)	0.11
Family history CAD, n (%)	46 (63)	30 (58)	0.64
Smoking			
Former	11 (15)	4 (8)	0.16
Current	28 (37)	28 (52)	
Testosterone	437 ± 163	395 ± 149	0.59
CRP	2.16 ± 3.36	0.7 ± 1.12	0.013
Aspirin, n (%)	42 (55)	47 (87)	0.19
ACE inhibitor, n (%)	10 (13)	19 (35)	0.021
B- blockers, n (%)	21 (28)	21 (39)	0.36
Ca ²⁺ Channel blocker, n (%)	28 (37)	26 (48)	0.86
Statins, n (%)	30 (39)	29 (54)	0.07
Diuretics	7 (9)	4 (7)	0.71
% CBF	81.7 ± 120	25.4 ± 71.3	0.0026
% CAD	-15.4 ± 22.0	-22.7 ± 22.1	0.065
CFR	3.3 ± 0.88	3.0 ± 0.75	0.068

Values are mean ± SD or n (%). BMI indicates body mass index, % CBF indicates percent change in coronary blood flow to acetylcholine, % CAD indicates percent change in coronary artery diameter to acetylcholine, and CFR indicates coronary flow reserve.

Table 3
Univariate Analysis of Risk Factors for Erectile dysfunction (ED)

Variable	Odds Ratio (95% CI)
Age, per- 10 year increase	1.6 (1.2 to 2.5)
Hyperlipidemia	2.02 (0.96 to 4.38)
Diabetes	6.74 (1.98 to 31)
Hypertension	2.02 (0.96 to 4.38)
Family history of CAD	1.08 (0.53 to 2.22)
Microvascular dysfunction	2.4 (1.18 to 4.99)