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·*Original Article*·

Efficacy and limits of sildenafil citrate in patients with arterial erectile dysfunction: role of peripheral arterial disease and cardiovascular comorbidities

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Abstract

Aim: To evaluate whether the response to sildenafil administration in patients with arterial erectile dysfunction (ED) was related to their peak systolic velocity (PSV), peripheral atherosclerosis, cardiovascular risk factors (RF) and/or comorbidities at low cardiovascular risk. **Methods:** We enrolled 97 patients with 1–2 RF and comorbidities, combined with arterial ED alone (group A, $n = 27$), ED plus atherosclerotic carotid artery (group B, $n = 23$), ED plus lower limb artery abnormalities (group C, $n = 25$), and ED plus carotid and lower limb artery abnormalities (group D, $n = 22$). Sildenafil efficacy (100 mg twice a week for 12 weeks) was also examined in patients with ≥ 3 RF, peripheral atherosclerosis and no cardiovascular comorbidities (group E, $n = 20$). **Results:** Median PSV was 24.1, 21.0, 19.3, 14.5 and 17.5 cm/s in groups A, B, C, D and E, respectively. Sildenafil response was higher in group A patients (77.8%), intermediate in groups B and C (65.2% and 56%) and lowest in groups D (45.4%) and E (50%), and the response in latter two groups was significantly lower than in the other three groups. In addition, sildenafil response was negatively influenced by: ≥ 3 RF, peripheral atherosclerosis and no systemic comorbidity, or presence of 1–2 RF associated with extended atherosclerosis and comorbidities. The number of comorbidities was positively related to atherosclerosis localization or extension (25, 35, 38 and 47 in groups A, B, C and D, respectively). **Conclusion:** Low sildenafil efficacy in patients with arterial ED was associated with extended atherosclerosis. These patients should undergo extensive ultrasonography and a full cardiovascular examination. *(Asian J Androl 2008 Nov; 10: 847–853)*

Keywords: arterial erectile dysfunction; cardiovascular comorbidities; peripheral atherosclerosis; sildenafil efficacy

1 Introduction

A growing body of studies has highlighted the relationship between erectile dysfunction (ED) and cardiovascular disease [1–3]. ED shares common risk factors (RF) with coronary artery disease (CAD). These RF (smoking, hypertension, diabetes, hyperlipidemia) trigger endothelial dysfunction and subsequently atheroscle-

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rosis progression. Furthermore, it has been suggested that ED, which is frequently caused by pelvic arterial insufficiency owing to atherosclerosis (revealed by an increased intima-media thickness [IMT] of the common carotid artery) [4], may be considered an early marker of silent vascular disease (ischemic heart disease, stroke, and claudication), or of a generalized vascular disease also affecting penile arteries [5–7]. The presence of arterial ED in an otherwise asymptomatic man now represents an important educational step in recognizing patients at risk of vascular disease [8, 9], but it was only towards the end of the 1990s that consensus guidelines recommended that all men with ED and cardiovascular RF should undergo a full medical assessment [5–7]. Recently, on selected and consecutive patients affected by ED, an isolated penile arterial dysfunction was found in a lower percentage of cases, whereas about 75% of them had a concomitant peripheral atherosclerosis [10]. Furthermore, patients with ED and more generalized atherosclerosis had the most severe penile artery insufficiency, since they exhibited the lowest cavernousal peak systolic velocity (PSV) [11].

Sildenafil citrate (Viagra; Pfizer, New York, NY, USA), a selective phosphodiesterase type-5 (PDE5) inhibitor, was the first oral erectogenic agent approved by the Food and Drug Administration (FDA) and the European Medicine Evaluation Agency (EMEA) for ED treatment and was first approved in 1998. The drug has an efficacy of 60%–80% [12–13]. However, the response rate is influenced by ED etiologies and patient comorbidities [12]. Despite almost 10 years of utilization, it remains difficult to predict which patients will fail to respond to this drug. Since its action is due to nitric oxide (NO) and to cavernous nerve integrity, its efficacy is also influenced by a vascular insufficiency. This explains why the best response rate has been observed in men with normal vascular component and presumptive psychogenic ED (80%), compared with a 50.7%–53.0% success rate in ED patients with vascular abnormalities [12–14]. In patients with vascular ED, the best responders are those with arteriogenic ED, with an overall efficacy to sildenafil treatment ranging from 65.0% to 74.5% [15–16]. Although these studies [15–16] demonstrate that sildenafil success rate negatively correlates with the severity of PSV, a stratification of the efficacy results, after taking into account vasculogenic factors (≤ 3 major RF), cardiovascular diseases stratified into low vascular risk [5], and vascular peripheral comorbidities (carotid and/or low limb atherosclerosis), is lacking. Therefore, the present study was undertaken to evaluate whether the response rate to sildenafil in patients with arterial ED was related to their PSV, associated or not to arterial abnormalities in other districts and/or presence of comorbidities at low cardiovascular risk [8–9].

2 Materials and methods

2.1 Patients

2.1.1 Patient selection

We retrospectively reviewed the medical records of 117 consecutively selected patients (mean age 61 years, range 52–78 years) with arterial ED (median duration 3.6 years, range 1.6–7.0 years) due to penile arterial insufficiency. The diagnosis was made using dynamic duplex Doppler ultrasound of the penile arteries with pulsed Doppler analysis following intracavernous administration of 20 μg of alprostadil (Caverject; Pfizer, New York, NY, USA). Following injection, PSV was measured every 10 min for 20–30 min. A PSV < 30 cm/s and a non-temporal peak systolic progression suggested the presence of an arterial disease [17].

Patients with initial arterial ED underwent duplex flussimetry of the carotid and lower limb arteries to evaluate the presence of coincidental, more extended peripheral atherosclerosis. To this end, carotid and lower limb arterial circulation assessments were performed by B-mode ultrasonography, using a 7.5 MHz high resolution transducer, as recently reported [11] and according to specific general ultrasound principles [18], involving both a grading of any stenosis and an attempt to characterize the plaque or the IMT.

The above comprehensive approach allowed us to recognize the following four groups of patients with one or two arterial RF. Group A (the control group): penile arterial ED alone (n = 27), but no evidence of atherosclerosis (at duplex flussimetry of the carotid and lower limb artery). Group B: arterial ED plus atheromasic plaques and/or increased IMT of the common carotid artery (n = 23). Group C: arterial ED plus lower limb artery abnormalities (n = 25). Group D: arterial ED plus carotid and lower limb artery abnormalities (n = 22).

Furthermore, we examined a group of patients (mean age 58 years, range 53–70 years) with arterial ED (ED duration: mean 36.6 months, range 26–60 months) and the following cardiovascular profile: presence of ≥ 3 RF, asymptomatic peripheral atherosclerosis (including arte-

rial ED plus carotid atherosclerosis, n = 7; arterial ED plus lower limb artery abnormalities, n = 8; or arterial ED plus carotid and lower limb artery abnormalities, n = 5), but no case of cardiovascular diseases (group E, n = 20).

Patients with cardiovascular disease (groups A, B, C and D) were required to be at low risk for adverse cardiovascular events during sexual activity, according to the published guidelines [8, 9].

2.1.2 Exclusion criteria

Patients with arterial ED were excluded if they also had: 1) hypogonadism (defined as a low serum total testosterone in two blood samples taken 1 week apart and/or reduced testicular volume (< 12 mL using Prader's orchidometer); 2) Peyronie's disease; 3) radical pelvic surgery; 4) venogenic ED (also known as corporo-venocclusive dysfunction or venous leak, suspected by the presence of an end-diastolic velocity > 5 cm/s); 5) high cardiac risk or a recent history of uncompensated chronic heart failure (CHF) classified New York Heart Association (NYHA) class II (with slight limitation of physical activity), or major cardiovascular events [8, 9], as well as severe (World Health Organization [WHO] stage III) hypertension and/or complicated multi-drug anti-hypertensive regimen; 6) been treated with β-blockers and/or thiazide diuretics; 7) severe hyperlipidemia (total serum cholesterol concentration exceeding 280 mg/dL and/or serum triglyceride concentration exceeding 350 mg/dL); or 8) poorly controlled diabetes (fasting plasma glucose > 140 mg/dL and/or hemoglobin A1c > 7.5%).

The protocol was approved by the Institutional Review Board and an informed written consent was obtained by each patient.

2.2 Methods

2.2.1 Study examination

All patients presenting with ED and selected criteria underwent a comprehensive medical history and physical examination. All patients also answered the five-item version of the International Index of Erectile Function questionnaire (IIEF-5) [19]. Answers, recorded at weeks 0 and 12, were scored from 1 (almost never/never) to 5 (almost always/always) frequency or ability, with 0 indicating no sexual activity.

2.2.2 Sildenafil administration and evaluation

All patients were treated with sildenafil and met the criteria for low cardiovascular risk [8]. Briefly, comorbid conditions, stratified as vasculogenic problems, included: 1) < 3 RF (smoking, hypertension, diabetes and/or hyperlipidemia) and cardio-vascular conditions graded as low risk (such as controlled hypertension [pharma-cologi cally treated without β-blockers and thiazide diuretics that predispose to ED] and/or with values < 160/95 mmHg, mild risk (stable angina pectoris, post-revascularization and/without significant residual ischemia, mild valvular disease, post-myocardial infarction > 6–8 weeks, LVD [stable mild CHF, classified as NYHA class I]) (groups A, B, C and D); and 2) three RF (smoking, hypertension, diabetes and/or hyperlipidemia) but absence of cardio-vascular conditions graded as low or mild risk.

Sildenafil (100 mg) was prescribed twice a week for 12 weeks continuously and to be taken about 1 h before the anticipated sexual activity, but no more than once daily. Patients were instructed not to consume more than two units of alcohol before sexual activity (one unit of alcohol equals one glass of wine, one half-pint of beer or one measure of spirits).

The primary outcome included the percentage of patients achieving more than a five-point gain from baseline in the erectile function domain of the IIEF-5. The secondary efficacy assessment considered the responses to Q3 (ability to achieve an erection) of the IIEF-5 in each treatment group.

2.2.3 Statistical analyses

Results are shown as mean ± SEM throughout the study unless otherwise indicated. The data were analyzed by one-way analysis of variance (ANOVA) followed by Duncan's Multiple Range test and Fisher's exact test. The software SPSS version 9.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical evaluation. A statistically significant difference was accepted when the $P < 0.05$.

3 Results

No significant differences were observed between the mean age of the control group (group A) and that of patients of groups B, C, D and E. Patients of group D had a significantly longer duration of ED than that observed in patients of groups A and E, whereas the severity of ED, evaluated by the IIEF-5 questionnaire, was similar in the five groups (Table 1).

A single RF (but never smoking) was found in 40.7% of group A patients, but no patient had a single RF in

groups D and E (Table 2). Two RF were found in 59.3% of patients in group A. A significantly higher percentage of patients with two RF was found in other groups: 78.3%, 80.0% and 100% in groups B, C and D, respectively. All patients of group E had ≥ 3 RF (Table 2).

Patients with arterial abnormalities at the carotid (group B) or lower limb (group C) arteries had a PSV similar to each other and to that of the control group. Interestingly, patients with signs of peripheral atherosclerosis in both districts had a PSV not only lower than controls, but also significantly lower than patients of groups B and C. This suggests that a more severe peripheral atherosclerosis is associated with a stronger impairment of penile artery blood flow (Table 2).

Interestingly, patients of group E, arbitrarily chosen in the present study for the lack of cardiovascular comorbidities, had similar PSV values, IIEF-5 score frequency distribution and sildenafil response to patients of group D, even though they were relatively younger and had a shorter ED duration (Tables 1 and 2).

The overall efficacy rate of sildenafil was 59.8% (70 out of 117 patients). However, patients with higher PSV (likely having a lower degree of arterial insufficiency) had the best response to sildenafil treatment both in terms of > 5 points IIEF-5 score increase (81.5%) and IIEF-5 Q3 response (81.5%). On the other hand, patients with lowest PSV (likely having the greatest degree of arterial insufficiency) had the worst response rate to sildenafil both in terms of >5 points IIEF-5 score increase (40.9%) and IIEF-5 Q3 (45.4%) (Table 2).

Although the overall number of RF was similar among the groups (in spite of a prevailing rate of patients with blood hypertension in group A, diabetes in groups C and D and blood hypertension and cigarette smoking in group E), the total sum of comorbidities at low cardiovascular risk was different among groups A, B, C and D. This number seems positively associated with atherosclerosis localization or diffusion, being 25, 35, 38 and 47 in groups A, B, C and D, respectively (Table 3). The cardiovascular profile of patients with

Table 1. Clinical characteristics of patients with arterial erectile dysfunction (ED) alone (group A), ED plus carotid abnormalities (group B), ED plus lower limb artery abnormalities (group C) or ED plus carotid and lower limb artery abnormalities (group D). Group E included patients with arterial ED and ≥ 3 risk factors (RF), peripheral atherosclerosis and lack of cardiovascular comorbidities. $^{c}P < 0.01$, compared with group A or group E (ANOVA followed by the Duncan's test). IIEF-5, five-item International Index of Erectile Function questionnaire.

Group (*n*)	Age (years)	ED duration (months)	IIEF-5 score (%, *n*)		
			Severe (0–10)	Moderate (11–16)	Mild (17–21)
A (27)	57.4 (51–71)	32.8 (18–48)	40.75 (11)	40.75 (11)	18.5 (5)
B (23)	60.4 (52–75)	42.5 (28–75)	43.5 (10)	39.1 (9)	17.4 (4)
C (25)	62.5 (55–78)	45.3 (36–75)	44.0 (11)	40.0 (10)	16.0 (4)
D (22)	64.6 (58–77)	51.5 (36–84)^{c}	45.4 (10)	36.4 (8)	18.2 (4)
E (20)	58.0 (53–70)	36.6 (26–60)	45.0 (9)	40.0 (8)	15.0 (3)

Table 2. Percentage and number (in parentheses) of arterial risk factors (RF), peak systolic velocity (PSV; cm/s), 95% confidence interval (CI), and sildenafil response registered in patients with arterial erectile dysfunction (ED) alone (group A), ED plus carotid abnormalities (group B), ED plus lower limb artery abnormalities (group C) or ED plus carotid and lower limb artery abnormalities (group D). Group E included patients with arterial ED and ≥ 3 RF, peripheral atherosclerosis and lack of cardiovascular comorbidities. $^{c}P < 0.01$, versus group A patients (ANOVA followed by the Duncan's test); $^{e}P < 0.01$, versus each other group (Fisher's exact test). IIEF-5, five-item International Index of Erectile Function questionnaire.

Group (*n*)	Arterial RF (%, *n*)			PSV(cm/s)	Sildenafil response (%, *n*)	
	One	Two	Three or more	Median (95% CI)	IIEF-5 (> 5 points)	IIEF-5 (Q3)
A (27)	40.7 (11)	59.3 (16)	0	24.0 (17–29)	81.5 (22)	81.5 (22)
B (23)	21.7 (5)^{e}	78.3 (18)^{e}	0	21.0 (11–26)	65.2 (15)	65.2 (15)
C (25)	20.0 (5)^{e}	80.0 (20)^{e}	0	19.3 (14–26)	56.0 (14)	56.0 (14)
D (22)	0 (0)^{e}	100 (22)^{e}	0	14.5 (9–22)^{e}	40.9 (9)^{e}	45.4 (10)^{e}
E (20)	0 (0)^{e}	0 (0)^{e}	100 (20)^{e}	17.5 (12–25)^{e}	50.0 (10)^{e}	50.0 (10)^{e}

ED, yielded by the sum of RF and mainly by the concomitant cardiovascular diseases, reflects on sildenafil efficacy, with a response rate highest in groups A (81.5%) and B (65.2%), intermediate in group C (56.0%), and lowest in group D (47.6%) (Table 4).

No patient in each group discontinued treatment be-

Table 3. Percentage and number (in parentheses) of comorbidities found in groups of patients with arterial erectile dysfunction (ED) alone (group A), ED plus carotid abnormalities (group B), ED plus lower limb artery abnormalities (group C) or ED plus carotid and lower limb artery abnormalities (group D). Group E included patients with arterial ED and ≥ 3 risk factors (RF), peripheral atherosclerosis and lack of cardiovascular comorbidities. [A]Pharmacologically treated (without β-blockers and thiazide diuretics which may predispose to ED) and/or with values < 160/95 mmHg. [c]$P < 0.05$, compared with group A patients (ANOVA followed by the Duncan's test); [d]$P < 0.05$, compared with group A patients (Fisher's exact test). LVD, left ventricular dysfunction; NYHA, New York Heart Association classification.

Comorbid conditions	Groups (%, *n*)				
	A (*n* = 27)	B (*n* = 23)	C (*n* = 25)	D (*n* = 22)	E (*n* = 20)
Controlled[A] arterial hypertension complicated	70.4 (19)	73.9 (17)	72.0 (18)	68.2 (15)	0 (0%)
Mild, stable angina pectoris	3.7 (1)	17.4 (4)[c]	16.0 (4)	18.2 (4)[c]	0 (0)
Post-revascularization and/without significant residual ischemia	0.0 (0)	13.0 (3)[d]	8.0 (2)[d]	22.7 (5)[d]	0 (0)
Mild valvular disease	0.0 (0)	4.3 (1)	8.0 (2)[d]	9.1 (2)[d]	0 (0)
Post-myocardial infarction > 6–8 weeks	0.0 (0)	13.0 (3)[c]	8.0 (2)[c]	22.7 (5)[c]	0 (0)
LVD (NYHA class I)	25.9 (7)	52.2 (7)[c]	40.0 (10)[c]	72.7 (16)[c]	0 (0)
Total co-morbid conditions	27	35	38	47	0
Hypertension	70.4 (19)	73.9 (17)	72.0 (18)	68.2 (15)	85 (17)[c]
Diabetes	37.0 (9)	52.2 (11)	48.0 (12)	77.3 (17)[c]	65 (13)[c]
Hyperlipidemia	25.9 (4)	17.4 (6)	16.0 (4)	22.7 (5)	30 (6)
Cigarette smoking	33.3 (8)	34.8 (7)	44.0 (11)	27.3 (6)	85 (17)[c]
Total RF	40	41	45	43	53

Table 4. Sildenafil response rate (%) stratified with cardiovascular comorbidities. [*]Within cardiovascular risk graded low (Second Princeton Consensus Conference). LVD, left ventricular dysfunction; NYHA, New York Heart Association classification.

		Group (%, *n*)			
		A (*n* = 27)	B (*n* = 23)	C (*n* = 25)	D (*n* = 22)
Overall	Responders	81.5 (22)	65.2 (15)	56.0 (14)	47.6 (10)
	Non-responders	18.5 (5)	34.8 (8)	44.0 (11)	52.4 (12)
Comorbid conditions[*]					
Controlled arterial hypertension complicated	Responders	84.2 (16/19)	41.2 (7/17)	55.5 (10/18)	46.7 (7/15)
	Non-responders	15.8 (3/19)	58.8 (10/17)	45.5 (8/18)	53.3 (8/15)
Mild, stable angina pectoris	Responders	0 (0/1)	40 (2/5)	50 (2/4)	25 (1/4)
	Non-Rresponders	100 (1/1)	60 (3/5)	50 (2/4)	75 (3/4)
Post-revascularization and/without significant residual ischemia	Responders	0	66.7 (2/3)	50 (1/2)	40 (2/5)
	Non-responders	0	33.3 (1/3)	50 (1/2)	60 (3/5)
Mild valvular disease	Responders	0	100 (1/1)	100 (2/2)	100 (2/2)
	Non-responders	0	0 (0/1)	0 (0/2)	0 (0/2)
Post-myocardial infarction > 6-8 weeks	Responders	0	33.3 (1/3)	50 (1/2)	40 (2/5)
	Non-responders	0	66.7 (2/3)	50 (1/2)	60 (3/5)
LVD (NYHA class I)	Responders	85.7 (6/7)	57.1 (4/7)	50 (5/10)	37.5 (6/16)
	Non-responders	14.3 (1/7)	42.9 (3/7)	50 (5/10)	62.5 (10/16)

cause of adverse reactions. Overall, 12 patients (10.2%) (one from group A, three from groups B, C, and D and two from group E) developed transient and mild treatment-related symptoms (headache in eight cases, rhinitis in one case and facial flashing in three cases).

4 Discussion

A growing body of evidence suggests that ED is an early manifestation of atherosclerosis and a precursor of systemic vascular disease. Indeed, atherosclerosis accounts for nearly half of all cases of ED in patients older than 50 years [2]. The assumption of ED as sign of atherosclerosis is also supported by a correlation between retinal vascular disease and low penile PSV [20].

Atherosclerotic lesions may progress over decades and their progression in various arterial districts seems to be associated with the presence of cardiovascular RF and/or the host's response (chronic low-grade inflammation state) to clinical management (dietetic and pharmacological strategies) of these factors [21].

Recently, on selected and consecutive patients affected by ED, we found an isolated penile arterial dysfunction in a low percentage of cases, whereas the vast majority of patients had a concomitant peripheral atherosclerosis [10]. Furthermore, patients with ED and more generalized atherosclerosis had the most severe penile artery insufficiency, since they exhibited the lowest penile PSV [11].

The present study focused on ED as a symptom of systemic atherosclerosis and examined whether the efficacy of sildenafil citrate administration in patients with arterial ED was related to their PSV and/or other peripheral atherosclerosis and/or cardiovascular comorbidities. Although the patients with arterial ED and pluridistrictual atherosclerosis enrolled in this study had a mean age similar to that of patients with arterial ED alone or in combination with carotid or lower limb artery abnormalities, they had a significantly longer ED duration, higher number of patients (up to 100% in group D) with two, variously combined arterial RF and a lower PSV. The lowest penile PSV in patients with more generalized atherosclerosis (group D), as well as the worst cardiovascular profile in these patients (suggested by the sum of the RF and mainly by concomitant cardiovascular diseases), in addition to identifying arterial insufficiency as the organic cause of ED, affects sildenafil outcome, with response rate relatively lower in group D (47.6%), higher in groups A (81.5%) and B (65.2%) and intermediate in group C (56%).

The systemic effects of arterial RF, such as cigarette smoking, hypertension, hyperlipidaemia and diabetes, are progressive, and their continuous presence accentuates the patho-physiological processes known to cause ED and concomitant or subsequent cardiovascular comorbidities. In addition, these RF may work in an additive or synergistic fashion to further reduce penile blood flow, to enhance endothelial oxidative stress and atherosclerosis progression and to influence negatively the response to ED treatment. The lack of endothelial response to PDE5 inhibitors could be in part explained by cavernous corpora fibrosis [22], reduction > 35% of cavernous smooth muscle at penile biopsy [23] and advanced oxidative stress (overproduction of radical oxygen species unopposed by direct or indirect, via increased number of endothelial precursors stem cell on damaged endothelial wall, effects of NO availability).

Recently, Solomon *et al*. [24] explored the relationship between cardiovascular RF and acute (a single 50 mg dose) and chronic responses to sildenafil in 45 patients with ED. They found that acute and chronic effects of sildenafil on erectile function and pulse wave profiles were related to metabolic cardiovascular RF. In particular, the improvement in erectile function in response to sildenafil was dependent on initial erectile function and baseline apolipoprotein B. On the other hand, acute changes in stiffness index were related to apolipoprotein A-1, B and lipoprotein(a) concentrations, whereas reflection index was related to pulse pressure, albumin-to-creatinine ratio and lipoprotein(a).

In conclusion, the present study showed that patients with penile artery insufficiency and atherosclerosis in other arterial districts also have a significantly lower PSV and a reduced sildenafil efficacy explained by the presence of ≥ 3 RF, asymptomatic peripheral atherosclerosis and no systemic comorbidity, or presence of at least two RF combined with both increased atherosclerosis extension and presence of cardiovascular comorbidities even if judged at low risk, therefore meeting the criteria for PDE5 inhibitor treatment. Hence, patients with arterial ED alone may be regarded as an important clinical model of atherosclerosis prevention through early management of their RF, and sildenafil response could be useful in screening of systemic atherosclerosis in arterial ED patients. In particular, ED patients with a severe arterial insufficiency and/or low

sildenafil response should undergo extensive Doppler ultrasonography and a full cardiovascular examination.

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