# EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

# Contractile Function of the Smooth-Muscle Wall and Its Adrenergic Regulation in Megaureter

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We demonstrated disordered contractile capacity of megaureters formed against the background of reflux, organic or functional obstruction. The rhythmic and tonic contractions were suppressed in the megaureters with organic obstruction in comparison with megaureters caused by reflux. Norepinephrine stimulation induced pronounced pressor responses in obstructive megaureters. The state of the smooth-muscle walls of megaureters with functional obstruction was characterized by high tone, weak phase contractions, and increased capacity to pressor tonic reactions induced by norepinephrine.

**Key Words:** *megaureter; isometric contractions in vitro; norepinephrine*

Megaureter (dilated, elongated, and convoluted ureter) develops as a result of disordered urinary discharge caused by reflux, mechanical obstruction, or incompetence of the neuromuscular system of the ureteral wall [2-4]. Structural and ultrastructural studies reveal different abnormalities of the megaureter muscular wall: sclerosis, hypertrophy, hyperplasia, atrophy, muscle cell dysplasia and decrease in the number of these cells. However, few reports describe the contractile function of the megaureter smooth-muscle wall and its neurohumoral regulation. The data on the functional manifestation and hypertrophy and hyperplasia of the ureteral tissue caused by infravesical obstruction showed intensification of the contractile function *in vitro* [6]. On the other hand, decreased amplitude of the ureteral wall contractions and increased muscle tone in megaureter result from neuromuscular dysplasia in the ureter [1]. Contradictory data suggest different mechanisms of contractile dysfunction in megaureter depending on the causes of this condition, stage of development, and patient age. More precise understanding of the mechanisms of formation of a wide ureter can be important both theoretically and practically and specifically, for choosing the pathogenetic treatment.

We studied contractile activity of the ureteral wall *in vitro* and its adrenergic regulation in children with obstructive and refluxing megaureter.

## MATERIALS AND METHODS

The contractile function of isolated ureter fragments obtained during surgery in children were examined in an experimental device [1]; 3 groups of preparations from patients with different diagnoses were examined. Group 1 included fragments of refluxing megaureters (RMU), group 2 included fragments of obstructive megaureters (OMU) with organic abnormalities in the ureterovesical anastomosis, and group 3 consisted of megaureter fragments with functional, but not mechanical obstruction (FMU). The fragments contracted in oxygenated Locke's solution at 37°C during electrical stimulation. The fragments were stretched to a length at which the strength of contractions was the maximum. The strength was measured by a mechanoelec-

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trical converter (6 MX 2B) and recorded on a N3038 autorecorder. Active tension (strength of isometric contraction standardized for the area of transverse section of the fragment) during rhythmic electric stimulation and after 1-min rest, tonic contraction tension in high-potassium solution (contracture) served as indicators of contractile activity of the ureter wall. The strength of megaureter fragments stretched to the maximum length served as the indicator of their tone. Adrenergic regulation of the megaureter function was evaluated by changes in the contractions and tone after addition of norepinephrine ($10^{-5}$ M) into the solution.

The results were statistically processed using Student's *t* test.

## RESULTS

Comparison of physical parameters of the fragments showed that the weight/length ratio reflecting tissue weight per unit of length was minimum in RMU group, 56% higher in OMU group, and 127% higher in FMU group (Table 1). This ratio did not correspond to the content of functionally active muscle tissue, because the intensity of tonic contraction in response to potassium depolarization of the cell membrane (reflecting the maximum possible contraction) was 2-fold lower in the OMU compared to RMU group, while in FMU group potassium contracture virtually did not differ from that in the RMU group. These data suggest structural and functional differences in megaureters caused by organic and functional obstruction. The increase of the weight/length ratio indicates increased diameter of the ureter, which in FMU is determined by increased number of muscle cells capable of contracting, while in OMU is associated with relative shortage of these cells in the megaureter wall. The tone of FMU fragments was appreciably higher in comparison with that of RMU and OMU fragments, which attests to incomplete relaxation of FMU muscle cells. Rhythmic contractions of OMU and FMU fragments were suppressed by 62.3 and 83.9% compared to those in RMU fragments. Rest-potentiated contractions decreased by 67.5 and 83.6%, respectively. Comparison of the contractile capacity of the megaureters showed that the strength of RMU contractions during rhythmic stimulation was 71.4% and the strength of rest-potentiated contractions was 99.8% of their maximum possible strength (potassium contraction). These data indicate that smooth-muscle cells can realize the contractile reserve sufficiently completely. For OMU fragments the above ratios were 55.2 and 66.5%, respectively, which confirms their limited potentialities for the realization of the existing contractile reserve. In FMU potassium contraction was virtually the same as in RMU, but the ratio of the mean values of phase contractions to tonic contractions was only 10.8 and 15.4% for phase and rest-potentiated contractions, respectively.

These data indicate that capacity to tonic contractions predominates in smooth-muscle cells of the megaureter wall, while the capacity to rhythmic contractions is poorly realized. These peculiarities attest to replacement of smooth-muscle cells with connective tissue cells and deficit of energy needed for the contractile process in OMU. Decreased contractions can be a result of suppressed oxidative phosphorylation and desensitization of myofibrils [5]. Different functional status of the smooth-muscle cells in FMU can be due to hypertrophy, disorders in the subcellular distribution of potassium and modification of intracellular mechanisms regulating contraction and relaxation.

Differences in the adrenergic regulation of contractions of different types of megaureters were detected (Table 2).

Norepinephrine stimulated phase contractions of 100% RMU fragments by 20.4%, while rest-potentiated contractions increased less intensely (by 7.8%) in 75% samples. FMU fragments reacted to norepinephrine by an increase in rhythmic contractions (40.8%) in 38% cases, rest-potentiated contractions increased by 40.6% in 46% cases. Positive inotropic

**TABLE 1.** Characteristics of Isolated Fragments of Megaureter Wall from Children (Lock solution, 37°C; $M \pm m$)

| Parameter | RMU ($n$=5) | OMU ($n$=9) | FMU ($n$=21) |
|---|---|---|---|
| Length | 2.0±0.2 | 1.4±0.2* | 2.5±0.1 |
| Weight | 65.0±3.2 | 71.2±3.1 | 184.7±7.2*** |
| Weight/length | 32.5 | 50.8 | 73.9 |
| Tone, mg | 275.3±112.6 | 291.6±43.6 | 1666.8±120.6*** |
| Potassium contraction tension, mg/mm² | 21.7±5.6 | 10.6±1.7 | 23.1±1.4 |
| Rhythmic contraction tension, mg/mm² | 15.5±6.1 | 5.8±1.0 | 2.5±0.3 |
| Rest-potentiated contraction tension, mg/mm² | 21.6±7.0 | 7.0±1.3 | 3.5±0.5** |

**Note.** *$p$<0.05, **$p$<0.02, ***$p$<0.001 compared to RMU.

**TABLE 2.** Reactions of Children's Isolated Megaureter Fragments to Norepinephrine ($M\pm m$)

| Fragments of | | Phase contractions during rhythmic electrical stimulation, mg/mm² | Rest-potentiated contractions mg/mm² | Tone, mg |
|---|---|---|---|---|
| RMU | positive reaction | 3.2±1.9 (4) | 1.2±0.3 (3) | 190.0±116.3 (4) |
| | negative reaction | (0) | (0) | (0) |
| | no reaction | (0) | 0 (1) | 0 (1) |
| OMU | positive reaction | 2.3 (1) | 0.9±0.4 (3) | 245.7±57.0 (7) |
| | negative reaction | -2.1±1.0 (4) | -1.7±0.6 (3) | (0) |
| | no reaction | 0 (3) | (0) | 0 (1) |
| FMU | positive reaction | 0.9±0.4 (5) | 1.6±0.5 (6) | 420.3±46.2 (13) |
| | negative reaction | -0.5±0.2 (4) | -0.6±0.1 (6) | (0) |
| | no reaction | 0 (4) | 0 (1) | (0) |

**Note.** Number of fragments is shown in parentheses.

effect of norepinephrine was observed in only 12% of tested OMU fragments, and in 50% cases norepinephrine decreased the rhythmic contractions. Rest-potentiated OMU contractions increased by 14.8% in 50% samples, in other samples they decreased by 24.1%. Tonic reactions to norepinephrine were less pronounced in FMU: 2.21 and 1.95 times increased compared to those in RMU and OMU, respectively.

Our findings suggest that adrenergic stimulation of megaureter contractions is possible only within the range of its functional potential. Initially decreased contractions of OMU mainly decreased after addition of norepinephrine. This confirms a previous hypothesis about a lesser number of muscle elements capable of contractions in the OMU wall in comparison with RMU wall. Failure to increase phase contractions in the presence of retained (to a certain extent) capacity to stimulate the rest-potentiated contractions confirms previous hypothesis about deficiency of energy transport for the contractile process, energy delivery being better realized during rare contractions. Disorders in the receptor mechanisms of contraction regulation by catecholamines are also possible.

Notably suppressed contractile function of FMU was stimulated by norepinephrine, but in less number of cases than that of RMU, that is, the regulation of phase contractions of FMU was retained within the range of their contractile capacity. Strong pressor tonic reactions of FMU fragments to the adrenomimetic corresponded to its peculiar functional status (high liability to slow tonic contractions). This feature of the FMU contractile function can underlie the mechanism of development of the megaureter syndrome without mechanical obstruction: discharge from the kidney is impaired as a result of spastic contractions of the ureter.

The observed functional differences in the obstructive and refluxing megaureters indicate specific features of contractile characteristics of hypertrophic smooth muscles of dilated ureter and necessitate individual approach to evaluation of its wall function.

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