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Full Length Research Paper

Dynamic observation of penile hemodynamic change in patients with vasculogenic erectile dysfunction after prostaglandin E_1 treatment

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To dynamically observe the hemodynamic features in different subtypes of vasculogenic ED after intracavernous injection of prostaglandin E_1 (PGE1). 358 of ED patients were involved in this study, including 119 psychogenic ED, 75 arteriogenic ED, 78 venogenic ED, 54 mingle vasculogenic ED and 32 other causes ED. For all of these ED patients, intracavernous injection of 10 µg PGE1 was used to induce penile erection. Then we employed color duplex ultrasonography to monitor the penile hemodynamic changes (including peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI)) at 5, 10, and 20 min after treatment. Psychogenic ED patients displayed normal hemodynamic response to PGE1 treatment (PSV> 25 cm/s and EDV <5 cm/s) and served as control. Statistic analysis demonstrated that the PSV levels in venogenic ED at all time points are dramatically lower than them in psychogenic ED and the PSV levels at 10 and 20 min in venogenic ED are significantly lower than 5 min after treatment. The EDV levels at 10 and 20 min after treatment in mingle vasculogenic ED is significantly lower than them in venogenic ED. The RI values are consistently lower than 0.9 in both venogenic ED and mingle vasculogenic ED at all time points. This study helps us better understand the hemodynamic features in different subtypes of vasculogenic ED during penile erection.

Key words: Vasculogenic erectile dysfunction, penile hemodynamic observation, color duplex ultrasonography.

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent inability to achieve and maintain an erection sufficient for satisfactory sexual activity, and it affects as many as 30 million American men. The disorder is highly associated with age, it is reported that the prevalence of ED at the age of 40 years old is 39% and at the age of 70 years old is 67% (Feldman et al., 1994).

Based on the etiology, erectile dysfunction can be classified as psychogenic, neurogenic, hormonal, vasculogenic, drug-induced and other cause erectile dysfunction (Lue, 2000). The clarification of the underlying cause is very important for ED patients before application of appropriate treatments. Penile vascular dysfunction (vasculogenic ED) is a common cause of ED, which consists of arteriogenic ED (cavernosal artery insufficiency) and venogenic ED (penile veno-occlusive dysfunction). In fact, both of these two mechanisms often coexist in the same patient, namely mingle vasculogenic ED (Grein and Schubert, 2002; Siroky and Azadzoi, 2003).

Color duplex ultrasonography was firstly employed to diagnose vasculogenic ED in 1985 (Lue et al., 1985). Diagnostic evaluation of ED by color duplex ultrasonography is now considered as an important approach for ED patients due to the fact that hemodynamic change monitored by color duplex ultrasonography after intracavernous injections of vasodilator agents could provide important information about the patients' erectile capacity and vasculogenic

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abnormalities. Not only can it measure blood flow velocity in the cavernosal arteries in both contracted and relaxed states, but also veno-occlusive abnormalities can be identified. Through color duplex ultrasonography test, the subtypes of vasculogenic ED including arteriogenic ED, venogenic ED and mingle vasculogenic ED can be clarified. A common used vasodilator drug for color duplex ultrasonography test is prostaglandin E1 (PGE1). PGE1 via its receptor activates the adenyl cyclase to upregulate cAMP level, which relaxes the artery and smooth muscle in corpus cavernosum and finally induces penile erection (Shah et al., 2007). After intracavernous injection of PGE1 to induce full erection, the levels of peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) values of RVA blood flow are measured by color duplex ultrasonography and abnormalities in PSA, EDV and RI can provide evidences for diagnosis of vasculogenic ED.

Moreover, intracavernous injection of PGE1 is also one of the main medical treatments for vasculogenic ED with satisfactory safety and efficacy (Kim and McVary, 1995; Levine et al., 1989; Waldhauser and Schramek, 1988). Although oral PDE5 inhibitors are widely accepted to be the first-line treatment of erectile dysfunction (Kouvelas et al., 2009), it is still considered as second-line treatment when oral PDE5 inhibitors therapy fails or PDE5 inhibitors are contraindicated (Bennett et al., 1991; Sundaram et al., 1997; Vardi et al., 2000).

PGE1 is most often used agent today for both diagnostic and therapeutic injections for the production of erection. However, very little attention has been paid to dynamic observation of penile hemodynamic change in vasculogenic ED patients after intracavernous injection of PGE1. In this study, we aim to dynamically observe hemodynamic change in vasculogenic ED by monitoring the blood flow velocity and veno-occlusive abnormalities in corpus cavernosum at different time points after PGE1 treatment. We believe this study may help us further understand the hemodynamic features in different subtypes of vasculogenic ED.

PATIENTS AND METHODS

From January 2007 to June 2009, 358 married patients aged from 22 to 55 years old (average age: 28.9±7.8 years old) were diagnosed as ED in our outpatient service. The history of ED ranged from 6 to 87 months with the average of 12.1 months. For diagnosis of ED, the thorough history was taken and physical examinations including evaluation of the breasts, hair distribution, penis, and testes; palpation of the femoral and pedal pulses; and testing of genital and perineal sensation were performed. Laboratory tests included blood routine, urine routine, hepatic function, renal function, cholesterol, triglycerides, blood glucose, urine glucose and testosterone. International Index of Erectile Function Questionnaire (IIEF-5) was applied to evaluate the severity of ED (Rosen et al., 1999). Other special tests for ED diagnosis included nocturnal penile monitoring by Rigiscan (Obson company, California, USA) (Hatzichristou et al., 1998), access of penile vascular function by color duplex ultrasonography (The Knoll/MIDUS™ System, PJR Inc, Minnesota, USA).

Dynamic observation of penile hemodynamic change by color duplex ultrasonography

For all of the 358 ED patients, color duplex ultrasonography (The Knoll/MIDUS™ System, PJR Inc, Minnesota, USA) equipped with 8 MHz probe was employed to evaluate the vascular function of penis. The patient was in a supine position and the basal levels of peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) values of RVA blood flow were measured by color duplex ultrasonography before intracavernous injection of PGE1.

10 µg of PGE1 (Alprostadil, Pharmacia & Upjohn Inc, New Jersey, USA) was dissolved to 1 ml saline and built in an insulin syringe. It was directly injected into corpus cavernosum near the radix penis, then the punctured site was pressed with medical cotton buds for 1 min and penis was massaged to make the drug spread into contralateral corpus cavernosum. Color duplex ultrasonography was used to monitor the penile hemodynamic change (including PSV, EDV and RI) at 5, 10 and 20 min later.

Diagnosis criteria

Psychogenic ED: The results of nocturnal penile tumescence test (NPT) were considered normal in case of at least one episode of penile tip rigidity greater than 60% and more than 10 min in duration during two consecutive nights of recording (Hatzichristou et al., 1998). If NPT result is normal and no other abnormalities were indicated by color duplex ultrasonography and laboratory tests, diagnosis of psychogenic ED was achieved (Wespes et al., 2006).

Vasculogenic ED: Arteriogenic ED was diagnosed when PSV was lower than 25 cm/s. Venogenic ED was diagnosed when EDV was higher than 5 cm/s and RI was lower than 0.9. Mingle vasculogenic ED was diagnosed when PSV was lower than 25 cm/s and concomitant EDV was higher than 5 cm/s (wespes et al., 2006).

Statistical analysis

All data were expressed as the mean ± SEM. Data were analyzed for statistical significance using SPSS 11.0. Student's *t* tests were applied in two-group analysis. Differences between the means of multiple groups were compared by the one-way analysis of variance (ANOVA). A value of $P < 0.05$ was considered significant and was the threshold to reject the null hypothesis.

RESULTS

The IIEF-5 score for all of the 358 ED patients is less than 21. Among them, 119 patients were finally diagnosed as psychogenic ED, with the mean age of 26.7±7.2 years old. 75 of them were diagnosed as arteriogenic ED, 78 were venogenic ED and 54 were mingle vasculogenic ED. 32 ED patients were attributed to hormonal, neurogenic factors or other causes. IIEF-5 score for different groups of ED patients is showed in Table 1. No significant difference was indicated for the mean IIEF-5 score among arteriogenic ED, venogenic ED and psychogenic ED. The IIEF-5 score in mingle vasculogenic ED and others are

Table 1. Characterization of 358 ED patients.

Category	Cases	Age (years)	History (months)	IIEF-5 score
Arteriogenic ED	75	28.3±7.5	10.3±5.1	13.4±1.7
Venogenic ED	78	30.6±8.0	12.1±6.3	14.2±1.2
Mingle vasculogenic ED	54	31.2±8.7	10.2±4.9	11.4±1.0
Psychogenic ED	119	26.7±7.2	13.5±6.5	15.2±1.6
Others	32	31.1±7.9	14.1±7.3	11.3±1.1

Table 2. Dynamic observation of penile hemodynamic changes in vasculogenic erectile dysfunction patients after PGE1 treatment.

Category	Before injection			5 min after injection			10 min after injection			20 minutes after injection		
	PSV (cm/s)	EDV (cm/s)	RI	PSV (cm/s)	EDV (cm/s)	RI	PSV (cm/s)	EDV (cm/s)	RI	PSV (cm/s)	EDV (cm/s)	RI
Arteriogenic ED	11.6±1.1	0.1±0.0	0.99±0.0	22.4±2.0	0.5±0.0	0.97±0.06	22.0±3.5	0.4±0.0	0.98±0.03	21.1±3.7	0.1±0.0	0.99±0.02
Venogenic ED	12.8±1.8	0.2±0.0	0.99±0.01	34.1±3.5	5.3±0.6	0.84±0.06	23.0±2.1	8.6±0.8	0.63±0.03	23.0±1.3	4.9±0.5	0.79±0.04
Mingle vasculogenic ED	12.9±1.1	0.1±0.0	0.99±0.2	20.9±2.0	5.2±0.4	0.74±0.07	23.9±2.8	2.3±0.2	0.89±0.04	20.0±1.7	2.0±0.2	0.88±0.01
Psychogenic ED	18.3±1.9	0.1±0.0	0.99±0.01	44.5±2.1	0.1±0.0	0.99±0.01	47.4±4.6	0.0±0.0	0.99±0.01	43.4±2.4	0.1±0.0	0.99±0.01

lower than psychogenic ED groups. The characterization of each group of patients was summarized in Table 1.

For these ED patients, color duplex ultrasonography was employed to dynamically observe the penile hemodynamic change after intracavernous injection of PGE1. Specifically, PSA, EDV and RI were measured by color duplex ultrasonography before and 5, 10 and 20 min after intracavernous injection of PGE1. It is showed that the basal PSV in psychogenic ED patients is 18.3±1.9 cm/s and the PSA at 5, 10 and 20 min were 44.5±2.1, 47.4±4.6 and 43.4±2.4 cm/s, respectively (Table 2). Psychogenic ED patients displayed normal hemodynamic response to PGE1 treatment (PSV >25 cm/s and EDV <5 cm/s) and served as control group. However, the basal PSV and PSV levels at 5, 10 and 20 min after PGE1 treatment in venogenic ED were 12.8±1.8, 34.1±3.5, 23.0±2.1 and 23.0±1.3 cm/s respectively (Table 2). Statistic analysis demonstrated that the PSV levels in venogenic ED at all time points are dramatically lower than them in psychogenic ED ($P<0.05$). Furthermore, the PSV levels at 10 and 20 min in venogenic ED are significantly lower than 5 min after PGE1 treatment ($P<0.05$), which does not happen in psychogenic ED patients (Figure 1). For arteriogenic ED and mingle vasculogenic ED, the PSV levels in different time points are less than 25 cm/s.

The EDV levels before and 5, 10 and 20 min after PGE1 treatment in venogenic ED were 0.2±0.0, 5.3±0.6, 8.6±0.8 and 4.9±0.5 cm/s respectively (Table 2). And the EDV levels before and 5, 10 and 20 min after treatment in mingle vasculogenic ED were 0.1±0.0, 5.2±0.4 , 2.3±0.2 and 2.0±0.2 cm/s respectively (Table 2). Statistic analysis demonstrated that the EDV levels at 10 and 20 min after treatment in mingle vasculogenic ED are significantly lower than them in venogenic ED (Figure 2). The EDV levels are almost undetectable in arteriogenic ED and psychogenic ED (Figure 2).

The RI values in venogenic ED and mingle vasculogenic ED at different time points after PGE1 treatment are consistently lower than 0.9 and in arteriogenic ED and psychogenic ED they are close to 1 (Table 2 and Figure 3).

DISCUSSION

Since Lue et al. (1985) firstly used vasodilator drugs to induce penile erection and then employed

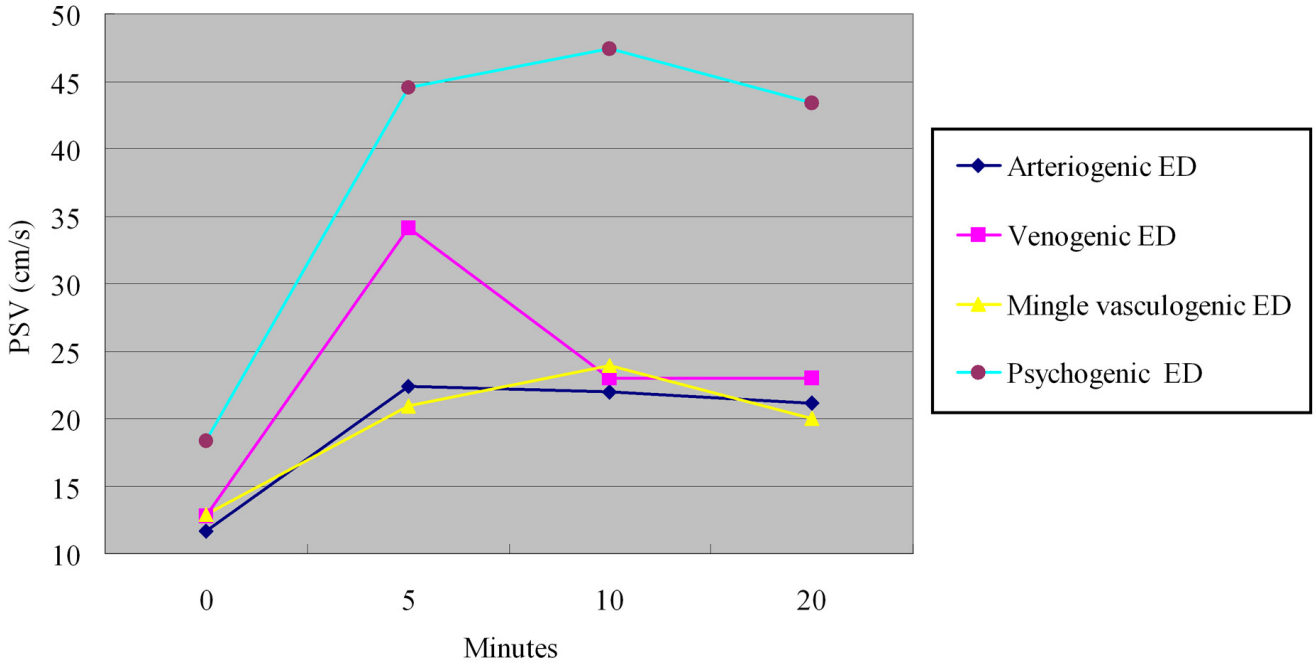

Figure 1. Dynamic observation of PSV levels after intracavernous injection of PGE1 in vasculogenic ED. The PSV levels in venogenic ED at all time points are dramatically lower than them in psychogenic ED.

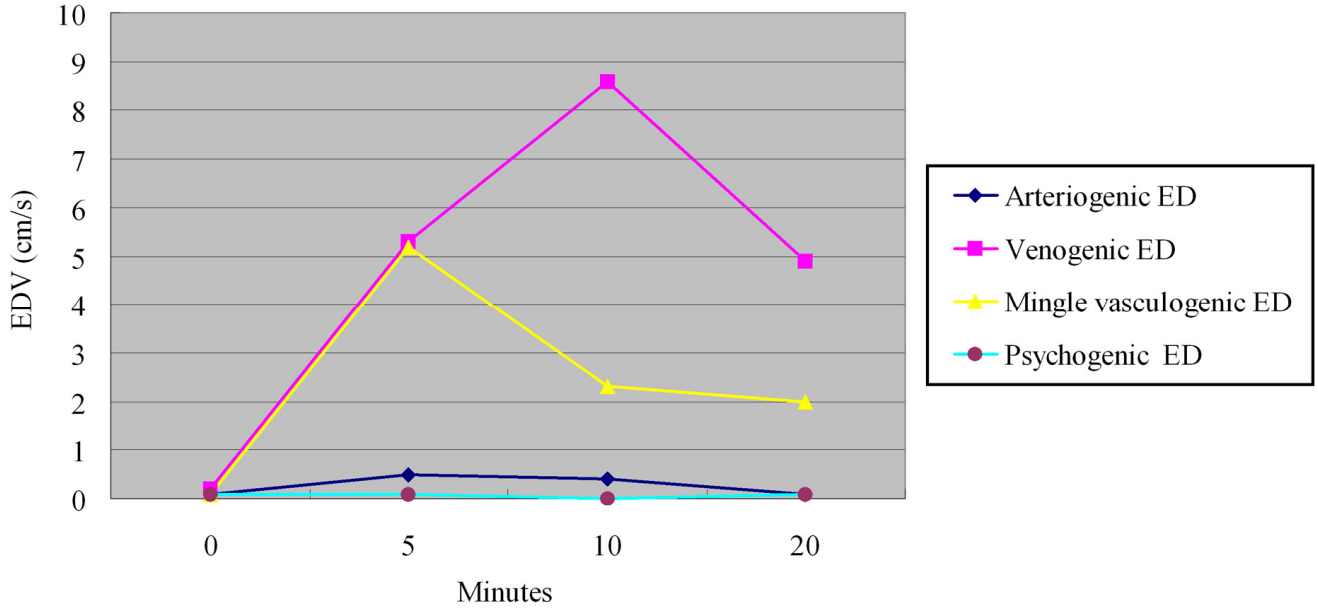

Figure 2. Dynamic observation of EDV levels after PGE1 treatment in vasculogenic ED. The EDV levels at 10 and 20 min after treatment in mingle vasculogenic ED are significantly lower than them in venogenic ED.

duplex ultrasonography to diagnose suspected vasculogenic ED, this technique has been developed as a standard method for quantitative assessment of hemodynamics changes after penile erection (Migaleddu

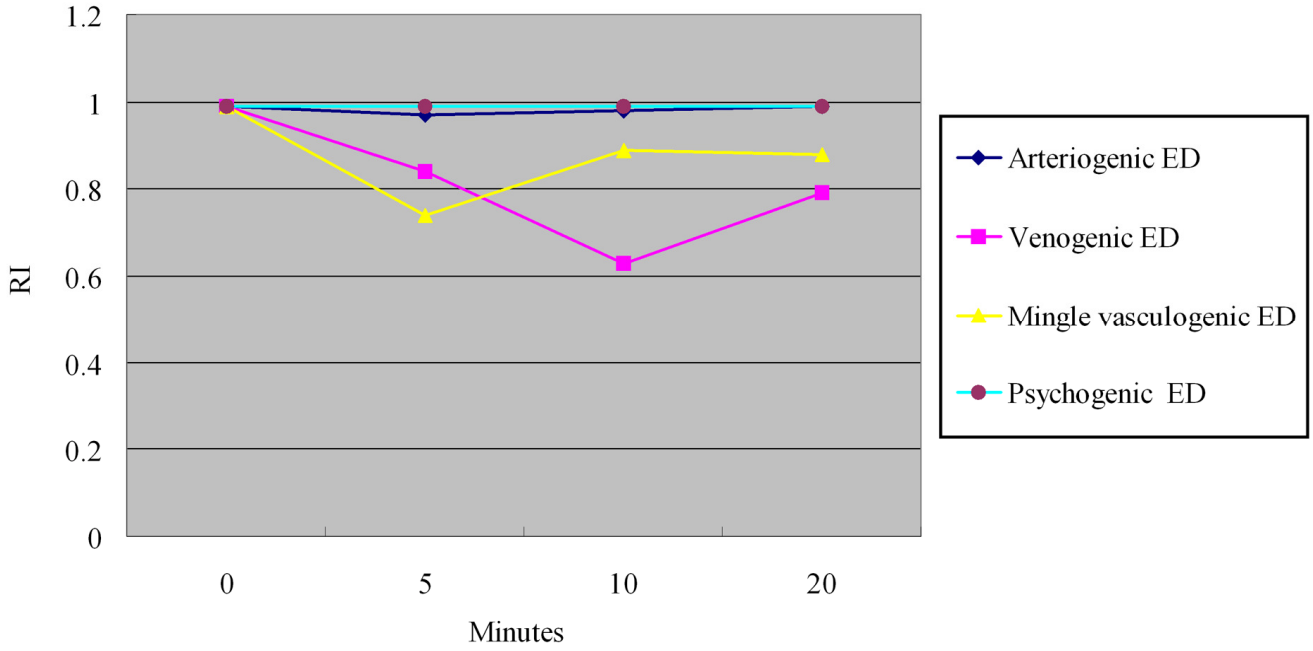

Figure 3. Dynamic observation of RI after PGE1 treatment in vasculogenic ED. The RI values are consistently lower than 0.9 in both venogenic ED and mingle vasculogenic ED at all time points.

et al., 2000). At present, it is well-accepted that the application of color duplex ultrasonography to detect the hemodynamics changes after intracavernous injection of vasodilator drugs is the first-line option to evaluate vascular function of penis and to distinguish arteriogenic ED and venogenic ED.

Penile erection is a complex neurovascular phenomenon that may be affected by hypercholesterolemia, atherosclerotic vascular occlusive disease, veno-occlusive dysfunction and cavernosal fibrosis (Siroky and Azadzoi, 2003). Vasculogenic abnormalities are one of the most common causes of ED. Several parameters have been used to quantify penile blood flow including peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI). Among these indexes, the peak systolic velocity is the most commonly used. It is generally agreed that a PSV less than 25 cm/s indicates arterial insufficiency. This criterion is used in this study to diagnose arteriogenic ED. The PSV levels at 5, 10 and 20 min after PGE1 intracavernous injection are all less than 25 cm/s in arteriogenic ED, which indicates this criterion is reliable for diagnosis of arteriogenic ED. Interestingly, we found that PSV levels in venogenic ED at all time points are dramatically lower than them in psychogenic ED, which means veno-occlusive dysfunction may negatively affect blood flow in corpus cavernosum.

Veno-occlusive dysfunction (venous leakage) is an important form of vasculogenic ED, namely venogenic ED. The main index for diagnosis of venogenic ED is EDV. In the presence of normal arterial function, persistent EDV higher than 5 cm/s measured by color duplex ultrasonography usually indicates veno-occlusive dysfunction. In this study, we designed to dynamically measure penile hemodynamics changes at different time points after PGE_1 treatment. The result shows that EDV value in venogenic ED achieved maximal value at 10 min after PGE_1 intracavernous injection. This suggests that measurement of EDV at 10 min after PGE1 treatment may have high sensitivity to diagnose venogenic ED. Moreover, the EDV levels at 10 and 20 min after treatment in mingle vasculogenic ED are significantly lower than them in venogenic ED (Figure 2), which indicates that reduced blood flow caused by cavernosal artery insufficiency in mingle vasculogenic ED could attenuate veno-occlusive dysfunction and lead to decreased EDV.

RI is another index for diagnosis of venogenic ED. The RI value is less than 0.9 in 95% venogenic ED patients, so 0.9 is generally accepted to be the cutoff value for diagnosis of venogenic ED. In this study, the RI values in venogenic ED at different time points after PGE1 treatment are consistently lower than 0.9, which demonstrates that this cutoff value shows excellent specificity and sensitivity for diagnosis of venogenic ED. In addition, the lowest RI value occurs 10 min after PGE1 treatment in venogenic ED, which means the RI values at 10 min after treatment may have high sensitivity to diagnose venogenic ED. Several vasoactive drugs have

been used to induce penile erection for color duplex ultrasonography test, such as papaverine, α-adrenergic blockers (phentolamine) and PGE_1. In this study, we injected PGE_1 into corpus cavernosum to induce erection, and found PGE_1 had less side-effect, rarely resulted in priapism and other serous complications.

Conclusion

In this study, we dynamically observed hemodynamic changes in vasculogenic ED by monitoring the blood flow velocity and veno-occlusive abnormalities in corpus cavernosum after intracavernous injection of PGE. We believe this study may help us better understand the hemodynamic features in different subtypes of vasculogenic ED.

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