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On the terminology for describing the length-force relationship and its changes in airway smooth muscle

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"optimal length" (or any other term implying a unique length that correlates with maximal force generation) for airway smooth muscle be avoided. Instead, the in situ length or an arbitrary but clearly defined reference length should be used. We propose the usage of "length adaptation" to describe the phenomenon whereby the length-force curve of a muscle shifts along the length axis due to accommodation of the muscle at different lengths. We also discuss frequently used terms that do not have commonly accepted definitions that should be used cautiously.

smooth muscle contraction; adaptation; plasticity; cytoskeleton; contractile apparatus

THE CAPACITIES OF AIRWAY SMOOTH MUSCLE to generate force and to shorten are not a unique function of muscle length. Instead, they change appreciably depending on the histories of muscle loading, length, and activation. These changes can occur over the course of days, hours, and even seconds (9, 11–14, 24, 35, 41, 44, 46). As a result, the length-force relationship of airway smooth muscle is highly mutable, and its characterization is meaningful only when the histories on which the relationship is derived are included. Length-dependent force generation in other smooth muscles is also known to be influenced by various factors (18, 29, 34, 36, 39), with the extent of influence varying from one type of smooth muscle to another. The following description of phenomena and terminology is based on and intended for airway smooth muscle, and it may or may not apply to other smooth muscle types.

Current terminology that describes the length-force characteristic in airway smooth muscle is borrowed from the physiology of striated muscle but is inadequate, and in some cases ill-suited, to depict the mutable relationship in airway smooth muscle. Thus there is a need to seek a consensual agreement among scientists working in the field of airway smooth muscle biomechanics concerning a nomenclature for defining the relationship between muscle length and the corresponding isometric force. The current terminology for the length-force relationship in smooth muscle includes terms that are not clearly defined and for which there is no commonly accepted usage. Without a standardized nomenclature, it is inevitable that there will be confusion and misunderstanding in communication. A solution to this problem requires collective effort. Faulkner (7) has recently reviewed the terminology for muscle contraction and alluded to the fact that a permissive attitude toward the use of unclearly defined terminology can be counterproductive. Once an incorrectly defined term has been widely used for an extended period of time, it is extremely difficult to eliminate the misuse from literature. The purpose of this article is to *1*) propose a standardized nomenclature for describing the observations regarding the dependence of isometric force on muscle length, *2*) define the characteristics of the dynamic length-force relationship, and *3*) remind readers that there are many commonly used terms in the literature that do not have commonly accepted usage and that care should be taken to prevent misunderstanding. The result will be improved efficiency and accuracy of communication among interested investigators.

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BACKGROUND

Applicability of striated muscle terminology to smooth muscle. In smooth muscle, the lack of structurally identifiable "sarcomeres" and the presence of a relatively broad plateau in the length-force relationship make the definition of optimal muscle cell length (L_o) arbitrary at best. Moreover, the dependence of isometric force on length in smooth muscle varies greatly from one preparation to another and even within the same muscle measured at different times. Other variables include the type of smooth muscle used, the method used, the history of loading, and the state of activation (2, 11–14, 18, 29, 36–37, 43–45, 47), as well as the orientation of cells within the tissue (30, 31, 38) and stress relaxation of the viscoelastic elements within the tissue (27). To make the relationship even more difficult to define, isometric force measured in smooth muscle after a length change is dynamic. That is, it increases with each activation as the muscle "adapts" to the new length (35, 39, 41, 46). One of the consequences of the length adaptation is the broadening of the force-length plateau and a potential shift in L_o.

In contrast, striated muscle possesses a structurally stable and well-defined contractile apparatus, which in turn gives rise to a stable length-force relationship, at least when the relationship is elicited by the classical methods of Gordon et al. (10). Although shifting of L_o is known to occur in striated muscle, it happens only under unphysiological conditions and over a long period of time (hours or days) (6, 21). In smooth muscle, such shifts can occur in a much shorter period of time (35, 39, 41, 46). More importantly, it appears that this rapid length adaptation is part of the normal physiological function of smooth muscle. The "fluidity" of the length-force relationship in smooth muscle renders some definitions for the classical length-force relationship (borrowed from striated muscle nomenclature) invalid. For example, a unique L_o in smooth muscle does not exist. The slopes of the ascending and descending limbs of the length-force curve in smooth muscle are not constant; they vary with time, unlike those in striated muscle (10).

L_o of smooth muscle: a shifting target. In studies that require measurement of smooth muscle mechanical properties, it is important to know the length (or a range of lengths) of the muscle that corresponds to the generation of maximal active isometric force. From reviewing the literature, this length has often been called L_o for optimal length or the length where maximal active isometric force is generated (L_{max}). L_o and L_{max} are often loosely used in smooth muscle studies. The protocols used in these studies are usually not adequate to ensure that L_o is unique for that muscle preparation and that there are no other lengths that can be considered equally optimal under different

conditions. Figure 1 illustrates the typical behavior of airway smooth muscle, showing the muscle's ability to shift its length-force curve. The shifting length-force curve not only makes finding L_o problematic, it brings into question the very legitimacy of the definition of L_o for the muscle.

The length-force curve of passive airway smooth muscle has also been shown to shift with the active length-force curve when muscle length is changed while relaxed (32, 46), as illustrated in Fig. 1. The intra- and/or extracellular structures responsible for maintaining the physical integrity of the muscle tissue (and conferring resistance to stretch in a resting muscle) therefore are not static: they appear to be in a perpetual state of reorganization and readjustment in an attempt to accommodate externally applied strain.

Time for new terminology (and maybe a new paradigm) for smooth muscle contraction? In light of evidence suggesting that the length-force relationship in smooth muscle is readily alterable, it appears that we have no choice but to abandon the terminologies based on the static length-force relationship of striated muscle. The change may not necessarily be limited to terminology; some of our concepts regarding mechanisms of smooth muscle contraction as well as our protocols to study smooth muscle may also have to be changed. For example, the widespread practice of applying a constant preload to smooth muscle for a fixed period of time to establish L_o should be reevaluated given that length increases indefinitely with time.

Nevertheless, in pursuing a consensus on terminology for describing smooth muscle properties, one must not forget that the underlying mechanisms governing the dynamic length-force relationship in smooth muscle are mostly unknown at present. By restricting the use of terminology at this stage, there is a danger of stifling discussion or even suppressing new or different ideas. Thus, altough we are looking to promote the use of a uniform nomenclature in the field of airway smooth muscle biology, we also acknowledge that differences will remain among investigators (and, in fact, among the coauthors of this paper) in the definitions of some frequently used terms such as cytoskeleton and contractile apparatus. A collective agreement on some definitions at the present time is therefore neither obtainable nor desirable.

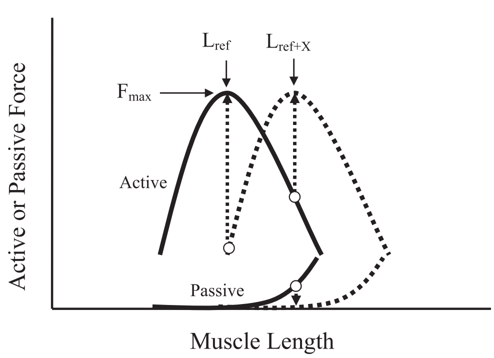

Fig. 1. Schematic illustration of muscle adaptation and the resulting shifts in both the active and passive length-force relationships. The muscle is initially adapted at an arbitrary reference length (L_{ref}), and the active and passive length-force relationships (solid curves) are then assessed in the absence of length adaptation. Stretching the muscle in the relaxed state by the amount of X to a new length (L_{ref+X}) results in an immediate decrease in active force and an increase in passive force to the respective levels indicated by the circles on the solid curves. Full adaptation of the muscle at the new length returns the active and passive forces to their original levels (indicated by the arrows originating from the solid curves). Reassessment of the length-force relationship of the muscle at this newly adapted length indicates a shift in the relationship (comparison between solid and dotted curves). Returning the muscle (in the relaxed state) back to L_{ref} causes an initial decrease in the ability to generate active force to the level indicated by the circle on the active length-force curve (dotted line). Readaptation of the muscle at this length returns the active force to its original maximal level (F_{max}) (dotted arrow originating from the dotted curve).

SUGGESTED TERMINOLOGY

Reference length. For a muscle preparation where there is not a unique L_o, an arbitrarily chosen length is still needed as a reference for normalization purposes. The reference length may or may not be associated with maximal force generation; however, a length that can be uniquely defined and duplicated in different experiments (such as the in situ length in trachealis) will serve better as a normalization length. We propose that L_o and L_{max} be avoided unless it can be shown that they represent unique, length-history- and time-independent lengths where isometric force is maximal. Instead of L_o and L_{max}, the in situ length or an arbitrarily chosen reference length should be used and defined as such. L_o sometimes is used to denote a length optimal for a chosen experimental condition but not necessarily optimal for force generation. If one prefers the symbols L_o and L_{max} for one's own definition of reference (or optimal) length, care should be taken to ensure that the readers do not confuse the length definition with that traditionally associated with these symbols. Insofar as the active isometric force is actually a moving target in smooth muscle, when a reference length is used, the history of length change, loading, and activation need to be clearly specified.

Although it may be possible to measure the length of tracheal smooth muscle in situ, it is more difficult in the bronchi, especially under dynamic conditions in which its length changes due to the action of tidal breathing or deep inspirations. The in situ length of bronchial smooth muscle, therefore, cannot be estimated easily and accurately. Many investigators have their own methods of selecting the reference length for their muscle preparations (3, 9, 11–14, 18, 24, 25, 29, 32, 35–41, 43–47). In the absence of proof that one particular method is better than all others, it is inappropriate for us to suggest a standard method for obtaining the reference length.

Muscle adaptation to length change and mechanical plasticity. The ability of airway smooth muscle to accommodate to changes in length (within a certain range) while retaining the capability for generating maximal isometric force has been well documented (8, 35, 41, 46). However, the isometric force generated immediately after a length change imposed while the muscle was relaxed is often found to be submaximal; force recovers only after a period of time during which the muscle is maintained at the new length (35, 41, 46). When the muscle is subsequently allowed to return to its original length, the isometric force is again submaximal, and another period of recovery is needed to bring the isometric force to maximal (see Fig. 1). Changes in isometric force in response to step changes in length therefore produce time-dependent shifts in the length-force relationship. We propose to define this time-dependent force recovery and the subsequent shift in the length-force relationship as the process of length adaptation. The word adaptation connotes modification according to external conditions. In length adaptation, the change in conditions is specifically related to a change in muscle length.

The nonstatic nature of the length-force relationship in airway smooth muscle has inspired some authors to use the term plasticity to describe the relationship and to imply specific mechanisms for the observed plastic behavior (8, 13, 14, 35). Because the mechanism underlying the muscle's plastic behavior is not yet clear, the term plasticity currently has no commonly accepted definition, even in the field of airway smooth muscle. There are many uses for plasticity in the current muscle and nerve literature. For example, typing in the phrase "smooth muscle plasticity" in a PubMed search results in many references, most of which deal with changes in the degree of cell differentiation and innervation. Halayko and Solway (16), based on functional evidence, have defined mechanical plasticity as changes in the number and organization of contractile filaments in a muscle cell in response to a length change and differentiated that from phenotypic plasticity, which was defined as the reversible modulation and maturation of smooth muscle cells between a synthetic and contractile state. Phenotypic plasticity can also refer to changes in protein isoform expression or other alterations in gene expression. Still another specific use of the term plasticity is to denote a deformation that persists after the load is removed, often associated with yielding of stress-bearing elements. We therefore recommend that the term plasticity be used in a context where its specific meaning is understood by the general readers of smooth muscle literature, and we recommend that the term length adaptation be used to describe the general plastic behavior of smooth muscle, especially when the underlying mechanism is not certain.

Plasticity is also a term used in engineering disciplines to describe a particular mechanical property of a material in a nonbiological context; in this case, it refers to a nonrecoverable deformation that results from an externally applied force and is essentially a deviation from ideal elastic behavior. Smooth muscle can show such changes, but they are more likely to arise from physical damage than from a specific physiological mechanism.

One phenomenon that can potentially be confused with length adaptation is observed during the conditioning or preconditioning period (sometimes, it is referred to as "equilibration" or "running-in" period) where muscle force increases with time and number of stimulations. The conditioning protocol is usually performed at the beginning of an experiment when muscle conditions such as temperature, intracellular pH, ionic gradients, and calcium loading of the sarcoplasmic reticulum are being brought to a desired state. Although such protocols usually lead to increased force generation in the muscle over time, the underlying mechanism for this improvement may not be the same as that for length adaptation. Length adaptation refers to the asymptotic increase in force seen in muscle adaptation after a length change in a preconditioned muscle. We therefore suggest that the time-dependent increase in force observed during the conditioning period be distinguished from that observed during length adaptation and that separate terminology be used in their description.

Length range within which adaptation is observed. The above-described adaptive behavior of smooth muscle can only be observed when changes in muscle length are made within an adaptable length range, i.e., a length range within which the muscle is able to regain all or most of its capacity to generate maximal force and shortening through adaptation. For reasons not yet certain, the adaptable length range varies from one type of smooth muscle to another and even within the same type of muscle (18, 35, 41, 45, 46). Beyond the adaptable range, the muscle's mechanical memory of the length history cannot be entirely erased with time (3).

Length-force relationships obtained under different conditions. Because of the adaptive behavior of airway smooth muscle, different experimental methods (mimicking different in vivo conditions) used to measure the muscle's length-force relationship often produce different results. Caution is therefore required when interpreting these relationships. For example, in the presence of force (or length) oscillation, the length-force relationship of the muscle is markedly different from that obtained under isometric conditions; the ability of the muscle to shorten or generate force is impaired by the presence of oscillation in an amplitude-dependent manner (9, 40). The expressions force fluctuation-induced lengthening or length fluctuation-induced force reduction are often used to describe deviations in length-force relationship observed under these oscillatory conditions, with implicit reference to that under static conditions. The biological significance of the differences in behavior of smooth muscle under dynamic vs. static conditions derives from the fact that the dynamic behavior likely has more relevance for the in vivo situation, particularly with respect to the control of airway caliber during breathing. In any case, the relationships among muscle length, airway geometry, and lung volume vary substantially depending on how force is measured (23).

A length-force relationship can also be obtained by allowing the muscle to shorten isotonically against different loads. However, force generated at a particular length is consistently lower under isotonic conditions than under isometric conditions (20, 44). In describing a length-force relationship of smooth muscle, it is therefore important to indicate the experimental method by which the relationship is obtained.

Cytoskeleton and contractile apparatus. Airway smooth muscle cells in vivo function as a group, a mechanical syncytium (25). When the muscle length is changed, several intra- and extracellular components are affected. The terminology describing these components is currently not standardized. Traditionally (at least in the smooth muscle community), the elements in smooth muscle responsible for force generation and shortening are considered to make up the contractile apparatus, whereas the structural elements responsible for maintaining cell shape and integrity are considered to make up the cytoskeleton (1). However, the view of the cytoskeleton as a passive scaffold supporting the contractile filaments is now being replaced with one that regards the cytoskeleton as a dynamic structure capable of adapting to changes in cell length (42). Small and Gimona (42) have assigned specific smooth muscle proteins to either contractile or cytoskeletal domains, in contrast to many cell biologists who prefer the concept of an all-encompassing cytoskeleton that also includes contractile proteins such as myosin.

Currently, there is no clear definition, especially from the structural point of view, of the contractile apparatus in smooth muscle. The boundary between the contractile apparatus and the cytoskeleton is also poorly defined. Caution should therefore be exercised when using the terms contractile apparatus

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and cytoskeleton, especially where structural (or even functional) components of the muscle are assigned to these domains. In the absence of commonly accepted definitions, the best way to avoid confusion is to carefully define one's use of the terms.

Airway remodeling and length adaptation in airway smooth muscle. Airway remodeling has been defined as a reparative process that occurs in the airways during chronic inflammation (28, 33). Remodeling of the airways usually involves persistent thickening or an altered composition of the various components of the airway wall, including the muscle layer (2, 5, 22, 26). Airway remodeling must not be confused with length adaptation in airway smooth muscle. Nevertheless, it is conceivable that airway remodeling could lead to length adaptation in airway smooth muscle. For example, mechanical constraints on the smooth muscle surrounding an airway could be altered during airway remodeling, which in turn could change muscle length and lead to length adaptation. Airway remodeling might also trigger changes in the muscle itself, leading to hypertrophy and hyperplasia of the muscle cells (4). These changes can cause a rearrangement of the cells, leading to an altered length-force relationship for the muscle as a whole. Airway remodeling can also be associated with the changes in the phenotype of airway smooth muscle cells (16, 17, 19), which can affect their force-generating capacity (15). We suggest that the term remodeling not be used to describe the phenomenon of length adaptation of airway smooth muscle.

FINAL REMARKS

In recognition of the fact that the length-force relationship of airway smooth muscle is dynamic, we have examined the definition of several terms associated with the adaptive behavior of smooth muscle in response to length changes. The underlying mechanism for length adaptation is still not entirely clear but likely involves reorganization of cellular, subcellular, and extracellular elements. With collectively agreed-on terminology, investigators can be more effective in communicating with each other. With careful use of terms that do not (yet) have a commonly accepted usage, confusion can be avoided. We hope this will translate into an increased efficiency in our efforts to understand the contractile mechanisms in airway smooth muscle and the roles they play in both health and disease.

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