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

Reriani, M; Flammer, A J; Li, J; Prasad, M; Rihal, C; Prasad, A; Lennon, R; Lerman, L O; Lerman, A

Abstract: BACKGROUND: Erectile dysfunction (ED) is associated with an increased risk for cardiovascular disease, stroke, and all-cause mortality, independent of conventional cardiovascular risk factors. Coronary endothelial dysfunction is independently associated with ED in men with early coronary atherosclerosis. We aimed to investigate whether coronary microvascular dysfunction predicts development of ED in patients presenting with coronary atherosclerosis without critical stenoses. PATIENTS AND 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: In all, 68 (50%) men had microvascular endothelial dysfunction at baseline; 35 (51%) men with microvascular endothelial dysfunction developed ED on follow-up compared with 19 (31%) men without microvascular endothelial dysfunction. Men who developed ED had a lower coronary blood flow response (% [INCREMENT]CBF) compared with men who did not develop ED, with mean+/-SD of 25.4+/-71.3 versus 81.7+/-120 (P=0.003). In univariate analysis, microvascular endothelial dysfunction was a predictor for the development of ED, with relative risk of 2.4 (1.2-4.9) (P=0.016). In multivariate logistic regression adjusting for traditional cardiovascular risk factors (age, hypertension, hyperlipidemia, diabetes, vascular disease, and family history of coronary artery disease), 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.

DOI: 10.1097/MCA.0000000000000145

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

Martin Reriani[a], Andreas J. Flammer[a], Jing Li[a], Megha Prasad[a], Charanjit Rihal[a], Abhiram Prasad[a], Ryan Lennon[c], Lilach O. Lerman[b] and Amir Lerman[a]

Background **Erectile dysfunction (ED) is associated with an increased risk for cardiovascular disease, stroke, and all-cause mortality, independent of conventional cardiovascular risk factors. Coronary endothelial dysfunction is independently associated with ED in men with early coronary atherosclerosis. We aimed to investigate whether coronary microvascular dysfunction predicts development of ED in patients presenting with coronary atherosclerosis without critical stenoses.**

Patients and 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 **In all, 68 (50%) men had microvascular endothelial dysfunction at baseline; 35 (51%) men with microvascular endothelial dysfunction developed ED on follow-up compared with 19 (31%) men without microvascular endothelial dysfunction. Men who developed ED had a lower coronary blood flow response (% ΔCBF) compared with men who did not develop ED, with mean ± SD of 25.4 ± 71.3 versus 81.7 ± 120 ($P = 0.003$). In univariate analysis, microvascular endothelial dysfunction was a predictor for the development of ED, with relative risk of 2.4 (1.2–4.9) ($P = 0.016$). In multivariate logistic regression adjusting for traditional cardiovascular risk factors (age, hypertension, hyperlipidemia, diabetes, vascular disease, and family history of coronary artery disease), 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.** ***Coron Artery Dis*** **25:552–557**

Coronary Artery Disease 2014, **25**:552–557

Keywords: endothelium, erectile dysfunction, prognosis

[a]Division of Cardiovascular Diseases, [b]Division of Nephrology and Hypertension and [c]Unit of Biomedical Statistics and Informatics, Mayo Clinic and College of Medicine, Rochester, Minnesota, USA

Correspondence to Amir Lerman, MD, Division of Cardiovascular Diseases, Mayo Clinic and College of Medicine, 200 First Street, SW, Rochester, MN 55905, USA
Tel: + 1 507 255 4152; fax: + 1 507 255 2550; e-mail: lerman.amir@mayo.edu

Received 25 March 2014 **Revised** 29 May 2014 **Accepted** 6 June 2014

Introduction

Erectile dysfunction (ED) has a high prevalence worldwide, affecting 40% of men above 40 years of age [1] 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 years [8–10], 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 for 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 with 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.

Patients and methods

Study design

This study was a prospective single-center cohort study. The Mayo Clinic Institutional Review Board approved

0954-6928 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MCA.0000000000000145

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, were found to have nonobstructive disease, and had a comprehensive coronary physiology study, including the assessment of endothelial function and nonendothelium-independent coronary flow reserve (CFR) [22–25].

Exclusion criteria included significant coronary artery stenosis (>40%), ejection fraction less than 45%, unstable angina, previous myocardial infarction, use of radiographic contrast agents within 12 h, and significant systemic disease. Medications that may affect CV hemodynamics were discontinued for at least 48 h before the study.

Study protocol

At baseline, diagnostic coronary angiography and determination of endothelium-dependent changes in coronary blood flow (CBF) and endothelium-independent CFR were performed as previously described [24,26,27]. A Doppler guide wire (0.014 inch diameter, FloWire; Volcano Corporation, San Diego, California, USA) within a 2.2 F coronary infusion catheter (Ultrafuse; SciMed Life System, Maple Grove, Minnesota, USA) was advanced and positioned in the middle portion of the left anterior descending coronary artery (LAD). Intracoronary bolus injections of incremental doses (18–36 μg) of adenosine (Fujisawa, Kanagawa Prefecture, Japan), 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 acetylcholine (ACh) into the LAD. ACh (Iolab Pharmaceuticals, Peterborough, Ontario, Canada), 10^{-6}, 10^{-5}, and 10^{-4} mol/l, was infused at 1 ml/min for 3 min [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, Abbott Park, Illinois, USA) [30].

Quantitative coronary angiography

Coronary artery diameter was analyzed by quantitative coronary angiography from digital images with modification of a previously described technique from our institution [24, 26,27]. The 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 performed, 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 were analyzed online to determine the time-averaged peak velocity. Volumetric CBF was determined from the following relation: CBF = cross-sectional area × average peak velocity × 0.5 [31]. Endothelium-dependent microvascular function was calculated as % ΔCBF in response to ACh as previously described [32].

Microvascular endothelial dysfunction

As in previous studies, microvascular endothelial dysfunction was defined as 50% or less increase in 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 mean ± SD or counts and percentages as appropriate. Variables with heavily skewed distribution are reported as the median with first and third quartiles in parenthesis. Comparison of demographic and baseline clinical data between the groups was performed using Student's *t*-test for continuous data and Pearson's χ^2-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 years. History of hypertension was present in 44%, hyperlipidemia in 64%, diabetes in 10%, and family history of coronary artery disease in 60% of patients enrolled. The mean duration of follow-up was 8.4 ± 4.7 years.

Coronary microvascular function and erectile dysfunction

The study population was divided into two groups: those with microvascular endothelial dysfunction (% ΔCBF to ACh ≤ 50%, $n = 68$) and those with normal microvascular endothelial function (% ΔCBF 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 with patients with normal endothelial function, 50 versus 30% ($P = 0.016$) (Table 1).

During the follow-up period, 54 (40%) patients 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 with those who did not develop ED. ΔCBF and CFR were lower in patients who developed ED compared with those who did not (Table 2 and Figs 1 and 2), but there was no difference in the percentage change in coronary artery diameter (% ΔCAD) (Fig. 3).

Univariate and adjusted models

Univariate analysis identified the presence of microvascular endothelial dysfunction [odds ratio (OR) 2.4, 95% confidence interval (CI) 1.18–4.99, $P = 0.016$], diabetes (OR 6.74, 95% CI 1.98–31, $P = 0.0017$), high-sensitive C-reactive protein ($P = 0.0047$), and increasing age (OR 1.6 for 10-year increase, 95% CI 1.2–2.5, $P = 0.019$) 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 1.13–6.6, $P = 0.024$) and age ($P = 0.0458$) were independent predictors of development of ED.

Table 1 Baseline patient characteristics

	Normal endothelial function ($n = 62$)	Microvascular dysfunction ($n = 68$)	P
Age (years)	49 ± 12.4	51 ± 10.5	0.27
BMI (kg/m^2)	27.7 ± 4.6	29.1 ± 5.6	0.12
Hypertension	25 (40)	33 (49)	0.33
Diabetes	4 (6)	10 (14)	0.12
Hypercholesterolemia	42 (68)	44 (66)	0.71
Family history coronary artery disease	28 (47)	48 (75)	0.0012
Smoking			
Former	25 (40)	31 (46)	0.0308
Current	12 (19)	3 (4)	
Testosterone	399 ± 187	418 ± 139	0.81
C-reactive protein	1.69 ± 3.4	1.34 ± 1.90	0.55
Aspirin	33 (53)	45 (66)	0.13
ACE inhibitor	13 (21)	13 (19)	0.79
β-Blockers	17 (27)	23 (34)	0.43
Ca^{2+} channel blocker	19 (31)	30 (44)	0.13
Lipid lowering	25 (40)	35 (51)	0.20
Oral hypoglycemic	3 (5)	7 (10)	0.93
Diuretics	5 (8)	6 (9)	0.88
% ΔCBF	135.8 ± 102	−12.3 ± 40.3	–
% ΔCAD	28.2 ± 22.7	−7.6 ± 16.1	< 0.001
CFR	3.3 ± 0.83	3.0 ± 0.72	0.049

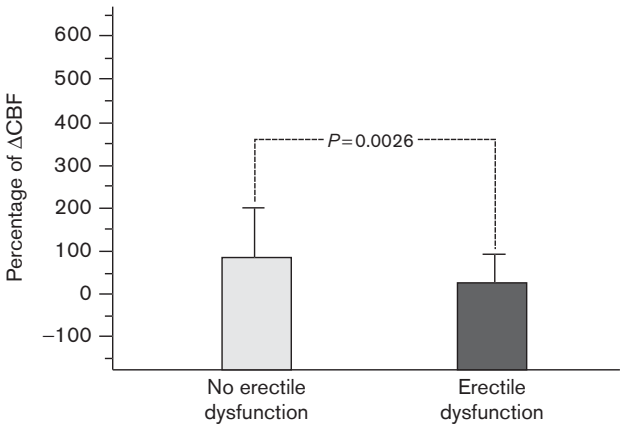
Values are expressed as mean ± SD or n (%).
ACE, angiotensin-converting-enzyme; % ΔCAD, percent change in coronary artery diameter to acetylcholine; % ΔCBF, percent change in coronary blood flow to acetylcholine; CFR, coronary flow reserve.

Table 2 Patient characteristics by erectile dysfunction

	No ED ($n = 76$)	ED ($n = 54$)	P
Age (years)	47.7 ± 12	54 ± 9.7	0.002
BMI (kg/m^2)	27.8 ± 5.6	29.5 ± 4.4	0.06
Hypertension	31 (41)	27 (50)	0.33
Diabetes	3 (4)	11 (20)	0.0029
Hypercholesterolemia	46 (61)	40 (74)	0.11
Family history coronary artery disease	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
C-reactive protein	2.16 ± 3.36	0.7 ± 1.12	0.013
Aspirin	42 (55)	47 (87)	0.19
ACE inhibitor	10 (13)	19 (35)	0.021
β-Blockers	21 (28)	21 (39)	0.36
Ca^{2+} channel blocker	28 (37)	26 (48)	0.86
Statins	30 (39)	29 (54)	0.07
Diuretics	7 (9)	4 (7)	0.71
% ΔCBF	81.7 ± 120	25.4 ± 71.3	0.0026
% ΔCAD	−15.4 ± 22.0	−22.7 ± 22.1	0.065
CFR	3.3 ± 0.88	3.0 ± 0.75	0.068

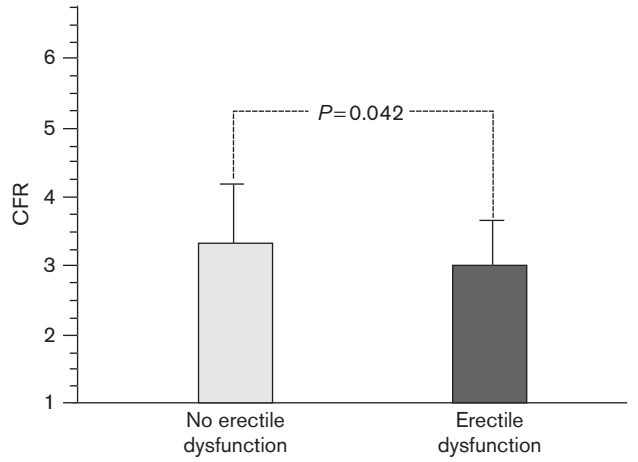
Values are expressed as mean ± SD or n (%).
ACE, angiotensin-converting-enzyme; % ΔCAD, percent change in coronary artery diameter to acetylcholine; % ΔCBF, percent change in coronary blood flow to acetylcholine; CFR, coronary flow reserve; ED, erectile dysfunction.

Fig. 1



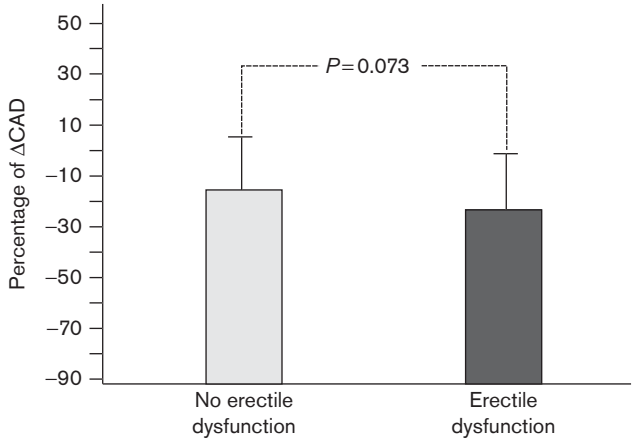
Percent change in coronary blood flow (% ΔCBF) by erectile dysfunction.

Fig. 2



Percent change in coronary flow reserve (CFR) by erectile dysfunction.

Fig. 3



Percent change in coronary artery diameter (% ΔCAD) by erectile dysfunction.

Table 3 Univariate analysis of risk factors for erectile dysfunction

Variables	Odds ratio (95% CI)
Age, per 10-year increase	1.6 (1.2–2.5)
Hyperlipidemia	2.02 (0.96–4.38)
Diabetes	6.74 (1.98–31)
Hypertension	2.02 (0.96–4.38)
Family history of coronary artery disease	1.08 (0.53–2.22)
Microvascular dysfunction	2.4 (1.18–4.99)

CI, confidence interval.

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. % ΔCAD 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 of 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 by 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 [6,7,17].

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 peripheral artery tonometry, predicts adverse events in the coronary circulation [37] 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 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 ED 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 ED [40].

ED is an independent risk factor for CVD, and its diagnosis precedes cardiac events by about 3–5 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 diabetes [42], 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 lifestyle modification for CV risk reduction. In addition, the use of phosphodiesterase inhibitors for management of ED may also improve systemic endothelial function [42]; however, more studies are needed to determine whether this therapy positively impacts CVD.

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 may be 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 for recall bias from patients who were diagnosed with ED or were embarrassed to report such a diagnosis.

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

Third, our study was not designed to measure whether 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 potential therapeutic target in CVD.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Jackson G. Erectile dysfunction and coronary disease: evaluating the link. *Maturitas* 2012; **72**:263–264.
2 Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int* 1999; **84**:50–56.
3 Sullivan ME, Keoghane SR, Miller MA. Vascular risk factors and erectile dysfunction. *BJU Int* 2001; **87**:838–845.
4 Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. *J Urol* 2000; **163**:460–463.
5 Moinpour CM, Lovato LC, Thompson IM Jr, Ware JE Jr, Ganz PA, Patrick DL, *et al*. Profile of men randomized to the prostate cancer prevention trial: baseline health-related quality of life, urinary and sexual functioning, and health behaviors. *J Clin Oncol* 2000; **18**:1942–1953.
6 Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2011; **58**:1378–1385.
7 Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, Aznaouridis KA, Stefanadis CI. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. *Circ Cardiovasc Qual Outcomes* 2013; **6**:99–109.
8 Hodges LD, Kirby M, Solanki J, O'Donnell J, Brodie DA. The temporal relationship between erectile dysfunction and cardiovascular disease. *Int J Clin Pract* 2007; **61**:2019–2025.
9 Inman BA, Sauver JL, Jacobson DJ, McGree ME, Nehra A, Lieber MM, *et al*. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc* 2009; **84**:108–113.
10 Montorsi F, Briganti A, Salonia A, Rigatti P, Margonato A, Macchi A, *et al*. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* 2003; **44**:360–364, discussion 364–365.
11 Jackson G, Boon N, Eardley I, Kirby M, Dean J, Hackett G, *et al*. Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. *Int J Clin Pract* 2010; **64**:848–857.
12 Aversa A, Rossi F, Francomano D, Bruzziches R, Bertone C, Santiemma V, Spera G. Early endothelial dysfunction as a marker of vasculogenic erectile dysfunction in young habitual cannabis users. *Int J Impot Res* 2008; **20**:566–573.
13 Ucar G, Secil M, Demir O, Demir T, Comlekci A, Uysal S, Esen AA. The combined use of brachial artery flow-mediated dilatation and carotid artery intima-media thickness measurements may be a method to determine vasculogenic erectile dysfunction. *Int J Impot Res* 2007; **19**:577–583.
14 Reriani MK, Lerman LO, Lerman A. Endothelial function as a functional expression of cardiovascular risk factors. *Biomark Med* 2010; **4**:351–360.
15 Halcox JP, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, *et al*. Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; **106**:653–658.
16 Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005; **111**:363–368.
17 Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000; **101**:948–954.
18 Targonski PV, Bonetti PO, Pumper GM, Higano ST, Holmes DR Jr, Lerman A. Coronary endothelial dysfunction is associated with an increased risk of cerebrovascular events. *Circulation* 2003; **107**:2805–2809.
19 Bocchio M, Desideri G, Scarpelli P, Necozione S, Properzi G, Spartera C, *et al*. Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *J Urol* 2004; **171**:1601–1604.
20 Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL, Bank AJ. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol* 2004; **43**:179–184.
21 Elesber AA, Solomon H, Lennon RJ, Mathew V, Prasad A, Pumper G, *et al*. Coronary endothelial dysfunction is associated with erectile dysfunction and elevated asymmetric dimethylarginine in patients with early atherosclerosis. *Eur Heart J* 2006; **27**:824–831.

22 Lavi S, Bae JH, Rihal CS, Prasad A, Barsness GW, Lennon RJ, *et al*. Segmental coronary endothelial dysfunction in patients with minimal atherosclerosis is associated with necrotic core plaques. *Heart* 2009; **95**:1525–1530.

23 Raichlin E, Prasad A, Mathew V, Kent B, Holmes DR Jr, Pumper GM, *et al*. Efficacy and safety of atrasentan in patients with cardiovascular risk and early atherosclerosis. *Hypertension* 2008; **52**:522–528.

24 Reriani M, Raichlin E, Prasad A, Mathew V, Pumper GM, Nelson RE, *et al*. Long-term administration of endothelin receptor antagonist improves coronary endothelial function in patients with early atherosclerosis. *Circulation* 2010; **122**:958–966.

25 Rubinshtein R, Yang EH, Rihal CS, Prasad A, Lennon RJ, Best PJ, *et al*. Coronary microcirculatory vasodilator function in relation to risk factors among patients without obstructive coronary disease and low to intermediate Framingham score. *Eur Heart J* 2010; **31**:936–942.

26 Hasdai D, Gibbons RJ, Holmes DR Jr, Higano ST, Lerman A. Coronary endothelial dysfunction in humans is associated with myocardial perfusion defects. *Circulation* 1997; **96**:3390–3395.

27 Yoon MH, Reriani M, Mario G, Rihal C, Gulati R, Lennon R, *et al*. Long-term endothelin receptor antagonism attenuates coronary plaque progression in patients with early atherosclerosis. *Int J Cardiol* 2013; **168**:1316–1321.

28 Hori M, Kitakaze M. Adenosine, the heart, and coronary circulation. *Hypertension* 1991; **18**:565–574.

29 Lerman A, Holmes DR Jr, Bell MR, Garratt KN, Nishimura RA, Burnett JC Jr. Endothelin in coronary endothelial dysfunction and early atherosclerosis in humans. *Circulation* 1995; **92**:2426–2431.

30 Harrison DG, Bates JN. The nitrovasodilators. New ideas about old drugs. *Circulation* 1993; **87**:1461–1467.

31 Doucette JW, Corl PD, Payne HM, Flynn AE, Goto M, Nassi M, Segal J. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 1992; **85**:1899–1911.

32 Ofili EO, Labovitz AJ, Kern MJ. Coronary flow velocity dynamics in normal and diseased arteries. *Am J Cardiol* 1993; **71**:3D–9D.

33 Elesber A, Lerman A, Bybee KA, Murphy JG, Barsness G, Singh M, *et al*. Myocardial perfusion in apical ballooning syndrome correlate of myocardial injury. *Am Heart J* 2006; **152**:469.e9–469.e13.

34 Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003; **23**:168–175.

35 Reriani MK, Lerman LO, Lerman A. Endothelial function as a functional expression of cardiovascular risk factors. *Biomark Med* 2010; **4**:351–360.

36 Mahmud FH, Earing MG, Lee RA, Lteif AN, Driscoll DJ, Lerman A. Altered endothelial function in asymptomatic male adolescents with type 1 diabetes. *Congenit Heart Dis* 2006; **1**:98–103.

37 Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, *et al*. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J* 2010; **31**:1142–1148.

38 Chade AR, Brosh D, Higano ST, Lennon RJ, Lerman LO, Lerman A. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. *Kidney Int* 2006; **69**:266–271.

39 Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, *et al*. The assessment of endothelial function: from research into clinical practice. *Circulation* 2012; **126**:753–767.

40 Cellek S, Cameron NE, Cotter MA, Fry CH, Ilo D. Microvascular dysfunction and efficacy of PDE5 inhibitors in BPH-LUTS. *Nat Rev Urol* 2014; **11**:231–241.

41 Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, *et al*. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2012; **87**:766–778.

42 Aversa A, Vitale C, Volterrani M, Fabbri A, Spera G, Fini M, Rosano GM. Chronic administration of Sildenafil improves markers of endothelial function in men with type 2 diabetes. *Diabet Med* 2008; **25**:37–44.