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## ORIGINAL ARTICLE

# The application of color Doppler flow imaging in the diagnosis and therapeutic effect evaluation of erectile dysfunction

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We aim to investigate the correlations between hemodynamic parameters, penile rigidity grading, and the therapeutic effects of phosphodiesterase type 5 inhibitors using color Doppler flow imaging after intracavernosal injection in patients with erectile dysfunction. This study involved 164 patients. After intracavernosal injection with a mixture of papaverine (60 mg), prostaglandin $E_1$ (10 μg), and lidocaine (2%, 0.5–1 ml), the penile vessels were assessed using color Doppler flow imaging. Penile rigidity was classified based on the Erection Hardness Score system as Grades 4, 3, 2 or 1 (corresponding to Schramek Grades V to II). Then, the patients were given oral sildenafil (50–100 mg) and scored according to the International Index of Erectile Function (IIEF-5) questionnaire. The number of patients with penile rigidities of Schramek Grades II to V was 14, 18, 21, and 111, respectively. The IIEF-5 score was positively correlated with the refilling index of the penile cavernosal artery ($r = 0.79$, $P < 0.05$), the peak systolic velocity ($r = 0.45$, $P < 0.05$), and penile rigidity ($r = 0.75$, $P < 0.05$), and was negatively correlated with the end diastolic velocity ($r = -0.74$, $P < 0.05$). For patients with erectile dysfunction, both the IIEF-5 score after sildenafil administration, which is correlated with penile rigidity, and the hemodynamic parameters detected using color Doppler flow imaging may predict the effects of phosphodiesterase type 5 inhibitor treatment and could provide a reasonable model for the targeted-treatment of erectile dysfunction.

## INTRODUCTION

Targeted-treatment for erectile dysfunction (ED) is convenient for both patients and physicians. The emergence of phosphodiesterase type 5 inhibitor ($PDE_{5i}$) is a revolutionary advance in the treatment of ED.[1] This treatment is simple and practical, and the clinical efficacy of nonselective treatment for ED has improved from 20%–30% to 60%–80%.[2,3] Despite this, ED can be attributed by a variety of factors, and each patient may have different and specific needs. Therefore, a suitable strategy for diagnosis and treatment is still demanded for patients who do not respond to $PDE_{5i}$ treatment.

The combination of color Doppler flow imaging (CDFI) parameters and the Schramek grading system provides a reasonable model for the diagnosis and targeted-treatment of ED. CDFI can assess whether blood is moving toward or away from the probe and its relative velocity via the Doppler effect. It can detect hemodynamic parameters such as the peak systolic velocity (PSV), end diastolic velocity (EDV), and refilling index (RI) of the penile cavernosal artery. Meanwhile, Schramek grading is a valid evaluation system for penile rigidity. This study sought to investigate the correlations between CDFI hemodynamic parameters and penile rigidity grading during CDFI after intracavernosal injection (ICI) as well as their ability to predict the therapeutic effect of $PDE_{5i}$.

## MATERIALS AND METHODS

A total of 164 patients with ED were recruited from our institution between December 2002 and December 2009. First of all, a detailed history of the patients was compiled, including the cause of disease, sexuality, occurrence of trauma and/or surgery, presence of diabetes or hypertension, and the use of erectile-related drugs. Every patient received comprehensive physical examinations performed by an experienced physician. Next, CDFI was performed after ICI with a vasoactive agent, and penile rigidity was assessed concurrently. Following this, all patients received oral $PDE_{5i}$ (sildenafil) and completed the IIEF-5 scoring questionnaire. The follow-up time was 6 to 49 months to assess the therapeutic effect of vasoactive agent treatment. All patients gave written informed consent, and the procedures were reviewed and approved by the Medical Ethics Committee of the hospital.

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### CDFI examination and rigidity grading[4]

Patients were placed in a supine position and remained at rest at room temperature, and were encouraged to be physically and mentally relaxed while viewing erotic pictures. The base of the penis was constricted by a rubber band with an appropriate degree of tension. A mixture of papaverine (60 mg), prostaglandin $E_1$ ($PGE_1$; 10 μg) and lidocaine (2%, 0.5–1 ml) was dissolved in normal saline (2 ml) and injected into the base of penis with a fine needle to reach into the cavernosum. After ICI, the base of the penis was massaged for 30 s, then the rubber band was removed. CDFI was performed by a professional sonographer in our hospital under the supervision of Doctor Xuan, using a Doppler ultrasonic diagnostic apparatus (Acuson l28, USA) with a probe frequency of 7.5 MHz, sampling volume of 2 ml, and ultrasound beam and vessel angle within 60°. The probe was placed on the ventral side of the base of the penis, and the PSV, EDV, RI of the penile cavernosal artery were consecutively measured at intervals of 1–3 min, 3–5 min, 5–10 min, 10–15 min, 15–20 min, and 20–30 min. The PSV, EDV, and RI of the dorsal artery and the velocity (V) of the deep dorsal vein were also measured at the same time points.

Meanwhile, during the CDFI measurement, penile rigidity was also observed. Based on the Schramek grading system (1990),[5] the rigidity was classified from Grade V (complete erection) to Grade I (no response). Patients were considered as Schramek Grade V when an Erection Hardness Score (EHS) of Grade 4 lasted for more than 10 min, and Grades IV, III, and II when EHS Grades 3, 2, and 1, respectively, lasted for more than 10 min. During each measurement interval, 7 data points were collected, including the PSV, EDV, and RI for both the penile cavernosal artery and the dorsal artery, and the velocity (V) of the deep dorsal vein. The mean values were analyzed then. Patients with a Schramek grading <5 after the first injection were reexamined in 1 week. The outcome with a higher grading was used for statistical analysis.

### CDFI, IIEF-5 criteria, and statistical analysis[6–8]

The CDFI was performed after the oral administration of sildenafil citrate. A dosage of 50 or 100 mg was used depending on the patient's needs.[9] The cut-off values for the penile cavernosal artery hemodynamics were defined as: PSV >25 cm $s^{-1}$, EDV <5 cm $s^{-1}$, and RI >0.90. Patients were considered normal when all the three cut-off standards were met or abnormal when any of the cut-off standards was not met.[10] Criteria for IIEF-5 scoring were set as follows: a score of 22–25 was considered normal; 12–21 indicated mild ED; 8–11 indicated moderate ED, and a score of 5–7 was considered severe ED. All analyses were performed using SPSS 16.0* software (IBM). Quantitative data were expressed as the mean ± standard deviation. Statistical methods including $t$-tests, $\chi^2$-tests, $F$-tests, and a new

multiple range method were also applied. Any $P < 0.05$ was considered statistically significant.

### RESULTS

The mean age of the subjects was 44 years old (range 22–71 years old) with a disease course ranging from 6 months to 10 years (mean 21 months). After ICI, the patients were classified into four groups based on penile rigidity. To this end, 111 patients were classified as Schramek Grade V, 21 patients as Grade IV, 18 as Grade III, 14 as Grade II, and no patients were Grade I in the current study. The PSV, EDV, and RI of the penile cavernosal artery showed statistically significant differences across the four groups ($P < 0.001$, **Table 1**). Moreover, for each pairwise comparison, the RI showed a statistically significant difference ($P < 0.05$), and was closely related to the elastic pressure around the blood vessel to assess penile rigidity (**Table 2**). All patients were given oral sildenafil (50–100 mg), with a minimum recommended dose of 50 mg and the dosage adjusted according to the parameters of penile blood flow, penile rigidity, and patient compliance. After oral sildenafil administration, the mean IIEF-5 scores for patients with rigidity Grades V, IV, III, and II were 22.04 ± 2.94, 16.33 ± 4.89, 9.67 ± 1.75, and 5.79 ± 0.89, respectively ($P < 0.0001$, **Tables 1** and **2**).

Rigidity grading and hemodynamic parameters after ICI were statistically significantly correlated (**Table 3**). Moreover, both of them were also statistically significantly correlated with the IIEF-5 score after $PDE_{5i}$ treatment (**Table 3**). Specifically, the RI and PSV of the penile cavernosal artery show positively correlation with the IIEF-5 score ($r = 0.79$, $P < 0.05$), and the rigidity grading also positively correlated with the IIEF-5 score ($r = 0.75$, $P < 0.05$).

### DISCUSSION

Targeted-treatment for ED, also known as goal-oriented therapy,[11] has been established and has higher success rates, fewer complications, lower costs, and greater satisfaction for patients and their sexual partners.[12] And a better understanding of the etiology and pathophysiology of ED could contribute to improve the targeted-treatment efficacy. Based on etiology, symptoms, and patient expectations, the current therapeutic process of ED may be developed into a model routine for target-oriented outcomes. The initial examination for an ED diagnosis includes the history of present illness, physical examination, serum sex hormone examination (Testosterone, Prolactin, *etc.*), and CDFI. Treatment strategies provided to the patients include sex behavior therapy, oral medication, a vacuum constriction device (VCD), ICI, vascular surgery to treat physical causes, and implantation of a penile prosthesis.[13] For patients with ED caused by vascular abnormalities, invasive vascular examination can be performed if desired by the patient. If these patients refuse further surgical treatment, ICI,

**Table 1: Comparison of rigidity-related parameters after vasoactive agent injection and IIEF-5 score after oral administration of $PDE_{5i}$**

| Rigidity | n | After ICI | | | | | | | IIEF-5 |
|---|---|---|---|---|---|---|---|---|---|
| | | Cavernosal artery | | | Dorsal artery | | | Deep dorsal vein | |
| | | PSV | EDV | RI | PSV | EDV | RI | V | |
| V | 111 | 38.47±8.54 | 2.17±1.03 | 0.94±0.03 | 51.56±7.61 | 10.37±2.88 | 0.80±0.06 | 8.58±2.66 | 22.04±2.94 |
| IV | 21 | 26.63±4.22 | 5.23±1.34 | 0.80±0.05 | 49.28±8.86 | 10.54±2.41 | 0.78±0.06 | 8.64±2.36 | 16.33±4.89 |
| III | 18 | 28.38±2.40 | 6.63±1.53 | 0.77±0.04 | 52.22±8.90 | 11.12±4.37 | 0.79±0.07 | 9.25±2.64 | 9.67±1.75 |
| II | 14 | 20.06±3.83 | 7.10±2.22 | 0.65±0.07 | 47.89±4.80 | 11.41±2.92 | 0.76±0.05 | 10.25±2.32 | 5.79±0.89 |
| F | | 40.80 | 128.14 | 365.17 | 1.44 | 0.73 | 1.43 | 1.94 | 93.26 |
| P | | <0.0001 | <0.0001 | <0.0001 | 0.23 | 0.54 | 0.24 | 0.13 | <0.0001 |

Note: (1) the numbers shown are mean±s.d.; (2) Statistical method: ANOVA; (3) Units for PSV, EDV and Velocity: cm $s^{-1}$. PSV: peak systolic velocity; EDV: end diastolic velocity; RI: resistance index; V: velocity; ANOVA: analysis of variance; IIEF-5: international index of erectile function-5; $PDE_{5i}$: phosphodiesterase type 5 inhibitor; s.d.: standard deviation; ICI: intracavernosal injection

VCD, and oral medication can still be used to maintain satisfactory sexual intercourse. Invasive diagnostic examinations, such as corpus cavernosum imaging or selective internal pudendal arteriography, are avoided with goal-oriented therapy.[14]

Regardless of the cause, ED ultimately results from an inability to maintain penile blood supply, leading to a failure to hold a spontaneous erection.[15] Penile erection requires normal physical functioning and depends on the blood supply in the corpus cavernosum, the normal function of sinus endothelial cells and smooth muscles, and the correct closure mechanism of the penile tunica albuginea.[16] Penile erection is also regulated by nonadrenergic and noncholinergic signal transduction.[17] ICI with a vasoactive agent allows the blood supply to the corpus cavernosum to closely approximate that of normal physiological conditions, while the response is related to the dose of vasoactive agent used.[18] In 1982, Virag[19] first reported treatment with papaverine ICI for patients with ED, and in 1986, Ishii *et al.*[20] introduced $PGE_1$ ICI to these patients. The clinical efficacy of both treatments was 50%–80.3%.[21] In our ICI study, we included lidocaine (2%, 0.5–1 ml) in the treatment to reduce the incidence of pain, while the doses of papaverine (60 mg) and $PGE_1$ (10 µg) were consistent with the routine dosage.[22] The mechanism of $PGE_1$ involves its binding to the $PGE_1$ receptor on the smooth muscle cells of the corpus cavernosum, thereby activating adenylate-activating enzymes to convert ATP to cAMP, which increases intracellular cAMP but decreases intracellular calcium, leading to smooth muscle relaxation. Papaverine is a nonspecific PDE inhibitor of all $PDE_{5,3,2}$ involving in both the cGMP/PKG and cAMP/PKA pathways,[23] thus inhibiting the degradation of cGMP and cAMP, which results in decreased calcium concentration in the cytoplasm and smooth muscle relaxation.[24] The combined mechanism of $PGE_1$ and papaverine is similar to that of $PDE_{5i}$, leading to smooth muscle relaxation in the corpus cavernosum.[25,26] In this study, we did not choose the commonly used vasoactive agent phentolamine, because its method of action is less similar to the physiological mechanism of an erection. Phentolamine acts as an $\alpha_1$-receptor antagonist, inhibiting

both adrenaline and norepinephrine, which results in a reduction in sympathetic tension. This effect acts directly on the vascular smooth muscle cells and increases blood flow to the penile artery, resulting in a penile erection. This mechanism is not in compliance with the physiological mechanism of erection regulated by nonadrenergic and noncholinergic signal transduction[27] or oral $PDE_{5i}$. The reaction caused by the intracavernosal vasoactive agent injection combining $PGE_1$ and papaverine provides blood supply to the corpus cavernosum, similar to what happens under physiological conditions. Thus, the penis reaches an erect condition in a manner similar to the physiological mechanism (**Figure 1**[28]), excluding the effect of mental factors on penile erection. As a result, the accompanying CDFI examination can better reveal the structural and functional changes of the vascular tissue in the corpus cavernosum in patients with ED.

Penile rigidity can be graded based on both rigidity and the ability for vaginal penetration, which makes it practical for the diagnosis and treatment of ED.[29] The Schramek[5] grading system (with a total of five grades) and the EHS grading system[30] (with a total of four grades) can be applied for penile rigidity classification. The EHS Grades 1, 2, 3, and 4 correspond to Schramek Grades II, III, IV, and V, respectively. Because the Schramek grading system is more detailed, we have been using this system for the CDFI examinations since 1995. In 1989, Quam *et al.*[31] used CDFI for the diagnosis of ED, and showed that the use of CDFI for vascular ED screening was associated with high specificity and sensitivity. The most significant findings between patients with ED and healthy individuals were the differences in PSV, EDV, and RI of the penile cavernosal artery after ICI,[32] which concured with our results.

In our study, we combined the results from CDFI with the penile rigidity findings, and showed that differences in penile rigidity after ICI were associated with variable hemodynamics. The PSV, EDV, and RI of the penile cavernosal artery varied significantly with the rigidity grades ($P < 0.05$).[33] The difference between the CDFI parameters after ICI and the Schramek grading provides a basis for diagnosis.

Generally, PSV represents the blood supply function of the penile cavernosal artery, and EDV represents the venous function of the penile corpus cavernosum.[34] Moreover, PSV or EDV reflects some aspects of the function of the penile cavernosal artery and venous echo status. RI is a value calculated by the equation (PSV-EDV)/PSV, and reflects the vascular resistance in the vessels, which is related to various factors including the peripheral pressure of the vessels, blood supply to the corpus cavernosum, blood reflux, and the overall status of corpus cavernosum function.[35] Our results revealed a statistically significantly

**Table 2: Intergroup comparison of PSV, EDV, and RI after vasoactive agent injection**

| Groups | *P* | | |
|---|---|---|---|
| Inter-comparison | PSV | EDV | RI |
| V-IV | <0.05 | <0.05 | <0.05 |
| V-III | <0.05 | <0.05 | <0.05 |
| V-II | <0.05 | <0.05 | <0.05 |
| IV-III | >0.05 | <0.05 | <0.05 |
| IV-II | <0.05 | <0.05 | <0.05 |
| III-II | <0.05 | >0.05 | <0.05 |

Note: statistics: rank sum test for multiple quantitative data. PSV: peak systolic velocity; EDV: end diastolic velocity; RI: resistance index

**Table 3: Correlations between hemodynamic parameters (PSV, EDV, and RI), rigidity grading, and IIEF-5 score**

| | Rigidity grading | | IIEF-5 | |
|---|---|---|---|---|
| | $r_s$ | P | $r_s$ | P |
| PSV | 0.67 | <0.001 | 0.45 | <0.001 |
| EDV | −0.79 | <0.001 | −0.74 | <0.001 |
| RI | 0.82 | <0.001 | 0.52 | <0.001 |
| IIEF-5 | 0.71 | <0.001 | - | |

Note: (1) values were considered statistically significant when *P*<0.05; (2) Statistical method: spearman rank correlation analysis. PSV: peak systolic velocity; EDV: end diastolic velocity; RI: resistance index; $r_s$: spearman correlation coefficient; IIEF-5: international index of erectile function-5
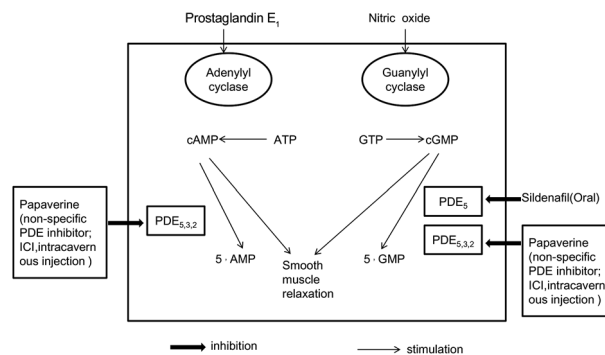


**Figure 1:** The erection-related signal transduction mechanism. $PDE_5$: 5-type phosphodiesterase; $PDE_{5,3,2}$: 5,3,2-type phosphodiesterase; ICI: intracavernous injection; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate.

positive correlation between RI and rigidity. Therefore, RI appears to be the most valuable hemodynamic parameter for evaluating penile rigidity. The use of RI to quantitatively diagnose ED may increase the consistency and accuracy of the ED grading diagnosis. After oral administration of $PDE_{5i}$ in patients with rigidity Grades V–II, the IIEF-5 scores were 22.04, 16.33, 9.67, and 5.79, respectively (**Table 1**). The corresponding score was statistically positively correlated with RI ($r = 0.79$, $P < 0.05$) and PSV ($r = 0.45$, $P < 0.05$), but statistically negatively correlated with EDV ($r = -0.74$, $P < 0.05$) (**Table 3**). The IIEF-5 scores for patients with Grade V were normal, because the mean PSV, EDV, and RI values decreased within the normal range. The EDV for Grades IV and III were 5 cm s$^{-1}$ greater than normal, and the EDV for Grade III was greater than that for Grade IV. The PSV and EDV for Grade II were abnormal. Thus, the IIEF-5 scores for Grades IV, III, and II were lower than normal (**Table 1**). The correlation of penile rigidity grading, RI, and IIEF-5 scores after oral administration of $PDE_{5i}$ suggests that penile rigidity and hemodynamic parameters after ICI might serve as predictive indicators for the therapeutic effect of $PDE_{5i}$, thereby improve the predictability and specificity of $PDE_{5i}$ treatment in clinical practice.

Consequently, for a patient with a chief complaint of ED, CDFI examination after ICI can be performed while the patient undergoes the basic diagnostic tests for penile rigidity, and hemodynamic parameters can be obtained before treatment. If the rigidity is lower than Schramek Grade V and the hemodynamic parameters are abnormal, the clinical effect of oral $PDE_{5i}$ administration is likely to be poor. Based on changes in PSV and EDV, an examination of the penile cavernosal artery or vein would be then recommended. If the hemodynamic parameters are normal and the rigidity is Schramek Grade V, $PDE_{5i}$ treatment can be recommended to the patient. For a patient who is reluctant to undergo the initial CDFI examination after ICI, $PDE_{5i}$ treatment can be recommended as the primary option. Based on the IIEF-5 score after $PDE_{5i}$ treatment, the patient's blood supply in the corpus cavernosum or endothelial cellular function can be evaluated. If the IIEF-5 score is not satisfactory after oral $PDE_{5i}$, CDFI examination after ICI will be recommended for further diagnostic confirmation and prognosis determination.

## CONCLUSION

As there is no existing model for the targeted-treatment of ED, we propose that combining CDFI examination and penile rigidity grading after ICI can provide a reasonable model for targeting the diagnosis and treatment of ED.

## AUTHOR CONTRIBUTIONS

XJX and GB contributed equally to this study and share first authorship; they designed the research study and participated in all procedures related to this research. CHH and JC provided financial support, selected the patients, and wrote the manuscript. CXZ, JC, CX, CHH, FDL and YP performed the color Doppler flow imaging examinations. CXZ and JC analyzed the data. CXZ drafted the figures. GM performed the statistical analyses.

## COMPETING INTERESTS

None.

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