Association between urodynamic study parameters and effective renal plasma flow in chronic spinal cord injury patients with neurogenic detrusor overactivity

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ABSTRACT

Association between urodynamic study parameters and effective renal plasma flow in chronic spinal cord injury patients with neurogenic detrusor overactivity

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Background: Neurogenic detrusor overactivity can cause renal function deterioration. Urodynamic study (UDS) is the gold standard for the evaluation of lower urinary tract function. We aim to investigate for UDS parameters that can predict upper urinary tract change.

Methods: Data of 232 evaluations of UDS and renal studies of 85 chronic spinal cord injury patients with neurogenic detrusor overactivity were collected, and rearranged into 147 pairs of consecutive evaluations. Four UDS parameters (cystometric capacity, reflex volume, compliance, maximal detrusor pressure)

and effective renal plasma flow (ERPF) results were collected. Based on the total ERPF, data pairs were divided into a favorable outcome group and an unfavorable outcome group. Change of UDS parameters were compared by linear mixed model analysis between the two groups.

Results: The two groups showed a difference of change in maximal detrusor pressure. A comparison of initial and follow-up results showed a decrease of maximal detrusor pressure in the favorable outcome group, and an increase in the unfavorable outcome group

Conclusion: Maximal detrusor pressure should be monitored most closely to predict upper urinary tract deterioration in chronic spinal cord injury patients with neurogenic detrusor overactivity.

Key Words : spinal cord injury; urinary bladder, neurogenic; urodynamics; renal plasma flow

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Ⅰ. INTRODUCTION

Neurogenic detrusor overactivity is a common complication in spinal cord injury (SCI) patients[1], neurogenic detrusor overactivity can cause renal function deterioration and renal failure[2], and renal failure used to be one of leading causes of mortality in SCI patients[3, 4]. Therefore, the most important goal in the treatment of neurogenic bladder in SCI is the prevention of upper urinary tract complications and the maintenance of renal function[5].

Urodynamic study (UDS) has been recommended as the gold standard for the evaluation of lower urinary tract function[6], and regular follow-up of UDS was stated to be mandatory for the maintenance of renal function[7].

Previous studies have revealed association between some of the UDS parameters and upper urinary tract complications. In the most prominent study of them, McGuire et al. reported that intravesical leak point pressure greater than 40cmH_2O was associated with upper urinary tract complications[8]. In another study McGuire et al. reported detrusor pressure greater than 6 cmH_2O that persists for a period of longer than 10 seconds are thought to present a potential risk factor for upper urinary tract complication[9]. Association between low compliance and upper urinary tract disorder was reported by Hackler et al., who defined low compliance as at or below 20 ml/cmH_2O[10], and later again by Weld et al., who defined it as below 12.5 ml/cmH_2O[11]. Killorin et al. suggested a new UDS parameter called maximum urethral pressure gradient (MUPG) and demonstrated in a small group of patients that patients with a MUPG greater than 80 cmH_2O were at greater risk for upper urinary tract distress[12]. Shingleton et al. reported detrusor pressure greater than 40 cmH_2O was associated with upper urinary tract deterioration[13] and Linsenmeyer et al. reported an association between duration of uninhibited bladder contraction and upper urinary tract stasis[14].

However, most of these studies detected upper urinary tract complications by assessing its morphological change only, thus lacking in any direct assessment of renal functions. Linsenmeyer et al. has presented the only study so far, in which upper urinary tract stasis was used to assess any association between UDS parameters with upper urinary tract complication[14]. Yet, commonly abnormality in renal function precedes morphological change of the upper urinary tract, so

that upper urinary tract complication can be detected at an earlier stage[15-18].

Thus, in this study, association between UDS parameters and upper urinary tract complication was assessed by analyzing the association between UDS parameters and renal function, to reveal UDS parameters that can predict change of upper urinary tract function, more sensitively.

Technitium-99m mercaptoacetyltriglycine (Tc-99m MAG3) renal studies are a safe, noninvaseive, sensitive, and valuable urological screening for SCI patients[15]. However, effective renal plasma flow (ERPF) in SCI patients normally show a change over time, a sharp decrease shortly after the initial injury, a slow increase during two years following the injury, and again a decrease thereafter[19]. So, to eliminate the confounding variable of difference in change of ERPF, only evaluation data of SCI patients, who sustained their injury more than two years ago, were included.

Ⅱ. MATERIALS AND METHODS

1. Subjects

A retrospective chart review was done. Included in this study were in- and outpatients with SCI at a single university hospital, who underwent UDS and Tc-99m MAG3 renal studies at least twice between January 1, 2006 and January 31, 2013, and who had sustained their injury at least two years before the evaluations. Each patient underwent neurological examination according to American Spinal Injury Association

Impairment Scale (AIS). Only patients with neurogenic detrusor overactivity caused by a suprasacral lesion (without an accompanied sacral lesion) were included. Suprasacral spinal cord injury without an accompanied sacral lesion was confirmed with electrodiagnostic studies (bulbocavernous reflex latencies and pudendal nerve somatosensory evoked potentials), and if electrodiagnostic studies were not available, it was confirmed with neurological examination (bulbocavernous reflex).

Exclusion criteria were history of any urologic disorders or decline of renal function prior to the spinal cord injury, combined traumatic brain injury, language or cognitive impairment which inhibits one-step verbal command obey, and failure of UDS.

2. Methods

A. UDS

Two urodynamic systems were used in this study. From the beginning of the study up to February 25, 2010, UDS was performed with Duet Encompass (Mediwatch, Rugby, UK). On February 26, 2010 the urodynamic system was switched to Duet Logic G2 (Mediwatch, Rugby, UK), which was used to perform UDS during the rest of the study period.

With either urodynamic system, the patient was in supine position, and room temperature normal saline was infused into the bladder through a double lumen catheter at a rate of 30ml/min.

Abdominal pressure was recorded via a rectal balloon catheter.

Four parameters were collected for this study: cystometric capacity, reflex volume, compliance, and maximal detrusor pressure. The parameters were defined according to the standardization of terminology by the International Continence Society[20, 21].

Cystometric capacity was defined as the bladder volume at the end of the filling cystometrogram. Bladder filling was ended if the patient showed leakage, if the patient reported urgency, which made further infusion difficult, or if 450 ml of normal saline had been infused. The cystometric capacity is the volume voided together with any residual volume.

Reflex volume was defined as the infused volume at starting of first hyperreflexive detrusor contraction.

Compliance was defined as the relationship between change in bladder volume and change in detrusor pressure, and was calculated by dividing the volume change by the change in detrusor pressure during that change in bladder volume. Two standard points were used for compliance calculations: 1.) The detrusor pressure at the start of bladder filling and the corresponding bladder volume (usually zero), and 2.) the detrusor pressure (and corresponding bladder volume) at cystometric capacity or immediately before the start of any detrusor contraction.

Maximal detrusor pressure was defined as the maximum value of detrusor pressure during the filling cystometrogram. Detrusor pressure is estimated by subtracting abdominal pressure from intravesical pressure.

B. Effective renal plasma flow

Tc-99m MAG3 renal studies were carried out with Vertex EPIC (ADAC, Milpitas, California, USA).

Effective renal plasma flow (ERPF), for each and both kidneys were recorded, which were calculated by using the Gates method, were collected for this study.

3. Statistical analysis

Data collected were encoded and statistical analysis was performed with SAS statistical software package (version 9.2; SAS Institute Inc, Cary, NC, USA).

First, frequencies, means and standard deviations were determined for baseline characteristics of the study population and general summary of evaluations.

Then, the evaluation data were arranged into pairs of consecutive evaluations. As patients underwent evaluations different number of times during the study period (two to six times), and as they suffered SCI at different points of time before the study, for statistical analysis, the change between two consecutive evaluations was considered

independent from spinal cord injury onset duration, and from change between previous or later evaluations. Data were uniformly arranged into pairs of two consecutive evaluations, regardless of the interval between each two evaluations. Three or more consecutive evaluations of the same patient were divided into several pairs of consecutive evaluations and all pairs were included in the data set. Thus a total of 85 patients underwent a total of 232 evaluations, which yielded 147 data pairs.

In UDS evaluations, in which involuntary detrusor contraction was not observed, reflex volume was not available. Instead of performing the statistical analysis with missing data, missing values were replaced with corresponding values of cystometric capacity to increase the accuracy of the statistical analysis.

So, each data pair consisted of an initial and a follow-up result of four UDS parameters and three ERPF parameters. Frequencies, means and standard deviations were determined before and after dividing in pairs and initial and follow-up study results after dividing in pairs were compared with paired samples T-test at a significance level of $p < 0.05$.

Data pairs were then divided into two groups, a favorable outcome group and an unfavorable outcome group, the analysis criteria used by Phillips et al. [22]. The favorable outcome group contained data pairs with either total effective renal plasma flow increased, maintained, or

decreased less than 20% on follow-up compared to the initial evaluation, and the unfavorable outcome group contained data pairs with total effective renal plasma flow decreased 20% or more on follow-up compared to the initial evaluation. Frequencies, means and standard deviations were determined, and initial and follow-up study results were compared with paired samples T-test at a significance level of $p < 0.05$.

Finally, to analyze for any differences between the two groups in change of UDS parameters over time, repeatedly measured UDS parameters were analyzed using linear mixed model for numerical measures, with fixed effect and random effect. When the interaction of group by time of the variables showed statistical significance, post hoc analysis was carried out with Bonferroni correction for the adjustment for multiple comparison. All probabilities were two-tailed, and the level of significance was defined as $p<0.05$.

Ⅲ. RESULTS

1. Baseline characteristics of the study population and general summary of evaluations

Demographic data of the study subjects enrolled in this study were summed up in table 1. Evaluation data of a total of 85 patients were collected. Age and neurologic status in this table were based on the data collected at the time of the first evaluation. Suprasacral spinal cord lesion without accompanied sacral lesion was confirmed electrodiagnostically in 70 patients (82.4%).

Table 1. Baseline characteristics of subjects

Age[1]	Mean ± standard deviation	36.73 ± 10.8
	Range	18~65
Gender[2]	Male	62 (72.9%)
	Female	23 (27.1%)
American Spinal Injury Association Impairment Scale[2]	A	43 (50.6%)
	B	24 (28.2%)
	C	8 (9.4%)
	D	10 (11.8%)
Level of injury[2]	Tetraplegia	44 (51.8%)
	Paraplegia	41 (48.2%)
Etiology of injury[2]	Trauma	71 (83.5%)
	Transverse myelitis	5 (5.9%)
	Neoplastic	3 (3.5%)
	Syringomyelia	2 (2.4%)
	Vascular	2 (2.4%)
	Infectious	1 (1.2%)
	Ossification of the posterior longitudinal ligament	1 (1.2%)

[1] values are in years

[2] values are in number of patients and percentage

General characteristics of evaluations were summed up in table 2. Total numbers of evaluations each study subject had undergone varied between two and six, which added up to a total number of 232 evaluations.

Table 2. General summary of evaluations[1]

Total number of evaluations of each patient[2]	2 evaluations	43 (50.6%)
	3 evaluations	26 (30.6%)
	4 evaluations	13 (15.3%)
	5 evaluations	2 (2.4%)
	6 evaluations	1 (1.2%)
Duration between onset and first evaluation[3]	Mean ± standard deviation	3066.08 ± 2106.18
	Range	764~10283
Interval between two consecutive evaluations[3]	Mean ± standard deviation	726.89 ± 447.55
	Range	148~2239

[1] each evaluation consisted of a urodynamic study and technitium-99m mercaptoacetyltriglycerine renal studies

[2] values are in number of patients and percentage

[3] values are in days

2. Summary of UDS and ERPF results before and after dividing in pairs

UDS and ERPF results before and after dividing in pairs are shown in table 3.

The reflex volume was observed in 180 of 232 evaluations. Missing values were replaced by corresponding values of cystometric capacity.

After dividing in pairs, among UDS parameters, a significant increase of cystometric capacity and a significant decrease of maximal detrusor pressure on follow-up compared to the initial evaluation were observed. Involuntary detrusor contraction, reflex volume, and compliance did not show any significant differences. Among ERPF, left ERPF and total ERPF showed a significant decrease.

Table 3. Summary of UDS and ERPF results before and after dividing in pairs of two consecutive evaluations

Study	Parameter	Before dividing in pairs	After dividing in pairs		
			Initial study	Follow-up study	p-value
UDS	Cystometric Capacity[1]	385.02 ± 122.98	371.75 ± 124.99	401.22 ± 117.98	**0.006***
	Reflex Volume[1]	275.62 ± 138.66	272.01 ± 140.79	287.07 ± 135.92	0.134*
	Compliance[2]	41.22 ± 52.95	34.72 ± 35.41	44.37 ± 59.54	0.078*
	Maximal detrusor pressure[3]	40.14 ± 31.43	45.16 ± 32.14	36.55 ± 30.57	**0.004***
ERPF	Rt ERPF[4]	210.28 ± 55.20	214.39 ± 52.84	206.19 ± 51.71	0.061*
	Lt ERPF[4]	212.53 ± 51.42	215.57 ± 49.08	206.08 ± 50.01	**0.022***
	Total ERPF[4]	422.81 ± 89.02	429.97 ± 85.88	412.27 ± 86.94	**0.030***

[1] values are in ml, expressed in mean ± standard deviation

[2] values are in ml/cmH_2O, expressed in mean ± standard deviation

[3] values are in cmH_2O, expressed in mean ± standard deviation

[4] values are in ml/min, expressed in mean ± standard deviation

[*] Statistical significance test was done by paired samples T-test

UDS: urodynamic study

ERPF: effective renal plasma flow

After classification based on the outcome of ERPF, the favorable outcome group included 113 pairs (76.9%) and the unfavorable group included 34 pairs (23.1%).

Table 4. Number of data pairs categorized into a favorable outcome group and an unfavorable outcome group[1]

Group	Number of data pairs
The favorable outcome group	113 (76.9%)
The unfavorable outcome group	34 (23.1%)

[1] The favorable outcome group contained data pairs with either effective renal plasma flow increased, maintained, or decreased less than 20% on follow-up compared to the initial evaluation. The unfavorable outcome group contained data pairs with effective renal plasma flow decreased 20% or more on follow-up compared to the initial evaluation.

[2] values are in number of data pairs and percentage

3. Comparison of initial and follow-up results after classification

Initial and follow-up results in each group were compared. In both groups an increase of cystometric capacity was observed, of which only the favorable group showed statistical significance. Maximal detrusor pressure showed a significant decrease in the favorable outcome group, and in the unfavorable outcome group an increase was observed, which however was not statistically significant

Table 5. Comparison of UDS parameters of initial and follow-up evaluations after dividing data pairs into a favorable outcome group and an unfavorable outcome group[1]

Group	UDS parameter	Initial	Follow-up	P value
The favorable outcome group	Cystometric capacity[2]	371.83 ± 122.18	397.50 ± 114.95	**0.033***
	Reflex volume[2]	266.25 ± 137.79	284.35 ± 131.27	0.145*
	Compliance[3]	34.57 ± 36.91	42.21 ± 51.94	0.179*
	Maximal detrusor pressure[4]	46.90 ± 34.13	33.67 ± 28.54	**0.001***
The unfavorable outcome group	Cystometric capacity[2]	371.47 ± 135.82	413.59 ± 128.57	0.076*
	Reflex volume[2]	291.15 ± 150.89	296.15 ± 152.13	0.726*
	Compliance[3]	35.19 ± 51.57	51.57 ± 80.38	0.261*
	Maximal detrusor pressure[4]	39.73 ± 24.59	45.55 ± 35.15	0.374*

[1] The favorable outcome group contained data pairs with either effective renal plasma flow increased, maintained, or decreased less than 20% on follow-up

compared to the initial evaluation. The unfavorable outcome group contained data pairs with effective renal plasma flow decreased 20% or more on follow-up compared to the initial evaluation.

[2] values are in ml, expressed in mean ± standard deviation

[3] values are in ml/cmH_2O, expressed in mean ± standard deviation

[4] values are in cmH_2O, expressed in mean ± standard deviation

[*] Statistical significance test was done by paired samples T-test

UDS: urodynamic study

4. Linear mixed model analysis, comparing UDS parameters in two groups

Linear mixed model analysis was carried out to analyze any difference of change between the two groups. Cystometric capacity was significant for time only. Maximal detrusor pressure was significant for the interaction of time and group.

Table 6. Linear mixed model analysis, comparing UDS parameters in the favorable outcome group and the unfavorable outcome group[1]

UDS parameter		F-value	p-value
Cystometric capacity	Group	0.15	0.699
	Time	7.29	**0.008**
	Group * Time	0.43	0.513
Reflex volume	Group	0.57	0.453
	Time	0.94	0.333
	Group * Time	0.46	0.500
Compliance	Group	0.50	0.483
	Time	3.45	0.065
	Group * Time	0.46	0.500
Maximal detrusor pressure	Group	0.35	0.556
	Time	1.49	0.224
	Group * Time	8.26	**0.005**

[1] The favorable outcome group contained data pairs with either effective renal plasma flow increased, maintained, or decreased less than 20% on follow-up compared to the initial evaluation. The unfavorable outcome group contained data pairs with effective renal plasma flow decreased 20% or more on follow-up compared to the initial evaluation.

UDS: urodynamic study

Post-hoc analysis, carried out for maximal detrusor pressure comparing the two groups, is shown in table 7. It showed statistical significance for the interaction of time and group.

Table 7. Post-hoc analysis for comparing maximal detrusor pressure in the favorable outcome group and the unfavorable outcome group[1]

	Estimate	p-value	Adj p-value
Group (the favorable outcome group) * Time (initial) vs Group (the unfavorable outcome group) * Time (initial)	6.4809 (6.1061)	0.2904	>.9999
Group (the favorable outcome group) * Time (initial) vs Group (the favorable outcome group) * Time (follow-up)	13.5699 (3.2403)	<.0001	**<0.0001**
Group (the favorable outcome group) * Time (initial) vs Group (the unfavorable outcome group) * Time (follow-up)	1.0064 (6.1636)	0.8705	>.9999
Group (the unfavorable outcome group) * Time (initial) vs Group (the favorable outcome group) *	7.089 (6.095)	0.2469	>.9999

Time (follow-up)			
Group (the unfavorable outcome group) * Time (initial) vs Group (the unfavorable outcome group) * Time (follow-up)	-5.4745 (5.7793)	0.3452	>.9999
Group (the favorable outcome group) * Time (follow-up) vs Group (the unfavorable outcome group) * Time (follow-up)	-12.5634 (6.1525)	0.0431	0.2586

[1] The favorable outcome group contained data pairs with either effective renal plasma flow increased, maintained, or decreased less than 20% on follow-up compared to the initial evaluation. The unfavorable outcome group contained data pairs with effective renal plasma flow decreased 20% or more on follow-up compared to the initial evaluation.

Ⅳ. DISCUSSION

In this study, a significant difference in change of maximal detrusor pressure was observed between the group with ERPF increased, maintained, or decreased by less than 20% compared to the group with ERPF decreased 20% or more. The favorable outcome group showed a significant decrease of maximal detrusor pressure on follow-up compared to the initial evaluation. The unfavorable outcome group showed a relative increase, which however was not significant. Previous studies on association between maximal detrusor pressure and upper urinary tract deterioration include the study by McGuire et al. in which detrusor pressure greater than 6 cmH_2O that persists for a period of longer than 10 seconds are thought to present a potential risk factor for upper urinary tract complication[9] and the study by Shingleton et al., in which detrusor pressure greater than 40 cmH_2O was associated with upper urinary tract deterioration[13]. Especially the study by Shingleton et al. was compatible with our results, as the ERPF increased, maintained, or decreased by less than 20% had a mean initial maximal detrusor pressure of below 40 cmH_2O, a mean follow-up maximal detrusor pressure of above 40 cmH_2O, and the group with ERPF decreased 20% or more had the opposite results.

Other studies which investigated the parameters included in this study were reported by Hackler et al. [10] and Weld at al. [11]. They reported low compliance to be a risk factor for upper urinary tract complication. In this study we were not able to find any significant association between change of compliance and upper

urinary tract deterioration. In fact, an increase of compliance was noted generally, and also in each group, which however was not significant. This may be due to difference of statistical analysis, as in this study there was not a normal value for compliance. Rather, compliance was analyzed as a continuous variable.

Another parameter, potentially of clinical significance, which however was not investigated in this study, is the observation of involuntary detrusor contraction. Reflex volume, which is the infused volume at starting of first hyperreflexive detrusor contraction[21], did not show any statistical significance in this study. In our opinion, this was odd, as we expected that change of reflex volume would reflect change of detrusor overactivity. Investigating the change in observation of involuntary detrusor contraction (i.e. involuntary detrusor contraction observed in the initial evaluation but not observed in the follow-up evaluation, or vice versa) could reveal undiscovered association between UDS parameters and ERPF.

In this study 'normal' values were not specified as there is a lack of established range of normal values in UDS parameters[23]. We merely analyzed any impact by change of values, and found out that change of maximal detrusor pressure may help to predict renal function change in SCI patients. Thus, the results of this study may not suffice as evidence when interpreting the results of a single UDS evaluation. However, they are the best so far, when interpreting results of consecutive UDS evaluations.

Also this study shows that change of UDS parameters in a patient can indicate

change of renal function. This again shows UDS in spinal cord injury patients is essential not just as a baseline evaluation, but also as a follow-up assessment. Although UDS is recommended as the gold standard for the evaluation of urinary tract dysfunction in spinal cord injury patients[6], and regular follow-up of UDS is warranted for protection of the upper urinary tract and maintenance of continence[7], often it is not used in practice[24-26]. The European Association of Urology recommends in neurogenic lower urinary tract dysfunction a follow-up UDS every two years in patients without detrusor overactivity and with normal bladder compliance, and at least once per year in patients with detrusor overactivity and/or low bladder compliance[27]. On the other hand a proposed guideline by the 'SCI Think Tank' in the UK recommends a baseline UDS between three and six months after spinal cord injury, and follow-up UDS only in high-risk patients[28]. Reference about desirable interval of UDS is still lacking[29], and demands further research in the future.

Ⅴ. CONCLUSION

Association between UDS parameters and ERPF in chronic spinal cord injury patients with neurogenic detrusor overactivity was analyzed in a retrospective chart review. Among the four UDS parameters investigated in this study, a significant inverse relationship between ERPF and maximal detrusor pressure was observed. Thus, maximal detrusor pressure should be monitored most closely, when managing neurogenic detrusor overactivity in chronic spinal cord injury patients. This study can also serve as evidence for the recommendation of regular follow-up of UDS in chronic spinal cord injury patients with neurogenic detrusor overactivity

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ABSTRACT (in Korean)

과활동성 신경인성 방광을 보이는 만성 척수손상환자에서 요류동태검사 척도와 유효신혈장류량의 연관성

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배경 : 과활동성 신경인성 방광은 신기능의 저하를 초래할 수 있다. 요류동태검사는 하부 요로 기능의 평가를 위한 가장 표준적인 검사이다. 본 연구에서 저자들은 상부 요로 기능의 변화를 예측할 수 있는 요류동태검사 지표를 조사해보고자 하였다.

방법 : 과활동성 신경인성 방광이 있는 85 명의 만성 천수 상부 척수손상환자를 대상으로 요류동태검사 및 신장촬영을 시행하여 232 례의 자료를 수집하였으며, 이들을 147 쌍의 연속적 평가 자료로 재분류하였다. 4 가지 요류동태검사 척도 (방광 용적, 불수의적 배뇨근의 수축이 나타나기 시작하는 단계, 순응도, 최대 배뇨압) 및 유효신혈장류량 결과를 수집하였다. 유효신혈장류량 결과를 토대로 짝지어진 자료를 양호한 결과를 보인 집단과 불량한 결과를 보인 집단으로 나누었다. 두 집단 사이의 요류동태검사 척도의 변화를 선형혼합모형분석을 통해 분석하였다.

결과 : 두 집단은 최대 배뇨압의 변화에서 의미 있는 차이를 보였다. 초기 측정값과 추적시 측정값의 비교에서 양호한 결과 집단에서는 최대 배뇨압이 감소하는 것으로 나타났으며, 불량한 결과 집단에서는 증가를 하는 것으로 나타났다.
결론 : 과활동성 신경인성 방광을 보이는 만성 척수손상 환자에서 상부 요로기능의 악화를 예측하기 위해 최대 배뇨압의 변화를 유의하여 관찰해야 할 것으로 생각된다.

핵심되는 말: 척수손상, 신경성 방광, 요류동태, 신혈장류량