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ORIGINAL ARTICLE

Sexual Function

# No effect of abstinence time on nerve electrophysiological test in premature ejaculation patients

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The nerve electrophysiological tests may differentiate the treatment of primary premature ejaculation (PPE) in our previous studies. However, no study verifies if the results will be affected by abstinence time. From January to December in 2016, fifty PPE patients ejaculated within 2 min and 28 control subjects were enrolled. The nerve electrophysiological tests, including dorsal nerve somatosensory evoked potential (DNSEP), glans penis somatosensory evoked potential (GPSEP), and penile sympathetic skin response (PSSR), were recorded before and immediately after ejaculation. The abstinence day was not correlated with the latencies of SEPs or PSSR neither in PE group ( $P = 0.170, 0.064, \text{ and } 0.122$ , respectively) nor in control group ( $P = 0.996, 0.475, \text{ and } 0.904$ , respectively). No statistically differences were found in the latencies of SEPs and PSSR before and after ejaculation in PE patients ( $P = 0.439, 0.537, \text{ and } 0.576$ , respectively) or control subjects ( $P = 0.102, 0.198, \text{ and } 0.363$ , respectively). Thus, abstinence time does not interfere with the nerve electrophysiological test, which is stable in determining the nerve function of PPE patients.

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**Keywords:** abstinence time; penile sympathetic skin response; postejaculation refractory time; premature ejaculation; somatosensory evoked potential

## INTRODUCTION

Premature ejaculation (PE) is one of the most common male sexual dysfunctions, which affects 20%–30% people worldwide.<sup>1,2</sup> PE is defined and updated by the International Society of Sexual Medicine (ISSM) in 2014 as follows: (1) ejaculation that always or nearly always occurs prior to or within approximately 1 min of vaginal penetration from the first sexual experience (primary PE or lifelong PE), or a clinically significant reduction in the latency time, often to approximately 3 min or less (secondary PE or acquired PE); (2) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (3) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.<sup>3</sup> Although the etiology of PE is still uncertain, the neurophysiology of ejaculatory function has been catching the attention of researchers. Previously, we have found that the latencies of the dorsal nerve somatosensory evoked potential (DNSEP), glans penis somatosensory evoked potential (GPSEP), and penile sympathetic skin response (PSSR) in primary PE (PPE) patients were shorter than those in control subjects, indicating a difference in the status of nerve pathways. The efficacy of local anesthetics was better in patients with abnormal latency of GPSEP and/or DNSEP than those with normal latency, while the efficacy of selective serotonin reuptake inhibitors (SSRIs) was better in patients with abnormal latency of PSSR than those with normal result.<sup>4–6</sup> Interestingly, a

study showed that longer ejaculatory abstinence may lead to a shorter intravaginal ejaculatory latency time (IELT) in healthy people.<sup>7</sup> In addition, there is a postejaculation refractory time (PERT), or male refractory period (MRP), even after a single ejaculation in most human males, during which erection and ejaculation is inhibited.<sup>8</sup> Thus, we expect to determine if abstinence time, as well as immediately after ejaculation (abstinence time = 0), will interfere with the results of the SEPs and PSSR. We conducted a prospective study to determine whether the result of a nerve electrophysiological test is correlated with the abstinence time or change before and just after ejaculation, as a stable objective test for PE.

## PATIENTS AND METHODS

### Subjects

From January 2016 to December 2016, 50 PPE patients in the Department of Andrology (Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China) and 28 control cases were consecutively enrolled (age: 21–49 years). All subjects signed informed consent, and the ethics committee of Drum Tower Hospital approved the investigations. All subjects had been in stable heterosexual, monogamous relationships for at least the previous 6 months. Waldinger<sup>9</sup> reported that most men with PPE ejaculated within 1 min, but approximately 10% of an entire random cohort ejaculated

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within 2 min. Rowland and Kolba<sup>10</sup> proposed that it was reasonable to extend the 1-min cutoff to 2 min, as the men with IELT 1–2 min shared more similar characteristics to men ejaculating within 1 min with regard to the other two criteria (occurrence frequency and distress frequency), when compared with men having IELT >2 min. Thus, patients who ejaculated within 2 min of vaginal penetration from the first sexual experience were enrolled. Control cases were selected from the patients referred to the same department to determine the quality of semen or for circumcision who had no complaint about PE or other sexual dysfunctions, and the premature ejaculation diagnostic tool (PEDT)<sup>11</sup> score was no more than 8. Neither control subjects nor patients had erectile dysfunction (total score of 5-item version of the International Index of Erectile Function [IIEF-5]  $\leq 21$ ),<sup>12</sup> genitourinary tract infection, systemic (such as diabetes mellitus, hypertension, hyper- or hypothyroidism, and others) or neurological disorders, or obvious psychological problems or continuous drug use that might alter sexual activities. The Chinese versions of PEDT and IIEF-5, validated previously, were used in this study.<sup>13,14</sup> Physical examinations, including the genitalia, were normal. Demographic data, abstinence time, score of PEDT, and the results of nerve electrophysiological tests were recorded.

#### Method of nerve electrophysiological tests

The methods of the SEPs and PSSR were previously described in detail.<sup>5,6</sup> All the tests were carried out using the Nicolet Viking Quest Electromyograph/Evoked Potential machine (Natus Medical Inc., Middleton, WI, USA). SEPs consisted of DNSEP and GPSEP, with stimulatory electrodes on different places. For GPSEP, a pair of surface electrodes was placed at the glans penis; for DNSEP, the anode ring was put on the subcoronal region and the cathode was placed on the shaft 2 cm proximal to the anode. The duration of stimuli was 1.0 ms and the frequency was 3 s. First, the penile shaft sensory threshold value was detected, which was determined by gradually increasing from 0 mA until the subject sensed tiny synchronous prickle stimulation. Subsequently, it was decreased step by step until the subject just could not feel the stimulation. The decreasing intensity was considered as the critical value. The same procedure was repeated 3 times, and all the critical values were recorded and averaged to estimate the sensory threshold of the penile shaft. Following the determination of penile shaft sensory threshold, electrical stimuli were delivered to the penile shaft via ring electrodes with an intensity of about three times than that of the threshold value.

Recording electrodes consisted of two cup electrodes. According to the international 10–20 electrode placement protocol,<sup>15</sup> the active recording electrode was placed on the scalp 2 cm behind the Cz electroencephalographic recording site, and the reference electrode was placed in the midline of the forehead (Fpz). The cup electrodes were pasted on the skin with Conductive Neurodiagnostic Electrode Paste (Weaver and Company, Aurora, CO, USA). The ground electrode (a metallic band) was placed around the right arm. Responses were recorded on the skin treated with Skin Prep Gel (Weaver and Company) with an impedance of <5 k $\Omega$ . Both GPSEP and DNSEP were performed twice and each time 200 cortical potentials were averaged. When there were significant differences between the two tests, the test was repeated three or four times to evaluate test-to-test variability. Results were recorded in latencies and amplitudes of SEPs. The latency was measured at the time of the stimulus to the first cerebral response (P40, the level of the first positive peak). The amplitude was measured from the first positive peak to the first negative peak points of the tracing.

To record PSSR, ring electrodes were placed around the proximal (negative site) and distal (positive site) region of the penile

shaft, with 2 cm distance (almost the same placement with that of DNSEP). Skin impedance was reduced below 5 k $\Omega$  with Skin Prep Gel. We obtained the PSSR waveforms using an electrical shock consisting of a single square wave pulse of 1 ms duration and 70 mA intensity, which is sufficient to produce a slightly painful sensation. The electric stimulation was applied to the right median nerve through superficial electrodes. Four stimuli were administered at irregular randomized intervals of more than 30 s. PSSR latencies were measured from the origin of the trace to the first deflection of the trace from the baseline, while the amplitudes were assessed by peak-to-peak analysis (between the first peak and the following opposite peak).

All patients and control subjects received the initial nerve electrophysiological tests, which took about 20 min. Then, they were access to erotic video and ejaculated by masturbation in the semen collection rooms for routine semen analysis just beside the room for nerve electrophysiological tests. They were requested to collect the semen with semen collection tubes as the evidence of ejaculation. After the ejaculation, a second test was conducted within 5 min.

#### Statistical analyses

The Kolmogorov–Smirnov test was applied to examine the normality of the distribution. Continuous variables that were normally distributed were expressed as the mean  $\pm$  standard deviation (s.d.) and compared using Student's *t*-test between two groups. Nonnormally distributed quantitative data were presented as median (interquartile range) and compared using nonparametric tests. Spearman's correlations were estimated for analyses involving two variables. Multiple linear regression was used for those factors considered to be related to the test results. Paired *t*-tests were used to compare the results before and after ejaculation. The interaction of factors was assessed using two-way ANOVA. All statistical analyses were performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). A two-sided  $P < 0.05$  was considered statistically significant.

## RESULTS

#### Subject characteristics

The self-estimated IELT of PE patients was shorter than that of control subjects ( $P < 0.001$ ) and the PEDT score of the patient group was significantly higher than that of the control group ( $P < 0.001$ ), showing that the sexual function of patients was worse than that of the control subjects on ejaculation. In addition, there was no statistically difference in age, height, weight, marital status, and IIEF-5 score between the PE and control groups (**Table 1**). The results of the SEPs were all obtained in all subjects, while the results of the PSSR were not detectable in 7 PE patients and 3 control subjects.

#### Correlations of abstinence time with the latencies of the SEPs and PSSR

The latencies and amplitudes of SEPs and PSSR of both groups before and after ejaculation are presented in **Table 2**. Since the amplitudes of the SEPs and PSSR (a type of evoked potential) fluctuate significantly in the normal population and are considered to be of much less diagnostic importance than the latency measurement,<sup>16</sup> we only assessed the correlations between abstinence time and the latency of the SEPs and PSSR. Before ejaculation, the abstinence time was neither correlated with GPSEP ( $r = 0.170$ ,  $P = 0.239$ ), DNSEP ( $r = 0.264$ ,  $P = 0.064$ ), or PSSR ( $r = -0.240$ ,  $P = 0.122$ ) of PE patients, nor correlated with the latency of the GPSEP ( $r = -0.001$ ,  $P = 0.996$ ), DNSEP ( $r = -0.141$ ,  $P = 0.475$ ), or PSSR ( $r = -0.026$ ,  $P = 0.904$ ) of control subjects (**Figure 1**). Further analysis with multiple linear regression (respectively for latencies of the GPSEP,

**Table 1: Demographic and clinical characteristics of patients with primary premature ejaculation and control subjects**

Characteristic	PE patients (n=50)	Control subjects (n=28)	P
Age (year), mean±s.d.	30.22±6.93	31.64±6.21	0.370
Height (cm), mean±s.d.	172.68±5.00	173.57±5.68	0.474
Weight (kg), mean±s.d.	68.45±8.22	70.43±10.32	0.356
Marital status, n (%)			
Married	36 (72.0)	22 (78.6)	0.524
Single	14 (28.0)	6 (21.4)	
Abstinence time (day), median (interquartile range)	4.00 (1.50, 10.00)	3.00 (1.00, 6.50)	0.180
Self-estimated IELT (min), n (%)			
>5		9 (32.1)	<0.001
2–5		16 (57.1)	
1–2	25 (50.0)	3 (10.8)	
0.5–1	15 (30.0)		
0–0.5	10 (20.0)		
PEDT, mean±s.d.			
Q1	3.24±0.66	0.89±0.74	<0.001
Q2	3.28±0.81	0.57±0.69	<0.001
Q3	2.32±1.13	0.50±0.79	<0.001
Q4	3.32±0.71	1.21±1.00	<0.001
Q5	3.30±0.65	1.25±0.89	<0.001
Total	15.46±2.64	4.43±2.95	<0.001
IIEF-5, mean±s.d.	23.34±1.21	23.43±1.00	0.742

Student's *t*-test was used to compare the results normally distributed, while nonparametric tests were used to compare nonnormally distributed quantitative data. IELT: intravaginal ejaculatory latency time; IIEF-5: 5-item version of the International Index of Erectile Function; PE: premature ejaculation; PEDT: premature ejaculation diagnostic tool; s.d.: standard deviation

**Table 2: Comparison of latencies and amplitudes of somatosensory evoked potentials and penile sympathetic skin response before and after ejaculation**

Variable	PE patients			Control subjects		
	Before, mean±s.d.	After, mean±s.d.	P	Before, mean±s.d.	After, mean±s.d.	P
GL	41.86±1.94	41.73±1.96	0.439	45.03±2.45	44.78±2.30	0.102
GA	1.50±0.65	1.46±0.56	0.710	1.22±0.49	1.32±0.60	0.490
DL	39.50±2.07	39.60±2.15	0.573	43.10±2.64	42.77±2.76	0.198
DA	1.47±0.61	1.45±0.72	0.907	1.22±0.51	1.35±0.62	0.410
PL	1308.84±144.67	1315.23±148.32	0.552	1402.60±142.72	1394.80±140.60	0.600
PA	73.44±63.15	58.39±51.08	0.194	56.50±62.72	46.21±51.61	0.547

GL: latency of GPSEP; GA: amplitude of GPSEP; DL: latency of DNSEP; DA: amplitude of DNSEP; PL: latency of PSSR; PA: amplitude of PSSR; PSSR: penile sympathetic skin response; GPSEP: glans penis somatosensory evoked potential; DNSEP: dorsal nerve somatosensory evoked potential; PE: premature ejaculation; s.d.: standard deviation

DNSEP, and PSSR) showed that tests had no difference with abstinence day ( $P = 0.427, 0.249, \text{ and } 0.457$ , respectively), but had significant difference within groups (all  $P < 0.001$ ).

#### Comparison of the latencies of the SEPs and PSSR before and after ejaculation

There were no statistically significant differences in the mean latencies or amplitudes of the SEPs and PSSR before and after ejaculation in PE patients or in control subjects. In addition, the latencies of the SEPs and PSSR of PE patients are significantly shorter than those of control subjects, both before and after ejaculation. Analysis with 2-way ANOVA showed no significance between the latencies of the GPSEP, DNSEP, and PSSR and abstinence day ( $P = 0.361, 0.497, \text{ and } 0.457$  respectively), while significant difference between PE and control groups (all  $P < 0.001$ ) (Figure 2).

#### DISCUSSION

Ejaculation consists of two phases: emission and expulsion.<sup>17</sup> The emission phase involves parasympathetic responses, in the form

of secretion of seminal fluids from accessory sex glands, as well as sympathetic responses, in the form of moving the seminal fluids to the proximal urethra, which includes contraction of the ductus deferens and closure of the bladder neck. The expulsion phase is the consequence of rhythmic contractions of striated perineal muscles, primarily the bulbospongiosus muscle, which involves both sympathetic and somatic outputs.<sup>18</sup> The determinants of PE are complex and multivariate, each type with its own etiology, so we only enrolled the patients with PPE. Somatosensory evoked potential testing has been used in several different superficial peripheral nerves, such as the median, ulnar, radial, and posterior tibial nerves.<sup>19</sup> The DNSEP is an electroencephalographic response that sends stimuli to the somatic sensory area of penile dorsal nerve, and the GPSEP is a modification of the DNSEP that sends stimuli to the glans penis.<sup>6</sup> The PSSR is widely considered as a functional test of the sympathetic nervous system, as an assessment of small fiber function, and is frequently used for the diagnosis of thin, unmyelinated fiber lesions in diabetic neuropathy and uremic neuropathy in clinical neurological practice. It is a multisynaptic somatic sympathetic reflex,

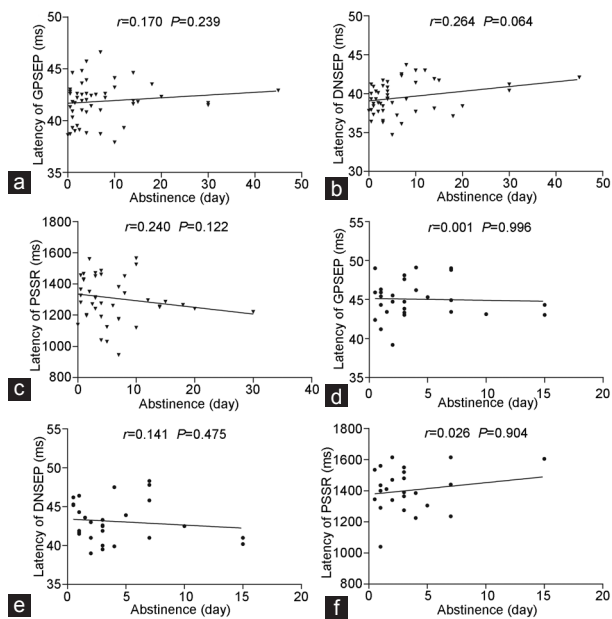
and the central control is located in the brain.<sup>5,20</sup> The sympathetic fibers innervating sweat gland activity in the genitalia and those involved in emission activity are close in their anatomical pathways. These pathways all originate from the lumbar spinal cord, via lumbar sympathetic ganglia, and connect to the postganglionic fibers governing the genital region.<sup>21,22</sup> PSSR may, therefore, reflect the functional state of the sympathetic nervous system associated with ejaculation. In this study, the latencies of SEPs and PSSR of PE patients were shorter than those of control subjects; these findings correspond with our previous studies.<sup>4-6</sup>

In previous studies, ejaculatory abstinence has usually been discussed in the context of semen analysis (2–7 days recommended by WHO<sup>23</sup>), but it has been seldom discussed in cases of PE. Palmieri *et al.*<sup>7</sup>

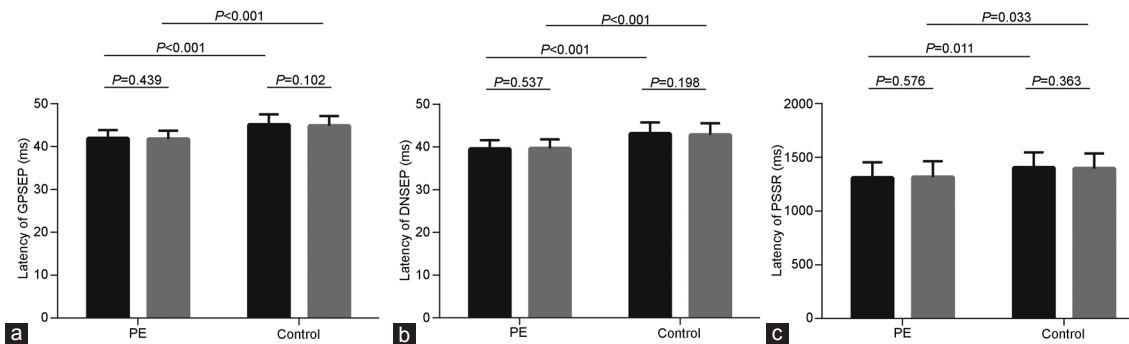
demonstrated that a 10-day abstinence period led to a significantly lower mean IELT and a significantly higher mean total PEDT score than a twice-a-week abstinence in healthy people. They suggested that ejaculatory abstinence may influence the physiology of both male sexual organs (such as the prostate, seminal vesicles, and vas deferens) and the nervous system. In this study, the latencies of the SEPs and PSSR were not correlated with ejaculatory abstinence and did not change significantly immediately after ejaculation (abstinence time = 0) in either PE patients or control subjects. The results indicated that abstinence time did not affect the somatosensory pathway of penile function and the penile sympathetic skin response which reflected the function of sympathetic nervous system. We hypothesized that the SEPs and PSSR only reflect the conductive function of the “wire” of the nerve – the somatosensory pathway of penile function and the sympathetic nervous system – associated with ejaculation, but not with the status of the prostate, seminal vesicles, and vas deferens. Future studies to assess these parts of the ejaculation may provide useful insights for further studies.

The postejaculation refractory time, or the male refractory period, during which further erections and ejaculation are inhibited, exists in rats after a single ejaculation, as well as in most human males.<sup>8</sup> The function of the PERT in the male has been assumed to conserve sufficient spermatozoa to enable as many fertile coital encounters with females as possible.<sup>24</sup> However, the precise mechanism of the PERT is still unknown. In the Yilmuz and Aksu’s study,<sup>25</sup> the authors recorded the activity of the cortical somatosensory evoked potential (the same method as the DNSEP in this study) of the penile dorsal nerve in healthy men before and after ejaculation. They found a small but significant decrease in its conduction properties but no significant change in the latency of the P1 (same with P40 in this study), which is consistent with our findings. In this study, PPE patients were enrolled, and the PSSR, which reflects the function of the sympathetic nerve involved in ejaculation, was conducted. In line with the findings of previous studies, no significant change was found before or after ejaculation. This may also indicate that during the PERT, the function of the somatosensory pathway of penile function and the sympathetic nervous system was not affected. Thus, we supposed that the delay of somatosensory pathway of penile function and the sympathetic nervous system was not the reason for the PERT. Further studies are recommended to clarify these mechanisms.

There are some limitations in this study. First, a small sample was used in this study. As there are no existing data on the effect of abstinence time on the results of SEPs and PSSR, sample size assessment



**Figure 1:** Correlations of abstinence time with the Latencies of the SEPs and PSSR before ejaculation. The correlations of abstinence time with the latencies of the (a) GPSEP, (b) DNSEP, and (c) PSSR, in PE patients; the correlations of abstinence time with the latencies of the (d) GPSEP, (e) DNSEP, and (f) PSSR, respectively, in control subjects. SEP: somatosensory evoked potential; PSSR: penile sympathetic skin response; GPSEP: glans penis somatosensory evoked potential; DNSEP: dorsal nerve somatosensory evoked potential; PE: premature ejaculation.



**Figure 2:** Comparison of the latencies of the SEPs and PSSR before and after ejaculation. The latencies of the (a) GPSEP, (b) DNSEP, and (c) PSSR, before and after ejaculation in PE patients and control subjects. PE: premature ejaculation; SEP: somatosensory evoked potential; PSSR: penile sympathetic skin response; GPSEP: glans penis somatosensory evoked potential; DNSEP: dorsal nerve somatosensory evoked potential. Student’s *t*-test was used to compare the results between two groups. Paired *t*-tests were used to compare the results before and after ejaculation.

was not conducted. *Post hoc* power analysis showed a high probability of making a type II error. Thus, further studies with more subjects are needed. Second, the range of abstinence day varied from 1 day to 45 days, which may affect the comparing of the results before and after ejaculation. Third, the nerve electrophysiological test for one subject lasted for approximately 20 min, which may be too long to detect some changes immediately after ejaculation for some subjects. Fourth, as the IELT of subjects were not accurate to seconds (self-estimated IELT), the correlation of IELT and nerve electrophysiological test was not assessed.

## CONCLUSION

Based on the results of this study, we supposed that the latencies of the SEPs and PSSR are not correlated with the ejaculatory abstinence time in either PPE patients or control subjects, as well as before and after ejaculation. When conducting the SEPs and PSSR tests, there is no need to consider an ejaculatory abstinence time. In conclusion, abstinence time does not interfere with the results of the nerve electrophysiological test, which is stable in determining the nerve function of PPE patients. Further studies with more subjects are needed to confirm these conclusions.

## AUTHOR CONTRIBUTIONS

BBY and YTD participated in the design of the study. BBY, ZZ, YFH, and YC participated in data collection. JDX, ZWH, ZZ, and YTD performed the statistical analysis. JDX, ZWH, and YC drafted the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declared no competing interests.

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