BRIEF REVIEWS

Critical Closure Reexamined

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WHEN PRESSURE-FLOW curves are constructed from organ perfusion data, the curves usually intercept the pressure axis at a positive value, indicating cessation of flow well before the pressure gradient has declined to zero. The most commonly cited explanation for this phenomenon is the "critical closure" theory of Burton. His theory was developed from the classical experiment in which soap bubbles are blown on two ends of a Y-tube. The pressure within the closed tube will equilibrate with the surface tension of the bubbles. Since this surface tension is a property of the soap solution and is therefore the same for both bubbles, it becomes impossible for the two bubbles to persist because of the Laplacian relationship between luminal pressure (P) and wall tension (T) as a function of bubble radius (r):

\[ T = \frac{Pr}{2}. \]

Whichever of the two bubbles is slightly smaller will have a higher pressure, forcing air into the opposite arm of the Y-tube. This will lead to enlargement of the bigger bubble and diminution of the smaller bubble. As the size discrepancy between the bubbles increases, the pressure differential becomes greater until the smaller bubble collapses completely into the larger bubble.

The Theory

The application of this model to blood vessels is most clearly visualized by expressing the Laplacian relationship for cylindrical tubes in terms of vessel circumference (c):

\[ T = \frac{Pc}{2 \pi r}. \]

Burton proposed that contraction of the vascular smooth muscle adds a fixed active tension to the passive elastic tension in the wall. This would raise intravascular pressure and displace blood toward other regions of the vascular bed. If the active wall tension created by muscular contraction was modest in reference to the systemic vascular pressure, vasoconstriction would reduce vessel circumference with a consequent lowering of the passive elastic tension until an equilibrium between wall tension and intraluminal pressure had been reestablished as defined by Equation 2. If the increase in active tension was relatively great and the vascular pressure low, Burton demonstrated that an equilibrium becomes impossible, the circumference reducing to the point of complete closure of the vessel before the pressure could come into equilibrium with wall tension. For any fixed level of active tension, the pressure at which this disequilibrium and closure of the vessel occurs was defined as the "critical closing pressure" and was represented by the positive intercept of the pressure-flow curve.

In the original formulation, the blood vessel was considered a thin-walled cylinder whose radius and circumference both approached zero as closure occurred. To apply this to real blood vessels, Burton and his students demonstrated that closure was actually produced by a concertina folding of the internal elastica and bulging of the endothelial cells into the lumen as the vessel circumference becomes severely reduced (cf. also VanCitters et al.). Verification of the closure phenomenon was carried out in frog and rabbit preparations with the demonstration that higher closing pressures were exhibited as active vascular tone increased. It is also noteworthy that closure was achieved with saline perfusions, indicating that the obstruction to flow was not merely a reduction in the lumen to the point at which plugging with blood cells occurred.

The Challenge of the Theory

Johnson challenged this concept by pointing out that muscle does not possess the properties assumed by the theory. The muscle machine is primarily a contractile element capable of shortening; this shortening will be associated with tension development as a function of the stretch of elastic elements in series with the contractile elements. When muscle activation increases this tension, Equation 2 tells us that the vessel circumference will decrease to equilibrate with the existing vascular pressure. This constrictive reduction of wall circumference will reduce the stretch of the series elasticity and thereby decrease the active wall tension as the new equilibrium is established. Burton did not accept this extrapolation of the properties of skeletal muscle to vascular smooth muscle, because he interpreted the high dynamic distensibility exhibited by constricted blood vessels in the normal pressure range as evidence of different properties of the vascular series elasticity. Recent work of Dobrin and Canfield demonstrates a series elastic element in muscular blood.
vessels quite comparable to that of skeletal muscle. Furthermore, even the dynamic distensibility data show that constricted blood vessels have a stiff series elasticity in the low pressure range where critical closure would occur. In contradistinction to the assumptions of the critical closure theory, therefore, the reduction in vessel circumference by vasoconstriction should be associated with a reduction in both active and passive wall tensions. Not only does this fail to predict critical closure, but in a sense it protects against critical closure.

A Test of the Theory

To examine just how these factors would interact in an artery, it is necessary to have data for both passive and active forces in the wall as a function of wall circumference. Assuming that only passive forces are present in a dilated blood vessel, Wiederhielm has provided data for the passive elastic behavior of a small muscular artery as a function of relative increase in vascular dimensions, relating wall tension to the midcircumference of the wall (cₘ) with the aid of the relationship

\[ cₘ = \frac{Wₐ}{W_t}, \]  

which assumes that the decrease in wall thickness (Wₐ) as the vessel distends does not alter the cross-sectional area of the wall (Wₐ). For any wall tension, the corresponding pressure in the lumen of the vessel may be calculated by application of the Laplacian relationship in the form

\[ P = T \frac{2\pi W_0}{1.35 cₘ}. \]

in which the constant of 1.35 yields pressure values in mm Hg when tension is expressed in g/cm². By this method, the Wiederhielm data have been used to describe the passive properties of a dilated muscular artery which, at zero pressure, has a radius of 100 μm, a wall thickness of 20 μm, and a length of 1 cm, yielding the “dilated” pressure-volume plot in Figure 1.

Adequate data for small blood vessels are not available to describe the active component of wall tension in a constricted blood vessel as it is distended by increasing pressures. For larger muscular arteries, however, considerable data are available. I have chosen the excellent data recently published by Cox for the active tension-length response of vascular smooth muscle which he obtained from the iliac artery of the dog. His data demonstrate that in the unstressed vessel (pressure = 0), vasoconstriction reduces the circumference by 30%, or to 70% of its dilated circumference. As the circumference increases with distention, active wall tension increases as a fairly linear function to a peak of 1.2 × 10⁶ dynes/cm² at a distention of 150% of the unstressed dilated circumference. This represents an active tension-length factor of 0.015 × 10⁶ dynes/cm² for each 1% increase in wall circumference above 70% of the dilated unstressed circumference. I have applied this constant to a series of arbitrarily chosen circumference values to calculate the pressure-tension relationship in the actively constricted blood vessel, using the same basic vascular dimensions as before. When vessel distention stretches the constricted vessel beyond 100% of its dilated unstressed circumference, the Wiederhielm passive tension value for that circumference was added to the active tension. The sum of the active and passive tensions for each circumference was then related to the corresponding intravascular pressure by application of Equation 4. The “constricted” curve of Figure 1 shows the result of these calculations. It is evident that equivalent wall tensions correspond with greater pressures in the constricted vessel than in the dilated vessel, as is implicit in the Laplacian relationship. The corollary of this should be noted: at any equivalent pressure, there is less wall tension in the constricted vessel than in the dilated vessel. Direct evidence that vasoconstriction reduces wall tension at equivalent pressures in real blood vessels has been provided by Wiederhielm.

Since the data of Figure 1 were calculated from a series of arbitrarily selected values of midwall vascular circumference, it is straightforward geometry to calculate the internal volume of the vessel at any pressure, assuming that the vessel is longitudinally tethered to confine volume changes to the radial dimension. This yields the pressure-volume values plotted in Figure 2. The “dilated” plot demonstrates the typical behavior of a dilated vessel which becomes less distensible as pressure increases. In contrast, the “constricted” pressure-volume curve exhibits the characteristic sigmoid form that has been reported for constricted blood vessels. The crucial point for our immediate concern, however, is that the constricted vessel does not exhibit closure, or any tendency toward closure, as pressure is reduced.

These relationships in a small muscular artery prompted extension of the analysis to the arteriole level where critical closure would be more likely to occur. Vessel dimensions were selected to correspond with a typical arteriole with a radius of 10 μm and a wall thickness of 4 μm at zero pressure, retaining the length dimension of 1 cm to simplify calculations. As before, the Wiederhielm data were

\[ FIGURE 1 \quad \text{Pressure-tension plots for a muscular artery with a radius of 100 \( \mu \text{m} \) and a wall thickness of 20 \( \mu \text{m} \); the “dilated” curve calculated from the passive tension data of Wiederhielm, and the “constricted” curve adding the active tension-length data of Cox for the contracted vascular muscle.} \]
used to define the passive tension in the vascular wall and the Cox data were used to quantify the active tension produced by vasoconstriction. The calculated pressure-volume values for the "dilated" and "constricted" arteriole are shown in Figure 3. In a vessel of these dimensions, wall tension in the constricted state remains purely active throughout the normal physiological pressure range, since the vessel never becomes sufficiently distended to encounter the restraint of the passive elastic elements which govern the properties of the dilated arteriole. Again it is observed that the constricted vessel exhibits no tendency toward critical closure as the pressure is lowered.

Critique of the Test

While this analysis reaffirms the fundamental importance of the Laplacian principle which Burton introduced into the thinking of cardiovascular physiologists, it does nothing to support his specific theory of critical closure. Failure to substantiate his theory might prompt dismissal of the closure phenomenon as some sort of laboratory artifact, recognizing that normal vascular function can scarcely be anticipated when blood flow is artificially reduced to zero to provide unequivocal evidence of closure. Indeed, autoregulatory mechanisms in the peripheral tissues, which protect against tissue ischemia by inhibiting vascular tone as pressure is lowered, provide cogent arguments against accepting a closure mechanism. Levy et al., for example, demonstrated the fallacy of extrapolating pressure-flow data to a zero flow intercept at a positive pressure without allowing for the autoregulatory vasodilation which intercedes as the intercept is approached. However, while recognizing the soundness of these arguments for being cautious in the evoking of any theory for vascular closure, it is difficult to discount the many descriptions by students of the microcirculation reporting directly observed closure of arterial elements. Indeed, autoregulatory mechanisms in the peripheral tissues, which protect against tissue ischemia by inhibiting vascular tone as pressure is lowered, provide cogent arguments against accepting a closure mechanism. Levy et al., for example, demonstrated the fallacy of extrapolating pressure-flow data to a zero flow intercept at a positive pressure without allowing for the autoregulatory vasodilation which intercedes as the intercept is approached. However, while recognizing the soundness of these arguments for being cautious in the evoking of any theory for vascular closure, it is difficult to discount the many descriptions by students of the microcirculation reporting directly observed closure of arterial elements.

This direct evidence of closure dictates a critical examination of the assumptions involved in the analysis presented in Figures 1-3. Since arterioles contain a higher percentage of muscle in their walls than do the larger arteries, extrapolation of the large artery data of Cox to arterioles might well be underestimating the active tension generation per cm$^2$ of the arteriole wall, as suggested by somewhat greater active tension development reported for some other analyses of smooth muscle. Use of a higher value for active tension development, however, would only serve to increase the pressure values calculated for the distended vessel; it would not help to achieve closure at zero pressure. The assumption that volume changes are restricted to the radial dimension and do not involve the longitudinal dimension is justified by the fact that longitudinal tethering actually maintains the smaller vessels under considerable longitudinal traction. Should imperfect tethering permit some shortening of the constricted blood vessel, the calculated values would not be significantly altered because the compromise in circumferential shortening would be offset by an increase in wall thickness.

A more critical assumption for closure is the assumed capacity of the muscle for shortening. Values in the neighborhood of 30% shortening of the unstressed vascular muscle, as found by Cox, have been reported by numerous investigators. Studies of vascular strips have reported maximum shortenings of 27% for rabbit aorta, 40% for bovine mesenteric arteries, and 25% for cat portal vein. In experiments in which there seems to have been somewhat more than minimal loading, Somlyo et al. reported maximum shortening of dog iliac artery strips of 57%, but in the same paper reported shortening of dog renal arteries of 33% and dog femoral arteries of...
30%. Isolated smooth muscle filaments uncoiled from the pig carotid show a maximum shortening of 34% of their unstressed length (W.H. Johnson, personal communication). Herlihy and Murphy\textsuperscript{22} were able to produce a shortening of something over 50% in isolated muscular media from the hog carotid by inducing a potassium contracture in a high calcium solution, but observed significantly less contractile response with the use of physiological stimuli. In the hypothetical arteriole analyzed in Figure 3, circular muscle fibers would have to contract by 60% to achieve closure at zero pressure, and even further to produce closure at positive pressures. In the real arteriole directly analyzed by VanCitters et al.\textsuperscript{4} (their Fig. 2) there was a 68% shortening of the midwall circumference and a 60% shortening of the outermost muscular elements in the constricted state. It is certainly conceivable that the smooth muscle in arterioles could possess such capacities for shortening. On the other hand, the very substantial crimping of the inner layers of the wall of a constricted arteriole\textsuperscript{23} suggests that active tension significantly greater than the wall tension predicted from the Leplacian relationship must be required to produce the amount of tissue distortion that is observed in the closed vessel. This would demand a still greater shortening capacity of the muscle.

An Alternative Mechanism

An assumption that could have far greater consequence for the mechanics of the smooth muscle is the angular orientation of the contractile elements. Up to this point the analysis has implied that muscle shortening occurs in an axis tangential to the wall, at right angles to the long axis of the vessel. In blood vessels, such circular muscle fibers are "rare indeed."\textsuperscript{24} The microdissections by Strong\textsuperscript{25} provided unequivocal evidence that vascular smooth muscle forms helical coils. These coils are the basis of the elegant technique of Bohr et al.\textsuperscript{26} for unwinding the coil so as to obtain filaments of relatively pure vascular smooth muscle. Many of the helices illustrated by Strong appear to have angles on the order of 45° from the transverse axis of the vessel, although reliable dimensions could not be obtained from the dissected preparations. Rhodin\textsuperscript{27} describes helices in the femoral artery of the mouse with an angle of 60° from the transverse axis, while in a study of bovine mesenteric arteries, Fischer\textsuperscript{28} concluded that in the larger vessels the helix angle averaged a little less than 45°. The angle becomes less in small vessels,\textsuperscript{27} but Fischer emphasized that careful examination of the "circular" muscle of the smaller arterial vessels reveals angles of 15°-30°. Indeed, he defended the thesis that an angular orientation of the muscle was the only arrangement that would permit effective control of the vascular wall. At the cellular level, the situation is further complicated by the fact that the contractile fibrils do not appear to be oriented in the long axis of the cells, but insert at attachment zones distributed along the sarcolemma.\textsuperscript{27} This creates angular orientations of the contractile fibrils within the cells themselves which can profoundly influence their mechanical action.\textsuperscript{29}

The consequence of this angular orientation of the muscular element in blood vessels was explored by Fischer,\textsuperscript{28} although his theoretical development did not take into consideration the external tethering of the vessels which minimizes their changes in length. Vascular geometry can be simplified by visualizing a longitudinal cut which permits flattening the cylindrical wall into a rectangle whose width is wall circumference and whose length equals one complete turn of the helix (Fig. 4). Retaining the assumption that the muscle itself is capable of shortening to 70% of its diluted length, there is a modest augmentation of the circumferential shortening of the wall as the angle of the helix increases from 0°-30°. Beyond 30°, Figure 4 demonstrates that the same percentage shortening of the muscle fiber has a marked effect on the circumference, with complete closure of the vessel at a helix angle of 45°.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{circumference.png}
\caption{Schematic diagrams of the arterial wall spread out as a flat sheet with the muscle oriented at progressively greater angles from the transverse axis of the vessel. Dashed lines indicate the reduction in circumference that would be achieved by a 30% shortening of the muscle, assuming no change in vessel length.}
\end{figure}
When this effect of helix angle is applied to the arteriole analyzed in Figure 3, taking wall thickness into consideration but neglecting any tendency for the endothelium to crimp and bulge into the lumen, closure is found to occur at a helix angle of 38.6° at zero pressure. Neglecting a minor correction of wall tensions because of the angular orientation of the force, with a helix angle of 39° closure would be maintained up to a pressure of 20 mg Hg; with an angle of 40° the vessel would not open until intraluminal pressure exceeds 50 mm Hg. The calculated volumes at pressures above this level for a 40° helix are shown by the dashed curve in Figure 3, assuming 30% shortening of the dashed curve in Figure 3, assuming 30% shortening of the helical muscle in the vasoconstricted state. Reducing the helix angle to 30° would avoid absolute closure, but a pressure of over 30 mm Hg would be required to allow free passage of red blood cells through this vessel. With allowance for the buckling of the endothelium that would occur,3 23 this pressure requirement might reasonably be doubled. These pressures are well within the range that could be associated with closure in the microcirculation.

Angular muscular elements, therefore, seem capable of explaining the closure phenomenon, though there are other factors that might be considered. Our simplifying assumption that the Laplacian tension can be assigned to the midpoint of the wall may be leading us astray in the analysis of very small vessels with relatively thick walls. Unfortunately, more rigorous techniques for defining the tension in thick-walled vessels30 assume a homogeneity of the wall that does not accord with the architecture of blood vessels. Their architectural complexity includes a distinct group of muscle elements which connect with elastic fibers in a configuration that could yield unique mechanical advantages for tension development with muscle contraction.3 18 31 37 It should be appreciated, nevertheless, that the functional resultant of these intimate details of wall structure are already being accounted for in the "active" tension data derived from laboratory measurements. Therefore these structural complications do not necessarily invalidate the use of simplified models to identify the salient features of the active and passive tension components that govern vascular function.

There is an obvious need for more direct quantitative data to clarify these functional characteristics of the small vessels of the microcirculation, which must await the technological advances necessary to obtain such data. In the meantime, the available evidence suggests that a plausible mechanism to account for the closure of small blood vessels could relate to the consequences of the helical arrangement of the vascular smooth muscle; an implausible mechanism to account for the closure of small blood vessels of the microcirculation, which must await the technical advances necessary to obtain such data. In the meantime, the available evidence suggests that a plausible mechanism to account for the closure of small blood vessels could relate to the consequences of the helical arrangement of the vascular smooth muscle; an implausible mechanism to account for the closure of small blood vessels could be associated with closure in the microcirculation. With allowance for the buckling of the endothelium that would occur,4 23 this pressure requirement might reasonably be doubled. These pressures are well within the range that could be associated with closure in the microcirculation.

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