Fundamental Instability of the Small Blood Vessels and Critical Closing Pressures in Vascular Beds*

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It was shown in a previous paper (1) that the application of the physical law of Laplace \( P = \frac{T}{R} \) to the blood vessels predicts that under vasomotor tone they can have only a limited stability, so that gradation of their constriction is possible only over a certain range of diameters of the vessels. If the tension in the wall of a blood vessel increases above a critical value (given by Laplace's law), there must be an abrupt and complete closure of the vessel. The relation between the tension in the wall \( T_c \), the pressure in the vessel \( P_c \) and the ‘unstretched radius \( R_o \) of the vessel’ (at which there is no elastic tension) at the critical point, is approximately:

\[
P_c = \frac{T_c}{R_o}
\]

According to this prediction, it is in the very small vessels, in the walls of which considerable tension can be developed by reason of the smooth muscle coats, that this ‘critical closure’ will occur at relatively high pressures. Obviously the arterioles would appear to be the vessels where evidence of this fundamental instability should be sought.

Verification of these predictions has been made following two main lines of investigation: a) Direct observation, with microphotography, has been made on the living small vessels of the mesentery of the frog, while these were perfused under decreasing pressure, so that evidence of closure when the pressure reached a critically low level could be obtained. b) Evidence of closure of small vessels has been sought by the less direct method of measuring the resistance to flow, i.e. the ratio of pressure gradient to the flow that results, as the pressure is reduced. This has been done in the perfused hind limb of the frog, the isolated perfused ear of the rabbit, and the

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* While this paper was in press, our attention was drawn to a series of papers by Gomez and co-workers, which seem to supply confirmatory evidence. Their “static pressure” would appear to coincide with the “critical closing pressure,” though the theoretical approach is very different and the closure of vessels is not specifically discussed. In humans they find a “normal static pressure” between 6 and 8 mm Hg which would agree with our “residual critical closing pressure.” References:


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'Intact' hind limb of the rabbit. Flow pressure curves have been obtained down to the point where the flow becomes zero. The existence of a critical closing pressure is demonstrated if the flow becomes zero while there is still a positive head of perfusion pressure, and the critical closing pressure is measured by the pressure head at this point (since with no flow the pressure will be the same throughout the patent vessels without any drop of pressure 'down the line').

In this paper, only those experimental results will be discussed which, in our opinion, demonstrate the existence of 'critical closure' and discount the possibility of explaining the cessation of flow on other grounds than this (as for instance in terms of 'plastic flow' or blockage of the vessels by thrombi). Once the fundamental phenomena and their interpretation are established, the measurement of critical closing pressures offers a new tool for the study of vasomotor tone. Its systematic use for this purpose will be reported in separate, more intensive papers.

While the fundamental prediction from the physical law might be expected to be verified, it was not certain that critical pressures that actually existed would be sufficiently high in comparison to the available blood pressure to be of any physiological importance. We were therefore anxious to determine how high critical pressures might be under conditions of great vasomotor tone.

METHODS

Direct Microscopic Observation. This has so far been confined to the vessels of the mesentery of the frog. Arterial cannulation of the mesenteric artery was made by a cannula constructed from a no. 24 hypodermic needle. As soon as it was completed, flow was maintained by perfusion from a bottle placed at appropriate heights. Ringer's solution buffered to pH 7.4 (phosphate buffer) with 3 per cent gum acacia was routinely used. Evans blue was sometimes added to increase contrast in the wall of the vessels for microphotography. The microscope was fitted with a demonstration eyepiece so that the vessels under observation could be kept in focus and photographed at any time. The magnification most used was 64 diameters. The image of an eyepiece scale, with graduations effectively 7.4 μ apart, appeared on each photograph. Diameters of vessels were measured by projection from the negatives onto paper and tracing of the vessel walls. Great care was taken to observe the directions of flow in the various vessels and to note any cessation or reversal of flow as the pressure of perfusion was lowered. Statistical evaluation of the measurements of diameters was made possible by taking 6 photographs at each pressure 15 seconds apart. Each final diameter was the average of a number of diameters measured at equal distances along a given segment of blood vessel in the field.

Measurements of Resistance to Flow. The perfusion of the isolated hind limb of the frog has been often described. The classical Trendelenburg preparation was used. The isolated rabbit ear perfusion is also well known. In both cases as soon as the arterial cannulation by a modified hypodermic needle was complete, blood was expelled by forcing through Ringer's solution with a syringe and continuous perfusion then maintained from a bottle mounted on a vertical stand so that it could be set at different levels above the blood vessels. It was found that it was not necessary to use rabbit serum in the case of the ear, since this would remain normally responsive.
to adrenaline for as long as 8 hours when perfused merely with buffered mammalian Ringer's solution at room temperature. No special oxygenation was required (2). For the measurement of flow, a simple microflowmeter of the differential-pressure type using the deflection of a mirror on a rubber membrane was employed. This has very great sensitivity, (down to 0.001 ml/min.) and yet relatively high
speed of response (time constant less than 10 seconds) and has already been described (3). In the early experiments the perfusion bottle was set at a given level, 30 seconds was allowed for the flow to become steady and be recorded, and then the level altered abruptly. Later a much more convenient method of obtaining the whole pressure-flow curve in one continuous operation was devised, and this was used in the case of the ear and in a modified form on the 'intact' leg of the rabbit. We have called this the 'vertical-tube method' and find it unexcelled for simplicity, accuracy and rapidity of determinations.

**Vertical-Tube Method.** The principle of this is illustrated in figure 1. In the experiments on the perfused ear, a T-tube was inserted just behind the arterial cannula, and connected to a vertical glass tube so that the pressure at the cannula was shown by the height of the liquid in this tube. It was then realized that if the reservoir were cut off by a tap placed just behind the vertical tube, the rate of fall of the meniscus in the tube, multiplied by the cross sectional area of the tube $a$ would give the rate of flow through the ear. The level on the tube was therefore recorded every 10 seconds as it fell until the flow ceased. This gave an exponential-like curve (fig. 1) from which by drawing tangents at points corresponding to different pressures the complete pressure-flow relation could be deduced. As figure 1 indicates, it happens that the resistance to flow is measured in the same diagram by the subtangent $(BC)$. The zero on the vertical scale was determined at the end of the experiment by placing the cannula in a dish of water at the level of the ear and allowing the level in the vertical tube to fall to its final value. This zero then included all capillarity corrections for the tube as well as for differences of levels. By choosing a suitable diameter for the vertical tube the time taken to describe the whole curve could be adjusted to suit the particular vascular bed under study. Three to 10 minutes was the usual time employed. For the study of flow under high pressure (which was necessary in experiments with high vasomotor tone) the top of the vertical tube was connected by rubber tubing and air transmission to a mercury manometer with a reservoir which could be compressed by a screw device. The total pressure was that shown on this manometer plus that due to the column of perfusion fluid in the vertical tube.

**Modified Vertical-Tube Method.** For the study of the resistance to flow in the leg of the rabbit the vertical-tube method was modified as illustrated in figure 2. A double cannulation of the femoral artery was made with cannulae of plastic tubing (polythene) so that a loop of plastic was interposed into the course of the arterial blood. At one point in the loop the tubing entered a bag of slack rubber through which the arterial pressure was transmitted to a column of water, which transmitted the pressure either to a vertical tube or to a mercury manometer provided with float and writing point for kymograph recording. This recorded the level of the femoral blood pressure. When the loop was occluded on the central side, the flow through the leg continued from the blood in the rubber bag, driven by the pressure of the column in the manometer. Thus the curve of fall of pressure in the manometer was recorded and could be analyzed, as already explained, to give the complete pressure-flow relation. For investigation of critical pressures, the whole of the tissues of the leg above the point of cannulation was occluded by a clamp, except
for the artery, the femoral vein and sciatic nerve. Otherwise the existence of collateral arterial connections would mean that the pressure in the manometer would cease to fall when it reached the level existing at the junction of the femoral system with a collateral artery, and so falsely indicate a high critical pressure. After a curve had been obtained with the blood of the animal, the artery could be occluded on both sides of the bag, and the contents of this replaced by Ringer's solution by successive filling and releasing. Thus in a few minutes the resistance-flow curve could be obtained also with Ringer's solution. Comparison with the results with blood allowed the role of viscosity in the resistance to be measured. Heparin had of course to be used, but the use of Polythene tubing reduces the amount needed to a minimum.

**Direct Observation of Small Vessels.** The results obtained for the changes in diameter of the vessels, as the perfusion pressure fell, at first suggested that our method must be invalid. Though at higher pressures the diameters showed a good consistency (though remarkably little decrease with reduced pressures) when the pressure fell below about 20 cm. of saline, bizarre fluctuations in diameter were measured. Figure 3 gives an example. The sudden changes in diameter were considerably and statistically greater than any seen in repeated measurements at the same pressure, or under any circumstances at higher pressure. In general the smaller vessels in the field tended to show decreases in diameter while at the same time larger vessels were increasing in size, in spite of the fact that the pressure was falling. Close observation revealed that when the pressure was low the flow in specific vessels would cease and there was often reversal of flow. The contents of one set of vessels, which were decreasing in diameter, were being pushed into other vessels. This is just what one would expect from a system of connected tubes in the condition of instability predicted by the law of Laplace at pressures below the critical value.

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* We are indebted to Professor O. G. Edholm for first pointing this to us.
The behavior of two soap bubbles blown at the two ends of a connecting tube is strictly analogous. Because of the law of Laplace, they cannot long co-exist, and the air in the smaller bubble will ‘bleed’ into the larger until the smaller has disappeared. Vertical tube experiments on the same mesenteric vascular bed showed that it was in the region of pressures where these phenomena occurred that the total flow through the system ceased, indicating complete closure of the channels (though we were seldom fortunate enough to have the vessels which closed completely in the field of the microscope).

These experiments led us to two conclusions: 1) that the small vessels were remarkably indistensible, and at higher pressures than the critical pressure behaved like rigid tubes. 2) Critical closure of vessels and instability of their equilibrium, as predicted by theory, occurred when the perfusion pressure was below several cm. of saline. (The pressure in the vessels would of course be less than that of the perfusion pressure as long as there was still flow in the system.)

**Flow-Pressure Relations in the Frog’s Leg.** Figure 4 shows the results for the perfused hind limb of the frog. The reservoir was successively set at different levels at intervals of a minute and the flow measured as soon as it was steady. The points lie very close to a straight line whether the reservoir is being raised or lowered. It will be seen that the flow became zero while the reservoir was still some 5 cm. above the level of the leg. When the reservoir was set to a lower level less than this but still above the leg, the flow was negative, i.e. solution was forced by the blood vessels ‘up-hill’ into the reservoir. Unlike the positive flows found at high pressure, these negative flows did not become steady, but gradually decreased (numerically) to zero. Figure 5 shows how this negative flow changed when the reservoir was abruptly lowered from a high level to a level less than 5 cm. above the leg. Integration of the area of the curve below the line of zero flow gave the total quantity of fluid forced out by the closure of the vessels. As seen in the inset, this increased as the initial level of the reservoir, from which it was lowered, was raised. There seemed to be no doubt that the vessels were closing down actively when the pressure in them fell below a critical closing pressure, and that the back flow could not be
explained by a ‘passive’ blockage of the vessels. Even after perfusion for several
hours, when there could be no remaining vasomotor tone in the leg, this ‘residual’
critical closing pressure remained. In 29 determinations the mean value was 3.3 cm.
of saline, with a standard deviation of ±1.7 cm. The range was from 0.9 to 7.0 cm.
Its value was quite independent of the physiological state of the vessels (as indicated
by the sensitivity to adrenaline) and remained the same up to 24 hours of
perfusion. It was unchanged after the vessels were perfused by 0.01 per cent sodium
cyanide, which removes all tone of the smooth muscle in the wall of the blood vessels.

This suggested that the residual critical closing pressure was due to a tension
that was physico-chemical rather than physiological, existing because there was an
interfacial tension between the Ringer’s solution and the vessel walls, which were
not completely wetted. Such an interfacial tension would, by the law of Laplace,
have to be of magnitude of only about 3 dynes per cm. for vessels of diameter 10 μ

to close, and this is a very low value compared to interfacial tensions between liquids
that do not ‘wet’ each other at all (as for water and ether where it is 35 dynes/cm.)
or in comparison with the tension between water and an unwettable surface (drilfilm
on glass, where it is up to 75 dynes/cm.). This view of the origin of the residual critical
pressure was confirmed by the finding that it could be removed by the addition
of a wetting agent, such as bile salts, to the perfusion fluid. (fig. 6). The interpretation
is complicated by the constriction initially produced by these agents, but this
does not last long, and the crossing over of the curve clearly shows that eventually
there is no longer any critical closing pressure. Exactly similar residual critical
closing pressures have been found in the case of the mammalian blood vessels, and
again they are removed by the use of wetting agents, but not by cyanide. Thus we
have demonstrated that neither Ringer’s solution nor rabbit serum completely
wets the blood vessels, and have a means of estimating the magnitude of the inter-
facial tension from the residual critical pressure.

Under vasomotor tone produced by sympathetic stimulation, by adrenaline and
other pressor agents, the vessels of the frog’s leg show elevated critical closing pres-
sure, but most such agents are soon toxic to frog vessels and the effect of vasomotor
tone is much better demonstrated on the mammalian vessels.

Flow-Pressure Relations in the Rabbit’s Ear. Curves obtained by the vertical-
tube method always became flat while there was still a positive pressure, indicating
a critical closing pressure which was never less than 3 or 4 cm. of saline. Under
vasomotor tone we have produced critical closing pressures ranging from this mini-
mum value up to 130 mm. Hg. It is easily demonstrated that the cessation of flow
is due to an active closure. When the level in the vertical tube has ceased to fall,
some fluid is removed by a side tube, lowering the meniscus by 2 or 3 cm. The level
then is seen to rise steadily to close to the original level at which flow ceased, i.e.
more vessels must be closing, forcing fluid ‘uphill’ back into the tube. By this means,
the value of the critical closing pressure could be ‘bracketed’ and it was routinely
used to arrive at the final value without delay of obtaining the whole curve (fig. 7).

For about half an hour after the excision of the ear, critical closing pressures
as high as 30 cm. of saline were found which steadily declined. These are probably
due to vasomotor tone from the stimulation by cutting and trauma to the vasomotor
plexus on the central artery. Agents used to produce sustained vasomotor tone have included Privine (giving a very long lasting constriction), calcium, heat injury, and perfusion with foreign serum (horse, beef and human) and by egg albumin added to Ringer’s solution. The case of adrenaline is of interest as it suggests why other investigators using only this agent to produce vasomotor tone have failed to discover the existence of critical closing pressures. Figure 8 shows how the vertical-tube curve looked as if it were approaching a plateau at a high level, but would accelerate again and again until eventually the low ‘residual’ value of critical pressure was reached, giving the curve a ‘scalloped’ appearance never seen in experiments with other agents. But when ephedrine was added, a drug which is known specifically to occupy the tissue enzyme which destroys adrenaline, the curve has a very definite plateau, though after several minutes the vessels open once more and the curve descends to a new plateau indicating a new critical closing pressure. (Ephedrine alone does not produce any constriction in the blood vessels of the rabbit ear, though it greatly potentiates the effect of adrenaline.) When adrenaline alone is used, the decrease in the supply, bringing fresh adrenaline to the tissues, as the critical closing pressure is approached, allows the destruction of adrenaline to outstrip its arrival, and the smooth muscle of the walls relaxes. Thus adrenaline can produce only ‘potentially’ high critical closing pressures, and physiologically as well as experimentally the actual closure of vessels may not take place, or be only very brief (2).

Considerable attention was paid to determining points on the pressure-flow curves as close as possible to the point where flow became zero, at the critical closing
pressure, to see whether the curves might actually turn and proceed to the origin very close to the flow axis. This is definitely not the case. Indeed, a great number of the curves are actually concave to the pressure axis where they intersect the axis of zero flow. Critical closure is an abrupt event as predicted by the theory.

**Pressure-Flow Relations in the Rabbit’s Hind Limb.** In these experiments vasomotor tone was always present in some degree, even after the sciatic nerve was cut, probably due to the presence of pressor substances in the circulating blood. A variety of critical closing pressures were obtained in the course of experiments, due to natural vasomotor tone, enhanced when ether administration brought reflexes into play. Figure 9 shows the type of pressure-flow curves deduced from the vertical-tube curves. The increase in the critical closing pressure as vasomotor tone

![Fig. 9. Flow and resistance vs. pressure. Rabbit leg.](http://ajplegacy.physiology.org/)

(indicated by the resistance to flow) increases is seen. An illuminating way of presenting the results is to plot the resistance to flow against the pressure (also shown in fig. 9). These plots show that the resistance at pressures well above the critical value is remarkably independent of the pressure. This must mean that the small vessels, where most of the resistance resides, act like rigid tubes. Yet when the pressure approaches the critical value the resistance increases quite abruptly to infinity. These curves are in marked contrast to those of the standard views on hemodynamics, which suggest that the resistance should rise steadily as the pressure is reduced, but remain finite down to zero pressures.

When curves were taken with Ringer’s solution as well as with the animal’s blood (fig. 10) the pressure-resistance curves showed how the resistance was increased by the viscosity factor, and rose less abruptly as the critical pressure was approached. However the critical pressure might be the same with Ringer’s solution.
as with blood. It was sometimes less, indicating the presence of pressor substances in the blood. Indeed, a comparison of the critical closing pressures with blood and with Ringer's solution offers a quantitative method for measuring the amount of pressor substances in the circulating blood.

With this preparation, we were able to add further fundamental information as to what was occurring at the critical closing pressure. In addition to the artery, the femoral vein was cannulated and connected to a long horizontal capillary tube. By injecting a bubble into this near the vein, the outflow could be measured during the course of the measurement of inflow by the vertical-tube method. The results (fig. 11) showed that when the critical pressure was reached and the inflow ceased the outflow continued for some time. The vessels which close force the fluid out the vein as well as damming it back on the arterial side, and when the arterial side is cut off from the venous by closure, vessels on this side progressively close until all the vessels, peripheral to the original closure, are empty.

**Relation of Resistance to Critical Closing Pressure.** Since the diameter of all the vessels depends upon the equilibrium between the pressure within them and the tension in their walls, the resistance to flow is a function of that tension. The critical closing pressure however is dependent on the tension in the wall only of these vessels which are the first to close (for which the ratio of tension to radius is greatest).
We should expect therefore that there would be a correlation between the critical closing pressure and the resistance to flow (at high pressures well above the critical value) but not necessarily a very close correlation. The vessels which first close might not be those which contribute a major part of the resistance of all the vessels in the flow-path.

Figure 12 is a scatter graph of simultaneous measurements of the critical closing pressure in the rabbit's ear and the degree of constriction expressed as the percentage reduction in flow from the maximal vasodilation value found in that ear. The figure shows that the critical closing pressure, which is never below the 'residual' value due to the interfacial tension, does not rise appreciably until the reduction in flow in more than 70 per cent, but then increases rapidly to values which may be well above the available blood pressure. In order to have a measure of the degree of correlation, the same data (46 points) were plotted as the critical closing pressure vs. the logarithm of relative resistance (the reciprocal of the reduction in flow), since this gives an approximately linear relation. The coefficient of correlation was 0.87 with a standard error of 0.05. A similar plot with data from the rabbit's leg, where the agents used to produce constriction were less varied, gave a coefficient of correlation of 0.86 ± 0.03. The high correlation would indicate that the 'critical' vessels which close when the pressure is reduced are the same as those which offer the major resistance to flow, namely the arterioles. On the other hand, when vasomotor tone is small, it may well be that the capillaries rather than the arterioles become the critical vessels which close, and this is why the critical closing pressure rises very little until a fairly great constriction is present.

**DISCUSSION**

It is concluded therefore that there is no substantial contrary evidence in the existing literature, in view of the fact that studies of flow with the perfusion pressure less than 20 mm Hg have been seldom made, and also that such studies were rarely made in conditions where there would be any considerable degree of vasomotor tone. In the absence of vasomotor tone the experiments here reported show a residual critical closing pressure amounting to only about 5 mm Hg. The accuracy
of previous experiments is insufficient to decide whether or not such a low critical pressure was present. On the other hand there are several indications in the literature of high critical closing pressure though the authors did not so interpret their findings.

The existence of a critical closing pressure is suggested in the work of a number of investigators, but there has been no general agreement as to its interpretation. It was noted by Whittaker and Winton in pressure-flow studies on the isolated leg of the dog that, with Ringer solution, the curve appeared to pass through the origin, while with blood it appears to intersect the pressure axis at 22 mm. Hg (4). However, in the case of the Ringer solution, the lowest pressure actually measured was about 35 mm. Hg at a flow of 140 ml. per minute and the long extrapolation to the zero flow position seems scarcely justified. Although the pressure-flow curve in areas of high flow and pressure was linear, there was no experimental basis for assuming that this relation held at low flows and pressures. The positive pressure in the case of blood was explained by these investigators as due to the colloid osmotic pressure or the concentration of red cells but such explanations were speculative.

Pappenheimer and Maes studied the pressure-flow relationships in the hind leg of the dog perfused with defibrinated blood (5). They confirmed the work of Winton and noted as well that the extrapolated intercept of the linear part of the curve
increases with increasing vasoconstriction, i.e. an apparent tendency for the vasoconstrictor to increase the pressure at which flow ceases. However, as in the work of Winton, no pressure of less than 25 mm. Hg was used and the smallest flow measured was 10 ml. per minute.

Green and associates have discussed the work of Pappenheimer and Winton and carried out similar experiments (6). They measured flows right down to the zero value and show that many of these zero flows occur at a positive pressure. These curves show that the pressure-flow curves, instead of going towards zero pressure, curve away in a sigmoid fashion to some positive value.

We feel that the cessation of flow while a positive pressure of perfusion still exists cannot be explained in terms of a blockage of the small vessels, because of the demonstration of 'back-flow.' It might be thought that an increased tissue pressure could be responsible for the apparent critical closing pressure when this is low, as in the case of the residual closing pressure. However this too is ruled out by the fact that no steady increase in critical pressure over many hours was found when Ringer's solution without osmotic balance was used and edema amounting to up to 30 per cent of the weight of the tissues was produced. In any case, the very rapid production and disappearance of higher critical closing pressures under vasomotor tone could not be explained in terms of edema. Review of pressure-flow curves that have been previously published by other investigators shows many cases where, had there been a theoretical reason to suggest it, the data would have indicated a critical closing pressure, but measurements were seldom made at the very low flows necessary to establish it without a doubt.

While the phenomena of critical closure in these experiments, where the perfusion pressure is lowered, seem established without doubt, the physiological importance of this intrinsic instability of blood vessels remains to be discussed. Where vasomotor tone is sufficient to raise the critical closing pressure above the normal mean blood pressure (100 mm. Hg), complete closure of a vascular bed must take place. This gives us a new view of the nature of vascular spasm. It is to be thought of as indicating that the critical closing pressure has risen above the maximum arterial pressure available. If the pressure were artificially raised (as by intra-arterial transfusion) the vessels would open up and the flow (judging from our experiments) would not be at all negligible. In contrast, the classical view of spasm is that the resistance to flow has become so great that the flow, though still proportional to the pressure, is negligibly small. On this view, an increase in pressure would result only in a proportional increase in the very small flow that existed before.

Does critical closure have physiological significance where the vasomotor tone is less than that required to raise critical closing pressures above the arterial pressure? It might be thought that if vessels began to close, the flow would be reduced so that the pressure gradient became less, and the pressure within the vessels would rise towards the arterial pressure sufficiently to keep them always open. However, it must be remembered that actual vascular beds are not the simplified circuits of our elementary explanation in hemodynamics, consisting of a set of resistances of artery, arteriole, capillary, venule and vein, each set in parallel with other such
critical circuits. There are so many arterial interconnections and arterial-venous shunts that the picture of a ‘fish-net’ or syncytium is often more appropriate. In such a system, the cessation of flow in one part will raise the pressure within it only to the level of pressure that exists at the nearest connection to a circuit in which flow is still proceeding. The pressure at this connecting point may be far below the arterial pressure. Thus we conclude that critical closing pressures much less than the arterial pressure may result in closure of portions of the vascular bed. The existence of critical closing pressures may be the explanation of the local cessation of flow, and reversals of flow in other parts that have so often been observed in the small vessels. It may also be the mechanism of operation of the control by arterial-venous anastomoses and ‘shunts’ as observed in the kidney.

While these investigations in establishing the existence of critical closing pressures have provided a new index of vasomotor tone that has the advantage over ‘resistance’ in being independent of viscosity, at the same time they have increased our confidence in the use of resistance. This has been criticized as a valid index of vasomotor tone on the grounds that, because of the distensibility of the blood vessels, resistance might change ‘passively’ when the pressure changed. We find however that the resistance is almost independent of the pressure, so long as this is well above the critical closing pressure. Simultaneous measurement of both critical closing pressure and resistance to flow at high pressures gives the best information at to vasomotor tone yet available.

**SUMMARY AND CONCLUSIONS**

Microscopic observations and measurement of the diameter of the small vessels of the mesentery of the frog show that though these act almost like rigid tubes at higher perfusion pressures, when the pressure falls below about 10 cm. of saline they are remarkably unstable. Some vessels close and empty their contents into others and cessation and reversal of flow are often seen. This instability is that predicted by the application of the law of Laplace. Careful measurement of the flow-pressure curve for the perfused hind limb of the frog shows that flow ceases when the pressure head is less than 3 to 6 cm. of saline. At lower pressures the vessels actively close and force fluid uphill back through the artery. This residual critical closing pressure is due to an interfacial tension between the perfusate and the wall of the vessels, which it does not completely wet. Analogous residual interfacial tensions have been found in the perfusion of mammalian vessels of the rabbit with Ringer’s solution, serum and blood. In the blood vessels of the rabbit’s ear and in the hind limb, vasomotor tone raises the critical closing pressure above the residual value to pressures which may exceed the arterial pressure. There are many demonstrations that the closure of the vessels is an active one and cannot be explained in terms other than that of the prediction from the law of Laplace.

The level of the critical closing pressure and the resistance to flow at higher pressures are closely correlated. Critical closing pressure begins to rise considerably when the degree of reduction of flow is more than 75 per cent. In general the vessels which close are the same as those supplying the greatest part of the resistance to
flow, i.e. the arterioles. Closure of small blood vessels when the pressure within them falls below a critical value is of physiological importance, not only when the critical pressure exceeds the available blood pressure (spasm) but also at much lower pressures.

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