

# Impaired Brachial Artery Endothelium-Dependent and -Independent Vasodilation in Men With Erectile Dysfunction and No Other Clinical Cardiovascular Disease

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<b>OBJECTIVES</b>	The goal of this study was to determine whether patients with vascular erectile dysfunction (ED) and no other clinical cardiovascular disease have structural and functional abnormalities of other vascular beds.
<b>BACKGROUND</b>	In many ED patients, vascular disease is the major underlying cause. It may be that ED is an early marker of atherosclerosis in patients without clinical cardiovascular disease.
<b>METHODS</b>	We assessed systemic vascular structure and function in 30 patients with ED and 27 age-matched normal control (NL) subjects. We measured vascular parameters, including: 1) carotid and brachial artery diameters, intima-media thickness, compliance, and distensibility; 2) aortic pulse wave velocity; 3) coronary calcification; and 4) brachial artery endothelium-dependent and -independent vasodilation.
<b>RESULTS</b>	There were no significant differences in baseline demographics, coronary artery risk score, or lipid values between the two groups. Most structural and functional vascular parameters were similar in the ED and NL groups. Brachial artery flow-mediated vasodilation (FMD) (1.3 vs. 2.4%, $p = 0.014$ ) and vasodilation to nitroglycerin (NTG) (13.0 vs. 17.8%, $p < 0.05$ ) were significantly reduced in ED patients, compared with NL subjects. In addition, there was a significant correlation between FMD and vasodilation to NTG in ED patients ( $r = 0.59$ , $p < 0.05$ ) but not in NL subjects.
<b>CONCLUSIONS</b>	Patients with ED but no clinical cardiovascular disease have a peripheral vascular defect in endothelium-dependent and -independent vasodilation that occurs before the development of other overt functional or structural systemic vascular disease and is independent of other traditional cardiovascular risk factors. (J Am Coll Cardiol 2004;43:179–84) © 2004 by the American College of Cardiology Foundation

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Erectile dysfunction (ED) is present in up to 30 million men in the U.S. and approximately 100 million men worldwide (1) and affects up to 52% of men between the ages of 40 and 70 years (2,3). It is now recognized that vascular disease of the penile arteries is the most common cause of ED, accounting for up to 80% of cases (4–6). The nitric oxide–cyclic guanosine-3'5'-monophosphate (NO-cGMP)

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system is important in producing the arterial and venous dilation necessary to attain and sustain an erection. Abnormalities of this vasodilator system are present in atherosclerosis and play an important role in the pathophysiology of ED (7–9). In addition, drugs such as sildenafil, which serve to enhance vasodilation by inhibiting the breakdown of cGMP, are very effective in treating ED (1).

Most previous clinical studies of ED have focused on patients with multiple risk factors for atherosclerosis or

patients with known cardiovascular disease (5,6,10). These studies have led to the perception that ED is a disease of patients with advanced atherosclerosis. However, we have observed that many relatively young patients presenting with ED do not have clinical cardiovascular disease or major risk factors for atherosclerosis. We hypothesize that these patients have systemic vascular disease and that ED is the first clinical manifestation of this disease. The present study was thus designed to determine whether patients with ED and no other clinical cardiovascular disease have structural and functional abnormalities in other vascular beds.

## METHODS

**Study groups.** Thirty patients with ED and 27 age-matched normal control (NL) subjects were recruited from a sexual dysfunction urology clinic and from newspaper advertisements. All subjects were without a clinical history or physical examination providing evidence of cardiovascular disease. Exclusion criteria for ED patients and NL subjects included recent smoking history (previous five years), known hypertension, hyperlipidemia, and diabetes mellitus. Patients with neurogenic causes of ED were excluded based on their history and physical examination. Patients with psychiatric causes of ED were excluded based

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**Abbreviations and Acronyms**

CAD	= coronary artery disease
ED	= erectile dysfunction
EDV	= end-diastolic velocity
FMD	= flow-mediated vasodilation
HDL	= high-density lipoprotein
IIEF-15	= 15-item International Index of Erectile Function
IMT	= intima-media thickness
LDL	= low-density lipoprotein
NL	= normal control subjects
NO-cGMP	= nitric oxide-cyclic guanosine-3'5'-monophosphate
NTG	= nitroglycerin
PGE <sub>1</sub>	= prostaglandin E <sub>1</sub>
PSV	= peak systolic velocity
PWV	= pulse wave velocity
RI	= resistance index

on a psychosocial questionnaire that assessed performance anxiety, stress, depression, and relationship issues.

**Study protocol.** Patients with ED underwent a urologic evaluation and penile Doppler examination to exclude nonvascular causes of ED. All subjects then underwent a series of tests, including a blood draw, ED questionnaire, and measurement of vascular parameters: 1) coronary calcification; 2) aortic pulse wave velocity (PWV); 3) brachial and carotid artery diameters, intima-media thickness (IMT), compliance, and distensibility; and 4) brachial artery endothelium-dependent and -independent vasodilation. The ED questionnaire response was also measured after two months or more of 50 mg oral sildenafil therapy to determine whether therapy designed to improve the NO-cGMP system would successfully improve the symptoms of ED in these patients.

**Penile Doppler examination.** Penile Doppler studies were performed in the ED group only, using the Knoll/Midus ultrasonic velocitometric system (Urometrics, St. Paul, Minnesota). This system incorporates a penile ultrasonic velocitometer that uses two moveable, fixed-angle, 8-MHz transducers to measure cavernosal artery velocity as an indicator of penile blood flow. Measurements using this system have previously correlated well with duplex ultrasonography with respect to peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistance index ( $RI = [PSV - EDV]/PSV$ ) (11). All ED patients received 10 to 20  $\mu$ g of intracavernosal prostaglandin E<sub>1</sub> (PGE<sub>1</sub>; Caverject, Pharmacia, New Jersey), and measurements were performed at 5 and 15 min after injection to determine the PSV, EDV, and RI. Erectile dysfunction was determined to be vascular in origin if PSV was <35 cm/s or RI was <0.9 (12,13).

**Blood tests.** The following laboratory tests were performed: fasting lipid panel (low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, total cholesterol), lipoprotein(a), fasting glucose, and homocysteine. For each participant, fasting blood

samples were drawn into a serum tube and an EDTA-containing tube that were separated within 30 min. Serum and plasma aliquots were frozen immediately at  $-70^{\circ}\text{C}$  until analyzed. Cholesterol, triglycerides, HDL cholesterol, and glucose were measured in serum by colorimetric reflectance spectrophotometry, using the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, New York). For HDL cholesterol, the non-HDL cholesterol was first precipitated with magnetic 50,000 molecular weight dextran sulfate and magnesium chloride. The LDL cholesterol was calculated in serum with a triglyceride value <400 mg/dl, using the formula of Friedewald et al. (14). Fasting homocysteine was measured in EDTA plasma by a fluorescence polarization immunoassay (IMx homocysteine Assay, Axis Biochemicals ASA, Oslo, Norway), using the Imx Analyzer (Abbott Diagnostics, Abbott Park, Illinois).

**The ED questionnaire.** The 15-item International Index of Erectile Function (IIEF-15), a validated, self-administered questionnaire, was used for the clinical assessment of ED (15,16). In this questionnaire, symptoms of ED are assessed in five domains, with each domain having a maximum score of 5.

**Aortic PWV.** Pulse wave velocity was measured along the descending thoraco-abdominal aorta using the foot-to-foot velocity method, as previously published and validated (17,18). Briefly, waveforms were obtained transcutaneously over the common carotid artery and right femoral artery, and the time delay (t) was measured between the feet of the two waveforms. The distance (D) covered by the waves was measured between the two recording sites. Thus, PWV was calculated as:  $PWV = D \text{ (m)}/t \text{ (s)}$ . The mean  $\pm$  SD difference between PWV measurements obtained 5 min apart was  $0.18 \pm 1.47 \text{ m/s}$  ( $p = \text{NS}$ ).

**Coronary calcification.** Electrocardiographically gated helical computed tomography (GE Multislice Lightspeed, GE Medical Systems, Milwaukee, Wisconsin) was used for noninvasive quantification of coronary artery calcium (19). The image acquisition consisted of a scan from the base of the heart to the apex, using cine loops of 4 slices, 11 images/slice, and a slice thickness of 2.5 mm. The rotation time was 0.8 s, with 0.1 s between images. The field of view was 25 cm, with a  $512 \times 512$  matrix size. Image processing was performed with SmartScore (GE Medical Systems), using the conventional Agatston method with a threshold of 130 Hounsfield units. A coronary calcium score >5 was considered abnormal.

**Brachial and carotid artery mechanical properties.** Arterial diameter, change in diameter ( $\Delta D$ ), and IMT were imaged using a wall-tracking system (PIE Medical WTS V2, Maastricht, The Netherlands), with a 10.0-MHz linear array ultrasound transducer held in place by a stereotactic device (20). The system consists of software running on a standard personal computer equipped with a data acquisition card for the acquisition of radiofrequency ultrasound signals obtained with a conventional echo scanner (Biosound AU5). Arterial pressure, diameter,  $\Delta D$ , and IMT of

the brachial artery were measured with the subject resting in the supine position. The nondominant arm was fixed level with the heart at an angle of 45° from the head to feet axis and supported by a tilt-table arm brace. An arterial pressure waveform was obtained using a tonometer placed over the radial artery and calibrated to a standard blood pressure cuff placed on the contralateral arm (Colin Medical, San Antonio, Texas). The diameter,  $\Delta D$ , and IMT of the carotid artery were measured with the subject resting in the supine position with the head turned 45° from the side being scanned. The reference point for measurement of the carotid artery was at the common carotid artery 2 cm proximal to the beginning of the dilation of the bulb (21). Compliance was defined as the change in area ( $\Delta A$ ) for a given change in pressure ( $\Delta P$ ). Distensibility was defined as the compliance divided by the vessel area in diastole:  $(\Delta A/\Delta P)/A$ . The final values reported for all mechanical properties were the average of three measurements. Reproducibility of diameter,  $\Delta D$ , and IMT were assessed using the Bland-Altman technique (22). The mean  $\pm$  SD differences between brachial artery diameter,  $\Delta D$ , and IMT measurements obtained 5 min apart were  $0.005 \pm 0.188$  mm,  $-0.6 \pm 17.8 \mu\text{m}$ , and  $-0.01 \pm 0.06$  mm, respectively ( $p = \text{NS}$ ). The mean  $\pm$  SD differences between carotid artery measurements obtained 5 min apart were  $0.120 \pm 0.388$  mm,  $-19.3 \pm 75.3 \mu\text{m}$ , and  $-0.02 \pm 0.15$  mm for diameter,  $\Delta D$ , and IMT, respectively ( $p = \text{NS}$ ).

**Brachial artery endothelium-dependent and -independent vasodilation.** Assessment of brachial artery vasodilation was done using the ultrasound system described earlier. Arterial diameter was recorded over time, as previously shown (23,24). Endothelium-dependent, flow-mediated vasodilation (FMD) was produced by releasing a blood pressure tourniquet around the wrist, which was inflated for 5 min at a pressure of 250 mm Hg (25,26). The diameter was tracked over time, beginning 10 s before cuff release and lasting  $\sim 90$  s. Endothelium-dependent vasodilation was expressed as the percent change from the diameter immediately after cuff deflation to the diameter at 60 s after cuff deflation. The mean  $\pm$  SD percent differences between the diameter before cuff inflation and the diameter immediately after cuff deflation were  $-0.5 \pm 5.7\%$  and  $-0.2 \pm 4.6\%$  for the NL and ED groups, respectively ( $p = \text{NS}$ ). The short-term mean  $\pm$  SD relative difference in FMD measured 10 min apart was  $0.15 \pm 2.49\%$  ( $p = \text{NS}$ ). In a subgroup of 38 individuals, the mean  $\pm$  SD relative differences in measurements made an average of  $130 \pm 43$  days apart were  $-0.117 \pm 0.346$  mm for baseline diameter and  $0.42 \pm 1.50\%$  dilation for FMD ( $p = \text{NS}$ ). After a 10-min rest, 0.4 mg sublingual nitroglycerin (NTG) was administered, and the diameter of the brachial artery was measured three times at 5 min after administration. Endothelium-independent vasodilation was defined as the percent change from resting baseline to the average of the three post-NTG diameters. The dose used has previously been shown to cause maximum vasodilation (27).

**Table 1.** Baseline Characteristics

Demographics	NL Subjects (n = 27)	ED Patients (n = 30)
Age (yrs)	46.2 $\pm$ 2.4	46.6 $\pm$ 1.7
BMI (kg/m <sup>2</sup> )	27.6 $\pm$ 1.2	28.4 $\pm$ 1.0
Systolic pressure (mm Hg)	124.2 $\pm$ 2.8	123.1 $\pm$ 2.5
Diastolic pressure (mm Hg)	72.6 $\pm$ 1.9	72.9 $\pm$ 1.8
Mean pressure (mm Hg)	87.8 $\pm$ 2.9	89.2 $\pm$ 1.9
Pulse pressure (mm Hg)	51.6 $\pm$ 1.7	50.2 $\pm$ 1.9
Heart rate (beats/min)	60 $\pm$ 1.3	64 $\pm$ 1.6*
CAD score	3.2 $\pm$ 0.8	3.5 $\pm$ 0.6
Penile Doppler PSV (m/s)	—	28 $\pm$ 3
IIEF-15	21.3 $\pm$ 1.2	13.7 $\pm$ 1.2†

\* $p < 0.05$ . † $p < 0.01$ . Data are presented as the mean  $\pm$  SEM.

BMI = body mass index; CAD = coronary artery disease by Framingham cardiac risk score; ED = erectile dysfunction; IIEF-15 = 15-item International Index of Erectile Function questionnaire; NL = normal control; PSV = peak systolic velocity.

**Statistical analysis.** Statistical analysis was performed using SPSS version 8.0. Demographic data, blood tests, and vascular measures were assessed using the unpaired  $t$  test. Brachial artery endothelial function curves for ED patients and NL subjects were compared using two-way analysis of variance, with group as a fixed factor and time as a repeated measures factor. Simple linear regression was used to assess the relationship between endothelium-dependent and -independent vasodilation within the two groups. Statistical significance was defined as  $p < 0.05$ . Data in the figures and tables are presented as the mean value  $\pm$  SEM.

## RESULTS

Table 1 shows the baseline characteristics of the 30 patients with ED and the 27 NL subjects. Heart rate was significantly increased in the ED group. There were no other significant differences in baseline demographics between the two groups. The Framingham cardiac risk score for coronary artery disease (CAD) tended to be slightly higher in the NL subjects, but this trend was not statistically significant. The patients with ED had objective evidence of significant clinical and penile vascular disease. Mean PSV measured by penile Doppler was  $28 \pm 3$  m/s (normal  $>35$  m/s). The mean  $\pm$  SD IIEF-15 score was  $13.7 \pm 6.5$  in the ED group versus  $21.3 \pm 5.3$  in the NL group ( $p < 0.0001$ ), indicative of moderate symptoms of ED. The mean IIEF score increased by  $3 \pm 5$  after two months or more of sildenafil therapy ( $p = 0.001$ ).

Table 2 shows blood tests and vascular study results for the two groups of subjects. Lipid values were similar in the two groups. Structural vascular parameters, including coronary calcium score, carotid and brachial artery diameters, and IMT, were similar between the two groups. Functional vascular parameters, including brachial and carotid artery compliance and distensibility and aortic PWV, were similar between the two groups.

Figure 1 shows the mean FMD curves for the ED and NL groups. Brachial artery FMD was significantly reduced in ED patients versus NL subjects, whether comparing over

**Table 2.** Study Results

	NL Subjects (n = 27)	ED Patients (n = 30)
Laboratory results		
Total cholesterol (mg/dl)	193.1 ± 8.6	203.6 ± 7.6
Triglycerides (mg/dl)	130.7 ± 18.4	115 ± 11.5
HDL cholesterol (mg/dl)	47.9 ± 3.9	47.7 ± 2.4
LDL cholesterol (mg/dl)	118.5 ± 7.0	128.2 ± 6.8
Lipoprotein(a) (mg/dl)	24.3 ± 10.3	22.4 ± 3.7
Glucose (mg/dl)	92.9 ± 2.1	90.0 ± 1.6
Homocysteine (mg/dl)	9.2 ± 0.3	8.9 ± 0.5
Vascular results		
Coronary calcium (% with score >5)	20%	27%
PWV (m/s)	7.9 ± 0.3	7.8 ± 0.4
Carotid (baseline)		
Compliance (mm <sup>2</sup> /mm Hg)	111.3 ± 9.1 × 10 <sup>-3</sup>	100.6 ± 8.0 × 10 <sup>-3</sup>
Distensibility (mm Hg <sup>-1</sup> )	2.67 ± 0.20 × 10 <sup>-3</sup>	2.47 ± 0.17 × 10 <sup>-3</sup>
Diameter (mm)	7.30 ± 0.17	7.14 ± 0.16
IMT (mm)	0.62 ± 0.03	0.65 ± 0.03
Brachial (baseline)		
Compliance (mm <sup>2</sup> /mm Hg)	9.4 ± 1.0 × 10 <sup>-3</sup>	9.2 ± 1.0 × 10 <sup>-3</sup>
Distensibility (mm Hg <sup>-1</sup> )	0.58 ± 0.04 × 10 <sup>-3</sup>	0.54 ± 0.04 × 10 <sup>-3</sup>
Diameter (mm)	4.48 ± 0.11	4.59 ± 0.13
IMT (mm)	0.40 ± 0.01	0.41 ± 0.01

Data are presented as the mean value ± SEM.

HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; PWV = pulse wave velocity measured at carotid and femoral arteries; other abbreviations as in Table 1.

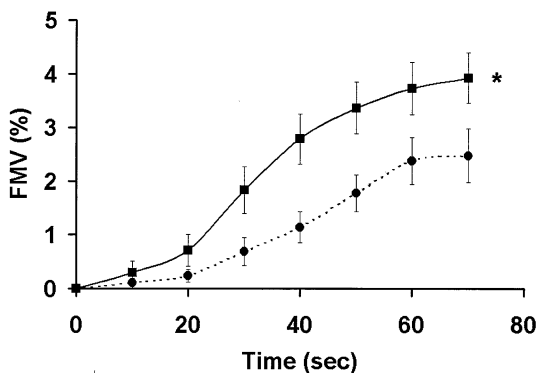
the entire 90-s period after cuff release ( $1.3 \pm 0.3\%$  vs.  $2.4 \pm 0.3\%$ ,  $p = 0.014$ ) or at 60 s after cuff release ( $2.4 \pm 0.5\%$  vs.  $3.7 \pm 0.5\%$ ,  $p = 0.05$ ). The maximum response to 0.4 mg sublingual NTG was significantly impaired in ED patients versus NL subjects ( $13.0 \pm 1.4\%$  vs.  $17.8 \pm 1.4\%$ ,  $p = 0.02$ ) (Fig. 2). In addition, there was a significant correlation between FMD and vasodilation to NTG in ED patients ( $r = 0.59$ ,  $p < 0.05$ ) but not in NL subjects ( $r = 0.05$ ,  $p = \text{NS}$ ) (Fig. 3).

## DISCUSSION

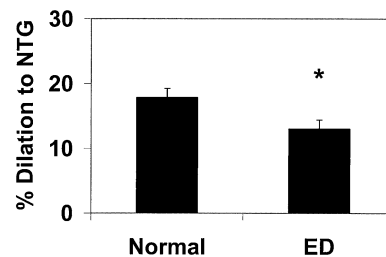
The main finding of this study is that patients with ED and no significant cardiac risk factors or other clinical cardio-

vascular disease have a peripheral vascular abnormality in the NO-cGMP pathway, as measured by brachial artery FMD and vasodilation to sublingual NTG. Flow-mediated vasodilation has previously been shown to be largely mediated by NO (28). This impairment in brachial artery endothelial-dependent and -independent vasodilation is present despite a normal CAD risk score, normal systemic vascular stiffness measures (compliance, distensibility, and PWV), and normal systemic vascular structure (diameter, IMT, coronary calcium score). These data suggest that an abnormality in the peripheral vascular NO-cGMP vasodilator system may result in ED as the first clinical manifestation of cardiovascular disease.

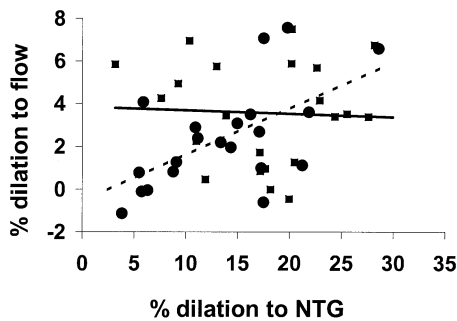
It is well known that patients with risk factors for cardiovascular disease or overt cardiovascular disease are at risk of developing ED. In one study, 64% of men who presented with myocardial infarction reported symptoms of ED before their heart problems, and in another study, 57% of men undergoing coronary artery bypass graft surgery



**Figure 1.** Brachial artery flow-mediated vasodilation (FMV) was significantly reduced in erectile dysfunction patients (circles) versus normal control subjects (squares) over the whole time period ( $p = 0.014$ ). The difference was also significant when comparing the percent dilation from baseline to 60 s after cuff release ( $p = 0.05$ ). \* denotes a significant increase compared to erectile dysfunction over the entire curve.



**Figure 2.** The vasodilator response to 0.4 mg sublingual nitroglycerin (NTG) was significantly impaired in erectile dysfunction (ED) patients versus normal control subjects ( $13.0 \pm 1.4\%$  vs.  $17.8 \pm 1.4\%$ ,  $p = 0.02$ ). \* denotes a significant decrease compared to normal.



**Figure 3.** There was a significant correlation between endothelium-dependent (flow-mediated vasodilation) and -independent (nitroglycerin [NTG]) vasodilation in erectile dysfunction patients (circles) ( $r = 0.59$ ,  $p < 0.05$ ) but not in normal control subjects (squares) ( $r = 0.05$ ,  $p = \text{NS}$ ).

reported ED symptoms before the operation (29). In these patients, ED was an early, or perhaps initial, clinical manifestation of atherosclerotic vascular disease. These studies raise the possibility that ED may serve as a clinical marker for the presence of future vascular disease or adverse cardiac events. However, there are little data available on the vasculature of patients with ED but no other clinical cardiovascular disease.

The patients with ED evaluated in this study clearly had a vascular etiology for their symptoms, as they had abnormal penile Doppler studies. They likely had impairment in the penile NO-cGMP system, because sildenafil treatment resulted in significant improvement in symptoms of ED. The finding of impaired endothelium-dependent and -independent vasodilation in patients with ED is similar to that found in patients with hypercholesterolemia (30) and early atherosclerosis (31). The abnormality noted in this study of ED patients could not be attributed to the presence of traditional cardiovascular risk factors, because the patients with ED were no different from the control subjects with respect to blood pressure, baseline lipid values, presence of diabetes mellitus, smoking status, and CAD risk score. Risk factors such as LDL particle size, high-sensitivity C-reactive protein, plasminogen activator inhibitor-1, and measures of oxidative stress (among others) were not measured and could possibly have contributed to the differences in vasodilation. The ED patients in this study were overweight, with a body mass index of  $28.4 \pm 1.0$ . We did not measure glucose tolerance or insulin sensitivity, so we cannot exclude the presence of abnormalities of these parameters in our ED patients. However, the NL subjects were similarly overweight, with a body mass index of  $27.6 \pm 1.2$ , so this potential risk factor is unlikely to account for the differences in vasodilation observed in this study.

The abnormality in the NO-cGMP system likely contributing substantially to ED was also present in the brachial artery. This abnormality appears to be a relatively early marker of atherosclerotic arterial disease, because other functional and structural parameters of three different systemic arteries were normal. There are several potential explanations for the presence of clinically significant vascu-

lar disease in the penile vascular bed before the presence of overt atherosclerotic vascular disease in other arteries. Penile arteries are relatively small, with the average cavernosal artery 0.5 mm in diameter, and helicine arteries, which run between the cavernosal artery and the sinusoids, are much smaller. These smaller arteries need to dilate up to 80% to provide the blood flow necessary to produce enough venous compression to sustain erection (32). This contrasts with other conduit arteries that dilate up to about 15% during FMD. In addition, the penile vascular bed is dependent on NO for vasodilation of arteries to produce rapid blood inflow, as well as for vasodilation of trabeculae smooth muscle of the lacunar spaces to prevent venous outflow. The relaxation of the lacunae and filling with arterial blood under high pressure cause the lacunae to swell and press the penile drainage veins against the resistant tunica albuginea, thus trapping the blood in the penis. In many other vascular beds, the role of NO on the venous side of the circulation is minimal. This high degree of dependence on NO for both normal and rapid arterial inflow and for prevention of venous outflow may account for the increased susceptibility of this vascular bed to deficiencies in the NO-cGMP vasodilator system.

Two stimuli of the NO-cGMP vasodilator system were assessed in this study: shear stress-induced FMD and NTG. Brachial artery vasodilation to both of these stimuli was abnormal in the patients with ED. The defect in the NO-cGMP vasodilator pathway must involve the smooth muscle, because vasodilation to the direct smooth muscle dilator NTG was impaired in the brachial artery of the patients with ED. There may also be a defect in endothelial NO bioavailability. However, the correlation between the vasodilator response to flow and NTG in ED patients suggests that the predominant defect in this vasodilator system is not in the endothelium.

It is unknown whether patients with ED have a specific defect in one vasodilator pathway or whether several pathway defects exist. We did not test other vasodilator stimuli in the peripheral vasculature of ED patients. However, we did demonstrate abnormal penile blood flow in response to intracavernosal PGE<sub>1</sub>, a vasodilator that works via increasing smooth muscle cyclic adenosine monophosphate (cAMP) levels. This test does not necessarily imply a specific defect in cAMP-mediated vasodilation, as the vasodilator response to PGE<sub>1</sub> may, in large part, depend on FMD as a result of endothelial NO release. One previous study showed that cGMP-dependent kinase I-deficient mice failed to relax corpora cavernosa smooth muscle on activation of the NO-cGMP signaling cascade (33). However, vasodilation remained intact via the cAMP-mediated pathway in these mice.

The FMD responses in our NL subjects are lower in our study than in some other laboratories' reports. This was because our technique for measuring FMD uses a wrist occlusion cuff instead of a forearm occlusion cuff to create the reactive hyperemic flow stimulus for FMD. This results

in a lower peak and total reactive hyperemia and thus a lower vasodilator response to flow. Our values for FMD are similar to those measured in other laboratories that use a wrist occlusion technique (34) and are consistent with normal endothelial function in our NL subjects.

**Conclusions.** This study demonstrates a defect in the peripheral vascular NO-cGMP system in patients with ED but no other clinical cardiovascular disease. This defect is predominantly in the smooth muscle and can occur before the development of other overt functional or structural systemic vascular disease. In addition, this abnormality in the patient population studied is not associated with traditional cardiovascular risk factors. Erectile dysfunction can be an early clinical marker for the presence of systemic vasodilator abnormalities. It remains to be seen whether patients with ED and abnormal NO-cGMP-mediated vasodilation will progress to clinically significant systemic cardiovascular disease or go on to have acute cardiovascular events such as stroke or myocardial infarction.

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