Coronary endothelial dysfunction is associated with erectile dysfunction and elevated asymmetric dimethylarginine in patients with early atherosclerosis

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Aims Coronary endothelial dysfunction (CED) precedes atherosclerosis and is associated with cardiovascular events. Both CED and erectile dysfunction (ED) are partly mediated by impairment in the nitric oxide pathway. ED is associated with established coronary atherosclerosis, but its relationship with early coronary atherosclerosis and CED is unknown. This study was designed to test the hypothesis that CED is associated with ED in men with early coronary atherosclerosis. Moreover, the role of the nitric oxide synthase inhibitor asymmetric dimethylarginine (ADMA) was investigated; ADMA is a novel endogenous competitive inhibitor of nitric oxide synthase and has been shown to be an independent marker for cardiovascular disease.

Methods and results Fifty-six men without obstructive coronary artery disease (CAD) who underwent coronary endothelial function testing were studied. ADMA levels were determined and all men were asked to complete the International Index of Erectile Function-5 questionnaire to assess erectile function. Patients were divided according to the presence (n = 32) or absence (n = 24) of CED. Men with CED had significant impairment of erectile function (P = 0.008) and significantly higher ADMA levels (0.50 ± 0.06 vs. 0.45 ± 0.07 ng/mL, P = 0.017) compared with men with normal endothelial function. Erectile function positively correlated with coronary endothelial function. This correlation was independent of age, body mass index, high-density lipoprotein, C-reactive protein, homeostasis model assessment of insulin resistance index, and smoking status.

Conclusion CED is independently associated with ED and plasma ADMA concentration in men with early coronary atherosclerosis. This study further supports the role of the endothelium in systemic vascular diseases and the role of ADMA in the systemic manifestations of endothelial dysfunction.

Introduction

Endothelial dysfunction may be considered as a systemic disorder and involves different vascular beds.¹ ¹² Coronary endothelial dysfunction (CED) precedes the development of coronary atherosclerosis² and is associated with an increased risk of cardiovascular events.⁴ - ⁷ Endothelial dysfunction is characterized by a reduction in endogenous nitric oxide (NO) activity, which may be attributed to an elevation in asymmetric dimethylarginine (ADMA) levels.⁸ ADMA is a novel endogenous competitive inhibitor of NO synthase (NOS) and has been shown to be an independent marker for cardiovascular risk.⁹ Thus, it may be speculated that the elevation of endogenous ADMA may be associated with the systemic manifestations of endothelial dysfunction in patients with cardiovascular risk factors.¹⁰

Erectile dysfunction (ED) is a common phenomenon in men with established CAD¹¹ and is believed to be another manifestation of atherosclerotic vascular disease.¹² - ¹⁴ In fact, recent data demonstrate that ED is associated with impaired endothelial-dependent flow-mediated vasodilation in the brachial artery,¹⁵ suggesting that ED is associated with peripheral endothelial dysfunction. However, there is a paucity of information regarding the prevalence and the relationship between ED, early coronary atherosclerosis, and CED.

Recently, elevated ADMA levels have been associated with peripheral and CED in hypertensive patients.¹⁶ However, the role of ADMA in men with ED and CED has not been fully explored. Thus, the current study was designed to test the hypothesis that coronary endothelial function is associated with ED and elevated ADMA levels in men with early coronary atherosclerosis.
Methods

Patient population

This study was approved by the Mayo Clinic Institutional Review Board, and consent was obtained from all patients enrolled. All men referred to the Mayo Clinic between January 1999 and July 2004 for cardiac catheterization for the evaluation of CAD, who were found to have no significant epicardial coronary stenoses (≤ 30%), and underwent coronary endothelial testing were offered to be included in this study. Females were excluded from this study.

Assessment of coronary vasoreactivity

Diagnostic coronary angiography was performed, as described elsewhere.

Coronary vascular reactivity responses were studied subsequently, as previously reported. In brief, a 0.014-in. Doppler-tipped guidewire (Volcano, Santa Ana, CA, USA) was introduced within a 2.2F coronary infusion catheter (Ultrasafe, SciMed Life System) into the left anterior descending coronary artery. After stable baseline flow velocities were obtained, assessment of non-endothelial coronary flow reserve (CFR) was determined by measuring dose responses to intracoronary adenosine boluses (18–48 μg) until maximal hyperaemia was achieved. The CFR was calculated by dividing the coronary mean flow velocity average peak velocity (APV) obtained from the Doppler tracing after adenosine injection by the baseline APV.

After allowing coronary blood flow (CBF) to return to baseline, selective intracoronary infusion of incremental doses of the endothelium-dependent vasodilator, acetylcholine (Ach), was performed to the maximum tolerable dose (10⁻⁶, 10⁻⁵, and 10⁻⁴ mol/L at 1 mL/min for 3 min), followed by intracoronary administration of 200 μg nitroglycerine (NTG). Selective angiography was performed following each dose of Ach and NTG.

Coronary artery diameter (CAD) was measured by quantitative coronary angiographic analysis by an independent investigator, 5 mm distal to the tip of the Doppler wire. CBF was calculated as CBF = (APV/2)(CAD Diam/2), where the coronary mean flow velocity was estimated as APV/2 by assuming a time-averaged parabolic velocity profile across the vessel. Endothelial-dependent changes in CBF were calculated by using the following equation: [CBF after intracoronary Ach-resting CBF/resting CBF > 100 %]. According to previous studies, linking the presence of CED to myocardial perfusion defects and an increased rate of cardiac events, CED was considered significant when there was an increase in CBF > 50% or a decrease in epicardial CAD > 20% after maximal Ach infusion. These two definitions led to identify endothelial dysfunctions reflected both macrovascular endothelial dysfunctions as reflected by the change in epicardial coronary diameter and microvascular endothelial dysfunction as reflected by the CBF that has been determined to be mostly regulated by the resistance of 200 μm or less arteries.

Erectile function assessment

All men were asked to complete questions 1–5 of the standardized International Index of Erectile Function-5 (IIEF) questionnaire either at the time of coronary angiography or after their angigram. The five questions asked were: How often were you able to get an erection?2 When you had an erection with sexual stimulation, how often were your erections hard enough for penetration?2 When you attempted sexual intercourse, how often were you able to penetrate your partner?2 During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?2 During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse? The IIEF score represents the sum of questions 1–5 with a maximum score of 25; a score of 21 or less is considered impairment of erectile function. The questionnaires were analysed in a blinded fashion independently of the results of the coronary endothelial function testing.

Blood samples

Fasting blood samples were taken at the time of coronary angiography and stored below freezing (−40 °C). Plasma ADMA concentrations were measured by liquid chromatography-tandem mass spectrometry (LC–MS/MS) method, using [15C]-ADMA as internal standard. An API 3000 bench top triple quadrupole tandem mass spectrometer with Turbo Ionspray source (positive mode) was employed. The intra-assay precision was determined at three different levels of ADMA (0.34, 0.64, and 1.81 μmol/L) with CVs of 5.6, 5.7, and 5.1%, respectively.22 The deuterated and C-13 labelled ADMA was synthesized as described elsewhere. The reagent trimethylsilylboronium iodide needed for synthesis of ADMA was prepared as reported in US Patent 5 686 390 (1997).

In addition, baseline samples were drawn for total cholesterol, LDL, HDL, triglycerides, creatinine, glucose, HbA1C, insulin, C-reactive protein, L-arginine. These assays were performed using standard laboratory techniques according to the established methodology. The homestasis model assessment of insulin resistance index (HOMA-IR) is a well-validated method to evaluate insulin sensitivity and was calculated for study participants. A highly sensitive latex-particle-enhanced immunoturbidimetric assay (Kamiya Biomedical, Seattle, WA, USA) was used to quantify the level of C-reactive protein.

Statistical analysis

Continuous variables with mildly skewed distributions were summarized as mean ± SD and were compared using Student's t-test. Those with heavily skewed distributions were summarized as median (first and third quartiles) and compared with the Wilcoxon rank sum test. Discrete variables were presented as frequency (group percentage) and compared using Pearson’s χ² test (if categorical) and the Wilcoxon rank sum test (if ordinal). Spearman’s correlation coefficient was used to describe the linear association between bivariate ranked values.

Logistic regression was used to estimate the odds ratios (marginal and partial) for CED based on IIEF score and ADMA values. Likelihood ratio tests were used to assess the overall model significance. The Hosmer–Lemeshow goodness-of-fit test was used to check that the model adequately fit the data. Linear regression was used to estimate associations between continuous variables. When residual diagnostics indicated a violation of the assumption of normality, transformations of the response were employed. Owing to the small sample size, only linear associations were entertained. Also owing to the small sample size, only an intercept and two parameters were estimated in the models to avoid overfitting. However, several covariates were deemed to be important for covariate adjustment. Data reduction on these covariates was accomplished by regressing the covariates on the independent variable of interest, either IIEF score or ADMA, an approach analogous to propensity score adjustment. The predicted values from these models were then used in the logistic regression models for covariate adjustment. Those covariates that were significantly different between the two endothelial function groups were included. These covariates were age, BMI, HDL, C-reactive protein (log-transformed), HOMA-IR (log-transformed), and smoking status.

Results

Patient population

A total of 160 men who underwent CFR studies between January 1999 and July 2004 were invited to complete the IIEF questionnaire and a total of 56 men agreed to complete them. Baseline characteristics are shown in Table 1. Men with...
CED had a significantly higher BMI, higher insulin resistance as calculated by the HOMA-IR, lower HDL, higher C-reactive protein, higher ADMA levels, and smoked more frequently than men with normal endothelial function. There was no difference in the glomerular filtration rate as calculated by the MDRD formula\(^25\) between the two groups.

Men with CED also had significantly lower IIEF scores compared with men with normal endothelial function. Results of the IIEF questionnaire are summarized in Table 2.

There was no difference between groups as far as use of different medications (Table 3).

### Association between coronary endothelial function, erectile function, C-reactive protein, and ADMA

**Coronary endothelial function and erectile function**

Twenty-four men were found to have an abnormal macrovascular endothelial function, CA Diam response to Ach (10\(^{-4}\) mol/L) (\( \leq 20\%\)). This group had a significantly lower IIEF score compared with the group who had normal macrovascular endothelial function (14.6 + 8.4 vs. 20.2 ± 4.6, \( P = 0.0026\)). The IIEF score positively correlated with CA Diam response to Ach (10\(^{-4}\) mol/L), \( r = 0.31\), \( P = 0.021\) (Figure 1). This correlation was independent of age, BMI, HDL, C-reactive protein, HOMA-IR, and smoking status (\( P = 0.004\)). Twenty-seven men were found to have abnormal microvascular endothelial function, CBF response to Ach (10\(^{-4}\) mol/L) (\( \leq 50\%\)). This group also had a significantly lower IIEF score compared with the group who had normal microvascular endothelial function (14.5 ± 8.3 vs. 20.9 ± 3.6, \( P = 0.0004\)). Similarly, the IIEF score positively correlated with CBF response to Ach (10\(^{-4}\) mol/L), \( r = 0.39\), \( P = 0.003\) (Figure 2). This correlation was independent of age, BMI, HDL, C-reactive protein, HOMA-IR, and smoking status (\( P = 0.019\)). Assessment of non-endothelial CFR in response to intracoronary adenosine boluses demonstrated no difference between men with ED (CFR = 3.0 ± 0.9) compared with men with normal erectile function (CFR = 3.3 ± 0.8, \( P = 0.23\)).

**Coronary endothelial function and ADMA**

Men who had an abnormal CBF response to Ach (10\(^{-4}\) mol/L) had significantly higher circulating ADMA levels than those who had a normal response (0.51 ± 0.07 vs. 0.46 ± 0.06 \( \mu \text{mol/L}, P = 0.01\)). There was a significant negative correlation between ADMA level and response of CBF to Ach (10\(^{-4}\) mol/L) (\( r = 0.39\), \( P = 0.0076\) (Figure 3)). This correlation was independent of age, BMI, HDL, C-reactive protein, HOMA-IR, and smoking status (\( P = 0.016\)). Men who had an abnormal CA Diam response to Ach (10\(^{-4}\) mol/L) had higher ADMA levels than those who had a normal response (0.50 ± 0.06 vs. 0.45 ± 0.06 \( \mu \text{mol/L}, P = 0.02\)). There was a significant negative correlation between ADMA level and % change of CA Diam in response to Ach (10\(^{-4}\) mol/L), \( r = 0.33\), \( P = 0.03\) (Figure 4). This correlation was independent of age, BMI, HDL, C-reactive protein, HOMA-IR, and smoking status (\( P = 0.023\)). Two-way ANOVA demonstrated that men who had both CED (either microvascular or macrovascular) and ED (IIEF < 21) were found to have significantly higher ADMA levels than those who had either CED, or ED, or neither (Table 4).

No significant correlation was seen between SDMA and response of CBF to Ach (10\(^{-4}\) mol/L) (Figure 3) and % change of CA Diam in response to Ach (10\(^{-4}\) mol/L) (Figure 4).

**Coronary endothelial function and C-reactive protein**

Men who had an abnormal CBF response to Ach (10\(^{-4}\) mol/L) had higher C-reactive protein levels than men who had a normal response (0.81 ± 1.24 vs. 0.21 ± 0.20 ng/mL, \( P = 0.02\)). A linear regression model that corrected for

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal CEF (n = 24)</th>
<th>Abnormal CEF (n = 32)</th>
<th>( P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.6 ± 11.2</td>
<td>49.8 ± 11.0</td>
<td>0.46</td>
</tr>
<tr>
<td>BMI</td>
<td>26.3 ± 4.4</td>
<td>30.1 ± 4.7</td>
<td>0.004</td>
</tr>
<tr>
<td>MAP (mmHg), median (Q1, Q3)</td>
<td>97.5 (87, 106)</td>
<td>98 (82, 111)</td>
<td>0.66</td>
</tr>
<tr>
<td>Glucose (mg/dL), median (Q1, Q3)</td>
<td>93 (87.5, 99)</td>
<td>99 (90, 108)</td>
<td>0.08</td>
</tr>
<tr>
<td>Insulin resistance (HOMA), median (Q1, Q3)</td>
<td>9.6 (6.1, 13)</td>
<td>13.8 (10.7, 29.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>MDRD-GFR</td>
<td>77.3 ± 14.7</td>
<td>72.2 ± 12.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>184.0 ± 45.5</td>
<td>173.8 ± 32.0</td>
<td>0.33</td>
</tr>
<tr>
<td>Triglycerides, median (Q1, Q3)</td>
<td>117 (93, 188)</td>
<td>153 (108, 174)</td>
<td>0.30</td>
</tr>
<tr>
<td>HDL</td>
<td>46.0 ± 12.9</td>
<td>38.1 ± 9.1</td>
<td>0.011</td>
</tr>
<tr>
<td>Homocysteine, median (Q1, Q3)</td>
<td>7.0 (6.0, 9.0)</td>
<td>8.0 (7.0, 10.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Folate</td>
<td>16.5 ± 5.3</td>
<td>16.8 ± 4.5</td>
<td>0.86</td>
</tr>
<tr>
<td>ADMA ((\mu\text{mol/L}))</td>
<td>0.45 ± 0.07</td>
<td>0.50 ± 0.06</td>
<td>0.017</td>
</tr>
<tr>
<td>SDMA ((\mu\text{mol/L}), median (Q1, Q3)</td>
<td>0.49 (0.45, 0.58)</td>
<td>0.50 (0.45, 0.60)</td>
<td>0.61</td>
</tr>
<tr>
<td>IIEF score, median (Q1, Q3)</td>
<td>22.5 (19, 24)</td>
<td>17 (9.5, 22.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>12 (50%)</td>
<td>16 (52%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>2 (8%)</td>
<td>8 (25%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>19 (79%)</td>
<td>21 (66%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Smoking status, no. (%)</td>
<td>0.039</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>12 (50%)</td>
<td>8 (25%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>10 (42%)</td>
<td>7 (22%)</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>107.1 ± 42.5</td>
<td>105.5 ± 29.9</td>
<td>0.87</td>
</tr>
<tr>
<td>C-reactive protein, median (Q1, Q3)</td>
<td>0.1 (0.0, 0.3)</td>
<td>0.4 (0.1, 0.6)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
age, BMI, HDL, C-reactive protein, HOMA-IR, and smoking status failed to show an independent relation between C-reactive protein and CBF response to Ach (10⁻⁴ mol/L, \( P = 0.42 \)).

Men who had an abnormal CA Diam response to Ach (10⁻⁴ mol/L) tended to have higher C-reactive protein levels than men who had a normal response, but this was not statistically significant (0.64 ± 1.10 vs. 0.36 ± 0.68 ng/mL, \( P = 0.27 \)). A linear regression model that corrected for age, BMI, HDL, C-reactive protein, HOMA-IR, and smoking status failed to show an independent relation between C-reactive protein and CA Diam response to Ach (10⁻⁴ mol/L, \( P = 0.41 \)).

**Erectile function and ADMA**

Spearman rank correlation analysis demonstrated no significant correlation between IIEF score and ADMA levels (\( r = -0.46, P = 0.013 \)) (Figure 5). A linear regression model correcting for age failed to show a significant correlation between IIEF score and ADMA levels (\( P = 0.11 \)).

No significant correlation was seen between IIEF score and SDMA (Figure 5).

**Erectile function and C-reactive protein**

Spearman rank correlation analysis demonstrated no significant correlation between IIEF score and C-reactive protein levels (\( r = 0.19, P = 0.20 \)). Nonetheless, patients with ED tended to have a higher C-reactive protein level than patients with no ED (0.69 ± 1.2 vs. 0.25 ± 0.31, \( P = 0.094 \)).

**ADMA and C-reactive protein levels**

Spearman rank correlation analysis demonstrated no significant correlation between ADMA and C-reactive protein levels (\( r = 0.20, P = 0.21 \)).

**Discussion**

This study demonstrates for the first time the association between CED and an increased prevalence of ED in men without obstructive CAD. Moreover, the increase in the endogenous ADMA levels may serve as a possible mechanism for these combined abnormalities. This study further supports the role of the endothelium in the regulation of vascular tone in different vascular beds, without involvement of
non-endothelial mechanisms as demonstrated by similar CFR response to adenosine in men with and without ED. It is generally accepted that ED has been associated with advanced atherosclerotic CAD. Several recent studies have reported that endothelial dysfunction in the penile circulation accompanies ED in association with various cardiovascular risk factors. However, no study to date has assessed the relationship between ED and the early stage of coronary atherosclerosis. Our data, therefore, extends previous studies, by demonstrating that men with early atherosclerosis and CED have increased prevalence of ED compared with men with normal coronary endothelial function. Furthermore, the current study demonstrates that the severity of CED correlates with the severity of ED.

Endothelial dysfunction is characterized by a tendency towards vasoconstriction and is associated with a proinflammatory, proliferative, and procoagulatory milieu all of which contribute to the mechanism of atherosclerosis. Increasing evidence suggests that endothelial dysfunction is a systemic disorder, affecting both conduit arteries and microvessels in various vascular beds. The key figure which regulates endothelial function is endothelial-derived NO. It is synthesized from the conversion of L-arginine by the enzyme NOS and is the key mediator of endothelium-dependent smooth muscle relaxation. Impaired NO activity appears to play a key role in both endothelial and ED. The ability of the phosphodiesterase type-5 inhibitors to improve endothelial dysfunction and ED through the upregulation of NO confirm these studies. Increasing attention is being focused on the endogenous NOS inhibitor ADMA as an important competitive inhibitor of NO formation. ADMA is a selective endogenous NOS inhibitor and is found to be elevated in many conditions associated with ED as well as impaired peripheral endothelium-dependent vasodilation in response to a high fat meal. In fact, elevated ADMA has been shown to cause endothelial dysfunction and predict an increase in cardiovascular mortality. As ADMA levels found in diabetes, cardiovascular disease, and renal failure are high enough to inhibit NO synthesis and cause endothelial dysfunction, it has been hypothesized that elevated ADMA levels may inhibit penile NO synthesis.

Multiple lines of evidence has now lead many investigators to believe that inflammation can explain the initiation and progression of atherosclerosis. The response-to-injury hypothesis of atherosclerosis postulates that multiple potential insults including oxidative stress, oxidized lipoproteins, infections, and haemodynamic effects among many others initiate the process of inflammation by injuring the endothelium. So, the injured endothelium initiates a series of steps that result in the recruitment of macrophages and lymphocytes through a process regulated by cytokines and cell adhesion molecules. The end result of this inflammatory response is atherosclerosis. One specific marker of inflammation, C-reactive protein, has attracted significant attention with accumulating...
evidence implicating its role in the pathogenesis of atherosclerosis. In our study, C-reactive protein levels were significantly higher in patients with CED compared with patients with normal endothelial function adding another line of evidence to the importance of inflammation in early coronary atherosclerosis. No significant association between C-reactive protein, on one hand, and ADMA and ED, on the other hand, could be detected. This is probably related to the relatively low number of patients and does not completely rule out a role of inflammation in ED as was pointed out by the non-significant but clearly higher C-reactive protein levels in patients with ED compared with patients with normal erectile function. The absence of a significant correlation between the ADMA and C-reactive protein levels points to the possibility of an inflammatory-independent pathogenetic mechanism for ADMA in atherosclerosis and ED.

In this study, men with CED have significantly elevated levels of ADMA, but similar levels of L-arginine to men with normal endothelial function (Table 1), suggesting that CED is associated with inhibition of NOS, and not a lack of L-arginine per se. Furthermore, this relationship was independent of age, BMI, HDL, C-reactive protein, HOMA-IR, and smoking status. Our data contrast with previous studies that have shown elevated ADMA levels in obese subjects which decrease after weight loss. In addition, ED is found to be associated with obesity, but improves after weight reduction. This difference could be explained by the fact that not all our patients specifically had obesity as a risk factor and that obesity is not the only risk factor for ED or an elevated ADMA level.

In addition, we observed a significant inverse relationship between ADMA levels and IIEF score. After accounting for the effect of age, this correlation was not significant anymore. More recently, Wierzbicki et al. investigated the relation between ADMA levels and cardiovascular risk factors in patients with ED. No relation was found between ADMA levels and the degree of ED as assessed by the IIEF score on both univariate and multivariate analyses. Possible reasons to explain this difference with Wierzbicki et al., univariate analysis results might lie in the difference between the populations studied. Our patient population was on average 10 years younger compared with Wierzbicki et al’s patient population. In addition, although Wierzbicki et al. looked exclusively at patients with ED where a history of CAD was present in up to 24%, our study looked at a patient population with no CAD and correlated the IIEF score in patients with and without ED to ADMA levels. Our results after correcting for the age, however, are similar to that of Wierzbicki et al.

This does not rule out completely the association between ADMA and ED as already pointed out by the univariate analysis in our study, but probably shows that age has a more important impact on ED and might be contributing to ED through a multitude of mechanisms.

More importantly, the subgroup of men in this study who had both CED and ED had significantly higher levels of ADMA. This provides further evidence that elevated ADMA levels are associated with ED and CED. In addition, this study supports the hypothesis that elevated ADMA levels may contribute to the inhibition of penile NO synthesis. The observed association between elevated ADMA levels, ED, and CED not only underscores the systemic nature of endothelial dysfunction, but also points out the importance of the vascular disease for the pathogenesis of ED.

So far, ED has been considered a marker for established coronary atherosclerosis. However, this study provides evidence to suggest that ED may occur in the early stages of atherosclerosis, characterized by CED as reflected by abnormalities at a macrovascular level detected by epicardial coronary artery vasodilatation and at microvascular level detected by changes in CBF. In contrast, a relationship between brachial artery endothelium-dependent vasodilatation and ED in patients with no clinical cardiovascular disease has been established. Hence it is conceivable that ED is part of the broad clinical spectrum of systemic diseases caused by endothelial dysfunction.

**Study limitations**

This is an observational study and subject to recall bias with regards to completion of the IIEF questionnaire. In addition, not all ED is vascular in origin, and hence not all men with ED will have elevated ADMA levels. The precise aetiology of ED can be difficult to elucidate, and may be due to a combination of organic as well as psychological factors. Taken together with the relatively small number of men in this study, this may account for the fact that no significant difference in ADMA levels was found in men with or without ED alone, even though a statistically significant correlation was shown.

**Conclusion**

The results of this study demonstrate that early coronary atherosclerosis, characterized by CED, is associated with

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**Table 4** ADMA levels according to coronary endothelial function and erectile function

<table>
<thead>
<tr>
<th>CED (ng/mL)</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IIEF score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 21</td>
<td>104.8 ± 13.0*</td>
<td>88.2 ± 11.6</td>
</tr>
<tr>
<td>&gt; 21</td>
<td>92.8 ± 8.5</td>
<td>93.7 ± 14.3</td>
</tr>
</tbody>
</table>

*ADMA level in this group is significantly elevated compared with other groups, P = 0.004.
ED and that ADMA levels are significantly elevated in men with CED and ED. These findings support the concept that endothelial dysfunction is a systemic disorder, which may be mediated by elevated ADMA levels.

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Conflict of interest: none declared.

References


