Erectile dysfunction in healthy subjects predicts reduced coronary flow velocity reserve

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Structured Abstract

Background Erectile dysfunction (Erectile dysfunction) is associated with, and may be the first sign of coronary artery disease. The objective of this study wasWe aimed to assess whether men with erectile dysfunction but without cardiovascular disease have reduced coronary flowvelocity reserve, as a sign of early coronary atherosclerosis.

Methods We investigated 12 men aged 68-73 years with erectile dysfunction, and 12 age-matched controls. Erectile function was evaluated using the validated IIEF-5 questionnaire. A score of ≤18 or less (of 25) was defined as erectile dysfunction, and a score of ≥21 or more was defined asconsidered normal. Patients with neurological or psychological reasons for erectile dysfunction were excluded, as were patients with symptoms of or prescribed medication for cardiovascular disease, hypertension or diabetes. Coronary flow velocity reserve was measured non-invasively with by Doppler in the left anterior descending artery, before and during aAdenosine infusion.

Results Coronary flow velocity reserve was significantly reduced in subjects with erectile dysfunction: (2.36 versus 3.19; P=0.024). In logistic regression analysis, compared to control subjects, men with erectile dysfunction had significantly increased risk of having abnormalreduced coronary flow velocity reserve (≤</=3.0): odds ratio 15.4, P=0.02. In multivariate analysis, adjusting for age, tobacco use, systolic blood pressure, heart rate and body mass index, erectile dysfunction was the only significant predictor of reduced coronary flow velocity reserve, P=0.016.

Conclusions Our study shows, for the first Men with erectile dysfunction but without diabetes or clinical cardiovascular disease have etime, early signs of coronary artery disease in men with ED but without diabetes or clinical cardiovascular disease. Our findings suggest that a cardiac risk evaluation may be indicated in men with suspected vasculogenic erectile

dysfunction, and these individuals should be considered for primary prevention measures regarding cardiovascular disease risk factors.

Key words: Ischemic heart disease. Echocardiography. Risk Factors. Coronary microcirculation.

Introduction

Erectile dysfunction is an under-diagnosed condition, estimated to affect up to 52% of men between the ages of 40 and 70 years[1, 2]. There is a close relationship between erectile dysfunction and coronary artery disease, and risk factors for both conditions are largely the same, including diabetes, hypertension, years[1, 2]. There is a close relationship between erectile dysfunction and coronary artery disease, and risk factors for both conditions are largely the same, including diabetes, hypertension, hyperlipoproteinemia and smoking[3, 4]. Recent studies on men with chronic stable coronary heart disease indicate that the presence of erectile dysfunction in this group of patients may be as high as 75%[5]. Like in early coronary artery disease, vascular endothelial- and smooth muscle dysfunction are believed to be key elements in smoking[3, 4]. Recent studies on men with chronic stable coronary heart disease indicate that the presence of erectile dysfunction in this group of patients may be as high as 75%[5]. Like in early coronary artery disease, vascular endothelial- and smooth muscle dysfunction are believed to be key elements in the pathogenesis of erectile dysfunction, and it is plausible that these disturbances are similar to the early changes seen in the process of coronary atherosclerosis[6, 7].
atherosclerosis[6, 7].

One of the first findings in subjects with atherosclerosis is reduced coronary flowvelocity reserve, i.e. the ability of the coronary arteries to increase flow in response to e.g. exercise. Coronary flow reserve is expressed as the ratio of the maximum coronary flow compared to the resting flow. Non-invasively assessed coronary flow reserve is a reliable method for assessment of impaired coronary circulation due to endothelial- and smooth muscle cell dysfunction[8, 9], which is one of the first findings in subjects with atherosclerosis[7,8]. Coronary flow reserve was recently found to be significantly reduced in diabetic men with erectile

dysfunction[10], howeverdysfunction[8, 9], which is one of the first findings in subjects with atherosclerosis[7,8]. Coronary flow reserve was recently found to be significantly reduced in diabetic men with erectile dysfunction[10], however coronary flow reserve has not previously been examined in men with erectile dysfunction, without diabetes, hypertension or clinical cardiovascular disease. It has previously been shown by our group that non-invasively assessed coronary flow *velocity* reserve has a good correlation to actual coronary flow reserve (ref Winter). It has previously been shown that non-invasively assessed coronary flow velocity reserve has a good correlation to actual coronary flow reserve[11], and the aim of the present study is was to examine if coronary flow velocity reserve is was affected by the presence of erectile dysfunction in otherwise healthy men.

Methods

Men aged 68-73 years were randomly selected from an observational population study (the Malmö Primary Prevention study, MPP-study) in Malmö, Sweden[11]. Original invitation into the MPP study included all men in Malmö from certain age groups. , and iInvitation to participate in this the present study was sent out to 200 randomly selected men Sweden[12]. Original invitation into the MPP study included all men in Malmö from certain age groups. , and iInvitation to participate in this the present study was sent out to 200 randomly selected men in the MPP cohort of men born between 1931 and 1936, and. 145 completed questionnaires (72,5%) were returned. Information regarding previously diagnosed diabetes, hypertension or heart cardiovascular disease, tobacco use, alcohol consumption, regular medication, anthropometrics, resting ECG, blood pressure, heart rate, serum-lipids and plasma-glucose were recorded. The validated IIEF-5 questionnaire[12] was used for evaluation of erectile function. All questionnaires were analyzed. We excluded , and ssubjects with symptoms or signs of cardiovascular disease, prescribed antihypertensive or other

cardiovascular medication, or with a previously known diagnosis of any cardiovascular questionnaire[13] was used for evaluation of erectile function. S, and subjects with symptoms or signs of cardiovascular disease, prescribed antihypertensive or other cardiovascular medication, or with a previously known diagnosis of any cardiovascular disease coronary heart disease or congestive heart failure or diabetes mellitus were excluded, were excluded. An IIEF-5 score of ≥>/=21 (of 25) was predefined as normal and ≤</=18 as significant erectile dysfunction. This yields a high accuracy for the diagnosis of true erectile dysfunction[13].
dysfunction[14].

Sample size calculation was based on the assumption that coronary flow velocity reserve is would be around 4.0 ± 0,6 (this describes relative maximum flow compared to resting coronary flow) in normalscontrols, and was expected to be around 3,0 ± 0.6 in subjects with erectile dysfunction. In order to have an 80% power to detect a significant difference between subjects with erectile dysfunction and controls at the 5% level, at least 7 patients were needed in each group. In order to increase the statistical power and allow for greater between- subject variability, we decided to includeaim for 125 patients in each group.

Standard echocardiography examination was carried out, and systolic and diastolic left ventricular function were evaluated. Categorization of diastolic flow profiles was based on standard clinical procedure, taking atrial size, maximum early/atrial contraction (E/A) transmitral flow velocity E/A ratio, maximum systolic/diastolic (S/D) pulmonary flow velocity ratio, early transmitral flow velocity deceleration time (Edt), tissue Ddoppler early to atrial contraction tissue velocity (Em/Am) ratio) and E/Em ratio into account[15, 16].

The cutoff values for this categorization was in accordance with the methods used by ?????? and associates (ref from Reidar here).

Coronary flow velocity reserve was assessed as describedpreviously[14]. In short, a standard 5MHz transducer (??) on a Philips ??? ultrasound machine and En Concert ver ?? software were used. The mid to distal left anterior descending artery was identified in an apical short axis projection, moving the transducer upward andmedially a few centimeters from the standard apical projection. LAD was then seen in the intraventricular sulcus, having predominantly diastolic flow, using color Doppler with the Nyquist limit set to 10cm/s. At this stage, intravenous during Sonovue® ultrasound contrast infusion was started at a rate of 0,4ml/second, thorough a venous cannule on the left forearm., pPulsed Doppler recordings of the flow profile in the distalpreviously[11]. In short, a standard S12 transducer probe, on a Sonos 5500 (Philips, Andover Massachusetts) ultrasound machine, and EnConcert Image Diagnosis Application Version B.2.1 (Agilent Technologies, Andover Massachusetts) were used. The mid to distal left anterior descending artery was identified in an apical short axis projection, moving the transducer upward and medially a few centimeters from the standard apical projection. The left anterior descending artery LAD was then seen in the interraventricular sulcus, having predominantly diastolic flow, using color Doppler with the Nyquist limit set to 10cm/s. At this stage, intravenous Sonovue® ultrasound contrast infusion was started at a rate of 0,4ml/second, through a venous cannule on the left forearm. Pulsed Doppler recordings of the flow profile in the distal left anterior descending coronary artery were performed before (baseline) and during Adenosine infusion (hyperemia). A standard adenosine dose of 140μg/kg/min was used in all subjects, and measurements were made at steady state of adenosine infusion (after 2-4 minutes). Coronary flow velocity reserve was defined as the ratio between hyperemia and baseline maximum diastolic flow velocity.

Digital off-line analysis was performed by one experienced interpreter, masked for IIEF-5 score and clinical data.

Coronary flow reserve decreases with increasing age, and proposed cut-off values for normal coronary flow reserve range from 4.30[15, 16] to 2.72[17]. Since reference values generally have been presented for individuals somewhat younger than those investigated in the present study, we predefined coronary flow 4.30[17, 18] to 2.72[19]. Since reference values generally have been presented for individuals somewhat younger than those investigated in the present study, we predefined coronary flow velocity reserve ≤</=3.00 as abnormalreduced.

Student's t-test and the Mann-Whitney U-test were used for to compare continuous variables, and the X^2 test for categorical variables. Uni- and multivariate logistic regression analysis with normal/abnormalreduced coronary flow velocity reserve as dependent variable was performed to identify predictors of abnormalreduced coronary flow velocity reserve. Linear regression analysis assessed correlations between continuous variables. P≤ <0,05 was considered significant. Data are presented as mean ± 1 SD, or as median value with [interquartile range] where appropriate. The study was approved by the regional Ethics Committee, and all participants signed a written informed consent form.

Results

There were no significant differences between men with erectile dysfunction and control subjects with regard to age, tobacco use, anthropometrics, blood pressure, heart rate, lipids or plasma-glucose (Table 1). The baseline echocardiographic measurements did not differ between the two groups (Table 2). The IIEF-5 score was significantly lower in men with erectile dysfunction (Table 1), and the mean duration of erectile dysfunction in this group was

3.5 years (range 1 to 15 years). Both maximumal coronary flow (during adenosine infusion) and coronary flow velocity reserve (P=0.0264) were significantly decreased in men with erectile dysfunction compared to controls (Table 3 and Fig 1). Abnormal Reduced coronary flow velocity reserve was found in 11 of 12 men with erectile dysfunction and in 5 of 12 controls. The positive predictive value forof erectile dysfunction to identify abnormalreduced coronary flow velocity reserve was 92% and the specificity was 88%. The only erectile dysfunction subject with normal coronary flow velocity reserve had an IIEF-5 score of 18. All patients with an IIEF-5 score <18 had abnormalreduced coronary flow velocity reserve. Among men with ED, IIEF-5 score and CFR were not significantly correlated. Men with ED since more than 2 years erectile dysfunction duration had borderline-significantly lower coronary flow velocity reserve compared to men with erectile dysfunction since duration 2 years or less: 1.81±0.69 vs 2.74±0.83; P=0.064 (t-test). In univariate logistic regression analysis, compared to control subjects, men with erectile dysfunction had significantly increased risk of having abnormalreduced coronary flow velocity reserve: Odds ratio 15.4, CI 1.5–167; pP=0.022. In multivariate logistic regression analysis, with forced adjustment for age, current tobacco use, systolic blood pressure, heart rate and body surface area, erectile dysfunction was the only significant predictor of reduced coronary flow velocity reserve, P=0.01625.

Discussion

There is rapidly growing evidence that erectile dysfunction may be an early clinical sign of coronary artery disease (coronary artery disease), and that vascular endothelial dysfunction is the common denominator[18]. The results of the present population-based study suggest that vascular wall dysfunction with reduced coronary flow velocity reserve is denominator[20]. The results of the present population-based study suggest that vascular wall dysfunction with

reduced coronary flow velocity reserve is indeed a common finding in men with erectile dysfunction, who do not have diabetes, clinical cardiovascular disease or any medication for cardiovascular disease or hypertension. This suggests that there is impaired vascular wall integrity in this group of patients, presumably due to atherosclerotic changes in endothelial- and smooth muscle cell- function. This is in line with recently published studies, showing both impaired brachial artery endothelial dependent- and independent dilation, and signs of pathological endothelial cell activation, in subjects with erectile dysfunction, but with no clinical coronary artery disease[21, 22].

Erectile dysfunction is very common among men around 70 years of age, and we found an abnormalreduced coronary flow velocity reserve in almost all of our men with erectile dysfunction who did not have diabetes or clinical cardiovascular disease. Consequently, a large proportion of "healthy" men in this age group may suffer from significant silent coronary artery disease, known to be a strong predictor of future coronary events and increased risk of premature death[23]. Using the IIEF-5 questionnaire, erectile dysfunction has been shown to be associated with total coronary artery plaque burden at coronary angiography[24]. If our results are confirmed in larger studies, there is a possibility that the IIEF-5 questionnaire could be used with high positive predictive value to identify men at risk of having endothelial dysfunction and possibly silent coronary artery disease without any clinical evidence of cardiovascular disease. It is an inexpensive, swift and readily available tool, which could easily be used in primary health care facilities as a complement to other cardiovascular risk stratification tools for male patients.

There are a few limitations to the present study. Primary prevention measures will probably be most beneficial in younger men. However, since we included men 68-73 years old, our

results need to be confirmed in younger men, before considering recommending screening for erectile dysfunction in them. Although we excluded all subjects with erectile dysfunction that was potentially due to neurological or psychological causes, it is not certain that the included erectile dysfunction subjects had true vasculogenic erectile dysfunction, since penile blood flow was not evaluated. If anything, this should have introduced a bias against an association between erectile dysfunction and decreased coronary flow velocity reserve. Individuals without sexual activity were excluded, without considering *why* they were not sexually active. Many of these individuals might have given up sexual activity due to longstanding severe erectile dysfunction. This might have caused an inclusion bias towards less severe erectile dysfunction as compared to the overall population with erectile dysfunction. Indeed, the mediaan IIEF-5 score among our erectile dysfunction subjects was 121, which only represents "moderate" erectile dysfunction[25]. This might also have resulted in a bias against an association between erectile dysfunction and decreased coronary flow velocity reserve.

A reduced coronary flow velocity reserve can be attributed to endothelial- and smooth muscle cell dysfunction or significant coronary artery stenosis. To accurately determine the pathological explanation underlying reason in each individual with reduced coronary flow velocity reserve, one would need to complement our investigations with a coronary artery angiography, which was not performed in this study. The fact that we were not able to invasively examine coronary artery diameter in this study is a limitation, and this means that we cannot be certain that the blunting in coronary flow velocity reserve reflects a true reduction in coronary artery blood flow. However in previous studies there has been a good correlation between coronary flow velocity reserve and actual reduction in coronary flow reserve seen in coronary arteries with significant stenoses[11].

Conclusions

Among men around 70 years of age without diabetes or clinical cardiovascular disease, the risk of reduced coronary flow velocity reserve was substantially increased in subjects with erectile dysfunction, compared to those without. This association was independent in multivariate analysis. The present study adds an important piece of evidence indicating that silent coronary artery disease is common among otherwise healthy men with erectile dysfunction. Our findings suggest that cardiac risk evaluation may be indicated in men with erectile dysfunction, at least in those with vasculogenic erectile dysfunction. These men should be considered for primary prevention measures regarding cardiovascular disease risk factors. However, before recommending general screening for erectile dysfunction, our findings need confirmation in larger studies with including younger subjects.

Table 1. Baseline variables

	Erectile dysfunction	*Control subjects*	*P*
Age (years)	69.1 ± 2.3	69.3 ± 2.5	0,85
IIEF-5 score	11.0 [7]± 3.8	24 [2]± 1.0	<0.0001
Current smoking (%)	25	8	0.30
Current snuffing (%)	25	8	0.30
Waist circumference (cm)	98 ± 8.7	100 ± 6.5	0.55
Hip circumference (cm)	104 ± 5.2	103 ± 4.5	0.59
Weight (kg)	84 ± 10.1	82 ± 9.8	0.54
Height (cm)	177 ± 4.4	173 ± 10.6	0.29
Systolic BP (mmHg)	148 ± 20.1	151 ± 18.7	0.68
Diastolic BP (mmHg)	88 ± 9.4	84 ± 9.8	0.30
Heart rate (bpm)	67 ± 11.7	70 ± 15.2	0.56
Total cholesterol (mmol/l)	5.94 ± 1.13	6.15 ± 1.13	0.66
LDL-cholesterol (mmol/l)	4.15 ± 0.93	4.28 ± 1.07	0.76
HDL-cholesterol (mmol/l)	1.21 ± 0.28[0.44]	0.98 [0.43]± 0.30	0.30
LDL/HDL	3.62 ± 0.92	4.23 ± 1.47	0.23
Triglycerides (mmol/l)	1.32 ± 0.29	1.74 ± 0.86	0.12
fP-Glucose (mmol/l)	5.54 ± 0.58	5.88 ± 0.68	0.21

ED= erectile dysfunction; BP= blood pressure. fP-Glucose = fasting plasma glucose.

Table 2.. Baseline echocardiographic data

Variable	*Erectile dysfunction*	*Control subjects*	*P (t-test)*
RVIDd (mm)	30.3 ± 3.0	30.3 ± 2.9	-
LVIDd (mm)	48.1 ± 6.2	48.8 ± 5.0	0.74
IVSDd (mm)	11.4 ± 1.4	10.8 ± 1.3	0.30
LVPWDd (mm)	9.8 ± 1.3	9.4 ± 1.4	0.47
LVEF (%)	67.5 ± 8.0	66.9 ± 4.7	0.84
Diastolic function (n)			
Normal	3	2	-
Relaxation disturbance	8	10	-
Pseudonormal pattern	1	0	-
Restrictive pattern	0	0	-

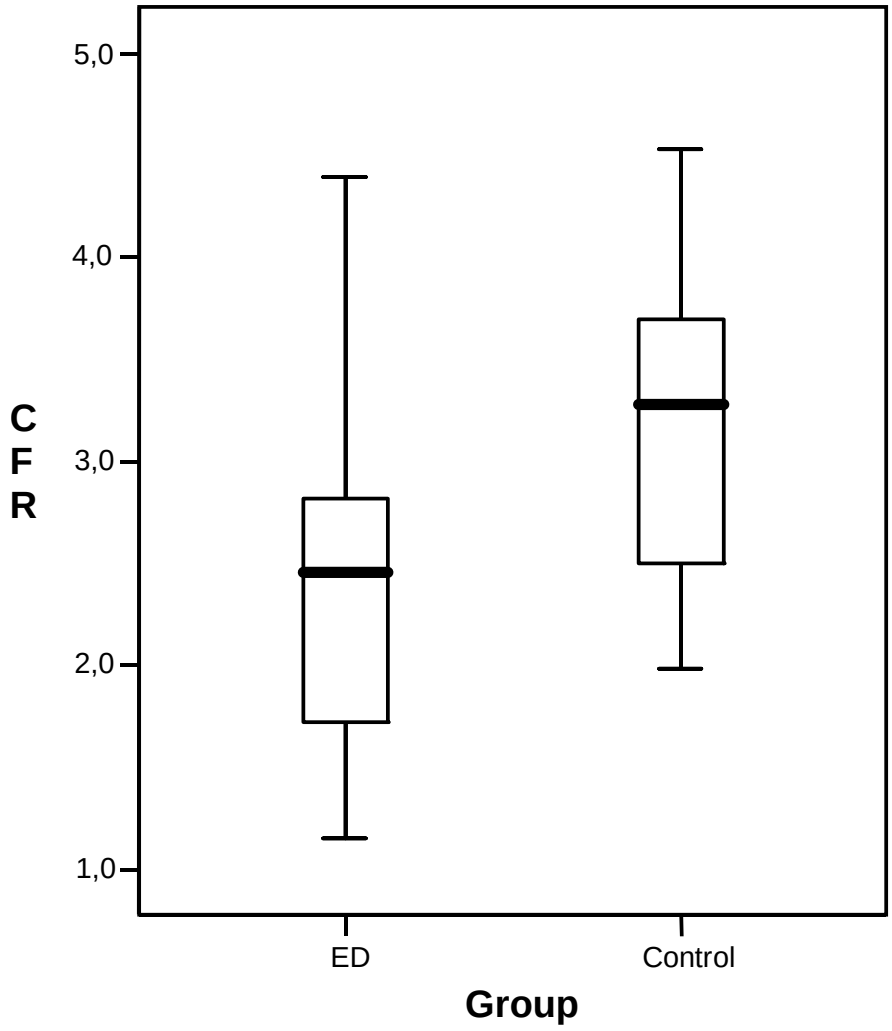
RVIDd= right ventricular internal diameter at end-diastole; LVIDd= left ventricular internal diameter at end-diastole; IVSDd= interventricular septum diameter at end-diastole; LVPWDd= left ventricular posterior wall diastolic diameter at end-diastole; LVEF= left ventricular ejection fraction.

Table 3. Coronary flow measurements

	Erectile dysfunction subjects	Control subjects	P (t-testM-W)
CF baseline (cm/s)	19.5 [12]21.8 ± 5.8	27.323.5 ± 9.8[15]	0.11804
CF adenosine (cm/s)	4650.7 ± 20.8[40]	87 [33]83.3 ± 22.0	0.0041
CF reserve	2.46 [1.18]36 ± 0.88	3.19 ± 0.793.28 [1.30]	0.0264

CF= maximum diastolic coronary flow velocity. M-W = Mann-Whitney U test.

Figure 1. Box plot for coronary flow velocity reserve measurements. ED= Erectile dysfunction. CFR= Coronary flow velocity reserve.



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