EXPERIENTIA

Vol. 31 – Fasc. 12 Pag. 1377 – 1476 15. 12. 1975

# GENERALIA

## Mechanics of Vascular Smooth Muscle Contraction

by BÖRJE JOHANSSON*

Department of Physiology and Biophysics, University of Lund, Sölvegatan 19, S–223 62 Lund (Sweden).

Much experimental work has been devoted to the problem of characterizing, in quantitative biophysical terms, the mechanical properties of the blood vessels with the purpose of reaching a better understanding of vascular functions in the intact circulation. A common approach has been to treat the vascular wall as a viscoelastic body with application of theories developed in the technology of elastomers. Mechanical properties are then presented as stress-strain relations, as static elastic moduli and POISSON ratios, and as frequency dependent dynamic elastic and viscous moduli. It turns out that the vascular wall cannot be represented by any simple viscoelastic model of springs and dashpots, and it has been particularly difficult to account for the influence of smooth muscle tone in terms of the elastomeric theory. It is important to realize that smooth muscle is not just a viscoelastic body but a chemomechanical transducer which, like a car engine, converts chemical energy to mechanical energy. Any description of the effects of the smooth muscle on vascular properties, the dynamic ones in particular, must consider the power output (mechanical work per unit time) from this machine and its dependence on the actual load.

The purpose of this paper is to review some recent studies on vascular smooth muscle mechanics and to discuss how the work on elastic and viscous properties may relate to the function of smooth muscle as a chemomechanical engine. It is the author's impression that communication has been poor between biophysicists or bioengineers who study the vessel wall as an elastomer and physiologists who approach vascular smooth muscle via concepts developed in research on striated muscle during the recent decades. Useful information comes from both approaches, but the relative importance of the contributions may depend on what vascular in vivo function one wants to elucidate. Data on static and dynamic elastic and viscous moduli will help in the understanding of arterial pressure waves and pulsatile flows whereas data on extent and rate of muscle shortening appear more relevant to resistance and capacitance responses in vivo.

*Fundamentals of the elastomeric theory*

The elasticity of a material such as steel is expressed as a Young's modulus ($E$) which is a ratio of stress ($S$) over strain ($\varepsilon$). Owing to the fact that $\varepsilon$ is dimensionless, representing the increase in length as a fraction of the unstrained length ($\Delta L/L_0$), $E$ gets the same dimension as $S$ which is force per unit cross sectional area (dyn/cm$^2$ or $N$/m$^2$). With an ideally elastic body Young's modulus remains constant for all degrees of stress up to the elastic limit, but biological tissues show highly non-linear stress-strain curves. Therefore, it has become customary to measure instead the incremental elastic modulus ($E_{inc}$) at different levels of the stress-strain curve, a limited section of which is thus considered approximately linear:

$$E_{inc} = \Delta S/\Delta\varepsilon \qquad (1)$$

If a piece of elastic material is subjected to simultaneous stress in more than one direction, the strain occurring on, say, the longitudinal axis will be less than longitudinal stress divided by the elastic modulus due to an influence of the perpendicular stresses. The magnitude of these influences depend on the so called POISSON's ratios which in turn reflect the relative distensibility of the elastic body in the different directions. Should the elastic modulus be the same in all three directions, the material is said to be isotropic and the POISSON ratios = 0.5; if not the material is anisotropic. For a presentation of the basic mathematics in this field see e.g.[1,2].

There may also be shearing strains between different parallel layers in the material, and the body may or

* The present study was supported by grants from the Swedish Medical Research Council (14X–28). I am grateful to Mrs MONICA LUNDAHL and Mrs TORA JOHANSSON for secretarial aid in the preparation of the manuscript.

[1] D. A. MCDONALD, *Blood Flow in Arteries*, 2nd edn (Arnold, London 1974).

[2] D. J. PATEL, J. S. JANICKI and T. E. CAREW, Circulation Res. *25*, 765 (1969).

may not change its volume when subjected to stress. It turns out that a full characterization of the elastic behaviour of such a body may require determination of as many as 21 constants. Fortunately, the situation with regard to the vascular walls appears simpler. As a result of its high water content the tissue is practically incompressible[3] and therefore does not change its volume. Furthermore, shearing strains appear to be negligible[4] so that studies of the stress-strain relations in the three main directions, longitudinal, circumferential, and radial, are sufficient to adequately characterize the elasticity of the tube.

The static incremental elastic moduli will decribe the elastic behaviour of the blood vessel in response to slow variations in pressure. When the blood pressure changes rapidly, as during systolic ejection, also the viscous properties of the vascular wall will influence the relation between stress and strain. Such viscoelastic responses may be characterized by determination of the dynamic modulus at different frequencies of sinusoidal oscillations. Following HARDUNG[5] and BERGEL[6,7] this dynamic modulus may be separated into one real component, $E_{dyn}$, representing storage of energy in the elastic element and one imaginary component representing dissipation of energy in the viscous part:

$$E_{inc} = E_{dyn} + i\omega\eta \tag{2}$$

or

$$E_{dyn} = E_{inc} \cos \eta \tag{3}$$
$$\omega\eta = E_{inc} \sin \varphi \tag{4}$$

where $\varphi$ is the phase angle by which the change in strain lags behind the change in stress, $\omega$ is the angular velocity and $\eta$ is the viscosity (see also e.g.[8,9]).

*Fundamentals of the mechanics of muscular contraction*

As pointed out in the foregoing, contraction implies a conversion of chemical energy to mechanical energy. The fundamental characteristics of the mechanical output from this chemomechanical transduction may be summarized in the following relationships which are reasonably well established and at least partly understood as far as skeletal muscle is concerned.

I. The ability to develop isometric force changes with the length of the muscle. The decline in active force at lengths greater than the optimal one can be attributed to decreasing overlap between actin and myosin filaments[10]. Active force also decreases at smaller lengths and this may be due to 'collision' of filaments[10] or perhaps to failure of excitation-contraction coupling[11].

II. At a given length and a given intensity of chemomechanical transduction the output from the contractile machine may be described by an instantaneous force-velocity curve which shows how the rate of shortening depends on muscle load. Mathematically these force-velocity relations have been approximated by HILL's[12] hyperbolic equation:

$$(P + a)(V + b) = b(P_o + a) \tag{5}$$

where $P$ is load, $V$ is shortening velocity, $P_o$ is isometric force, and $a$ and $b$ are constants with the dimensions of force and velocity, respectively, or by AUBERT's[13] exponential equation:

$$P = A \cdot e^{V/B} \pm F \tag{6}$$

where $P$ and $V$ have the same meaning as in HILL's equation, $A$ and $F$ are constants with the dimension of force and $B$ is a velocity constant. Little is known about the 'negative part' of the force-velocity curve i.e. the relation between force and rate of lengthening when the contracted muscle is stretched by an external force $> P_o$.

III. The intensity of the chemomechanical transduction, the active state, which follows a defined stimulus has a characteristic time course. To describe this time course without having to present a whole set of complete force-velocity curves it has been customary to use HILL's[14] definition of the active state as the force which the contractile element can bear without changing its length. Thus, the time course of the active state is given by the $P_o$ values of all the instantaneous force-velocity curves on which the muscle operates during the contraction-relaxation cycle.

Points I to III then indicate that the contractile response after a stimulus may be completely described as a function including four variables, e.g.:

$$P = f(L, V, t) \tag{7}$$

The length-active tension curve, the force-velocity curve, and the active state curve represent particular solutions to this complex relationship.

The mechanical output from the contractile proteins is transmitted to recording systems through passive elastic elements in the tissue. Recordings of length and force from the entire muscle can be interpreted as events in the contractile system proper, e.g. at the

[3] T. E. CAREW, R. N. VAISHNAW and D. J. PATEL, Circulation Res. *23*, 61 (1968).
[4] D. J. PATEL and D. L. FRY, Circulation Res. *24*, 1 (1969).
[5] V. HARDUNG, Helv. physiol. Acta *11*, 194 (1953).
[6] D. H. BERGEL, J. Physiol., Lond. *156*, 458 (1961).
[7] D. H. BERGEL, in *Biomechanics. Its Foundations and Objectives* (Prentice-Hall Inc., Englewood Cliffs 1974).
[8] R. D. BAUER and T. PASCH, Pflügers Arch. *330*, 335 (1971).
[9] D. L. PATEL, J. S. JANICKI, R. N. VAISHNAW and J. T. YOUNG, Circulation Res. *32*, 93 (1973).
[10] A. N. GORDON, A. F. HUXLEY and F. J. JULIAN, J. Physiol., Lond. *184*, 170 (1966).
[11] S. R. TAYLOR and R. RUDEL, Science *167*, 882 (1970).
[12] A. V. HILL, Proc. R. Soc., Lond. B *126*, 136 (1938).
[13] X. AUBERT, *Le couplage énergétique de la contraction musculaire* (Editions Arscia, Bruxelles 1956).
[14] A. V. HILL, Proc. R. Soc. Lond. B *136*, 399 (1949).

sarcomere level, only if the influence of the passive elastic structures is accounted for. Such accounting is mostly based on simple mechanical models of the muscle consisting of a contractile unit in series with an elastic element, and a parallel elastic element, the latter being responsible for resting tension. At low preload the parallel elasticity may be neglected and analyses of the contraction can then be based on a two-component model.

*Longitudinal and radial stresses and strains in blood vessels*

The variations in dimension, force and stiffness in the circumferential direction of the vascular wall are the most important ones, particularly with regard to those functions of the blood vessels which depend on caliber (e.g. resistance and capacitance). However, before we turn to that major topic, a few comments will be made on longitudinal and radial (intima to adventitia) events in the vessel.

In vivo the blood vessels do not change their length appreciably in response to pressure variations, but they are under *longitudinal stress* by being tethered to surrounding tissues. Understanding of configuration and propagation of the pulse wave in the large arteries requires that effects of both circumferential and longitudinal forces are considered. This brings us back to the difficult question of the possible anisotropy of the vessel wall. PATEL, JANICKI and CAREW[2] concluded from their study of the canine aorta that the incremental elastic modulus at physiological pressure levels is greater in the longitudinal than in the circumferential direction and smallest in the radial direction (cf. also[9]). On the other hand, ATTINGER[15] and DOBRIN and DOYLE[16] found that in the dog femoral and carotid artery, respectively, the longitudinal $E_{inc}$ is greater than the circumferential $E_{inc}$ only at low pressure while the circumferential modulus increases markedly at higher pressures. In the carotid artery it became twice the longitudinal modulus at 120 mm Hg. DOBRIN and DOYLE also calculated POISSON's ratio between the circumferential and longitudinal axes and obtained values of 0.25 to 0.45. The fact that the fibrous proteins of the vascular wall, elastin and collagen, are not randomly distributed, but largely arranged in concentric lamellae (especially so with elastin), suggests that the tissue may in fact be anisotropic. However, the studies referred to above indicate that no generalizing conclusions can be drawn in this respect due to differences between different vessels and influences of the pressure level. PATEL et al.[9] correctly point out that even if the vessel is isotropic in one situation, for instance at zero transmural pressure, one is likely to find anisotropy at a different pressure as the change is stress will not be the same in all directions and, therefore, different points will be reached on the curvilinear stress-strain curves. It appears difficult indeed to make corrections for vascular anisotropy in analyses of matters such as arterial pulsatile pressure and flow. MCDONALD[1] (p. 276) concludes that the treatment of the wall as isotropic is a reasonable compromise; he also considers analysis of a large number of elastic constants as mainly of theoretical interest.

The *distribution of stresses and strains in the different concentric layers* through the blood vessel wall also deserves a few comments. The incompressibility of the tissue enables us to calculate the strain in any part of the wall from measurements of the changes in external diameter which occur at variations in transmural pressure; if the vascular segment under study is kept at constant length the only additional information we need is one determination of wall thickness or wall volume. It is obvious that strains will always be greater at the intimal surface than in the adventitia. This would also imply that circumferential stress would be greatest at the luminal side and decrease towards the outside if the tissue were homogenous i.e. if all layers had the same stress-strain relation. However, the histological differences between the inner and outer portions of the wall may complicate this matter. For instance if the stress-strain curve were generally steeper for the adventitial collagenous elements than for the elastic lamellae in the inner half of the wall, the energy delivered by the distending pressure could be stored mainly in the adventitial coat and to a smaller extent in internal and medial structures despite that the latter would undergo more strain. Then the pressure drop along the radial axis through the vessel wall would not be linear but might be steepest in the adventitia. Also, when force is developed actively within the tissue by the smooth muscle, the highest circumferential stress will frequently occur in the contracting layer; narrowing of the lumen due to activation of smooth muscle in the outer media (the innervated part) might completely unload the internal elastica. It appears that the assumption of homogeneity, often made in elastomeric treatments of blood vessels, is very inadequate with regard to distribution of circumferential stress and pressure profile through the wall.

*Circumferential length-tension relations in the vascular wall. Static incremental elastic moduli.*

The mean circumferential stress of the vessel wall is given by the equation often referred to in the physiological literature as the law of LAPLACE:

$$\bar{S} = p \cdot r_i/(r_o - r_i) \qquad (8)$$

[15] F. M. L. ATTINGER, Circulation Res. *22*, 829 (1968).
[16] P. B. DOBRIN and J. M. DOYLE, Circulation Res. *27*, 105 (1970).

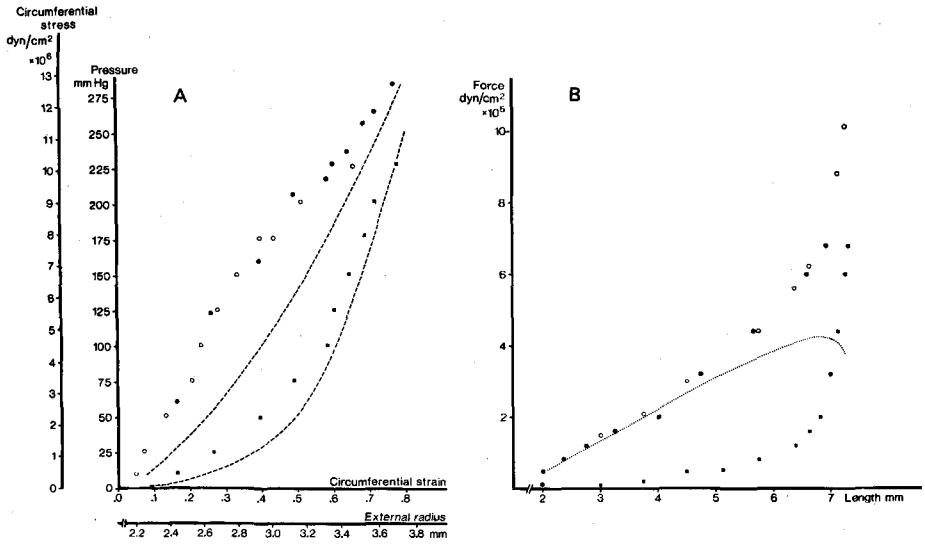


Fig. 1. A) Pressure strain relations of dog carotid artery under metabolic inhibition by KCN (square symbols) and at isometric (filled circles) or isobaric (open circles) contraction to noradrenaline. These original data, reported by DOBRIN[17] have been used to calculate circumferential stress-strain curves for the relaxed (lower broken line) and the contracted (upper broken line) carotid artery assuming an external radius of 2.1 mm at 0 mm Hg.
B) Length-tension relations obtained in isolated strip of rat portal vein at inhibition of contractile activity by Ca-free solution (square symbols) and at maximal isometric (open circles) or isotonic (filled circles) responses to $K^+$ depolarization at 5.0 m$M$ $Ca^{2+}$. Broken line represents active contractile force obtained as total minus passive force.

where $\bar{S}$ is mean stress, $p$ transmural pressure, and $r_i$ and $r_o$ internal and external radius respectively. Figure 1 A shows the relationship between pressure and increase in radius for the relaxed and the noradrenaline stimulated dog carotid artery. The figure is based on data originally reported by DOBRIN[17]. The pressure-radius curve of the relaxed vessel shows, in agreement with numerous other studies of this topic, an early slow and a later steep rise in pressure with graded inflations. Assuming a wall to lumen ratio of 0.1 and using an external radius of 2.1 mm at zero pressure, the pressure-radius curve has been translated into a stress-strain curve for the relaxed carotid artery (lower broken line in Figure 1A). This curve represents the characteristics of the parallel elastic element, which is the load-bearing component when the smooth muscle is at rest. Its curvilinear form implies that the incremental static elastic modulus is relatively small at low pressure (or low strain), but increases markedly in the range of physiological arterial pressure. Figure 1B shows length-tension relations for an isolated strip of portal vein at rest and in potassium contracture. Here again the resting state (square symbols) is characterized by an early slow and a late steep ascent. It is likely that the structural background of these relations is similar in the two preparations illustrated in A and B. There is some evidence that the early part of the resting curve is dominated by the relatively distensible elastin whereas the steep rise reflects the influence of the stiffer collagen[18]. It is difficult to say to what extent the smooth muscle cells may contribute to the resting tension. In the classical muscle model of HILL[12], the contractile element is considered fully extensible (plastic) at rest. If this element, on the basis of present knowledge, is structurally equated with the actin and myosin filaments we would then consider the two filament systems completely dissociated and unable to bear force in the resting muscle. Rest should be defined as total absence of chemomechanical transduction, i.e. no dynamic interaction of cross-bridges between actin and myosin. However, the possibility remains that static, rigor-like cross-bridge attachments are present in vascular smooth muscle at rest, and in that case the actomyosin filaments could contribute to resting stiffness (cf. D. K. HILL's studies[19] of short range stiffness in resting skeletal muscle). Other structures of the smooth muscle cells such as the plasma membrane may also carry part of the resting force.

The circular symbols in Figure 1 A show the changes in pressure and strain obtained by DOBRIN[17], in the carotid artery by isometric (closed symbols) and isobaric (open symbols) contractions, respectively. It should be noted that the noradrenaline stimulated vessel reaches the same pressure-strain relations no matter whether contraction causes increased pressure at a constant radius or whether it causes shortening to this radius against the constant pressure. The circular symbols thus summarize the equilibrium situations in which the constricting forces of smooth muscle and parallel elastic elements balance the distending forces of the transmural pressure. Isobaric contraction does not imply shortening of the smooth muscle against a constant load due to the fact that wall stress is also a function of radius (equation 8). The load on the muscle thus decreases during isobaric shortening except in the earliest phase of the response when the

[17] P. B. DOBRIN, Am. J. Physiol. *225*, 659 (1973).
[18] M. R. ROACH and R. C. BURTON, Can. J. Biochem. Physiol. *35*, 681 (1957).
[19] D. K. HILL, J. Physiol., Lond. *199*, 637 (1968).

transfer of force from the parallel elastic to the contractile element can predominate[20,21]. It is important to note that isobaric contraction, in spite of the apparent tendency to positive feedback by LAPLACE's law, does not lead to inevitable 'critical closure' as the smooth muscle will find a new equilibrium state at the shorter length. Obviously, this new length of the contracting cells in the outer media may be associated with closure of the lumen if the vessel has a thick wall.

The pressure-strain relations of the contracted carotid artery (circular symbols in Figure 1A) may be converted to an active stress-strain curve; its approximate course is shown by the upper broken line of Figure 1A. The corresponding length-active tension relation is shown for the simpler linear system of the portal vein strip in Figure 1B. Here isometric ('vertical') and isotonic ('horizontal') contractions also lead to a unitary length-tension relation showing that the muscle reaches the same equilibrium situations irrespective of its previous history. This may not be true if the muscle is brought to very large strains which may lead to more or less irreversible changes in contractility[22,23].

The differences between the active and passive length-tension curves in Figure 1A and B represent the force developed by the smooth muscle at the different lengths. In B this contractile force is shown by the broken line. There is in this preparation an almost linear increase in isometric force with increasing length up to an optimum after which the force appears to drop quite abruptly. It seems likely that this assymetry of the curve may not be a property of the contractile element itself but may relate to the distensibility and the arrangement of the series elasticity[20,24]. The maximal contractile force developed by vascular smooth muscle is of the order of $2–3 \cdot 10^6$ dyn/cm$^2$ (e.g.[25,26]), which is comparable to values obtained in striated muscle. The venous strip in Figure 1B developed much less tension, but only part of the cross sectional area of this preparation is smooth muscle with optimal orientation of the cells. Present knowledge concerning the organization of the myofilaments in vascular smooth muscle does not permit an ultrastructural interpretation of its length-active tension relation.

The stress-strain curves illustrated in Figure 1A may also be discussed in terms of the circumferential static elastic moduli of the arterial wall in the relaxed and contracted states. Under the assumption of isotropy the slope of the curves is proportional to $E_{inc}$ in the different stress-strain situations. As pointed out in the foregoing, the gradually increasing $E_{inc}$ with increasing stress (or strain) in the relaxed artery has been attributed to an increasing influence of stiffer collagen in relation to the more distensible elastin[18]. The effect of smooth muscle tone on vascular distensibility has been a matter of some confusion. If active and passive stress-strain or pressure-radius curves are compared along given levels of stress or pressure, smooth muscle contraction is often found to decrease $E_{inc}$ at physiological pressures. Several authors (e.g.[15,27,28]) have emphasized this decrease in the stiffness of the vascular wall. Many physiologists have found this effect difficult to accept, as the reduced stiffness does not seem to be a proper result of smooth muscle contraction. However, if comparisons are made at equal strains instead, contraction of the smooth muscle does indeed increase $E_{inc}$ over the major or even the entire range of strain values.

Many authors have published pressure-radius, stress-strain or length-tension curves for intact vessels, rings or strips from arteries and veins similar to the ones shown in Figure 1. Vascular smooth muscle from different locations thus seems to show the same general features of length dependence. The pressure-diameter relations from rabbit ear artery, recently reported by SPEDEN[21] are somewhat different as the active curves are very steep indicating that shortening of the muscle in this vessel is essentially independent of load over a large pressure range. One possible explanation for this could be that special changes occur in the distribution of stress between different layers of the vessel wall in the ear artery.

Isometric contraction does not imply that the contractile element itself maintains constant length as internal shortening is considered to occur in the muscle. The active isometric force recorded externally represents the tension produced in the series elastic element by this shortening of the contractile unit. Stress-strain relations and stiffness characteristics of the series elastic element can be revealed by quick release experiments on the contracted muscle; the analysis being simplest at low preloads (low resting tension) where the influence of the parallel elastic element is negligible (see further below). The series elastic component in blood vessels shows relatively high distensibility in comparison with skeletal muscle and heart. Strong isometric contractions in strips of vascular smooth muscle are associated with lengthening of the series elasticity corresponding to 7–20% of the total length of the preparation[25,29,30] and this can

[20] B. JOHANSSON, Fedn. Proc. *33*, 121 (1974).
[21] R. N. SPEDEN, J. Physiol., Lond. *248*, 531 (1975).
[22] P. B. DOBRIN, Am. J. Physiol. *225*, 664 (1973).
[23] J. W. PETERSON and R. J. PAUL, Am. J. Physiol. *227*, 1019 (1974).
[24] B. JOHANSSON, in *Microcirculation* (University Park Press, Baltimore, 1975), in press.
[25] L. LUNDHOLM and E. MOHME-LUNDHOLM, Acta physiol. scand. *68*, 347 (1966).
[26] J. T. HERLIHY and R. A. MURPHY, Circulation Res. *33*, 275 (1973).
[27] R. S. ALEXANDER, Circulation Res. *2*, 140 (1954).
[28] C. J. WIGGERS and R. WEGRIA, Am. J. Physiol. *124*, 603 (1938).
[29] B. JOHANSSON, Circulation Res. *32*, 246 (1973).
[30] J. T. HERLIHY and R. A. MURPHY, Circulation Res. *34*, 461 (1974).

only in part be attributed to injured tissue at the ends of the strips since DOBRIN and CANFIELD[31] report similar values from intact carotid arteries. As in the case of parallel elasticity discussed above, it is not yet possible to exactly define the structural localization of vascular series elasticity. Some of it certainly resides in elastin and collagen between the smooth muscle cells but part of it may be intracellular in the myofilaments and/or in their attachments to dense bodies and membranes. Speculations on the possible stretching of cross-bridges between actin and myosin filaments in vascular smooth muscle during contraction do not seem justified at the present stage.

It is not known exactly how the vascular contractile machine may operate when a constant vascular caliber is maintained by isometric contraction against the distending pressure. Perhaps the function of the chemomechanical transducer of the smooth muscle may then be compared to a rower's work at the oars when he just manages to prevent his boat from going downstream. There is no clear evidence from mammalian vascular smooth muscle that the force established in the series elasticity by shortening of the contractile element can be maintained thereafter by a passive or highly economic catch mechanism as has been described for some invertebrate smooth muscles[32].

*Application of the length-tension relations and of static elastic moduli to the in vivo circulation.*

The changes in the length-tension relation and in the stiffness of the vessel wall brought about by smooth muscle contraction are important for the understanding of adjustments of vascular functions in vivo. Some aspects of these adjustments will be considered at this point.

The smooth muscle cells of the *large elastic arteries* (the aorta and its major branches) are supplied with sympathetic vasoconstrictor fibres and they respond to circulating vasoactive agents. If these cells are engaged in reflex or central nervous adjustments of the circulation as in physical exercise, emotional excitement, response to bleeding etc. the resultant effects on arterial elasticity will obviously depend on how the mean arterial pressure is affected by the simultaneous changes in cardiac output and peripheral resistance. Figure 1A indicates that maintenance of mean pressure will permit the smooth muscle to reduce arterial diameter and elastic modulus whereas a concomitant rise in pressure may prevent lumen reduction and cause stiffness to increase. Variations of smooth muscle tone in the large elastic arteries can obviously affect the velocity of propagation of the pulse wave, but may seem to be of little importance for the overall function of the circulation. However, contraction of aortic smooth muscle can produce changes in Windkessel function (storage of systolic energy), in arterial impedance for left ventricular contraction[33], in impulse traffic from arterial mechanoreceptors[34], and in the dynamic stimulus for peripheral myogenic reactions[35,36], and these effects may not be homeostatically unimportant.

It is difficult to translate length-tension curves of isolated vascular preparations directly into *resistance and capacitance functions* of intact vascular beds. The difficulties are related not only to the influence of the law of LAPLACE but also to the high wall to lumen ratio of the resistance vessels[37] and to the fact that resistance and capacitance depend on the fourth and the second power, respectively, of the inner radius. It appears that the length-tension relations at rest and activity of the smooth muscle in small blood vessels resemble those of larger vessels exemplified in Figure 1 (see e.g.[8,38]). The responsiveness or reactivity of the resistance and capacitance vessels will obviously depend on whether their smooth muscle operates on an optimal or an unfavourable part of the length-tension diagram, and that, in turn, depends on the actual pressure level in the respective sections of the vascular tree. From in vivo experiments on frog mesenteric microvessels, GORE[39] concluded that the physiological pressure range corresponded to optimal conditions for active constriction in arterioles but not in larger precapillary vessels.

Examination of the passive and active length-tension relations, for instance in Figure 1B, tells us that the ability of the smooth muscle to develop force and its ability to shorten do not change in parallel when the passive stress is altered[20]. Force and shortening are different manifestations of the chemomechanical transduction in the smooth muscle and this must be kept in mind when results from studies with different recording techniques are compared. The following examples from the literature may illustrate the point.

In a study of the sympathetic vasoconstrictor fibre control of the vascular bed of skeletal muscle, MELLANDER[40] demonstrated a significant difference between the frequency-response curves of resistance and capacitance vessels when responses were measured as changes of flow at constant perfusion pressure and as plethysmographically recorded decreases in tissue volume, respectively. The curve for the capacitance vessels was steeper and displaced to the left of that for the resistance vessels. In a later study, BROWSE,

[31] P. B. DOBRIN and T. R. CANFIELD, Circulation Res. *33*, 444 (1973).
[32] J. LOWY and B. M. MILLMAN, Phil. Trans. R. Soc. *246*, 105 (1963).
[33] W. R. MILNOR, Circulation Res. *36*, 565 (1975).
[34] S. LANDGREN, Acta physiol. scand. *26*, 1 (1952).
[35] S. MELLANDER and S. ARVIDSSON, Acta physiol. scand. *90*, 283 (1974).
[36] B. JOHANSSON and S. MELLANDER, Circulation Res. *36*, 76 (1975).
[37] B. FOLKOW, G. GRIMBY and O. THULESIUS, Acta physiol. scand. *44*, 255 (1958).
[38] C. A. WIEDERHIELM, Fedn. Proc. *24*, 1075 (1965).
[39] R. W. GORE, Am. J. Physiol. *222*, 82 (1972).
[40] S. MELLANDER, Acta physiol. scand. *50*, Suppl. 176 (1960).

LORENZ and SHEPHERD[41] recorded resistance responses in the dog's limb by the constant flow-variable pressure technique and capacitance responses by measuring venous pressure elevation with the circulation temporarily arrested. These authors found, in contrast to MELLANDER, similar frequency-response curves for the two vascular sections. Such different conclusions may easily lead to arguments and confusion if it is not realized that the smooth muscle contracts under quite different conditions in the two studies. In MELLANDER's experiments the smooth muscle of the capacitance vessels shortened against a constant venous outflow pressure whereas it developed isometric force in the study of BROWSE et al. It is also known that resistance responses differ depending on whether they are obtained by the constant pressure-variable flow technique or by the constant flow-variable pressure technique[42]. The hemodynamic starting situation is an important but often neglected determinant of vascular responsiveness. An illustration of this point is the careful analysis of the effect of venous pressure on capacitance responses by ÖBERG[43]. He found that the total mobilization of blood from the capacitance vessels of the cat hind-quarter in response to a standardized vasoconstrictor fibre stimulation was greatly dependant on the venous outflow pressure, and so were the relative contributions of active and passive mechanisms to the total response. These observations illustrate how the active and passive length-tension relations apply to the in vivo situation.

*Dynamic viscoelastic moduli, force-velocity relations of vascular smooth muscle, and rates of change of vascular functions in vivo*

The rapid changes of pressure and diameter in the arterial system associated with each systolic ejection cannot be simply related to incremental static elastic moduli but require that the frequency dependent *dynamic moduli* be considered. BERGEL[6] examined pressure diameter relations of large canine arteries subjected to sinusoidal distensions at variable frequency. Assuming isotropy of the vessel wall he found that $E_{dyn}$ increased over the static $E_{inc}$ between 0 and 2 Hz and remained constant for further increases in oscillation frequency up to 20 Hz. The difference between the static and dynamic elastic moduli was greater in the more muscular carotid and femoral arteries than in the aorta. Surprisingly the viscous term remained virtually constant over the 2 to 20 Hz range. PATEL et al.[9] in their recent study of dog aorta considered the anisotropy of the tissue, but obtained results which did not deviate markedly from those of BERGEL. The attempts by PATEL et al. to fit their results to two different kinds of viscoelastic models of springs and dashpots were not particularly successful despite that also inversely frequency-dependant viscous elements were considered. 'In an 'orthodox' viscoelastic substance both $E_{dyn}$ and $\omega\eta$ rise steadily with frequency' (MCDONALD[1] p. 269).

Increased smooth muscle tone is generally considered to make the vascular wall 'more viscous'. BAUER and PASCH[8] who studied the small muscular rat tail artery found wider hysteresis loops when the vessel was contracted by noradrenaline than when it was relaxed by papaverin, but the $\omega\eta$ term which increased somewhat with frequency was found to be independent of smooth muscle tone. WIEDERHIELM[38] in his elegant study of microvascular distensibility points out that combinations of classical elastic and viscous elements do not adequately describe the influence of smooth muscle on vascular mechanics. He fitted his data to a different mathematical model which was based on the assumption that smooth muscle contraction could be described as a chemical reaction involving formation and breaking of bonds corresponding to a short and a long state. The model is entirely theoretical but it can possibly be reconciled with the physiological force-velocity relation of the smooth muscle (see further below).

*Stress relaxation* is one manifestation of viscosity in viscoelastic bodies and this phenomenon has been studied also in blood vessels at different levels of smooth muscle tone. Again, the time course of the events cannot be accounted for by simple models of springs and dash-pots but require more complex assumptions[1]. The decrease in force as a function of time does not follow any single exponential decay curve; instead it has often been reported that there is a linear relation between the fall in force and the logarithm of time e.g.[44]. (The kinetic implications of this dependence on log time are not at all clear to the present author. The only interpretation I have managed to come up with is the following: If you mount a piece of tissue in a bath and stretch it in order to study its stress relaxation, time seems to pass more slowly the longer you sit there watching the damned thing).

The length-tension diagrams discussed in connection with Figure 1 above reflect the steady-state situations in which the blood vessel can maintain a constant diameter when the smooth muscle is at rest (the passive curve) and when it is fully activated (the active curve). The rate at which a blood vessel with active tone can move from one steady state situation to another is largely determined by the *force-velocity relations* of the smooth muscle. The force-velocity relation shows how fast the muscle can shorten against

[41] N. L. BROWSE, R. R. LORENZ and J. T. SHEPHERD, Am. J. Physiol. *210*, 95 (1966).
[42] D. L. DAVIS and M. C. HAMMOND, Am. J. Physiol. *216*, 1292 (1969).
[43] B. ÖBERG, Acta physiol. scand. *71*, 233 (1967).
[44] M. ZATZMAN, R. W. STACY, J. RANDALL and A. EBERSTEIN, Am. J. Physiol. *177*, 299 (1954).

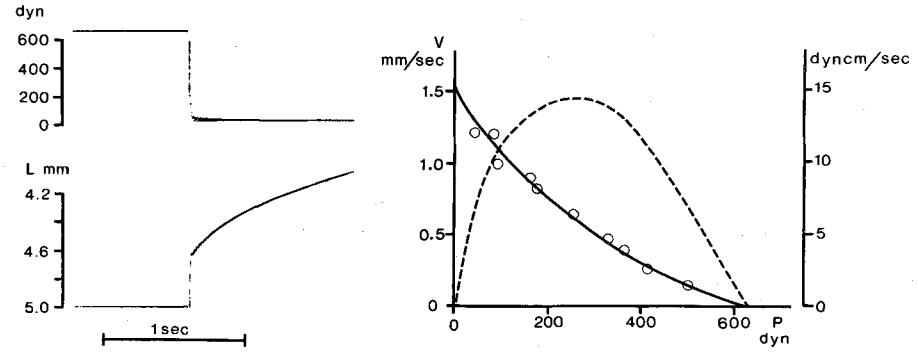


Fig. 2. Left panel shows original records of force and length at isotonic quick release of portal vein strip contracted by $K^+$ depolarization at low preload. The shortening response to the decrease in force occurs in two phases, the immediate series elastic recoil and the subsequent shortening of the contractile element. Right panel summarizes data (circles) for the early velocity of shortening of the contractile element at different loads. Full line is approximate force-velocity curve fitted to these data. Broken line refers to the right ordinate and represents the power output (mechanical work per unit time) corresponding to the force-velocity curve.

different loads and it therefore also reflects the power output (mechanical work per unit time) from the chemomechanical transduction process as a function of load. As will be indicated below it is not an easy matter to determine this relationship unequivocally by mechanical experiments on the smooth muscle. Let us start our analysis with a relatively simple case by considering a strip of vascular smooth muscle which from a negligibly low resting tension has developed an active and sustained isometric force in response to a supramaximal stimulus. The low preload permits us to disregard the parallel elastic element and to represent the muscle by the contractile and series elastic elements only. Moreover, the sustained isometric force is taken to indicate a constant (time independent) level of chemomechanical transduction in the contractile element which keeps the series elastic spring extended to a steady length. To study the ability of this muscle to shorten at the prevailing level of chemomechanical transduction we may perform a 'quick release' experiment which implies that the load on the muscle is suddenly reduced below the isometric force (Figure 2). The shortening which is then recorded occurs in two phases, an immediate one interpreted as a recoil in the series elastic element and a later, slower phase attributed to shortening of the contractile element. It is the rate of shortening in this second phase which reflects the power output from the contractile machine at the actual load. After letting the muscle return to its original isometric length and force we may repeat the quick release with different loads and thus obtain a whole set of points which together form the force-velocity curve. The shortening velocities are measured at a fixed, short interval (e.g. 100 msec) after the release.

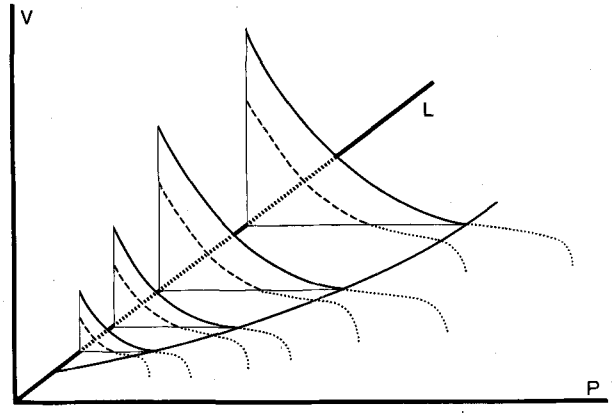


Fig. 3. Tentative three-dimensional diagram illustrating force-velocity curves of contractile element in vascular smooth muscle at different muscle lengths with maximal (full lines) and submaximal (broken lines) activation of the contractile machinery. Heavy line in the zero velocity plane represents the length-active force ($P_o$) relation at maximal contraction. Dotted lines below the zero velocity (or $PL$) plane illustrate the possible relations between force and lengthening velocity when the contracted muscle is stretched by forces greater than $P_o$.

It should be realized that the force-velocity curve illustrated in Figure 2 will only be representative of the mechanical output from the contractile element at its actual length and level of activation. Figure 1B showed that the isometric contractile force of the fully activated muscle depends on length. These active forces represent in fact the intercepts of the maximal force-velocity curves with the force axes and it is evident that these changes in $P_o$ with variations in length can lead to shifts of the entire force-velocity curve. Also, at any specified length of the contractile element a submaximal stimulus will elicit less isometric force than that obtained by full activation which again can imply a shift of the entire force-velocity relation. It is not known in detail whether the changes in isometric force will be associated with proportionate changes in the velocity at which the smooth muscle shortens against low loads. The problem has been considered in recent work on venous smooth muscle[45]. Figure 3 is a tentative illustration of how length, force and velocity of the contractile element may relate to one another in the rising part of the length-active tension curve (cf. Figure 1B). The diagram has been limited to this range where responses of the whole muscle can with some confidence be considered to reflect the events at the contractile element itself; at greater lengths where parallel elasticity cannot be

[45] P. HELLSTRAND and B. JOHANSSON, Acta physiol. scand. *93*, 157 (1975).

neglected the interpretation of quick release experiments becomes more complex. However, there is no reason why the general concept of the length-force-velocity relation indicated by Figure 3 should not apply to all lengths.

If the smooth muscle of a blood vessel maintains a constant length and force in a maximal isometric contraction and if the load is then decreasing, for instance through a fall in the intravascular pressure, the contractile element will move on the hyperboloid surface created by the maximal force-velocity curves in Figure 3 to reach a new equilibrium at a shorter length where isometric contractile force just balances the new load. Conversely if load increases above the initial isometric force due to increased transmural pressure the contractile element will lengthen, and the time course of this lengthening will be determined by the 'negative part of the force-velocity curves' (negative shortening velocities and loads $> P_o$). Again a new equilibrium of constant length and force can be reached, but it is evident that with large extensions an appreciable fraction of the additional load may be stored in the passive parallel elastic element rather than being carried by the contractile unit. Unfortunately the negative part of the force-velocity relation has not yet been studied in vascular smooth muscle, and, as mentioned earlier, it is not known in detail for other contractile systems either. It appears that this part is not just a simple continuation of the hyperbolic or exponential curve but deviates towards the force axis exept at loads which are so much greater than $P_o$ that the contractile process virtually breaks down and the muscle 'gives'[13,46]. A similar course has been indicated tentatively in Figure 3.

The force-velocity curves of vascular smooth muscle can be fitted to HILL's or AUBERT's equation suggesting that the chemomechanical transduction in this contractile system shares some of the principal features of that in skeletal muscle. From the quantitative point of view it appears that smooth muscle from different vessels varies with regard to its maximal rate of shortening at zero external load ($V_{max}$). In strips from pig carotid artery a $V_{max}$ of about 0.1 muscle length/sec was obtained[30] whereas rat portal vein showed values of 0.4 and 0.7 lengths/sec in tonic and phasic contractions, respectively[45,47]. LASZT[48] has reported $V_{max}$ data from a variety of arteries indicating that shortening velocity increases from around 0.1 length/sec in large central arteries to above 1 length/sec in small arteries. These differences in $V_{max}$ may be related to different internal loads which can resist shortening, or they may be due to true biochemical differences in the actomyosin system; comparison of a wide selection of muscles shows that a correlation exists between the maximal rate of shortening and the maximal ATPase activity of the isolated contractile proteins (for review see[49]). It may be appropriate to point out at this stage that quantitative data on the force-velocity relation ($V_{max}$ and values for the constants $a$ and $b$) should be judged with some caution in smooth muscle due to methodological differences between different studies. Direct measurements from afterloaded phasic contractions may yield curves which are incorrect because the different points can represent different lengths of the contractile element and different levels of activation. This methodological problem was illustrated in a recent study[45] where results from afterloaded contractions were compared with results from quick release experiments in phasic contractions of venous smooth muscle. In quick-release experiments it is essential to reduce the inertia of the lever to a minimum and it is often necessary to add a damping device[50].

The influence of neurohormonal control mechanisms and environmental physico-chemical factors on the force-velocity relation of vascular smooth muscle has not yet been studied to any great extent. Variations in temperature affect shortening velocity to a much greater degree than isometric force in the smooth muscle of portal vein[51], results which illustrate again a similarity between smooth and striated muscle. Contractures of portal vein in hyperosmolar solutions are associated with very low shortening velocities[52].

Our information on the force-velocity relation of vascular smooth muscle and its dependence on length and level of activation is still fragmentary, but there is little doubt that this characteristic feature of the chemomechanical-transduction must have a bearing on the dynamic responses of arteries and veins. The time course of stress relaxation in a contracted blood vessel reflects the adjustments of length in the series elastic and contractile elements where the latter 'moves' on the negative part of its force-velocity curves to reach a new steady state on the length-active force relation. Biophysicists and bioengineers who examine dynamic stress-strain relations in blood vessels subjected to sinusoidal oscillations or to other kinds of inflation-deflation cycles should keep the physiological force-velocity curve in mind. It must also be considered that stretch can act as a true stimulus for the vascular smooth muscle and that shortening can have an inhibitory effect[36,53,54].

[46] B. KATZ, J. physiol. Lond. *96*, 45 (1939).
[47] P. HELLSTRAND, B. JOHANSSON and A. RINGBERG, Acta physiol. scand. *84*, 528 (1972).
[48] L. LASZT, in *Physiology and Pharmacology of Vascular Neuroeffector Systems* (Karger, Basel 1971).
[49] J. C. RÜEGG, Physiol. Rev. *51*, 201 (1971).
[50] K. A. P. EDMAN and E. NILSSON, Acta physiol. scand. *85*, 488 (1972).
[51] U. PEIPER, R. LAVEN and M. EHL, Pflügers Arch. *356*, 33 (1975).
[52] C. ANDERSSON, P. HELLSTRAND, B. JOHANSSON and A. RINGBERG, Acta physiol. scand. *90*, 451 (1974).
[53] B. FOLKOW, Circulation Res. *15*, Suppl. 1, 279 (1964).
[54] H. V. SPARKS, Circulation Res. *15*, Suppl. 1, 254 (1964).

Moreover, in connection with sinusoidal oscillations it is worth noticing that vibrations of higher frequencies interfere directly with smooth muscle contractility[55]. It is evident that there are many physiological characteristics of vascular smooth muscle, both in its fundamental chemomechanical transducer machinery and in its cellular control system, which make the tissue so different from a passive viscoelastic substance that any simple model of springs and dash-pots is bound to fail. On the other hand, blood vessels may certainly contain elements with passive viscous characteristics and these would make our earlier mechanical tissue models more or less inadequate.

The pathway taken by the contractile element in the length-force-velocity space during a phasic contraction-relaxation cycle is determined by the load on the muscle and by the time course of the chemomechanical transduction (the active state), the latter in turn being determined by the temporal variations in intracellular [$Ca^{2+}$]. In a phasic contraction the contractile element may be visualized as starting from a resting length on the $L$ axis of Figure 3 and running through a continuous set of points on different force-velocity curves to reach a situation where external force equals the $P_o$ value of the instantaneous force-velocity curve. At this latter point, which would be the peak of the recorded response, contraction would end and relaxation start. Relaxation would then imply a return to the resting length via points on what we above have called the negative part of the force-velocity curves[56] (below the PL or zero velocity plane of Figure 3). In an isometric response the changes in length of the contractile element will be determined by the stiffness characteristics of the series-elastic element.

It may seem of little value to discuss the time-course of the active state in smooth muscles as their phasic contractions are notoriously variable due to the irregularities of the electrical membrane events. However, if the time course of the excitation process can be standardized by artificial electrical stimulation[57] or by other means[29], the time course of the mechanical events which follow is worth being studied in some detail. In the case of vascular smooth muscle, the results may tell us how fast a vessel can react with changes in caliber when external neurohormonal or local control factors change their influence. The time course of the active state in relation to electrical membrane activity and isometric force has been studied in phasic contractions of venous smooth muscle[29]. The results indicate that a short burst of action potentials can increase intracellular [$Ca^{2+}$] to levels which are supramaximal for contractile activation and that activator calcium is then eliminated by sequestration or extrusion at a half time of about 1 sec at 37 °C. Excitation was not synchronous in all parts of the preparation and the time course of the active state obtained in the study therefore does not exactly represent the events in the individual cell (see[45,56]).

With regard to the *in vivo circulation* it is evident that force-velocity curves and time-course of active state can have a bearing on the rate of change in vascular functions. For instance, it can be tempting to use the time course of variations in blood flow resistance in reactive or functional hyperemia to determine the rate of elimination of vasodilator metabolities from the interstitial space around the smooth muscle of the resistance vessels. Such calculations can be correct only if we may safely disregard as rate-limiting processes the intracellular events which are reflected in changes of active state and in subsequent adjustments of length and force according to the force-velocity relations. References cited in the foregoing sections may help to settle such problems of circulatory control.

*Zusammenfassung.* Die Beziehung zwischen passiven und aktiven Länge-Spannungsdiagrammen isolierter glatter Gefässmuskeln und Druck-Diameter- oder «stress-strain»-Kurven intakter Gefässe wird diskutiert. Diese Relationen werden auch mit Hinsicht auf statische, inkrementale Elastizitätsmodulen von dilatierten und konstringierten Gefässen behandelt. Der Beitrag solcher Ergebnisse bezüglich der stationären mechanischen Eigenschaften isolierter Gefässe zum Verständnis von verschiedenen Gefässfunktionen in vivo (Windkessel-, Resistanz- und Kapazitanzfunktion) wird kurz diskutiert. Die dynamischen Reaktionen der Gefässwand werden behandelt sowie mit Rücksicht auf Messungen der dynamischen Elastizitäts- und Viskositätsmodulen als auch mit Rücksicht auf neuere Untersuchungen über die Kraft-Geschwindigkeits-Relationen und den aktiven Zustand der glatten Gefässmuskulatur. Diese Information hat Bezug auf die Veränderungsrate verschiedener Gefässfunktionen in vivo.

[55] B. LJUNG and R. SIVERTSSON, Blood Vessels *12*, 38 (1975).
[56] B. JOHANSSON and P. HELLSTRAND, Acta physiol. scand. *93*, 167 (1975).
[57] A. R. GORDON and M. J. SIEGMAN, Am. J. Physiol. *221*, 1250 (1971).