Biomechanical characterization of the urethral musculature

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THE URETHRA IS A DYNAMIC TISSUE comprised of both circumferential and longitudinally oriented smooth and striated muscle within a connective tissue matrix. It serves a dual function by maintaining continence during bladder filling and aiding in the release of urine from the bladder during micturition. Unlike the smooth muscle layer, which is relatively uniform and continuous throughout the entire axial length, the striated muscle layer becomes much more dense within the midurethral region which has been termed the rhabdosphincter (15, 21, 25). Continence is maintained through the generation of urethral closure pressures that exceed intravesical pressures.

Experimental studies involving pharmacological neuromuscular blockade demonstrate the fundamental importance of the urethral musculature in maintaining continence, both at rest and during strenuous activities (35–37). Clinical associations have been established between the emergence of certain forms of incontinence (e.g., stress urinary incontinence) and deficits in the urethral musculature and/or associated nerves (1, 18, 22, 26–28, 40). Furthermore, the anatomic establishment of minimum limits on urethral structure and associated musculature necessary to maintain continence has been serendipitously revealed through required resections (e.g., orthotopic lower urinary tract reconstruction) (30). Despite such clinical observations and associations, the female urinary continence mechanism as a whole remains somewhat controversial. Experimental studies have yet to clearly discern the quantitative contribution of the structures that contribute to the generation of closure forces under normal and stressful (e.g., coughing, sneezing, straining) conditions (35). The lack of agreement on fundamental issues regarding the maintenance of continence speaks to the necessity of clarifying basic urethra structure-function relationships. To begin to address such deficiencies, and gain an improved understanding of urethral function, the experiments described herein were designed to quantify the individual contributions of both the urethral smooth and striated muscle layers in the female rat urethra in response to a wide range of applied transmural pressure loads. To accomplish this, a recently developed ex vivo whole urethra experimental model was utilized (19).

There remains a fundamental need for clear identification of structure-function relationships encompassing both the urethra and its supporting tissues. We demonstrate here, through the validation of traditional biomechanics methodology and concepts, how the activation of each individual muscle component can affect the overall function of this complex tissue. Our results embody the first known detailed ex vivo description and comparison of the biomechanical behavior of the active and passive female urethra.

MATERIALS AND METHODS

Animals. Urethras were obtained from adult female Sprague-Dawley rats (260–320 g, ~8–10 wk of age; Harlan) that were housed at the University of Pittsburgh under the supervision of the Department of Laboratory Animal Resources. The policies and procedures of the animal laboratory are in accordance with those detailed in the Guide for the Care and Use of Laboratory Animals published by the US Department of Health and Human Services.

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Procedural protocols were approved by the Institutional Animal Care and Use Committee.

**Urethra isolation and experimental testing apparatus.** Intact urethras were isolated under halothane anesthesia (4%), as previously described (19). To maintain in vivo length, a catheter (PE-50) was inserted into the urethral lumen before excision of the tissue and secured with sutures at the midbladder and at the urethral meatus. The entire bladder-urethra unit was removed and immediately placed into cold, oxygenated Medium 199 (Sigma) at 37°C and bubbled with a 95% O₂-5% CO₂ gas mixture. A chamber that was perfused with bathing medium (Medium 199; inside of the experimental apparatus and was enclosed within a described testing system (19). secured with sutures at the midbladder and at the urethral meatus. The tissue bath for a period of 30 min to completely inhibit smooth muscle activity as evidenced by dilation of the tissue to a new stable baseline OD. Both atropine (1 μM) and hexamethonium (100 μM) were also added along with the sodium nitroprusside, to further eliminate any possibility of cholinergic-induced smooth muscle activation, before stimulation with ACh (5 mM). Preliminary PE and ACh dose-response studies were performed to ensure maximal induced contractions and to ensure the effectiveness of the blocking agents at the stated concentrations.

For all active tissue experiments, immediately following confirmation of contraction, intraluminal pressure was increased from 0 to 20 mmHg in 2-mmHg increments. P-D data were collected at a 20-Hz sampling rate over a 10-s period for each 2-mmHg pressure step. The OD data were then averaged over the 200 data points obtained at each incremental pressure step to obtain discrete values associated with each applied pressure. The P-D collection period (100 s = 10 s × 10 pressure steps) was chosen to be within the duration of maximal striated muscle contraction based on preliminary measurements. The 20-mmHg pressure range was selected based on preliminary studies to identify the degree of tissue strain in the ex vivo system and to ensure that this degree of strain remains consistent with estimations of the normal physiological urethral strain (occurring during micturition). This pressure is consistent with normal physiological (non-stress) mean bladder pressure in the female rat (3.4 KPa ≈ 25 mmHg) (32).

**Passive state P-D measurements.** Immediately following collection of active state data, a passive state devoid of muscle tone was induced by addition of EDTA (3 mM final concentration) to the bath, allowing a 30-min equilibration period for elimination of muscle activity (19). To minimize viscoelastic effects, a mechanical preconditioning protocol, consisting of 10 pressure cycles from 0 to 4 mmHg at 5-s increments, was performed before collection of the passive P-D data. P-D responses became repeatable generally by the sixth to eighth inflation-deflation cycle, as observed through examination of resulting hysteresis loops. Note that preconditioning was not performed before the collection of active state data and is commonly avoided in studies of active mechanics due to concerns of compromising contractile function with repetitive stretching (12, 14, 17).

**Determination of muscle volume fraction and tissue thickness.** Immediately following collection of P-D data, and before tissue removal for histological processing, the location at which the laser was positioned for OD measurements was identified by marking the outside of the tissue with a permanent ink pen. The tissue was then fixed at the maintained in vivo length using 2% paraformaldehyde. The local content of smooth and striated muscle at the location of measurement was determined through immunofluorescent labeling of fast and slow myosin heavy chain and α-smooth muscle actin [protocols previously described (19); all antibodies from Sigma]. For each specimen, local muscle content and tissue thickness were determined by averaging values obtained from three cryosections taken over the marked segment, ~1 mm in axial length. The actual urethral wall cross-sectional area (WCSA) for each section was determined through image processing (Northern Eclipse software, v6.0; Epix Imaging,) from the difference in the cross-sectional areas (CSA) enclosed by manually drawn borders of both the lumenal and ablumenal surfaces. Unloaded tissue thickness, h, was calculated as the difference between the estimated unpressurized outer radius (Rₒ) and inner radius (Rᵢ) based on these CSA measurements and an approximation of the tissue to a cylindrical geometry, as described in equations 1–3.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Agent</th>
<th>Action</th>
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<tbody>
<tr>
<td>Smooth muscle alone</td>
<td>N⁵-nitro-1-arginine</td>
<td>NOS inhibitor</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>Phenylephrine</td>
<td>α-Adrenergic receptor agonist</td>
</tr>
<tr>
<td>Striated muscle alone</td>
<td>Sodium nitroprusside</td>
<td>NO donor</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>Atropine sulfate</td>
<td>Muscarinic antagonist</td>
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<td></td>
<td>Hexamethonium</td>
<td>Neuronal nicotinic antagonist</td>
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<td></td>
<td>Acetylcholine</td>
<td>Nicotinic receptor agonist</td>
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<tr>
<td>Smooth and striated</td>
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Protocols are listed in the order presented. NOS, nitric oxide synthase.
Estimation of inner radius. The tissue inner radius, \( R_i \), under a given pressure, \( P_o \), was estimated from application of the incompressibility assumption, which is commonly invoked in (and has been validated for) arterial mechanics studies (5). This assumption, that the cross-sectional area of the tissue wall will remain unchanged under the various levels of tissue strain, allows for the estimation of \( R_i \) at each pressure step (\( P_o \)) based on corresponding OD measurements (yielding outer radii, \( R_o \)) and from known tissue dimensions (\( R_{i0}, R_{o0} \)) taken at a reference pressure (\( P_o = 0 \) mmHg). Because the tissue was tethered at both ends, changes in axial length were not permitted. This constant tissue length, along with conservation of tissue volume, dictate that the tissue maintains a constant wall cross-sectional area (i.e., WCSA\(_{p}\) = WCSA\(_{p0}\)). Thus assuming an approximate cylindrical geometry yields the estimation of \( R_i \) at any pressure (\( P_o \)) based on the following equations 4–5:

\[
\pi (R_{o0}^2 - R_i^2) = \pi (R_o^2 - R_i^2) \quad (4)
\]

\[
R_i = \sqrt{R_{o0}^2 - R_i^2 + R_i^2} \quad (5)
\]

Previous estimations of \( R_i \) using these assumptions, specifically examined for various blood vessels over a wide range of pressure conditions, were found to be within a mean of less than 1% of actual measurements (13).

Muscle contraction parameters. Parameters descriptive of the relative contractile function of the active muscle element(s) over the entire applied pressure range were obtained from the P-D data. Each parameter is graphically depicted in Fig. 1.

The total contraction capacity (TCC), defined as the ratio of the area between the active and passive curves to the area under the passive curve alone (Fig. 1A), may be considered the relative ratio of the work performed by the activated muscle to the elastic energy stored by the passive elements of the tissue alone (14). To obtain this parameter, the OD data were normalized to the initial diameter value (i.e., \( D|D_{o0} = 1.0 \) at \( P = 0 \) mmHg) to attain a common starting point for each set of passive and active curves. To calculate the area under each curve, each set of P-D data was fit separately to a third-order polynomial function (yielding outer radii, \( R_o \)) and from known tissue dimensions (\( R_{i0}, R_{o0} \)) given pressure, \( P_o \) using nonlinear regression (SigmaStat, v2.0). Once the coefficients were determined, the function describing the P-D curve was integrated over the same normalized outer diameter range for each paired passive and active data set, given below in equation 6:

\[
\sigma_o = P_i \left( \frac{R_o^2}{R_{i0}^2} \right) \frac{1 + R_{o0}^2}{R_o^2} \quad (6)
\]

where \( P_i \) is the internal (transmural) applied pressure and \( R_{i0} \) and \( R_{o0} \) are the previously defined estimated and measured inner and outer radii, respectively.

Using equation 6, urethra midwall \( \sigma_o \) responses were calculated and were subsequently used to determine the maximum stress generated by each activated muscle component. To accomplish this, nonlinear regression was used to fit the experimental data to either an exponential (\( \sigma = a \exp^{bx} \), for active striated and all passive responses) or a third-order polynomial function (\( \sigma = ax^3 + bx^2 + cx \), for active smooth and smooth-striated responses), based on maximizing \( R^2 \) values, using SigmatStat (v2.0; Jandel Scientific). Active and passive fitted \( \sigma_o \) values were then obtained over the entire normalized diameter (OD/OD\(_{o0}\)) range at 0.02 increments. Maximum \( \sigma_o \) generated by the active muscle component alone for each tissue was determined as the maximum difference between the fitted active and passive \( \sigma_o \) values at each normalized diameter increment. Fitted \( \sigma_o \) vs. normal-

\[
R_o = \sqrt{\text{CSA}_{o0}/\pi} \quad (1)
\]

\[
R_i = \sqrt{\text{CSA}_{i0}/\pi} \quad (2)
\]

\[
h = R_o - R_i \quad (3)
\]
ized diameter responses, and subsequent estimation of maximum $\sigma_0$, were performed within the limits of the experimentally observed diameter range (i.e., requiring no extrapolation).

Statistical analysis. Comparison of OD and ID responses between active and corresponding passive tissue states at each applied pressure was performed using paired $t$-test, or the equivalent nonparametric Wilcoxon signed rank test. Comparison of the contraction parameters TCC and FCR among active tissue states (smooth, striated, and smooth striated) was performed using one-way ANOVA with Student-Newman-Keuls post hoc pairwise comparisons, or the equivalent nonparametric ANOVA on ranks with Dunn’s post hoc analysis. FCR comparisons were performed at each applied pressure, separately. $P$ values $<0.05$ are reported as significant, and data are expressed as means ± SE. All statistical comparisons were performed using SigmaStat (v2.0; Jandel Scientific) statistical software.

RESULTS

Tissue histology. The striated muscle layer within the mid-urethral region contained a prevailing alignment of myofibers in the circumferential direction (Fig. 2, left). Inspection of the smooth muscle layer within the midregion also revealed a predominant circumferentially oriented muscle layer, along with some longitudinally oriented fibers both intermingled within the circumferential layer and located closer to the lumen of the tissue. For tissues utilized in these experiments, smooth and striated muscle content in the midregion as a percentage of total cross-sectional area was within the same range as previously reported (smooth, 32.8–37.8%; striated 17.2–19.7%) (19). The striated muscle layer was predominantly composed of type II (fast) fibers, also as previously reported (19).

P-D responses. Average P-D plots displaying responses collected within the mid-urethral region for all three active and passive muscle states are provided in Fig. 3. In general, all active tissue states displayed an initial resistance to deformation on increased applied pressure, resulting in an S-shaped P-D curve. This was more pronounced in the presence of an activated smooth muscle component. In contrast, the presence of active striated muscle alone was not sufficient to provide resistance to deformation distinguishable from that of the corresponding passive state at both the lowest and highest applied pressures (Fig. 3, middle).

Muscle contraction parameters. Initial diameters, to which the OD diameter data were normalized, demonstrated consistency in both the tissue preparation and state of the tissue at the time of experimentation ($1.651 ± 0.182$). The nonlinear regression performed to obtain the TCC parameter provided an excellent fit for both the active and passive P-D data for all three experimental protocols ($r^2$: striated alone, $0.977 ± 0.020$ and $0.996 ± 0.001$; smooth alone, $0.954 ± 0.013$ and $0.994 ± 0.002$; smooth-striated, $0.941 ± 0.015$ and $0.993 ± 0.002$, for active and passive data fits, respectively). A significant difference in TCC was observed between tissues in which striated muscle alone was activated compared with those in which both smooth and striated muscle was activated (Fig. 4A). No statistically significant difference was apparent for smooth muscle-activated tissues in the presence or absence of striated muscle activity.

Comparison of contractile function between the activated muscle elements at each applied pressure step, as defined by the FCR parameter, is shown in Fig. 4B. Both striated and smooth muscle exhibit their maximal influence within approximately the same pressure range (from 4 to 10 mmHg). However, smooth muscle activation, either with or without concom-

![Fig. 2. Immunofluorescent labeled cross-sections of the female rat mid-urethra, representative of the muscle orientations found within the mid-urethra. Predominant circumferential layers of both smooth and striated muscle are apparent, as well as a mixture of longitudinally oriented smooth muscle. Striated muscle was revealed with antibodies against both fast and slow myosin heavy chain and smooth muscle with an antibody against α-smooth muscle actin.](http://ajprenal.physiology.org/)
itant striated activity, resulted in a significantly increased contraction within the 4- to 14-mmHg range, and again at 20 mmHg, compared with striated muscle activation alone (non-significant multiple comparisons: $P = 0.141, 0.051,$ and $0.055$ at 2, 16, and 18 mmHg, respectively). No significant differences were observed however for smooth muscle-activated tissues in the presence or absence of striated muscle activity.

**Maximum stress generation.** A good correlation between actual and fitted data were observed for all of the midwall circumferential stress ($\sigma_0$) vs. normalized diameter responses, which were subsequently used to calculate maximum $\sigma_0$ generated by each activated muscle component. The best fit for tissues with active striated muscle, as well as for all passive tissues, was obtained using an exponential function ($r^2$: striated active, $0.994 \pm 0.003$; striated passive, $0.996 \pm 0.001$; smooth passive, $0.993 \pm 0.002$; smooth-striated passive, $0.995 \pm 0.001$), whereas the best fit for smooth and smooth-striated active tissues was obtained using a polynomial function ($r^2$: $0.985 \pm 0.007$ and $0.987 \pm 0.004$, respectively). An example of these fitted passive and active plots for each of the activation protocols in relation to the measured data is shown in Fig. 5. Also shown in this figure are plots of the difference between the active and passive responses, which is representative of that which would be hypothetically observed from the activated muscle component alone (i.e., if the underlying passive component could be removed from the tissue).

From these responses, the average maximum $\sigma_0$ was estimated to be $748 \pm 379$ N/m$^2$ for striated muscle alone, $2,229 \pm 409$ N/m$^2$ for smooth muscle alone, and $2,335 \pm 239$ N/m$^2$ for smooth and striated muscle activated tissues; all of these maximum stresses occurred at a similar degree of mid-wall deformation for each activated tissue state ($\sim 0.1–0.25$ change in normalized OD). However, from Fig. 5, it can be seen that the active smooth muscle component generated a

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**Fig. 3.** Applied pressure vs. measured normalized outer diameter (OD/ODo) responses measured at the mid-urethra. Tissue responses measured in the absence (passive) and presence (active) of smooth muscle activity alone ($n = 8$), striated muscle activity alone ($n = 6$), and combined smooth and striated muscle activity ($n = 6$). *$P < 0.05$, **$P < 0.01$.**
more immediate and continuous amount of stress over a wider range of tissue deformation, in contrast to that observed for striated muscle activation alone.

**DISCUSSION**

Biomechanical characterization of the intact female rat urethra was performed through ex vivo experimental measures of changes in the outer diameter of active and passive tissues in response to controlled increases in intralumenal pressure. Previously, we demonstrated that such measurements performed during the application of a single fixed pressure can be used to delineate regional urethra contractile responses in relation to axial changes in muscle composition and content (19). In principal, we now demonstrate that the experimental methodology utilized herein, which has traditionally been employed to characterize vascular tissue responses (12, 14, 17), may also be applied for the investigation of urethra functional properties within a physiological pressure range. The results obtained utilizing this methodology indicate that the female rat intrinsic urethral smooth muscle, compared with striated muscle, is capable of imparting a greater influence on the long-term functional responses of the urethra; the smooth muscle generated higher levels of maximum circumferential stress and also sustained higher levels of stress over a broader range of applied opposing pressures.

This study represents a continuance of previous work performed with a primary goal of assigning biomechanical, and subsequently clinical, significance to the inherent structures of the urethra. It is generally believed that both the smooth and striated muscle of the urethra play a substantial role in the production of closure force at rest (2, 4, 33). It is also generally believed that the urethral striated muscle, along with that of the supporting pelvic floor, is a chief source of adjunct closure pressure required to maintain continence during stress episodes (35). Indeed, deficits of innate striated muscle function and composition, not smooth muscle, are most associated with the clinical presentation of stress-related incontinence (18, 23, 26, 27). Despite such clinical associations, the urinary continence mechanism in women as a whole remains a considerably controversial issue. Contradictions in the perceived relative importance of each of the intraurethral muscle layers (smooth and striated), including the potential quantitative contribution of each component toward the overall generation of urethral closure force, continue to persist within the urologic community without resolution. For instance, it has been proposed that both the smooth and striated musculature, as well as the external pelvic floor musculature, may all coordinately contribute to increased urethral closure pressures during stress episodes in a bladder-to-urethra reflex mechanism (20). Yet others have proposed that external compression of the urethra by pelvic floor contraction, rather than inherent contraction of urethral musculature, contributes to such increased pressures (38). Even during resting conditions some have asserted that the striated muscle, rather than the smooth muscle, provides the bulk of resting urethral closure pressure (11, 31).

Attempts to add clarity to these issues as well as to definitively quantify the contributions of each intraurethral muscle component have met with further discrepancy. Studies performed in the canine have estimated striated contributions to the urethral pressure profile to be one-third (3) to over one-half (34). In striking contrast, other studies, also performed in the canine, have been unable to detect any significant influence by this muscle component (6). Additionally, studies performed in the pig have also shown little contribution of striated muscle to resting pressures (16). The results presented herein in the female rat mid-urethra estimate the maximal striated muscle contribution to force generation to be approximately one-third of that of the smooth muscle; furthermore, sustainability of these contractions suggest that the striated muscle layer is more likely to act as an adjunct, shorter-term closure mechanism to...

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**Fig. 4.** Muscle contraction parameters: P-D-derived measures of relative muscle contractile function within the mid-urethra over the entire applied pressure range [total contraction capacity (TCC); A], or at each pressure step individually [functional contraction ratio (FCR); B]. Active tissue responses, compared with passive responses, measured in the presence of smooth muscle activity alone \( (n = 8) \), striated muscle activity alone \( (n = 6) \), and combined smooth and striated muscle activity \( (n = 6) \). A: \( *P < 0.05 \) striated vs. smooth-striated. B: \( *P < 0.05 \) striated vs. smooth-striated and \( **P < 0.05 \) striated vs. smooth.
the continuous principal influence of the smooth muscle during normal (nonstressful) urinary storage. However, it should also be stated the temporal role of the striated muscle’s contribution may ultimately be more relevant to the overall continence mechanism than absolute force generation capability. This is a topic requiring further research.

As has been astutely observed, animal studies cannot and should not simply be extrapolated unilaterally to the human clinical situation, owing to the least to differences in: species anatomy, receptor distribution and composition, and possible confounding effects of anesthesia during measurements (35). Although anesthesia effects are plainly absent during ex vivo measurements, there remain several important experimental issues to consider with regard to the conclusions presented herein, in particular, and the ex vivo or in vitro study of urethral striated muscle function, in general. First, although the female rat is a widely accepted model with which to perform functional urethra studies, the predominately fast (type II) myosin isotype of the striated muscle observed in the young rats utilized here is contradictory to the predominately slow (type I) isotype of striated muscle histological findings in both the human female and in older rats (2, 15, 29). The temporal nature of striated muscle is fundamentally influenced by the predominance of fiber type present. Our findings of a predominately type II urethral striated layer in the female rat, and a conclusion that this muscle is more suitable to responding to sudden and brief periods of applied stress, coincide with previous urethra strip studies in both the canine and sheep demonstrating fiber-type influence over contractile speed and sustainability (9). In addition, the use of pharmacological agents to induce striated muscle contraction can result in desensitization of the nicotinic cholinergic receptors, contributing to a more transient striated muscle response. Previous experience has demonstrated the length of maximal ACh-induced striated contraction to be of the same order of time required to complete the incremental pressure ramping (19). The priming volume of the system, together with chemically evoked receptor desensitization, precluded the possibility of challenging the contractile function of the tissue before initiation of the mechanical testing protocol. Thus no method of assessing uniform strength of contraction during application of the opposing intralumenal pressures was possible. Therefore, currently, we cannot rule out the possibility at this time of underestimation of striated maximum contractile responses or the duration of such responses. Modification of the system to allow electrical field stimulation (EFS)-induced muscle contractions may help to clarify and lessen the potential impact of such issues (39). Nonetheless, the overall experimental biomechanics approach described herein is adeptly suited toward delineating the quantitative contributions of the intrinsic muscle responses of the urethra and we have no reason to believe that this system is not perfectly suited at the present toward addressing smooth muscle functional responses in both an accurate and reliable manner.

Basic research should continue toward a full understanding of the coordinated efforts and biomechanical contributions of the urethral musculature and related structural components that comprise the continence securing mechanism. It is of fundamental importance to determine the magnitude of the effect caused by alterations of these components with regard to the overall mechanical properties of the tissue. This is true in both defining pathophysiological changes in tissue composition and function and subsequently devising therapeutic strategies to address such changes. The recent interest in cellular uromyoplasty therapy to regenerate functional urethral striated muscle illustrates this position (7, 10, 24, 31). Currently, estimation of the clinical impact imparted by increases in striated muscle cannot be gauged simply from evaluation of the currently available literature, which may confound the expectations of such a therapy in relation to the amount of regeneration which can be realistically attained through cellular transplantation techniques. Thus clarification of such fundamental issues will be indispensable to further the practical understanding of urethra pathophysiology, but also will be critical in the co-
continued development of strategies for the reconstruction, restoration, or functional replacement of the dysfunctional urethra.

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