Brief Review

Autoregulation of Blood Flow

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Autoregulation of blood flow, the tendency for blood flow to remain constant despite changes in arterial perfusion pressure, is a ubiquitous and much studied phenomenon. Autoregulation was first described in the kidney in 1931, but it had been anticipated by Bayliss 30 years earlier based on changes in hind limb volume during alterations in arterial pressure. Bayliss noted a secondary decrease of organ volume with arterial pressure elevation and suggested that "the peripheral powers of reaction possessed by the arteries is of such a nature as to provide so far as possible for the maintenance of a constant flow of blood through the tissues supplied by them, whatever may be the height of the blood pressure, except so far as they are directly overruled by impulses from the central nervous system." The widespread occurrence of autoregulation in various organs of the body began to be recognized in the 1950's as part of an intensified interest in local mechanisms of blood flow regulation. In 1963 a symposium on this topic, provided a detailed view of the field at that time.

Since the 1963 symposium, autoregulation has been a topic of continuing interest. New experimental techniques for studies in whole organs and in the microcirculation have provided a means for analyzing and quantifying behavior of vessels responsible for autoregulation. Also, new biochemical methods have become available to study purported vasodilators. Finally, the importance of autoregulation in clinical medicine has been explored. The purpose of this review is to examine the principal developments since that time.

In 1963 four mechanisms of autoregulation — myogenic, metabolic, tissue pressure, and tubulo-glomerular feedback — were recognized as potentially important while a fifth possible mechanism — local neural control — was noted but given little credence. The experimental evidence relevant to each of these four theories will now be reviewed.

Metabolic Hypothesis

According to this hypothesis blood flow and tissue metabolism are tightly coupled in such a way that any reduction in arterial inflow causes a buildup of vasodilator metabolites in the tissue. This buildup could be due to a reduced rate of washout of aerobic vasodilator metabolites such as CO₂ or increased production of vasodilator substances due to hypoxia or to both. Evidence to be presented subsequently indicates that washout is probably not a significant factor. There is substantial evidence that the dependence of tissue oxygen on blood flow is responsible for autoregulation in organs with high oxygen consumption.

Both myocardium and brain exhibit a high degree of autoregulation, and in both organs blood flow is highly dependent on tissue oxygen consumption. The latter observation suggests a tight coupling between blood flow and tissue PO₂, or vasodilator metabolite production. In myocardium the hypothesis has been suggested that blood flow is regulated to maintain a constant tissue PO₂. Laird et al. examined this hypothesis using venous PO₂ as an overall indicator of tissue PO₂. The relation between vascular resistance and venous PO₂ was identical under conditions of functional hyperemia and autoregulation, suggesting that the same mechanism may be operating in both circumstances.

Consistent with this concept is the observation that in some tissues elevated oxygen consumption greatly enhances autoregulation. This was shown in skeletal muscle by Stainsby, in stomach by Holm-Rutigli and in intestine by Norris et al. The key factor in the enhancement of autoregulation may be a lowering of tissue oxygen levels as oxygen consumption increases. Venous O₂ levels in resting skeletal muscle are relatively high (70% saturated), reflecting a high tissue PO₂. An increase in metabolism in skeletal muscle leads first to increased O₂ extraction and lowered venous O₂ content with modest increase in flow. This increased extraction is apparently aided by a more widespread perfusion of the capillary bed to include vessels previously without flow. Granger et al. have suggested that the terminal arterioles are more sensitive than the larger arterioles to reduction in tissue oxygen tension. This response would allow perfusion of more capillaries and greater oxygen extraction without substantially altering overall vascular resistance. Klitzman et al. have suggested that relatively small changes in tone of the distal arterioles may have a disproportionate effect on capillary perfusion. When the capillary network is well perfused and O₂ extraction is maximized, a drop in arterial pressure and flow would lower tissue PO₂ and lead to relaxation of the larger arterioles and restoration of blood flow. Available evidence suggests that low tissue PO₂, whether due to elevated metabolism or low blood flow, apparently favors autoregulation. Jones and Berne found in skeletal muscle that autoregulation was much better in preparations with high vascular tone and low venous
oxygen levels. Granger et al. found in a variety of circumstances that lowering tissue PO2 increased the autoregulatory flow response of a skeletal muscle vascular bed.

Tissue PO2 levels have not been examined extensively during autoregulation. However, in myocardium Schubert et al.16 found a number of hypoxic sites (<5 mm Hg PO2) at normal perfusion pressure in preparations that showed good flow autoregulation. The number of such sites increased as arterial pressure was reduced even though mean tissue PO2 was maintained. This study suggests that localized reduction in tissue PO2 may be responsible, at least in part, for flow autoregulation.

An argument against tissue PO2 as a determinant of autoregulation in the brain is that infusion of vasodilator substances that increase cerebral blood flow does not weaken blood flow autoregulation.17 This finding is surprising since it would be expected that the increased blood flow would elevate tissue PO2 and lower tissue metabolite concentration. It is also interesting that sustained reduction in cerebral blood flow can occur without affecting autoregulation. After a period of spreading cortical depression, cortical blood flow and vascular responsiveness to CO2 are reduced but the efficacy of autoregulation is not altered. In this case it is possible that flow is reduced in proportion to a fall in O2 consumption, maintaining a normal tissue PO2. In support of latter possibility, a normal tissue pH is seen in spreading depression. Also, when cerebral O2 consumption is reduced by 50% in pentobarbital comatose, cerebral blood flow also falls by 50% and autoregulation is not impaired.18 Similarly, in the heart, reduction in cardiac function leads to a fall in myocardial blood flow but the degree of autoregulation is not impaired.19

More direct evidence for a role of oxygen in blood flow autoregulation has involved suffusion of an oxygen-rich solution over a microcirculatory preparation. Elevating the O2 level typically causes vasoconstriction of arterioles and reduced flow. In such studies Kontos et al.20 found that the dilation of pial arterioles, which normally was quite prominent following arterial pressure reduction, was entirely abolished when an oxygen-rich solution was suffused over the tissue. Similar results were obtained by Sullivan and Johnson21 in the cat sartorius muscle microcirculation, while Morff and Granger22 found autoregulatory dilation in rat cremaster arterioles was diminished but not abolished. Since the autoregulatory dilation in two of these tissues was completely abolished with elevated oxygen, it appears that in those tissues production rather than washout of vasodilator metabolites is important in blood flow autoregulation. If washout were important, there should have been some residual autoregulation despite the fact that oxygen was supplied from an external source. The firmness of this conclusion, however, is tempered by the fact that washout of vasodilator substances from tissue near the surface may be quite different from that in deeper areas. The absence of any apparent role of washout in these studies does not prove it is unimportant in thicker tissue. The presence of residual dilation in Morff and Granger’s studies22 could indicate a role for washout in their preparation, but other evidence from those studies favored a myogenic mechanism as responsible for the remaining dilation.

Since O2 causes arteriolar constriction, it is also possible that the abolition of autoregulation is due to a nonspecific vasoconstrictor effect of oxygen. Klitzman et al.23 showed that norepinephrine suppressed the normal vasodilator response to stimulation of skeletal muscle fibers in the cremaster muscle. A nonspecific effect does not appear to be involved in the inhibitory effect of oxygen on autoregulation since autoregulation is enhanced rather than inhibited in preparations with elevated vascular tone.11,12

If tissue PO2 is the sole determining factor in blood flow autoregulation, it would seem logical that there be a detectable fall in flow as arterial pressure is reduced, in order to reduce O2 delivery and tissue PO2. However, in some vascular beds such as brain and myocardium, there is a substantial change in precapillary resistance in the absence of a measurable change in blood flow. Mosher et al.20 reported instances of no measurable change in myocardial blood flow in the dog in the arterial pressure range 80–120 mm Hg. Also, cerebral blood flow in man does not change significantly as arterial pressure is lowered from 130 to 60 mm Hg.24 The latter finding requires that total vascular resistance in this bed falls by half as arterial pressure is reduced. Since capillary and venous vessels do not participate in the response, precapillary resistance must fall by more than half. Tissue PO2 must change appreciably in order to alter vascular resistance to this degree. It is not immediately obvious how tissue PO2 could change appreciably in the absence of a change in blood flow. One possible explanation of this finding that would fit the tissue oxygen hypothesis is that there is continuous countercurrent exchange of oxygen from arterial to venous vessels.25 Such exchange would be greater at reduced arterial pressure when the arterioles are dilated and flow velocity is decreased. In these circumstances capillary PO2 would fall even though blood flow is maintained constant. This phenomenon would decouple flow from tissue O2 levels and flow might actually increase as arterial pressure is reduced. Such “superregulation” is seen in individual microcirculatory vessels in skeletal muscle26 and mesentery27 and has been reported in measurements of total blood flow in the intestine28 during absorption of foodstuffs.

The studies by Schubert et al.16 suggest that an increase in the number of hypoxic sites leads to production of anaerobic vasodilator metabolites as arterial pressure is reduced. One problem with this hypothesis is that the oxygen threshold for production of such vasodilators is thought to be very low. The critical PO2 for cytochrome oxidase in isolated mitochondria is known to be less than 1 mm Hg.29 However, if the intracellular diffusion coefficient is low, as suggested by studies in cardiac myocytes,28,29 the critical extracellular PO2 may be considerably higher (≈6 mm Hg).
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This factor, coupled with heterogeneous O₂ distribution in the tissue, could lead to localized regions where oxygen supply is inadequate for normal oxidative metabolism. In addition, there is a variety of enzyme systems that have a considerably higher $k_{m}$ for oxygen. If the latter play a role in blood flow regulation, they could sense changes at the hypoxic sites or in mean tissue PO₂, which is about 11 mm Hg in hamster cheek pouch and 19 mm Hg in rat cremaster muscle. In this connection, it may be significant that as the solution PO₂ is elevated over these preparations, the arterioles constrict and maintain a constant mean tissue PO₂. Oxygen causes generalized vasoconstriction in all orders of arterioles in the cat sartorius muscle.

In examining the tissue oxygen hypothesis of blood flow autoregulation, primary credence has been given to an indirect effect of oxygen on the arterioles, i.e., via an alteration of tissue metabolism and production of vasodilator metabolites. Relatively little work has been done to identify possible chemical mediators of this vasodilation. Morff and Granger found that theophylline reduced but did not abolish autoregulatory dilation of arterioles in rat cremaster muscle following arterial pressure reduction, suggesting a role for adenosine in autoregulation. Schrader et al. found that coronary venous levels of adenosine and inosine in the saline-perfused guinea pig heart increased at reduced arterial pressures. On the other hand, Dole et al. found that adenosine deaminase infused into the blood-perfused dog myocardium moderately reduced the magnitude of reactive hyperemia but did not significantly affect autoregulation. Hanley et al. also found that adenosine deaminase did not attenuate autoregulation, but the increase was statistically significant only at pressures below the autoregulatory range.

It is conceivable that changes in tissue PO₂ could bring about an autoregulatory response by a direct effect on the resistance vessels. Studies on larger vessels revealed a direct effect of oxygen on vascular tone. The importance of this observation for regulation of resistance vessels has been disputed since the larger vessels may have an anoxic core in the wall due to a larger diffusion distance from the vessel surface. The latter would not be a consideration in the arterioles. Moreover, local changes in periarteriolar PO₂ did not alter arteriolar diameter. However, evidence for a direct effect of oxygen on arterioles has been provided recently by Jackson and Duling, who reported oxygen-induced constriction of isolated arterioles and arterioles in a network dissected free from surrounding parenchyma. To date this effect has been demonstrated only when arteriolar PO₂ is substantially elevated. Whether this effect is operative at normal or reduced arteriolar PO₂ has not been determined.

If oxygen has a direct effect on arterioles, intraluminal PO₂ in these vessels as well as tissue PO₂ would be a factor in regulation. Since there is a longitudinal gradient of intraluminal oxygen along the arteriolar network to the capillaries, a reduction in flow would reduce arteriolar PO₂. The degree of PO₂ reduction in any arteriole with a fall in flow would depend on the location of the arteriole in the network and various other factors including the magnitude of flow reduction, the O₂-Hb dissociation curve and any associated change in tissue O₂ consumption.

Since it appears that oxygen may act directly on the arteriole, the possibility that it inhibits autoregulation by suppressing another mechanism such as a myogenic response must also be considered. However, as noted in the following section (myogenic hypothesis), elevation of tissue PO₂ does not inhibit the myogenic response.

There is an additional possible mechanism of autoregulation that involves flow but does not depend on metabolism per se. The endothelium of arteries is known to produce prostaglandins with vasodilator properties that tend to reduce basal tension. While blockage of prostaglandin production does not abolish autoregulation, it is possible that a steady rate of production of such a substance by the endothelium would enhance the degree of autoregulation, assuming that reduced flow would reduce the rate of washout by the bloodstream. Alternatively, if the plasma contains a vasoconstrictor substance, as suggested by studies of Bohr and Johansson, a reduction in flow would reduce the rate of delivery of the substance to the arterioles. Under these circumstances vasodilatation might occur in the arterioles with flow reduction.

Myogenic Hypothesis

According to this hypothesis the arterioles respond to intravascular pressure as a stimulus, with pressure elevation causing constriction. The response may be of a transient or sustained nature. Mellander and coworkers have extensively studied the transient activation of resistance vessels and portal vein strips by dynamic stretch. It appears that transient stretch caused by the arterial pulse pressure induces an especially pronounced response in the distal arterioles of skeletal muscle and may be particularly important in determining the basal vascular tone in those vessels. If arterial pressure to skeletal muscle is reduced, the metabolic mechanism apparently is quite effective in attenuating the arteriolar response to the arterial pulse.

The resistance vessels of certain vascular beds also respond in a sustained fashion to maintained pressure elevation. The sustained response is of special interest, as it would lead to autoregulation of blood flow, and will therefore be considered in detail in this section.

The evidence for a role of the sustained myogenic response in autoregulation comes about directly and also through exclusion of other possibilities. For example, in some vascular beds autoregulation persists under conditions of elevated oxygen. In rat cremaster muscle the autoregulatory dilation of arterioles was reduced but not abolished by elevated tissue O₂. Constriction of arterioles in hamster cheek pouch to elevat-
ed transmural pressure was enhanced by elevated oxygen although oxygen also caused these vessels initially to constrict.

Several techniques have been employed to test the hypothesis that arterioles constrict in response to elevated intravascular pressure. Venous pressure elevation (which increases arteriolar transmural pressure but reduces the arterio-venous pressure gradient) increases vascular resistance in some vascular beds (small and large intestine and liver) and causes arteriolar constriction in the rat mesoappendix, rat cremaster, and cat mesentery. In the rat mesoappendix and rat cremaster the constriction to venous pressure elevation is greatest in the terminal region of the arteriolar network where the pressure rise would presumably also be greatest. More recently, however, investigations that magnified the response of equal numbers of arterioles that experienced a large pressure increase and those that underwent little or no rise in local intraluminal pressure when venous pressure was elevated by a fixed amount. This observation would suggest that the mechanism of constriction of these vessels was not a myogenic response to local pressure rise. Alternatively, a myogenic constriction may have been propagated from arterioles that did experience a pressure rise. Propagated constriction is seen in the arteriolar network of the hamster skin flap during periodic vasomotion. Vasomotion in the hamster skin flap originates at vessel bifurcations, is propagated in a decremental fashion, and as a consequence, affects the vessels in the immediate vicinity most strongly.

In some vascular beds the arterial constriction to venous pressure elevation may be neurogenic in origin. A local venous-arteriolar reflex has been described in skin and skeletal muscle. However, the reflex response is abolished by increasing the level of sodium pentobarbital anesthesia. The possibility that a neural reflex is responsible for the precapillary constriction in intestine with venous pressure elevation is minimized by the fact that the experiments were done under pentobarbital anesthesia and also that sympathetic blocking agents and local anesthetics did not abolish the constrictor response. In rat cremaster muscle, venous pressure elevation also causes arteriolar constriction, which is more pronounced in the presence of elevated ambient oxygen. Other studies have also shown a sensitivity of arterioles to altered transmural pressure. Bouskela and Wiederhielm raised arterial and venous pressure simultaneously in the bat wing by placing the animal's body in a sealed chamber with the wing extended outside. Under these circumstances pressure elevation in the chamber caused arteriolar and precapillary sphincter constriction. The constriction is not likely to be due to a venous-arteriolar reflex such as seen in human skin since the terminal arterioles have inconsistent sympathetic innervation. In a somewhat similar type of experiment, lowering ambient pressure around the hamster cheek pouch preparation caused constriction of the arterioles.

Baez stopped flow in the rat mesoappendix and then elevated static intravascular pressure in the preparation. He found, under conditions of no flow, that pressure elevation caused arteriolar constriction. Johnson and Intaglietta also reported that static pressure elevation in cat mesentery caused arteriolar constriction. In addition, they found that arterioles in cat mesentery dilated moderately when flow was reduced or stopped by a microneedle applied to an arteriole at a point downstream to the site of observation, indicating that mesenteric arterioles possess a degree of flow sensitivity. However, after flow was stopped completely by microocclusion, the arteriole still dilated substantially when arterial pressure to the mesentery was reduced.

Isolated small arteries from brain show a myogenic type of constriction to intravascular pressure elevation. Vessel diameter tends to be maintained or decrease slightly as intravascular pressure is elevated in the range 55–110 mm Hg. This can best be explained as due to a stimulatory effect of the intravascular pressure. This response would aid the autoregulatory response of the brain circulation, but would appear to be too weak to account for the maintenance of constant flow seen in that organ.

The mechanism by which vascular smooth muscle senses the elevated intravascular pressure is an unsolved question. Bulbring observed that stretch of the taenia coli muscle of the guinea pig led to depolarization and increased spontaneous spike activity of the muscle. However, Bulbring found depolarization of the muscle cell to be better correlated with tension than muscle length. This observation led several workers to suggest that circumferential tension may be the controlled variable in the myogenic response of arterioles. When intravascular pressure is elevated, the myogenic response leads to a sustained shortening of the vascular smooth muscle. The sustained shortening may reflect the special geometry of smooth muscle in the arterioles and the dependence of circumferential tension on both the vessel radius and transmural pressure. This response would aid the autoregulatory response of the brain circulation, but would appear to be too weak to account for the maintenance of constant flow seen in that organ.

Several studies lend support to this hypothesis. Bouskela and Wiederhielm found that the constriction of arterioles and precapillary sphincters in the bat wing tended to maintain calculated wall tension constant during simultaneous elevation of arterial and venous pressures. Burrows and Johnson found that arterial pressure to the cat mesentery was reduced, arteriolar dilation tended to maintain wall tension. As noted by the latter authors, if the dilation were too pronounced with pressure reduction, wall tension would rise, which would not support the wall tension hypothesis. A rise in wall tension was rarely seen with arterial pressure reduction, and the results were considered consistent with the hypothesis. It would be expected that the degree of constriction of an arteriole would be proportional to the local rise in pressure in
that vessel. However, with a single step elevation of arterial pressure (or venous pressure as noted earlier) the magnitude of constriction in individual arterioles was not proportional to the local pressure change. Thus, wall tension did not appear to be well regulated when arterioles were compared with each other. As noted above, if the myogenic mechanism causes a spreading vasoconstriction, there may not be a close correlation between local pressure change and the myogenic response. However, the lack of correlation may also indicate that a variable other than wall tension is regulated.

A more critical examination of the wall tension hypothesis requires consideration of a possible transducing mechanism that would sense wall tension and stimulate the vascular smooth muscle cell to contract. Two sites on the smooth muscle plasma membrane have been proposed: 1) the myoendothelial junction and 2) the dense area on the plasma membrane where the actinomyosin filaments attach to the cell wall. In respect to the myoendothelial junction, the internal elastic lamina in many arterioles is fenestrated and allows direct contact between endothelium and vascular smooth muscle cells. It has been proposed that actual fusion of the two plasma membranes takes place in certain circumstances. As intravascular pressure rises, it is thought that the endothelial cell contents are extruded through the IEL fenestration, deforming and stretching the myoendothelial junction. This would possibly lead to a rise in membrane conductance for calcium and activation of the contractile machinery of the smooth muscle cell or alternatively to a change in conductance of other ions that influence transmembrane potential. The ensuing contraction of the vascular smooth muscle cell would tend to oppose the translocation of the endothelial cell across the internal elastic lamina and thus provide a negative feedback. However, it is not clear how such a mechanism would provide a well-modulated control system in which a rise in intravascular pressure would cause the vascular smooth muscle cell to shorten to less than its initial length. Despite this possible shortcoming, it is of interest that club-shaped protrusions of endothelial cells into vascular smooth muscle cells are common in arterioles of mesentery and interlobular arteries and afferent renal arterioles where experimental studies favor a myogenic mechanism. However, such an arrangement is more scarce in the efferent renal arterioles where a myogenic response is apparently absent. This mechanism cannot explain the stretch-induced tone in rabbit ear arteries that is not affected by removal of the endothelium.

The second proposed cellular site of transduction (the region of the plasma membrane near the dense bodies) has been suggested because this region is insensitive to the contractile machinery and, hence, the cell membrane in this vicinity should be deformed to a degree which depends on the circumferential wall tension. However, this deformation would depend on total wall tension only as a first approximation because other passive elements in the wall also are load bearing. Moreover, as the vascular smooth muscle cell contracts it would tend to unload these parallel elastic elements, and thus, the wall tension borne by the muscle would not fall as much as total wall tension when the muscle contracts. A further complicating factor is that the orientation of the contractile elements on the luminal side of the cell apparently becomes relatively more radial rather than tangential as the smooth muscle cell shortens and, therefore, relatively ineffective in load-bearing. This would suggest that those contractile filaments on the abluminal side and the associated dense bodies carry proportionately more of the load borne by the vascular smooth muscle cell. The effect of such a shift of load bearing in the cell on stretch of the cell membrane cannot be easily predicted.

Whatever the site of transduction of the myogenic response may be, there is evidence that intravascular pressure alters vascular smooth muscle transmembrane potential. Harder found that pressure elevation in isolated cerebral arteries caused membrane depolarization of 1.45 mV/10 mm Hg in vascular smooth muscle cells. The slope of this relation was directly dependent on external calcium concentration, suggesting that the latter cation may play a role in membrane depolarization. Under some circumstances these vessels also showed spontaneous spike activity that increased with pressure elevation. In respect to a possible role of calcium in the myogenic response, Baker et al and Cohen and Fray found that calcium was important in renal autoregulation under conditions where only the myogenic mechanism appeared to be involved. Addition of calcium channel blocking agents nifedipine or verapamil abolished autoregulation. Also, raising Ca++ in the perfusate from 0 to 1.8 mM did not alter vascular resistance at an arterial pressure of 50 mm Hg but did increase resistance at 100 and 150 mm Hg. Haws and Heistad showed that a calcium blocker, nimodipine, virtually abolished the autoregulatory response in pial arterioles to elevated arterial pressure.

Guharay and Sachs recently demonstrated single ionic channels in skeletal muscle that are activated by stretch. The channels are apparently not specific for calcium but provide a possible mechanism by which force applied to vascular smooth muscle might alter transmembrane ion fluxes and transmembrane potential.

In respect to the role of a myogenic mechanism in autoregulation of blood flow, a question remains as to how flow could be regulated effectively by a tension or pressure-sensitive mechanism. If the arteriolar network is regarded as a single resistance element which acts as a unit to constrict when internal pressure is elevated, a reasonable degree of autoregulation can be expected, provided that there is only a moderate range of variability of control system gain. However, if the system gain is high, an inverse relation between flow and arterial pressure would be expected and might lead to a vicious cycle, where constriction generally in the peripheral vasculature would lead to a further rise in arterial pressure which would beget further constriction, etc., as suggested by Hall. It is true that a rise in
total vascular resistance would tend to increase systemic arterial pressure. But a true vicious cycle could be induced only if the rise in total vascular resistance were greater than the rise in systemic arterial pressure. The possibility of this occurring is unlikely because baroreceptor reflexes would come into play. Also the autoregulatory mechanism has an upper limit (generally around 160 mm Hg) above which resistance declines with further pressure increase. In addition, some vascular beds autoregulate poorly and would attenuate the total resistance rise.

The degree of over-regulation in individual organs is limited by the fact that part of the total resistance of the peripheral vascular bed is relatively fixed (i.e., in capillaries, venous vessels, and perhaps large arteries). As a consequence, moderate changes of the gain in the arteriolar portion of the network would not cause a radical shift in the pressure–flow curve as described in earlier studies. This type of unitary myogenic controller could however explain the occasional report of increased flow in individual organs or microcirculatory vessels with reduced arterial pressure (super-regulation) cited above.

An alternative myogenic control system that provides for a higher degree of precision in flow autoregulation is the series-coupled independent effector system. In this model the individual arteriolar branches operate independently of each other and respond to internal pressure elevation by contracting. It is not required that the individual vessels sense tension. The behavior of this system can be illustrated by considering the response when arterial pressure is reduced modestly. Pressure in the larger arterioles will be affected more than distal vessels and the large vessels will dilate, reducing the pressure drop through them and tending to restore pressure in the mid-sized arterioles downstream. If the larger arterioles dilate sufficiently to restore normal pressure in the mid-sized arterioles to normal, the latter vessels will not dilate. However, if dilation of the larger arterioles is inadequate, pressure in the mid-sized arterioles will be reduced and they will also dilate to bring pressure in the more distal arterioles back to normal levels. Downstream from the point in the arteriolar network where pressure is restored to normal by dilation, the pressure profile and dimensions of the network will be identical to the control state. If this is the case, it follows that flow will also be returned exactly to control levels. If arterial pressure is reduced further the vasodilation will extend further downstream. When the vasodilation extends to the most distal branches of the arteriolar network the autoregulatory capability of the network will be exhausted and any further reduction in arterial pressure will lead to a decrease of flow. The detailed characteristics of such a model have been examined in respect to the interlobular arteries and afferent arterioles and good flow autoregulation is predicted by the model.

A noteworthy feature of this model is that blood flow can be perfectly regulated although flow itself is not sensed. Flow regulation is secondary to regulation of intravascular pressure in the myogenically active vessels. It also follows that pressure in the capillary network will be autoregulated so long as flow is held constant.

The fact that individual arteries and arterioles in vitro contract in response to pressure suggests that a network composed of independent myogenic effectors is not an unreasonable model. However, in vivo, periodic vasomotion seems to spread over localized regions of the arteriolar network. Moreover, this vasomotion is pressure dependent, i.e., the frequency of vasomotion increases when pressure is elevated. Thus, it is quite possible that the myogenic response of individual vessels to pressure elevation spreads to adjacent vessels and the response of each vessel to local pressure changes is enhanced by vasoconstrictor input from adjacent vessels. In this way the constriction of an individual arteriole to pressure elevation in the network may be more pronounced than would be seen in the same vessel in isolation. This may serve to increase the overall gain of the system. Speden has noted that the contractile response of the isolated rabbit ear artery to pressure elevation is less pronounced than reported for individual arterioles in a network. He suggested that the presence of the vessel in the network may enhance the response. While this may be the case, studies of vasomotion suggest that the spread is decremental and would not make the entire arteriolar network behave as a single unit.

**Tubuloglomerular Feedback (TGF) Hypothesis**

Autoregulation was first described in the kidney and that organ regulates blood flow extremely well in the arterial pressure range 70–140 mm Hg in the dog and 105 to 165 mm Hg in the rat. The main candidates for autoregulatory control in the kidney are the myogenic response and the tubuloglomerular feedback mechanism. According to the TGF hypothesis, an increase in arterial pressure leads first to increased glomerular filtration. According to Navar et al the increase in glomerular filtration rate would increase the solute and electrolyte concentration in the tubular fluid at the macula densa. Specialized cells in the macula densa are thought to sense changes in the tubular fluid. The sensed variable has been suggested to be solute or sodium chloride concentration. The nature of the constrictor stimulus from the macula densa to the smooth muscle cells of afferent arteriole is not known but appears not to be mediated by the renin–angiotensin system. Studies by Hall provide several lines of evidence which discount this mechanism as of importance in regulation of afferent arteriolar tone.

If a rise in solute and/or electrolyte concentration acts as a stimulus to the macula densa, the system should behave as a proportional controller. It might appear that perfect regulation of renal blood flow and hence glomerular filtration rate would require that the macula densa be exquisitely sensitive to the change in tubular fluid solute or electrolyte concentration. This need not be the case, however, since a small but sig-
significant fall in volume reabsorption was seen in hypovolemic animals when arterial pressure was elevated. This effect, whatever its cause, would provide a residual offset or error signal even in the face of perfect flow autoregulation. However, perfect flow autoregulation by this mechanism would require that the sensitivity of the macula densa receptor system and the fall in volume reabsorption be quantitatively matched so as to provide adequate arteriolar constriction with arterial pressure elevation. Otherwise the system would likely over- or under-compensate and renal blood flow would not be held constant in response to changes in arterial pressure.

There is evidence that the tubuloglomerular feedback mechanism does not act alone in regulating renal blood flow. Knox et al. found that autoregulation of the glomerular filtration rate persisted in superficial blood flow. Moreover, arterial arterioles in renal tissue transplants in the hamster cheek pouch constrict when vascular transmural pressure is elevated. A myogenic mechanism could be activated secondarily to constriction of the distal afferent arteriole by the TGF mechanism since such constriction would tend to elevate pressure in the arteriolar network immediately upstream and therefore lead to myogenic constriction in those vessels. TGF alone may be unable to regulate flow since the control is located at the distal end of the arteriole and therefore could not influence the total arteriolar network unless there is an ascending vasoconstriction of myogenic or other origin.

**Tissue Pressure Hypothesis**

If tissue pressure is to play a role in autoregulation it must vary with arterial pressure and be high enough in the initial state to be an appreciable fraction of arterial pressure. The best evidence for a role of tissue pressure was obtained by Hinshaw in the isolated, pump-perfused kidney. The importance of this mechanism has been questioned because pump-perfusion may have rendered the kidney preparation edematous and, therefore, tissue pressure may have been elevated above normal levels. However, such conditions may obtain in tissue injury, at least in encapsulated organs. In addition to the kidney, the brain would appear to be a likely organ for such autoregulation during tissue injury. In the case of head injury, autoregulation of cerebral blood flow is seen in areas of cortex where injury is more severe while it is absent in areas less severely injured. This observation led Enevoldsen and Jensen to suggest that head injury causes a general depression of vascular responsiveness, leading to autoregulatory loss in most areas. However, autoregulation due to changes in tissue pressure (as a result of capillary leakage), which the authors characterized as "false autoregulation," may occur in the most severely injured tissues. Decompression of the affected area abolishes this type of autoregulation.

**Maintenance of Capillary Pressure**

When blood flow is held constant by the autoregulatory response, it is to be expected that there will be a constant capillary pressure as well. From the relation \( P_c = P_v + F \cdot R_v \), where \( P_c \) = capillary pressure, \( P_v \) = venous pressure, \( F \) = blood flow, and \( R_v \) = venous resistance, it can be seen that capillary pressure can be expressed in terms of flow rather than in terms of arterial pressure. If arterial pressure changes and autoregulatory mechanisms are strong enough to maintain a constant flow, capillary pressure should be unaltered and independent of arterial pressure. There is evidence for this behavior, for example, in the kidney, where autoregulation maintains a constant glomerular capillary hydrostatic pressure by adjustment of afferent arteriolar resistance. Since efferent arteriolar resistance is also substantial, constant glomerular filtration depends on the latter remaining constant.

In other vascular beds (hind limb, intestine) capillary hydrostatic pressure as measured by the isogravimetric or isovolumetric method seems to be nearly independent of arterial pressure in the autoregulatory range. Microcirculatory pressure measurements, however, do not provide unequivocal support for this concept. Gore found instances in which capillary pressure in mesentery measured directly by the servo-null technique was not maintained as arterial pressure fell. Also, in capillaries where hydrostatic pressure was maintained it appeared that flow redistribution at the precapillary level was responsible. Redistribution could explain pressure maintenance in individual capillaries but would not seem to account for general maintenance of pressure in the capillary bed as reported in whole organ studies. The degree to which capillary pressure is autoregulated in a given vascular bed depends on the degree of flow autoregulation and also on whether postcapillary resistance remains constant or varies with changes in arterial pressure. These factors have not been examined in microcirculatory studies to the same extent as in whole organ studies.

It is likely that capillary pressure would be autoregulated to a different degree than flow if there were simultaneous changes in venous resistance. In skeletal muscle and intestine it has been shown that venous resistance rises as arterial pressure is reduced, especially below the range in which flow is regulated. In intestine a local arterio-venous reflex may be involved. In muscle, there is evidence that suggests that blood viscous resistance in the venules increases as blood shear rate decreases. The number of venules with flow or the diameter of the venules in skeletal muscle does not change significantly as arterial pressure is reduced. But direct measurements in small (4th order) venules show that pressure in these vessels is well maintained as flow falls.

**Localization of Autoregulatory Adjustments**

It has been shown that arterioles participate strongly in the autoregulatory response in brain, skeletal muscle, and cat mesentery. Studies in which pressure
was directly measured in small arteries and determined in the capillary bed by the isogravimetric method indicate that the larger arteries do not contribute to autoregulatory response in intestine. By contrast, in the kidney it appears that interlobar arteries and afferent arterioles but not efferent arterioles participate in the autoregulatory response. In the brain there is a substantial pressure drop in the large and small arteries and these vessels may contribute appreciably to the autoregulatory response.

**Interaction Among Control Systems**

In the brain there is evidence that the arteries are under myogenic control while the pial and smaller arterioles imbedded in the tissue are principally under metabolic control. This is an example of a series arrangement of myogenic and metabolic control. As noted above, constriction of the distal afferent arteriolar segment in the kidney by the TGF system may tend to raise upstream pressure and therefore cause further myogenic constriction. This would represent a series arrangement, in this case of myogenic and TGF control mechanisms. The myogenic and metabolic systems may also be present in parallel in some tissues. In the rat cremaster muscle it appears that both metabolic and myogenic mechanisms are present in the arterioles since elevation of PO₂ with a suffusing solution reduced but did not abolish arteriolar responses to arterial pressure changes. In cat mesentery the arterioles are sensitive to changes in both pressure and flow. In this instance it appears that the two mechanisms act somewhat independently since the arterioles dilate substantially with arterial pressure reduction even after flow is stopped locally by micro-occlusion.

In the presence of other types of vasomotor input, i.e., humoral and nervous vasoconstrictor stimuli, the myogenic and metabolic mechanisms may still be effective in producing autoregulation. In the brain, stimulation of the sympathetic fibers apparently causes only constriction of the large arteries and a transient fall in flow. The flow rapidly returns to normal as the autoregulatory adjustment occurs in the downstream vessels. The brain may be somewhat unusual in this respect as it lacks sympathetic innervation of the arterioles. In skeletal muscle there is histological evidence that sympathetic nerves extend to the smallest arterioles and induce constriction of those vessels when stimulated. However, there is also evidence that sympathetic innervation is not continuous in the terminal arterioles of the bat wing. Thus, it might be expected that this tissue would behave similarly to brain, with sympathetic stimulation lowering blood flow only transiently. This sympathetic escape phenomenon has been linked to autoregulation although it is not clear that the mechanism would be identical in all cases.

In skeletal muscle, sympathetic stimulation elicits constriction in both large and small arterioles as well as in large arteries but the constriction is not maintained in the smaller arterioles. The escape of the small arterioles is in the face of continuing sympathetic excitation and apparently represents an instance where local mechanisms dominate when there is direct opposition between central and local mechanisms. In the larger vessels in skeletal muscle apparently there is similar opposition but central mechanisms prevail.

The degree of autoregulation that occurs in various organs during systemic arterial pressure reduction will depend on the interplay of central and local mechanisms. When systemic blood pressure is reduced there is an increase in sympathetic outflow and circulating plasma levels of Angiotensin II and ADH which would cause vasoconstriction. At the same time the autoregulatory mechanisms should counteract the former. The net result in skeletal muscle arterioles is constriction in larger arterioles and dilation of the more distal arterioles. The latter can be prevented in thin muscle by elevating the O₂ level over the muscle surface. Sympathetic nerve stimulation does not inhibit autoregulation in the brain but does alter the autoregulatory range. Under these circumstances the arteries are constricted and the small resistance vessels are believed to be already dilated to a degree to maintain constant blood flow at normal arterial pressure. As a consequence, the lower limit of autoregulation in brain is reached at a higher than normal arterial pressure. But the upper limit is also elevated. Based on the considerations discussed above in respect to sympathetic escape, it is possible that vascular beds with innervation throughout all levels of the arteriolar network would also show an alteration of the autoregulatory range. It is believed that alteration of the autoregulatory range is of particular importance in the brain because the sympathetic constriction acts in concert with autoregulation to protect the capillary network against the disruptive effects of elevated capillary pressure.

**Long-Term Autoregulation and Structural Changes**

Most studies of blood flow autoregulation involve very short term pressure adjustments, sometimes of only a few minutes duration. Guyton and coworkers have pointed out that the vascular adjustments to sustained alteration in arterial pressure may differ in mechanism from acute changes. In the areflexic animal, autoregulatory responses are more pronounced over a period of hours than over a few minutes. Guyton suggests that the more slowly developing autoregulation is more important than the acute response since the latter is quite weak, at least in the areflexic animal. Moreover, when systemic arterial pressure is chronically elevated over a longer time period (i.e., days or weeks), structural changes take place in the walls of arteries and arterioles that elevate vascular resistance: Folkow and co-workers favor the view that this structural type of autoregulation is due to a thickening of the arteriolar wall with consequent narrowing of the arteriolar lumen. Microcirculatory studies have shown that in spontaneous hypertension there is a decrease in arteriolar density that could also serve to elevate resting vascular resistance. Whatever the nature of the structural change, arteriolar resistance increases and this tends to maintain a constant blood flow. If capil-
lary and venous circuits are not structurally altered, one would expect that capillary pressure would also be maintained at near normal levels. Studies by Meininger et al indicate that in some types of hypertension the elevated pressure is dissipated in the arteriolar network, leading to normal or near normal pressures in the capillary network.

Chronic reduction of pressure and flow by ligation of a feeding artery leads to a change opposite to that described above, that is, a reduction in structural vascular resistance in the downstream vascular bed. Microcirculatory studies after arterial ligation have shown a proliferation of arterioles and return of total blood flow in the cremaster muscle to normal levels. The stimulus for proliferation of arterioles in this circumstance is not known, although it is generally recognized that vasculogenesis is promoted under conditions where tissue PO<sub>2</sub> is below normal levels, perhaps due to activation of baroceptor reflexes. Autoregulat ory dilation of arterioles in cat mesentery was substantially weakened when a supplemental dose of Na pentobarbital was given. Given the clinical and experimental importance of the anesthetic effects, it is surprising that this area is not better understood.

**Abolition of Autoregulation**

Autoregulation is easily impaired, as those who have attempted to study it experimentally can testify. It is often abolished under experimental conditions that involve extensive perfusion circuitry. Surgical preparation of the tissue may also render arterioles unresponsive to arterial pressure reduction. There is also evidence in brain injury, as noted above, that autoregulation is impaired or abolished. Arterial hypoxia to less than 60% saturation abolished cerebral blood flow autoregulation in man according to one study, while in another study autoregulation was maintained with a comparable degree of hypoxia. By contrast, Granger et al found that arterial hypoxia (exact level undetermined) enhanced autoregulation in skeletal muscle due to a reduction of tissue PO<sub>2</sub>.

Anesthetics are known to adversely affect autoregulation although the results are variable depending on the depth of anesthesia and type of anesthetic. Smith et al found cerebral autoregulation was well maintained under light nitrous oxide anesthesia. With deep cyclopropane anesthesia cerebral autoregulation was maintained when arterial pressure was elevated above normal levels but not when pressure was reduced below normal levels, apparently because the resistance vessels were already nearly maximally dilated. Milteich et al also found that cerebral autoregulation was weakened as evidenced by a higher pressure threshold for autoregulation with enflurane and halothane under moderate anesthesia (0.5 MAC) but that as the anesthetic level with halothane was elevated (1.0 MAC) autoregulation was lost. Perhaps the anesthetic used is important since, as noted earlier, Donegan et al found cerebral autoregulation was maintained in sheep during pentobarbital coma. In the isolated kidney halothane (0.9%) did not abolish autoregulation, but when systemic pressure was altered by varying anesthetic depth, renal blood flow was not autoregulated, perhaps due to activation of baroceptor reflexes. Autoregulatory dilation of arterioles in cat mesentery was substantially weakened when a supplemental dose of Na pentobarbital was given. Given the clinical and experimental importance of the anesthetic effects, it is surprising that this area is not better understood.

**Significance of Short-Term Autoregulation**

When systemic arterial pressure is acutely reduced to an organ, flow is better maintained in vital organs such as brain, skeletal muscle, liver and the gastrointestinal tract. This comes about because autoregulation is stronger in brain and myocardium and also because sympathetic innervation is considerably weaker in the latter organs.

When systemic arterial pressure is acutely elevated, the autoregulatory response in kidney, brain, and myocardium would tend to prevent an increase in flow while organs that do not autoregulate well would experience overperfusion. Assuming nutritional supply is adequate initially, perhaps the most important homeostatic consequence of the elevated flow in poorly autoregulating organs would be the rise in capillary pressure. The fact that some vascular beds do not autoregulate well provides a safety valve for the arterial circuit that would tend to attenuate the pressure increase. From a homeostatic standpoint it would seem optimal if the less vital organs had a lesser degree of autoregulation than the vital organs such as brain. In respect to the brain, when arterial pressure is above the autoregulatory range, the rise in capillary pressure can lead to disruption of the blood–brain barrier.

Organs which autoregulate blood flow incompletely in the resting state (skeletal muscle, intestine) are capable of a high degree of autoregulation under conditions of increased metabolic demand. Under such conditions these organs would behave, to a large degree, like brain and myocardium when systemic pressure is altered, with the proviso that their greater sympathetic innervation would probably render them more susceptible to baroceptor reflex control.

An obvious beneficial aspect of autoregulation that apparently has not been fully explored to date is the ability of the vascular bed to compensate for increased resistance in the large arteries in atherosclerosis. When arteries become stenosed to the degree that downstream pressure is appreciably reduced, it is to be expected that there will be dilation of the arterioles and maintenance of constant flow, although the vasodilator reserve of these vessels will be diminished. In accordance with this, a study of atherosclerosis in monkeys indicated that cerebral blood flow autoregulation was not impaired in the pressure range of 86–51 mm Hg and control blood was normal. However, maximal vasodilator response to hypercapnia was impaired.

**Conclusions**

Over the past 20 years, substantial new evidence has been obtained in support of the metabolic, myogenic,
and tubuloglomerular feedback mechanisms of blood flow autoregulation. The relative contribution of the metabolic and myogenic mechanisms varies considerably among vascular beds, and in a few tissues, apparently, a single mechanism is responsible for autoregulation. In organs where both mechanisms are present we do not have a good idea of their relative importance. Moreover, the contribution of each may vary according to the metabolic activity of the tissue as well as experimental conditions of the study.

The metabolic or flow-dependent mechanism of blood flow autoregulation appears to depend on tissue levels of oxygen, probably acting through alterations in tissue metabolism. However, a direct effect of oxygen on the resistance vessels cannot be excluded. The heterogeneous nature of tissue PO2 distribution suggests that areas of low oxygen tension may act as primary sites of flow regulation by producing vasodilator substances as oxygen delivery fails. The identity of specific chemical mediators produced in such hypothesized areas remains to be determined.

The myogenic mechanism may be due to a sensitivity of the vascular smooth muscle cell to tension in the arteriolar wall. How this takes place is not clear, but stretch-sensitive ionic channels in the cell membrane such as described in skeletal muscle could act as the force sensor. Changes in smooth muscle transmembrane potential observed with transmural pressure elevation suggest that a membrane event may be involved. Clearly, more information is needed at the cellular level to understand the operative mechanisms.

The tubuloglomerular feedback mechanism contributes importantly to autoregulation in the kidney, apparently by sensing changes in tubular solute concentration. The nature of the stimulus to the juxtaglomerular apparatus and from the latter to the tubuloglomerular feedback mechanism also contributes importantly to other aspects of renal function it will not doubt continue to be an area of intensive research.

The homeostatic importance of autoregulation has usually been seen in terms of maintaining constant blood flow and nutrient supply. However, it can also maintain a relatively constant capillary pressure that is important for tissue fluid balance. Autoregulation also serves an important protective role in preventing capillary pressure from rising to levels that would damage the exchange vessels, especially in the brain, with acute elevation of arterial pressure.

The importance of the autoregulatory mechanism in disease states has been examined to a relatively small extent. While it doubtless serves as a valuable local homeostatic mechanism when arterial pressure is altered, it is possible that it accentuates at least modestly the systemic arterial pressure rise in acute hypertension by contributing to the increase in total vascular resistance.

Clarification of the uncertainties that still surround the phenomenon of autoregulation will probably arise in part from studies of other fundamental questions rather than autoregulation itself. It is to be expected, however, that autoregulation of blood flow will continue to interest many researchers because of its normal and pathophysiological importance and because it reveals the behavior of local mechanisms of flow regulation without the complication of simultaneously involving other, i.e., central, control mechanisms.

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