Int J Physiol Pathophysiol Pharmacol 2015;7(1):34-43
www.ijppp.org /ISSN:1944-8171/IJPPP0005150

Original Article

Regional differences of energetics, mechanics, and kinetics of myosin cross-bridge in human ureter smooth muscle

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Received December 23, 2014; Accepted March 9, 2015; Epub March 20, 2015; Published March 31, 2015

Abstract: This study provides information about baseline mechanical properties of the entire muscle and the molecular contractile mechanism in human ureter smooth muscle and proposed to investigate if changes in mechanical motor performance in different regions of isolated human ureter are attributable to differences in myosin cross-bridge interactions. Classic mechanical, contraction and energetic parameters derived from the tension-velocity relationship were studied in ureteral smooth muscle strips oriented longitudinally and circularly from abdominal and pelvic human ureter parts. By applying of Huxley's mathematical model we calculated the total working cross-bridge number per mm^2 (Ψ), elementary force per single crossbridge (Π_0), duration of maximum rate constant of crossbridge attachment $1/f_1$ and detachment $1/g_2$ and peak mechanical efficiency ($Eff._{max}$). Abdominal longitudinal smooth muscle strips exhibited significantly higher maximum isometric tension and faster maximum unloaded shortening velocity compared to pelvic ones. Contractile differences were associated with significantly higher cross-bridge number per mm^2. Abdominal longitudinal muscle strips showed a lower duration of maximum rate constant of crossbridge attachment and detachment and higher peak mechanical efficiency than pelvic ones. Such data suggest that the abdominal human ureter showed better mechanical motor performance mainly related to a higher crossbridge number and crossbridge kinetics differences. Such results were more evident in the longitudinal rather than in the circular layer.

Keywords: Human ureter smooth muscle, actomyosin crossbridge, shortening velocity, Huxley's model, Hill's equation, ureteral motility

Introduction

Ureteral peristalsis, the principal motor event that propels urine along the ureter, is the result of coordinated contractions of longitudinal and circular smooth muscle inside the organ wall. Longitudinal smooth muscle is responsible for ureteral shortening and may play a role in movement of urine; circular smooth muscle contractions are responsible for coapting the ureteral walls and generating pressure.

In the last decade, numerous investigations have focused on the effects of autonomic drugs in the modulation of ureteral motility in animal [1, 2] and in human models [3, 4].

The major improvement in our understanding of mechanical properties of urinary tract smooth muscle mostly derives from experiments carried out by means of "in vivo" and "in vitro" techniques in animal models [5-8]. Indeed, the literature gives very few publications on human ureter biomechanical characteristics [9].

Although knowledge on ureteral motility has advanced considerably, the molecular contractile mechanism of ureteral smooth muscle cells is not fully understood.

The state of contraction and relaxation, both in smooth muscle and striated muscle cells, depends on the attachment-detachment cycle between the crossbridges (CBs) on the thick filament and the thin filament [10]. The actin-myosin interaction in human ureteral smooth muscle cells occurs according to the general

kinetic scheme proposed for skeletal muscle. This interaction represents the molecular motor of force generation and mechanical performance depends on turning on both the number and unitary force of CBs.

Assuming that the fundamental characteristics of actomyosin CBs do not differ between smooth and striated muscle [11], to analyse the CB mechanics and kinetics in human ureteral smooth muscle strips, we proposed the formalism of Huxley's equations [10] adapted to non-sarcomeric muscle [12]. The application of Huxley's mathematical model not only takes into account many characteristics of muscle such as force, velocity and heat production, but also correlates these properties with its structural and biochemical properties [11]. In doing so, the total number, single force and kinetics of CBs were determined in longitudinal and circular smooth muscle strips obtained from human ureter segments isolated from abdominal and pelvic regions.

Therefore, besides providing information about baseline mechanical properties at the level of both the entire muscle and the molecular contractile mechanism in longitudinal and circular smooth muscle of human ureter, the aim of this study was to investigate, for the first time, if changes in mechanical motor performance in different regions of isolated human ureter could be attributed to differences in CBs interactions.

Materials and methods

This study, in accordance with the standards set by the *Declaration of Helsinki of the World Medical Association*, was approved by the Ethics Committee of Cagliari University and all patients signed the informed consent form.

At first, mechanical experiments were performed on isolated smooth muscle strips of human ureter. Tension and velocity were measured in living muscle strips throughout the overall load continuum to determine the Hill hyperbolic relationship, which is characterized by the two asymptotes, *a* and *b*, and the G curvature [13, 14].

Then, these experimental parameters were introduced into Huxley's equations [10] to determine myosin CB characteristics in living smooth muscle cells of human ureter.

Human ureteral smooth muscle preparations

Human ureter specimens were taken from 11 male and 4 female patients (mean age 58.4 ± 14 yr) undergoing radical nephroureterctomy due to cell carcinoma confined to renal parenchyme. Soon after surgical resection, the kidney was dissected and the ureter segments were tied at conventional levels, removed and put in a 100 ml airtight container filled with a Krebs solution (in mM: NaCl 118, KCl 4.7, $CaCl_2$ 2.52, $MgSO_4$ x $7H_2O$ 1.64, $NaHCO_3$ 24.88, glucose 5.55) previously aerated with a gas mixture of 95% O_2-5% CO_2. Then they were moved to the laboratory at room temperature where circular and longitudinal oriented muscle strips (8-10 mm long, 3-4 mm wide) were cut from abdominal and pelvic parts of the ureter. In this study the portion of ureter located between kidney basin and lower border of pelvic bone was named the abdominal part and the remaining portion to the urinary bladder was defined as the pelvic part.

Each muscle strip was clamped between two small metallic clips (Fine Science Tools, Vancouver, Canada) and vertically suspended in a 10 ml organ bath containing the same Krebs solution bubbled with 95% O_2 - 5% CO_2 and maintained at 37 °C and pH 7.4.

All tissue specimens appeared macroscopically normal with no sign of tumour or inflammation. Pathologic analysis of ureteral sections near the tissue used for the experiment was performed to ensure normality of tissue on the microscopic level.

While the metallic clip of one edge of the specimens was attached to a force transducer, the other clip was fastened to the lever of a linear displacement transducer as previously described [15].

Each strip was gradually stretched until a stable resting tension of 20 mN was obtained, and then equilibrated for at least 2 hours.

After equilibration, electrical field stimulation (EFS) was applied by means of two platinum plate electrodes placed parallel to the muscle preparation. The pulse trains were 300 ms at an interval of 150 s and supramaximal impulses of 80-200 mA with a duration of 6 ms at a frequency of 30 Hz applied by a constant cur-

rent source (Multiplexing Pulse Booster, Basile, Comerio, Italy).

All experiments were performed at optimal length of muscle strips (L_{max}; mm). L_{max} was defined as the resting muscle length at which the maximum peak value of active isometric tension was measured. This was determined by carrying out a conventional length-tension study.

Mechanical parameters, force-velocity relationship

Isotonic and isometric mechanical signals (shortening and force) were simultaneously recorded at L_{max} in longitudinal and circular muscle strips, according to the conventional afterloaded technique. Eight to ten EFS evoked contractions were performed against increasing afterloads, from preload up to the fully isometric contraction.

Calculated maximum shortening velocity was measured with necessary preload to obtain L_{max} (Vc_{max}; $L_{max} \times s^{-1}$) as well as for maximum extent of shortening (ΔL; % L_{max}). Peak isometric tension normalized per cross-sectional area (P_0; $mN \times mm^{-2}$) was measured from the full isometric contraction. For each contraction, peak shortening velocity (V) was plotted against total isotonic load (P) normalised per cross-sectional area. Maximum unloaded shortening velocity (V_{max}; $L_{max} \times s^{-1}$) was computed by means of Hill's equation [13]:

$$(P + a)(V + b) = (P_0 + a)\, b \quad (1)$$

where *a* and *b* represent the asymptotes of the hyperbola and P_0 is the peak isometric tension for V = 0. Shortening velocity was normalized to muscle length. The curvature of the force-velocity relationship (G) was calculated as P_0/a. In striated muscle, the G value reflects the myothermal economy of force generation, such that the higher the G the more economical the contraction. Peak mechanical efficiency ($Eff._{max}$), calculated as $[G/(G+2)]^2$ [16], was defined as the maximum ratio of the rate of mechanical work to the rate of total energy.

Work and power of shortening were calculated from the data. Work was defined as the product of the shortening and the load lifted (W_{max}; $\mu J \times mm^{-2} \times L_{max}^{-1}$). The power output was defined as the product of the velocity and the load lifted (P_{output}; $\mu W \times mm^{-2} \times L_{max}^{-1}$).

Crossbridge characteristics

Force and shortening in striated and smooth muscle are generated by cycling interactions of contractile filaments (crossbridges, CBs). Myosin head interacts with the active site on the actin filament, a process fuelled by one molecule of ATP. Huxley's equations represent the most widely accepted mathematical model of striated muscle mechanics. Recently, Huxley's model was also used for smooth muscle [11, 12]. This mathematical model not only accounts for many macroscopic properties of muscle (force, velocity and heat production) but it also connects these parameters with its structural and biochemical characteristics.

In accordance with the most widely accepted theory of contraction [10], muscle force depends on the elementary CB force and the total number of CBs; consequently the maximum force developed by a muscle (P_0) is the product of the number of cycling CB/mm^2 and the force of a single CB. Huxley's model allows computing of the number, unitary force and kinetics of myosin CBs in living smooth muscle as a function of velocity (V). Considering the values of Huxley's equations *h* (CB step size equal to 11 nm), *e* (free energy required to split an ATP molecule equal to 5.1×10^{-20} J), *l* (the distance between two actin sites equal to 36 nm) and *w* (the maximum mechanical work of a unitary CB equal to 3.8×10^{-20} J), it is possible to calculate the peak value of the rate constants for CB detachment g_1 and g_2 (s^{-1}) and the maximum value of the rate constant for CB attachment f_1 (s^{-1}).

$$g_2 = \frac{2V_{max}}{h} \quad (2)$$

$$g_1 = \frac{2wb}{ehG} \quad (3)$$

$$f_1 = \frac{-g_1 + \sqrt{g_1^2 + 4g_1g_2}}{2} \quad (4)$$

Consequently, $1/g_2$ and $1/f_1$ are the duration of maximum rate constant of CB detachment and attachment respectively.

This approach provides a system for estimating the unitary force per CB (π_0; pN), the number of CBs per mm^2 at peak active tension ($\Psi \times 10^9$) and the total duration of CB cycle (T_c; ms).

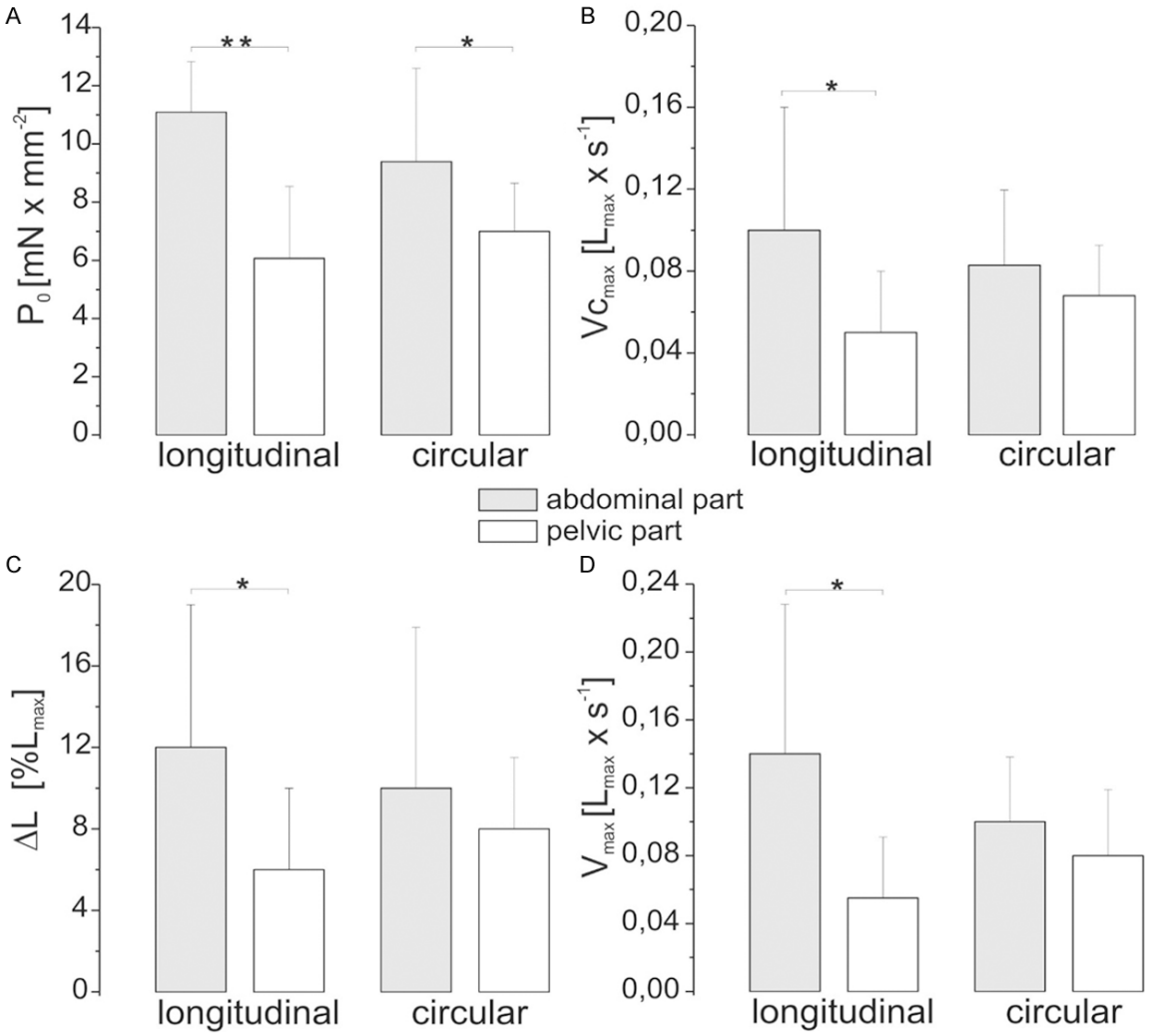

Figure 1. Mechanical and energetic parameters in longitudinal and circular muscle strips from abdominal and pelvic parts of human ureter. A: Normalized peak isometric developed tension (P_0). B: Calculated maximum shortening velocity (Vc_{max}). C: Maximum extent of shortening (ΔL). D: Maximum unloaded shortening velocity (V_{max}). Lmax: optimal muscle length. Values are means ± S.D. *; p < 0.05, **; p < 0.001.

$$\pi_0 = \frac{w}{l} \times \frac{f_1}{f_1 + g_1} \quad (5)$$

$$\Psi = ab/(e\,\frac{h}{2l} \times \frac{f_1 g_1}{f_1 + g_1}) \quad (6)$$

$$t_c = 1/\frac{h}{2c} \times \frac{f_1 g_1}{f_1 + g_1} \quad (7)$$

Statistical analysis

Data are presented as mean values ± S.D. Statistical significance was assessed by ANOVA variance analysis. P < 0.05 was taken to indicate statistical significance. Linear regression was based on the least squares method.

Results

Mechanical and energetic parameters in human ureteral smooth muscle

Mechanical and energetic parameters of human ureteral smooth muscle strips are presented in **Figure 1**. The abdominal part of human ureter exhibited a maximum peak isometric tension normalised per cross-sectional area, P_0, significantly higher than those of the pelvic part (longitudinal strips, from abdominal part: 11.09 ± 1.74 mN × mm^{-2}, from pelvic part: 6.07 ± 2.47 mN × mm^{-2}, n = 14, P < 0.001; circular strips from abdominal part: 9.39 ± 3.21 mN × mm^{-2}, from pelvic part: 7.00 ± 1.65 mN × mm^{-2}, n = 14, P < 0.05) (**Figure 1A**). The longitu-

Table 1. Values of mechanical and energetic parameters of longitudinal and circular muscle strips from abdominal and pelvic parts of human ureter

	Longitudinal		Circular	
	Abdominal	Pelvic	Abdominal	Pelvic
a ($mN \times mm^{-2}$)	4.83 ± 1.42	4.45 ± 1.11	4.04 ± 0.83	4.18 ± 1.09
b ($L_{max} \times s^{-1}$)	0.08 ± 0.035	0.11 ± 0.037*	0.11 ± 0.039	0.16 ± 0.21*
G	2.94 ± 1.39	1.23 ± 0.65*	2.04 ± 0.69	1.19 ± 0.56*
W_{max}	0.21 ± 0.14	0.07 ± 0.06*	0.16 ± 0.12	0.09 ± 0.03*
P_{output} ($mW \times mm^{-2} \times L_{max}^{-1}$)	0.17 ± 0.11	0.05 ± 0.04*	0.13 ± 0.07	0.07 ± 0.02*

Data are presented as means ± S.D. *a* and *b*: the asimptotes of the Hill's hyperbola; G: the curvature of the hyperbola; W_{max}: the normalized maximum mechanical work; P_{output}: the normalized maximum power output. *; p<0.05.

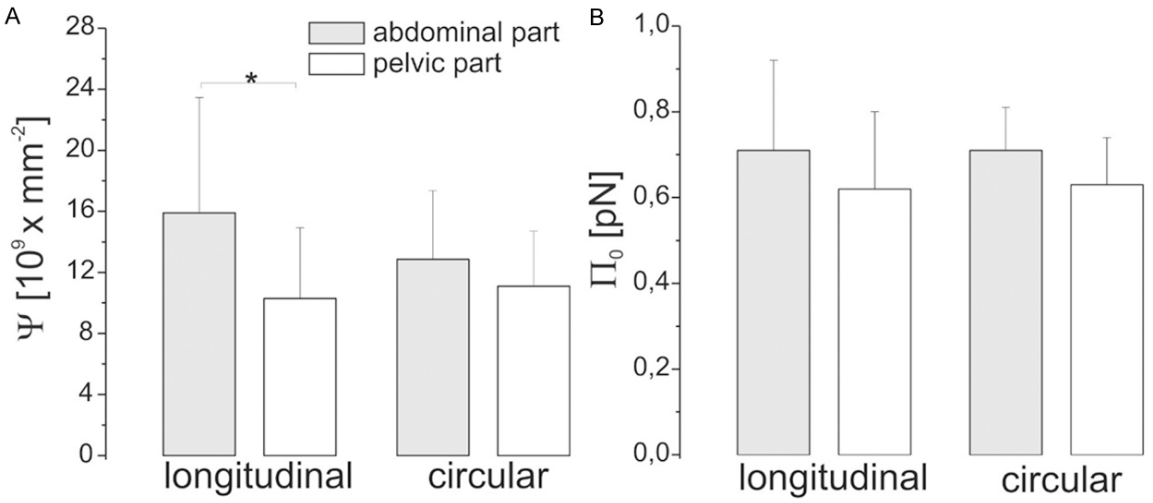

Figure 2. A: Total number of CB (Ψ) per mm^2 at peak isometric tension; B: Single CB force (Π_0) calculated in longitudinal and circular muscle strips from abdominal and pelvic parts of human ureter. Values are means ± S.D. *; p < 0.05.

dinal strips from abdominal part exhibited significantly faster Vc_{max} (~117%, P < 0.05; **Figure 1B**), greater ΔL (~100%, P < 0.05; **Figure 1C**) and faster maximum shortening velocity, V_{max}, (~154%, P < 0.05; **Figure 1D**) than pelvic ones. Hill's constants, G curvature and energetic parameters are given in **Table 1**. The analysis of force-velocity constants revealed that the *a* value was similar in all smooth muscle strips, while the *b* constant was significantly smaller in both longitudinal and circular strips from abdominal part compared to pelvic ones (P < 0.05). The G curvature of the force-velocity hyperbola was significantly higher in both longitudinal and circular strips from the abdominal part when compared to longitudinal and circular strips from the pelvic part (P < 0.05). The normalised maximum mechanical work, W_{max}, and maximum power output, P_{output}, were significantly higher in longitudinal and circular muscle strips from abdominal part compared to pelvic ones (P < 0.05).

Myosin CB number, force and kinetics

Significant differences were observed between longitudinal muscle strips from the abdominal part and pelvic ones as concerns the total number of CBs per mm2 (Ψ) at peak isometric tension as shown in diagrams of **Figure 2A** (P < 0.05). However, the single CB force (π_0) did not significantly differ between abdominal part and pelvic part of smooth muscle of human ureter (**Figure 2B**). As shown in **Figure 3A** there was a strong linear relationship between P_0 of the muscle strip and Ψ (R^2 = 0.98; P < 0.001); there was no correlation between P_0 and π_0 (R^2 = 0.0018; **Figure 3B**). The duration of CB attach-

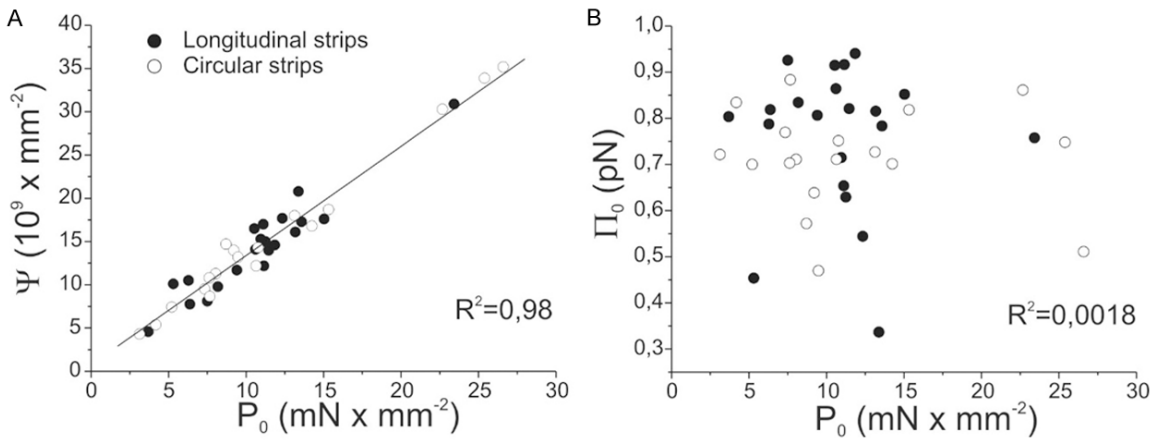

Figure 3. A: Relationships between peak isometric tension (P_0) of longitudinal and circular muscle strips and the number of CB ($\Psi \times 10^9$). B: Relationships between P_0 and the unitary force per single CB (π_0) at peak active tension in abdominal part of human ureter.

ment, $1/f_1$, and CB detachment, $1/g_2$, the total duration of the CB cycle, T_c, and the peak mechanical efficiency, $Eff._{max}$, are depicted in diagrams of **Figure 4**. $1/f_1$ (**Figure 4A**) and $1/g_2$ (**Figure 4B**) were significantly ($P < 0.001$) shorter in the abdominal part of human ureter ($1/f_1$ in longitudinal strips from the abdominal part was 0.023 ± 0.005 s, from the pelvic part was 0.04 ± 0.009 s; $1/g_2$ in longitudinal strips from the abdominal part was 0.006 ± 0.003 s, from the pelvic part was 0.016 ± 0.005 s). T_c, was similar in both parts of human ureter (**Figure 4C**). The $Eff._{max}$ was significantly higher ($P < 0.001$) in both longitudinal and circular strips from the abdominal part when compared to longitudinal and circular strips from pelvic ones (**Figure 4D**).

Discussion

In the human ureter alterations of static and dynamic biomechanical properties of the ureteral wall lead to pathological states compromising regular urine transportation from kidney to bladder.

Mechanical factors, such as megaureter, vesicoureteral reflux and diuresis, are involved in presence of pathological states. Renal damage associated with urinary stones is the result of a sequence of pathophysiological events starting from obstruction. Mechanical factors, such as cycling contraction and relaxation of ureteral smooth muscle, are involved in the partial or total obstruction of the ureteral lumen. Chronically obstructed ureter shows altered active (smooth muscle contraction) and passive (hydrostatic pressure) forces. Therefore, ureter is no longer able to produce a propulsive force within its lumen, so that its ability to transport urine is somewhat reduced [17]. The peristaltic contraction waves become smaller and are unable to coapt the ureteral wall. Moreover, hypertrophy and increase in thickness were found in presence of stones in the ureteral wall [18].

Abnormal distension of ureteral diameter is commonly named megaureter. Histological studies using light and electron microscopy have mostly shown hypoplasia and atrophy of the ureteral muscle and an increased amount of collagen between muscle cells with abnormal cell-to-cell contact in the megaureter [19, 20]. Such structural alterations cause a disrupted and ineffective ureteral peristalsis [21]. The dilated ureter is incapable of coapting its lumen and efficiently propelling the urine bolus.

Moreover, a loss of compliance of ureterovesical junction is an important mechanical factor connected to vesicoureteral reflux [22].

Obstruction, megaureter, vesicoureteral reflux and diuresis directly affect ureteral muscle fiber length and thus may change the ability of the ureter to transport urine from kidney to bladder.

Thus the right choice of therapy is guaranteed by complete knowledge of ureter anatomy, physiology and biomechanical characteristics.

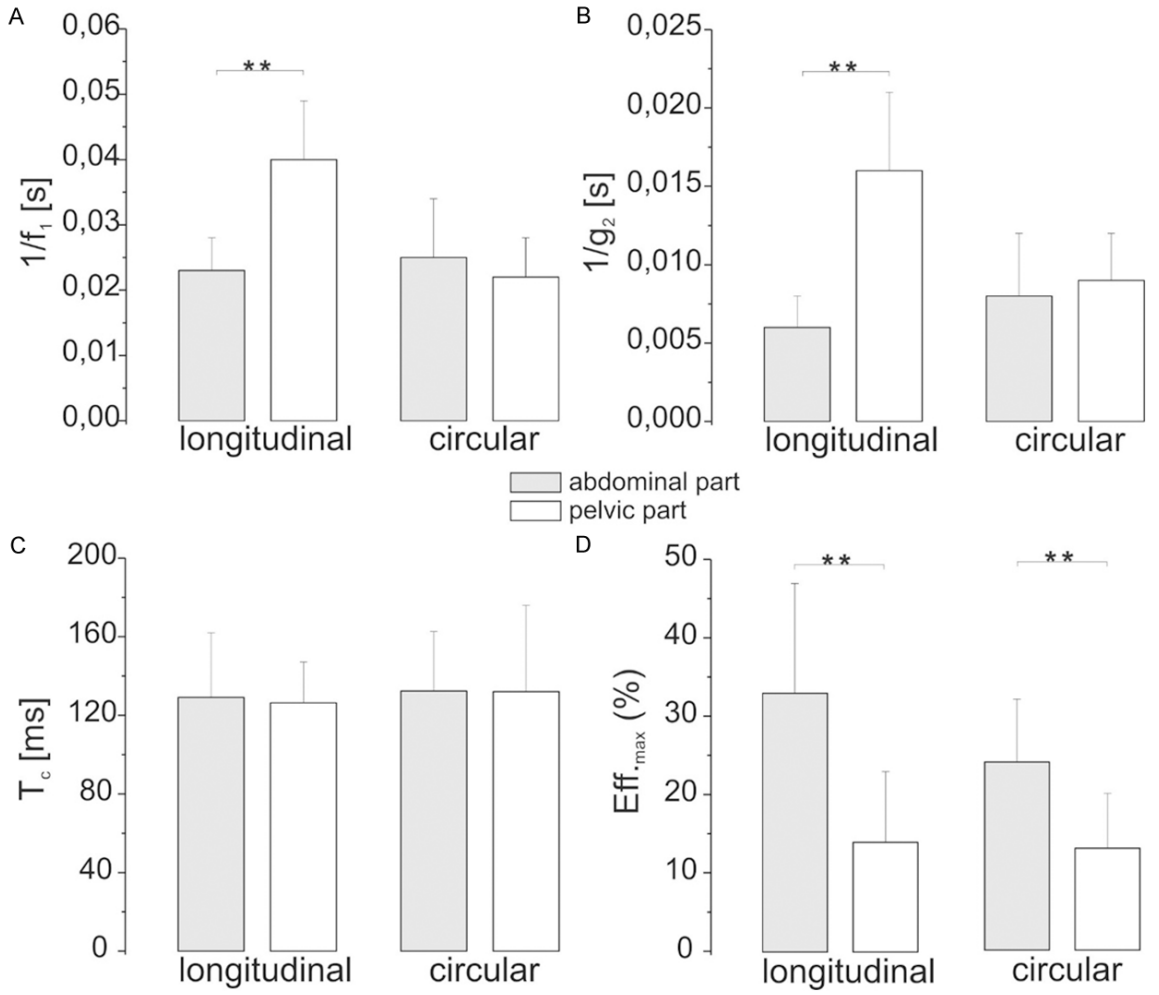

Figure 4. A: The duration of maximum rate constant for CB attachment ($1/f_1$); B: The duration of maximum rate constant for CB detachment ($1/g_2$); C: The total duration of the CB cycle (T_c); D: The maximum mechanical efficiency ($Eff._{max}$, in %) calculated in longitudinal and circular muscle strips from abdominal and pelvic parts of human ureter. Values are means ± S.D. *; $p < 0.05$, **; $p < 0.001$.

Our goal in the current study was to undertake experiments in an attempt to obtain a complete picture of biomechanical characteristics at the level of the entire muscle and the molecular contractile mechanism in the human ureter. For this purpose, in one time mechanical experiments were first carried out using isolated muscle strips oriented in the longitudinal and circular direction and removed from the abdominal and pelvic region of the human ureter. Tension and shortening velocity were measured in living muscles throughout the overall load continuum to determine the Hill hyperbolic relationship [15, 23]. Following this, these experimental parameters were introduced into Huxley's formalism [10] to see if changes in mechanical motor performance in different regions of the human ureter could be attributed to differences in CB interactions.

We found that although no substantial differences exist in structural, biochemical and histological characteristics along the muscular wall of the human ureter [24-26], the abdominal smooth muscle region showed a better mechanical performance than the pelvic one resulting in a higher maximum peak of active isometric force, greater shortening, faster shortening velocity and higher maximum peak of work and power output.

Analysis of the force-velocity constants revealed that in longitudinal and circular smooth muscle strips from the abdominal part

of the human ureter the *b* constant values were smaller compared to pelvic ones. Since the constant *b* is a measure of the rate of extra energy liberation during shortening, this observation may reflect the lower rate of energy expenditure for this region when compared to the pelvic part. Also taking into account that the G curvature of the force-velocity relationship was found to be higher in all muscle preparations of the abdominal part compared to those of the pelvic part, these results suggest that smooth muscle of the human ureter exhibited economy of force generation in the abdominal part.

The force-velocity relationship obtained in isotonic conditions depends on the rate of formation and breakdown of the CBs between the myofilaments. Mathematical models of muscle mechanics provide an informative system for estimating the number, unitary force and kinetics of myosin CBs in living muscle [11, 27]. Huxley's model has been used in many mechanical experiments [28] and can also contribute to better understanding CB interactions in human ureter smooth muscle cells.

According to AF Huxley's theory of contraction, the CBs act as independent force generators and muscle force depends both on total number of cycling CBs and the force produced per single CB [10, 11, 12, 23]. In our experiments the single CB force was similar in all muscle preparations, thus the enhanced P_0 found in the longitudinal smooth muscle strips from the abdominal part implies that the total number of active CBs per mm^2 was higher during contraction in these preparations. These results are consistent with data obtained from Huxley's mathematical model showing a higher number of CBs in longitudinal strips from the abdominal part.

Muscle contraction is caused by the attachment-detachment cycle between the cross-bridges on the thick filament and the thin filament coupled with ATP hydrolysis. During myofilament sliding, the attachment of cross-bridge to the thin filament occurs after ATP hydrolysis. Then myosin rapidly dissociates from actin after ADP release. Thereafter, one molecule of ATP binds the nucleotide site of the myosin head (ATP-binding pocket).

In our study, the duration of maximum rate constant of CB attachment ($1/f_1$) and detachment ($1/g_2$) was found to be markedly shorter in longitudinal smooth muscle strips from the abdominal part than in pelvic ones. This result may account, at least in part, for increased shortening velocity at the muscle level. Indeed, since V_{max} is proportional to the maximum value of g_2, consequently the higher g_2 leads to the lower $1/g_2$, thus the detachment step is shorter. Therefore, the detachment phase is a critical step in determining of maximum velocity of shortening in human ureter smooth muscle. $1/g_2$, rather than T_c, would thus strongly influence the shortening capacity of the whole muscle [11].

Such results are common to a previous study in which it was demonstrated that the proximal portion of dog ureter appeared to develop a higher tension than the distal portion [8].

Furthermore, other authors [29] observed that the longitudinal smooth muscle also plays an essential role. Indeed, contraction of longitudinal layer distends passively the uppermost portion of the ureter forming a "ureteral diastole" that helps filling, instead the longitudinal contraction of the lower portion, followed by the contraction of circular layer, helps to inject urine into the bladder.

A complete knowledge of ureter anatomy, physiology and biomechanical properties is important in presence of pathological states to guarantee the right choice of therapy as well as the appropriate choice of a minimally invasive method in each clinical case. This knowledge allows a good choice of the right molecule for selective action on ureteral smooth musculature, reducing side effects and increasing therapeutic efficacy. Currently, alphalythic drugs utilised to facilitate the removal of ureteral stones are used off-label. Moreover, other authors [30] demonstrated recently that the α_1-receptors density was significantly smaller in the abdominal human ureter than in its pelvic part.

Our results presented also a better motor performance in terms of greater force developed, more rapid speed and greater extension of shortening of smooth abdominal ureter muscle compared to the pelvic ureter. In physiological states these biomechanical characteristics of the human ureteral wall ensure the urinary bolus a rapid progression to the bladder. In pathologic states, such as obstruction by ure-

teral stones, the administration of alphalythic drugs, which act primarily in the pelvic ureteral region, and the increased contractility of the abdominal region contribute to a better performance of stone expulsion.

The biomechanical characteristics of the ureteral wall from this point of view are not yet present in the literature.

Our work not only confirmed the important role of longitudinal smooth muscle in ureteral peristalsis, which has been reported by some authors [31, 32] but it showed for the first time and with an innovative theoretical and experimental approach, that in the human ureter the differences in mechanical motor performance found between abdominal and pelvic parts could be attributed to differences in myosin crossbridge (CB) interactions.

We believe that our results will be useful to understand better the physiology and dysfunction of ureteral smooth muscle at the level of the whole muscle and at the level of the molecular motors, as well as improving the evaluation of pharmacological, surgical and cellular therapies in particular clinical cases. These new outcomes allow a better description of the biomechanical behavior of the human ureter in congenital diseases such as stenosis of the pyeloureteral joint and in acquired diseases such as megaureter. Moreover, a detailed knowledge of mechanical characteristics of the whole ureteral muscle permits the development of new surgical techniques and new materials for increased versatility and biocompatibility of ureteral stents. Several ureteral substitutes have been already proposed, including blood vessels, fallopian tubes and the appendix.

Nevertheless, all these solutions and corresponding procedures are related to a significant morbidity with a lower kidney function in many patients. Currently, partial or complete ureteral replacement with small bowels is indicated as a secondary treatment after failure of ureter-sparing surgery. However, those neoureters are frequently associated to Ileoureteral reflux, strictures at the ureteroileal anastomosis and recurrent infections.

In the future, the newly known mechanisms that regulate smooth muscle ureteral layers activity may represent a novel approach to find other tissues or materials that are most appropriate in reconstructive surgery.

Disclosure of conflict of interest

None.

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