Relation of size of seminal vesicles on ultrasound to premature ejaculation

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Myriad biological factors have been proposed to explain premature ejaculation (PE). However, data correlating PE with seminal vesicles (SVs) are sparse. The study aimed to evaluate the relationship between the size of SV and PE. The cross-sectional study included 44 outpatients with PE and 44 volunteers without PE, and the size of SV was compared. Self-reported intravaginal ejaculatory latency time, the Premature Ejaculation Diagnostic Tool (PEDT), the International Index of Erectile Function-15, and the National Institutes of Health-Chronic Prostatitis Symptom Index were used for assessment of symptoms. Compared to the control group, the PE group had significantly higher mean anterior-posterior diameter (APD) of SV (P < 0.001). The optimal mean APD of SV cutoff level was 9.25 mm for PE. In the PE group, PEDT was also higher with a mean APD of SV ≥9.25 mm compared with mean APD of SV <9.25 mm. PEDT was significantly correlated with the mean APD of SV (r = 0.326, P = 0.031). The seminal plasma proteins were compared between six PE and six matched control cases by mass spectrometry and it was shown that 102 proteins were at least 1.5-fold up- or down-regulated. Among them, GGT1, LAMC1, and APP were significantly higher in the PE group. These results indicated that men with a larger mean APD of SV might have a higher PEDT score. Transrectal ultrasound of SV should be considered in the evaluation of patients with premature ejaculation. SV might be a potential target for the treatment of patients with PE and ultrasound change in SV.

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INTRODUCTION
Premature ejaculation (PE) is probably the most prevalent sexual complaint in men, affecting 20%–30% of sexually active men.1–3 According to the International Society for Sexual Medicine (ISSM), PE is defined as male sexual dysfunction characterized by (i) ejaculation that always or nearly always occurs prior to or within about 1 min of vaginal penetration from the first sexual experience (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 min or less (acquired PE); (ii) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (iii) negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy.4

Myriad biological factors have been proposed to explain PE including hypersensitivity of the glans penis,5 disturbances in central serotonergic neurotransmission,6 erectile difficulties7,8 and other sexual comorbidities, prostatitis,9 chronic pelvic pain syndrome,10 and thyroid disorders.11,12 However, data correlating PE with seminal vesicles (SVs) are sparse.

The ejaculatory process is typically subdivided into three phases: emission, ejection (or penile expulsion), and orgasm.13 Emission consists of contractions of epididymis, vas deferens, SVs, and prostate, with expulsion of sperm and seminal fluid into the posterior urethra.

Ejection involves closure of bladder neck, pulsatile contractions of the bulbocavernosus and pelvic floor muscles, together with relaxation of the external urinary sphincter. The disorders of these organs may result in ejaculation disorder. Moreover, a higher frequency of sexual dysfunction was detected in male patients with change in ultrasound in male accessory gland.14 Thus, we are curious about whether the size of SV on ultrasound is related to PE.

Nowadays, many factors are considered to be related to SV volume: age and sexual abstinence,15 PRL,16 smoking,17 testosterone,18 thyroid hormones,19 and inflammation.20 We aimed to avoid the effect of these confounders on SV to evaluate the relationship between the size of SV and PE and to explore the preliminary mechanism of the relationship.

MATERIALS AND METHODS

Subjects
The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Jingling Hospital. From November 2014 to May 2015, patients who sought treatment for the complaints of premature ejaculation were enrolled from andrology clinics. Individuals who met the following criteria were included in the study, as reported in previous studies, if they21–23 (i) were aged ≥18 years in a heterosexual, stable, and monogamous
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Detection of differently expressed seminal plasma proteins

All semen specimens were collected by masturbation into sterile containers after 2–7 days of sexual abstinence. The semen was tested for C. trachomatis using immunochromatography and cultured for M. urealyticum and M. hominis. The samples were centrifuged at 1600 ×g for 5 min and supernatant seminal plasma was immediately stored at −80°C. Tandem mass tag (TMT) method followed by mass spectrometry analysis was used to compare the relative expression levels of seminal plasma proteins between the PE and control groups. Proximal seminal plasma samples (six cases for acquired PE and six matched cases for control) were extracted and digested using trypsin. Later, the proteins were labeled with the TMT reagent. Peptide analysis was performed using the LTQ-Orbitrap instrument (Thermo Finnigan, San Jose, CA, USA) connecting to a Nano AQUITY UPLC system via a nanospray source. Raw files of proteomics data were processed using MaxQuant (version 1.2.2.5). The false discovery rate (FDR) of the identification was estimated by searching against the databases with the reversed protein sequences. The site, peptide, and protein FDR were all set to 0.05. One-way analysis of variance was used to calculate significant differences in abundance among groups.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± s.d. when normally distributed and as median (quartiles) for parameters with nonnormal distribution. Differences of means of normally distributed parameters between two groups were assessed using unpaired Student’s t-test or one-way analysis of variance with post hoc least square differences. In all other cases, the Mann–Whitney U-test was used for comparisons between the groups. Comparison of proportions was performed using the Chi-square test. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) of ROC was calculated for the anterior-posterior diameter (APD) of SV before ejaculation. The optimal cutoff values for the mean APD of SV for detecting PE (according to the patients with PE and control cases) were identified using the maximum of the Youden index [(sensitivity + specificity) − 1]. Correlations were assessed using Spearman’s or Pearson’s method whenever appropriate. Multiple linear regression analyses were used for those factors considered to be related to SV parameters, whenever appropriate.

RESULTS

Sociodemographic, clinical, and color Doppler ultrasound characteristics of the patients with PE and control cases before ejaculation

The sociodemographic, clinical, and color Doppler ultrasound characteristics of the whole sample before ejaculation are summarized in Table 1. No statistically significant differences in serum lipids and hormonal levels were observed between these two groups. The PEDT score in patients with PE was significantly higher than that in the control group (12.7 ± 3.0 vs 2.6 ± 2.2, P < 0.001). The mean APD (10.6 ± 2.7 mm vs 8.8 ± 1.9 mm, P < 0.001) and SV volume (P < 0.001) in the PE group were significantly higher than that in the control group. Patients with PE also had significantly higher incidence of areas of endocapulation and of wall thickening and septa than the control cases (P = 0.031 and P = 0.029, respectively). The ultrasound image of control cases and PE patients is shown in Figure 1. In addition, mean APD of SV was not significantly different between the acquired PE group and lifelong PE group.

Demographic characteristics and questionnaires

Before their participation, all participants provided written informed consent. Later, all patients underwent a complete andrological and physical examination. The participants were also asked to complete questionnaires including demographics, self-estimated intravaginal ejaculatory latency time (IELT), the Premature Ejaculation Diagnostic Tool (PEDT), the IIEF-15, and the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI). Patients were categorized as current smokers if they had smoked at least 1 year, past smokers if they had smoked at least 1 year and were not current smokers, and never smokers if they had never smoked or smoked <1 year, according to a previous study. Both past smokers and never smokers were counted as nonsmokers.

Transrectal ultrasound imaging

All patients and control cases underwent ultrasonography following 2 to 7 days of sexual abstinence. The prostate-vesicular region was assessed at rectal ultrasonography using a 6 MHz monoplane and linear transducer through transverse, longitudinal, and oblique scans, with patients placed in the left lateral decubitus (nemio-XG580, Toshiba, Tokyo, Japan). The prostate-vesicular region was assessed at rectal ultrasonography before ejaculation as reported by Lotti et al. Both seminal vesicle and prostate were calculated according to previous report. To prevent bias on the part of the examiner, the ultrasonographer was unaware of the clinical data.

Serum lipids and hormonal evaluation

Blood samples were drawn in the morning (between 8:00 and 10:00 a.m.) after an overnight fast. The biochemical analyses included the triglycerides, the total cholesterol (TC), the low-density lipoprotein cholesterol, and the high-density lipoprotein cholesterol (HDL-C) level. Total testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels were evaluated using chemiluminescent immunoassay system (Beckman Coulter, Inc., Brea, CA, USA). The intra- and inter-assay coefficients of variation for progesterone, estradiol, testosterone, and prolactin were 8.18% and 7.89%, 5.13% and 6.23%, 2.56% and 5.19%, and 5.52% and 3.53%, respectively.
Table 1: Sociodemographic, clinical, and CDU characteristics of the patients with PE and control cases before ejaculation

| Characteristic                              | PE (n=44) | Control (n=44) | P   |
|---------------------------------------------|-----------|----------------|-----|
| Age (years)                                 | 30.2±6.4  | 29.3±4.1       | 0.420 |
| Height (cm)                                 | 173±6.4   | 174±5.2        | 0.391 |
| Weight (kg)                                 | 71.2±11.1 | 72.3±8.4       | 0.585 |
| Smoking                                     |           |                | 0.574 |
| Current smokers                             | 25 (56.8) | 23 (52.3)      |     |
| Past smokers                                | 0 (0)     | 1 (2.3)        |     |
| Never smokers                               | 19 (43.2) | 20 (45.5)      |     |
| Sexual abstinence (days)                     | 3.4±2.0   | 4.1±1.6        | 0.099 |
| Total testosterone (nmol l⁻¹)               | 14.1±5.1  | 13.7±2.9       | 0.704 |
| PRL (mIU l⁻¹)                               | 222.3±128.7 | 197.7±64.8 | 0.312 |
| LH (IU l⁻¹)                                 | 4.0±1.7   | 3.9±1.6        | 0.811 |
| FSH (IU l⁻¹)                                | 5.2±3.0   | 5.1±2.1        | 0.935 |
| TC (mmol l⁻¹)                               | 4.4±0.9   | 4.3±0.7        | 0.849 |
| TG (mmol l⁻¹)                               | 1.3±1.3   | 1.4±0.9        | 0.584 |
| LDL (mmol l⁻¹)                              | 1.2±0.2   | 1.3±0.3        | 0.459 |
| HDL (mmol l⁻¹)                              | 2.5±0.7   | 2.5±0.7        | 0.700 |
| PEDT                                        | 12.7±3.0  | 21.2±2.6       | <0.001 |
| IIEF-15 erectile function score             | 27.7±1.3  | 28.1±1.1       | 0.163 |
| NIH-CPSI pain domain score                  | 0 (0–2.5) | 0 (0–0)        | 0.509 |
| NIH-CPSI voiding domain score               | 1.5 (0–3.0) | 1.0 (0–2.0) | 0.064 |
| NIH-CPSI quality of life domain score        | 2.0 (0–3.0) | 1.0 (0–2.0) | 0.078 |
| Self-estimated IELT (min)                   |           |                | <0.001 |
| ≤1                                          | 16 (36.4) | 0              |     |
| 1–2                                         | 25 (56.8) | 8              |     |
| 2–3                                         | 3 (6.8)   | 0              |     |
| 3–4                                         | 0         | 1 (2.3)        |     |
| 4–5                                         | 0         | 2 (4.5)        |     |
| ≥5                                          | 0         | 41 (93.2)      |     |
| Mean self-estimated IELT (min)              | 1.2±0.6   | 9.3±5.4        | <0.001 |
| Type of PE                                  |           |                |     |
| Lifelong                                    | 27 (38.6) |                |     |
| Acquired                                    | 17 (61.4) |                |     |
| Duration of PE (years)                      | 3.4±2.9   |                |     |
| CDU parameters                              |           |                |     |
| Prostate                                    |           |                |     |
| Prostate volume (ml)                        | 16.6±3.9  | 15.7±3.9       | 0.265 |
| Prostate calcifications (%)                 | 7 (15.9)  | 6 (13.6)       | 0.764 |
| Inhomogeneous prostatic texture (%)         | 14 (31.8) | 1 (18.2)       | 0.140 |
| Utricular cyst (%)                          | 0         | 1 (2.3)        | 0.315 |
| Seminal vesicles                            |           |                |     |
| Mean LD before ejaculation (mm)             | 36.3±4.2  | 35.2±4.1       | 0.206 |
| Mean APD before ejaculation (mm)            | 10.6±2.7  | 8.8±1.9        | <0.001 |
| Total volume (ml)                           | 4.2 (2.4–6.4) | 2.5 (2.0–3.3) | 0.001 |
| Areas of endocapsulation (%)                |           |                | 0.031 |
| Unilateral                                  | 2 (4.5)   | 0              |     |
| Bilateral                                   | 12 (27.3) | 5 (11.4)       |     |
| Wall thickening and septa (%)              | 1 (2.3)   | 0              | 0.029 |
| Unilateral                                  |           |                |     |
| Bilateral                                   | 9 (20.5)  | 2 (4.5)        |     |
| Ejaculatory ducts                           |           |                | 0.360 |

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ROC curve analysis of the mean APD before ejaculation for PE
AUC of ROC analysis of the mean APD of SV before ejaculation for diagnosing PE was 0.697 (95% confidence interval [95% CI]: 0.586–0.808) (Figure 2). The optimal mean APD of SV cutoff level as identified by the maximal Youden index was 9.25 mm for PE with modest sensitivity (61.4%) and specificity (77.3%). AUC of ROC curve analysis of SV volume for PE was the same as that of APD (data not shown). Thus, we preferred APD to volume for the following analysis.

Comparison of SV size between patients with PE with APD cutoff of 9.25 mm before ejaculation
Table 2 shows the comparison in patients with PE between the mean APD of SV ≥9.25 mm and the mean APD of SV <9.25 mm. The PEDT scores were 13.5 ± 3.0 for patients with PE with the mean APD of SV ≥9.25 mm and 11.4 ± 2.4 with the mean APD of SV <9.25 mm (P = 0.016). The mean LD (37.7 ± 4.0 mm vs 34.1 ± 3.6 mm, P = 0.004) and SV volume (P < 0.001) before ejaculation with the mean APD of SV ≥9.25 mm were higher than the mean APD of SV <9.25 mm. Compared with the mean APD of SV <9.25 mm group, patients with PE with the mean APD of SV ≥9.25 mm had significantly higher incidence of areas of endocapsulation and of wall thickening and septa (P < 0.001 and P = 0.003, respectively). Patients with PE with the mean APD of SV ≥9.25 mm also had significantly lower TC and LDL-C and significantly higher HDL-C (P = 0.014, P < 0.001, and P = 0.041, respectively). No statistically significant differences between the two groups with regard to self-estimated IELT and type of PE were observed.

Relationships between the PEDT and age, mean APD of SV, IIEF-15, and NIH-CPSI
The statistical analysis revealed that PEDT was significantly correlated with mean APD of SV before ejaculation (r = 0.326, P = 0.031) and IIEF-15 erectile function score (r = -0.413, P = 0.005) (Table 3). After adjusting for age, IIEF-15 erectile function score, NIH-CPSI pain domain score, NIH-CPSI voiding domain score, sexual abstinence, smoking, testosterone, and prolactin, PEDT was found still to be significantly correlated with mean APD of SV before ejaculation (r = 0.442, P = 0.009) (Supplementary Table 1).

Detection of differentially expressed proteins in seminal plasma of patients with PE and control cases
The sociodemographic, clinical, and color Doppler ultrasound characteristics of the six patients with acquired PE with mean APD of SV ≥9.25 mm and six matched control cases for TMT are summarized in Supplementary Table 2. No differences were found except PEDT and the mean APD of SV (12.7 ± 2.9 vs 2.0 ± 1.0 and 12.3 ± 0.6 mm vs 8.2 ± 0.6 mm, respectively). Examination of the mass spectrometry data using the MaxQuant 1.2.2.5 software revealed that 102 proteins were at least 1.5-fold up- or down-regulated (P < 0.05).
Table 2: Sociodemographic, clinical, and CDU characteristics of the patients with PE with mean APD of SV ≥9.25 mm and mean APD of SV <9.25 mm before ejaculation

|                     | Mean APD of SV ≥9.25 mm (n=27) | Mean APD of SV <9.25 mm (n=17) | P       |
|---------------------|---------------------------------|--------------------------------|---------|
| Age (years)         | 29.7±6.3                        | 31.1±6.7                        | 0.490   |
| Height (cm)         | 174.3±4.8                       | 172.5±4.3                       | 0.209   |
| Weight (kg)         | 72.4±12.4                       | 69.3±8.6                        | 0.381   |
| Smoking             |                                 |                                 | 0.402   |
| Current smokers     | 14 (51.9)                       | 11 (64.7)                       | 0.016   |
| Never smokers       | 13 (48.1)                       | 6 (35.3)                        | 0.784   |
| Sexual abstinence (days) | 3.6±2.2                      | 3.2±1.7                        | 0.003   |
| Total testosterone (nmol l⁻¹) | 15.0±6.0                   | 12.6±2.9                        | 0.018   |
| PRL (mIU l⁻¹)       | 251.9±150.0                     | 174.5±64.7                      | 0.089   |
| LH (IU l⁻¹)         | 4.2±2.0                         | 3.7±1.2                         | 0.400   |
| FSH (IU l⁻¹)        | 5.1±3.3                         | 5.2±2.5                         | 0.951   |
| TC (mmol l⁻¹)       | 4.1±1.0                         | 4.9±0.5                         | 0.014   |
| TG (mmol l⁻¹)       | 1.4±1.6                         | 1.1±0.4                         | 0.633   |
| HDL-C (mmol l⁻¹)    | 1.3±0.2                         | 1.1±0.2                         | 0.041   |
| LDL-C (mmol l⁻¹)    | 2.2±0.7                         | 3.1±0.3                         | <0.001  |
| PEDT                | 13.5±3.0                        | 11.4±2.4                        | 0.016   |
| IIEF-15 erectile function score | 27.7±1.2               | 27.8±1.3                        | 0.694   |
| NIH-CPSI pain domain score | 0 (0–3.0)           | 0 (0–1.5)                       | 0.656   |
| NIH-CPSI voiding domain score | 2.0 (0–3.0)     | 1.0 (0–2.5)                     | 0.179   |
| NIH-CPSI quality of life domain score | 3.0 (1–5.0) | 1.0 (0–3.0)                     | 0.069   |
| Self-estimated IELT (min) |                                 |                                 | 0.504   |
| ≤1                  | 8 (29.6)                        | 8 (47.1)                        |         |
| 1–2                 | 17 (63.0)                       | 8 (47.1)                        |         |
| 2–3                 | 2 (7.4)                         | 1 (5.9)                         |         |
| 3–4                 | 0                               | 0                               |         |
| 4–5                 | 0                               | 0                               |         |
| ≥5                  | 0                               | 0                               |         |
| Mean self-estimated IELT (min) | 1.3±0.6                     | 1.1±0.6                         | 0.308   |
| Type of PE          |                                 |                                 | 0.784   |
| Lifelong            | 17 (63.0)                       | 10 (58.8)                       |         |
| Acquired            | 10 (37.0)                       | 7 (41.2)                        |         |
| Duration of PE (years) | 3.1±2.2                      | 4.0±3.9                         | 0.403   |
| CDU parameters      |                                 |                                 |         |
| Prostate            |                                  |                                 |         |
| Prostate volume (ml) | 17.0±3.7                      | 16.0±4.2                        | 0.404   |
| Prostate calcifications (%) | 5 (18.5)                     | 2 (11.8)                        | 0.689   |
| Inhomogeneous prostatic texture (%) | 10 (37.0)                   | 4 (23.5)                        | 0.349   |
| Utricular cyst (%)  | 0                               | 0                               |         |
| Seminal vesicles    |                                  |                                 |         |
| Mean LD before ejaculation (mm) | 37.7±4.0                   | 34.1±3.6                        | 0.004   |
| Total volume (ml)   | 5.7 (4.4–8.0)                   | 2.2 (1.8–2.7)                   | <0.001  |
| Areas of endocapsulation (%) |                                  |                                 | <0.001  |
| Unilateral          | 2 (7.4)                         | 0                               |         |
| Bilateral           | 12 (44.4)                       | 0                               |         |
| Wall thickening and septa (%) | 1 (3.7)                      | 0                               | 0.003   |
| Unilateral          | 1 (3.7)                         | 0                               |         |
| Bilateral           | 9 (33.3)                        | 0                               |         |
| Ejaculatory ducts   | Dilated ejaculatory duct (%)    | 1.0                             |         |

Table 2: Contd...

|                     | Mean APD of SV ≥9.25 mm (n=27) | Mean APD of SV <9.25 mm (n=17) | P       |
|---------------------|---------------------------------|--------------------------------|---------|
| Unilateral          | 1 (3.7)                         | 0                               |         |
| Bilateral           | 0                               | 0                               |         |

Data are expressed as mean±s.d. or as median (quartiles) when appropriate and as number (percentage) when categorical. APD: anterior-posterior diameter; CDU: color Doppler ultrasound; FSH: follicle-stimulating hormone; HDL-C: high-density lipoprotein cholesterol; IELT: intravaginal ejaculatory latency time; IIEF-15: International Index of Erectile Function-15; LD: longitudinal diameter; LD-C: low-density lipoprotein-cholesterol; LH: luteinizing hormone; NIH-CPSI: National Institutes of Health-Chronic Prostatitis Symptom Index; PE: premature ejaculation; PEDT: premature ejaculation diagnostic test; PRL: prolactin; s.d.: standard deviation; SV: seminal vesicle; TC: total cholesterol; TG: triglyceride

Among them, 101 proteins were upregulated and 1 protein was downregulated (Supplementary Table 3). Ingenuity® Pathway Analysis (IPA; Ingenuity® Systems, www.ingenuity.com) was used to further analyze the networks among PE, SVs, and the 102 differentially expressed proteins. Among them, GGT1, LAMC1, and APP were significantly higher in the PE group. A pathway map can be drawn for better visualization and understanding (Figure 3). Additional enzyme-linked immunosorbent assay was performed to verify key proteomic differences discovered using mass spectrometry analysis. It was confirmed that APP in seminal plasma was altered and the result was in agreement with mass spectrometry analysis (data not shown).

DISCUSSION

The results of this study indicate that the ultrasound change in SVs is associated with PE. A recent study demonstrated that in patients with male accessory gland infection (MAGI), patients with PE showed a mean value of the SVs APD detected before ejaculation, which was significantly higher compared to those without PE.²³ These results here represented the higher mean APD of SV in the patients with PE compared to healthy volunteers and confirmed that the peculiar ultrasound phenotype of SV may be associated with PE. In addition, these results revealed a positive linear relationship between PEDT score and the APD of SV, which was consistent with their results despite the difference in the correlation coefficient.²⁴ Thus, the ultrasound change in SV is possibly associated with PE. This study demonstrated that the mean APD of SVs in the patients with PE was significantly higher than that in the control cases, with higher incidence of areas of endocapsulation before ejaculation and of wall thickening and septa. These changes in morphology may be associated with premature ejaculation. SV dilation was defined as a SV anterior-posterior diameter >14 mm,²⁵ suggestive of male accessory gland infection or ejaculatory duct obstruction.²⁶ In our study, the mean APD of SV in the PE patients was larger than that in the control group although the mean APD of SV in most PE patients was no more than 14 mm. In addition, both areas of endocapsulation and wall thickening and septa of SV were associated with male accessory gland infection.²⁷,²⁸ The aim of this study was to evaluate the relationship between the size of SV on ultrasound and PE. Thus, we tried to avoid other causes for PE. In this study, patients with PLS and infection of Chlamydia or Mycoplasma were excluded to avoid the impact of infection. Since transrectal ultrasound is a valuable diagnostic technique for evaluating indirect signs of ejaculatory duct obstruction, such as dilatation, and the volume of all semen samples were more than 1.5 ml, we assumed that these patients did not have distal seminal tract obstruction. In addition, patients with other disorders that were associated with PE such as ED and hormonal disorders were excluded.
Therefore, the changes in SV are associated with PE and might be the idiopathic cause for PE in the patients with ultrasound change in SV. It needs further study to explore the cause of the changes of SV in the patients with PE. It was notable that APD of SV in this study was not that large as previous studies. This may be due to the different races and inflammatory status.

These results demonstrated that patients with PE had larger mean APD of SV. We proposed that the enlargement of SV might be related to a stronger SV contraction with ejaculation, resulting in a more likely tendency to propel the seminal fluid into the posterior urethra, thus accelerating the phase of emission. Therefore, at equal stimulus, cases with large SV may ejaculate more quickly. It was reported that SV pressure response to electrical nerve stimulation could be inhibited by selective serotonin reuptake inhibitors or alpha-adrenergic blocker in rat,35–37 which could be the potential mechanism of the treatment for PE. Thus, it is speculated that the SV pressure plays an important role in ejaculation and the larger mean APD of SV could result in the change in SV contraction, which further causes PE. The detailed mechanism needs to be studied in the future.

Seminal plasma proteins are secreted from SVs (~65% of semen volume), prostate (~25%), testis and epididymis (~10%), and bulbourethral and periurethral glands (~1%).38 Thus, the change in SV may be associated with different expression of seminal plasma proteins. Later, the seminal plasma proteins were determined and several differentially expressed proteins associated with SV and PE were found.

Among the 102 differentially expressed proteins, the expression of GGT1 and LAMC1 was significantly higher in the seminal plasma of the PE group compared with the control group. These two genes may be associated with SV structure. A previous study showed that homozygous mutant mouse GGT1 gene (knockout) in mouse decreases the size of SV in male mouse.39 Mutant mouse LAMC1 gene (homozygous knockout) increases lack of SV in mouse.40 Thus, GGT1 and LAMC1 may be associated with SV structure, and overexpression of these two genes may result in the enlargement of SV’s, which could result in the change in SV pressure. In this study, the expression of APP was significantly higher in the seminal plasma of the PE group compared with the control group. A previous study showed that 3xTgAD mice treated with paroxetine significantly reduced the levels of amyloid beta-peptide (Aβ) and numbers of Aβ immunoreactive neurons in the hippocampus of male and female mice compared to 3xTgAD mice treated with saline.41 Dysfunction and death of neurons in brain regions resulted in behavioral abnormalities in Alzheimer’s disease, which are associated with extracellular accumulations of Aβ (plaques).42 It was noticeable that paroxetine was effective in delaying ejaculation.43 Therefore, it seems that paroxetine may delay ejaculation by reducing the levels of APP, and the higher expression of APP could be associated with the neural dysfunction, which could result in the change in SV pressure. The mechanism needs further exploration.

Several limitations of the present study should be considered. First, the cross-sectional nature of the dataset makes causal inferences problematic. Second, SV diameters were not evaluated both before and after ejaculation. Third, the NIH-CPSI was used to measure PLS in this study. However, the NIH-CPSI was not specifically developed to diagnose CP although the index had a significant power to distinguish and identify men with PLS.21 No laboratory examinations such as Meares-Stamey four-glass test were performed in the present study to exclude bacterial prostatitis. Therefore, prostatitis was not excluded strictly. Forth, we just excluded hypothyroidism and hyperthyroidism according to the physical examination and did not measure thyroid hormones in this study. Thyroid hormones had a positive effect on SV35 and this could be a potential bias. Fifth,
lifelong PE might be related to several other confounders, including psychological status. We did not take them into consideration because it is difficult during clinical practice. Sixth, this study included data from a single institution; hence, a potential selection bias may have occurred. To address this limitation, a well-designed, larger-scale assessment of the relationship of SVs and PE is warranted to validate the results of this study.

CONCLUSIONS
This study demonstrated the relationship between the size of SV and PE. Men with a larger mean APD of SV might have a higher PEDT score. Transrectal ultrasound of SV should be considered in the clinical evaluation of patients with PE. The treatment for SV might be useful in the treatment for the patients with PE and with ultrasound change in SV. SV might be a potential target for the treatment of patients with PE and ultrasound change in SV. Further studies are needed to explore the mechanism.

AUTHOR CONTRIBUTIONS
ZWH, BY, and ZCXC participated in the design of the study. ZWH, YMF, XCH, and JMS participated in data collection. ZWH, YFG, JJ, and LPP performed the statistical analysis. ZWH drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
All authors declared no competing financial interests. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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**Supplementary Table 1: Multiple linear regression test of the relationship between PEDT and mean APD of SV before ejaculation**

|            | PEDT | β     | Standard error | P   |
|------------|------|-------|----------------|-----|
| Mean APD of SV before ejaculation |      |       |                |     |
| Model 1    |      | 0.343 | 0.166          | 0.044 |
| Model 2    |      | 0.395 | 0.151          | 0.013 |
| Model 3    |      | 0.423 | 0.147          | 0.007 |
| Model 4    |      | 0.442 | 0.159          | 0.009 |

APD: anterior-posterior diameter; IIEF-15: International Index of Erectile Function-15; NIH-CPSI: national Institutes of Health-Chronic Prostatitis Symptom Index; PEDT: premature ejaculation diagnostic tool; SV: seminal vesicle. Model 1: adjusting for age; Model 2: adjusting for age; IIEF-15 erectile function score; NIH-CPSI pain domain score; and NIH-CPSI voiding domain score; Model 3: adjusting for age; IIEF-15 erectile function score; NIH-CPSI pain domain score; NIH-CPSI voiding domain score; sexual abstinence and smoking; Model 4: adjusting for age; IIEF-15 erectile function score; NIH-CPSI pain domain score; NIH-CPSI voiding domain score; sexual abstinence; smoking; testosterone and prolactin.

**Supplementary Table 2: Sociodemographic, clinical, and CDU characteristics of the PE patients with PE and matched control cases for TMT**

|                     | PE (n=6) | Control (n=6) | P      |
|---------------------|----------|---------------|--------|
| Age (years)         | 31.3±10.5| 35.0±4.4      | 0.606  |
| Height (cm)         | 174.0±4.4| 176.0±9.2     | 0.756  |
| Weight (kg)         | 64.0±10.6| 79.3±16.2     | 0.252  |
| Sexual abstinence (days) | 4.7±2.5  | 5.3±1.5      | 0.715  |
| Total testosterone (nmol l⁻¹) | 11.3±3.6  | 9.6±2.7      | 0.549  |
| PRL (mIU l⁻¹)       | 317.7±241.0 | 176.3±46.8 | 0.377  |
| LH (IU l⁻¹)         | 5.3±2.8  | 4.6±1.3       | 0.687  |
| FSH (IU l⁻¹)        | 4.5±1.9  | 5.7±1.1       | 0.412  |
| TC (mmol l⁻¹)       | 4.9±0.3  | 4.7±0.5       | 0.592  |
| TG (mmol l⁻¹)       | 1.5±1.2  | 1.5±0.2       | 0.962  |
| HDL (mmol l⁻¹)      | 1.3±0.3  | 1.1±0.2       | 0.308  |
| LDL (mmol l⁻¹)      | 2.6±0.5  | 2.9±0.4       | 0.372  |
| PEDT                | 12.7±2.9 | 2.0±1.0       | 0.004  |
| IIEF-15 erectile function score | 27.3±1.5  | 29.0±1.0 | 0.189  |
| NIH-CPSI pain domain score | 0±0 | 0±0 |        |
| NIH-CPSI voiding domain score | 2.7±0.6 | 1.0±1.0 | 0.067  |
| NIH-CPSI quality of life domain score | 2.3±0.6 | 0.7±1.2 | 0.089  |

**CDU parameters**

**Prostate**

- Prostate volume (ml): 17.4±2.4 vs. 20.3±1.3, P=0.143
- Prostate calcifications (%): 0 vs. 0
- Inhomogeneous prostatic texture (%): 0 vs. 0
- Utricular cyst (%): 0 vs. 0

**Seminal vesicles**

- Mean LD before ejaculation (mm): 34.0±3.5 vs. 32.3±2.8, P=0.552
- Mean APD before ejaculation (mm): 12.3±0.6 vs. 8.7±0.6, P=0.001
- Total volume (ml): 5.5±0.8 vs. 2.3±0.5, P=0.004

**Areas of endocapsulation before ejaculation (%)**

- Unilateral: 0 vs. 0
- Bilateral: 0 vs. 0

**Ejaculatory ducts**

- Dilated ejaculatory duct (%): 0 vs. 0
- Unilateral: 0 vs. 0
- Bilateral: 0 vs. 0

Data are expressed as mean±s.d. or as median (quartiles) when appropriate and as number (percentage) when categorical. A statistical analysis comparing patients with PE to control cases was performed. PE: premature ejaculation; TMT: tandem mass tag; APD: anterior-posterior diameter; CDU: color Doppler ultrasound; FSH: follicle-stimulating hormone; HDL: high-density lipoprotein; IELT: intravaginal ejaculatory latency time; IIEF-15: International Index of Erectile Function-15; LD: longitudinal diameter; LDL-C: low-density lipoprotein-cholesterol; LH: luteinizing hormone; NIH-CPSI: national Institutes of Health-Chronic Prostatitis Symptom Index; PEDT: premature ejaculation diagnostic tool; PRL: prolactin; s.d.: standard deviation; TC: total cholesterol; TG: triglyceride.