Arterial function and intima-media thickness in hypertensive patients with erectile dysfunction
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Introduction
Erectile dysfunction is a highly prevalent disorder in the general population, as it affects almost 50% of men aged 40–70 years [1,2]. Erectile dysfunction is now increasingly perceived as a sign of generalized arterial disease and frequently coexists with subclinical or symptomatic coronary artery disease (CAD) [3–5]. Interestingly, erectile dysfunction often precedes the appearance of chronic atherosclerotic disease or presentation of an acute cardiovascular event [5,6]. Recent prospective studies have shown that erectile dysfunction is independently associated with a high rate of cardiovascular events [7]. This high risk may be mediated, at least in part, by endothelial dysfunction, which is a common denominator in the pathophysiology of both erectile dysfunction and atherothrombotic cardiovascular disease [8,9], and/or by an activated systemic endothelial and inflammatory state, which characterizes erectile dysfunction, as we have recently shown [10].

Vasculogenic erectile dysfunction and atherosclerotic cardiovascular disease share common risk factors [1]. Essential hypertension is a disorder with a high prevalence of erectile dysfunction [11] and a high incidence of atherosclerosis. In hypertensive patients, it is currently unknown whether erectile dysfunction is related to an additional risk on top of hypertension. Several studies have shown that arterial functional and structural characteristics and endothelial/inflammatory activation are important determinants of cardiovascular performance.

Methods
We evaluated arterial structural and functional characteristics and measured systemic endothelial/inflammatory markers in 52 hypertensive men with vasculogenic erectile dysfunction and in 34 hypertensive men with normal erectile function, matched for age, blood pressure, risk factors and treatment.

Results
Hypertensive patients with erectile dysfunction had higher common carotid intima-media thickness (0.95 ± 0.19 vs. 0.83 ± 0.18 mm, P = 0.003) and carotid–femoral pulse-wave velocity (8.89 ± 1.38 vs. 8.11 ± 1.10 m/s, P = 0.007), lower flow-mediated dilation of the brachial artery (absolute values of 2.96 ± 1.64 vs. 4.07 ± 1.68%, P = 0.003) and a higher level of the systemic endothelial dysfunction marker asymmetric dimethylarginine (0.67 ± 0.13 vs. 0.57 ± 0.16 μmol/l, P = 0.003), and the inflammatory markers high-sensitivity C-reactive protein [2.03 (1.16–2.89) vs. 1.23 (0.67–1.90) mg/l, P = 0.029] and interleukin-6 (4.13 ± 2.38 vs. 2.77 ± 1.92 pg/ml, P = 0.011). Multivariable analysis adjusting for age, mean pressure, other risk factors and treatment showed independent associations between erectile dysfunction and parameters of arterial structure and function. In the erectile dysfunction group, there were no significant relationships between the severity of erectile dysfunction (as expressed by the Sexual Health Inventory for Men score) and the above arterial indices and level of circulating markers (all P = NS).

Conclusion
In hypertensive men, the presence but not the severity of vasculogenic erectile dysfunction is associated with subclinical atherosclerosis, impairment of arterial function and systemic endothelial and inflammatory activation. J Hypertens 26:1829–1836 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.
and predictors of risk [12–18]. Accordingly, in the present study, we sought to investigate whether the presence of erectile dysfunction is associated with an altered structure and function of the arterial system in patients with uncomplicated hypertension. For this purpose, we employed a thorough approach including studies of arterial stiffness and wave reflections, endothelium-dependent vasodilation, and arterial wall thickness, as well as measurements of circulating levels of certain endothelial/inflammatory markers/mediators.

Methods
Study participants
In this study, we screened consecutive patients with essential hypertension and symptoms suggestive of erectile dysfunction with no history, symptoms or other evidence of cardiovascular disease, who were referred to the Cardiovascular Diseases and Sexual Health Unit of our department for evaluation of erectile dysfunction, and consecutive patients with uncomplicated essential hypertension who attended the Hypertension Unit of our department for management of hypertension. In all participants, a full medical history was taken and physical examination was performed. Patients who had evidence of antihypertensive drug-related hypotension, secondary hypertension, heart failure, history of a cerebrovascular event, endocrinopathy, renal insufficiency (creatinine >2mg/dl), or an acute or chronic inflammatory-infectious disease were excluded. During recruitment, all patients were evaluated comprehensively for presence of subclinical CAD with two noninvasive tests (exercise stress test and stress echocardiography) [6,10]. Patients with positive tests were excluded from the study so as to avoid a potential confounding effect on our findings. All participants were clinically well and taking no phosphodiesterase-5 inhibitors, antioxidant vitamins, or anti-inflammatory or steroid substances.

Office brachial systolic and diastolic blood pressure (SBP and DBP) in the sitting position were measured with a mercury sphygmomanometer on three occasions 1 min apart, after the participants had rested for 15 min, and the mean value was calculated. The first phase and the fifth phase of the Korotkoff sounds were used to identify the SBP and DBP, respectively. Hypertension was diagnosed when blood pressure (BP) was above 140/90 mmHg [19] on two different visits 2 weeks apart, or if chronic use of antihypertensive drugs was documented. In that case, medication was not withdrawn, but the participants did not receive any medication during the day of the arterial studies. Participants abstained from caffeine, ethanol and flavonoid-containing beverages for at least 12 h before the vascular study.

Study design
In this cross-sectional study, participants without exclusion criteria underwent a thorough vascular evaluation. Controls (hypertensive patients without erectile dysfunction) were selected so as to match the erectile dysfunction group for age and other risk factors. All participants were studied in the morning after an overnight fast in a quiet, temperature-controlled room at 23°C. After a 20-min rest period, measurements for evaluation of aortic stiffness, pulse-wave analysis, carotid wall thickness and endothelial function of conduit brachial artery were taken in the supine position, in this fixed order. After the vascular studies had been completed, blood was drawn for measurement of certain endothelial/inflammatory markers/mediators. Furthermore, hypertensive patients with erectile dysfunction were also referred for hormonal and penile Doppler studies.

The study complies with the Declaration of Helsinki, the study protocol was approved by our Institutional Research Ethics Committee, and all patients gave informed consent.

Evaluation of erectile dysfunction
In all participants, a full sexual history was taken. Erectile dysfunction was diagnosed according to the score of the five-item form of the International Index of Erectile Function (IIEF), the Sexual Health Inventory for Men (SHIM score, <21 indicates erectile dysfunction) [20]. In patients with erectile dysfunction, vasculogenic erectile dysfunction was diagnosed on the basis of the absence of certain causes of erectile dysfunction, such as psychological, neurologic or anatomic abnormalities, pelvic surgery or trauma, or antihypertensive drug-induced hypotension; the absence of clinical symptoms and signs suggestive of endocrinopathies known to cause erectile dysfunction (hypogonadism or pituitary tumour) and negative hormonal testing (total testosterone and prolactin); and findings of penile Doppler ultrasonography. Doppler studies were performed using 20 mg intracavernous prostaglandin E1 and audiovisual stimulation [10]. Vascular erectile dysfunction was diagnosed when either the penile peak systolic velocity was less than 35cm/s or when the end-diastolic velocity was greater than 5cm/s or both.

Evaluation of aortic elastic properties
Pulse travels at a higher velocity in a stiff aorta. Carotid-femoral pulse-wave velocity (PWV), an established index of aortic stiffness [12,21,22], was calculated from measurements of pulse transit time and the distance travelled between two recording sites (PWV equals distance in metres divided by transit time in seconds) with a validated noninvasive device (Complior, Artech Medical, Paris, France), as previously described [21,22]. Two different pulse waves were obtained simultaneously at two sites (at the base of the neck for the common carotid and over the right femoral artery) with two transducers. Distance was defined as the distance from the suprasternal notch to the femoral artery minus the distance from the carotid artery to the suprasternal notch.
Measurement of wave reflection indexes
Central (aortic) BPs and augmentation index (AIx), a composite index of wave reflections and arterial stiffness, were calculated using a validated, commercially available system (SphygmoCor, AtCor Medical, Sydney, Australia), which employs the principle of applanation tonometry, as previously described [12,17,21,22]. In brief, from radial artery recordings, the central arterial BP was derived with the use of a generalized transfer function, which is an accurate estimate of the central arterial pressure waveform. Waveforms of radial pressure were calibrated according to sphygmomanometric SBP and DBP measured in the brachial artery because there is practically negligible pressure pulse amplification between the brachial and radial arteries. Augmented pressure is the pressure added to the incident wave by the returning reflected one and represents the pressure boost with which the left ventricle must cope at systole. AIx was calculated as the augmented pressure divided by pulse pressure and was expressed as a percentage. Large values of AIx indicate increased wave reflection from the periphery and/or earlier return of the reflected wave as a result of increased PWV (owing to increased arterial stiffness) and vice versa.

Measurement of carotid wall thickness
Intima-media thickness (IMT) of the right and the left common carotid arteries, a marker of subclinical atherosclerosis [14], was measured in the 1-cm segment proximal to the carotid dilation with B-mode ultrasonography, using a high-resolution, linear-array ultrasonic transducer of 7.5–10.5 MHz (Sonos 5500, Hewlett-Packard, Andover, Massachusetts, USA). In brief, three measurements of the maximal IMT in the far wall were averaged. For each patient, mean common carotid IMT was calculated as the average of six measurements (three in the right and three in the left common carotid artery).

Evaluation of endothelial function
Flow-mediated dilatation (FMD) of the brachial artery is predominantly dependent on endothelial nitric oxide release and can be used as an estimate of endothelial function [23]. Resting and postocclusion arterial diameters and flows, reactive hyperaemia (the stimulus for the postocclusion diameter response) and FMD of the conduit brachial artery were determined as previously described [23,24], using the same ultrasonic transducer and device as described for the carotid study. FMD was calculated as the percentage change of brachial artery diameter from baseline: FMD (%) = [(postocclusion diameter resting diameter)/resting diameter] × 100. Endothelium-independent nitrate-induced dilatation (NID) was measured after delivering a single 0.4 mg dose of nitroglycerin spray sublingually.

Measurement of inflammatory and endothelial prothrombotic markers
Immediately after acquisition of venous blood, plasma or serum was separated by centrifugation (3000 g at 4 °C for 15 min), placed in aliquots and stored at −70 °C for the measurement of endothelial and inflammatory markers. High-sensitivity C-reactive protein (hsCRP) and fibrinogen were measured by immunonephelometry (Dade Behring, Marburg, Germany). High-sensitivity interleukin-6 (IL-6) and asymmetric dimethylarginine (ADMA) were measured in 77 participants (48 erectile dysfunction patients and 29 controls) using enzyme-linked immunosorbent assay (ELISA; BioSource, Camarillo, California, USA and Immundiagnostik AG, Bensheim, Germany).

Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and glucose were measured with standard methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

Statistical analysis
Sample size calculation was based on the hypothesis that erectile dysfunction would be associated with a difference in the level of each arterial parameter and each endothelial/inflammatory marker of at least 0.75 SD. Therefore, we estimated that a minimum of 43 hypertensive patients with erectile dysfunction would provide 80% power at the 5% level of significance to detect a true difference of that magnitude between groups with and without erectile dysfunction, with a nonerectile dysfunction/erectile dysfunction subject ratio of at least 0.5.

Continuous variables are expressed as mean value ± SD. Normality was tested using the Kolmogorov–Smirnov criterion. Skewed variables are expressed as median value (interquartile range). To compare continuous parameters between the erectile dysfunction and nonerectile dysfunction groups, Student’s t-test for unpaired measures or the nonparametric Mann–Whitney U-test were used for normally distributed and skewed variables, respectively. Multivariable linear regression analysis (backward model) was applied to evaluate the association between arterial indices (dependent variable) and erectile dysfunction (main independent variable), after adjusting for potential confounders (age, mean BP, total and HDL cholesterol, fasting glucose, smoking status, BMI and use of angiotensin-converting enzyme (ACE) inhibitors, diuretics and β-blockers). The association of erectile dysfunction with categorical clinical variables was assessed with the Chi-squared test or the Fischer’s exact test. Multivariable logistic regression analysis was used to estimate the predictors of erectile dysfunction (dependent variable) among

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clinical characteristics, arterial parameters, blood levels of inflammatory/endothelial markers and drugs (independent variables). Correlations between continuous variables were evaluated by calculation of the Pearson’s or Spearman’s correlation coefficient.

All tests were two-tailed and exact \( P \) values less than 0.05 were considered statistically significant. Data analysis was performed with SPSS software, version 10.1 (SPSS Inc., Chicago, Illinois, USA).

Results

Study group characteristics

Clinical characteristics of the study groups are shown in Table 1. Overall, the 52 hypertensive patients with erectile dysfunction had similar age, peripheral (brachial) SBP and DBP, lipid and risk factor profile and frequency of antihypertensive drug use compared with the 34 hypertensive patients with normal erectile function.

<table>
<thead>
<tr>
<th>Study group characteristics</th>
<th>Erectile dysfunction ((N = 52))</th>
<th>No erectile dysfunction ((N = 34))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.4 ± 8.6</td>
<td>59.0 ± 7.2</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.06</td>
<td>1.73 ± 0.07</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89.1 ± 16.6</td>
<td>84.9 ± 9.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.3 ± 4.6</td>
<td>28.3 ± 2.8</td>
</tr>
<tr>
<td>Brachial SBP (mmHg)</td>
<td>141 ± 15</td>
<td>136 ± 14</td>
</tr>
<tr>
<td>Brachial DBP (mmHg)</td>
<td>84 ± 8</td>
<td>84 ± 8</td>
</tr>
<tr>
<td>Brachial pulse pressure (mmHg)</td>
<td>58 ± 14</td>
<td>54 ± 11</td>
</tr>
<tr>
<td>Aortic SBP (mmHg)</td>
<td>129 ± 14</td>
<td>125 ± 15</td>
</tr>
<tr>
<td>Aortic DBP (mmHg)</td>
<td>84 ± 8</td>
<td>85 ± 8</td>
</tr>
<tr>
<td>Aortic pulse pressure (mmHg)</td>
<td>44 ± 12</td>
<td>40 ± 12</td>
</tr>
<tr>
<td>Mean pressure (mmHg)</td>
<td>103 ± 10</td>
<td>103 ± 10</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>69 ± 11</td>
<td>69 ± 9</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.4 ± 1.02</td>
<td>5.13 ± 0.92</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.58 ± 0.87</td>
<td>3.42 ± 0.89</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.15 ± 0.22</td>
<td>1.12 ± 0.20</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.55 ± 0.73</td>
<td>1.30 ± 0.84</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>6.51 ± 1.64</td>
<td>5.86 ± 1.31</td>
</tr>
<tr>
<td>Erectile function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHIM score</td>
<td>12 (10–15)</td>
<td>22.5 (22–24)</td>
</tr>
<tr>
<td>Doppler PSV (cm/s)</td>
<td>32.4 ± 8.7</td>
<td>–</td>
</tr>
<tr>
<td>Doppler EDV (cm/s)</td>
<td>6.6 ± 4.1</td>
<td>–</td>
</tr>
<tr>
<td>Risk factors, ( N (%) )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (35)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Pack-years in smokers</td>
<td>45 (32–64)</td>
<td>37 (23–56)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (52)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (21)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Current treatment, ( N (%) )</td>
<td>48 (92)</td>
<td>34 (100)</td>
</tr>
<tr>
<td>Two or more antihypertensive drugs</td>
<td>24 (46)</td>
<td>15 (44)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>21 (40)</td>
<td>16 (47)</td>
</tr>
<tr>
<td>AT-1 antagonists</td>
<td>8 (15)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>23 (44)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>11 (21)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>13 (23)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Statins</td>
<td>13 (25)</td>
<td>7 (21)</td>
</tr>
</tbody>
</table>

Comparisons between groups were done with Student’s \( t \)-test for unpaired measures or Mann–Whitney \( U \)-test (for continuous dependent variables) and Chi squared test or Fisher’s exact test (for categorical dependent variables); ACE, angiotensin-converting enzyme; AT-1, angiotensin-II receptor-1; DBP, diastolic blood pressure; EDV, end-diastolic velocity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PSV, peak systolic pressure; SBP, systolic blood pressure; SHIM, Sexual Health Inventory for Men. Categorical variables are presented as absolute (relative) frequencies; continuous variables are presented as mean ± SD or median (interquartile range). * \( P \) value less than 0.001.

Table 1. Clinical characteristics of the study groups according to the presence of erectile dysfunction

Relationship of erectile dysfunction with arterial structure and function

Aortic stiffness and central haemodynamics

Carotid-femoral PWV was significantly higher in erectile dysfunction patients (8.89 ± 1.38 vs. 8.11 ± 1.10 m/s, \( P = 0.007 \), Fig. 1), indicating an association of erectile dysfunction with aortic wall stiffening. Multivariable regression analysis showed that age (standardized \( \beta = 0.266, P = 0.012 \)), mean BP (\( \beta = 0.220, P = 0.034 \)) and erectile dysfunction (\( \beta = 0.245, P = 0.018 \)) were independent determinants of PWV.

Central (aortic) BPs were similar in the two groups (Table 1). Furthermore, we observed no significant differences in central (aortic) augmented pressure (12.4 ± 5.0 mmHg, \( P = 0.51 \)) or AIx (absolute values of 27.1 ± 11.3 vs. 27.0 ± 8.7%, \( P = 0.97 \), Fig. 1).

Conduit artery endothelial function

There were no differences between the two groups regarding resting brachial artery diameter (0.476 ± 0.048 vs. 0.479 ± 0.048 mm).

Fig. 1

Box-and-whisker plots of arterial structure and function indices according to erectile dysfunction presence. The centerline of the box denotes the median value, the extremes of the box the interquartile range, and the bars the upper and lower limits of 95% of the data. The circles represent outlying data (between 1.5 times the interquartile range and 3.0 times the interquartile range beyond the 25th or 75th percentile). AIx, aortic augmentation index; ED, erectile dysfunction; FMD, flow-mediated dilatation; IMT, intima-media thickness; PWV, pulse-wave velocity.
0.482 ± 0.042 cm in erectile dysfunction and nonerectile dysfunction patients, respectively, \( P = 0.56 \), resting flow and the degree of reactive hyperaemia induced by the ischaemic occlusion of the forearm. However, in patients with erectile dysfunction, both postocclusion brachial artery diameter \( [0.484 (0.452–0.519) \text{ vs. } 0.495 (0.477–0.536)] \) cm in erectile dysfunction and nonerectile dysfunction patients, respectively, \( P = 0.05 \) and FMD (absolute values of 2.96 ± 1.64 vs. 4.07 ± 1.68\%, \( P = 0.003 \), Fig. 1) were significantly lower, indicating an impairment of endothelial function in patients with erectile dysfunction. In multivariable analysis, adjustment for age, mean BP and other risk factors did not alter the association of erectile dysfunction with impaired FMD \( (P = 0.003) \). There was no difference in NID between the two groups (12.13 ± 7.91 vs. 11.75 ± 7.27\%, \( P = 0.82 \)), indicating a similar response of brachial artery smooth muscle to vasodilatory stimuli.

**Relationship of erectile dysfunction with endothelial/inflammatory markers/mediators**

Compared with patients with normal erectile performance, we observed higher circulating levels of hsCRP \( [2.03 (1.16–2.89) \text{ vs. } 1.23 (0.67–1.90) \text{ mg/dl, } P = 0.029] \), IL-6 \( (4.13 ± 2.38 \text{ vs. } 2.77 ± 1.92 \text{ pg/ml, } P = 0.011) \), ADMA \( (0.67 ± 0.13 \text{ vs. } 0.57 ± 0.16 \text{ µmol/l, } P = 0.003) \) and fibrinogen \( (326 ± 76 \text{ vs. } 244 ± 59 \text{ mg/dl, } P < 0.001) \) in erectile dysfunction patients (Fig. 2).

**Determinants of erectile performance**

Overall, a model of risk (multivariable logistic regression) adjusting for age, mean BP, arterial parameters, levels of endothelial/inflammatory variables and use of diuretics, \( \beta \)-blockers and ACE inhibitors showed that only FMD [odds ratio (OR) 0.73 per 1% increase, 95% confidence interval (CI) 0.52–0.98, \( P = 0.05 \)] and fibrinogen (OR 1.019 per 1 mg/dl increase, 95% CI 1.009–1.029, \( P < 0.001 \)) remained independent predictors for presence of erectile dysfunction.

In the erectile dysfunction group, erectile performance expressed by the SHIM score (the inverse of erectile dysfunction severity) correlated marginally with FMD \( (r = 0.23, \ P = 0.10) \) but did not correlate with IMT \( (r = -0.013, \ P = 0.92) \), PWV \( (r = -0.014, \ P = 0.92) \) or AIx \( (r = 0.083, \ P = 0.56) \). Furthermore, we did not observe any significant correlation between SHIM score and endothelial/inflammatory markers/mediators (all \( P = NS \)).

**Discussion**

Our data indicate that in hypertensive men, erectile dysfunction is related to increased carotid thickness, aortic stiffening, impaired endothelium-dependent vasodilation and higher circulating levels of certain important endothelial and inflammatory markers compared with men with normal sexual function. However, the values of these variables do not correlate with the severity of erectile dysfunction. These findings elucidate pathological links and may have important clinical implications for increased cardiovascular risk in hypertensive patients with erectile dysfunction.

**Clinical implications**

The findings of the present study may have important implications for the risk stratification and management of hypertensive men with erectile dysfunction. Essential hypertension is a disorder with a high prevalence of vasculogenic erectile dysfunction [11], which in its own right is a manifestation of generalized arterial disease. Indeed, we and others have shown that erectile dysfunction is associated with a high prevalence of subclinical CAD, it usually precedes the clinical onset of CAD when both conditions coexist [5,6], and also it is an independent predictor of cardiovascular outcomes [7]. In hypertensive patients, it is currently unknown whether erectile dysfunction is related to any additional risk on top of hypertension. Several studies have shown that arterial functional and structural characteristics are important determinants of cardiovascular performance and predictors of risk in several populations, including hypertensive patients [12–14,17,22]. Furthermore, a high level of endothelial/inflammatory markers has been related to increased risk [10,15,16]. Our findings suggest that in hypertensive men, erectile dysfunction is accompanied by an unfavourable profile of arterial structure and function, and provide some evidence to hypothesize that in hypertensive men erectile dysfunction may be associated with a higher cardiovascular risk, beyond the risk of hypertension. Accordingly, diagnosis of vasculogenic erectile dysfunction should call for more...
aggressive antiatherosclerotic treatment. Furthermore, clinicians should seek and treat erectile dysfunction in patients with uncomplicated hypertension, as specific treatment (phosphodiesterase-5 inhibitors) is effective and safe, and also as we and others have shown that this treatment may be associated with beneficial effects on the overall cardiovascular health [24–27].

The present study has the following strengths. First, we performed a thorough evaluation and targeted different aspects of arterial structure and function. Second, we meticulously evaluated our patients for occult CAD so as to avoid the confounding effect of atherosclerotic disease on our investigations. This is crucial, given that we have previously shown that almost 20% of participants without known atherosclerotic disease who present with vasculogenic erectile dysfunction may have occult CAD documented by coronary arteriography [6]. Finally, in our study, we evaluated patients with erectile dysfunction of vasculogenic origin exclusively, as was documented with appropriate penile Doppler studies.

Pathophysiological considerations

FMD of the brachial artery is mainly a nitric-oxide-dependent response [23]. In hypertensive patients, FMD is impaired due to lower nitric oxide availability [28] and corresponds to future cardiovascular risk [13]. In our hypertensive patients with erectile dysfunction, FMD was significantly lower compared with patients with hypertension of a similar severity but with normal erectile performance. This is mainly attributed to decreased postocclusion response of the brachial artery, as other parameters that may interfere with FMD, such as resting brachial diameter, the degree of reactive hyperaemia (the stimulus of FMD) and the ability of arterial smooth muscle to dilate (expressed by NID) [23] were similar in hypertensive patients with or without erectile dysfunction. Thus, low FMD in our patients with erectile dysfunction is presumably due to impaired nitric oxide availability [28], and this is corroborated by our finding of a higher level of ADMA in these patients, which is a competitive inhibitor of endothelial nitric oxide synthase. Our data are in line with other studies showing that in men with erectile dysfunction and risk factors, ADMA level is associated with endothelial dysfunction of both the peripheral and the coronary circulations [29,30]. These data reinforce the notion that erectile dysfunction represents a generalized arterial endothelial disease not confined to the penile vasculature [8,9].

Aortic stiffness (expressed by PWV) was higher in hypertensive patients with erectile dysfunction, and this may be attributed, at least in part, to impaired nitric oxide activity, as nitric oxide is an important determinant of arterial elastic properties [31]. Furthermore, inflammatory activation in patients with erectile dysfunction may also contribute to aortic stiffening, either directly or through impaired nitric oxide action, as we and other investigators have observed that stiffness of large, elastic-type arteries deteriorates in parallel with increasing levels of CRP and fibrinogen in hypertensive patients [18,21,32]. On the contrary, we observed no association between erectile dysfunction and wave reflection indices in our study. AIx is a composite marker of wave reflections that integrates the amount of the wave that is reflected back to the aorta (depending on the tone of the resistance arteries, which are the main peripheral reflecting sites) and the velocity of this reflected wave (arterial stiffness), but it also depends on heart rate and the effective length of the arterial system [12,17,21,22]. In our study, the two groups did not differ in heart rate and anthropometric characteristics, but despite the higher aortic stiffness in erectile dysfunction patients, AIx was similar in the two groups. Consistent with this, we observed no relationship of erectile dysfunction with central (aortic) pressures. These data suggest that erectile dysfunction may be related to increased large artery stiffness but not to wave reflections from the periphery. Indeed, several studies indicate that PWV and AIx do not always change in parallel [21,32]. Specifically for inflammation, the response of these two variables may even be in opposite directions in the acute setting [21], whereas in the chronic one, some studies have shown that there is no correlation of wave reflection indices with inflammatory markers, despite a positive correlation with PWV [32]. Thus, the inflammatory activation that we observed in patients with erectile dysfunction may explain in part why erectile dysfunction is associated with aortic stiffening but not with increased wave reflections and central pressures.

The association between erectile dysfunction and the degree of subclinical atherosclerosis as expressed by IMT may be accounted for by a more prominent systemic inflammatory activation in patients with erectile dysfunction. Furthermore, this expands previous studies showing that presence and severity of erectile dysfunction are related to CAD extent [5].

Our findings are in line with other studies confined to specific indices or evaluating populations with different characteristics [33–37]. However, in a previous comprehensive clinical study, it was observed that erectile dysfunction was not accompanied by higher IMT or PWV [38]. This is not necessarily in contradiction of our results, as that study referred to a population without cardiovascular risk factors [38]. On the contrary, all patients of our matched groups were hypertensive patients and, furthermore, some of them had other risk factors, and thus they resemble the usual erectile dysfunction patient encountered in everyday clinical practice. In other recent studies, no association of erectile dysfunction with large artery elasticity and inflammatory markers was observed [39,40]. However, it appears that no discrepancy exists with our findings, as there
are important differences regarding the evaluated parameters of arterial function [39], and the risk profile of the population studied [39,40]. Importantly also, in these studies [39,40] there was no confirmation that erectile dysfunction was vasculogenic.

Specific comments: limitations

Most patients were on antihypertensive treatment. Antihypertensive treatment may be related to erectile dysfunction, either because of overtreatment, hypotension and hyperperfusion of the penile cavernous bodies (nondrug-specific effect) or because of drug-specific effects of certain classes of antihypertensive drugs (β-blockers and diuretics) [41]. On the contrary, the patient’s knowledge about the side-effects of specific drugs and other psychological factors may perhaps confound the association of certain drugs with erectile dysfunction [42], so many aspects remain unclear. Although we cannot certainly rule out a possible effect of antihypertensive drugs on erectile performance in our patients, it is rather unlikely that the principal findings of our study were influenced by treatment, as there were no differences in the frequency of drug use between the two groups, and as we also meticulously excluded patients with treatment-induced hypotension or patients with erectile dysfunction of nonvasculogenic origin.

All participants were instructed to avoid taking any drug on the study day. Although there is some evidence that withholding nonnitrate vasoactive drugs before studying indices of vascular function may not be necessary [43], we cannot exclude a possible effect of previous drug intake on the absolute values of vascular function variables. However, the observed differences in arterial function between erectile dysfunction and nonerec tic dysfunction groups are unlikely to be accounted for by previous treatment, as there was no difference in the frequency of using drugs that may improve arterial function after chronic or even acute administration, such as ACE inhibitors [28,44,45].

We used a 0.4 mg dose of nitroglycerine during the brachial artery study. A lower dose would result in a lower endothelium-independent vasodilation that would be comparable to FMD [28]. However, our finding of an almost identical nitroglycerin-induced vasodilation (even with this high dose) between hypertensive patients with and without erectile dysfunction is a strong indication for a lack of significant differences in the responsiveness of the arterial smooth muscle layer between these two groups.

Although hypertension is not defined simply by the values of BP [19], the conventional threshold of 140/90 mmHg was used in untreated patients for ensuring similarity of characteristics between the two groups of patients.

In conclusion, this is the first study to demonstrate that in hypertensive patients with erectile dysfunction, carotid IMT, aortic stiffness and endothelium-dependent vasodilation are more impaired compared with hypertensive patients with normal erectile performance, possibly either due to lower availability of nitric oxide or activation of inflammatory mechanisms or both. In hypertensive patients, the diagnosis of vasculogenic erectile dysfunction is clinically essential and may be regarded as a state of increased overall cardiovascular risk that calls for more aggressive treatment, as arterial structure and function indices are important risk predictors. Accordingly, sexual history and evaluation of erectile function could be valuable components of the assessment and management of hypertensive patients.

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References


