Length-Tension Relationship of Smooth Muscle of the Hog Carotid Artery

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ABSTRACT
The length-tension relationships for arterial smooth muscle were determined using vascular strips teased from the media of hog carotid arteries. Histological examination revealed that the strips were (1) free of adventitia and (2) composed of smooth muscle cells oriented parallel to the long axis of the strips. Measurements from electron micrographs indicated that 60% of the cross-sectional area consisted of smooth muscle. At $L_o$ (the optimal length for tension development) the total cross-sectional area of the strips varied from 0.3 to 0.8 mm². Potassium-induced depolarization was the most effective stimulus for force development. Norepinephrine and electric field stimulation elicited responses which were 70% and 30%, respectively, of that produced by potassium-induced depolarization. At $L_o$, the intrinsic load-bearing capacity ($P_o$) of the contractile system was $2.22 \times 10^5$ dynes/cm². Tension development fell off gradually at lengths shorter than $L_o$ and more rapidly at lengths greater than $L_o$. Passive length-tension curves were determined after quick releases from higher to lower lengths to avoid complications arising from tone. Passive tension was negligible at lengths below 0.9 $L_o$. At $L_o$, the passive tension was 10% of $P_o$.

KEY WORDS vascular smooth muscle mechanics isometric force parallel elastic component potassium-induced depolarization norepinephrine electric field stimulation contractile component

\[ V \] The contractile system of vascular smooth muscle is poorly understood. One approach to characterizing this system is the measurement of its mechanical properties. Although the arterial wall has been subjected to such measurements (1), the actual contribution of the muscle component of this complex tissue to the observed mechanics remains uncertain.

Several inherent difficulties are involved in obtaining suitable preparations and experimental techniques for measuring the mechanics of vascular smooth muscle. The vascular wall contains large amounts of connective tissue which complicates most mechanical observations. For the most part, the smooth muscle cells of the arterial wall possess a complex helical orientation around the lumen (2), and in some vessels (e.g., mesenteric vein) the system is further complicated because both circular and longitudinal muscle layers are present. Accurate determination of muscle force and length depends on a uniform orientation of the individual muscle cells whose axes preferably are parallel with the axis in which force is measured. To obtain true passive stress-strain curves, the contractile system should be completely inactivated. With vascular smooth muscle, this criterion is difficult to satisfy, since the usual presence of tone indicates partial activation of the contractile system. The resting tension of a muscle strip which exhibits tone is thus a combination of passive stress and active force development. Finally, measurement of the stress-strain curve for the contractile component of a muscle requires stimulation procedures which fully activate this element. However, vascular smooth muscle responds to various stimuli in a graded manner (1) and the inherent load-bearing capacity of this muscle ($P_o$) is therefore difficult to assess.

The present study is a systematic attempt to develop a preparation and experimental techniques which overcome these difficulties and to obtain length-tension curves which reflect the characteristics of the contractile system of vascular smooth muscle.
Methods

Preparation and Apparatus.—Carotid arteries were gently excised from hogs weighing approximately 90 kg 20-60 minutes after slaughter. They were immediately immersed in physiological salt solution at 0°C and, after transit to the laboratory, were trimmed of loose connective tissue and immersed in fresh physiological salt solution for storage, at 4°C until use. Strips prepared from arteries generally showed consistent responses for 2-3 days after collection.

Muscle strips were obtained in the manner shown diagrammatically in Figure 1 (left), which is essentially the technique introduced by Wolinsky and Daly (3) for obtaining the media of rat aortas for biochemical studies. We used the hog carotid artery because of its large muscular media and the ease with which its media and intima could be separated from the adventitia (2). The less muscular central and distal ends of the carotid artery were removed and discarded; the remaining segment was slit longitudinally. The media was grasped at one edge with a plain forceps, and a strip having a rectangular cross section was teased from the adventitial layers along naturally occurring separations. The first strip was discarded because parallel strips could then be removed with less force. The thickness and the length of the strips were proportional to the size of the artery used; the width of the strips could be varied at will. Generally strips 8-12 mm long were teased from the arteries, and the thickness of the unstretched strips was about 0.8 mm. With an oxygen tension (Po2) exceeding 600 mm Hg, oxygen diffusion was not limiting in these strips which had a low rate of oxygen consumption (4).

Strips were mounted as shown in Figure 2A and securely held by stainless steel-nylon clips. The lower clip was attached to a vertical glass rod mounted on a micrometer electrode carrier with a 35-mm drive calibrated in units of 0.01 mm. The upper clip was attached by a very light stainless steel jewelry chain to...
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FIGURE 2
A: Apparatus for mounting muscle strips. Water-jacketed bath, gas supply, and electrode leaders are not shown. The enlarged side view of clip (left) shows the stainless steel spring being forced away from the nylon block with a removable screw prior to muscle mounting.

B. Tracing of a typical initial response of the strips when they were mounted and stretched 100% at t = 0. The ordinate on the right was calculated using the cross-sectional area of this strip (0.48 mm²).

a Grass FT.03C strain gauge. The overall compliance of the system was 16 µg. The strips were quickly mounted and stretched to a length 100% greater than their slack length and equilibrated for 2 hours in physiological salt solution. After the equilibration period the strips were stimulated electrically (see below) at 15-minute intervals until a constant isometric response was obtained. The response to such stimulation was highly reproducible even without continued washings. Force was recorded by a Grass model 7 polygraph. The frequency for half-maximal response of the driver amplifiers was 35 Hz.

Several factors were important for obtaining good contractile responses. First, the strips had to be rapidly (<90 seconds) removed, mounted, and stretched. When handled in this way, they exhibited more consistent responses and higher force values than those leisurely mounted or removed from arterial segments which had been slit and left for even a short period in physiological salt solution. The initial spontaneous activity of viable strips followed a definite pattern which could be reliably used to evaluate the condition of the strip. After the initial stretch of 100%, stress relaxation occurred. Within 1–2 minutes tension development was evident and increased for 10–20 minutes; it then spontaneously decreased over a period of 20–40 minutes to an equilibrium level which was usually lower than any earlier value (Fig. 2B). Strips which did not exhibit this initial response contracted poorly or not at all on stimulation and were judged unfit for experimentation. The initial response was not repeated following later stretches and probably reflected an adjustment to warming and other equilibration effects.

Stimuli.—Transverse electric field stimulation was applied to the muscle using two 5 × 10-mm platinum electrodes placed parallel to the muscle strip (Fig. 2A). In earlier experiments, the distance between the electrodes was 1.0 cm, but this distance was later reduced to 0.5 cm. Alternating current was supplied to the electrodes by a power amplifier whose voltage and frequency were controlled by a function generator. A variable line transformer was employed in a standard 115-v circuit to supply 60-Hz current. Stimulus durations were set with a control timer. Preliminary experiments showed that maximal response of the strips to electric field stimulation was obtained at 20–30 v/cm, 50–100 Hz, and stimulus durations of 20 seconds. Cumulative dose-response curves for norepinephrine (I-Arterenol bitartrate, Sigma) established that maximal response was obtained at 10⁻⁵M. For high-potassium solutions, KCl was substituted for NaCl on an equimolar basis. The millimolar composition of the normal physiological salt solution was: NaCl 110, KCl 4.7, KH₂PO₄ 1.18, MgCl₂ 1.17, NaHCO₃ 14.9, dextrose 5.5, CaNa-ethylenediaminetetraacetic acid (EDTA) 0.026, and CaCl₂ 1.6. The solution was bubbled continuously with 95% O₂–5% CO₂ giving a pH of 7.4 at 37°C. The addition of up to 50 m-equiv sucrose to this slightly hypotonic solution had no effect on the contractile response.

Electron Microscopy and Histology.—Strips were equilibrated as described above and initially fixed in isosmotic 2% glutaraldehyde solution at 4°C for 2 hours. The strips were then removed from the clips and left in the fixative for 1–2 hours at 4°C. After two rinses in cacodylate buffer solution and postfixation with osmium tetroxide, they were embedded in Epon. Sectioned on a Porter-Blum MT2B ultramicrotome, and stained with uranyl acetate and lead citrate. Electron micrographs were obtained at ≤ 1800x magnification on a Zeiss EM9A microscope. Relative cross-sectional areas occupied by smooth muscle were obtained by carefully cutting the cells from the photograph and weighing the fractions.

Light microscopy was done on unstretched whole artery segments and muscle strips stretched by hanging a 1-g weight from the lower end. They were fixed in 10% formalin and embedded in Paraplast (Biological Research, Inc.). Serial 7µm sections were stained with either Weigert's-van Gieson solution for collagen and
elastin or with hematoxylin-eosin for the smooth muscle nuclei.

Cross-Sectional Analysis.—The cross-sectional areas of the strips were calculated by weight and also optically in one series of experiments. For weight measurements, strips were blotted without pressure between two pieces of Whatman no. 10 filter paper for 5 seconds and weighed on a Mettler balance (H10T) accurate to ± 10^-4 g. Mean cross-sectional area was determined according to the following relationship:

\[ \text{Area (cm}^2\text{)} = \frac{\text{mass}}{\left(\frac{\text{density}}{\text{length}}\right)} = \frac{\text{g}}{\left(\frac{\text{g/cm}^3}{\text{cm}}\right)} \]

A value of 1.05 g/ml was assumed for the density of the muscle strips. Multiple measurements of the width and thickness of the strip, whose cross section was rectangular, were made with a Filar micrometer eyepiece mounted on a Bausch and Lomb (Stereo- zoom) microscope. Cross-sectional area was obtained by multiplying the average values for width and thickness. Over the range of strip sizes used in the present study (0.3–0.8 mm² at optimal length), there was no significant difference between the two methods. Therefore, in the following experiments, weight rather than optical measurement was employed for cross-sectional calculation, because the former measurement could be performed more easily and with greater precision.

Normalization of Length-Tension Data.—The experimental points for each strip were plotted and optimal length (Lₒ) was graphically determined as the length at which maximal tension (Pₒ) was developed. The data were then replotted with tension expressed as a fraction of Pₒ and length as a fraction of Lₒ, to normalize the data. For statistical purposes, the variation in tension development by different strips at various fixed lengths (i.e., 0.9 Lₒ, 1.2 Lₒ, etc.) could be estimated by interpolated values taken from the normalized plots.

Results

Smooth Muscle Content.—The photomicrograph in Figure 1 (top right) shows a transverse section of a whole artery stained for connective tissue which appears in the wavy intimal layer (left), in arrays within the media, and intensively in the adventitia (right). The separation line for the muscle strip is illustrated in this section where a portion of the adventitia came loose during handling of the section. Such separations were noted in a number of sections taken from different vessels. Moreover, sections taken from teased muscle strips showed no indication of adhering adventitia. A certain amount of connective tissue, however, was present within the media as shown in the same photomicrograph. Electron microscopic examination of randomly chosen areas of the teased strips indicated that 60 ± 2% (SE, N = 15 fields) of the strip cross section was composed of muscle cells and that the extracellular space contained both collagen and elastin.

Passive Properties of the Strips.—To obtain an accurate length-tension curve for the unstimulated muscle strip, the contractile component must be functionally inactivated. Such measurements on vascular smooth muscle are complicated by the presence, often unrecognized, of tone. Three approaches for obtaining passive length-tension curves were tested (Fig. 3). (A) The muscle was stretched to the desired length, stress relaxation was allowed to proceed for 15 minutes, and then the tension was measured. This approach assumes that the contractile system was fully relaxed. (B) The strip was stretched to a length 0.5 mm (about 5% Lₒ) greater than desired, and stress relaxation was allowed to proceed for at least 15 minutes. Then the strip was rapidly (about 3 seconds) shortened by 0.5 mm, using the micrometer, to the desired length, and the minimal tension value obtained at the end of release was measured. This method, used by Gordon and Siegman (5), assumes that tension equilibration in the parallel elastic components during release was complete and that a partially activated contractile system in this very slow muscle did not have time to redevelop any active tension. Thus, the minimal tension after release may be an improved estimate of strictly passive elastic components. (C) The strip was gradually stretched to the maximal length which could be sustained without pulling it from the clips, and after equilibration a 0.5-mm release was applied so that the desired length was always less than previous lengths in the experiment. Passive tension was estimated as the minimal value obtained after release. This protocol is based on the same assumptions as those for protocol (B) but avoids stretching the strip during the experiment.

The three protocols were randomly tested on each of four strips. The average stress-strain curves for the unstimulated strips are shown in Figure 4. For any given strip the relative positions of the stress-strain curves obtained were identical regard-
physiological salt solution containing 1.0 mM ethyleneglycol bis(β-aminoethyl ether)-N, N'-tetra-acetic acid (EGTA). Passive length-tension curves were then constructed according to protocol C (Fig. 3); the result is shown as curve D in Figure 4. In most strips there was no significant difference between the results obtained in normal or calcium-free physiological salt solution. Therefore protocol C was adopted for the studies shown in Figure 6.

Length-Tension Relationship.—In an effort to produce maximal activation of the contractile element, we studied the efficacy of various stimuli in eliciting maximal responses from the muscle strips in both high (5 mM) and normal (1.6 mM) CaCl₂. A comparison of the responses is shown in Figure 5. Maximal response was obtained with potassium-induced depolarization with 10⁻⁵M norepinephrine and 5 mM CaCl₂ present in the bathing medium. Although the mean response for potassium-induced depolarization without norepinephrine but with high CaCl₂ was lower, no statistical difference at the 0.05 level existed between the two. The

![Figure 3](image-url)

**FIGURE 3**

Example of changes in force in an unstimulated strip (bottom record in each section redrawn to rectify the curvilinear recording obtained from the Grass polygraph) as a consequence of imposed length (l) changes (graphically represented in the top portion of each section) in a typical experiment. A, B, and C show the results of three protocols for altering strip length. The final length of this strip was the same in all cases: l_a = l_b = l_c = 9.0 mm. The force recorded as that corresponding to the 9.0-mm length in the unstimulated strip is indicated by the broken lines in each section. Note that F_a > F_b > F_c. See text for additional details.

![Figure 4](image-url)

**FIGURE 4**

Length-tension curves obtained from unstimulated strips by protocols A, B, and C depicted in Figure 3. Curve D was obtained using protocol C after overnight equilibration in calcium-free solution. Tension (P) is plotted on the ordinate as a fraction of the maximal active tension (P_a). For each of the four strips, protocol C (Fig. 3) was employed in calculating P_a. The stress-strain curves obtained by all the protocols were then normalized to this reference point.
presence of high CaCl₂ had no effect on the response to any of the stimuli except potassium-induced depolarization, and the difference between high and normal CaCl₂ was significant at the 0.05 level. The mean response to potassium-induced depolarization in normal CaCl₂ was greater than that obtained with norepinephrine either in normal or high CaCl₂. In this series of experiments the poorest response was obtained with electric field stimulation. Potassium-induced depolarization in the presence of increased CaCl₂ (from 1.6 to 5.0 mM) was adopted for use in the length-tension determination. This stimulus provided tensions comparable to those obtained from striated muscle (see below) and was readily reversible.

Figure 6 shows the length-tension curves for the preparation. Tension is plotted on the ordinate as a fraction of maximal developed tension (Pₒ). Length is plotted on the abscissa as a fraction of Lₒ, where Lₒ is defined operationally as that length at which Pₒ occurs. Only two determinations were made at the longer length of 1.2 Lₒ because of the high forces at these lengths. The broken line (open circles) represents the developed tension curve. Tension development was a function of length, and it passed through a maximum at Lₒ and fell off on either side of this length. For this series of 11 strips, tension development was 2.22×10⁶ dynes/cm² (2.27 kg-wt/cm²), a value equivalent to that for skeletal muscle. The strips were capable of considerable tension development at lower lengths; at 0.5 Lₒ, for example, tension development was approximately 0.2 Pₒ. Resting tension at Lₒ was low (approximately 10% of Pₒ), a characteristic of the strip which is advantageous for force-velocity and other mechanical measurements. The resting tension curve rose sharply at lengths greater than Lₒ.

Discussion

For characterizing the contractile system of vascular smooth muscle, direct measurement of the mechanics of vascular strips is preferable to indirect measurements made on whole artery segments. The former approach simplifies the measurements of force and length and avoids many of the uncertain-
ties (6) associated with whole artery experiments. Unfortunately, the number of mechanical experiments that have been carried out on arterial strips is small and confined almost exclusively to the mesenteric artery (7-9). Notwithstanding the advantages of using strips, the complexities of the vascular wall and the nature of the smooth muscle component are such that further precautions must be taken to ensure that the mechanical output of the strips faithfully mirrors the activity of the contractile system. Much of the present study was devoted to overcoming the difficulties discussed in the Introduction, and these attempts met with varying success.

The smooth muscle content (60%) of the media of hog carotid arteries reported in this paper is the same as that reported earlier by Prosser et al. (10), using the same electron micrograph techniques. This value is within the range reported for vascular smooth muscle (1), but it is still somewhat lower than the 75% muscle content reported for the mesenteric artery (7). In spite of their lower muscle content, the carotid strips developed slightly greater isometric force per cross section ($2.22 \times 10^4$ dynes/cm$^2$, Fig. 6) at $L_o$ than do bovine mesenteric arteries ($2$ kg/cm$^2$) (1). The differences between these values might reflect differences in the modes of stimulation or calculation of cross-sectional area. The presence of connective tissue in the intima and adventitia in the carotid strips resulted in a sizable reduction in the passive elastic component (6) associated with whole artery experiments. Unfortunately, the number of mechanical experiments that have been carried out on arterial strips is small and confined almost exclusively to the mesenteric artery (7-9). Notwithstanding the advantages of using strips, the complexities of the vascular wall and the nature of the smooth muscle component are such that further precautions must be taken to ensure that the mechanical output of the strips faithfully mirrors the activity of the contractile system. Much of the present study was devoted to overcoming the difficulties discussed in the Introduction, and these attempts met with varying success.

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The strips exhibited a uniform cell orientation parallel to the axis in which force and length changes were measured (Fig. 1, bottom right). The organization of the contractile system within a smooth muscle cell is not known, but it is generally assumed that force development and shortening are directed toward the ends of the cell. As shown in Figure 4, the route taken to reach a final length had a profound influence on the "passive" tension recorded at that length and, consequently, on the calculated developed tension. The top curve in Figure 4 was constructed under sequential length increments, and the bottom two curves were determined during length decrements. This hysteresis phenomenon, indicated by the difference between the curves, has been previously reported for both vascular smooth muscle (1) and skeletal muscle (12, 13). Incomplete inactivation of the contractile component (incomplete relaxation) has been proposed as one cause of this hysteresis phenomenon (9, 13). Likewise, the pronounced stress relaxation seen with vascular smooth muscle (Fig. 3A and B) might be an expression of the same phenomenon, namely, the breaking of contractile links during stretch. Support for this hypothesis is evident from the work of Lundholm and Mohme-Lundholm (7) who reported that the ascending and descending limbs of the passive curves were superimposed in iodoacetate-poisoned mesenteric strips. However, even in the EGTA-treated strips we observed some rebound or recovery of tension after quick release (Fig. 3C). This observation suggests that EGTA treatment might not completely inactivate the contractile system. However, curve D in Figure 4, obtained in EGTA-containing solutions, would appear to more closely reflect the passive characteristics of the carotid strips. Curve C, which was obtained under reversible conditions, is similar to curve D and therefore would be more acceptable than protocols A or B (Fig. 3). An additional cause for the observed hysteresis might be some irreversible stretch on the noncontractile elements within a strip (9, 13). The high tensions recorded at the longer stretches in the present experiment might have brought about such changes. In this case, curves C and D would be spuriously low, but tension development was not altered by such stretch.

We chose protocol C (Fig. 3C) and the corresponding length-tension curve (Fig. 4C) in the present study since (1) it was more reproducible than the other curves, (2) it avoided problems arising from stretch activation as well as stress relaxation, and (3) any irreversible stretch or slippage which arose at longer lengths took place prior to rather than during the experiment. Just as it is difficult to decide when the contractile system of vascular smooth muscle is totally inactive, so too, maximal activation is an experimental uncertainty. In the present study an attempt was made to obtain a stimulus which would at least approach complete activation (Fig. 5). The stimulus used for the active length-tension curves was potassium-induced depolarization in high CaCl$_2$. Norepinephrine was omitted since (1) no statistically significant difference in the response was evident when norepinephrine was omitted, (2) tachyphylaxis was a potential problem with norepinephrine, and (3) high doses of this agent cannot easily be washed out of the bath. The high tensions...
obtained with potassium-induced depolarization (2.22 × 10^6 dynes/cm², Fig. 5) were comparable to tetanic tension developed by skeletal muscle (14), which suggests that near maximal activation was obtained.

The care taken to satisfy the criteria discussed above produced clear, practical results in removing much of the variability between individual arterial strips reported previously (8). Figure 6 represents the composite data for the length-tension relationships of 11 carotid artery strips, and, for purposes of quantification and comparison, these data are an improvement over the length-tension curves for arterial smooth muscle generally exemplified by the individual experiments (7-9). The considerable variability in resting tension between strips at longer lengths largely reflects the difficulty in precisely determining the value of L_o. Small differences in length have a very large effect on the passive (but not the developed) tension of stretched strips.

In many respects the length-tension curves shown in Figure 6 are similar to examples given for arterial strips (7-9), and, indeed, most muscles studied. The resting tension curve rose monotonically with increasing length. The steeply rising portion of this curve was characteristic of muscle tissue containing substantial amounts of connective tissue (Fig. 1, top right) with a low compliance at longer lengths. The active length-tension curve was also similar to that for other muscles in that tension development was a function of strip length. The carotid strips were capable of substantial tension development at lengths shorter than 0.6 L_o where skeletal muscle ceases to develop tension, and this capability appears to be characteristic of smooth muscle in general (1). Maximal tension development (P_o) was equivalent to that for skeletal (14) and other types of vascular smooth (1) muscle. The overall shape of the active length-tension curve would tend to indicate that a sliding filament mechanism operates in the contraction of vascular smooth muscle. However, the correct shape of the active length-tension curve is a necessary, but by no means sufficient, cause for applying this hypothesis to vascular smooth muscle. The active length-tension curve for skeletal muscle forms the physiological basis for the sliding filament hypothesis in that tension changes are directly correlated with ultrastructural changes (15). The organization of the contractile system in vascular smooth muscle is still largely unknown, although the recent demonstration of thick and thin filaments in this tissue (16) is encouraging. More information on the organization of the contractile system is needed before the sliding filament hypothesis can be applied to vascular smooth muscle.

To what extent the asymmetrical length-tension curve for the strips reflects that of the contractile component of this tissue is difficult to assess, in spite of the precautions taken in this study. Deviations between the measured length-tension relationship of strips and that of the contractile component could arise from at least two factors. Unlike the study of Gordon et al. (15) where a single-cell preparation was employed, the present study used muscle strips composed of a large number of cells. It is entirely possible that at a given strip length the individual muscle cells are at different points on their particular length-tension curves so that some average response is obtained. This fact could partially account for the rather broad range of lengths over which active contraction is possible. The asymmetry seen in the active length-tension curve (Fig. 6) may be in part due to the series elastic component present within the strips and to dead tissue at the point of attachment to the apparatus. The presence of significant elasticity in series with the contractile system would shift the top part of the curve to the right but have little effect on those parts of the curve where tension development is low. Estimates of the series elastic component for isolated smooth muscle preparations generally run from 10-20% of L_o (7, 17), although more recent estimates in intact dog carotid arteries (18) place the value at 3-4% of L_o. Since the series elastic component of the hog carotid strips has not been characterized and the complete length-tension relationship for vascular smooth muscle has not been successfully measured, further investigation on this point is necessary.

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