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·*Clinical Experience*·

Different hemodynamic responses by color Doppler ultrasonography studies between sildenafil non-responders and responders

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Abstract

Aim: To determine if there are different penile hemodynamic patterns between sildenafil non-responders and responders by using color Doppler ultrasonography. **Methods:** A total of 69 erectile dysfunction (ED) patients aged 22–79 years were enrolled into the present study. Thirty-eight (55.1%) men with ED who did not respond to four attempts of treatment with 100 mg sildenafil after re-education were classified as sildenafil non-responders. A combination of three vasodilator drugs, 1.25 mg papaverine, 0.4 mg phentolamine and 5 μg prostaglandin E1, was given by intracavernous injection before penile Doppler ultrasonography was carried out. The erectile response to intracavernous injection and vascular parameters including peak systolic velocity (PSV), resistance index (RI), end diastolic velocity (EDV) and cavernosa artery diameter (CD) were measured and the results between sildenafil non-responders and responders were compared. **Results:** No statistical difference in vascular parameters measured by Doppler ultrasonography studies between non-responders and responders was noted. Sildenafil non-responders had a poorer penile rigidity response to intracavernous injection than responders ($P < 0.05$). Among patients with adequate PSV (≥ 30 cm/s) and abnormal EDV (> 5 cm/s), individuals in the non-responder group had fewer positive responses to intracavernous vasodilator injection than in the responder group (35.3% *vs.* 72.2%, $P < 0.05$). Advanced age and comorbidity with diabetes mellitus were significantly associated with sildenafil non-response ($P < 0.05$). **Conclusion:** Sildenafil non-responders were characterized by a poorer penile rigidity response to intracavernous injection and had an associated impaired veno-occlusive mechanism. Advanced age and comorbidity with diabetes mellitus were two common factors associated with non-response. *(Asian J Androl 2007 Jan; 9: 129–133)*

Keywords: color Doppler ultrasonography; erectile dysfunction; impotence; sildenafil citrate; ultrasonography

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1 Introduction

Normal penile erectile function depends on adequate relaxation of smooth muscle in the corpora cavernosa. Vasodilatation occuring after relaxation of the smooth

muscle in arterioles results in increased blood flow within the corpora cavernosa. A veno-occlusive mechanism enables the corpora to retain blood within the expanded sinusoids by relaxation of trabecular smooth muscles and compression of emissary venules against the tunica albuginea [1]. Sildenafil citrate was the first type of phosphodiesterase 5 (PDE5) inhibitors introduced to treat male erectile dysfunction (ED). Sildenafil citrate prevents cyclic guanosine monophosphate (cGMP) degradation and enhances smooth muscle relaxation within the corpora cavernosum. In healthy young men, oral sildenafil citrate can reduce the interval between first and second nocturnal erections and prolong the duration of the last nocturnal erection [2]. Oral sildenafil citrate has been extensively prescribed as the first line of ED treatment since its release in 1998; however, not all patients with ED treated with oral sildenafil citrate have a satisfactory response, that is, adequate penile rigidity for vaginal penetration. Patients with severe neurologic damage, diabetes mellitus or severe vascular disease might be resistant to PDE5 inhibitors. In a dose-response study, 84% of the men receiving 100 mg of sildenafil had improved erection as compared with 25% of those receiving placebo [3]. Approximately 40% of individuals who do not have an adequate response to sildenafil achieve satisfactory penile rigidity after re-education and/or proper instruction [4].

Intracavernous injection of vasodilators has become a salvage treatment for individuals who do not respond to sildenafil after re-education. A response of 88.1% to intracavernous self-injection of alprostadil has been noted in a prospective study of sildenafil non-responders [5]. However, a direct comparison of penile hemodynamics between sildenafil non-responders and responders has never been carried out. Color Doppler ultrasonography studies (CDUS) were used to measure penile blood velocity and have become a useful tool for the diagnosis of penile vasculogenic insufficiency.

For a better understanding of the penile hemodynamic differences between sildenafil non-responders and responders, we retrospectively analyzed ED patients who were referred to our department for CDUS of the penis during the past 6 years. We compared the erectile response to intracavernous injection of a combination of three vasoactive drugs and the parameters measured from penile blood flow studies between sildenafil non-responders and responders.

2 Materials and methods

2.1 Study population and design

The penile hemodynamics of pharmacologically induced erection in 69 ED patients evaluated with CDUS in our department since 1999 were studied. The mean patient age was 50.4 years (range 22–79 years). Patients referred to our department as a result of an unsatisfactory sildenafil response were re-educated and challenged with 100 mg sildenafil citrate. Patients who did not reach satisfactory rigidity after a fourth challenge were classified as non-responders. ED patients who reached satisfactory penile rigidity after sildenafil treatment were classified as responders. A successful response to sildenafil was defined as the ability to achieve vaginal penetration in ≥ 75% of attempts. Patients diagnosed to have Peyronie's disease were excluded from the present study. Penile CDUS were carried out in an outpatient clinic. Intracavernous injection of 0.5 mL of a solution containing 1.25 mg papaverine, 0.4 mg phentolamine and 5 μg prostaglandin E1 was given before the start of penile blood flow measurement. Semiquantitative clinical grading of an erection was carried out throughout the Doppler evaluation. Erectile response was documented using a 5-grade scale: 0, flacid; 1, mild tumescence; 2, moderate tumescence but inadequate rigidity for vaginal penetration; 3, full tumescence with moderate rigidity allowing vaginal penetration with some difficulty; and 4, full tumescence and full rigidity allowing vaginal penetration without difficulty. The same physician (STH) carried out all the studies. Patients classified as grade 3 or 4 were regarded as having a positive response to intracave-rnous injection.

2.2 CDUS

All CDUS were carried out in a quiet, private room with minimal distractions by the same urologist (STH) using an Acuson 128XP machine (Mountain View, CA, USA) and an L7 (7.0 MHz) small piece transducer. In order to reduce measurement variation, the transducer was always positioned at the penile base. Grayscale scanning of the penis was carried out at the beginning of each study to document any structural abnormality. Color mapped Doppler ultrasonography was then used to measure the proximal cavernosa arteries. After intracavernous injection, assessment of the corpora cavernosa was carried out at 1, 5, 10, 15, 20, 25 and 30 min. All injections were carried out in the left corpora. Measurements of peak systolic velocity (PSV), end diastolic velocity (EDV), cavernous artery diameter (CD) and resistance index (RI) over both sides of the proximal cavernous arteries were

carried out during the CDUS. The measurement angle was 55 degrees.

2.3 Vascular diagnosis of ED by CDUS

Patients with normal PSV (≥ 30 cm/s) and normal EDV (≤ 5 cm/s) were classified as having a normal penile blood flow study. Arterial insufficiency type ED was defined as PSV < 30 cm/s with normal EDV (≤ 5 cm/s). The diagnosis of veno-occlusive type erectile dysfunction was defined as normal PSV (≥ 30 cm/s) with abnormal EDV (> 5 cm/s). Patients who could not be classified into the above categories were defined as having mixed type ED [6–8].

2.4 Analysis of data

Comparison of age and vascular parameters between sildenafil non-responder and responder groups was carried out using unpaired *t*-test. Categorical data was analyzed using χ^2-test or Fisher's exact test. Differences were considered significant when $P < 0.05$. Statistical analysis was carried out with commercial software SPSS 11.0 (SPSS, Chicago, IL, USA).

3 Results

Thirty-eight (55.1%) patients with a mean age of 57.3 years were included in the sildenafil non-responder group, and 31 (44.9%) patients with a mean age of 41.9 years were in the sildenafil responder group (Table 1). Of the 38 patients in the non-responder group, 21 (55.3%) had no comorbid disease, nine (23.7%) had diabetes mellitus, three (7.9%) had both diabetes and hypertension, three (7.9%) had undergone prostatectomy, one (2.6%) had coronary artery disease and one (2.6%) had cerebrovascular disease. Of the 31 patients in responder group, 25 (80.6%) had no comorbid disease, three (9.7%) had coronary artery disease, one (3.2%) had dyslipidemia, one (3.2%) had diabetes mellitus and one (3.2%) had multiple sclerosis.

There was no statistical difference in vascular parameters (PSV, EDV, CAD and RI) between the two groups (Table 2). Veno-occlusive ED was the commonest type in both non-responder and responder groups (44.7% *vs.* 58.1%, respectively), followed by normal type (23.7% *vs.* 22.6%), arterial type (23.7% *vs.* 12.9%) and mixed type (7.9% *vs.* 6.5%). No patients diagnosed with mixed type ED in either group were able to achieve adequate rigidity (grade 3 or 4). Overall, the rigidity response to intracavernous injection of three vasodilators

Table 1. Distribution of study population according to age, vascular parameters and associated diseases. PSV, peak systolic velocity; EDV, end diastolic velocity; RI, resistance index; CD, cavernous artery diameter; CAD, coronary artery disease.

	Sildenafil non-responders (n = 38)	Sildenafil responders (n = 31)	P value
Age (years)	57.3 ± 12.2	41.9 ± 12.6	< 0.05
PSV (cm/s)	39.4 ± 13.7	38.3 ± 11.3	> 0.05
EDV (cm/s)	7.5 ± 5.4	7.0 ± 4.0	> 0.05
RI	0.81 ± 0.09	0.81 ± 0.09	> 0.05
CD (mm)	6.0 ± 1.4	6.4 ± 2.2	> 0.05
Rigidity response (*n*, %)			< 0.05
Grade 1	4 (10.5)	2 (6.5)	
Grade 2	21 (55.3)	8 (25.8)	
Grade 3	8 (21.1)	9 (29.0)	
Grade 4	5 (13.2)	12 (38.7)	
Diabetes mellitus (*n*, %)			< 0.05
Yes	12 (31.6)	1 (3.2)	
No	26 (68.4)	30 (96.8)	
CAD (*n*, %)			> 0.05
Yes	1 (2.6)	3 (9.7)	
No	37 (97.3)	28 (90.3)	

Table 2. Vascular classification of erectile dysfunction (ED) by color Doppler ultrasonography study (CDUS) and the rigidity response to intracavernous injection. *"Yes" as positive response in grade 3 or 4 rigidity and "No" as negative response in grade 1 or 2 rigidity.

ED vascular diagnosis and rigidity response* to CDUS	Sildenafil non-responders (n = 38)	Sildenafil responders (n = 31)	P value
Arterial (*n*, %)			> 0.05
Yes	3 (33.3)	2 (50.0)	
No	6 (66.7)	2 (50.0)	
Mixed (*n*, %)			
Yes	0 (0)	0 (0)	
No	3 (100.0)	2 (100.0)	
Normal (*n*, %)			> 0.05
Yes	4 (44.4)	6 (85.7)	
No	5 (55.6)	1 (14.3)	
Veno-occlusive (*n*, %)			< 0.05
Yes	6 (35.3)	13 (72.2)	
No	11 (64.7)	5 (27.8)	

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had a significant difference in favor of the sildenafil responder group ($P = 0.032$). Only 34.2% (13/38) of non-responders, but 67.7% (21/31) of responders, had a positive response to intracavernous vasodilator injection (Table 2). Fewer patients with veno-occlusive type ED in the non-responder group had a positive response to intracavernous injection than in the responder group (35.3% *vs.* 72.2%, $P = 0.044$). No prolonged erections (more than 4 hours) or priapism occurred in any individual in the present study.

4 Discussion

Color Doppler ultrasonography is an excellent non-invasive method to evaluate the arterial and venous components of ED. Intracavernous injection of vasoactive agents before CDUS has been noted to provide a better response and higher blood flow in cavernosa arteries than oral sildenafil with audiovisual stimulation [9]. In the present study, we used a solution of three vasodilators (1.25 mg papaverine, 0.4 mg phentolamine and 5 μg prostaglandin E1) to enhance smooth muscle relaxation of corpus cavernosum. There was no statistical difference in vascular parameters (PSV, EDV, CAD and RI) as measured by color Doppler ultrasonography between sildenafil non-responders and responders. Using a PSV < 30 cm/s and EDV ≤ 5 cm/s as the diagnostic criteria, our data also showed a low incidence of arterial insufficiency in both non-responders and responders (23.7% and 12.9%, respectively). This finding was comparable to the results of a previous study by McCullough *et al.* [10]. In the aforementioned study, a low incidence of arterial insufficiency (19%) in sildenafil non-responders receiving nerve-sparing radical prostatectomy using a PSV < 25 cm/s as the diagnostic criteria was also noted.

Interestingly, in the present study no patient categorized with mixed type ED in either group had a positive erectile response to intracavernous vasodilator injection. Thus, mixed type ED might represent the most severe form of vascular insufficiency. It has also been noted that only 6% of patients diagnosed with mixed type ED respond to sildenafil [11].

A high incidence of veno-occlusive type ED (44.7% in the non-responder group and 58.1% in the responder group) was noted in the present study. This might be overestimated as a result of inadequate smooth muscle relaxation induced by intracavernous vasodilator injection. In patients having a normal PSV (≥ 30 cm/s) and abnormal EDV (> 5 cm/s), more sildenafil responders reached adequate penile rigidity in response to intracavernous vasodilator injection. Six of the 69 patients classified as having normal CDUS did not have an adequate penile rigidity response after intracavernous vasodilator injection. Five of these six patients were in the sildenafil non-responder group. Therefore, a subgroup of sildenafil non-responder patients characterized by adequate PSV (≥ 30 cm/s), normal EDV (≤ 5 cm/s) and negative response to intracavernous injection were identified in the present study.

Psychogenic suppression during examination might cause a false negative response to intracavernous vasodilator injection. Complete cavernous smooth muscle relaxation is essential for normal erection and without a normal erection, the diagnosis of venous insufficiency might be overestimated. A second injection of vasodilators can reduce this type of overestimation, but the risks of prolonged erection must be weighed against potential benefits. A second intracavernous vasodilator injection was not given to any patient in the present study. More than 75% of our non-responders had adequate flow velocity (PSV ≥ 30 cm/s), but the erection response to intracavernous vasodilator injection was poorer than in the responder group. Patients with normal PSV, but an incomplete erectile response, are considered to have a veno-occlusive dysfunction [6].

It had also been postulated that men with an intact veno-occlusive mechanism can maintain an erection in response to intracavernous vasodilator injection despite arterial insufficiency [12]. Veno-occlusive dysfunction alone, or combined with arterial disease, is the hemodynamic abnormality causing non-response to intracavernous pharmacotherapy [13]. However, non-response to intracavernous vasodilator injection in an older patient with a long duration of ED is most likely to the result of venous insufficiency [14]. Age and the competence of smooth muscle relaxation to vasoactive agents might play a major role in the difference of erectile response in the present study, that is, the mean age of patients in the non-responder group was 15 years older than in the responder group. Partial androgen deficiency might also be a factor contributing to poorer erectile response an aging male. Older men might require higher levels of testosterone for normal sexual function and testosterone replacement might possibly improve the therapeutic response to PDE5 inhibitors [15].

Diabetes mellitus might be another major factor contributing to sildenafil non-response. Diabetic patients with erectile dysfunction have autonomic and endothelium dependent smooth muscle relaxation impairment [16].

Diabetes mellitus was present in 31.6% (12/38) of sildenafil non-responders in the present study; however, the PSV of our diabetic non-responders was similar to that in responders. In a longitudinal observation study, diabetic men with erectile dysfunction had more severe function impairment and lower intercourse satisfaction than non-diabetic men [17]. Diabetes mellitus has been noted to negatively impact the response to intracorporeal injection and is associated with low PSV and poor penile axial rigidity [18]. In a 10-year follow-up study, diabetic patients using self-injection to treat ED had the tendency to switch from a single vasodilator to a combination of vasodilators in order to reach maximal cavernous smooth muscle relaxation and a better erection response [19]. In a recent prospective morphometric study, severe vascular lesions with reduction of cavernous smooth muscle (< 35%) were observed in sildenafil non-responders [20]. Further immunohistochemical or molecular studies in sildenafil non-responders and responders are needed to confirm the role of cavernous smooth muscle in the pathogenesis of sildenafil non-response.

In conclusion, the present study has shown that sildenafil non-responders had a poorer rigidity response to intracavernous injection of vasodilators than responders. Most sildenafil non-responders were characterized by adequate PSV (≥ 30 cm/s) and abnormal EDV (> 5 cm/s). Older age and diabetes mellitus are two common factors associated with non-response.

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