J. Physiol. (1960), **153**, *pp.* 290–305
With 9 text-figures
Printed in Great Britain

THE MEASUREMENT OF TENSION IN VASCULAR SMOOTH MUSCLE

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(*Received* 3 *February* 1960)

An aim of physiological research is to establish quantitative relations between physiological 'responses' and the amount of 'stimulus' that elicited them, as in terms of the concentration of a drug administered. The experimental results are most concisely and completely described, in many cases, by an equation. This may be purely empirical. When the results are examined, it may be that a logarithmic relation or a rectangular hyperbola gives a reasonable fit over the range of the variables used in the experiments. Such an empirical equation is useful over that range, for prediction of the magnitude of response from the intensity of stimulus. A familiar example is the pharmacologists' relation, found to hold over a very limited range, between logarithm of 'dose', and 'response' (Gaddum, 1953). The usefulness of such empirical equations is limited, and we cannot hope to interpret their mathematical form in terms of basic mechanisms of the response, unless that particular mathematical form is the result of some basic hypothesis, and of analysis of behaviour of a 'model' operating on this hypothesis. Since there are usually many different forms of mathematical relation that might fit the data equally well over the range, it becomes important to choose, from among these, one which might be consistent with some such hypothesis and model.

For this process to be useful, the particular response measured should obviously be 'primary' to the hypothesis and to its application to model behaviour.

An example may make this clear. Where vasomotor effects of pressor drugs are concerned, the 'primary response' might be considered to be the tension developed by the smooth muscle of the vessel wall when a given concentration of drug is presented to the 'receptor substance' of that muscle. The tension could be related to the concentration of the drug by an equation based on some plausible theory, e.g. of reversible formation of an activated complex between drug and receptor substance. The index of response measured, however, would usually be the change in resistance to

flow of a vascular bed, when a given concentration of the drug was present in the perfusate. There are three ways in which such data have been obtained. (*a*) by using perfusion at constant pressure, of an isolated vascular bed, and measurement of the decrease in flow when the perfusate contains a pressor substance in a known concentration; (*b*) by using one of the constant-flow pumps now available, again with an isolated preparation, and measuring the increase in 'driving pressure', from artery to vein, when the pressor agent is present; or (*c*) in the 'intact' circulation of an animal, where neither driving pressure nor flow are constant when the pressor agent is given.

The results of all three methods can be expressed in common terms as the change in resistance to flow (i.e. in the ratio of driving pressure to flow). As demonstrated in this paper, however, the relations between the response, in terms of change of resistance, and concentration of the drug, e.g. adrenaline, found by these three methods of experiment, will be completely different.

Figure 1, which anticipates results obtained by the methods described later in the paper, illustrates this difficulty. The data were obtained by measuring the increase in resistance to flow in the vascular bed of an isolated rabbit's ear at constant flow, repeated at several different values of that flow. Figure 1*A* shows flow–pressure curves for given concentrations of the drug. These curves closely resemble previous results obtained in this laboratory by a variety of methods (Nichol, Girling, Jerrard, Claxton & Burton, 1951; Girling, 1952). This graph contains all the data, from which we can deduce also the change of resistance that would have been measured if constant-pressure determinations had been used, instead of constant flow. Figure 1*B* shows, from the same data, the change in resistance versus concentration of drug plotted for constant pressure of perfusion, Fig. 1*C* for constant flow. Three different levels of flow and of pressure were chosen to derive these curves from Fig. 1*A* (e.g. broken lines on Fig. 1*A*). It is seen that the shapes of the resistance–concentration curves are quite different according to the method used to analyse the data. Indeed, Fig. 1*B* suggests that the response to adrenaline increases more and more as the concentration is increased, while Fig. 1*C* might suggest, for higher rates of flow, that the response was proportional to concentration. Actually, as verified in subsequent work with higher concentrations, the response eventually reaches a 'saturation' value.

Obviously we could not base the verification of any kinetic theory of action of the drug on the results of either method of experimentation, without proving which, if either, of the methods, i.e. constant-pressure or constant-flow perfusion, was related directly to the tension of the muscle. The factor that makes the curves of Figs. 1*B* and 1*C* so different is, of

course, the distensibility of the blood vessels. When constant-pressure perfusion is used, the increasing tension with higher concentrations of drug eventually causes 'critical closure' of the vessels (Burton, 1951). With constant flow, closure can never occur, since when increasing concentrations of the drug increase the tension the perfusion pressure and thus the 'transmural pressure' of the vessels also increases. This distends the vessels passively, and partially offsets the constrictive effect of the increase in

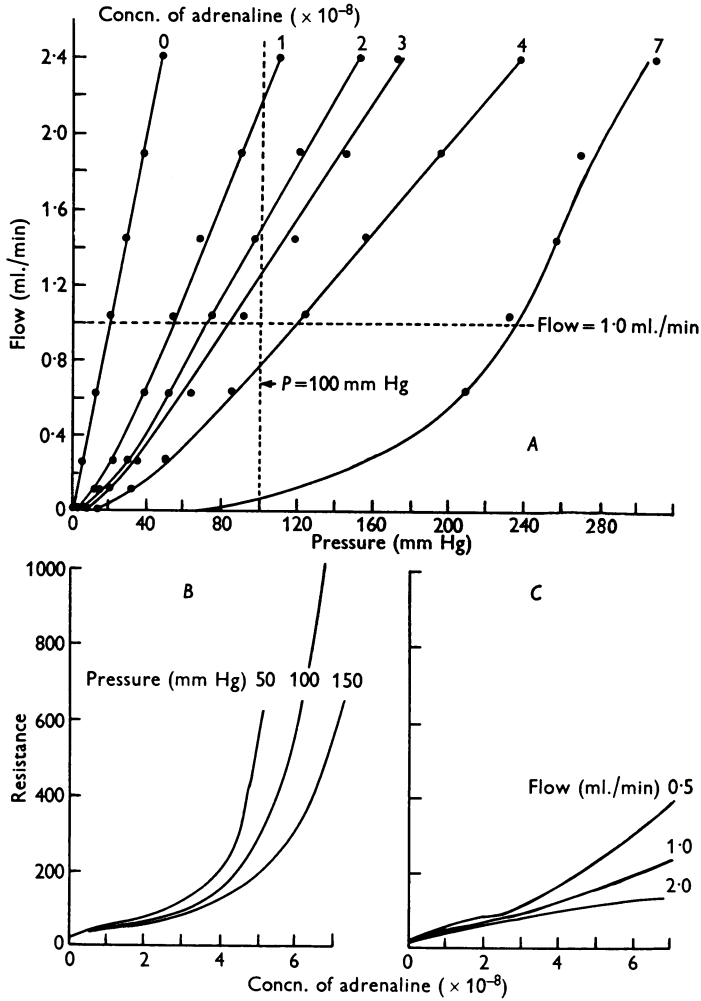

Fig. 1. *A*. Flow–pressure curves for an isolated rabbit ear, perfused with different concentrations of adrenaline. A series of values of constant flow was used.

B. Resistance to flow versus concentration of adrenaline, derived from *A*, at three different values of constant driving pressure.

C. The same for three different values of constant flow.

tension. This consideration suggested a possible method of measuring the 'active tension' of the muscle directly, in which the passive distension would be made to compensate completely for the active constriction.

Theory of a method of measuring tension of the vascular smooth muscle

To simplify the discussion we have replaced the vascular bed of the ear by a single equivalent vessel which would give the actual total resistance to flow (Fig. 2). The total tension in the wall (T), must be related to the

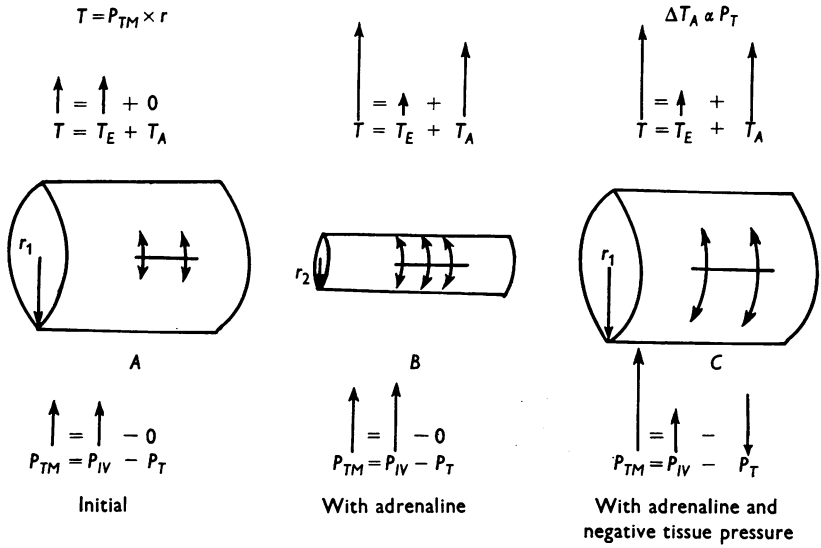

Fig. 2. To illustrate the theory of the 'null method' for measuring active tension in the vessel wall.

'transmural pressure' (P_{TM}), which is the intravascular pressure P_{IV} minus the tissue pressure P_T, by the law of Laplace (*ca.* 1806), $T = P_{TM} \times r$, where r is the radius of the equivalent vessel (Burton, 1951). The total tension T can be considered as the sum of two tensions: the 'elastic tension', T_E, which depends on the degree of stretch of the wall, plus the 'active tension', T_A, due to contraction of the smooth muscle.

By our definition, 'active tension' is independent of the degree of stretch of the wall. Vascular smooth muscle, the contraction of which supplies the 'active tension', also possesses 'elasticity', i.e. change of tension with stretch, but its contribution in this respect can be included under the 'elastic tension', most of which is probably due to the other elements of the wall (Burton, 1954). Thus the division into 'active' and 'elastic' tensions is 'functional' and convenient, and not on an anatomical basis, nor does it involve any approximation. Without the presence of the vasoactive drug,

T_A may be considered to be zero, as in Fig. 2*A* (the result does not depend on this assumption).

When the drug is present in a given concentration, the active tension increases, and the vessel contracts, as in Fig. 2*B*. The total tension has increased. However, the increase in active tension T_A has been partially offset by a decrease in the elastic tension, T_E, due to the reduction in stretch of the wall. Thus the change in total tension cannot be used as an index of the primary response, i.e. of the active tension, unless the details of the concomitant decrease in the elastic tension are known. This would involve knowing the details of the distensibility curves of the resistance vessels.

However, if the vessel can be made to return to its original radius in the presence of the pressor drug, then the elastic tension will also return to its original value (Fig. 2*C*). It is possible that this assumption may not be correct, for there is evidence that the contraction of the smooth muscle may 'tighten up' the elastic fibres of the wall (see Appendix) so that even though the radius is the same as before, the elastic tension may be greater. Making this assumption is the best that can be done. The increase in total tension will now equal the change in active tension induced by the drug, i.e. $\Delta T = \Delta T_A$. Since the radius of the vessel depends on the transmural pressure, P_{TM}, which is the difference between intravascular and tissue pressure ($P_{TM} = P_{IV} - P_T$), the vessel may be distended to its original size by decreasing the tissue pressure, i.e. by lowering the pressure in a box in which the rabbit's ear is placed (Fig. 3). If a 'negative pressure' sufficient to reduce the driving pressure to its original pressure be found, and the flow is constant, the resistance to flow must be once more at its original value. Since the resistance to flow depends on the radius of the vessel, this must also be at its original value, as was desired (except for the reservation below).

The law of Laplace is

$$T = P_{TM} \times r.$$

If r has been kept constant by the procedure above, then

$$\Delta T_A = \Delta T = \Delta P_{TM} \times r,$$

and since the intravascular pressure will be the same as before

$$\Delta P_{TM} = -\Delta P_T.$$

Thus, in this 'null method',

$$\Delta T_A = -r(\Delta P_T).$$

Since the parameter r in this null method is a constant, the negative tissue pressure required to reach the null point will therefore be a measure of the active tension produced by the drug in the vascular smooth muscle.

This analysis is, of course, based on a 'lumped parameter', the 'single equivalent vessel', and in the real situation several categories of vessel contribute to the total resistance to flow. Since distensibilities of different categories of vessel are not the same, the final situation when negative tissue pressure is applied might give the same total resistance, yet the arterioles might not be exactly at their original radii, because other vessels contributing to the resistance were now distended. This statistical consideration is a valid criticism of the method, but the method is the best that can be devised. The error is unlikely to be great, since there is abundant evidence, from calculations based on the sizes of vessels, and from the pressure gradients down the line of resistances in vascular beds, that one category of vessels, the arterioles, contributes by far the greatest part of the total resistance (probably at least 70%), especially when there is vasomotor tone.

The null method, which employs negative tissue pressure, is not very convenient, and cannot be used for long periods of time, e.g. to establish a large number of tension–concentration relations, because oedema of the ear occurs quite rapidly as a result of the increased capillary transmural pressures. However, this method provides a means of testing measures more easily available, such as the increase of resistance produced by the drug when either constant-pressure or constant-flow perfusion is used, as to their relation to the active tension. Fortunately it turns out that the rise of resistance, at constant flow, is an excellent measure of active tension.

METHODS

Rabbits, weighing 1·8–3 kg, were anaesthetized with urethane (7·5 ml./kg of a 20% solution, intraperitoneally). Heparin (2 mg) was injected intravenously. The central and the major peripheral veins of the ear were first cannulated with polyethylene tubes and then the central artery near the root of the ear. The blood was forced out of the ear by a syringe, and the ear was then cut off. In the 'null method' it was essential that venous outflow, other than through the cannulae, should be occluded, since otherwise the effective venous pressure might be indeterminate. A paraffin-wax plug was poured into the auricular cavity at the root of the ear, and a tight ligature was tied over the skin, holding it against this plug. A coat of collodion was also applied to seal off any seepage of blood. In spite of these precautions, leaking sometimes occurred when high concentrations of adrenaline were used, necessitating very high values of the negative pressure to reach the null point. Leakage was easily detected, and where it occurred the data were rejected.

All the plastic tubes of the cannulae, arterial and venous, were led through a glass tube in a rubber stopper in the wall of the chamber. The venous cannulae drained into a test-tube, to preserve a constant level of venous pressure. The artery was connected through a constant-flow pump (sigmamotor) to a funnel containing a known volume of buffered Ringer's solution, at pH 7·4. This solution was prepared by mixing two stock solutions which were stored at 4° C until required. One part of a solution of $CaCl_2$ (2·16 g/l.) was added to 8 parts of a solution of 76·5 g NaCl, 3·78 g KCl, 4·50 g anhydrous Na_2HPO_4, and 1·5 to 2·5 ml. M-H_3PO_4 to pH 7·4 in 8 l. of water.

The total volume of fluid in the system could be reduced to less than 5 ml. of which only 0·1–0·2 ml. was in the vessels of the ear. The pump delivers a pulsatile flow, the mean value of which is accurately known from the calibration of a continuously variable gear on its motor. The output is completely independent of the resistance to flow into which it pumps.

The driving pressure was measured by a strain-gauge electromanometer (Statham) connected to the arterial cannula and was recorded on an ink-writing recorder (Varian).

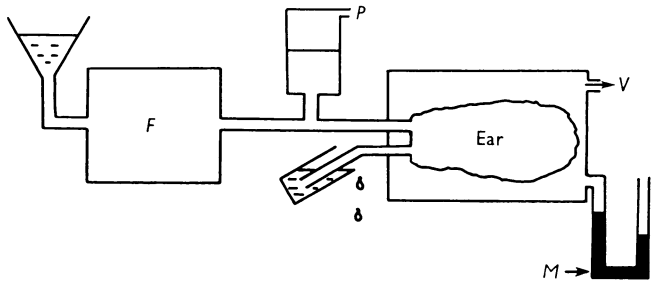

Fig. 3. Diagram of apparatus used in the null method. *F*, constant-flow pump; *M*, manometer showing negative tissue pressure; *P*, pressure transducer for driving pressure; *V*, vacuum pump.

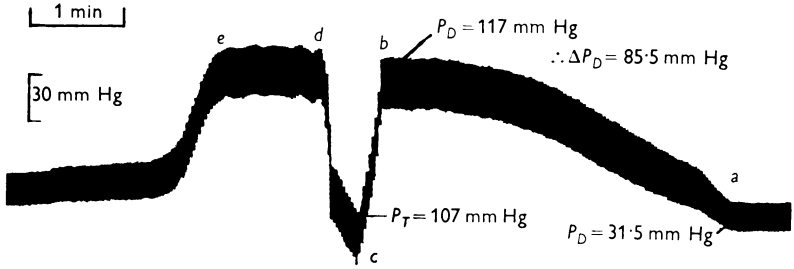

Fig. 4. Record obtained by the 'null method'. For explanation, see text.

Solutions of fresh adrenaline (Parke, Davis and Co; epinephrine hydrochloride solution C.S.D. 1/100) were made up in concentrated form (1 in 10^5 or 1 in 10^6) at pH 4·0, in which the *in vitro* oxidation is inhibited. Small volumes of these solutions were added to the funnel of Ringer's solution, which was quickly stirred to give the various concentrations of drug desired. It was found early in the research that the addition of as little as 1 part in 200 of blood or plasma (or of a 0·8 mg % glutathione solution) to the perfusate removed any evidence of *in vitro* oxidation of the drug during its passage through the ear, and made the concentration–response curves much more consistent, as well as increasing the responsiveness.

As has been general experience, the isolated ears, perfused by cold Ringer's solution, were responsive to concentrations of adrenaline as low as 10^{-9} g/ml. Oxygenation of the perfusing solution by bubbling O_2 in the funnel made no appreciable difference to this responsiveness. There was very little change in responsiveness in the 1–2 hr period of an experiment.

Operation of the 'null method' for measuring the tension

Figure 4 is a typical record from an experiment at a constant flow of 2·5 ml./min. At the point marked '*a*', the reservoir funnel was emptied and the solution was replaced by Ringer's solution containing a concentration of 2×10^{-8} of adrenaline. When the subsequent

rise of pressure reached a steady level, at point '*b*', the pressure in the chamber was reduced (by a vacuum pump) until the driving pressure was below the original value, point '*c*'. As soon as the box pressure was lowered the venous outflow ceased, and some fluid from the outflow test-tube was observed to flow back into the ear to fill the distended vessels. For up to 30 sec, the record of driving pressure showed a rise as the new steady state of flow was reached. Air was then allowed to leak into the chamber until the mean driving pressure

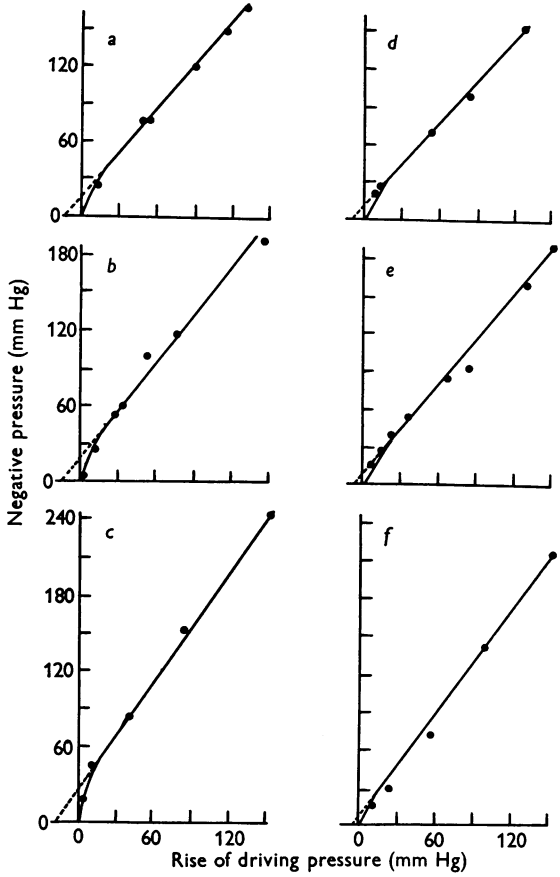

Fig. 5. Relation of negative pressure in the chamber to rise of driving pressure at constant flow for six different ears.

reached its original value. The pressure in the chamber was rapidly returned to atmospheric, and the driving pressure rose to the original value (point '*d*'). Finally (point '*e*') the solution in the funnel was replaced by fresh Ringer's solution, and the driving pressure returned to its original value. The measurements of the records, and of a mercury manometer attached to the chamber, gave the simultaneous values of the rises of driving pressure P_D at constant flow, and of the increased transmural pressure (the negative pressure in the chamber) required to bring the vessels back to their original resistance.

RESULTS

The graphs of the negative tissue pressure, for the 'null' point, proportional by the theory to the tension of the smooth muscle, versus the rise in driving pressure for six different ears, are shown in Fig. 5. Graphs *a*, *b*, *c* and *d* are at the same constant-flow rate; *e* and *f* are at two other rates of flow. It may be seen that if the drug produces rises of pressure of

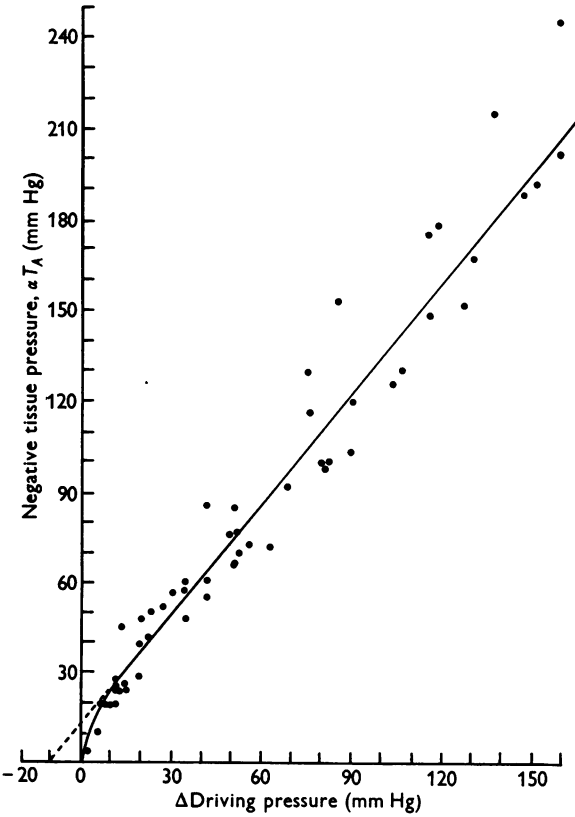

Fig. 6. Results for ten different ears, each at a constant flow of 2·52 ml./min. The coefficient of linear correlation for abscissae greater than 20 mm Hg is 0·96. $-P_T = 1{\cdot}26P_D + 12$, $\therefore T_A \propto (\Delta P_D + 10)$ for $\Delta P_D > 20$.

more than 20 mm Hg the relation is remarkably linear. The straight line, when extrapolated, has an intercept of about minus 10 mm Hg, for the flow rate of 2·5 ml./min. In this range, therefore, the tension of the smooth muscle is accurately proportional to the rise of arterial pressure plus a small constant added pressure (10 mm Hg in this case). In the case of the other rates of flow used, the added constant is less, and could be neglected.

The results of many experiments at the intermediate flow rate of 2·5 ml./min on ten different ears are shown on a scatter graph in Fig. 6. The linearity for pressure rises of more than 20 mm Hg is evident even when many ears are included. The coefficient of correlation was 0·96 (37 degrees of freedom). Similar scatter graphs were made for flow rates of 1·72 and 3·50 ml./min. The coefficients of correlation were again very high, 0·98 (16 degrees of freedom) and 0·97 (14 degrees of freedom) respectively. The slope of the regression line for the flow rate of 1·72 ml./min was significantly different from that of the data at a flow rate of 2·52 ml./min, and in the case of the highest and lowest flow rates the intercepts of the regression lines on the pressure axis were between 0 and -5 mm Hg, which would be negligible for practical purposes.

DISCUSSION

It is evident that when the method of perfusion at constant flow is used, the increase in driving pressure (or in the proportional resistance to flow) is a very good measure of the increase in 'active tension' of the vascular smooth muscle when a given concentration of adrenaline is present in the perfusate. There is very little error in assuming strict proportionality between the rise in driving pressure and the active tension. Greater accuracy for the flow rate of 2·5 ml./min used in the majority of the experiments is achieved by adding a constant 10 mm Hg to the observed increase of pressure, for pressure increases greater than 20 mm Hg. Proportionately less should be added for increases of less than 20 mm Hg, say 3 mm Hg for ΔP_D between 0 and 10 mm Hg, and 7 mm Hg for ΔP_D between 10 and 20 mm Hg. For the two other flow rates (1·72 and 3·50 ml./min) no correction is necessary.

Since the concentration–response curves when the experiments are made with constant perfusion pressure, rather than with constant flow, are completely different, it is obvious that the constant-pressure method offers no possibility of measuring the 'primary response'.

The linearity of the relation with 'active tension' in the constant-flow method is not to be thought of as arising from any simple basic relations, but as an 'accidental' result of many factors concerned with the vascular resistance. The degree of distensibility (change of radius with transmural pressure) is one of these factors, the fourth power relation between radius of vessel and viscous resistance is another, and mathematical analysis (see Appendix) indicates that a decrease in distensibility when the smooth muscle contracts is also involved. It should be emphasized, therefore, that this fortunate linearity in the case of the rabbit's ear, at the rates of flow employed, must not be taken as an indication that a similar linearity

would exist in other vascular beds under different circumstances of pressure and flow. A generalization that the method of constant flow would be more likely to give such linearity than the more common method of perfusion at constant pressure would, however, be justified. The mathematical analysis given in the appendix encourages the hope that approximate linearity would be found in other vascular beds.

SUMMARY

1. The need is pointed out for a method of measuring the 'active tension' of vascular smooth muscle in response to a given concentration of a pressor drug, or to nervous stimulation, if interpretation in terms of kinetics of drug action is to proceed.

2. It has been shown that if the 'response' is measured by a change of resistance to flow of the vascular bed, the relation between response and concentration of adrenaline is quite different if constant-pressure perfusion is used, from the results with perfusion at constant flow.

3. A 'null method' for measuring the 'active tension' directly has been devised, based on a 'lumped parameter' theory of a single equivalent vessel having the same resistance to flow as the vascular bed.

4. When the results of this 'null method' are compared with the rise in driving pressure obtained under constant flow, in a range of concentrations of adrenaline from threshold concentrations to those giving maximal response, it is found that the relation is linear for all but the smallest responses (increases in driving pressure of less than 20 mm Hg). In contrast, the changes of resistance observed when constant perfusion pressure is used are not at all linearly related to the active tension.

5. It is concluded that for the rabbit ear preparation the measurement of responses to adrenaline as increases of driving pressure, or of resistance, at constant flow should permit interpretation in terms of basic theories of action of the drug on the smooth muscle.

The work was made possible by the granting of leave of absence to one of us (R.H.S.) from Ontario Agricultural College, Department of Physics. We are grateful to Mrs D. Elston for technical assistance. This research was supported by a grant of the Medical Division of the National Research Council of Canada.

APPENDIX

Theory of constant pressure and of constant flow perfusion

The concept of a 'single equivalent resistance vessel' is used, as already explained in the text. The total tension, T, per centimetre length of vessel, is given by

$$T = T_E + T_A, \tag{1}$$

in which the 'elastic tension', T_E, is a function of the radius of the vessel (Fig. 7); i.e.

$$T_A = T - f(r). \tag{2}$$

For the total tension T we have the law of Laplace,

$$T = P_{TM} \times r, \tag{3}$$

where P_{TM} is the transmural pressure of the single equivalent vessel.

It is easily shown that if the use of the 'single equivalent vessel' is justified, i.e. most of the total resistance to flow resides in one set of vessels (the arterioles), then the mean intravascular pressure at the single equivalent vessel must be midway between arterial and venous pressures. If venous pressure be taken as zero, then

$$P_{TM} = P_D/2, \tag{4}$$

where P_D is the 'driving pressure', arterial minus venous pressure. By substitution, equation (2) becomes

$$T_A = \frac{P_D \cdot r}{2} - f(r). \tag{5}$$

Equation (5) applies whether constant-pressure or constant-flow methods of perfusion are employed.

Perfusion at constant driving pressure

Here P_D is constant in equation (5). A graphical solution of the equation has been given elsewhere (Burton, 1951), and is repeated in Fig. 7*A*. The curve represents the rise of elastic tension with increase of the radius r of the vessel, beyond its unstretched radius r_0. The straight line (Laplacian line) through the origin, with slope equal to $P_D/2$, represents the total tension that must be present if the law of Laplace is to be obeyed. The intersection at point A represents the radius and elastic tension of the vessel when it is in equilibrium under elastic tension only, without any vasomotor tone ($T_A = 0$). Suppose that under vasomotor tone the vessel contracts to radius r', then the new total tension is represented by the vertical distance BD. Of this, CD represents the now reduced elastic tension. The remainder, BC, must represent the active tension T_A required to reduce the radius from r to r'. On the basis of this diagram the possibility of 'critical closure' was predicted, since when the intercept BC has reached its maximum value ($B'C'$), at a value of r close to r_0, no greater active tension than this will be required to cause complete closure of the vessel, unless new forces intervene.

Elastic diagrams of blood vessels (Roach & Burton, 1957) are such that at a moderate degree of stretch beyond the 'unstretched radius' r_0, the

line of elastic tension reaches its maximum slope, since all the collagenous fibres in the wall are now being stretched. Except for the lowest values of active tension and of transmural pressure, therefore, we may use an approximation for $f(r)$,

$$f(r) = k(r-r_0), \tag{6}$$

where k is the maximum elastic modulus of the wall. Substituting this in equation (5) yields

$$T_A = kr_0-(k-P_D/2)r,$$

$$\therefore \quad r = \frac{kr_0-T_A}{k-P_D/2} \tag{7}$$

(k must be greater at $P_D/2$, as inspection of the diagram will show; otherwise there will be no intersection, indicating 'blow-out' of the vessel under too high a pressure).

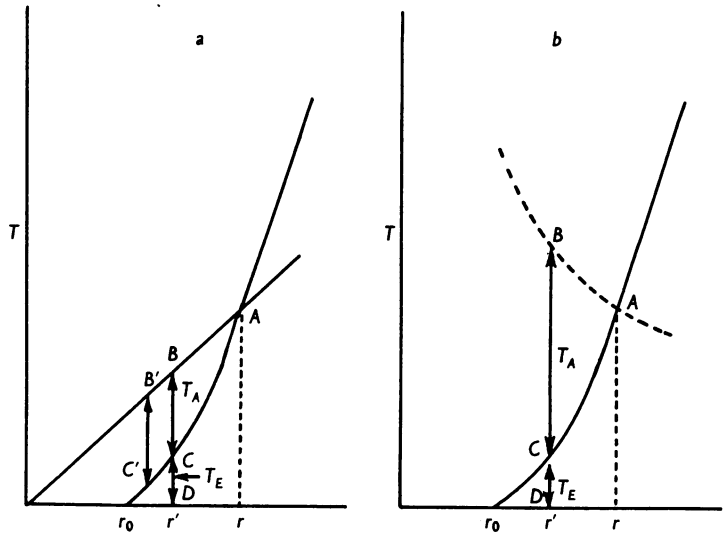

Fig. 7. Illustrating the equilibrium of the single equivalent resistance vessel. *a*, with perfusion at constant pressure; *b*, with perfusion at constant flow.

We may deduce how the resistance to flow will depend on the active tension, T_A, by using the Poiseuille–Hagen formula,

$$R = \alpha r^{-4}, \quad \text{where} \quad \alpha = \frac{8\eta l}{\pi}. \tag{8}$$

Finally,

$$R = \frac{\alpha(k-P_D/2)^4}{(kr_0-T_A)^4}. \tag{9}$$

Equation (9) predicts a very accelerated rate of increase of resistance as T_A increases, because the fourth power is involved, until finally, when

$T_A = P_D/2 \times r_0$, the point of critical closure is reached. Such a very curvilinear relation between resistance and concentration of adrenaline (related to T_A) was found experimentally (Fig. 1*B*) when constant-pressure perfusion was used.

Perfusion at constant flow

Equation (5) applies, but P_D is no longer constant. Instead,

$$P_D = F \times R = \alpha F r^{-4}, \tag{10}$$

where F is the constant-flow rate. Substituting in equation (5),

$$T_A = \frac{\alpha F}{2} r^{-3} - f(r). \tag{11}$$

The solution of equation (11) is represented graphically in Fig. 7*B*, where the broken line represents the first term (in r^{-3}). The intercept BC is now much greater than in Fig. 7*a*, i.e. much more active tension is required to reduce the radius of the vessel. This is, of course, because of the compensatory rise of transmural pressure that occurs in the constant-flow method. There is now no maximum value of the intercept $B'C'$ (as in Fig. 7*a*), and so no possibility of 'critical closure'.

Again we may use the approximation for $f(r)$, equation (6), and find

$$T_A = kr_0 + \frac{\alpha^{\frac{1}{4}} F R^{\frac{3}{4}}}{2} - k\alpha^{-\frac{1}{4}} R^{-\frac{1}{4}}. \tag{12}$$

How can this equation represent an almost linear relation, except for very small values of T_A, between T_A and the resistance R? (The driving pressure P_D plotted in Fig. 5 is proportional to the resistance R if the flow is constant.) In a plot of T_A versus R, the term $R^{\frac{3}{4}}$ will give a relatively slight curvature towards the axis of R over the whole range. The term in $R^{-\frac{1}{4}}$, which is smaller, decreases rapidly as R is increased. Subtraction of this term from the other will tend to straighten the line, over the range in which the term is not negligible. To illustrate this, numerical calculation has been made of the function

$$y = nR^{\frac{3}{4}} - R^{\frac{1}{4}}$$

with n having values of 1, 2, 3 and 4 (Fig. 8).

The working range of the experiments at constant flow corresponds to an increase of the resistance of, at the most, five times, as the maximal effect of adrenaline is reached before this. The linearity and correspondence to the experimental curves is moderately good. There is, however, evidence of a further factor that makes the linearity more marked. This is the evidence that when there is vasomotor tone the value of k increases.

The sigmamotor pump supplies a constant fluctuation in volume flow, which is shown by the fluctuation in driving pressure on the records, i.e. the 'pulse pressure'. The records by the 'null method' for the active tension (e.g. Fig. 4) show that, even when the vessels are brought back to their original size, the pulse pressure increases with the concentration of adrenaline. This indicates an increase in the elastic modulus, k, brought about by the 'tightening-up' of the 'slack' in the collagenous fibres when

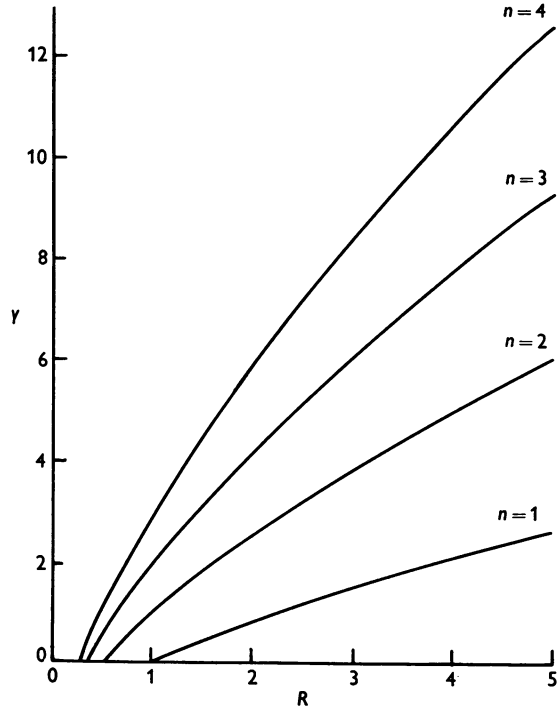

Fig. 8. Plot of the function $y = nR^{\frac{1}{2}} - R^{-\frac{1}{2}}$ for values of n of 1, 2, 3 and 4.

the smooth muscle contracts. There is an increase in pulse pressure to about twice its original value as the resistance increases three times (Fig. 9B). We therefore corrected the numerical calculation to

$$y = nR^{\frac{1}{2}} - f(R^{-\frac{1}{2}}),$$

where f increased from 0·5 to 1·0, as indicated in Fig. 9A. The result is a marked straightening of the line, except for the lowest values of T_A. It now resembles the experimentally determined curves of Fig. 5 very closely indeed.

It is concluded, therefore, that the remarkable linear relation found experimentally, with perfusion at constant flow, is consistent with the

theory, and that the same theory predicts that the method of perfusion at constant driving pressure would give no such convenient linear relation between active tension and response. While it is not at all conclusive, the theory does offer hope that other vascular beds than that of the isolated rabbit's ear might obey similar linear relations if the method of constant flow were employed.

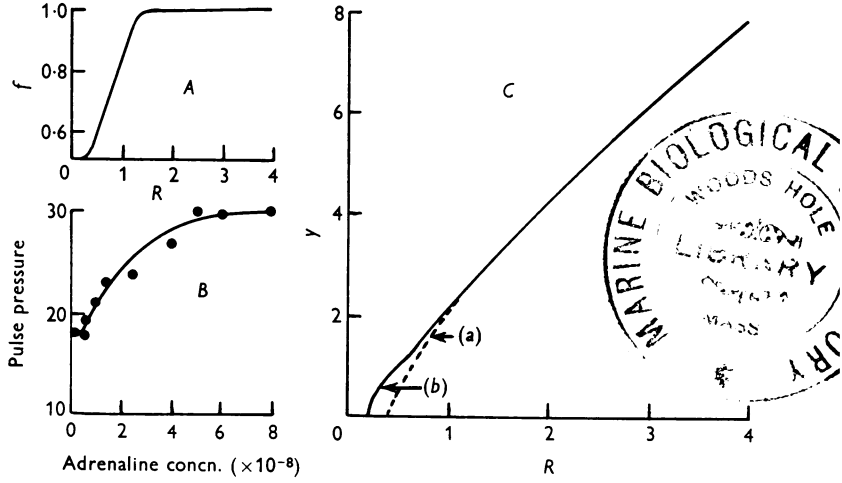

Fig. 9. *A*. Assumed variation of the factor f in the relation $y = nR^{\frac{1}{2}} - fR^{-\frac{1}{2}}$. *B*. Experimental results for pulse pressure versus concentration of adrenaline. The pulse pressure was measured at the 'null point', i.e. with the single equivalent vessel at the same size. *C*. Application of the correcting factor f to the curve of Fig. 8 ($n = 3$). (*a*) broken line, uncorrected ($y = 3R^{\frac{1}{2}} - R^{-\frac{1}{2}}$; (*b*) solid line, corrected, ($y = 3R^{\frac{1}{2}} - fR^{-\frac{1}{2}}$).

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