Heterogeneity of Morphological and Functional Changes in Various Compartments of Rat Urinary Bladder in Infravesical Obstruction of the Urinary Tract

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 147, No. 1, pp. 108-112, January, 2009
Original article submitted August 8, 2008

Infravesical obstruction of the lower urinary tract was simulated in rats by dosed constriction of the prevesical portion of the urethra. The functional and morphological changes in various urinary bladder compartments were evaluated after 1 week and 3 months. The development of compensatory hypertrophy of the detrusor was associated with an increase in the number of hypertrophic, atrophic, and young leiomyocyte forms and their transformation into myofibroblasts, with the formation of connective tissue laminae between myofibril bundles mainly in the zone of urinary urinary bladder neck. Specific contractility of the detrusor strips decreased with increasing their tone, which was most pronounced in the neck zone. The relaxing effect of norepinephrine was significantly lower after 3 months of obstruction and virtually disappeared in the zone of the urinary bladder body and neck. Blockade of α-adrenoceptors after adrenostimulation with norepinephrine stimulated contractions of the hypertrophic detrusor against the background of reduced tone of the urinary bladder neck, in contrast to intact urinary bladder where this treatment reduced contractions.

Key Words: *prostatic adenoma; infravesical obstruction; detrusor hypertrophy; adrenoregulation of contractions*

Persistent obstruction of the lower urinary tract (infravesical obstruction; IVO) developing in prostatic adenoma, urethral strictures or valves, sclerosis of the urinary bladder (UB) neck, leads to stable hyperfunction of the detrusor and its hypertrophy because of the need to overcome the urethral hyperresistance during urination. The use of α-adrenoblockers facilitates urination in these patients, but in many cases surgery has to be resorted to because of inefficiency or failure of conservative therapy. In about 30% of all operated on patients urination disorders persist after open or transurethral prostatectomy, this reducing patient's quality of life [1-5].

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These data indicate various degrees of functional disorders developing in a hypertrophic detrusor determined by the severity and duration of IVO and the individual reactivity of the patients. The involvement of different UB compartments in urination and possible heterogeneity of the developing changes are important.

We studied the dynamics of functional changes in various UB compartments in simulated IVO and their correlations with developing hypertrophy of the detrusor and changes in the adrenergic regulation of contractions.

MATERIALS AND METHODS

Experiments were carried out on outbred male albino rats (n=30; 260-300 g) due to easier avail-

0007-4888/09/1471-0100

ability of the prevesical portion of the urethra, easy catheterization of UB, and more reliable dosed obstruction in these animals. The prevesical urethra was mobilized in rats narcotized with ether and Dacron thread No. 1 was brought under it. Cubital catheter No. 3 was inserted into the urethra and the thread was tied around the urethra on the catheter, thus narrowing the urethral lumen (dosed stenosis). After removal of the catheter, the operation wound was tightly sutured.

Ascending urethrocystography was carried out 1 week and 3 months after surgery in order to confirm the development of IVO, after which UB function was evaluated by recording the dynamics of intravesical pressure during gradual filling of UB with saline and its maximum volume was evaluated. UB was then resected and annular fragments of its bottom, body, and neck were cut out. The fragments were placed into a cell of an experimental device with flowing oxygenated warm (37°C) Lock's solution (pH 7.2). The study was carried out in an isometric mode. To this end, a fragment was fixed to an immobile rod and the other end was connected to a 6MX2B mechanoelectrical force transducer for evaluating the distention effort (tone) and contraction force under conditions of electric stimulation with rectangular pulses of 500 msec duration, 6 pulses/min frequency, and voltage 20% higher than the threshold. After stabilization of the contraction amplitude, norepinephrine (10^{-5} M) or α-adrenoblocker (doxazosin; 2 mg/liter) were added to the perfusion solution for characterization of the detrusor adrenoreactivity. The final step of the study was registration of changes in strip tension after complete replacement of sodium with potassium in the nutrient solution. Histological study of the cystic wall was carried out by the standard method. Leiomyocyte morphometry was carried out on a MOP-Videoplan device with applied software. In control series, all studies were carried out on intact rats.

RESULTS

The formation of IVO was confirmed by urethrocystography, showing urethral stenosis in the prevesical zone and an enlargement of UB volume. Cystometry showed that the maximum volume of UB increased from 0.63±0.07 to 0.87±0.09 ml 1 week after IVO formation, reaching 1.23±0.06 ml 3 months after the intervention ($p<0.001$).

Histological study of UB wall showed signs of detrusor hypertrophy as early as 1 week after IVO formation. The muscular layer was thickened; smooth-muscle fiber bundles grew more massive. Some smooth-muscle fibers were swollen to 18×7 μ in size. Apart from hypertrophic smooth-muscle cells, the overwhelming majority of the cell population was presented by more or less normal leiomyocytes. Few young cell forms were detected (Table 1). The changes in the proportion of cell populations during this period were most intense in the UB neck. After 3 months, hypertrophy of the muscular layer progressed. Smooth-muscle fibers were enlarged to 24×9 μ. The concentration of young cells increased, myofibroblasts appeared (Table 1), which were virtually absent in the intact UB and 1 week after the beginning of experiment. As a result of myofibroblast appearance, thick bundles of smooth-muscle fibers were enveloped with connective tissue layers, rather substantial in some rats. In these cases, some leiomyocytes had signs of atrophy. Morphological changes in leiomyocytes were more pronounced in UB wall, where the share of modified cells approached 50%.

Study of detrusor function *in vitro* in a testing unit showed that the specific capacity of detrusor

TABLE 1. Distribution of Various Leiomyocyte Types in the Bladder Detrusor in IVO (%)

Fragment origination	Group	Leiomyocyte type				
		normal	hypertrophic	atrophic	myofibroblasts	young
Bottom	Intact	98.74	1.21	0.13	—	—
	IVO, 1 week	82.24	16.80	0.91	—	0.05
	IVO, 3 months	62.34	17.23	8.36	7.58	4.49
Body	Intact	98.42	1.48	0.10	—	—
	IVO, 1 week	76.13	22.54	1.02	—	0.31
	IVO, 3 months	63.71	19.72	9.17	2.19	5.21
Neck	Intact	99.73	0.22	0.05	—	—
	IVO, 1 week	61.52	35.14	2.67	—	0.68
	IVO, 3 months	51.82	24.52	11.76	4.56	7.34

TABLE 2. Detrusor Function Evaluated *In Vitro* (mg/mm^2)

Parameter	Bottom			Body			Neck		
	normal value	IVO, 1 week	IVO, 3 months	normal value	IVO, 1 week	IVO, 3 months	normal value	IVO, 1 week	IVO, 3 months
Amplitude of contractions	6.2±3.1	0.8±0.4*	6.3±4.4	14.2±6.3	6.0±3.5*	6.6±3.8*	14.9±6.7	6.5±3.8*	2.5±1.8*
Tone	165±73	739±427*	604±349*	265±119	429±248	1728±998*	321±143	244±141	724±418*
Potassium contraction	25.3±14.6	47.3±27.3	25.5±14.8	80.2±35.9	47.5±27.4	38.5±22.2*	49.2±22.0	65.4±37.7	20.2±11.7*

Note. *$p<0.05$ compared to normal value.

strips to phasic contractions decreased after 1 week of IVO, this reduction being maximum in the fragments cut out from UB bottom (from 6.2 to 0.8 mg/mm^2; Table 2). The reduction of contraction force was about the same in the other compartments (from 14.2 to 6.0 mg/mm^2 in the body and from 14.9 to 6.5 mg/mm^2 in the neck). By contrast, the detrusor tone increased from 165 to 739 mg/mm^2 in the bottom area, from 265 to 429 mg/mm^2 in the body area, and decreased from 321 to 244 mg/mm^2 in the neck zone. After 3 months, the strength of detrusor contractions in the UB bottom normalized, remained reduced similarly as during the early period after IVO formation in the body, and decreased further in the neck zone, where it was just 2.5 mg/mm^2. The detrusor tone was sharply elevated in all compartments (Table 2).

The increase in the detrusor tone in response to leiomyocyte membrane depolarization with potassium ion excess (characterizing the bulk of actively functioning cells) after 1 week of obstruction did not differ much from the control values. After 3 months, it decreased by 51% for the UB body zone and by 57% for the neck zone.

Study of detrusor adrenoreactivity showed (Fig. 1) that after 1 week of IVO norepinephrine caused not relaxation, but a 25% increase of the contraction amplitude for UB bottom fragments. It virtually did not modulate contractions of UB body fragments, while the amplitude of contractions of UB neck fragments decreased by 30% under the effect of norepinephrine. The detrusor tone decreased less than in the control (by 10-11% in the bottom and body fragments and by 30% in the neck fragment). After 3 months of obstruction, norepinephrine reduced the UB bottom contraction amplitude by 52% and virtually did not change the contraction amplitudes of UB body and neck fragments. The tone decreased by 48-78%, more markedly in the fragments from the UB body.

Doxazosin treatment of normal UB wall increased the amplitude of contractions of the detrusor fragments from different compartment of intact UB by 11-56% without appreciably changing the tone. After 1 week of IVO, doxazosin increased contractions of UB bottom by 60%, but not of other compartments. After 3 months, the drug stimulated contractions of all compartments by 24-56% and increased the tone (Fig. 1).

Doxazosin blockade of a-adrenoreceptors after norepinephrine stimulation of α- and β-adrenoreceptors in normal detrusor led to a 17-36% reduction of contractions in the presence of reduced (by 30-44%) tone of the UB body and neck. After 1 week of IVO, this treatment virtually did not mo-

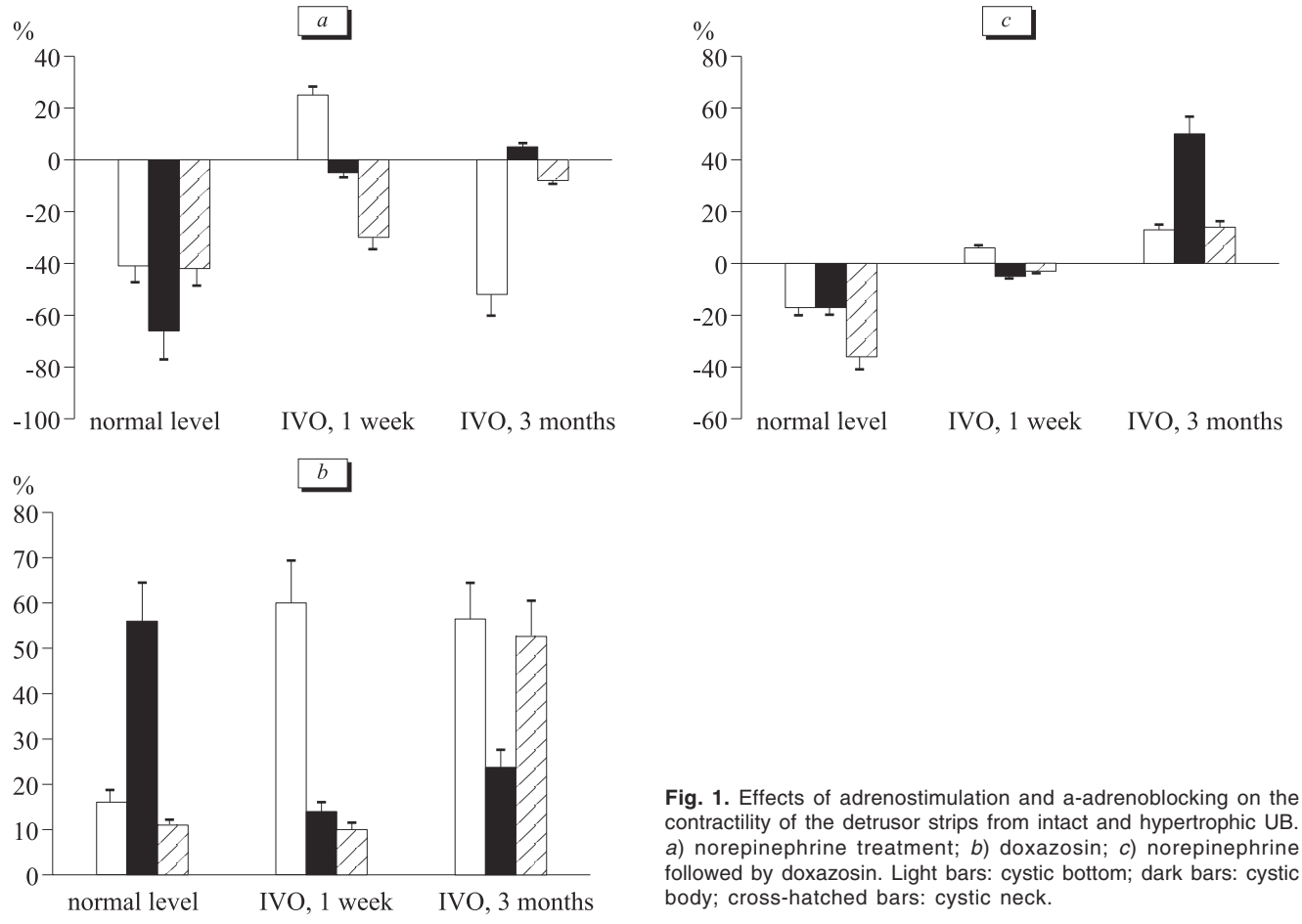

Fig. 1. Effects of adrenostimulation and a-adrenoblocking on the contractility of the detrusor strips from intact and hypertrophic UB. *a*) norepinephrine treatment; *b*) doxazosin; *c*) norepinephrine followed by doxazosin. Light bars: cystic bottom; dark bars: cystic body; cross-hatched bars: cystic neck.

dify the contractile activity of hypertrophic detrusor, the tone of the cystic neck being 14% reduced. After 3-month obstruction and treatment with norepinephrine and doxazosin, the contractions increased in the presence of the detrusor hypertone in the cystic bottom and body and hypotone in the cystic neck zone.

Hence, our experimental model of the urinary tract status in benign prostatic hyperplasia demonstrated the development of detrusor hypertrophy in UB during the earliest period of IVO development. Hypertrophy progressed in persistent obstruction and was paralleled by hypofunction of UB (specifically, of its evacuatory constituent). This is largely explained by progressing degenerative changes in the detrusor smooth-muscle cells and their transformation into myofibroblasts, paralleled by connective tissue growth. A significant reduction of the contractile activity of the cystic neck in parallel with its hypertone creates conditions for acute ischuria. Disorders in detrusor adrenoreactivity manifesting in lower sensitivity to norepinephrine, particularly in the neck zone, promote the development of this condition. α-Adrenoblockers increase detrusor contractility with reduction of its tone in the neck zone, this facilitating urine evacuation from UB. These data confirm the efficiency of α-adrenoblockers in acute ischuria in patients with benign prostatic hyperplasia.

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