Effect of Aramine-Induced Smooth Muscle Contraction on Length-Tension Diagrams of Venous Strips

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The elastic properties of helically cut strips of peripheral veins of dogs were studied. Length-tension diagrams of relaxed venous strips are compared with those obtained when the smooth muscle of the strip is contracted in the presence of a long-acting sympathomimetic agent, Aramine. Sustained strong, muscular contraction is always associated with a change in the shape of the length-tension curve and a marked decrease in the extensibility of the tissue. The contribution to total strip tension of the smooth muscle relative to that of other tissue elements appears to be greater in this preparation than it is in certain previously described arterial tissues. Aramine causes smooth muscle contraction of the isolated vein strip in concentrations comparable to those probably achieved in vivo. This fact supports the hypothesis that Aramine can alter the pressure-volume characteristics of the venous bed in intact animals.

THE experiments reported are a study of the length-tension relationships of isolated, dog, peripheral venous strips examined in vitro under controlled conditions. The effect on this system of Aramine,* a long-acting sympathomimetic agent, is also described.

METHODS

A segment of vein from the lateral aspect of the lower leg of a dog anesthetized with Nembutal was quickly dissected out and placed in Krebs-bicarbonate solution. The segment was 15–20 mm. in length, approximately 1–2 mm. in diameter, contained no branches and was free of surrounding connective tissue. By cutting the segment in the form of a helix, a strip about 2 mm. wide was obtained. Those muscle fibers which had been circularly oriented in the intact vein are thus longitudinally oriented in the strip. A 5–10 mm. length of the strip was suspended between two clamps in Krebs-bicarbonate solution. The distance between the two clamps could be varied, and the tension exerted by the strip continuously recorded with a strain gage, strain analyzer and a direct-writing oscillograph. The details of the method are described elsewhere.[1]

Dilutions of Aramine were made in distilled water so that addition of about ⅟₁₀₀ of the tissue bath volume would give the desired final concentration. Data for dose-response curves were collected by increasing the bath concentration of Aramine

in tenfold steps, allowing the tension to stabilize between each addition.

The length-tension experiments were performed by decreasing strip length to l_0 (the length at which no tension is exerted) and then increasing the length in 0.5 mm. increments, waiting 1 or 2 min. between each length change so that a reasonably steady state was achieved. Each length increase was made over a period of 5 sec. This sequence was followed for one or two control runs, then in the presence of Aramine and once again after the Aramine had been washed out of the bath.

In some preparations spontaneous rhythmic small contractions occurring at a rate of 3–5/min. appeared, especially following stretch. These occurred in 2 of the 9 venous strips studied and were abolished in those preparations by lowering the calcium ion concentration from 5.0 to 2.5 mEq./L. at the beginning of the experiment.

RESULTS

Effect of Aramine on Tension at Constant Strip Length. When Aramine is added to the bath in which the venous strip is suspended, a relatively rapid increase in tension occurs. This is followed by a slower rise that may continue for 10 to 15 min. before a plateau is reached. In some preparations the initial rise is followed by a moderate decline in tension before a steady level is achieved. The final plateau tension is quite stable, with no significant change over 30 to 50 min. periods of observation. The peak response is comparable to the maximum that can be obtained with l-epinephrine.

A record which demonstrates the relationship between the final tension and the bath
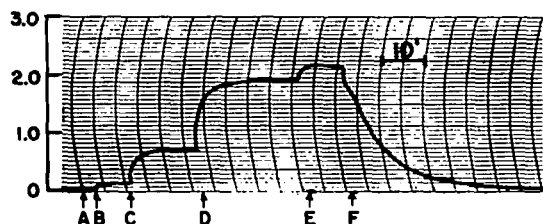
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Fig. 1. Effect of increasing Aramine on strip tension. Original tracing. X-axis time, 10 min. time mark drawn on tracing; Y-axis, tension (Gm.). At arrows, Aramine was added to achieve a final concentration in micrograms/milliliter: $A = .005$; $B = .055$; $C = .56$; $D = 5.6$; $E = 55.6$; $F =$ washout.
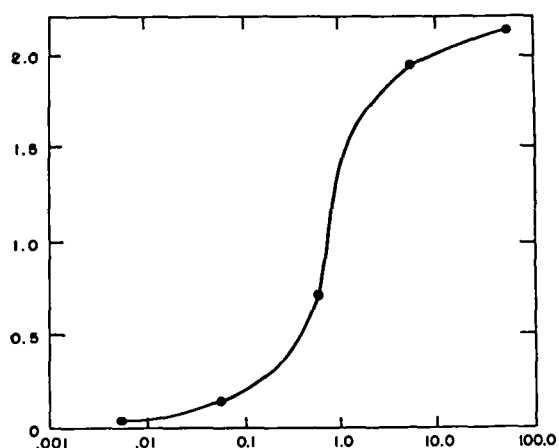

Fig. 2. Aramine dose-response curve. X-axis, Aramine concentration γ/ml., logarithmic scale; Y-axis, strip tension (Gm.).

Fig. 3. Experimental records for length-tension diagrams. X-axis, time, 2 min. time mark drawn on tracing; Y-axis, tension. Numbers along the X-axis, strip length in millimeters. Each sharp upswing in the tracings coincides in time with a 0.5 mm. increase in strip length.

Record A, control; B, Aramine 0.1 μg./ml.; C, Aramine, 5.0 μg./ml.; D, post-Aramine control.

concentration of Aramine is presented in figure 1. When the logarithm of Aramine concentration is plotted against tension, an S-shaped curve is obtained (fig. 2).

Effect of Aramine on the Length-Tension Diagram of the Venous Strip. Figure 3 shows records representative of the 12 experiments performed on 9 venous strips, from which the data for length-tension diagrams were obtained. Record A is a pre-Aramine control. Records B and C were made at two different concentrations of Aramine. The last tracing was obtained after the drug was washed out of the bath. In all records each increment in strip length caused a sharp rise in tension followed by a fall to a plateau level. The fall has been described previously for many tissues[2-5] and is sometimes called stress relaxation.[6] Figure 4 shows the curves obtained from the data of figure 3 when strip length is plotted against
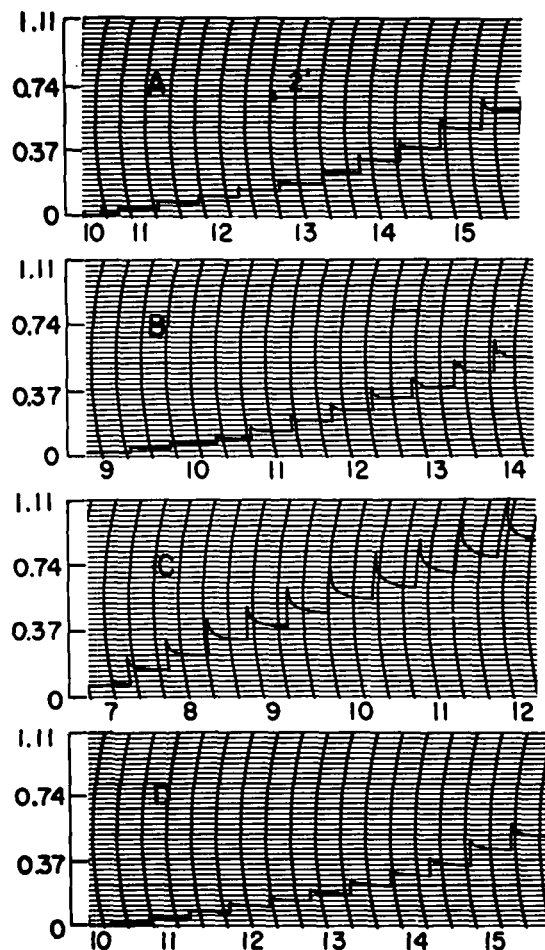
tension. The dashed curves are a joining of points which represent the peak tension achieved after each length change. The solid curves show the relationship between strip length and plateau tension values. The sustained muscle contraction induced by Aramine causes an obvious shift in the position of the curves, so that l_0 (the length at which no tension is exerted) for curve C is reduced to about 65 per cent of the control value. This is simply an indication of the extent of shortening which can occur in the presence of the drug. It can also be seen that when the muscle is strongly contracted the relationship between length and

tension approaches linearity. The post-Aramine control curve is practically identical with the pre-Aramine control.

The range of strip tensions studied includes and exceeds the range of physiologic venous pressure (from 0 up to 30–50 mm. Hg), according to calculations based on the relationship between pressure and tangential tension in the vessel wall.[7] Such calculations can provide only an approximation of the pressure range because of the uncertainty in estimating the radius of the vein under consideration.

For wire or long strips in which the cross-sectional area is small, elasticity is generally expressed in terms of Young's modulus. Only the change in length is considered, changes in cross-sectional area being ignored. The formula is $Y = \dfrac{F l_0}{A \Delta l}$, in which F is the force in grams applied, A is the cross-sectional area, l_0 is the unstretched length, and Δl is the change which occurs when the force is applied. Extensibility may be considered the reciprocal of this ratio. The less extensible the strip, the greater is Young's modulus. In applying these definitions to a strip of tissue with heterogeneous components, the meaning of A presents a problem, since not all the elements which make up the cross-sectional area share the stress equally. Thus, when the strip contracts, only the smooth muscle and the tissue to which it is attached in series contribute to the tension; and the cross-sectional area of this stress-bearing element is an unknown fraction of the total. If the point of physiologic interest is the comparison of the change in extensibility of a given strip in contracted and relaxed states, rather than Young's modulus for the stress-bearing elements in the strip, then the more useful expression is simply $\dfrac{F l_0}{\Delta l}$, the tension exerted for a fractional length change of the strip under study. Extensibility in this paper, therefore, refers to the reciprocal of this quantity for a strip of given width.

In accordance with the foregoing argument, a distinction must be made between a decrease in extensibility of the strip and a shift of the length-tension curve without such a decrease. As an example of the latter, comparison may be made between curves A and B in figure 4. Curve B is similar in shape to curve A, but is shifted down the length axis so that if the strip is stretched to, say, 13 mm. a greater tension is exerted than that exhibited in the control
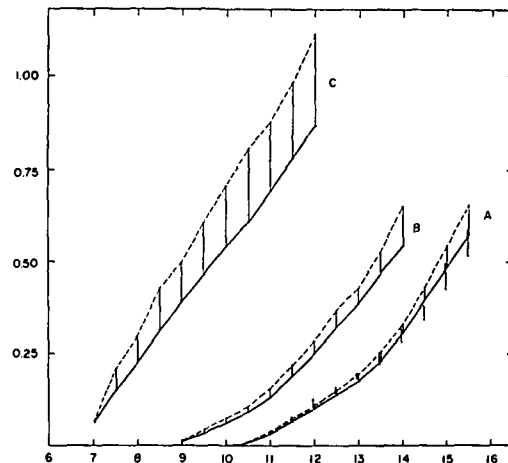

FIG. 4. Length-tension diagrams plotted from data of figure 3. *Dashed curves*, a joining of points which represent the peak tension achieved after each length change. *Solid curves*, plateau tension values. *X-axis*, strip length (mm.); *Y-axis*, tension (Gm.). *A*, control, *B*, Aramine, 0.1 μg./ml.; *C*, Aramine, 5.0 μg./ml.

The post-Aramine control points from record *D* in figure 3 are also shown, peak and plateau values at each strip length being joined by vertical lines. These latter curves (*D*) have not been drawn, however, because of their close proximity to curves *A*.

state at 13 mm. If an estimate is made of the slopes of the early portions of the two curves, one can calculate the quantity $\dfrac{\Delta l / l_0}{F}$, the fractional length change per gram of tension, which is a measure of the extensibility of the tissue. It is 1.6 for curve A, 1.8 for curve B. These differences may not be significant; there was insufficient data to determine whether minimal contraction is generally associated with an increased extensibility, because of the uncertainty in determining the slopes of the early portions of the curves. When the control is compared with the maximally contracted state, however, the differences are unequivocal: for all specimens examined the strongly contracted strip is less extensible than the control. The ratio

$$\frac{extensibility,\ relaxed\ state}{extensibility,\ strongly\ contracted\ state}$$

had a mean value of 2.7 ± S.D. 1.2, based on the 7 venous strips for which the slopes of the early portions of the length-tension curves could be readily estimated. Thus, strong con-

traction is always accompanied by a marked decrease in extensibility.

The magnitude of stress relaxation, that is the drop in tension to a plateau from the peak value attained immediately after a length change, is greater in the contracted than in the relaxed state.

DISCUSSION

The elastic properties of vascular tissue have frequently been a subject for study in the past. Much of the information contained in the length-tension diagrams of the dog vein strips can be found in the load-extension curves of aortic strips published by Roy in 1880.[8] This author discussed the slow rate at which such smooth muscle organs reach a new equilibrium length after loading, the description of which as "elastische Nachwirkung" Roy attributed to E. Weber in 1841. It is obviously related to the stress relaxation which is seen in the vein strips after stretching (fig. 3). Roy also noted the difference between the pressure-volume curve of a tubular segment of aorta and the length-tension curve of a strip and explained the now well-known sigmoid shape of the former on the basis of the geometry of the organ, a consideration which has been recently emphasized by Burton.[7]

Our studies showed that, over a physiologic range of tensions, dog peripheral venous strips always exhibit diminished extensibility in the strongly contracted state. Similar findings were described by Winton,[9] whose length-tension curves for dog retractor penis and guinea pig uterus showed that the muscles became less extensible when contracted.

Since the smooth muscle fibers in the wall of a blood vessel are very short (about 50 μ) and must in effect be joined end to end by collagen or elastic tissue, no conclusions can be drawn about the elasticity of the muscle cells without some reference to their arrangement in the vascular wall. The studies of Benninghoff on arteries suggest that the cells are not connected directly, but insert into elastic tissue.[10] For purposes of this discussion, the venous strip may be considered in terms of a generally used simple model as (1) a chain of muscle cells in series with an inert elastic element interspersed

between them (the series component of the strip), and (2) a parallel elastic component running from one end of the strip to the other, without connections to the muscle. The strip length at which no tension is exerted may be defined as l_0. When the unstimulated tissue is stretched beyond l_0, the tension which develops is due to the stretch of both series and parallel components. But if the muscle is stimulated to contract, and the strip is allowed to shorten to some length below the unstimulated l_0, the parallel elastic elements are now all slack and the load is carried only by the series component.

The extensibility of the venous strip during contraction below the unstimulated l_0 reflects then, the extensibility of the contracted series component alone, and it was found to be less than the extensibility of the series plus parallel components in the relaxed state. The elastic modulus of the venous smooth muscle cells must, therefore, have increased significantly during contraction. The results also suggest that the elastic modulus of the contracted muscle fibers is greater than that of elastic tissue. The latter conclusion cannot be drawn with certainty, however, because the cross-sectional areas of the different tissue elements sharing the stress and their relative elongations during extension of the strip are unknown.

There are few studies in the literature which compare the mechanical properties of relaxed and contracted blood vessels, if observations under such unphysiologic conditions as post mortem shortening[11] are excluded. The available data, obtained from aorta[12, 13] and carotid sinus,[14] have in common the fact that distensibility for stimulated vessels was found to be *greater* than that for unstimulated vessels over a certain pressure range,* results which are the opposite of those provided by the dog venous strips. The divergent findings may be related

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* Volume distensibility, D, may be defined as $\dfrac{\Delta V}{V \Delta P} \times 100$. The word is frequently used loosely, and sometimes V is not known. In the studies quoted, however, even though a strictly quantitative answer was not always available, it is clear that $\dfrac{\Delta V}{\Delta P}$ (or a related function) was greater in the contracted than in the relaxed state, at a time when V had decreased.

to the difference in the tissues studied. From Alexander's data on aorta,[13] it would appear that the contribution to total tension of the contracted smooth muscle in his preparation is small compared to that of the parallel elastic tissue in the vessel wall. Thus, muscular contraction induced by addition of epinephrine in high dosage increased by only 1.5 times the tangential tension in the wall of the unstimulated vessel stretched, say, 10 per cent above l_0. In contrast, for the dog peripheral venous strip, contraction of the muscle caused an eleven-fold rise in tension above that of the unstimulated tissue stretched a comparable amount above l_0.

On the basis of the data on aorta and carotid sinus,[13, 14] Burton concluded that smooth muscle, whether relaxed or contracted, contributes very little directly to the total elastic tension of the vessel wall.[7] The present study shows that this is not true for peripheral venous strips. It appears likely that smooth muscle can contribute significantly to vascular wall tension in all but the large elastic vessels.

Stress relaxation was found to be greater for the contracted strip than for the relaxed one; suggesting that among the elements in the vessel wall, the smooth muscle is mainly responsible for this phenomenon. The fact that stress relaxation of muscular umbilical artery was much greater than that of carotid artery with its larger proportion of elastic tissue led Zatzman and his colleagues to a similar conclusion.[15] This observation may have meaning in the interpretation of in vivo pressure volume relationships in veins in which varying degrees of smooth muscle contraction are present.

Recent studies have shown that the circulatory depression accompanying high levels of positive pressure breathing can be counteracted by the administration of Aramine.[16] It was thought that one of the effects of this agent might be to decrease the distensibility of veins, thus diminishing the displacement of blood from lung to periphery which occurs during uncompensated pressure breathing. The fact that Aramine causes a decrease in the extensibility of isolated veins supports this hypothesis. The concentrations of drug used in vitro are comparable to those which were achieved in vivo. The experiments showing the effects of Aramine on the circulatory depression of positive pressure breathing provide one example among many of how the pressure-volume characteristics of the venous bed have substantial consequences for circulatory homeostasis.

SUMMARY

Length-tension diagrams of peripheral venous strips from dogs have been presented. It has been shown that a sympathomimetic agent, Aramine, causes contraction of the muscle in the isolated venous strip. Over the range of lengths studied, strong muscular contraction is always associated with a decrease in extensibility of the tissue, and it is apparent that the smooth muscle is capable of contributing significantly to the total tension of the vessel wall. The effect of Aramine on isolated vein is consistent with the hypothesis that the drug has an effect on peripheral venous tone in the dog.

SUMMARIO IN INTERLINGUA

Es presentate diagrammas de tension longitudinal de peripheric bandas venose ab canes. Esseva monstrate que le agente sympathomimetic 'Aramina' causa contractiones del musculo in isolate bandas venose. Intra le limites de longitude studiate, forte contractiones muscular es semper associate con un reduction del extensibilitate del histo, e il es apparente que le musculo lisie es capace a contribuer significativemente al tension total del pariete vascular. Le effecto de Aramina super vena isolate se trova de accordo con le hypothese que le droga exerce un effecto super le tono venose peripheric in le can.

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