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Reversible Plasticity of Detrusor Smooth Muscle: Evidence for a Key Role of "Slipping" Actomyosin Cross-Bridges in the Control of Urinary Bladder Compliance

Thomas Eddinger
Marquette University, thomas.eddinger@marquette.edu

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Reversible plasticity of detrusor smooth muscle: evidence for a key role of "slipping" actomyosin cross-bridges in the control of urinary bladder compliance

Thomas J. Eddinger
Marquette University, Milwaukee, Wisconsin

To examine biomechanical properties of soft biological materials such as smooth muscle, tissues secured between a force transducer and micrometer are often preconditioned by subjecting them to a protocol involving sequential stretch-release cycles while the tissue is in a relaxed (i.e., unstimulated) state (4); that is, the tissue is stretched to a longer length and then released back to the original length sequentially several times (9). Preconditioning causes a reduction in measured force for a given tissue length termed strain softening, or the Mullins effect (1). The decline in force is large after the first stretch-release cycle, and thereafter, the decline is less such that after several cycles the difference in force over the length/range of the stretch between repeated cycles is negligible, and the force-length

relationship of this preconditioned tissue is termed pseudoelastic (7). In addition to pseudoelasticity, which is time independent, biological soft tissues display time-dependent viscosity often measured as a phase shift of force and length during imposed sinusoidal length oscillations (8). In arteries, the viscosity is thought to originate in the smooth muscle cells. Thus, smooth muscle tissues have long been considered visco (pseudo)elastic materials. The force "lost" during preconditioning has been attributed to an artifact related to the preparation and not to a characteristic of the muscle. The paper in a recent issue of *AJP-Renal Physiology* by Neal et al. (6) presents evidence that detrusor smooth muscle within the urinary bladder wall is not simply viscoelastic but is instead viscoelastic-plastic. They argue that the force component lost during preconditioning is not an artifact but represents smooth muscle plasticity, a novel component of detrusor smooth muscle behavior that is subject to regulation and thus may be a participant in bladder pathology.

The strict definition of plasticity is an irreversible gain in length during a stretch-release cycle. What is unique about the plasticity of detrusor smooth muscle is that the length gain (and force "loss") is reversed when the muscle is contracted at its original (short) length, which would occur as the bladder shortens during the voiding phase of the bladder fill-void cycle. In short, the lengthening (and force decline) during muscle stretching (bladder filling) represents plasticity caused by slipping actomyosin cross-bridges, which extends the repertoire of activities of cross-bridges from shortening and developing force (3) to slipping while providing some "holding" force. This activity is perhaps not unlike the behavior of latch bridges that maintain force despite low cycling rates (5). Smooth muscle cells express several isotypes of smooth and nonmuscle myosins that display a broad range of shortening vs. holding capabilities (3). One issue left unresolved in the paper by Neal et al. (6) is the determination of which myosin isotype(s) participates in the actomyosin cross-bridge activity responsible for detrusor smooth muscle plasticity.

Behaving as both a viscoelastic and reversibly plastic biomaterial may explain how the bladder can maintain a roughly spheroid shape while also exhibiting a very high degree of compliance (10). According to this working model, slowly cycling cross-bridges ensure that the organ maintains tension, and as the bladder fills, slippage of these cross-bridges permits lengthening of the cells and increases in vesical volume without developing additional wall tension (crossbridge "slippage" model; Fig. 1*B*). In the current "standard" model (Fig. 1*A*), extracellular matrix proteins contribute a parallel elastic component that would develop force when the muscle is lengthened and would not be acutely regulated. One significant aspect of plasticity is that the Laplace relationship (wall tension is proportional to hollow organ pressure multiplied by organ radius) applies only to elastic and viscoelastic materials and not to plastic materials. This is relevant to work on bladder (or any hollow organ) because wall tension cannot be measured in vivo. The brain senses the bladder fill state through mechanoreceptors within the bladder wall (2). Wall tension can be calculated using the Laplace relationship and measurements of vesicular pressure performed during bladder cystometry and bladder radius using sonography. If the bladder wall has a plastic component (and is not solely viscoelastic), then the Laplace relationship will not provide an accurate measure of wall tension. From a physiological perspective, the data presented by Neal et al. (6) suggest that wall tension during bladder filling is dependent on (and likely regulated by) actomyosin cross-bridge activity and that the voiding contraction and the degree of cross-bridge activity that remains at the end of the voiding contraction "sets" the degree of subsequent bladder compliance during the filling phase. In short,

cross-bridge regulation appears not only to participate throughout the entire bladder cycle but to play unique roles during voiding and filling. Bladder overactivity is a major cause of incontinence, and precisely what mechanisms cause this chronic disorder remain to be determined. Knowledge that actomyosin cross-bridges play a significant role in compliance regulation during the filling phase provides a novel physiological/biochemical target for future studies designed to identify new therapeutic interventions for lower urinary tract syndromes.

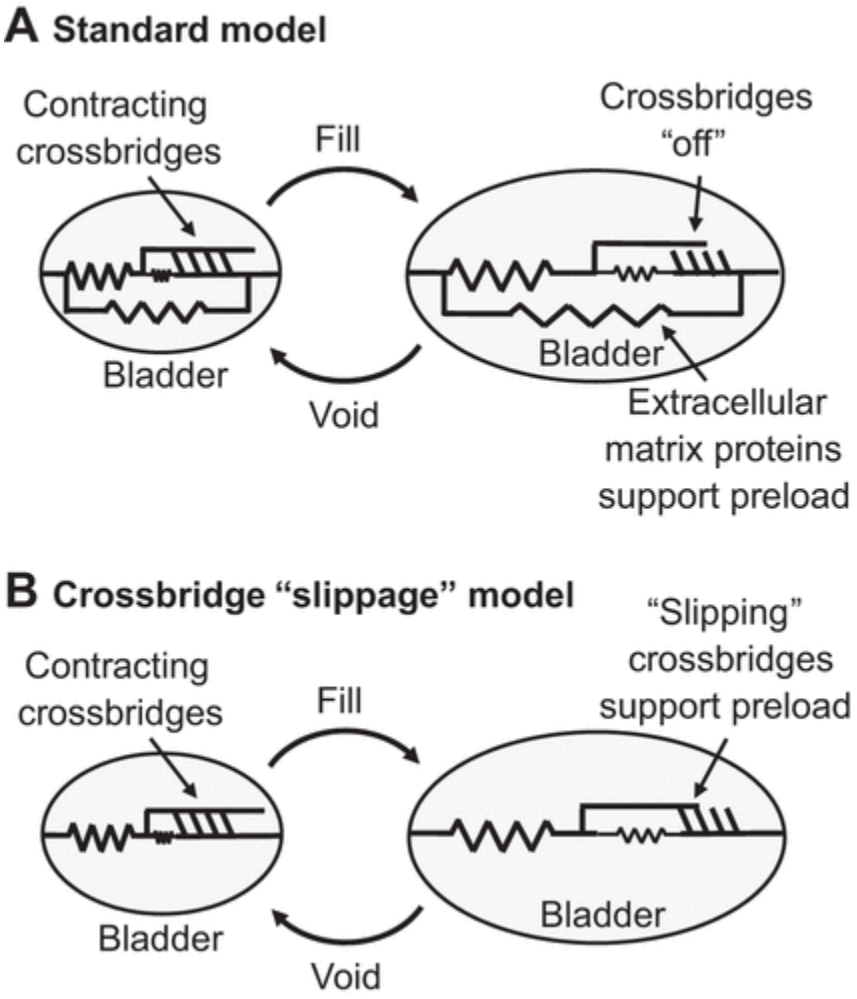

Fig. 1.*A*: in the "standard" model, actomyosin cross-bridges are inactive ("off") during the urinary bladder filling phase, and extracellular matrix proteins support preload (a.k.a, "passive" force). *B*: in the proposed "cross-bridge slippage" model, cross-bridges support preload as the bladder fills and also slip with each incremental increase in bladder volume, permitting high compliance and accommodation. In both models, active cross-bridge cycling causes detrusor smooth muscle shortening and bladder emptying. For clarity, a viscous component known to be present is not shown in either model.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.J.E. prepared figures; T.J.E. drafted manuscript; T.J.E. edited and revised manuscript; T.J.E. approved final version of manuscript.

AUTHOR NOTES

- Address for reprint requests and other correspondence: T. J. Eddinger, Marquette University, 530 N. 15th St., Milwaukee, WI 53233 (e-mail: thomas.eddinger@marquette.edu).

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