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Time-effect of penile color duplex Doppler ultrasound for diagnosing vascular erectile dysfunction

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Abstract

Introduction: This study aimed to explore the time-effect of color duplex Doppler ultrasound (CDDU) in the diagnosis of vascular erectile dysfunction (ED). **Material and methods**: Using a self-control study, we included patients who underwent penile CDDU and cavernosography in our hospital. We compared the arterial peak systolic velocity (PSV) of CDDU among different intervals for the diagnosis of arterial ED. We included 357 patients who were under consideration for vascular ED. **Results**: We found significant differences in all the pairwise comparison of PSV in the 1st (0–5 min), 2nd (6–10 min), 3rd (11–15 min), and 4th (16–20 min) 4 intervals after the injection of prostaglandin E1 ($p<0.001$), except the 11–15 min vs. the 16–20 min interval ($p=0.387$). Using cavernosography, 294 patients were diagnosed with venous ED. Compared with other intervals, the diagnosis of CDDU 11–15 min after the intracavernous injection of 20 ug prostaglandin E1 (PGE1) had the best consistency with cavernosography (Kappa=0.761; $p<0.001$). Compared with other intervals, CDDU at 11–15 min had the highest specificity (93.65%), the highest Youden index (0.85), positive likelihood ratio of 14.46, positive predictive value of 98.54%, negative predictive value of 71.08% and a coincidence rate of 92.16%. **Conclusions**: Our findings support the increased utilization of CDDU for the diagnosis of both arterial and venous ED. The diagnosis at 11–15 min after intracavernous injection of PGE1 is accurate and stable, which would help to simplify the process and shorten the time of CDDU.

Keywords: color duplex Doppler ultrasound; erectile dysfunction; time-effect; cavernosography

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [1]. Epidemiological data have shown a high prevalence and incidence of ED worldwide [2]. As a male sexual dysfunction, ED may affect physical and psychosocial health and may have a significant impact on the quality of life for sufferers and their partners. Moreover, ED can be the first presenting symptom of multi-organ endothelial dysfunction. The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic [2].

Although phosphodiesterase-5 inhibitors (PDE5i) have been utilized as the first-line therapy for ED, in clinical practice 20–30% of patients with ED do not adequately respond to orally-administered PDE5i [3,4]. Objective vascular testing that provides a physiological diagnosis may help direct appropriate therapy [5]. Certain comorbidities associated with one or more risk

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factors may require further hemodynamic investigation, and in selected cases, this can be followed by an invasive penile angiographic evaluation [5]. Color duplex Doppler ultrasound (CDDU), first described by Lue et al [6], is an objective and reliable diagnostic method for documenting penile hemodynamics. CDDU of the penis can also help differentiate psychogenic from organic ED [5]. Veno-occlusive mechanisms and arterial insufficiency can be assessed using peak systolic velocity (PSV), end-diastolic volume (EDV) and spectral patterns on pulsed wave Doppler ultrasound examinations [7].

The lack of standardized measures often prevents the accurate clinical diagnosis of patients undergoing hemodynamic assessment of the penis using CDDU [5]. This also leads to variability in data interpretation when comparing the results among various centers. Sikka et al established standard operating procedures in 2012 and recorded data for arterial PSVs, EDVs, and resistance indices of the corpus cavernosum within 30 min after intracavernous injection (ICI) with prostaglandin E1 (PGE1) [5]. However, it is not clear which interval was the most suitable for diagnosis. Therefore, this study aimed to identify the optimal time interval for the diagnosis of ED after ICI, using CDDU.

Materials and methods

We employed a self-control study design. Because cavernosography is the most commonly used technique and can evaluate the venous occlusion function of the corpus cavernosum [8], we used the diagnostic capability of cavernosography as the gold standard to explore the time-effect of the CDDU. Informed consent was obtained from all participants and confidentiality was ensured. The study was approved by the local Ethics Committee.

Subjects

Patients with indication for CDDU and cavernosography were included in study if they 1) scored <22 on the 5-item version of the International Index of Erectile Function (IIEF-5) questionnaire thereby confirming ED; 2) could not take or failed to respond to PDE5i, which is required to determine the cause of the disease before treatment, or expected complete healing without the use of medicines; 3) did not suffer from neurogenic ED; 4) did not suffer from drug-induced ED; 5) did not suffer from hypertension, hyperlipidemia or liver and chronic kidney dysfunction; 6) did not suffer from severe psychological problems; 7) did not have an allergic reaction to the contrast medium (Ioversol); and 8) visited our clinic between June 2014 and March 2017.

Neurogenic ED was diagnosed by identifying a history of spinal cord lesions or pelvic surgery [9]. To evaluate the patients' psychological issues, we used a Chinese version of the Symptom Checklist-90 [10-12], a multidimensional symptom self-reporting inventory composed of 90 items, each rated on a 5-point scale of distress from 0 (not at all) to 4 (extremely) [13]. The global severity index (GSI) provided a summary score for the number and intensity of psychological distresses, and was determined by adding raw scores from all dimensions divided by the total number of items (90) [14]. If a patient's GSI was >2, he was referred to a psychologist and excluded from the study.

CDDU

With the patient in a supine position, a physician with 10 years' experience performed ICI of 20 ug PGE1 with a 27G needle [15].Dynamic CDDU was performed in all subjects by Philips IU22 machine using a linear transducer L12-5MHz. The sonographer gently lifted the patient's penis upwards toward the pubic symphysis, placed the probe at the crus of the penis and obtained an ultrasonographic B-mode image of the bilateral origin of the cavernous artery. The changes in arterial PSVs, EDVs and resistive indices in the 1st (0–5 min), 2nd (6–10 min), 3rd (11–15 min), and 4th (16–20 min) intervals after PGE1 injection were recorded. The PSV was calculated as the mean PSV value of the left and right arteries in each patient. After pharmacological stimulation, the diagnosis of arterial ED was made if a PSV value of <25 cm/s was obtained [7]. The diagnostic standard for venous ED using CDDU was considered PSV $\geq$ 25 cm/s, EDV $\geq$ 5 cm/s and RI $\leq$ 0.8 [16,17].

Cavernosography

After performing CDDU, patients underwent cavernosography within the next 72 h. The nurse performed the puncture with a 24G needle in the left corpora cavernosum anterior coronary sulcus, 1-2 cm from the proximal segment at the back side of the 10–11 o'clock position of the penis. When the erection hardness score [18] attained 3, the nurse injected 320 mg/ml dilute loversol (30%) into the penis at a rate of 30–60 ml/min. An X-ray cavernosograph using a Shimadzu Flexavision multi-function digital X-ray machine (75kv, 4mAs) was then performed on all patients with an erection hardness score of 4. All procedures were conducted by a nurse and physician. All images were diagnosed by a physician according to the vascular anatomy of the penis [19].

Assessment

During CDDU, the changes in the arterial PSV, EDV, and RI at four different intervals: 0–5 min, 6–10 min, 11–15 min, and 16–20 min after the injection of PGE1.The diagnoses obtained using cavernosography and CDDU at the different time intervals were compared.

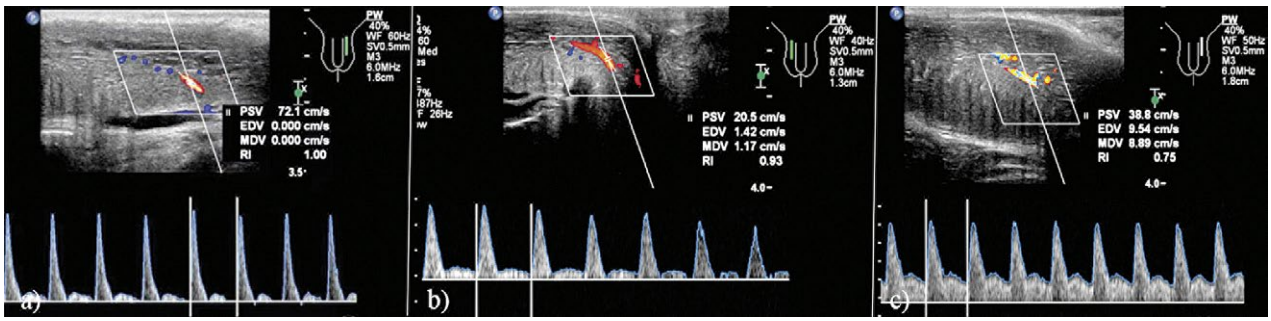

Fig 1. a). The normal image of a patient with PSV of 72.1 cm/s; b) The image of arterial ED with PSV of 20.5 cm/s; c) The image of venous ED with PSV of 38.8 cm/s, EDV of 9.54 cm/s and RI of 0.75.

Statistical analysis

We analyzed the data using the Statistical Package for the Social Sciences, Version 11.0 (SPSS, Chicago, IL). Quantitative data were expressed as the mean ± standard deviation. We performed analysis of variance for univariate repeated measurement data to compare the PSVs among the four CDDU intervals. If statistical significance was found, we performed a Student-Newman-Keuls test for pairwise comparisons. The consistency between the two tests was assessed using Cohen's kappa coefficient and Youden index. The kappa value was interpreted as follows: over 0.75, excellent; 0.40 to 0.75; fair to good, and below 0.40; poor [20]. $p<0.05$ was considered to be statistically significant. The sensitivity (%), specificity (%), Youden index, positive and negative likelihood ratios, positive and negative predictive values (%) and the coincidence rate (%) of CDDU during the 4 intervals were also analyzed.

Results

In total, 372 patients were enrolled to undergo CDDU and cavernosography. Seven patients refused to undergo the tests and 8 patients were found to be allergic to loversol and were excluded. Finally, 357 patients with ED were included in the study. After undergoing CDDU and cavernosography, 10 patients (2.8%) had foreskin hematomas, 3 (0.8%) had priapism and 15 (4.2%) experienced pain. In figure 1 are exemplified 3 different ED cases (normal CDDU parameters, venous and arterial ED).

The patient characteristics are detailed in Table I.

The means PSV in the 4 intervals were 19.3±3.5 for 1–5 min, 24.9±3.7 for 6–10 min, 31.2±5.1 for 11–15 min, and 30.5±4.8 for 16–20 min. There were significant differences in the PSVs values obtained in the 4 intervals ($p<0.001$). Significant differences were also found in all pairwise comparisons of the 4 intervals ($p<0.001$), with the exception of the 11–15 min vs. 16–20 min pairing ($p=0.387$) (Table II).

Table I. Baseline characteristic of included patients

Characteristic	
Age (years)	31.05±6.37
Course of disease (years)	4.16±1.34
Marriage age (years)	6.35±5.53
Smoking history	282(79)
Drinking history	277(77.6)
Scores of IIEF-5	11.21±5.59
GSI of SCL-90	0.63±0.47
Time for penis began erection (min)	3.51±1.62
Time to reach maximum erection (min)	11.23±1.14

The results are expressed as mean±standard deviation or number (%). IIEF-5, 5-item version of the International Index of Erectile Function; SCL-90, Symptom Checklist 90; GSI, Global severity index.

Table II. Comparison of PSV between the four intervals in color duplex Doppler ultrasound (Student-Newman-Keuls)

	Mean difference	q	p
1-5 min vs. 6-10 min	5.6	12.39	<0.001
1-5 min vs. 11-15 min	11.9	30.23	<0.001
1-5 min vs. 16-20 min	11.2	29.31	<0.001
6-10 min vs. 11-15 min	5.3	11.27	<0.001
6-10 min l vs. 16-20 min	5.6	12.39	<0.001
11-15 min vs. 16-20 min	-0.7	1.67	0.387

As shown in Table III, 82.4% (284/357) of patients had venous ED. The agreement between 6-10 min interval and 11-15 min interval was good. Table IV shows detailed CDDU performances in all 4 intervals. Compared with the other intervals, CDDU at 11–15 min after ICI had the highest specificity (93.65%), Youden index (0.85), positive likelihood ratio (14.46), positive predictive value (98.54%), negative predictive value (71.08%), and coincidence rate (92.16%).

Table III. Diagnosis of ED with color duplex Doppler ultrasound (CDDU) and cavernosography in 4 intervals

		Cavernosography		Kappa	P
CDDU		+	-		
1-5 min	+	282	56	0.097	0.024
	-	12	7		
6-10 min	+	277	22	0.612	<0.001
	-	17	41		
11-15 min	+	270	4	0.761	<0.001
	-	24	59		
16-20 min	+	269	19	0.591	<0.001
	-	25	44		

Table IV. Comparison of diagnostic effectiveness of color duplex Doppler ultrasound in four intervals

	1-5 min	6-10 min	11-15 min	16-20 min
Sensitivity (%)	95.92	94.22	91.84	91.50
Specificity (%)	11.11	65.08	93.65	69.84
Youden index	0.07	0.59	0.85	0.61
Positive likelihood ratio	1.08	2.70	14.46	3.03
Negative likelihood ratio	0.38	0.09	0.09	0.12
Positive predictive value (%)	83.43	92.64	98.54	93.40
Negative predictive value (%)	36.84	70.69	71.08	63.77
Coincidence rate (%)	80.95	89.08	92.16	87.68

Discussion

For the correct diagnosis of vascular ED, CDDU is a useful and simple tool for differentiating organic from psychological causes. As far as we know, this is the first study to demonstrate the time-effect of CDDU in the diagnosis of vascular ED.

In the present study, the mean age of the included patients was 31.05±6.37 years, which implies that most patients with vascular ED are young Chinese adults. Similarly, in a cross-sectional real-life study among men seeking initial medical help for new-onset ED, one in four patients were younger than 40 years, with almost 50% of the young men complaining of severe ED [21]. Our results showed that PSVs become stable 11–20 min after ICI, which is the best time interval for diagnosing arterial ED using CDDU.

Cavernosography revealed a high rate (82.4%) of venous ED among the included patients, which is similar to the rate reported in a previous study conducted by Yafi et al [22]. For the diagnostic conformance of venous ED using cavernosography and CDDU, the 11–15 min interval after ICI had the highest Kappa value (0.761), representing excellent agreement. We found that all interval sensitivities were >90. Moreover, the 6–10 and 11–15 min intervals also had the lowest negative likelihood ratio (0.09). Compared to other intervals, CDDU at 11–15 min after ICI had the highest specificity and the best coincidence. Because the pressure inside the corpus cavernosum is small, EDVs more than 5 cm/s in 1–5 min lead to higher sensitivities for venous ED. However, at the same time, the possibility of false positives is high. Thus, the CDDU results indicated that the highest accuracy is attained for CDDU performed 11–15 min after ICI.

However, it is noteworthy to mention that the veno-occlusive mechanism may not function properly in some patients with arterial insufficiency thereby decreasing the intracavernous pressure and preventing closure of the emissary connections [7]. Kropman et al reported that many patients present with combined arterial and venous ED. In the subset of patients with significant arterial ED, the specificity of EDV correlated with pathologic venous ED significantly decreases [23].

Cavernosography uses radiological imaging to both diagnose and locate the sites of venous leaks in patients. However, because of its invasiveness, its utility is limited [24]. For this reason, in our opinion, CDDU following ICI with a vasodilator agent remains the most reliable and the least invasive test for the determination of the etiology of ED being a minimally invasive and accurate method for evaluating penile hemodynamics [17]. Cavernosonometry, cavernosography of cavernous bodies and selective pudental arteriography are advanced and rather invasive diagnostic tests that should be reserved for cases that cannot be definitively diagnosed using CDDU [7,25].

For patients with ED who cannot take PDE5i or fail to respond to PDE5i, in which the cause of the disease

must be determining before treatment, or for those patients who expect complete healing without the use of medicines, CDDU after ICI is recommended for further diagnostic confirmations and prognosis determinations. Our findings of time-effects while using CDDU in the diagnosis of both arterial and venous ED could make CDDU more convenient and accurate. It would help to avoid unnecessary waiting, improve its accuracy and be convenient for both medical staff and patients.

Strengths and limitations

Our study had some strengths. First, all included patients had undergone both CDDU and cavernosography assessments and it was a self-control design. Second, we provided a large sample size of patients with ED who either could not take PDE5i or failed to respond to PDE5i, or expected complete healing without the use of medicines. The findings of our study should also be noted in light of the following limitations. First, penile measurements might be affected by multiple factors including the degree of penile tumescence or rigidity, penile curvature, subjective variability in stretching and operator technique, although a single experienced physician performed all measurements. Second, single center data may lead to Berkson's bias and has an impact on its external validation. Third, the majority of our included subjects were young adults, which restricted the extrapolation of this study. Finally, while we used the cavernosography results as the standard for venous CDDU, false positive and negative results could occur.

Conclusion

Our findings demonstrated that CCDU is effective for the correct diagnosis of ED and support the increased utilization of CDDU for the diagnosis of both arterial and venous ED. A diagnosis of ED 11–15 min after ICI is accurate and stable which helps to simplify the process and shorten the CDDU time. Further studies are required to confirm the time-effect of CDDU in the diagnosis of vascular ED.

Conflict of interest: none

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