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Radical prostatectomy restores detrusor contraction pattern according to pressure flow parameters

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ABSTRACT

Objectives: Pressure flow studies are regarded as the gold standard for evaluating both bladder outlet obstruction and detrusor contractility, but none of the current methods for evaluating bladder contraction patterns are well validated. Impaired bladder contraction results in a lower peak Watts factor (WF) and poorly sustained detrusor contractions. From this viewpoint, the maximum WF (Wmax) and its pattern should be considered separately. We examined detrusor contraction pattern using multiple parameters.

Methods: We defined some parameters from WF curve throughout micturition. rV(Wmax) was the relative bladder volume when reach Wmax. A normal detrusor contractility pattern involves an increase in WF at the initiation followed by further gradual increases until the end of micturition. Thirty-seven patients with clinically localized prostate cancer underwent both pre- and post-radical prostatectomy (RP) urodynamic evaluations. The examined urodynamic parameters included the maximum flow rate (Qmax), post-void residual volume (PVR), detrusor pressure at maximum flow (PdetQmax), Wmax, and rV(Wmax).

Results: After RP, Qmax increased significantly (pre: 13.0±6.5, post: 17.3±7.7 ml/min; $P < 0.01$), whereas PdetQmax and PVR decreased significantly (pre: 49.6±21.6 and 31.4±18.2 cmH_2O; post: 48.6±66.1 and 10.1±28.5 ml; $P < 0.05$). Wmax did not change significantly after RP (pre: 10.5±3.1, post: 11.0±3.2 W/m^2), but rV(Wmax) decreased significantly (pre: 0.48±0.3, post: 0.20±0.20; $P < 0.001$). Wmax represents the maximum power of bladder contraction at a particular point in time, whereas rV(Wmax) can be used to detect changes in detrusor contraction pattern.

Conclusions: Evaluation of rV(Wmax) confirmed that RP restores normal detrusor contractility pattern in prostate cancer patients.

Keywords: detrusor contraction; detrusor underactivity; pressure flow study; radical prostatectomy

Introduction

Patients with early-stage prostate cancer have been reported to achieve long-term survival after combination treatment with radical prostatectomy (RP) and radiotherapy [1]. However, RP can also cause lower urinary tract symptoms (LUTS), and patients that undergo RP are often affected by bladder function abnormalities such as detrusor overactivity (DO) or decreased bladder compliance,[2] probably owing to bladder denervation during surgery and long-term bladder outlet obstruction (BOO). In addition, detrusor underactivity (DU) is seen in some patients that develop incontinence after RP [3,4]. It has also been reported that many patients acquire voiding behavior after RP as an adaptation to low urethral resistance and void after minimal detrusor contraction or abdominal straining. However, few studies have examined the effects of RP on detrusor function itself.

DU has received much less scientific attention than DO. The International Continence Society (ICS) defines DU as "contractions of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span" [5]. Such

symptoms can be caused by two different pathophysiological mechanisms, namely reduced detrusor contraction force or abnormally short detrusor contractions. Pressure flow studies (PFS) are regarded as the gold standard for evaluating BOO and detrusor contractility. We previously reported that RP improved urodynamic parameters by abrogating BOO without affecting detrusor contractility [6]. Precise changes of detrusor contraction remain to be completely elucidated.

In the present study, we investigated the changes in urodynamic parameters and LUTS in patients that were followed for one year after RP. These parameters were compared with preoperative urodynamic data, focusing on detrusor contraction pattern, which was measured using a WF curve throughout micturition. The contractility of the bladder was quantified using a parameter that approximates power per bladder wall area according to the Hill equation, which calculates detrusor pressure in relation to volume and flow rate. The Watts factor (WF) is the most widely used measure of detrusor contractility [7]. The WF was calculated throughout bladder emptying and plotted as a function of the volume of liquid in the bladder at each moment in time. A normal detrusor contractility pattern involves a marked increase in WF at the initiation of micturition followed

by further gradual increases until the end of micturition. We also determined the correlations between LUTS and parameters calculated from WF curve in this population.

Methods

Patient characteristics

The study was based on a retrospective review of urodynamic data. Thirty-seven consecutive patients (Table 1; median age 65 years**,** range 53–74 years) who had undergone RP and pre- and post-RP PFS were enrolled in the present study. The post-RP PFS were performed at 1 postoperative year. Of these 37 patients, 24 and 13 underwent laparoscopic RP and retropubic RP, respectively. And this patients group was not intentionally selected. The mean prostate volume was 39.9 ml (20.7-92.6 ml). Urodynamic analyses, including uroflowmetry and PFS, and questionnaires regarding LUTS were performed before and 1 year after RP. We used the International Prostate Symptom Score (IPSS) and the quality of life (QOL) score to analyze LUTS and QOL, respectively. The present study was approved by the Scientific Ethics Committee of Hokkaido University (#016-0098).

Pressure flow study

All urodynamic studies were performed according to a standardized protocol that followed the Good Urodynamic Practice guidelines recommended by the ICS [8].

Prior to PFS, free uroflowmetry and post-void residual volume (PVR) data were obtained. PFS tests were conducted using an Ellipse functional urodynamics system (Medizinische Systeme GmbH, Germany). During PFS, a 6 Fr double-lumen transurethral catheter was used to administer infusions and record intravesical pressure, and a 10 Fr single-lumen catheter was inserted into the rectum to measure intra-abdominal pressure. During cystometry, the patient was positioned in a convenient sitting position, and the bladder was filled with sterile normal saline solution (37°C) at a rate of 20 to 50 ml/min. After patient feel the strong desire to void, we stop the filling and the patient was asked to void. Afterwards, the patient voided according to their normal habits in the sitting or standing position, and pressure flow data were obtained. DO, maximum bladder capacity, and bladder compliance during water filling cystometry were then assessed. DO was defined according to the definition of the ICS.

The definition of parameters from WF curve

We defined some parameters from WF curve throughout micturition refer from previous study of Van Mastrigt et al. [9] (Fig. 1a). The volume of fluid in the bladder during emptying was expressed in a relative volume rV (rV = 1: completely full

bladder and rV = 0: the volume of residual urine). rV(Wmax) was the relative bladder volume when reach Wmax, W(Qmax) was the value of W at the moment of maximum flow rate, W80-W20 was the value of W at a relative volume rV = 0.80 minus its value at a relative volume rV = 0.20 and Line(W) was the slope of a straight line fitted to the W function between rV = 0.20 and rV = 0.80. A normal detrusor contractility pattern involves a sharp increase in WF at the initiation of micturition followed by further gradual increases until the end of micturition. However, patients with impaired detrusor contractility show a fading contraction pattern (WF decreases towards the end of micturition; Fig. 1b). Van Mastrigt *et al*. reported that in most patients, a preoperative fading contraction was replaced by a normal pattern after prostate surgery involving transurethral resection [9]. Parameters from WF curve could shows detrusor contractility patterns. The urodynamic parameters examined in this study included the maximum flow rate (Qmax), detrusor pressure at Qmax (PdetQmax), PVR, Wmax, W(Qmax), bladder contractility index (determined using the following formula: PdetQmax + 5 Qmax), rV(Wmax), Line (W) and W80-20. Of multiple parameters from WF curve, rV(Wmax) is simpler parameter compare to other parameters. rV(Wmax) can calculate only need bladder volume at peak of WF, bladder capacity and

residual urine volume(Fig. 1a). In this study, we mainly focused on the rV(Wmax). BOO was evaluated using the Abrams–Griffiths nomogram.

Statistical analyses

All data are presented as mean ± standard deviation values, and statistical analyses were conducted using the Student's t test. Comparisons between groups were performed by conducting Tukey analyses. P-values of <0.05 were considered to be statistically significant. Spearman's Rho (correlation coefficient) was calculated to analyze the strength of the correlations among variables. We also used the non-parametric Kruskal-Wallis test followed by pairwise comparisons analysis (performed using Dunn's procedure and Bonferroni's correction for multiple comparisons).

Results

Pressure flow study data

Qmax increased significantly after RP (13.0 vs. 17.3 ml/min, $P < 0.01$). Conversely, PdetQmax and PVR decreased significantly after RP (49.6 vs. 31.4 cmH_2O, and 48.6 vs. 10.1 ml, respectively; $P < 0.01$). Although neither Wmax, W(Qmax) nor the bladder contractility index changed significantly after RP, rV(Wmax), Line(W), and W80-W20 changed significantly after the procedure (0.48 vs.0.20; $P<0.001$, -0.0017 vs. -0.010; $P<0.05$ and -0.4 vs. -2.2; $P<0.05$, respectively). We observed DO in 11% (n = 4) of patients preoperatively and 8% (n = 3) of patients postoperatively (Table 2). Representative values for pre- and post-RP parameters are shown in Fig. 2.

IPSS and QOL scores

The patients' IPSS scores, including their IPSS subscores (which were used to assess LUTS), remained unchanged, whereas their QOL scores had improved significantly at 1 year after RP ($P = 0.007$; Table 3). No correlation was detected between rV(Wmax) and Wmax either before or after RP (Figs. 3a and b). Similarly, no correlation was detected between any IPSS parameter and

rV(Wmax) (Figs. 3c and d). However, QOL score correlated with rV(Wmax), i.e., significant differences were observed among the seven defined QOL groups ($P = 0.029$, Kruskal-Wallis test). In the post-hoc test, a significant difference in rV(Wmax) was detected between the patients with QOL scores of 0 and those with QOL scores of 4, 5, or 6 (Fig. 3e). Worsening QOL was associated with decreasing rV(Wmax). Both pre- and post-RP Qmax, PdetQmax and residual urine volume correlated with rV(Wmax) ($r = -0.52$, 0.43, 0.56, respectively; $P < 0.001$; Fig. 4 a, b, and c).

Discussion

In this study, evaluations based on multiple parameters from WF curve showed for the first time that RP changes the detrusor contractility pattern of prostate cancer patients. Decreased urine flow can be caused by BOO or impaired detrusor contractility. However, PFS is the only definitive way of distinguishing between these two entities [10]. Although PFS cannot measure detrusor contractility directly, as is possible with *in vitro* muscle strip assays, detrusor pressure and urine flow rate can be measured to assess detrusor contraction force and urethral resistance [5]. The methods used to assess BOO are well established, and several nomograms are in widespread use (e.g., the ICS [11] and Schafer nomograms [12]). Historically, most of these methods have been used for patients with benign prostate hyperplasia to evaluate BOO and detrusor contractility. However, they cannot be used to analyze the entire voiding cycle. During PFS, these nomograms only use PdetQmax and Qmax data for a single time point. Compared with the methods used to assess BOO, those used to quantify detrusor contraction force during voiding are less well verified [13]. Various methods for quantifying detrusor contractility have been developed, e.g.,

the stop test [14] and pressure-velocity plots [15], but none have met with widespread clinical acceptance.

With aging, the voided volume and maximum urine flow rate decrease continuously, and PVR increases [16]. The prevalence of BOO appears to be fairly consistent over different age groups [17], whereas DU increases with age [18]. The ICS definition of DU [5] contains two different pathophysiological causes, namely weak detrusor contraction force and abnormally short detrusor contractions. Each of the incidence and prevalence of the condition is highly dependent on both the definition and diagnostic methods used. Urodynamic studies have attempted to define DU, but no precise definition is widely accepted.

RP has the potential to affect both the anatomy and function of the bladder and urethra [19], which could affect LUTS, such as urinary incontinence, and urodynamic parameters. Urodynamic studies have demonstrated that RP improves urodynamic parameters by abrogating BOO without affecting overall detrusor contractility. In agreement with these findings, the present study found that RP abrogated BOO without affecting overall detrusor contractility (as

measured using Wmax and bladder contractility index), which resulted in improvements in other urodynamic parameters. However, Giannantoni *et al*. [2] reported that, whereas DU was detected in 43% of patients before RP, it was still seen in 29, 10, and 25% of patients at 1 month, 8 months, and 3 years after RP, respectively. RP can result in denervation of the bladder and urethra, which might explain the occurrence of DU [20]. Similarly, neurogenic voiding dysfunction can occur following bilateral extravesical ureteral neostomy [21]. In the current study, no significant changes were detected at 1 year after RP. Moreover, in our patient group postoperative residual urine volume was 10.1 ± 20.2 ml, this is significantly smaller volume. From this point of view, it is difficult to determine most patients in this study as DU patient. The development of refined RP surgical techniques, such as robot-assisted laparoscopic prostatectomy, might reduce the incidence of *de novo* DU. However, DU is caused by many factors, and further studies are necessary to examine this issue.

Detrusor contractility is often estimated using the WF, which represents detrusor pressure in relation to bladder volume and, urine flow rate and is calculated using the following formula [10]:

WF = (Pdet × Vdet + a × Vdet + b × Pdet) / 2 pai.

Vdet represents the detrusor shortening velocity, and a and b are the fixed constants 25 cmH_2O and 6 mm/sec, respectively, both of which are based on the findings of experimental and clinical studies. Conceptually, WF represents the mechanical power generated per unit area of the bladder wall surface. Therefore, Wmax is a measure of detrusor contraction strength at a single point in time, but it is necessary to produce a WF curve throughout micturition to assess overall detrusor contractility. Neither Wmax nor WF provides any information about detrusor contraction sustainability. The ICS definition of DU only considers two aspects of detrusor contraction, namely strength and sustainability. Generally speaking, bladder contractility is usually evaluated based on contractile strength alone because the utility of measuring contraction duration is not well validated [22]. Wmax is often used to characterize detrusor contractility, but this parameter does not refer to the entire contraction period, which can lead to erroneous diagnoses. As Pdet and Vdet vary throughout the voiding cycle, WF also varies. The advantages of WF are that it is nominally affected by bladder volume [23] and is not affected by the presence of BOO [24]. However, it does not provide a measure of contraction sustainability. Therefore, in the current study we have evaluated using parameters from WF curve such as

rV(Wmax), Line (W) and W80-20 as the first step of a future understanding of contraction of human bladder muscle.

Voiding pressure and maximal flow rate are usually used to define BOO for patients with benign prostate hyperplasia. Nevertheless, measurements obtained at only one point in the voiding cycle might only provide a snapshot of the complex physiological alterations occurring in the lower urinary tract. WF curves allow detrusor contraction power to be visualized throughout the entire duration of micturition. Intuitively, increasing WF values might indicate that the bladder muscles have sufficient physiological reserves. Conversely, decreasing WF values reflect poor contraction function, i.e., the inability to continue detrusor contraction. rV(Wmax) represents the pattern of bladder contraction using throughout the voiding cycle. Because WF usually gradually increases from the onset of voiding to the terminal phase of micturition [23], low rV(Wmax) values may represent detrusor contractions of an appropriate manner. However, bladder contraction duration (sustainability) could not evaluate only this one parameter. Moreover, the raw data of WF could be fluctuated in some patients, and could

not be a smooth line during emptying (because of biological data). This could affect the calculation of WF related parameters including rV(Wmax).

Previously, van Mastrigt *et al*. [9] reported the parameters not only rV(Wmax), but also Line (W) and WF80 – WF20, which is the slope and raw data of WF between WF at 20% of voided volume subtracted from the WF at 80% of voided volume. These parameters can also reveal how well a contraction is sustained. This concept is similar to rV(Wmax) parameter mathematically and represents the pattern of micturition. Because WF normally increases from the onset of voiding [24], Line (W) and WF80 – WF20 can be used to discriminate between well-sustained and weakening micturition contractions. Contractility during the latter stage of voiding is particularly important. However, personal computer is required to calculate Line (W) and WF80 – WF20 (to measure all of the parameters throughout the micturition cycle); therefore, rV(Wmax) is simpler parameter compare to other parameters. rV(Wmax) can calculate only need bladder volume at peak of WF, bladder capacity and residual urine volume (Fig. 1a). Moreover, in the current patients setting, rV(Wmax) is the most sensitive for compare pre and post RP detrusor contractility pattern.

Van Mastrigt *et al*. reported that in most patients, preoperative fading contraction patterns were replaced with normal patterns after prostate surgery involving transurethral resection [9]. Moreover, they concluded that when fading contraction patterns persist postoperatively they should probably be ascribed to structural changes in the detrusor muscle secondary to BOO. In this study we focus the change of detrusor activity after remove the prostate completely, even surgical intervention is more severe compare to transurethral resection of prostate.

It is well recognized that LUTS are not specific to BOO. Many previous studies have reported no correlation between IPSS and various urodynamic parameters associated with obstruction [25,26]. In the current study, IPSS remained unchanged after RP, whereas the QOL score improved significantly at 1 year after RP. Thus, it can be concluded that BOO is often abrogated and the anatomy and function of the bladder altered after RP. Qmax increased significantly, and PdetQmax and PVR decreased significantly after RP (Table 2). Efficient voiding can occur at low pressure, as seen in the female voiding pattern. As micturition efficiency is an important requirement for normal micturition or normal detrusor contractility [27], easy urination might be associated with increased QOL. As mentioned above,

Wmax represents the maximum bladder contraction power at a particular point in time, whereas rV(Wmax) can be used to detect changes in detrusor contraction patterns.

The limitations of this study include its retrospective nature, small patient population, and the fact that each subject only underwent one post-RP follow-up examination. In the future, a multicenter study will be critical to confirm our findings. To confirm our findings, a multicenter study will be critical, and further collection of data (various diseases or conditions) leads to enhancement of scientific reliability.

In conclusion, evaluation of rV(Wmax) confirmed that RP results in the restoration of a normal detrusor contractility pattern in prostate cancer patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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Legends

Fig. 1 (a) Definition of WF related parameters.

rV was defined as the volume of fluid during emptying was expressed in a relative volume (rV = 1: completely full bladder and rV = 0: volume of residual urine) .

(b) Normal and impaired detrusor contractility patterns.

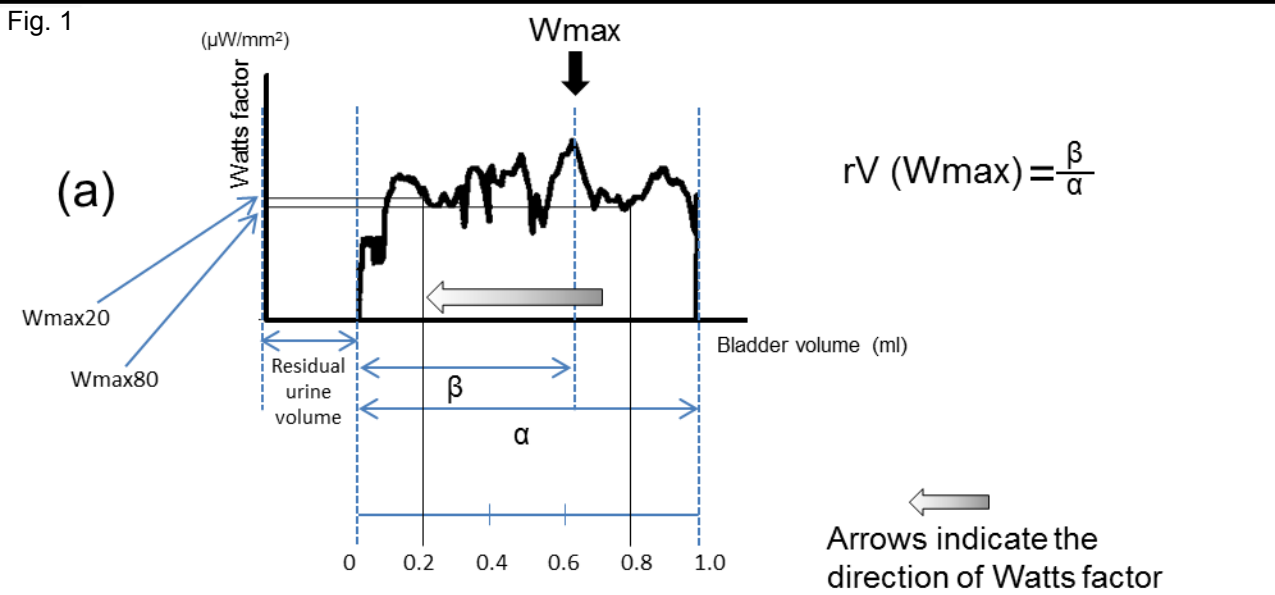
A normal detrusor contractility pattern involves a sharp increase in the WF at the initiation of micturition followed by further gradual increases until the end of micturition. However, patients with impaired detrusor contractility exhibit a fading contraction pattern towards the end of micturition.

Fig. 2 Representative examples of pre- and post-RP WF related parameters for the same patient. In the preoperative PFS, WF exhibited a fading contraction pattern (rV (Wmax) = 0.95, Line (W) = 0.0046, W80-W20 = 0.7). After surgery, rV (Wmax) decreased sharply at the initiation of micturition and then increased gradually until the end of micturition (rV (Wmax)= 0.11, Line (W) = -0.025, W80-W20 = -6.8). X-axis is bladder capacity, and y-axis is WF.

Fig. 3 Scatterplots of the patients' Wmax and rV (Wmax) values pre-RP (a) and post-RP (b), IPSS total score and rV (Wmax) values pre-RP (c) and post-RP (d). (e) Scatterplots of the patients' pre- and post-RP rV(Wmax) values for the seven QOL groups. rV (Wmax) differed significantly among the seven QOL groups according to the Kruskal-Wallis test ($P = 0.029$). In post-hoc testing, a significant difference was detected between the rV (Wmax) values of patients with QOL scores of 0 and those of the patients with QOL scores of 4, 5, or 6. *Significantly different from the QOL score 0 group ($P < 0.05$).

Fig. 4 Scatterplot showing the patients' pre- and postoperative (a) Qmax and rV (Wmax) values. The patients' pre- and post-RP Qmax values correlated with rV (Wmax) ($r = -0.52$, $P < 0.001$). (b) PdetQmax and rV (Wmax) values. The patients' pre- and post-RP PdetQmax values correlated with rV (Wmax) ($r = 0.43$, $P < 0.001$). (c) Residual urine volume and rV (Wmax) values. The patients' pre- and post-RP residual urine volume values correlated with rV (Wmax) ($r = 0.56$, $P < 0.001$).

Fig. 1


(μW/mm²)
Wmax
Watts factor
(a)
Wmax20
Wmax80
Residual urine volume
β
α
Bladder volume (ml)
0
0.2
0.4
0.6
0.8
1.0
rV (Wmax) = β/α
Arrows indicate the direction of Watts factor

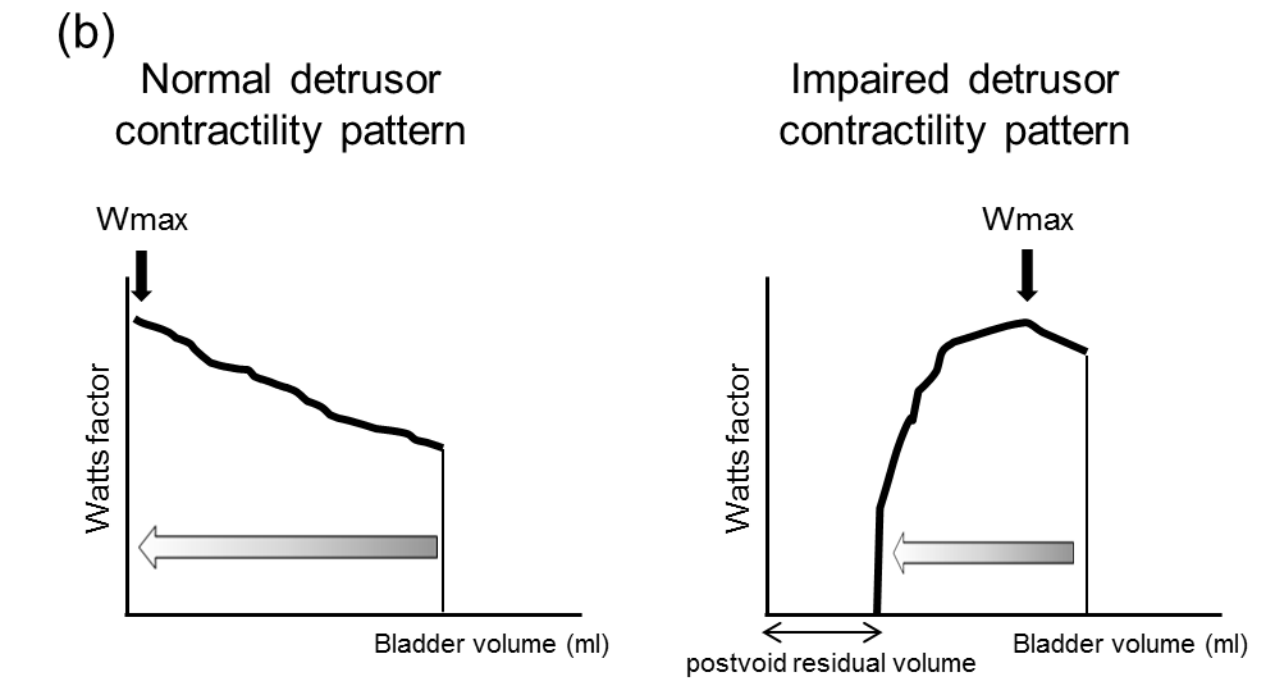

(b)
Normal detrusor contractility pattern
Impaired detrusor contractility pattern
Wmax
Watts factor
Bladder volume (ml)
Wmax
Watts factor
postvoid residual volume
Bladder volume (ml)

Fig. 2

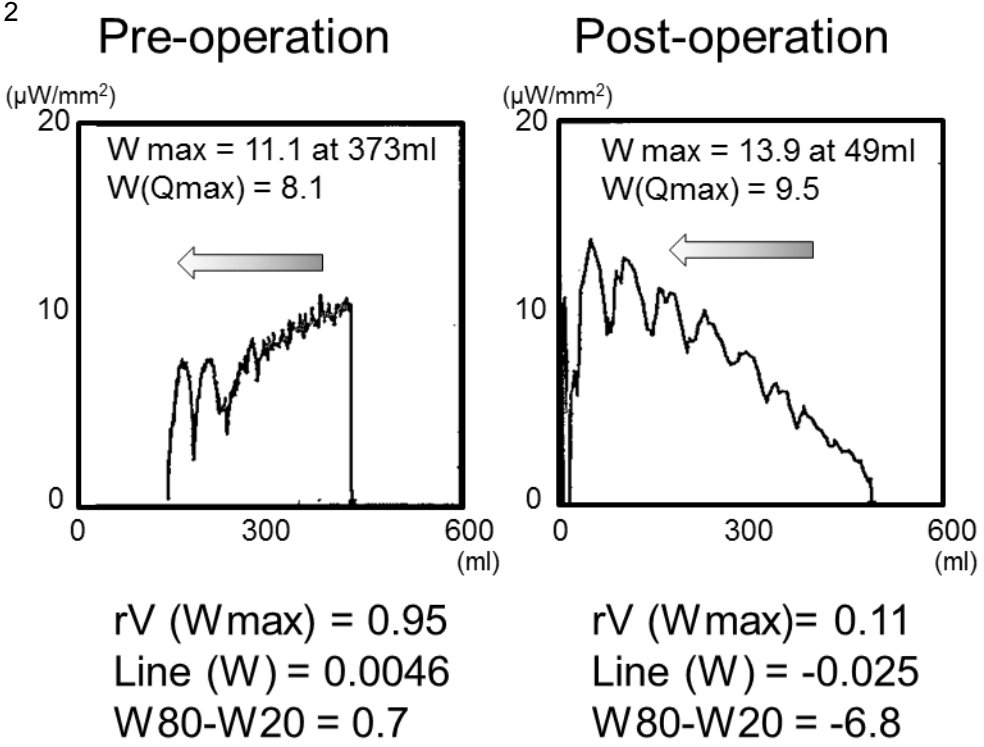

Pre-operation
Post-operation
(μW/mm²)
20
10
0
W max = 11.1 at 373ml
W(Qmax) = 8.1
0
300
600
(ml)
rV (Wmax) = 0.95
Line (W) = 0.0046
W80-W20 = 0.7
(μW/mm²)
20
10
0
W max = 13.9 at 49ml
W(Qmax) = 9.5
0
300
600
(ml)
rV (Wmax)= 0.11
Line (W) = -0.025
W80-W20 = -6.8

Fig. 3a

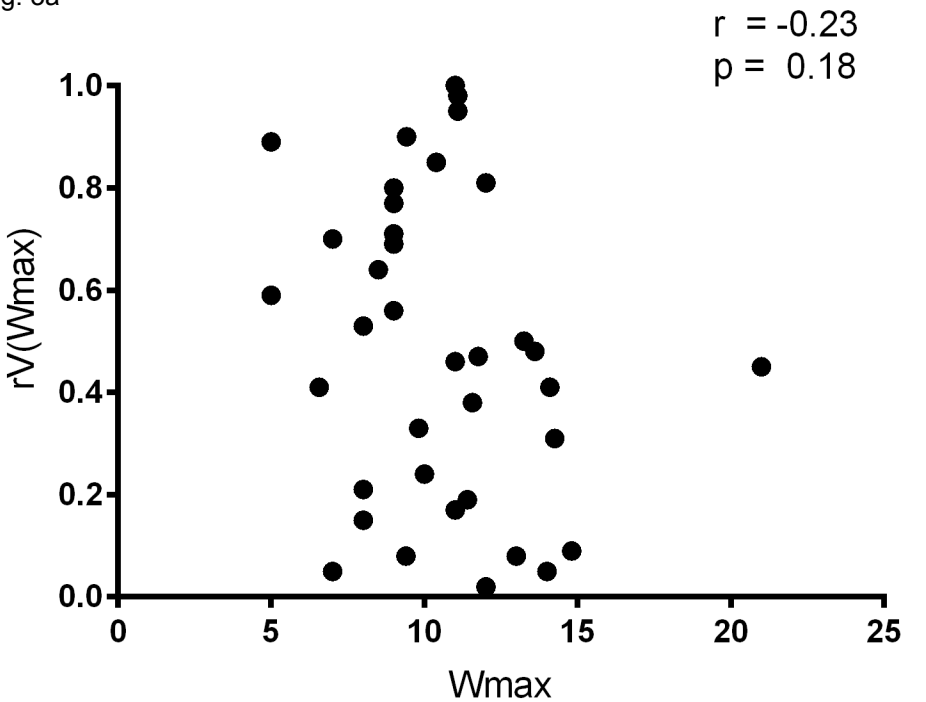


Fig. 3b

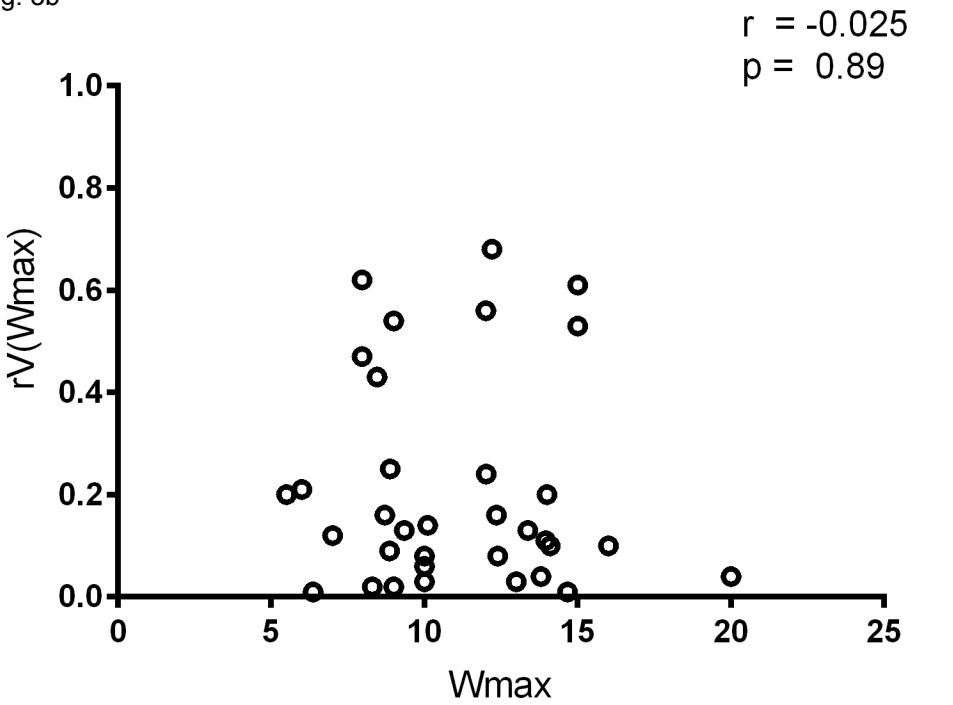


Fig. 3c

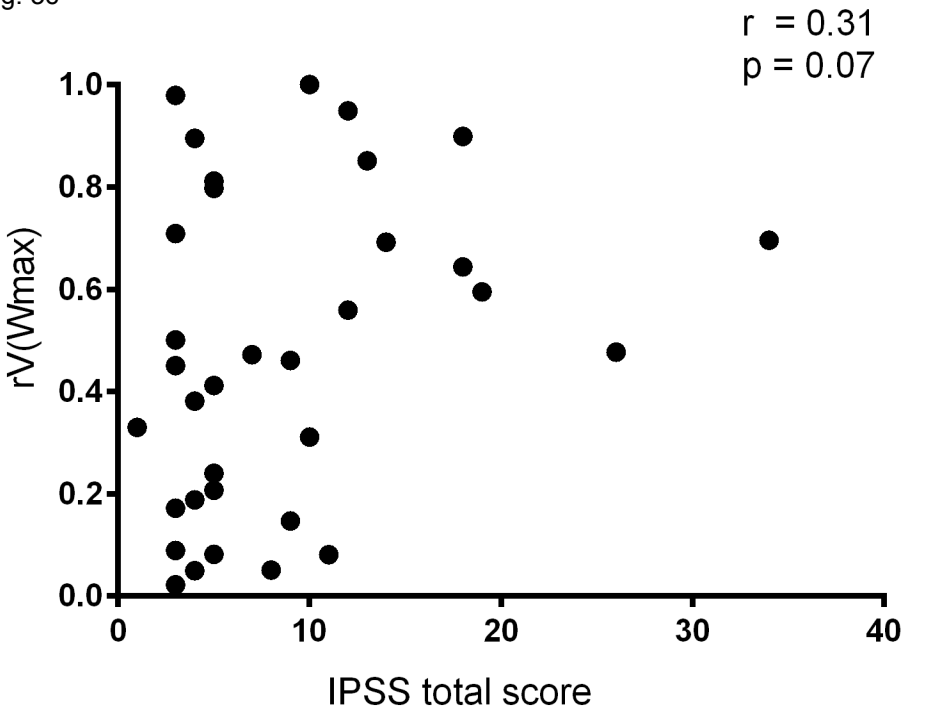


Fig. 3d

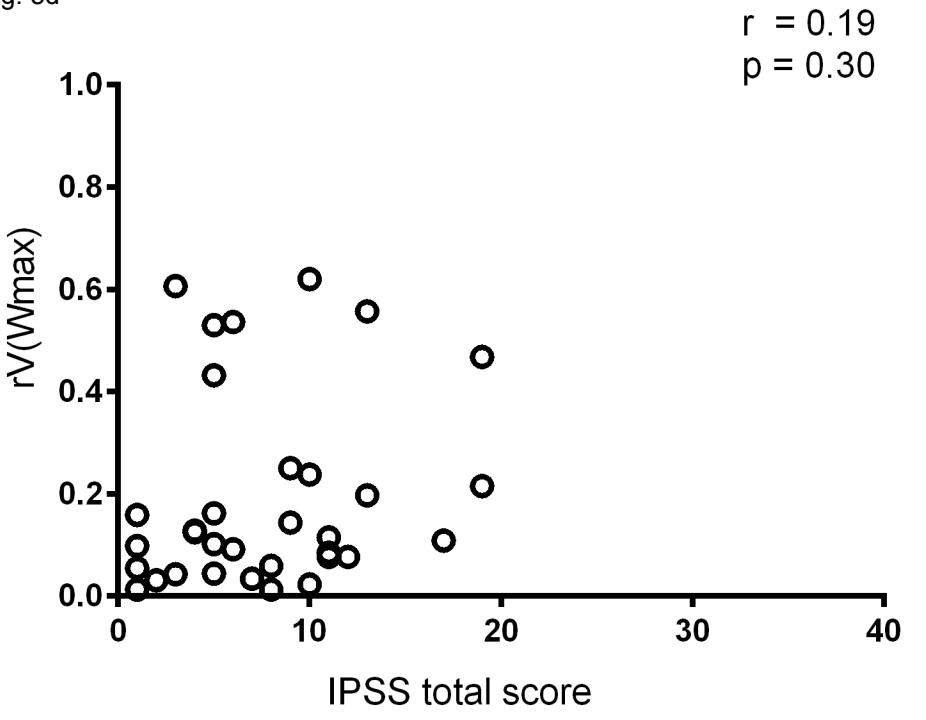


Fig. 3e

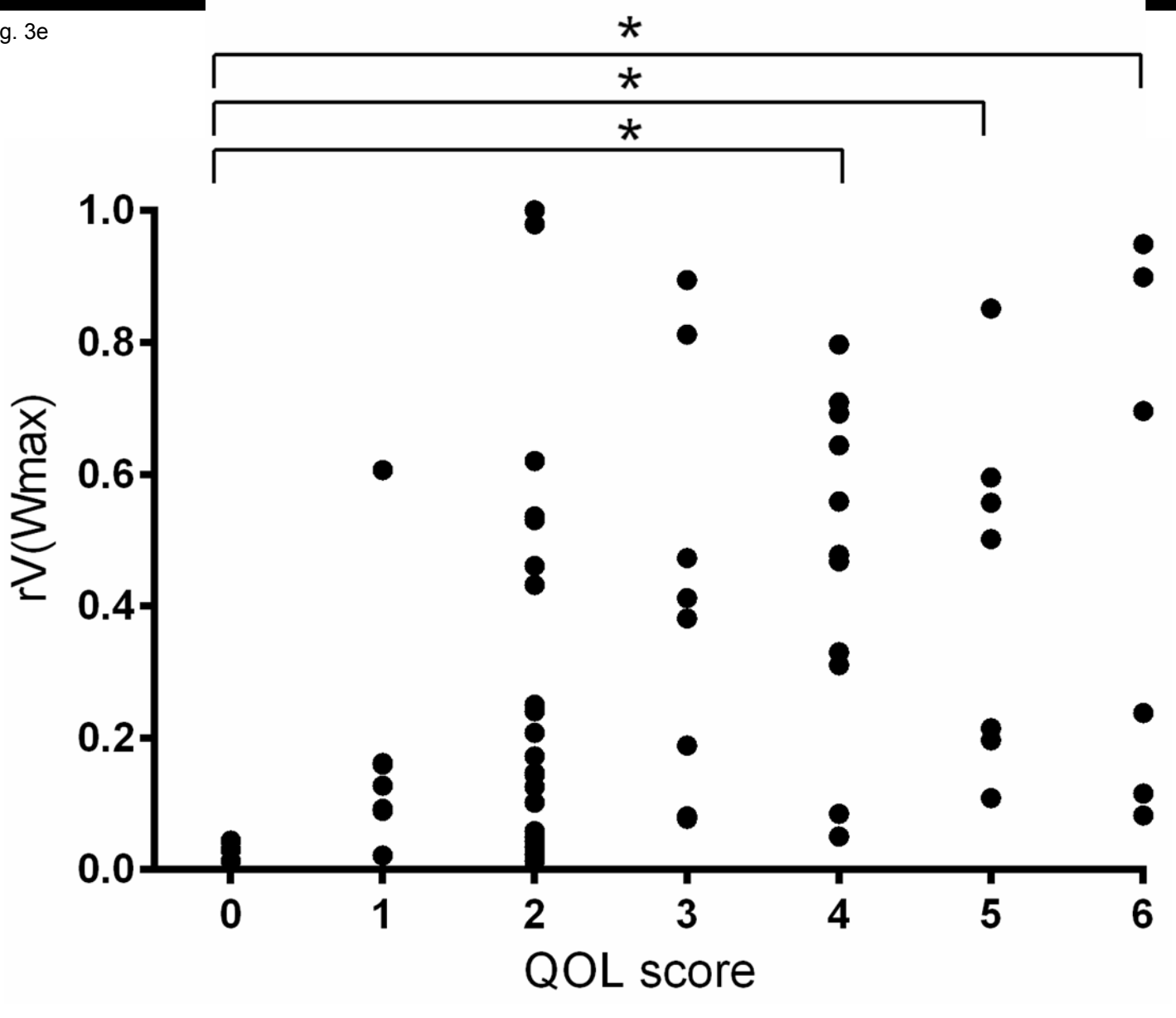


Fig. 4a

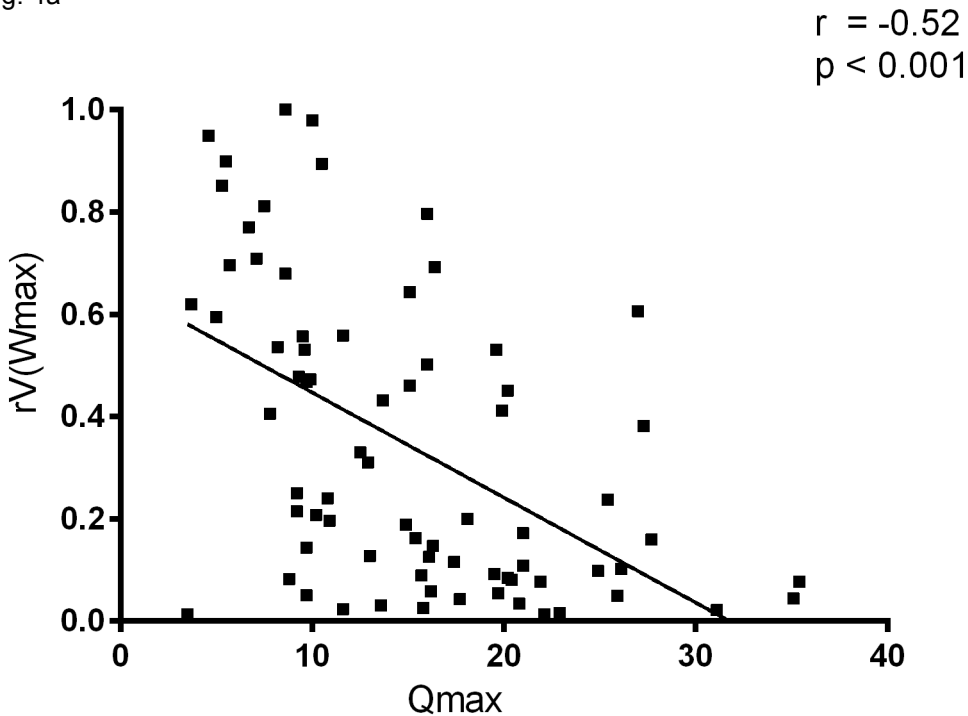


Fig. 4b

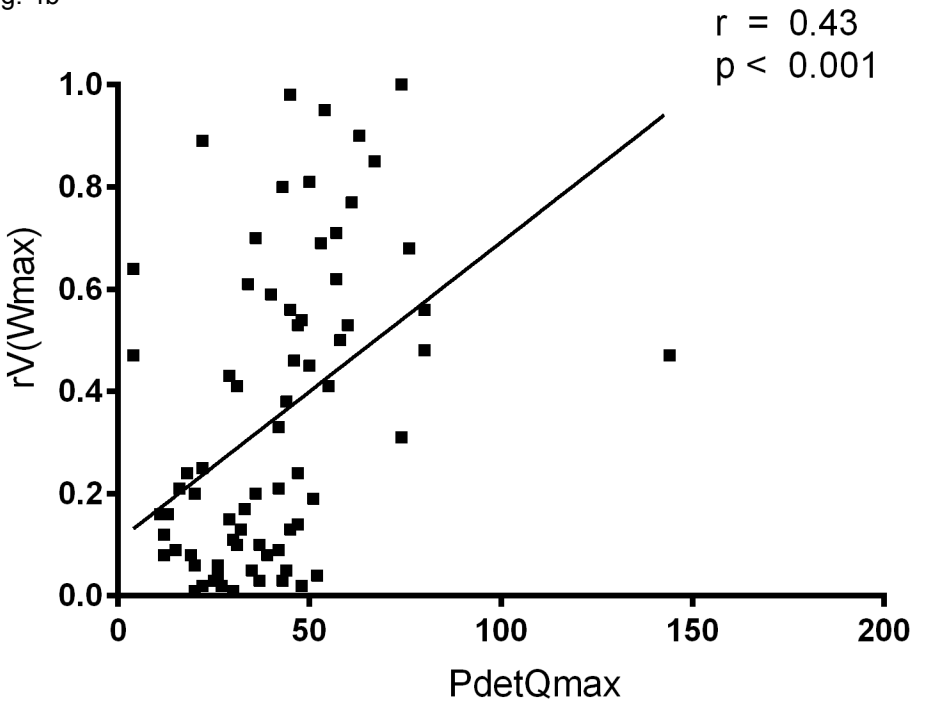


Fig. 4c

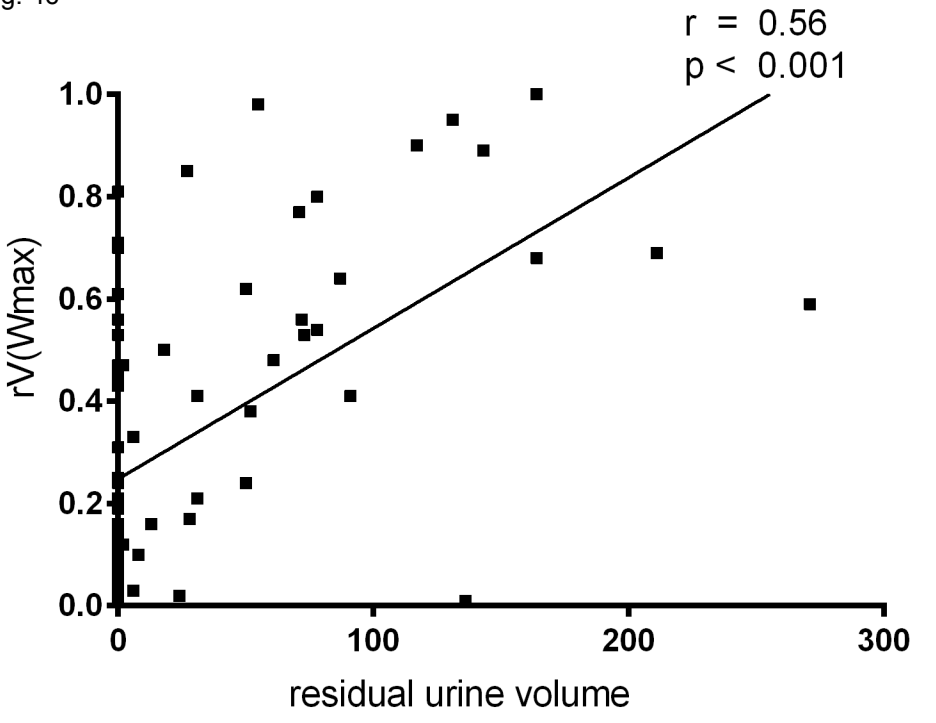

r = 0.56
p < 0.001
1.0
0.8
0.6
0.4
0.2
0.0
rV(Vmax)
0
100
200
300
residual urine volume

Table 1
Baseline characteristics of 37 men who underwent radical prostatectomy

Age at RP, years	65 (53, 74)
Type of surgery	
Open	13 (35%)
Laparoscopic or robotic	24 (65%)
Prostate volume (ml)	39.9 ± 18.4
Clinical stage	
≤T2a	35 (95%)
≥T2b	2 (5%)
Nerve-sparing status	
None	20 (54%)
Unilateral	5 (14%)
Bilateral	12 (32%)

Age is shown as median (interquartile range), mean and standard deviation and remaining data as frequency (percentage). RP: radical prostatectomy

Table 2
Results of the pressure flow studies

	Pre	Post	P
Bladder capacity (ml)	388 ± 139	351 ± 111	n.s.
Number of patients with DO (%)	4 (11%)	3 (8%)	
Qmax (ml/sec)	13.0 ± 6.5	17.3 ± 7.7**	0.005
PdetQmax (cmH_2O)	49.6 ± 21.6	31.4 ± 18.2**	<0.001
Residual urine volume (ml)	48.6 ± 66.1	10.1 ± 28.5**	0.004
Number of patients (%) with BOO (A-G nomogram)			
Unobstructive	12 (32%)	31 (84%)	
Equivocal	16 (43%)	3 (8%)	
Obstructive	9 (24%)	3 (8%)	
BCI	114.6 ± 35.6	115.4 ± 18.2	n.s.
Wmax (W/m^2)	10.5 ± 3.1	11.0 ± 3.2	n.s.
W（Qmax） (W/m^2)	8.9 ± 2.7	9.8 ± 3.2	n.s.
rV(Wmax)	0.48 ± 0.3	0.20 ± 0.20**	<0.001
Line(W) ($W/m^2/ml$)	-0.0017 ± 0.01	-0.010 ± 0.01*	<0.05
W80-W20 (W/m^2)	-0.4 ± 2.0	-2.2 ± 2.8*	<0.05

Comparison of the voided volume, maximum urinary flow (Qmax), detrusor pressure at the maximum flow rate (PdetQmax), and residual urine volume values obtained during preoperative and 1-year postoperative pressure flow studies. Data represent the mean ± SD and were compared with Student's t test. A–G nomogram: Abrams–Griffiths nomogram, BCI: bladder contractility index (PdetQmax + 5 Qmax), Wmax: max value of Watts factor (W), W（Qmax）: value of W at the moment of Qmax, rV(Wmax): relative bladder volume at which this maximum occurred, Line(W): slope of a straight line fitted to the W function between rV = 0.20 and rV = 0.80, and W80-W20: value of W at a relative volume rV = 0.80 minus its value at a relative volume rV = 0.20. *P < 0.05, **P < 0.01.

Table 3

Pre- and postoperative (1 year) lower urinary tract symptoms according to the patients' IPSS and QOL scores

IPSS	Pre	Post	P
Total	8.8 ± 7.3	8.1 ± 4.8	0.38
Incomplete emptying	1.0 ± 1.5	1.1 ± 1.1	0.99
Frequency	1.6 ± 1.2	1.4 ± 0.8	0.15
Intermittency	0.9 ± 1.4	0.7 ± 1.0	0.33
Urgency	0.9 ± 0.9	0.9 ± 1.3	0.99
Weak stream	1.4 ± 1.5	1.1 ± 1.2	0.24
Straining	1.2 ± 1.4	1.5 ± 1.6	0.93
Nocturia	1.7 ± 1.2	1.6 ± 1.1	0.13
QOL score	3.5 ± 1.5	2.5 ± 1.7*	0.007

*P < 0.01