COMMENTARY

# Muscle force is modulated by internal pressure

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Fluid pressure is generated in muscle during normal activity (1). This "intramuscular pressure" is correlated with the development of force during muscle contraction, but it is rarely considered in models of muscle function and its implications for muscle performance in vivo are unknown. Sleboda and Roberts (2) show that intramuscular pressure is not simply an indication of muscle activity; it also directly influences contractile force. While previous studies have shown that constraints that impede lateral bulging of muscle can reduce force and work (3, 4), Sleboda and Roberts' (2) study examines the implications of a radial constraint that actually exerts force and does work on the muscle during contraction. Sleboda and Roberts (2) report the unexpected result that intramuscular pressure modulates force in a length-dependent manner; increased intramuscular pressure decreases force at short muscle lengths but increases force at long muscle lengths. Sleboda and Roberts (2) tested a potential mechanism of transduction of this pressure using water-filled silicone cylindrical models wound with relatively inextensible helical threads. The orientation of the threads in the models mimics what has been observed previously in muscle extracellular matrix, which includes the connective tissues and especially the collagen fibers that wrap muscle fibers and groups of muscle fibers. Pressurization experiments on the models, analogous to those performed on the muscle, suggest that the forces transmitted to the extracellular matrix from intramuscular pressure may be an unrecognized, but important determinant of muscle force in the whole animal.

For their experiments, Sleboda and Roberts (2) used isolated muscles from bullfrogs. Skeletal muscles typically produce maximum force at an intermediate length, denoted $L_0$, with lower forces produced at longer lengths and at shorter lengths (5). To allow comparison between muscles this "length–force relationship," and thus $L_0$, was determined for each muscle by testing over a range of fixed muscle lengths. The middle third of the muscle belly was then enclosed in a neonatal blood pressure monitoring cuff. The muscle was stimulated and allowed to reach a force plateau and the cuff was then rapidly pressurized. Such local pressurization has not been attempted in previous studies and results in an increase in intramuscular pressure that likely simulates the pressures experienced by muscle in vivo. The pressurization experiments were performed at a series of fixed muscle lengths ranging from 0.9 $L_0$ to 1.25 $L_0$. The results show that at short lengths (0.9 $L_0$ to 1.05 $L_0$) squeezing the muscle belly significantly decreased active force. At long lengths (1.2 $L_0$ to 1.25 $L_0$), however, squeezing the muscle belly with the pressure cuff significantly increased the active force. Sleboda and Roberts (2) also performed a series of analogous experiments over a range of muscle lengths on unstimulated muscle. The results on these relaxed muscles are also length dependent, with significant increase in passive force at longer muscle lengths (1.15 to 1.25 $L_0$) but no change at shorter lengths (0.9 to 1.1 $L_0$).

Sleboda and Roberts (2) suggest that the modulation of force observed in their experiments is due to the effect of pressurization on the connective tissue fibers in the extracellular matrix. They base their argument not on previous research on muscle but instead on older studies of the support and movement of worms! The extracellular matrix of skeletal muscle includes collagen fibers that are arranged in a "crossed-fiber helical array" with the fibers wrapping the muscle fibers and fascicles in both right- and left-handed helixes. Such a pattern of helical reinforcing connective tissue fibers is commonly observed in the body wall of many worm-like soft-bodied invertebrates (6). These animals rely on a hydrostatic skeleton, the function of which depends on internal pressure.

The role of the helical connective tissue fibers in force transmission and controlling shape change in worms has been investigated previously (7, 8) and has been applied to many animals and structures with hydrostatic skeletons (6). A simple geometrical model

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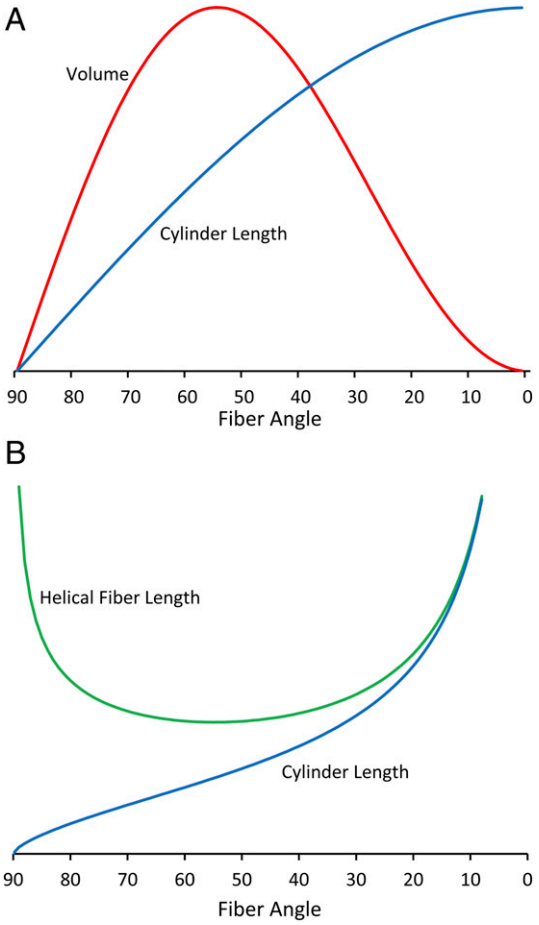


**Fig. 1. The control of shape change in cylinders wound with helical fibers. (*A*) Plot of the enclosed volume and length of a right circular cylinder wrapped by a single turn of a helical fiber of constant length, as a function of the fiber angle. The greatest enclosed volume occurs at a fiber angle of 54° 44′. If the initial fiber angle is less than this value and such a cylinder is pressurized, it will shorten; if the initial fiber angle is greater than this value, it will elongate. (*B*) Plot of the length of a helical fiber wrapping a cylinder of constant volume and the length of the cylinder, as a function of fiber angle. The minimum length occurs at a fiber angle of 54° 44′ and the fiber is stretched if the cylinder elongates or shortens from this point. Plots *A* and *B* are derived from modifications of the geometrical model described by Clark and Cowey (7).**

provides the insight needed. Consider a right circular cylinder wrapped with inextensible right- and left-handed helical fibers. The "fiber angle" is defined as the angle that the fibers make with the longitudinal axis of the cylinder. As the cylinder elongates, the fiber angle decreases and as it shortens the fiber angle increases. It is straightforward to calculate the volume of such a cylinder as a function of the fiber angle. Such a plot is shown in Fig. 1*A*. Note that the maximum volume that can be contained by the helical fiber array occurs at a fiber angle of 54° 44′ and that the volume decreases as the cylinder shortens or elongates from this maximum. Engineers have exploited these properties in McKibben actuators, which are flexible cylindrical tubes reinforced by a fabric of helical fibers or wires that generate force in response to being pressurized, typically by compressed air (9, 10). Indeed, the physical models employed by Sleboda and Roberts (2) were inspired by these actuators. Pressurizing a cylinder wrapped with a crossed-fiber array will cause the fiber angle to approach that of the maximum volume. Fig. 1*A* shows that the deformation and consequent force developed depend on the initial fiber angle, a characteristic that has been used to design actuators that either shorten or elongate (11). If the fibers are oriented at an angle greater than 54° 44′, pressurization generates force for elongation. If, however, the fibers are initially oriented at an angle of less than 54° 44′, force is produced that shortens the cylinder.

Measurements of collagen fiber angle in the extracellular matrix from different vertebrate skeletal muscles show fiber angles approaching 75° in shortened muscle and 25° in stretched muscle (12, 13). Using the simple geometrical analysis described above, one can predict the implications of pressurization for force production by muscle. Pressurizing a muscle at a short length, and thus a high fiber angle, should generate a force that opposes the active contractile force and the force output of the muscle will thus be decreased. Likewise, pressurizing muscle at a long length, and thus low fiber angle, should generate a force that augments the active contractile force and the force exerted by the muscle will be increased. This is indeed what Sleboda and Roberts (2) observed in their experiments.

In the geometrical model described above, the volume of the cylinder was allowed to vary. But muscles, and other tissues lacking gas spaces, are filled with an aqueous fluid that resists volume change. What are the implications of the fact that muscle fibers are essentially constant in their volume? To explore this issue we can modify the simple geometrical model and, rather than holding the helical fiber length constant and calculating the volume, hold the volume constant and calculate the helical fiber length as a function of the fiber angle (14). A plot of this relationship is shown in Fig. 1*B*. Note that the minimum helical fiber length occurs at a fiber angle of 54° 44′ and the helical fiber is elongated as the cylinder is either shortened or elongated from this length. The relationship plotted in Fig. 1*B* may explain previous observations of the appearance of collagen fibers in the extracellular matrix of muscle. At intermediate muscle lengths, the collagen fibers in the extracellular matrix show a crimped or wavy appearance (12, 15). These crimps disappear as the muscle is elongated or shortens, presumably because the fibers are being elongated and the crimps pulled out. Sleboda and Roberts (2) suggest that the crimping may thus be important in accommodating the length change of the fibers of the extracellular matrix that must occur as a muscle fiber changes length.

Sleboda and Roberts (2) thus show that forces transmitted by pressurized fluid in the muscle to the fibers of the extracellular matrix have a significant impact on the mechanics of both actively contracting and passively elongated muscle. It is notable that the perspective provided by Sleboda and Roberts' (2) study could not have been derived from an analysis of the molecular components of the myofilament lattice or from studies of isolated and skinned single muscle fibers. Sleboda and Roberts' (2) work thus emphasizes the crucial importance of employing an integrative approach to the study of muscle, incorporating analyses at multiple levels of organization. It is of interest now to explore the potential implications of this previously unrecognized effect on the in vivo performance of muscle.

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**1** T. M. Winters *et al.*, Correlation between isometric force and intramuscular pressure in rabbit tibialis anterior muscle with an intact anterior compartment. *Muscle Nerve* **40**, 79–85 (2009).
**2** D. A. Sleboda, T. J. Roberts, Internal fluid pressure influences muscle contractile force. *Proc. Natl. Acad. Sci. U.S.A.*, 10.1073/pnas.1914433117 (2020).
**3** T. Siebert, O. Till, N. Stutzig, M. Günther, R. Blickhan, Muscle force depends on the amount of transversal muscle loading. *J. Biomech.* **47**, 1822–1828 (2014).
**4** E. Azizi, A. R. Deslauriers, N. C. Holt, C. E. Eaton, Resistance to radial expansion limits muscle strain and work. *Biomech. Model. Mechanobiol.* **16**, 1633–1643 (2017).
**5** A. M. Gordon, A. F. Huxley, F. J. Julian, The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J. Physiol.* **184**, 170–192 (1966).
**6** W. M. Kier, The diversity of hydrostatic skeletons. *J. Exp. Biol.* **215**, 1247–1257 (2012).
**7** R. B. Clark, J. B. Cowey, Factors controlling the change of shape of certain nemertean and turbellarian worms. *J. Exp. Biol.* **35**, 731–748 (1958).
**8** J. E. Harris, H. D. Crofton, Structure and function in the nematodes: Internal pressure and cuticular structure in *Ascaris*. *J. Exp. Biol.* **34**, 116–130 (1957).
**9** F. Daerden, D. Lefeber, Pneumatic artificial muscles: Actuators for robotics and automation. *Eur. J. Mech. Environ. Eng.* **47**, 11–21 (2002).
**10** G. K. Klute, J. M. Czerniecki, B. Hannaford, "McKibben artificial muscles: Pneumatic actuators with biomechanical intelligence" in *Proceedings of the IEEE/ASME International Conference on Advanced Intelligent Mechatronics* (IEEE, Piscataway, NJ, 1999), pp. 221–226.
**11** M. B. Pritts, C. D. Rahn, "Design of an artificial muscle continuum robot" in *Proceedings of the IEEE International Conference of Robotics and Automation* (IEEE, Piscataway, NJ, 2004), pp. 4742–4746.
**12** P. P. Purslow, Strain-induced reorientation of an intramuscular connective tissue network: Implications for passive muscle elasticity. *J. Biomech.* **22**, 21–31 (1989).
**13** P. P. Purslow, J. A. Trotter, The morphology and mechanical properties of endomysium in series-fibred muscles: Variations with muscle length. *J. Muscle Res. Cell Motil.* **15**, 299–308 (1994).
**14** W. M. Kier, K. K. Smith, Tongues, tentacles and trunks: The biomechanics of movement in muscular-hydrostats. *Zool. J. Linn. Soc.* **83**, 307–324 (1985).
**15** R. W. D. Rowe, Collagen fibre arrangement in intramuscular connective tissue. Changes associated with muscle shortening and their possible relevance to raw meat toughness measurements. *Int. J. Food Sci. Technol.* **9**, 501–508 (1974).