의학석사 학위논문

신경인성방광에서 새로운 방광내시경적 방광육주화 분류체계의 설정

Establishment of the Novel Cystoscopic Classification for Bladder Trabeculation of Neurogenic Bladder

2014 년 7 월

서울대학교 의과대학원

의학과 비뇨기과학 전공

정 재 현

신경인성방광에서 새로운 방광내시경적 방광육주화 분류체계의 설정

Establishment of the Novel Cystoscopic Classification for Bladder Trabeculation of Neurogenic Bladder

지도교수 오 승 준

이 논문을 의학석사 학위논문으로 제출함

2014 년 7 월

서울대학교 대학원

의학과 비뇨기과학 전공

정 재 현

정재현의 석사학위논문을 인준함

2014 년 7 월

위 원 장 _____ (인)

부 위 원 장 _____ (인)

위 원 _____ (인)

ABSTRACT

Establishment of the Novel Cystoscopic Classification for Bladder Trabeculation of Neurogenic Bladder

Jae Hyun Jung

Student Number: 2012-23624

Department of Urology, College of Medicine, Seoul National University

Objective: To establish a cystoscopic grading system for trabeculation of neurogenic bladders

Materials & Methods: A total of 140 neurogenic bladder patients who had undergone both fluoroscopic urodynamic study and cystoscopic examination were retrospectively reviewed. Cystoscopic images were categorized into four grades according to the formation of muscle bundle layer and the height-to-width ratio of the muscle bundle: 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Test-retest reliability and inter-observer reliability were assessed. Cystoscopic grade of the trabeculated bladder were correlated with urodynamic results and the fluoroscopic grades of trabeculation.

Results: Median age of the patients was 62.4 (± 14.0, SD) years and the most common underlying disease was spinal disease. The test-retest reliability showed almost perfect agreement with all levels of Cronbach's alpha ranging from 0.927 to 0.984. The intraclass correlation coefficient was 0.986, indicative of an almost perfect level of inter-observer reliability. The grading system showed clinical significance by correlation with urodynamic parameters (Qmax, p value=0.016; PVR, p value<0.001; BOO index, p value=0.002).

Conclusion: Our results showed that this novel cystoscopic classification of bladder trabeculation is highly reliable. We anticipate that this grading system will be widely used in daily clinical practice and clinical research.

Keywords: Trabeculation, urinary bladder, muscles, cystoscopes, urodynamics

CONTENTS

List of Tables

Introduction

Patients with bladder dysfunction often show trabeculated bladder structures comprising an irregular contour with thick walls and hypertrophied muscle bundles.[1, 2] This bladder trabeculation reflects dysfunction of the detrusor muscle.[3-5] The clinical correlation of trabeculated bladder with urodynamic parameters was investigated in patients with lower urinary tract dysfunction.[6-8]

Differences in clinical parameters according to the severity of trabeculated bladders were evident.[2, 9] Khoury et al. reported[3] that the severity of bladder trabeculation in patients with neurogenic bladder could be a marker of bladder outlet resistance. Groutz et al.[10] found that in patients who had refractory detrusor overactivity without any alarming signs, diagnostic cystourethroscopy facilitated the identification of silent signs, such as bladder trabeculation and timely diagnosis; however, neither study used objective criteria of bladder trabeculation; the former study classified the condition into two grades, whereas the latter study classified it into three subjective grades. El Din et al.[11] reported cystoscopic grades based on representative images of each grade. However, neither study established the reliability of the grades of bladder trabeculation by using appropriate validation processes.

We previously established a system for the fluoroscopic grading system of bladder trabeculation and have proven its validity and reliability.[1] Since cystoscopic examinations are widely used in daily clinical practice, and allow for direct inspection of the intraluminal bladder, it is necessary to establish an objective cystoscopic classification system for the trabeculated bladder. The present study was undertaken to establish a cystoscopic classification system and to indicate the clinical significance of trabeculation graded by the cystoscopic classification according to urodynamic parameters in patients with neurogenic bladder.

Materials and Methods

Subjects and cystoscopic examination

This study was approved by the Institutional Review Board of Seoul National University Hospital (Approval No. H1305-636-492). A total of 411 patients were enrolled in this study, all of whom had neurogenic bladders and had undergone fluoroscopic urodynamic study with cystoscopic examination within a the previous 6 months to assess voiding dysfunction in our institute between September 2005 and December 2012. The medical records were retrospectively reviewed, and all cystoscopic and fluoroscopic images were collected by one investigator (JHJ) from the cystoscopic and urodynamic databases. The exclusion criteria were cases with anatomical changes (e.g., vesicoureteral reflux, urethral leak, or diverticulum), cases with previous urological surgery or with urethral stricture, and cases with unclear cystoscopic images due to aspects such as turbid urine and bleeding. The investigators (SJO, SYC, JHJ) read all images and randomly selected 140 cases – 40 from cystoscopic grade 0 (none), 40 from cystoscopic grade 1 (mild), 30 from cystoscopic grade 2 (moderate), and 30 from cystoscopic grade 3 (severe).

In all patients, history taking and physical examination were performed to identify underlying disease. The fluoroscopic urodynamic study and cystourethroscopy were performed sequentially. The study was performed in the same manner described previously[1] as recommended by the International Continence Society.[12] The urodynamic study was performed using the same protocol (UD-2000, Medical Measurement System, Enschede, The Netherlands) as described in a previous study.[1] In brief, with a dual-lumen catheter of 6Fr (Medtronic, Skovlunde, Denmark) and a rectal balloon catheter (Medical Measurement System, Enschede, The Netherlands), patients were positioned supine on a fluoroscopy table (Sonialvision 100 model ZS100I, Shimadzu, Kyoto, Japan) and evaluation of bladder appearance was performed during the filling and emptying phases.

Cystoscopic examinaion was performed in the dorsal lithotomy position. Cystourethroscopy using a 30-degree telescopic lens was performed using endoscopy (Karl-storz Endoscope, Tuttlingen, Germany) and was used to evaluate the whole urethra from the meatal opening to the bladder neck, to check any structural abnormalities. Then 70-degree cystoscopy was used to evaluate the bladder. Whole bladder inspection by cystoscopy was performed to identify both orifices, mucosal abnormalities (e.g., trabeculation), and other anatomical changes. The urinary bladder was typically filled with normal saline with natural gravity until 70-80% of the maximal voided volume is reached, which was determined by three-day voiding diary. Therefore, the bladder trabeculation is assumed to be assessed in approximately 70-80% of maximal voided volume. Cystoscopic findings were recorded using a digital recorder (Telecam SL II, Karl-Storz Endoscope) and still images were taken from midline trigone and various directions (i.e., 7, 9, 11, 5, 3, 1, and 12 o' clock) of the urinary bladder. Then, still images were taken from the dome and posterior wall area carefully to cover whole area.

Establishing new cystoscopic classification

To assess the severity of trabeculation, we distinguished between four grades: 0 (none), 1 (mild), 2 (moderate), and 3 (severe). We classified bladder trabeculation according to two criteria – namely, formation of muscle bundles and depth of mucosal layer (Table 1). Criteria A were as follows: if no formation of muscle bundle was detected by cystoscopic examination, then grade 0 is assigned. Grade 1 was assigned when just a single layer of muscle bundle formation was detected. If the muscle bundles were in two layers but comprised no more than 50% of the still image (i.e., overlapping bundles), it was assigned to grade 2. If two layers filled more than 50% of the cystoscopic field of a still image or if three layers were detected in the still image, it was assigned to grade 3. Criteria B were as follows: if the depth of mucosa was considerable but the height of the muscle bundle (near the mucosal base, from the

deepest portion of that mucosa) was smaller than the width between those muscle bundles, grade 2 was assigned. If the height was the same as or larger than the width, grade 3 was assigned (Table 1). Cystoscopic grade was determined according to a representative image of higher grade in the same patient. When the grades determined by criteria A and B are different, higher grades were adopted.

Validation of classification system

Inter-observer and test-retest reliability

To evaluate the inter-observer reliability, the trabeculation grades were read by nine participants: three urologic residents, three medical school students, and three nursing school students. One of the study investigators (JHJ) provided the participants with an illustrative outline of the grading system. Participants were trained to assess the trabeculation of the bladder for 30 minutes. Then randomly assigned cystoscopic still images of 140 cases (4 per case) were given to participants who had independently determined the grade of the bladder trabeculation of each case within 30 seconds. Test-retest reliability of the cystoscopic grading system of bladder trabeculation was assessed two weeks later. Reliabilities were analyzed by the intraclass correlation coefficient and Cronbach's alpha.

Correlation between fluoroscopic grades and cystoscopic grades

The fluoroscopic grade of bladder trabeculation was evaluated by the three investigators (SJO, SYC, JHJ) using the same protocol as the criteria determining cystoscopic trabeculation previously described.[1] Results of fluoroscopic grades were matched with cystoscopic grades. Analysis of statistical significance was performed using correlation analysis.

Urodynamic correlation

The clinical significance of this classification was evaluated by correlating

cystoscopic trabeculation grades with the urodynamic parameters using analysis of variance. Urodynamic parameters included free uroflowmetry, filling cystometry, and voiding cystometry.

All variables are presented as mean ± standard deviation. Statistical significance was defined by a p-value <0.05. All statistical analyses were performed using commercially available software (SPSS 19.0, Chicago, IL, USA).

Results

Patient demographics

Patient demographics were described in Table 2. Eighty one male and 59 female patients were included. Median age of the patients was 62.4 (± 14.0, SD) years. The most common underlying disease was spinal disease.

Inter-observer and test-retest reliability

There was an almost perfect level of reliability among the participants as evident by the inter-observer reliability of bladder trabeculation grades. The intraclass correlation coefficient was 0.986 (95% CI 0.98 – 0.99, $p<0.001$). There was a strong correlation between the initial grading and repeat trabeculation grading (Table 3). All values for Cronbach's alpha ranged from 0.927 to 0.984, which indicated an almost perfect level of agreement.

Correlation between fluoroscopic grades and cystoscopic grades

The cystoscopic grades and fluoroscopic grades were moderately well correlated (Table 4). Spearman's correlation coefficient was 0.79 ($p<0.001$). Cystoscopic grades and fluoroscopic grades were identical in 52.9% (74/140). Overall, 40% (56/140) of the cystoscopic grades were rated higher than fluoroscopic grades while 7.1% (10/140) of cystoscopic grades were rated lower than fluoroscopic grades. More than half of cystoscopic grades 1 and 3 – 57.5% (23/40) and 70% (21/30), respectively – were rated higher than fluoroscopic grades.

Urodynamic correlation

Table 4 shows the clinical significance of the cystoscopic classification of trabeculation by urodynamic results. As trabeculation grades increased, the bladder compliance decreased, especially in grade 3. Maximal flow rate (Qmax) was

significantly lower in free uroflowmetry, and postvoid residual (PVR) volume was increased in voiding cystometry in both grades 2 and 3 ($p<0.05$). Bladder contractility index was significantly lower in grade 3 ($p=0.005$) and the bladder outlet obstruction index (BOOI) was significantly higher in cystoscopic grades 2 and 3 ($p=0.002$).

Discussion

Changes in bladder structure and function are caused in a pathophysiologic cascade initiated by BOO. It is regarded as a compensatory response for the bladder to overcome the resistance for emptying of urine. Inui et al.[13] reported that bladder hypertrophy, bulking of detrusor muscle, is a consistent consequence of BOO in animal models and men. In case of severe trabeculation, the urinary bladder often shows a Christmas tree appearance in a cystographic image. Bai et al.[2] analyzed urodynamic parameters of female patients with and without bladder trabeculation and found that BOO may be a risk factor for bladder trabeculation. Liang et al.[9] reported clinical correlation of bladder trabeculation in patients with pelvic organ prolapse. They classified bladder trabeculation into four groups, but did not use objective criteria. El Din et al.[11] reported that findings at urethroscopy correlated with urodynamic results. Even though they graded trabeculation of the bladder using representative cystoscopic images, there were no objective criteria.

To our knowledge, the present study is the first to establish a cystoscopic classification of trabeculated bladder, show its reliability, and indicate a clinical correlation with the urodynamic study. This classification was based on the conception of mucosal layer weakening and muscle bundle strengthening if trabeculation presents. Our results demonstrated that even unspecialized individuals could interpret this classification, as six of nine participants were non-urologists who had never been trained to read cystoscopic images.

Cystoscopic grade did not display strong consistency with fluoroscopic grade (Table 2). Except for grade 0, fluoroscopic grades were often rated lower than cystoscopic grades. This is because mild trabecuation may not be readily evident in fluoroscopic images. Moreover, trabeculated bladder margin may often be overlapped and thus masked in fluoroscopy which can only show a two-dimensional antero-posterior view. Some over-graded cases in fluoroscopic images may be due to

observational errors where an irregular bladder contour was misinterpreted as trabeculation. These findings indicate that the fluoroscopic grading system has some limitations, including overlapped bladder contours, observational errors in measuring depth, and irregular bladder contours – all of which increase the chance of misinterpreting bladder trabeculation; however, this may not always mean that the fluoroscopic grading system is less accurate than the cystoscopic grading system. Not all patients with lower urinary tract dysfunction undergo both tests in real clinical practice. The cystoscopic exam and urodynamic study are completely different examinations.

This classification showed a correlation of urodynamic results with the grade of bladder trabeculation. These correlation with cystoscopic grade showed comparable significance to the correlation with fluoroscopic grade in previous study.[1] However, the grades did not always show significant differences, especially grades 2 and 3. In fact, grades 2 and 3 did not show significant differences in maximal flow rate and BOO index. In the BOO index there may be relatively more missing values of detrusor pressure at maximum flow (PdetQmax) in cystoscopic grade 3 with fluoroscopic grade 3 than in cystoscopic grade 2. Grades 2 and 3 showed differences in the bladder contractility index and compliance. It is likely that with a larger sample size, this classification would show differences between grades 2 and 3.

This study had some limitations. The present study included only patients with neurogenic bladder without anatomically abnormal factors, such as vesicoureteral reflux, urethral leak, and bladder diverticulum. Furthermore, there may be some need for further improvement of our cystoscopic grading system in the future since some urodynamic parameters showed insignificant difference between grades 2 and 3. Further studies should also address various diseases and anatomic factors with larger sample sizes. We anticipate that this newly developed cystoscopic grading system will be widely used in daily clinical practice and clinical research.

Conclusion

We established a novel cystoscopic classification system of trabeculated bladder. This grading system proved to be reliable and clinically meaningful.

References

1. Cho SY, Bae J, Yoo C, et al. Establishment of a grading system for bladder trabeculation. *Urology.* 2013;81(3):503-507.

2. Bai SW, Park SH, Chung DJ, et al. The significance of bladder trabeculation in the female lower urinary system: An objective evaluation by urodynamic studies. *Yonsei Med J*. 2005;46(5):673-678.

3. Khoury AE, Dave S, Peralta-Del Valle MH, et al. Severe bladder trabeculation obviates the need for bladder outlet procedures during augmentation cystoplasty in incontinent patients with neurogenic bladder. *BJU Int.* 2008;101:223-226.

4. Holm NR, Horn T, Smedts F, et al. The detrusor muscle cell in bladder outlet obstruction – ultrastructural and morphometric findings. *Scand J Urol Nephrol.* 2003;37:309-315.

5. Tse V, Wills E, Szonyi G, et al. The application of ultrastructural studies in the diagnosis of bladder dysfunction in a clinical setting. *J Urol.* 2000;163:535-539.

6. Andersen JT, Nordling J. Prostatism. II. The correlation between cysto-urethroscopic, cystometric and urodynamic findings. *Scand J Urol Nephrol.* 1980;14:23-27.

7. Simonsen O, Moller-Madsen B, Dørflinger T, et al. The significance of age on symptoms and urodynamic- and cystoscopic findings in benign prostatic hypertrophy. *Urol Res.* 1987;15:355-358.

8. Barry MJ, Cockett AT, Holtgrewe HL, et al. Relationship of symptoms of prostatism to commonly used physiological and anatomical measures of the severity of benign prostatic hyperplasia. *J Urol.* 1993;150:351-358.

9. Liang CC, Chang YL, Lin YH, et al. Significance of bladder trabeculation in postmenopausal women with severe pelvic organ prolapsed: Clinical and urodynamic assessments. *Menopause.* 2013;20:813-817.

10. Groutz A, Samandarov A, Gold R, et al. Role of urethrocystoscopy in the evaluation of refractory idiopathic detrusor instability. *Urology.* 2001;58:544-546.

11. El Din KE, de Wildt MJ, Rosier PF, et al. The correlation between urodynamic and cystoscopic findings in elderly men with voiding complaints. *J Urol*. 1996;155:1018-1022.

12. Schafer W, Abrams P, Liao L, et al. Good urodynamic practices: Uroflowmetry, filling cystometry, and pressure-flow studies. *Neurourol Urodyn.* 2002;21:261-274.

13. Inui E, Ochiai A, Naya Y, et al. Comparative morphometric study of bladder detrusor between patients with benign prostatic hyperplasia and controls. J Urol. 1999;161:827-830.

Table 1. Cystoscopic grading system of bladder trabeculation

Variables	Cystoscopic grades			
	0 (none)	1 (mild)	2 (moderate)	3 (severe)
Criteria A: formation of muscle bundle layer	No	One layer	Two layers (<50% of the image)	Two layers (>50% of the image) or more layers
Criteria B: ratio of "height" to "width"	N/A	N/A	"height" < "width"	"height" > "width"
Typical images				

"height" = the height of muscle bundle, measured from the deepest portion of the mucosa
"width" = the width between the muscle bundles described above

Table 2. Patient characteristics

Variables	Mean ± SD or Number (% or range)
Age (years)	62.4 ± 14.0 (21-86)
Sex	
Males / Females	81 (57.9%) / 59 (42.1%)
Underlying diseases	
Spinal disease	41 (28.1%)
Stenosis or spondylosis	14 (9.6%)
Tumor	12 (8.2%)
Cord injury	12 (8.2%)
Cauda equina syndrome	3 (2.1%)
Previous radical pelvic surgery	21 (14.4%)
Multiple systemic atrophy	15 (10.3%)
Diabetes mellitus neuropathy	14 (9.6%)
Cerebral infarction	13 (8.9%)
Other	42 (28.7%)

Table 3. Test-retest reliability

Participants	Cronbach's alpha	95% CI	p-value	Spearman's rho	p-value
Reader 1	0.984	(0.978-0.989)	<0.001	0.969	<0.001
Reader 2	0.958	(0.941-0.970)	<0.001	0.920	<0.001
Reader 3	0.927	(0.897-0.947)	<0.001	0.888	<0.001
Reader 4	0.933	(0.907-0.952)	<0.001	0.873	<0.001
Reader 5	0.941	(0.917-0.957)	<0.001	0.888	<0.001
Reader 6	0.940	(0.917-0.957)	<0.001	0.877	<0.001
Reader 7	0.961	(0.945-0.972)	<0.001	0.928	<0.001
Reader 8	0.940	(0.917-0.957)	<0.001	0.884	<0.001
Reader 9	0.963	(0.948-0.973)	<0.001	0.932	<0.001

CI, confidence interval

Table 4. Fluoroscopic and urodynamic correlation

Clinical parameters	Cystoscopic grades				Sum or p-value
	0 (Number or Mean ± SD)	1 (Number or Mean ± SD)	2 (Number or Mean ± SD)	3 (Number or Mean ± SD)	
Age	59.6±13.2	67.1±13.3	62.2±14.6	60.8±14.2	
Fluoroscopic grades†					
0	40 (100%)	23 (57.5%)	7 (23.3%)	0 (0%)	70 (50%)
1	0 (0%)	15 (37.5%)	5 (16.7%)	6 (20.0%)	26 (18.6%)
2	0 (0%)	2 (5%)	10 (33.3%)	15 (50.0%)	27 (19.3%)
3	0 (0%)	0 (0%)	8 (26.7%)	9 (30.0%)	17 (12.1%)
Total	40 (100%)	40 (100%)	30 (100%)	30 (100%)	140 (100%)
Free uroflowmetry					
Maximal flow rate (ml/sec)	9.6±6.8	7.8±7.0	5.0±5.5$^{\downarrow}$	5.5±6.6$^{\downarrow}$	0.016*
Postvoid residual urine (ml)	50.0±91.5	121.1±156.1	211.6±158.7$^{\uparrow}$	202.8±148.5$^{\uparrow}$	<0.001*
Filling cystometry					
First desire to void (ml)	168.5±96.9	209.7±135.3	236.9±140.9	238.2±121.3	0.082
Normal desire to void (ml)	267.4±284.7	284.7±126.0	342.5±210.1	318.1±117.3	0.206
Strong desire to void (ml)	353.9±113.5	339.8±112.3	384.8±140.9	386.4±134.4	0.543
Maximal cystometric capacity (ml)	358.8±115.2	323.0±147.7	328.0±156.9	320.1±157.1	0.667
Compliance (ml/cmH2O)	43.1±25.1	40.9±18.2	40.0±32.1	25.0±24.0$^{\downarrow}$	0.022*
Voiding cystometry					
PdetQmax (cmH2O)	35.2±15.7	43.5±15.5	48.7±19.8$^{\uparrow}$	46.3±21.6	0.038*
Opening pressure (cmH2O)	33.6±15.5	43.8±17.1	64.4±41.8$^{\uparrow}$	55.7±46.2$^{\uparrow}$	0.003*
Maximal flow rate (ml/sec)	10.3±7.0	7.9±5.4	5.9±4.0$^{\downarrow}$	5.2±3.7$^{\downarrow}$	<0.001*
Voided volume (ml)	261.2±168.3	181.3±115.2	123.6±117.1$^{\downarrow}$	103.3±135.1$^{\downarrow}$	<0.001*
Postvoid residual (ml)	105.5±120.4	147.7±156.0	239.0±186.9$^{\uparrow}$	272.9±179.8$^{\uparrow}$	<0.001*
Bladder contractility index	92.9±30.2	88.5±29.0	72.1±30.4	65.5±31.8$^{\downarrow}$	0.005*
BOO index	12.1±23.9	25.5±19.9	35.0±23.7$^{\uparrow}$	34.5±23.9$^{\uparrow}$	0.002*

† Spearman's correlation coefficient was 0.79 ($p<0.001$); BOO, bladder outlet obstruction; PdetQmax, detrusor pressure at maximum flow;
*$p<0.05$; $^{\uparrow}$ significantly higher than other parameters according to trabeculation grades; $^{\downarrow}$ significantly lower than other parameters according to trabeculation grades

국문초록

신경인성방광에서 새로운 방광내시경적 방광육주화 분류체계의 설정

정재현

학번: 2012-23624

서울대학교 의과대학 의학과 비뇨기과학교실

서론: 신경인성 방광에서 새로운 방광내시경적 방광육주화 분류체계를 설정하고자 하였다.

방법: 2005 년 9 월에서 2012 년 12 월 사이에 비디오 요역동학검사와 방광내시경 검사를 모두 시행한 신경인성방광 환자 140 명을 후향적으로 분석하였다. 방광내시경적 방광육주화의 정도는 방광 근육 다발의 층 형성과 높이-넓이 비율에 따라 0 (없음), 1 (경도), 2 (중등도), 3 (중증) 등 네 단계로 분류하였다. 검사-재검사 신뢰도와 관찰자간 신뢰도를 평가하였다. 방광육주화의 내시경적 분류체계와 방사선 투시적 분류체계의 상관관계를 분석하였고, 요역동학검사 지표와의 임상적 상관관계를 평가하였다.

결과: 대상 환자들의 평균 나이는 62.4(± 14.0, SD)세였고 가장 흔한 단일 기저질환은 척추질환이었다. 검사-재검사 신뢰도는 Cronbach's alpha 0.927 - 0.984 으로 높은 일치도를 보였다 ($p<0.001$). 등급내 상관계수는 0.986 으로 관찰자간 신뢰도가 매우 높았다 ($p<0.001$). 이 새로운 분류체계는 방사선 투시적 분류체계와의 상관관계 및 요역동학검사 지표와의 상관관계가 유의하게 나타났다 (Qmax, p value=0.016; PVR, p value<0.001; BOO index, p value=0.002).

결론: 위 결과는 새로운 방광내시경적 육주화 분류체계가 높은 신뢰성을 가지고 있음을 보여주었다.

주요어: 육주화, 방광, 근육, 방광내시경, 요역동학검사