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The response of the detrusor muscle to acetylcholine in patients with infravesical obstruction

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Summary. We previously examined the effects of overdistension on the neuromuscular system of canine urinary bladders and reported that bladder overdistension led to nerve degeneration and subsequent supersensitivity through a decrease of blood supply to the bladder. We have accordingly in this study evaluated these changes in human subjects with infravesical obstruction. The responses to acetylcholine of bladder strips obtained from patients with detrusor instability were not significantly different from those of bladder strips from patients without detrusor instability, but the dose-response curve of these groups showed a shift to the right compared to that of the unobstructed control patients. As compared with the response of bladder strips in patients without an episode of retention, the response in patients who received prostatectomy within 30 days demonstrated no significant difference, although in patients who received prostatectomy after more than 30 days there was a statistical difference. These results indicated a significant decrease in sensitivity of the detrusor muscle in patients with infravesical obstruction and suggest that bladder overdistension caused by infravesical obstruction may lead to supersensitivity of the detrusor muscle secondary to denervation.

Key words: Bladder overdistension – denervation supersensitivity – detrusor instability

Infravesical obstruction results in various changes in bladder structure and function, including trabeculation, increased wall thickness, and detrusor instability. We previously examined the effects of overdistension on the neuromuscular system of canine urinary bladders as a model of infravesical obstruction in terms of histological changes and pharmacological responses [1]. Bladder overdistension caused by lower urinary tract obstruction may lead to nerve degeneration and subsequent supersensitivity through a decrease in the blood supply to the bladder. In addition, fibrotic changes in the bladder wall following overdistension may also result in a decrease in detrusor muscle contraction [2]. Speakman and associates also reached the conclusion that denervation supersensitivity occurred as a consequence of obstruction, using the pig as an animal model [3]. In this study we have evaluated these changes in human subjects with infravesical obstruction.

Cystometric examination of patients with infravesical obstruction demonstrates various patterns, although these findings do not necessarily imply contractibility of the detrusor muscle itself. We classified the patients according to cystometric findings, history of cerebrovascular accident, and episode of urinary retention and examined the contractibility of the detrusor muscle pharmacologically.

Materials and methods

Studies were performed on 48 patients aged between 59 and 92 years (mean 71.3 years) who showed symptoms of benign prostatic hypertrophy and were subjected for transvesical prostatectomy during hospitalization (Table 1a). At prostatectomy bladder tissues were obtained from the anterior wall of the dome of the bladder. Bladder strips, $3 \times 3 \times 10$ mm in size, were prepared from the side of the outer longitudinal muscle layer. Freshly dissected bladder strips were placed in an isolated 50-ml organ bath. The bathing medium was Tyrode's solution composed of the following (per 1,000 g distilled water): 8.0 g NaCl; 0.2 g KCl; 0.1 g $MgCl_2$; 0.2 g $CaCl_2$; 0.005 g NaH_2PO_4, and 1.0 g glucose. The solution was maintained at 37°C and aerated with 95% O_2 + 5% CO_2. Contractions of the bladder strips were recorded isometrically with a force-displacement transducer connected to thermal-array recorder (Nihon-Koden Kogyo, Japan). Approximately 0.5 g of resting tension was applied to the strips, and 1 h was allowed for equilibration before the strips were exposed to acetylcholine. Acetylcholine was applied for 1 min and washed out thoroughly. The strips were washed two to three times with fresh medium before exposure to the next dose of acetylcholine. For the construction of the dose-response curve, the peak tension development after each dose was regarded as the response. Six male patients were referred for this study as controls (five with bladder tumors, one with primary vesicoureteral reflux, VUR, as a manifestation of a primary abnormality of the ureterovesical junction, excluding reflux caused by neurogenic bladder and infravesical obstruction). None of these patients showed evidence of

Table 1 a–d. Classification of patients in relation to cystometric findings, history of cerebrovascular accident, and episode of urinary retention

a	*n*	Mean age (years)
BPH	48	71.3 ± 6.5
Control	6	48.2 ± 6.5

b Cystometric findings in patients with BPH	*n*	Mean age (years)
Normal	27	68.4 ± 10.1
Detrusor instability	21	75.6 ± 6.2

c Patients showing detrusor instability on cystometry: History of cerebrovascular accident	*n*	Mean age (years)
(+)	5	73.4 ± 5.2
(−)	16	76.6 ± 6.6

d Episode of urinary retention		Days to prostatectomy after retention episode	
	n	Within 30 days	More than 30 days
(+)	20	11	9
(−)	17		

BPH, benign prostatic hypertrophy

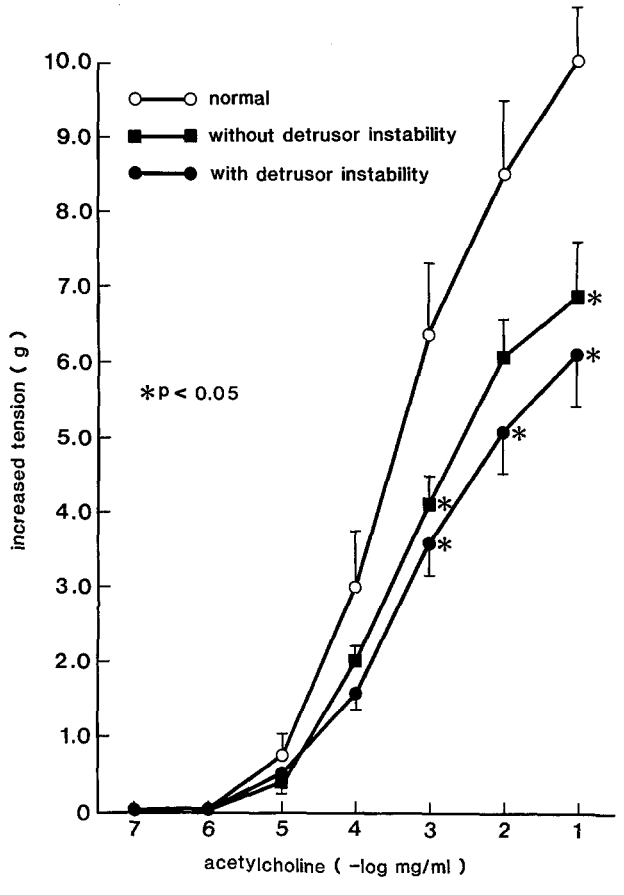

Fig. 1. Dose-response curve of bladder strips with acetylcholine from patients with and without detrusor instability, compared to normal detrusor function. Values represent means ± SE

infravesical obstruction on urodynamic study. The contractibility of the detrusor muscle obtained at operation was examined by the same method described above.

The patients with prostatic hypertrophy were divided into the following groups on the basis of cystometric findings and clinical history. The present study was performed by comparing the behavior of the detrusor strips in vitro.

1. Cystometric examination was performed before operation. We defined detrusor instability as the presence of involuntary, uninhibited detrusor contractions that exceeded 15 cm H_2O during cystometry. Patients were classified into two groups according to the presence of detrusor instability, and the detrusor muscle contractibility of the two groups was compared (Table 1b).
2. Patients demonstrating detrusor instability were classified into two groups according to the history of cerebrovascular accident and the two groups compared (Table 1c).
3. Patients were classified into two groups according to an episode of urinary retention. The patients with an episode of retention were divided into two further groups according to whether prostatectomy was performed within 30 days or more than 30 days after the retention episode. The former group received prostatectomy 16.9 days (average) after retention, and the later group 44.9 days (average) after retention. These two groups were compared as shown in Table 1d.

Statistical analysis of the differences was performed using Student's *t*-test for unpaired samples. Data were considered significant at the $P < 0.05$ level.

Results

The mean age of the patients with detrusor instability in this series was 75.6 years, slightly higher than that of the patients without detrusor instability (68.4 years; Table 1b). Figure 1 shows the increased tension of the bladder strips obtained from patients with or without detrusor instability as a function of increasing acetylcholine dosage, compared to the control group. The responses to

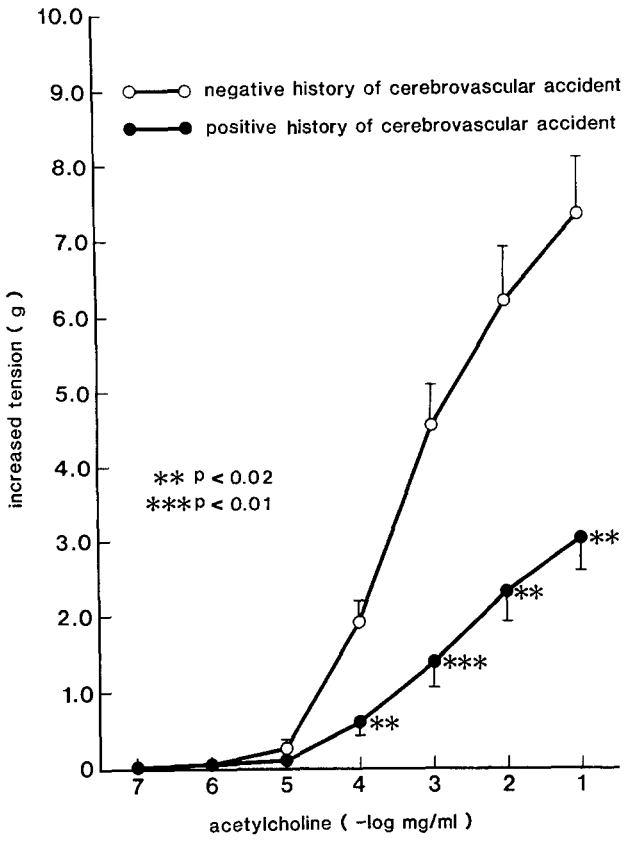

Fig. 2. Dose-response curve of bladder strips with acetylcholine from patients with and without a history of cerebrovascular accident, who demonstrated detrusor instability on cystometry. Values represent means ± SE

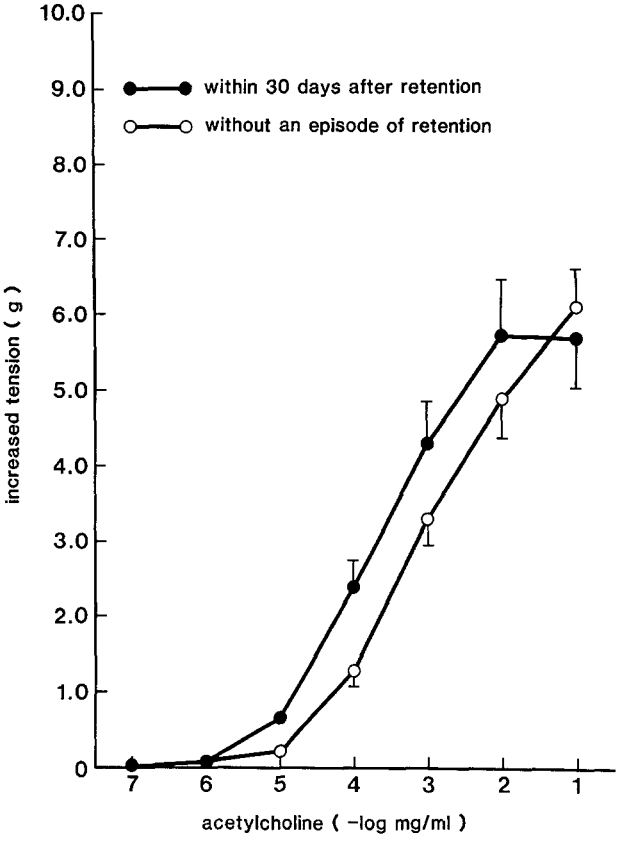

Fig. 3. Dose-response curve of bladder strips with acetylcholine from patients who underwent prostatectomy within 30 days after retention episode, compared to patients without an episode of retention. Values represent means ± SE

acetylcholine of bladder strips obtained from patients with detrusor instability did not significantly differ from those of bladder strips without detrusor instability. It was noted, however, that the dose-response curves of these groups showed a shift to the right when compared to those of the control group, indicating a significant decrease in sensitivity of bladder strips of patients with infravesical obstruction to acetylcholine in the range of 10^{-3} to 10^{-1} mg/ml (Fig. 1).

The diagnosis of detrusor instability was made in 21 patients, 5 of whom presented with concomitant cerebrovascular accident that may have been responsible for the uninhibited detrusor contractions. The mean age of patients with a history of cerebrovascular accident was 73.4 years versus 76.6 years for patients without such a history. The difference was not significant (Table 1c). The patients had been suffering from cerebral neurological disorders for an average of 7.8 years. As can be seen in Fig. 2, the response level of bladder strips obtained from the patients with such a history was low and was significantly different from that of the bladder strips without such a history in acetylcholine concentrations greater than 10^{-4} mg/ml (Fig. 2).

Twenty patients had an episode of acute urinary retention before operation, 11 of whom underwent prostatectomy within 30 days after retention, and 9 of whom after more than 30 days (Table 1d). The mean volumes of urine drained just after the urinary retention episode were 984 ml in the former and 839 ml in the latter. Seventeen patients had no acute urinary retention episodes before operation. As compared with the response of bladder strips in patients without an episode of retention, the response in patients who underwent prostatectomy within 30 days demonstrated no significant difference (Fig. 3), although in patients who underwent prostatectomy after more than 30 days there was a statistical difference in acetylcholine concentrations of greater than 10^{-4} mg/ml (Fig. 4).

Of 21 patients with detrusor instability, 9 (42.9%) had an episode of acute urinary retention, while of 27 patients without detrusor instability 12 (44.2%) had a episode of retention. There was no significant difference between them.

Discussion

It is widely believed that over 50% of patients with obstruction secondary to prostatic hypertrophy demonstrate detrusor instability urodynamically, however, over 60% of these patients regain normal bladder function after removal of the obstruction [4–6]. The etiology of

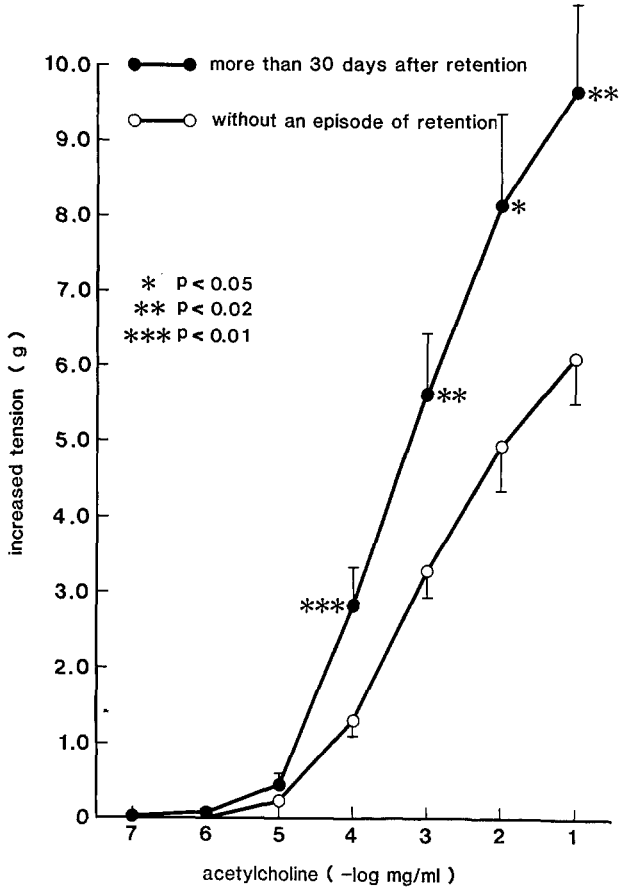

Fig. 4. Dose-response curve of bladder strips with acetylcholine from patients who underwent prostatectomy more than 30 days after retention episode, compared to patients without an episode of retention. Values represent means ± SE

detrusor instability is not clearly understood. However, it is known that the pathophysiological properties of the detrusor muscle undergo change in the presence of infravesical obstruction. In the present study the response to acetylcholine of the detrusor muscle obtained from patients with detrusor instability did not significantly differ from those without detrusor instability, while the dose-response curves of these patients showed a shift to the right when compared to the control patients. These results indicate a significant decease in sensitivity of detrusor muscle in patients with infravesical obstruction. Kinder and Mundy compared the in vitro behavior of human detrusor strips from urodynamically normal bladders and bladders exhibiting idiopathic (as distinct from obstructive) detrusor instability or detrusor hyperreflexia, by measuring spontaneous contractile activity, the response to electric field stimulation and acetylcholine [7]. They found that there were significant differences between normal and abnormal muscles with respect to spontaneous contractile activity and the response to electric field stimulation, but no significant differences in the response to acetylcholine. These results suggest that detrusor instability itself cannot lead to a decrease in the response to acetylcholine, but may cause a decrease in the response to acetylcholine in cases in which infravesical obstruction follows. Detrusor hyperreflexia is a urodynamic manifestation of the bladder caused by neuropathic disorders, for example cerebrovascular accident. In patients with infravesical obstruction with a history of cerebrovascular accident, it is very difficult, based only on cystometric examination, to ascertain whether the uninhibited detrusor contraction is due to infravesical obstruction or to the neuropathic disorders. However, since it has been shown that the response level of bladder strips from such patients is significantly low, patients should have the obstruction removed before detrusor function deteriorates. The patient should be warned that he may require a urine collection device or the administration of anticholinergic agents to avoid incontinence postoperatively.

Morphological studies of the obstructed urinary bladder have been carried out to some extent. Collagen fibrils in the smooth muscle probably play an important role in the intercellular transmission of active force [8], and a change in the collagen content may affect the contractile properties of the smooth muscle. Electron microscopy of bladder biopsies from patients with a variety of conditions revealed intercellular widening and collagen formation in infravesical obstruction, neuropathic bladder disorders, and after severe overdistension [9]. In an experimental study of chronically induced bladder neck obstruction in rabbits, marked intercellular collagen deposition could be seen in the ultrastructure of the hypertrophic bladder wall [10]. These morphological changes were identical to those found in the human trabeculated bladder described by Gosling and Dixon [11]. Gilpin and associates revealed that connective tissue infiltration of detrusor muscle bundles was a characteristic of obstructed, trabeculated human bladders exhibiting cellular hypertrophy [12]. Concerning the early changes in the rat urinary bladder induced by infravesical obstruction, Uvelius and Mattiasson found that the total amount of detrusor collagen increased, while the concentration of collagen decreased in the hypertrophic detrusor [13]. The decrease in collagen concentration in the hypertrophic detrusor might be seen following onset of infravesical obstruction, but in the chronically obstructed bladder the degree of collagen infiltration would tend to increase. The severity and duration of obstruction varies among patients, but the obstructions found in the present study were severe and of long duration. As the duration of obstruction increases, the contraction response level of the detrusor muscle may decrease because of collagen deposition, especially when accompanied by detrusor instability.

Comparison of the dose-response curve between patients who underwent prostatectomy more than 30 days after a urinary retention episode and patients with no episode of urinary retention showed a shift to the left, representing the increasing contractibility of the detrusor muscle with acetylcholine. This finding suggests that bladder overdistension caused by infravesical obstruction may lead to supersensitivity of the detrusor muscle secondary to denervation. In previous papers, we reported that bladder overdistension resulted in nerve degeneration with subsequent supersensitivity of the detrusor muscle to acetylcholine in dogs, which was thought to be denervation supersensitivity [1, 2]. Gosling and associates com-

pared the amount of autonomic nerve supplying the detrusor muscle between obstructed patients and unobstructed control patients by means of light and electron microscopic techniques. They found a significant reduction (of about 60%) in nerve density in the obstructed group and confirmed that the presence of outflow obstruction significantly reduced the amount of autonomic nerve supplying the detrusor muscle [14]. Speakman and associates, using smooth muscle from partially obstructed pig bladders, described cystometric evidence of bladder instability and an increase in sensitivity to exogenously applied agonists. From the morphological evidence of denervation, these changes were regarded as typical of postjunctional supersensitivity secondary to partial denervation [3]. In the presence of infravesical obstruction, the wall tension of the bladder increases and blood supply to the bladder decreases, parallel to the increasing micturition pressure. Infravesical obstruction, therefore, is thought to reduce the blood supply to the bladder and result in nerve degeneration (denervation) there. To clarify the relationship between the nerve degeneration and ischemic condition of the bladder, we produced ischemic bladders in dogs by means of bilateral ligation of the caudal vesical arteries and veins and performed morphological and pharmacological examinations [15]. Degeneration of cholinergic axons and changes in Schwann cells were observed by electron microscope; the contraction response level of the detrusor muscle to acetylcholine was significantly elevated 1 week after ligation. These findings suggest that a decrease in the blood supply to the bladder may lead to denervation and subsequent supersensitivity of the detrusor muscle to acetylcholine.

Finally, the results of the present study emphasize the importance of the removal of infravesical obstruction before detrusor function deteriorates.

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