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Coronary artery flow reserve in diabetics with erectile dysfunction using sildenafil

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Abstract

Background: Diabetics with erectile dysfunction have a high prevalence of microvascular disturbance of the coronary circuit as measured by coronary flow reserve (CFR).

Purpose: We aimed to evaluate the effects of the phosphodiesterase 5 inhibitor sildenafil on CFR in diabetics with erectile dysfunction.

Methods: Diabetics seeking diabetes refinement therapy were screened for vascular or neurogenic erectile dysfunction which was confirmed in 43 patients. No ischemic ECG changes were found in any of the ECG stress tests at the 100 W level. Cardiologic examinations raised suspicion of coronary artery disease in 16 patients; coronary angiography confirmed severe coronary artery lesions in 12, who were excluded from further analysis. CFR measurements were not possible in 10 participants. The 21 diabetics eligible for CFR measurements aged 60 years (50–69) had known diabetes for 11 years (3–30) and a BMI of 27 kg/m^2 (24–36). CFR of the left anterior descending artery was assessed at baseline and 1 hour after 50 mg sildenafil, using transthoracic Doppler echocardiography.

Results: Baseline CFR was at the lower level of the normal range (median 245%, range 210 – 490%). After sildenafil administration, CFR decreased insignificantly (ΔCFR -10%, $p = 0.3$). Patients with a BMI > 25 kg/m^2 and left ventricular hypertrophy exhibited the highest reduction of CFR after sildenafil. No decrease of CFR below 200 % was observed. Systemic blood pressure dropped from 130/80 mmHg to 120/72 mmHg ($p < 0.002$).

Conclusions: Diabetics with erectile dysfunction exhibit a CFR in the lower normal range indicating severe microvascular disturbance. Sildenafil did not alter CFR in those patients. A high prevalence of severe coronary macroangiopathy was identified in asymptomatic diabetic patients screened for contraindications for sildenafil.

Introduction

Diabetic patients have a high prevalence of erectile dysfunction which is mainly caused by disturbance of the microvascular bed [1,2]. This disturbance can be enhanced by hypertension, hyperlipoproteinemia and smoking, which are also risk factors for macroangiopathy [3,4]. Therefore diabetics with erectile dysfunction and the presence of other cardiovascular risk factors have a higher likelihood of having coronary artery disease [5,6]. Symptoms are often absent in those patients despite severe myocardial ischemia.

In earlier investigations it was demonstrated that the adenosine-mediated flow reserve (CFR) of the left anterior descending (LAD) artery is reduced to values in the lower normal range in most diabetic patients, indicating disturbance of microvascular flow dynamics [7]. Reduction of CFR below a cut-off value of 200% is closely correlated with exercise-induced myocardial ischemia by either microvascular dysfunction or significant coronary artery stenoses [8,9]. Our aim was to evaluate whether sildenafil alters CFR in diabetics with erectile dysfunction.

Methods

Study Population

Diabetic males aged 25–75 years who reported erectile dysfunction were eligible for the study. Patients who had diabetes less than 1 year, psychogenic erectile dysfunction, history of a myocardial infarction or significant coronary artery lesions, impaired systolic left ventricular function, right or left bundle block, or atrial fibrillation were not considered for the study. The study was approved by a local ethical rights committee. All patients gave written informed consent.

Study Protocol

Patients visiting our outpatient endocrinology department for refinement of anti-diabetic therapy were screened. Those suitable for enrollment were referred to the urology department to confirm erectile dysfunction. Patients were examined by color Doppler ultrasound of the penile blood supply before and after intracavernous injection of 10 μg PGE5. Only patients with vascular or neurogenic erectile dysfunction were included. For cardiac evaluation, patients were questioned by a cardiologist; an ECG and a transthoracic echocardiography were also performed. Left ventricular hypertrophy was determined to be present if the thickness of the interventricular septum was > 12 mm as assessed by echocardiography using the parasternal long-axis view. Diastolic dysfunction of the left ventricle was diagnosed if the ratio of the E and A waves of the transmitral flow profile was inverted and if the E wave deceleration time was > 250 ms, which was associated with an isovolumetric relaxation time of > 100 ms. A stress ECG had to be performed at a work load of at least 100 W or ≥ 5 METS. Patients with symptoms of angina pectoris or ischemic ECG changes were excluded from the study.

In patients with no contraindications, CFR baseline measurements were performed. Therefore, patients received a venous cannula and had to rest for 30 min in the supine position. Then blood pressure was measured and CFR measurement performed. Patients with a baseline CFR > 200% received 50 mg sildenafil (Viagra, Pfizer Inc., USA) and after 30 minutes were asked to rest again in the supine position for another 30 minutes. Repeat measurements of blood pressure and CFR were performed thereafter.

Assessment of Coronary Flow Reserve

The technique of CFR assessment by transthoracic echocardiography was described previously [10]. In brief, to visualize the mid or distal portion of the left anterior descending coronary artery (LAD) we used a 3.5 or 7 MHz transducer (Siemens-Acuson, Sequoia, C 256). First, the anterior groove was imaged in a modified parasternal short-axis view. Using color Doppler the LAD can be detected in the anterior groove area as a circularly shaped color Doppler signal with predominantly diastolic flow. Second, pulsed wave Doppler analysis was performed using color flow as a guide. Spectral Doppler tracings were recorded during the baseline condition and after adenosine-induced hyperemia. The dosage rate of adenosine (Adenoscan, Sanofi-Synthelabo, Berlin, Germany) was 0.140 mg/kg/min. CFR was calculated by dividing average peak velocity during adenosine infusion by that at baseline. CFR values were expressed in percent after multiplication with 100 (Figure 1). A CFR below 200% was regarded as pathologic according to previous findings [8].

Statistics

Data are presented as median values, with the minimum and maximum values given in parentheses. The Spearman correlation coefficient was calculated to compare continuous variables. The statistical significance of differences between groups was determined by the paired and unpaired Wilcoxon test, respectively. A p-value of ≤ 0.05 was regarded as statistically significant.

Results

We investigated 43 diabetic males who reported erectile dysfunction, which was confirmed by urologic measurements identifying a vascular origin in 39/43 patients and a neurogenic origin in 4/43. None of the patients had a history of myocardial infarction or reported typical symptoms of angina pectoris; however, 4 patients reported dyspnea during effort. Systolic function of the left ventricle was normal in all patients as determined by echocardiography. Stress ECG did not suggest myocardial ischemia at the 100 Watt level in any patient. However, at a higher

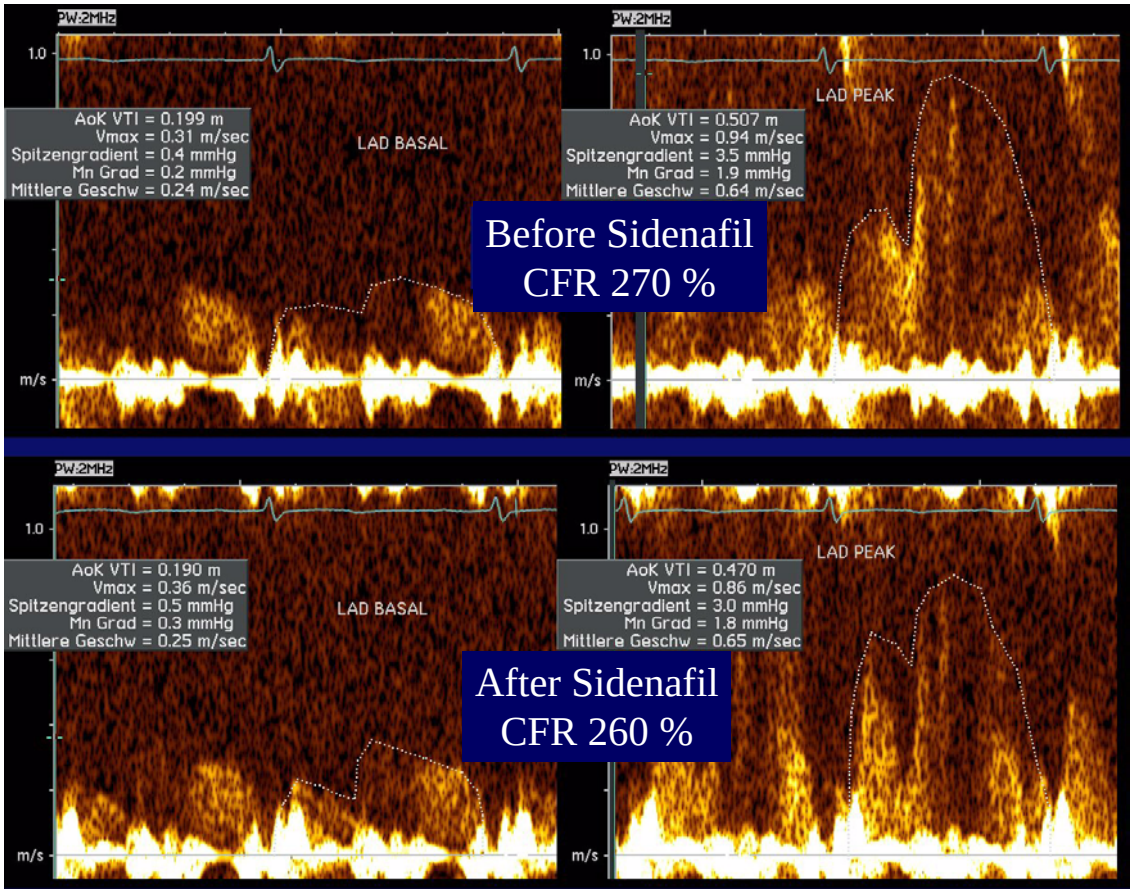

Figure 1
Pulse wave Doppler recording of blood flow in the left anterior descending coronary artery before (a) and after (b) adenosine infusion at baseline and corresponding recordings after sildenafil (c and d) in one patient.

work load it was positive in three asymptomatic patient in whom heart catheterization revealed coronary artery disease with indication for coronary intervention or bypass surgery in two. Stress ECG was inadequately negative in 11 patients who developed dyspnea during exercising. In the presence of cardiac risk factors, coronary angiography was advised and performed in all of those patients. Severe coronary 2- or 3-vessel disease was found in 8 patients necessitating coronary intervention in 2 patients, surgical revascularization in 4 and medical therapy in 2; all of those patients were excluded from further analysis. Insignificant coronary artery sclerosis was found in the other 3 patients. In these 3 and the remaining patients, CFR measurement was performed. Baseline CFR measurement revealed a pathologic reduction of coronary flow reserve in two patients. In both patients the study was halted. Heart catheterization was advised and performed in both, exhibiting a chronic total occlusion of the right coronary artery in one, and severe coronary 2-vessel disease with stenosis of the left main coronary artery in the other patient. Treatment included medical therapy and bypass surgery, respectively. Transthoracic Doppler signals were not sufficient to allow reproducible flow measurements in 8 patients, which was mainly caused due to extreme obesity. Those patients did not receive sildenafil. Adenosine infusion was not tolerated by two patients. Patient baseline characteristics for patients eligible to receive sildenafil and those who were not are summarized in Table 1.

CFR measurements at baseline and after sildenafil were performed in 21 patients. Minor side effects occurred in 5 patients including headache, flush and nasal congestion. Blood pressure decreased significantly after sildenafil (Δ RR syst. -10 mmHg, Δ RR diast. -8 mmHg, $p < 0.002$). One

Table 1: Baseline Characteristics

	Patients receiving sildenafil (n = 21)	Patients not receiving sildenafil (n = 22)	p
Age (years)	60 (50 – 69)	62 (35 – 74)	NS
Body Mass Index (kg/m^2)	27 (24 – 36)	28 (23 – 47)	NS
Diabetes type 2	17 (81 %)	21 (96 %)	NS
Duration of diabetes (years)	11 (3 – 30)	10 (2 – 39)	NS
HbA1c (%)	7.3 (5.8 – 10)	8.1 (5.2 – 10.4)	0.04
Hypercholesterinemia	10 (48 %)	10 (45 %)	NS
Smoker	1 (5 %)	8 (36 %)	< 0.01
Hypertension	14 (67 %)	17 (77 %)	NS
Family history of CAD	3 (14 %)	5 (23 %)	NS
Apoplex or periph. arterio-occlusive dis.	4 (19 %)	1 (5 %)	0.04
LV hypertrophy	11 (52 %)	14 (64 %)	NS
Diabetic organ dysfunction	14 (67 %)	18 (82 %)	NS
Vascular ED	17 (81 %)	19 (86 %)	NS
Maximum work load during stress test (W)	150 (75 – 200)	125 (100 – 200)	0.06
Max. heart rate at stress test (/min)	138 (103 – 161)	140 (109 – 166)	NS

Abbreviations: CAD: coronary artery disease, LV: left ventricle, ED: erectile dysfunction

patient experienced vasovagal syncope 30 minutes after ingestion of sildenafil which was treated by a rapid volume substitution. CFR measurements were repeated in this patient at a later time and were performed without complications. Baseline CFR values were within the lower normal range, except in 4 patients in whom it exceeded 300%.

At baseline, CFR correlated inversely with the value of individual HbA1c ($r = 0.5$, $p = 0.04$). The mean average coronary flow velocities at baseline and after adenosine were higher in obese patients and those with left ventricular hypertrophy ($p < 0.001$), and correlated with the body mass index ($r = 0.52$, $p = 0.01$). Furthermore, the increase of the mean and peak average coronary flow in response to the administration of adenosine correlated with the duration of the diabetes ($r = 0.6$, $p < 0.001$).

CFR after sildenafil administration decreased insignificantly in 11/21 patients (Δ CFR -10%, $p = 0.3$). Accordingly, there was a trend for a smaller average mean flow velocity response to adenosine after sildenafil compared to baseline measurements (Δ average mean flow velocity -0.06 m/s, $p = 0.06$). The decrease of CFR was more pronounced in obese diabetics (BMI > 25 kg/m^2) who had a HbA1c > 7.0 % and left ventricular hypertrophy, while for the other patients CFR tended to increase after sildenafil (Δ CFR -10 % vs 1 %, p = NS). None of the patients had the CFR drop below 200% after administration of sildenafil.

Discussion

Erectile dysfunction caused by microvascular or neurogenic disturbance can be improved by sildenafil and other phosphodiesterase type 5 inhibitors. Microvascular dysfunction is mostly caused by factors that enhance risk for cardiovascular disease. Not surprisingly, patients with overt cardiovascular disease exhibit a high erectile dysfunction rate [5]. In patients with symptomatic myocardial ischemia, nitrates are commonly prescribed to improve anginal status. The concomitant use of nitrates and sildenafil causes a potentiation of vasodilating effects inherent to both drugs [11,12]. Systemic hypotension aggravating myocardial ischemia in the presence of significant coronary artery disease after ingestion of both drugs is believed to be the cause for cardiac deaths [11,13,14]. Because the concomitant use of these drugs has been prohibited, patients with symptomatic myocardial ischemia can not be treated with sildenafil for erectile dysfunction. Vascular and metabolic effects of sildenafil in the presence of myocardial ischemia and the resulting risk potential is unknown since patients with significant and symptomatic heart disease have been excluded from most clinical trials [13]. Cardiac expenditure during sexual activity varies widely and silent myocardial ischemia does frequently occur during sexual intercourse in patients with chronic ischemic heart disease [15]. Myocardial ischemia enhances ventricular ectopy and thereby can cause sudden death. Ectopy might be enhanced due to the proarrhythmogenic effects which were shown to occur at high dosages of sildenafil by prolongation of cardiac repolarization [16]. Furthermore, sildenafil increases sympathetic activity resulting in elevated plasma norepinephrine levels and sympathetic nerve traffic [17]. With this knowledge, the effects of sildenafil on cardiac microcirculation are of interest, especially in diabetics who develop endothelial dysfunction during the course of the

disease and who more frequently have silent ischemic events.

Estimation of the coronary artery flow reserve utilizing adenosine permits detection of clinically relevant restriction of myocardial blood flow during maximum vasodilatation resembling hemodynamic changes during physical exercise [8,18]. The deterioration of CFR allows identification of severe stenoses of epicardial coronary arteries and microvascular disturbances due to endothelial dysfunction with high sensitivity. Previous investigations in diabetics demonstrated an inverse correlation between the duration and elevation of blood sugar levels and impairment of CFR [19,20]. Not surprisingly, patients of this study who had suboptimally adjusted long-standing diabetes exhibited a CFR which was uniformly in the lower normal range, indicating the presence of a microcirculatory disturbance. CFR measurements of the LAD in animal studies have demonstrated an increase of the mean flow velocity after sildenafil [21,11]. In contrast we found a modest reduction of the CFR due to sildenafil in half of the diabetic study patients, but in none of them did CFR decrease below 200 %, which is known to represent a cut-off value to indicate clinically relevant myocardial minor perfusion during exercising [8]. However, this is in accordance with CFR measurements performed in normal coronary arteries in animal models with sildenafil, indicating that cGMP-mediated dilatation of resistance vessels contributes little to the shear stress-induced vasodilatation augmented by adenosine [21,22]. Thus, sildenafil is unlikely to enhance myocardial ischemia during physical exercise in men with metabolically, severely reduced CFR.

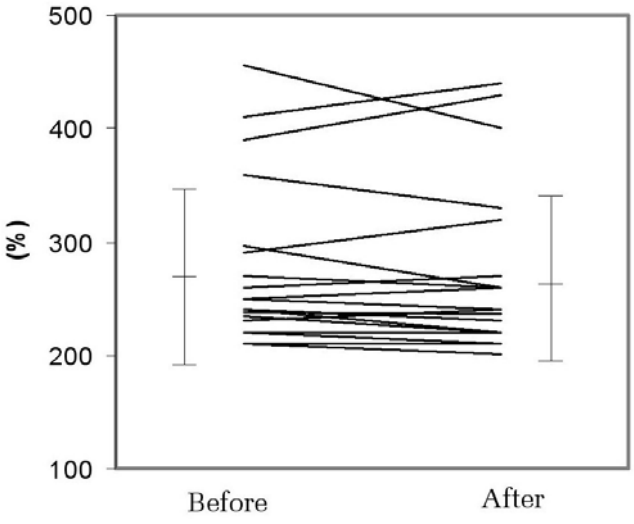

Figure 2
Individual values of CFR before and after sildenafil, including mean values and SD.

The risk of myocardial ischemia during sexual activity with a familiar partner is low, if the patient can achieve a minimum of 5–6 METS on an exercise test [23]. It was therefore recomended to perform a stress test with ≥ 5 METS in patients at risk of coronary artery disease, which should be completed without symptoms of angina pectoris or myocardial ischemia [13]. A work load of 100 W corresponds to this recommended metabolic equivalent. No evidence of myocardial ischemia at the 100 Watt level was observed in any patient during the stress test. We intended to perform a diagnostic stress test in each patient reaching the age adopted submaximal heart rate; however, most patients were not able to reach their maximal work load, although in 3 a positive result was obtained. Of those, two exhibited CAD in subsequent heart catheterization. Although not having objective signs of a coronary artery disease, invasive diagnostics were performed because of safety reasons in 16 patients reporting atypical chest pain or dyspnea with the presence of 3 or more cardiac risk factors. The surprisingly high number of patients who were demonstrated to have severe coronary artery stenosis or occlusion amounted to about 30% of all study patients. Routine examination would probably not have identified most of these severe CAD cases. Therefore, a critical revision of clinical findings on an individual basis should be made in diabetic patients. Furthermore, we were able to detect severe CAD in 2 patients, including a high grade stenosis of the left main coronary artery in one, by pathologic results of the CFR measurements while clinical assessment was unremarkable.

Recently, several studies investigated hemodynamic effects of sildenafil in the presence of high grade coronary artery stenoses. In an animal investigation sildenafil increased poststenotic blood flow due to lowering peripheral resistance in the presence of a flow limiting stenosis of the LAD [23], whereas in another study it did not [25]. In a human investigation, sildenafil increased CFR values 13 percent above baseline levels in the stenosed arteries and in undiseased reference vessels [26]. Contrary to the former investigation in which 43% were diabetics, CFR generally decreased in our study. The decrease of CFR was mainly seen in the presence of left ventricular hypertrophy, obesity and an inadequately adjusted diabetes, a constellation that is paralleled by severe disturbance of endothelial function. Since CFR results also diverged in the study of Hermann et al. [26], we speculate that more severe microcirculatory dysfunction in diabetics with a high risk profile is responsible for this lowered endothelial responsiveness. However, reduction of the adenosine-mediated increase of the mean flow velocity after sildenafil might be also a result of a more pronounced dilatation of epicardial coronary arteries, since a modest dilatation of coronary arteries induced by sildenafil was found in ex vivo studies [11,27].

Table 2: Coronary Artery Flow Measurements

	Baseline	Differences after sildenafil	p
CFR (%)	245 (210 – 490)	-10 (-90 – 40)	NS
Peak flow velocity baseline (m/s)	0.3 (0.15 – 0.50)	-0.005 (-0.15 – 0.005)	NS
Peak flow velocity adenosine (m/s)	0.72 (0.08 – 1.4)	0.03 (-0.7 – 0.05)	NS
Mean flow velocity baseline (m/s)	0.23 (0.12 – 0.43)	0.01 (-0.22 – 0.007)	NS
Mean flow velocity adenosine (m/s)	0.54 (0.31 – 0.94)	0.06 (-0.27 – 0.04)	NS
Systolic blood pressure (mmHg)	130 (110 – 170)	120 (100 – 150)	0.002
Diastolic blood pressure (mmHg)	80 (60 – 100)	72 (60 – 80)	0.002

Taking the results of these studies together, it can be stressed that sildenafil does not induce or enhance myocardial ischemia during rest or exercise in the presence of clinically significant coronary macro- or microangiopathy. However, patients with stress-induced myocardial ischemia and erectile dysfunction, who are enabled to resume sexual activity using sildenafil, are at risk of suffering from ischemia-induced cardiac events [14]. Therefore, in diabetics with an elevated cardio-vascular risk profile, intensive judgement of cardiac risk on an individual basis should be performed before administration of sildenafil.

Limitations of the Study

The CFR was measured only in the LAD, raising the question of representativity of measurements for the other coronary arteries. However, invasive measurements have shown that variation of individual CFR values is low among the coronary arteries unless a severe stenosis obstructs one of them [28].

Investigations were performed at a dosage of 50 mg sildenafil. Repetitive measurements with dosage escalation were not performed since studies of hemodynamic effects of sildenafil did not indicate clinically relevant effects with dosages exceeding 50 mg [29,30].

The study did lack a control group and no repetitive CRF measurements were performed. Validation of CFR measurements in a larger study has shown that the intraindividual variability and the day-to-day variability are low [10]; therefore, a statistical error is not likely to occur in the given setting. Also intra- and interoberver variability have been shown to be low (r = 0.95, and 0.91); in this study all measurements were made by the person who performed the validation studies.

Conclusions

Sildenafil does not alter coronary flow reserve in diabetic patients with erectile dysfunction having low coronary flow reserve at baseline. Diabetics with erectile dysfunction having two or more risk factors exhibited a high prevalence of severe coronary artery disease. Most of those patients have silent ischemia that was not detected by the recommended examination criteria. Examinations to determine eligibility of those patients for sildenafil use should be performed more intensively than in other males with erectile dysfunction.

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